UNIVERSITAT DE BARCELONA

DEPARTMENT OF PSYCHIATRY AND CLINICAL PSYCHOBIOLOGY

SCHOOL OF MEDICINE

STRUCTURAL BRAIN CHANGES, COGNITIVE DEFICITS AND VISUAL HALLUCINATIONS IN DEMENTIA WITH LEWY BODIES AND PARKINSON'S DISEASE WITH DEMENTIA

Cristina Sánchez-Castañeda

Barcelona, November 2009

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Structural Brain Changes, Cognitive Deficits and Visual Hallucinations in Dementia with Lewy Bodies and Parkinson's Disease with Dementia

Thesis presented to obtain the Degree of Doctor
in accordance with the requirements of the European PhD Diploma

Cristina Sánchez-Castañeda

Supervisors:
Dr Carme Junqué Plaja, University of Barcelona
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We, the undersigned,

Dr CARME JUNQUÉ PLAJA, Professor at the University of Barcelona, and
Dr RAMÓN REÑÉ RAMÍREZ, of Bellvitge University Hospital,

declare and confirm that we have supervised and guided the PhD thesis entitled **"STRUCTURAL BRAIN CHANGES, COGNITIVE DEFICITS AND VISUAL HALLUCINATIONS IN DEMENTIA WITH LEWY BODIES AND PARKINSON'S DISEASE WITH DEMENTIA"** presented by Cristina Sánchez-Castañeda. We hereby assert that this thesis fulfils the requirements to be defended for the Degree of Doctor.

Signatures,

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This thesis has been carried out at the Department of Neurology of Bellvitge University Hospital and at the Neuropsychology Group, Psychiatry and Clinical Psychobiology Department, School of Medicine, University of Barcelona. The groups belong respectively to the Institut d'Investigacions Biomèdiques de Bellvitge (IDIBELL) and the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS).

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En recuerdo a mi padre

"somos quienes somos por obra de lo que aprendemos y de lo que recordamos"

"we are who we are largely because of what we learn and what we remember. We learn the motor skills that allow us to master our environment, and we learn languages that enable us to communicate what we have learned, thereby transmitting cultures that can be maintained over generations."

ERIC R. KANDEL.
Principles of Neural Science. 4th edition.

A mi madre, a Francesco

Si uno empieza con certezas, acabará con dudas; pero si se conforma empezando con dudas, conseguirá acabar con certezas.

If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts he shall end in certainties.

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FOREWORD

This thesis, presented to obtain the degree of Doctor by the University of Barcelona, is the result of a research project carried out at the Bellvitge University Hospital and the Department of Psychiatry and Clinical Psychobiology, School of Medicine, University of Barcelona. During this period, I have obtained the Diploma d'Estudis Avançats (DEA) through the Neurosciences Program of the School of Medicine at the University of Barcelona.

The following papers has been published and/or accepted in 1st quartile international journals with a global impact factor (IF) of 7.796 (ISI of Knowledge, Journal Citation Reports inferred from 2008):

Study I:

Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, Campdelacreu J, Gascon J, Falcon C, Calopa M, Jauma S, Juncadella M, Junque C. ***Correlations between gray matter reductions and cognitive deficits in dementia with Lewy Bodies and Parkinson's disease with dementia.*** *Movement Disorders, 2009; 24(12):1740-6.* ***IF: 3.898.***

Study II:

Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, Campdelacreu J, Gascon J, Falcon C, Calopa M, Jauma S, Juncadella M, Junque C. ***Frontal and associative visual areas related to Visual Hallucinations in Dementia with Lewy Bodies and Parkinson's Disease with Dementia.*** *Accepted in Movement Disorders, 2009.* ***IF: 3.898.***

GLOSSARY OF ABBREVIATIONS

AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ChAT	Cholin acetyltransferase
ChEI	Cholinesterase inhibitor
CNT	Control subject
CSF	Cerebrospinal Fluid
DLB	Dementia with Lewy Bodies
DTI	Diffusion Tensor Imaging
DWMH	Deep White Matter Hyperintensities
FA	Fractional Anisotropy
GM	Gray Matter
IQ	Intelligence Quotient
LBD	Lewy Body Disease
LBs	Lewy Bodies
LNs	Lewy Neurites
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
MTL	Medial Temporal Lobe
PD	Parkinson's Disease
PDD	Parkinson's Disease with Dementia
PET	Positron Emission Tomography
PVH	Periventricular Hyperintensities
ROI	Region of Interest
rCBF	Regional Cerebral Blood Flow
SN	Substantia Nigra
SPECT	Single-Photon Emission Tomography
SPM5	Statistical Parametric Mapping
STN-DBS	Subtalamic Nucleus Deep Brain Stimulation
UPDRS	Unified Parkinson's Disease Rating Scale
VBM	Voxel-based Morphometry
WM	White Matter
WMH	White Matter Hyperintensities
WAIS	Wechsler Adult Intelligence Scale

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INTRODUCTION

1.1 Lewy Body Disease

Lewy Body Disease (LBD) refers to a spectrum of disorders characterized pathologically by the presence of neuronal intracytoplasmatic inclusions containing aggregated α-synuclein (McKeith *et al.* 1996; 2005). Proteinopathies are diseases in which certain protein become structurally abnormal. Thus, abnormalities of proteins (such as amyloid beta peptide, α-synuclein protein, and hyperphosphorylated tau protein) account for 70% of all dementias in elderly subjects and more than 90% of all neurodegenerative dementias (Cummings, 2003). These disorders share pathogenetic mechanism as aggregation of misfolded polypeptides that are not degraded appropriately by the ubiquitin-proteasome system and accumulate within affected and vulnerable cells. Soluble monomers of the disease proteins are converted into insoluble species that may be present for extended periods of time before they are converted into morphologically detectable inclusions. These aggregates may originate from post-translational modifications of crucial proteins, abnormal solubility, fibrillation and aggregation of single proteins (Ferrer, 2009). Different groups of proteinopathies have been described depending on the prevalent aggregated protein. Parkinson's disease (PD), Parkinson's Disease with dementia (PDD) and dementia with Lewy bodies (DLB) all present with an abnormal α-synuclein metabolism that leads to the formation of protein aggregates called Lewy Bodies (Cummings, 2003; Ferrer, 2009). These diseases have therefore been grouped into one single nosological entity called Lewy Body Disease (LBD) or more widely synucleinopathies.

Disorders of α-synuclein aggregation are the second cause of neurodegenerative dementia after Alzheimer's disease (AD) (McKeith *et al.* 1996; 2005; Galvin *et al*. 2006). It's prevalence has been estimated to range from 10 to 28.4% of all clinically demented patients (Wakisaka *et al.*, 2003; McKeith *et al*. 2005). Since PDD and DLB present with considerable clinical overlap of signs and symptoms, combining fluctuating cortico-subcortical neuropsychological impairment with neuropsychiatric features and motor parkinsonian symptoms, whether DLB and PDD may or not be different manifestations of the same disorder is nowadays debated.

1.1.1. Neuropathological studies

Lewy Body Disease postmortem diagnosis is based on histological evidence of specific inclusion bodies, which appears as spindle- or thread-like *Lewy Neurites* (LNs) in cellular processes, and in the form of *pale bodies* and *Lewy bodies (LBs)* in the cytoplasm of the neurons (Braak *et al*., 2006a). LBs are usually present as spherical or reniform, weakly acidophilic inclusion bodies with smooth surfaces, varying in shape and size (Braak *et al*., 2003). Figure 1.

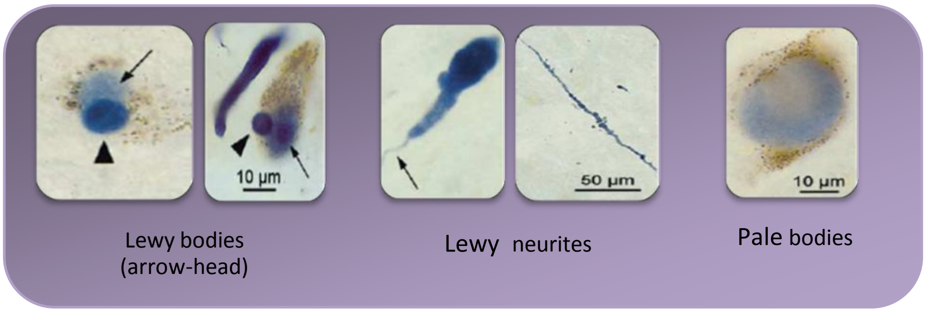


Figure 1. Specific inclusions in Lewy Body Disease (Modified from Braak *et al*., 2003)

LBs were described for the first time by Foster and Lewy in 1912 in the brain of patients with *parálisis agitans*, afterwards called PD (McKeith *et al*., 1996; McKeith *et al.*, 2005). Years later, Hassler *et al.* (1938) described cortical LBs in these patients, but it was not until 1961 that Okazaki suggested their possible relationship with dementia (Okazaki *et al*., 1961). LBs have been found in the cortex of nearly all PD patients, particularly in PD patients with dementia (Matilla *et al.*, 1998; Hurtig *et al*., 2000; Lippa *et al.,* 2007; Jellinger, 2009a).

The main component of LBs and LNs is an aggregated form of the presynaptic protein α-synuclein. The physiological functions of this protein are modulation of synaptic plasticity and control the transport and release of dopamine vesicles at the synaptic level (Braak *et al*., 2003; Cummings, 2003). Under physiological conditions α-synuclein is natively unfolded, but very sensitive to environmental and intrinsic factors such as genetic factors, mitochondrial abnormalities, exposure to oxidative stress, pesticides, metal ions, α-synuclein phosporilation that may cause a modification of its conformation, and trigger its folding in β-sheets, facilitating dimer formation, aggregation into soluble oligomers (protofibrillar species) and assembly into insoluble amorphous and fibril aggregates. Oxidative dimer formation represents the initial step in fibrillogenesis (Krishnan *et al*., 2003; Ferrer, 2009). Figure 2 illustrates the process of α-synuclein modification and aggregation.

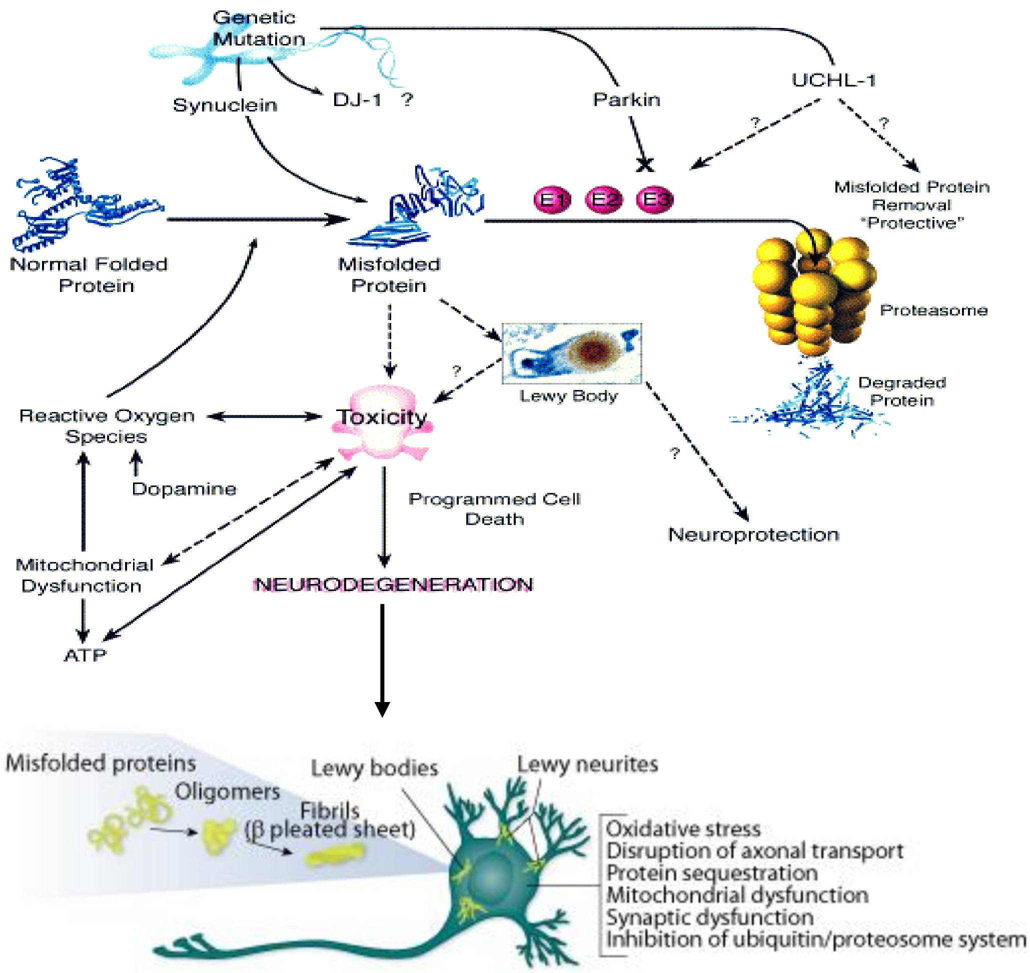


Figure 2. α-synuclein modification and aggregation (*Source*: Dauer and Przedborski, 2003; Lee and Trojanowski *et al.*, 2006)

Of the many nerve cell types within the nervous system, only a few develop inclusions, and this selective involvement reflects the regional distribution pattern of the pathology. PD is a multisystem disorder that not only affects the doparminergic nerve cells of the substantia nigra but also other regions and transmitter systems (Braak *et al.*, 2006a). Cells showing α-synuclein aggregates are: a) projection neurons that generate an axon that is disproportionately long and thin in relation to the size of the cell soma; b) long and thin unmyelinated or poorly myelinated axons; c) melano-neurons in the substantia nigra and other mesencephalic nucleus, whereas adjacent non-melanized nerve cells within the area of destruction do not develop LNs/LBs (Braak *et al.*, 2003; 2006a).

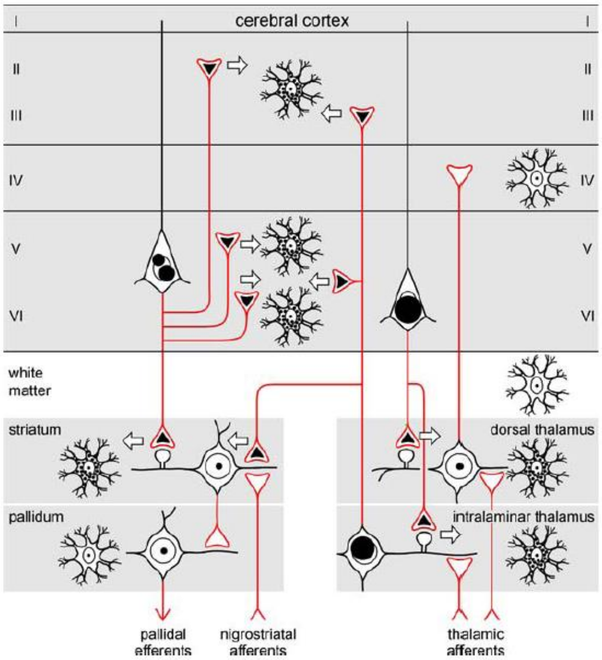


Figure 3. Selective neuronal vulnerability in Parkinson's Disease (*Source*: Braak *et al.,* 2006)

On the contrary a well-developed myelin sheath provides two potentially neuroprotective features (Braak *et al.,* 2006a): 1) a Reduced energy expenditure; a neuron with a well-myelinated axon requires less energy than a weakly myelinated one to transmit impulses. Less myelinated projection neurons are more exposed to increased levels of oxidative stress. 2) Greater structural stability; the interaction between the axon and oligodendroglial cells that produce and sustain the myelin sheath stabilizes the neuron and makes it less susceptible to pathological sprouting.

The inclusions themselves however may not be neurotoxic (Ferrer, 2009). New theories suggest that they may have a neuroprotective function (Windisch *et al*., 2007; Monti *et al.,* 2007; Batelli *et al.,* 2008), while others suggested that protein oligomers that precede the formation of intracellular deposits may exert a neurotoxic effect and in some cases protein accumulation itself may further interfere with normal cellular function (Lippa *et al*., 2007).

Table 1 and Figure 4 illustrate how the impaired metabolism of different proteins leads to different disease phenotypes. Synucleinopathies, or dysfunction of α-synuclein protein, include PD (sporadic and genetic forms with α-synuclein mutations), DLB, multiple system atrophies (Shy–Drager syndrome, striatonigral degeneration, olivopontocerebellar atrophy) (Gilman *et al.,* 2008), and neurodegeneration with iron accumulation type 1 (Hallervorden–Spatz syndrome, neuroaxonal dystrophy) (Cummings, 2003a).

Table 1. Protein Metabolism Abnormalities Characteristic of Major Neurodegenerative Disorders (Modified from Cummings, 2003; Ferrer, 2009)

Amyloid-β protein	• Alzheimer's disease
α-synuclein	• Parkinson's Disease • Dementia with Lewy Bodies • Multisistemic Atrophy • Neurodegeneration with Iron Accomulation
Hyperphosphorylated tau protein	• Alzheimer's Disease • Fronto-temporal lobar degeneration linked to MAPT gen mutations • Corticobasal degeneration • Supranuclear progressive Palsy • Parkinson's Disease • Pick Disease
Other proteins	• Prion proteins: Creutzfeld-Jakob disease, Kuru, Fatal familial insomnia.. • Increased repetition of triplets: Hungtinton's Disease, hereditary ataxia

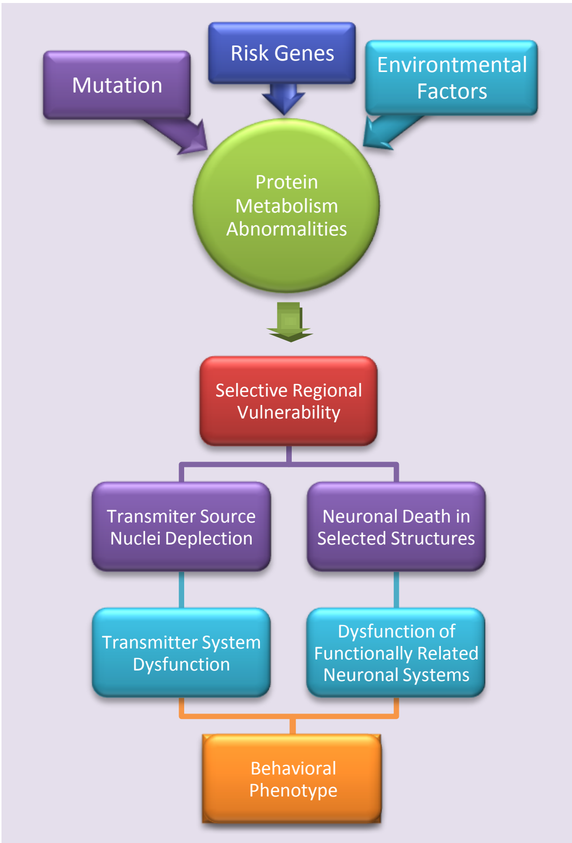


Figure 4. Schema of relationship between causative factors, proteotypes and phenotypes (*Source*: Cummings *et al*., 2003).

The most frequent α-synucleinopathies are *sporadic PD* and *DLB,* both manifest as progressive multisystem neurodegenerative disorders. For both diseases the clinical dysfunction showed a correlation with the distribution and progression pattern of Lewy-related/ α-synuclein pathology. It has been proposed that LBs may be localized in the brainstem in PD patients and extend to limbic and neocortical areas in DLB and PDD (Cummings, 2003; Lippa *et al.,* 2007). Staging and classification systems are based on these assumptions.

In **PD,** the Braak and Braak staging procedure (Braak *et al*., 2003; 2006) rests on the assumption that incidental LB pathology is the first step along a disease continuum. Sporadic PD is regarded as a dynamic biological process because: a) the pathological process increases in extent and severity with disease duration; b) severity of changes is not related to age.

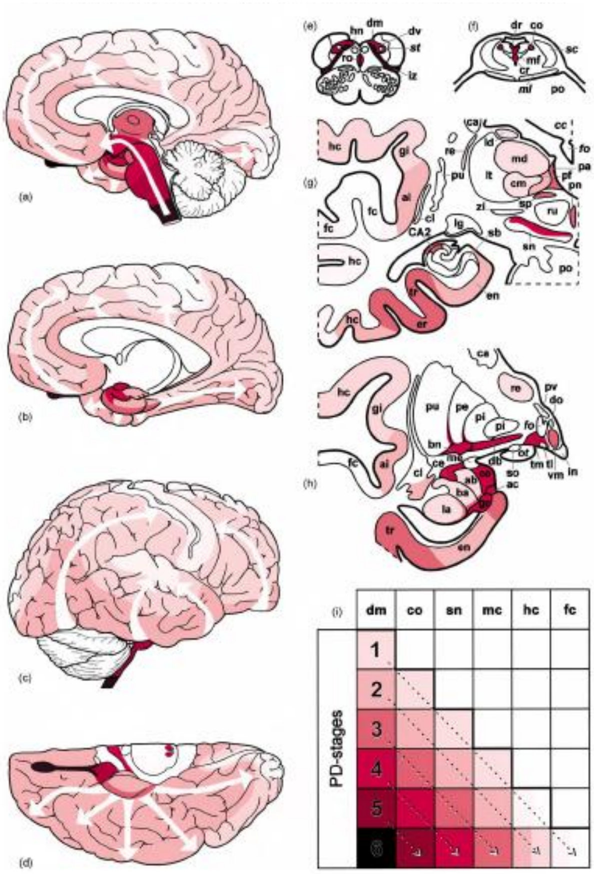


Figure 5. Porgession of PD-related intraneuronal pathology
(*Source*: Braak et al., 2003)

As illustrates Figure 5, in a scale of 6 stages the pathological process begins at specific predilection sites in the brain, and then advances in a topographically predictable sequence with ascending progression from medullary and olfactory nuclei to the cortex (Further details in *Section 1.2.*). The first two pre-symptomatic stages refer to incidental

LB disease (with LB pathology in the medulla oblongata: dorsal IX/X motor nucleus and olfactory bulb); motor symptoms appear in stages 3 (midbrain) and 4 (limbic); and the last two (neocortical stages) are frequently associated with cognitive impairment. In accordance with this hypothesis, PD and DLB are believed to represent two different phenotypes within a continuous spectrum of clinical manifestations of a unique disease the LB disorders, wherein the clinical manifestations predominantly depend on the anatomical distribution and load of α-synuclein pathology (Braak *et al.* 2003; 2006a).

Some studies report that this classification shows an acceptable correlation between pathological findings and clinical data (Lippa *et al.*, 2007; Halliday *et al.*, 2008; Ferrer, 2009). Other studies however, suggest that there is no correlation between Braak's Lewy body stages and clinical severity of PD or dementia (Jellinger, 2009a; 2009b) and that the degree of dementia is largely dependent on AD pathology rather than on LB distribution (Leverenz *et al*., 2008a).

On the other hand, **Dementia with Lewy Bodies** is pathologically defined according to the Consensus pathologic guidelines (McKeith *et al*., 1996; 2005), that distinguishes three phenotypes (brainstem, transitional/limbic and diffuse neocortical) by semiquantitative scoring of α-synuclein pathology in specific brain regions, considering also concomitant Alzheimer-related pathology. *See Section 1.3.*

To date, it is not clear if PD and DLB are different diseases or different manifestations within the same disease (Halliday *et al*., 2008; Jellinger 2009a). DLB exhibits a clinical phenotype that is apparently at variance with PD. However, the subcortical and cortical regions involved in DLB closely overlap with those of PD, specifically with PDD, corresponding to Braak LB stages 5 and 6. Moreover, further studies evaluated the validity of these classifications (Jellinger, 2009a; 2009b) and even in the majority of cases, there was a reasonable pathological and clinical correlation; it did not occur universally, as some cases with large numbers of cortical LBs were manifestly non-demented, showing no relationship between Braak LB stages and the clinical severity of PD (Lippa *et al*., 2007; Jellinger, 2000a; 2009b). Furthermore, the predictive validity of this concept is doubtful, since large unselected, retrospective autopsy series reported no definite neuropsychiatric symptoms in 30-55% of elderly subjects with widespread α-synuclein/Lewy-related pathology, suggesting the presence of a considerable cerebral compensatory mechanism (Leverenz *et al.,* 2008; Jellinger, 2004; Parkkinen *et al*., 2008). Earlier studies (Forno, 1969) showed LBs in the brains of 50 elderly persons without extrapyramidal symptoms, α-synuclein pathology in the *substantia nigra* in about 10% of neurologically unimpaired elderly persons and in the midbrain and limbic cortex in 31%

of asymptomatic aged controls with a mean age of 82 years. The risk of extrapyramidal symptoms increases with disease progression, though not to the same extent as previously believed. On the other hand, the clinical relevance of cortical α-synuclein pathology in relation to cognitive impairment is a matter of intense debate. Some authors emphasized its key causative role, whereas others have reported abundant LB cortical inclusions in non-demented PD patients and in neuropsychiatrically unimpaired elderly subjects (Jellinger, 2009a). Retrospective clinico-pathological studies, although confirming the staging system, particularly for younger onset PD with long duration, showed that from 6.3 to 43% of the cases α-synuclein pathology did not follow the proposed caudo-rostral progression. Applicability and clinical relevance has recently been criticized as both staging systems, the Braak hypothesis of LB staging in PD and the DLB consensus guidelines, were developed in non-population-based cohorts (Jellinger 2009a). Moreover, reliability of these staging procedures could be limited because of incomplete clinical information in a number of autopsy cases, the lack of neuron counts, quantitative methods, and immunohistochemistry to identify neuronal types could undermine the validity of the Braak hypothesis of LB staging in PD (Jellinger, 2009a; 2009b).

1.1.2. Neuropathological basis of cognitive dysfunction

The number of α-synuclein positive Lewy inclusions in certain brain regions correlates with dementia. These regions include frontal (Matilla *et al*., 1998; Kovari *et al*., 2003a) and temporal cortices (Matilla *et al.,* 1998; Harding and Halliday 2001; Kovari *et al.,* 2003b; Halliday and McCann, 2008). Clinicopathological studies show a correlation between cognitive impairment and both cortical LB pathology and Alzheimer type changes; other studies found a correlation between cognitive dysfunction and presynaptic α-synuclein aggregates (Jellinger, 2009b).

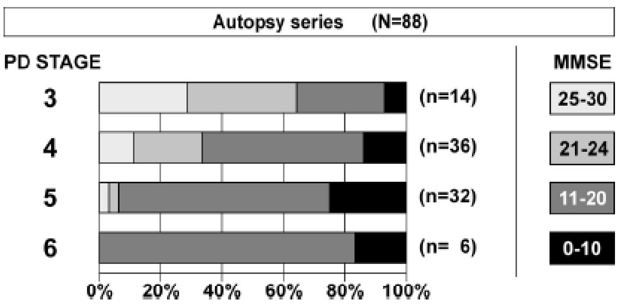


Figure 6. Correlation of PD stages with MMSE scores *(source:* Braak *et al*., 2006b)

Age may play a role in regional susceptibility, because younger individuals are more likely to present without cognitive impairment, whereas significant cognitive changes (either in PDD or DLB) occur in the older adult. Severity of dementia in PDD/DLB showed to correlate with the presence and distribution of cortical LBs and LNs (Mattilla *et al.*, 1998; Hurtig *et al.*, 2000; Lippa *et al.*, 2007).

In a study from Braak *et al.* (2006b), neuropathological stages of PD correlated with the Mini-Mental State Scale (MMSE) scores in a linear trend (see Figure 6). Two-thirds of the patients with stage 4 pathology were moderately or severely demented. This means that cognitive decline may already develop in the presence of relatively few cortical LBs/LNs. However, two stage 5 patients did not fulfil the MMSE criteria for cognitive decline, although these cases showed abundant cortical LBs/LNs. Finally, 100% of stage 6 patients were moderately to severely demented. None of the individuals showed involvement of the cerebral cortex in the absence of subcortical lesions.

In the brains of sporadic PD patients, the cortex displayed a hierarchical susceptibility across different regions. As Figure 7 and 8 illustrate, the first cortical area involved was the temporal mesocortex, followed by the anterior cingulate gyrus, the agranular insula and subgenual mesocortex, high order sensory association areas, and finally first order sensory association areas.

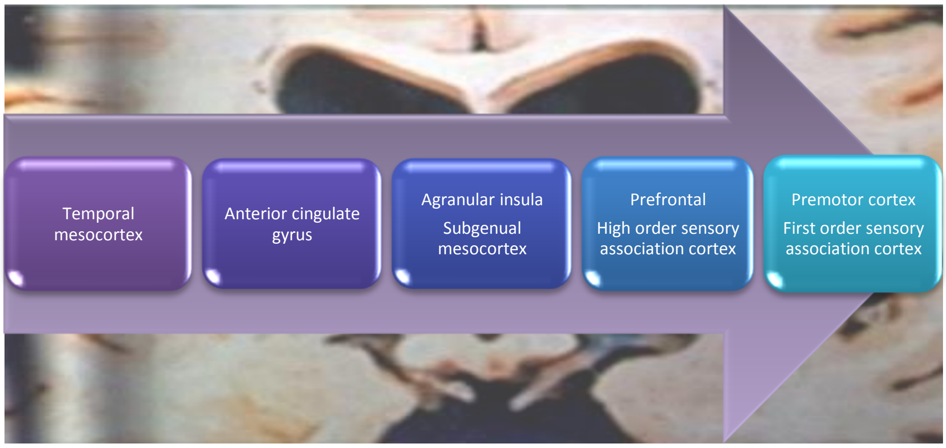


Figure 7. Evolution of LB/LN pathology in the cortex (Based on Braak *et al.*, 2006b)

Since DLB patients display this same sequence of cortical involvement, the neuropathological distinction between PD and DLB does not appear to be entirely convincing. The gradually increase in the severity of brain lesions may contribute to a decline of cognitive functions long before symptoms have become severe enough to warrant the diagnosis of dementia, so that a prodromal phase, such as mild cognitive impairment, presumably precedes dementia (William-Gray *et al.,* 2007; Caviness *et al.,* 2007; Verleden *et al.,* 2007; Song *et al.,* 2008).

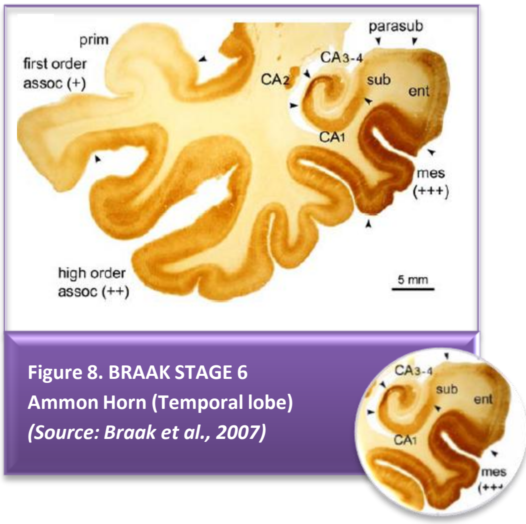


Figure 8. BRAAK STAGE 6
Ammon Horn (Temporal lobe)
(Source: Braak et al., 2007)

Furthermore, LBs and LNs have been shown to be only a part in the pathology of LBD and the visualization of morphological lesions depends on the methods and antibodies used. Novel α-synuclein antibodies have shown abundant striatal pathology in LBDs, suggesting that α-synuclein pathology exceeds LB pathology in PD and DLB (Ferrer 2009). And also AD pathology has been related to cognitive dysfunction (Leverenz *et al*., 2008; Jellinger 2009b).

In conclusion, current neuropathological methods do not yet provide a definite basis for explaining cognitive impairment in PD.

1.1.3. Neuropathological studies "in vivo". Analysis of global and regional atrophy using Magnetic Resonance Imaging

Due to the similarity of the symptoms, many physicians find it difficult to distinguish cases of DLB from PDD. Neuropathological studies are often perceived as the best strategy to solve such controversies. However, DLB and PDD share many qualitative neuropathological features with widespread α-synuclein inclusions from the brainstem to the neocortex. Moreover, pathological diagnosis can only be made postmortem. For those reasons, MRI represents a powerful, non-invasive technique for *in vivo* soft tissue imaging with detailed anatomical resolution. Comparing MRI biomarkers in DLB and PDD could help in determining if there are indeed morphological cerebral differences between these two syndromes.

Furthermore, structural brain imaging offers the possibility of measuring macroscopic cerebral changes in an indirect but quantitative way being a useful tool to evaluate the cerebral risk factors or predictors for developing dementia in PD.

With the development of neuroimaging processing techniques, a large number of approaches have emerged to characterize differences in brain morphology. Table 2 illustrates some characteristics of these approaches:

Table 2. Approaches to study brain morphology using MRI

Techniques/Aim	• differences in brain shape • differences in the local composition of brain tissues, after differences in shape have been discounted
Structures analyzed	• whole brain • Region of interest (ROI)
Degree of rater's manipulation	• manual segmentation techniques • semiautomated techniques • automated techniques

a) <u>Techniques:</u> those that deal with differences in brain shape and those that deal with differences in the local composition of brain tissues, after differences in shape have been discounted. The former use the deformation fields that map any individual brain onto a standard reference as the characterization of neuroanatomy, while the latter compare images on a voxel basis after the deformation fields have been used to spatially normalize the images (Ashburner and Friston, 2000).

b) <u>Structures analyzed</u>: whether whole brain analysis, which does not need a prior hypothesis, or Region of Interest (ROI) analysis, according to a prior hypothesis.

c) <u>Degree of rater's manipulation</u>: manual segmentation techniques (visual rating scales or ROIs manually draw), semi-automated or automated techniques.

As Figure 9 shows, different techniques of structural and functional MRI have been used to evaluate the cerebral characteristics of PDD and DLB patients. Current section is focused only on the structural ones. PET and SPECT studies will be described in the *1.2.7 section* for PDD and *1.3.5.* for DLB.

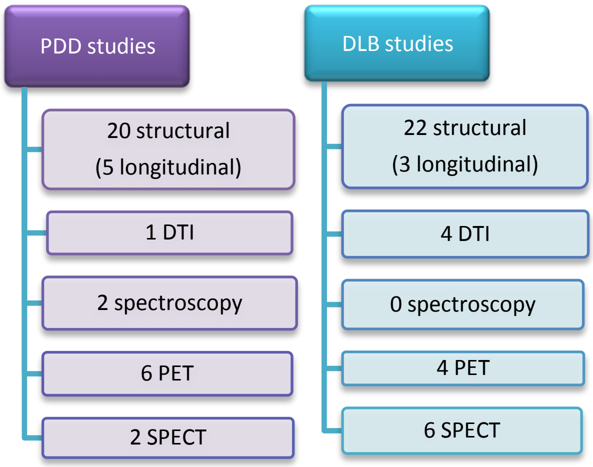


Figure 9. MRI studies exploring PDD and DLB patients

Below, a brief mention of the brain structures more frequently studied through MRI in PDD and DLB and the different techniques used to measure them.

1.1.3.1. Whole brain approach

Voxel-based morphometry

The majority of studies assessing the whole-brain pattern of change underlying DLB and PDD use an automatic technique called voxel-based morphometry (VBM). VBM detects differences in the regional concentration of gray matter at a local scale having discounted global differences in anatomy and position (Ashburner and Friston, 2000). The pre-processing steps are: **1)** spatial normalization of all subjects' images into the same stereotactic space by registering each of the images to the same template image. In neurodegenerative diseases, due to the high degree of atrophy in comparison with healthy control brains, a customized template is recommended based on the average of the scans of the sample to study (Crinion *et al.*, 2007); **2)** segmentation of the spatially normalized images into gray matter, white matter and cerebrospinal fluid (Acosta-Cabronero *et al.*, 2008; Ashburner and Friston, 2005); **3)** smoothing of the gray matter images by convolving with an isotropic Gaussian Kernel (Kiebel *et al.*, 1999); **4)** modulation of the images that aim to correct for volume change that occurred during the spatial normalization step and **5)** statistical analysis to localize and make inferences about group differences. The result is a statistical parametric map showing regions where gray matter or white matter concentrations differ between groups. This statistical parametric map comprises the results of many statistical tests, so it is necessary to correct for these multiple dependent comparisons (Ashburner and Friston, 2000). Some modifications and updates of these processes have been developed, but the main steps are the ones described above. *For further details of this technique see the Methods section (3. 3. MRI protocol).*

The advantages of VBM are that it allows a statistical analysis of the brain volume with an automatic procedure (avoiding the bias introduced by the rater in manual techniques) and performing an exploratory assessment of the whole-brain without an *a priori* hypothesis. However, the limitations of this technique are that it is affected by the variability among individuals and that errors may be introduced by the pre-processing steps. These limitations may be addressed by normalizing all images to a customized template, which is the mean of the subjects included in the analysis, and by checking all the output images after each step of the pre-processing.

Other techniques have been used to analyze the whole-brain volume. For example, one study (Ballmaier *et al.*, 2004) used Cortical Pattern Matching to evaluate regional brain difference between DLB, AD and control subjects. This is an automatic procedure which has similar steps to the ones previously described in VBM. Furthermore, very few studies have tried to assess differences in brain morphology by semiautomated threshold-based procedures (Burton *et al.*, 2005) or semiautomatic brain segmentation algorithms (O'Brien *et al.*, 2001; Cousins *et al*., 2003; Whitwell *et al.*, 2007a). Finally, atrophy visual rating scales have also been used to assess changes in brain morphology associated with DLB and PDD in comparison to control subjects, but commonly they are used to evaluate small regions of the brain (Tam *et al.,* 2005; Meyer *et al.,* 2007; Burton *et al.,* 2009). The advantage of these visual rating scales over automatic procedures is that they can be applied individually and can be used in clinical practice, but they also include the bias of the rater criteria and the statistical analyses performed are based on qualitative variables. To overcome these limitations, all the studies that have applied visual rating scales in the study of brain atrophy in DLB and PDD have used two blind-to-diagnosis raters and have evaluated the inter-rater reliability.

The findings of the whole-brain MRI studies will be described in *section 1.2.7* for PDD and *1.3.5.* for DLB.

1.1.3.2. <u>Regions of Interest analysis: main target areas</u>

When there is an *a priori* hypothesis, it is possible to delineate a ROI, reducing the number of voxels entering the statistical computation. ROI analysis provides an estimated proportion of the gray matter volume within a defined region.

The ways of measuring these regions range from automatic segmentation techniques (f. e. Pick Atlas implemented in SPM that allows performing VBM of a ROI) to semiautomatic or manually traced ROIs. Among the programs available for manually drawing ROIs, the most frequently used in the reviewed literature have been analyze, MRIcro or MIDAS.

Furthermore, the Scheltens' scale has also been widely used. As Figure 10 describes, it is a scale for visually rating atrophy extensively used to rate atrophy in the hippocampus, but as well being adapted to other cortical areas. It ranges from 0 (no atrophy) to 4 score (severe atrohy). It offers a score for each side of the brain, and the sum of both marks gives the total score. The advantage of these visual rating scales is that are easy, fast and can be used individually, but the limitation is that are rater-dependent, so less objective.

Below, studies that used ROIs to explore brain atrophy in PDD and DLB will be described in more detail, summarizing the main findings:

Medial temporal lobe

The structures within the medial temporal lobe (MTL), namely the hippocampus, amygdala and entorhinal cortex, have been extensively studied in DLB and PDD as ROIs. Hippocampal volume has been consistently correlated with memory impairment, especially with episodic memory and recall deficits, in both diseases (Riekkinen *et al.*, 1998; Barber *et al.*, 2001; Camicioli *et al.*, 2003; Junque *et al.*, 2005; Bouchard *et al.*, 2008; Jokinen *et al.*, 2009). Age has been related with decreased volume in the hippocampus in both diseases (Barber *et al.*, 2001; Bouchard *et al.*, 2008). Moreover, Braak stages and age at death have been suggested to be good predictors of medial lobe atrophy (Burton *et al*., 2009).

In DLB, the relative preservation of the MTL related to AD has been widely documented (Hashimoto *et al*., 1998; Barber *et al.*, 1999a; Barber *et al.*, 2000a; Barber *et al.*, 2001; Ballmaier *et al.*, 2004; Burton *et al.*, 2009) and for that reason the degree of MTL atrophy has been proposed as an index to differentiate the two diseases that correctly predicts 74.1% of DLB patients and 70.4% of AD patients (Hashimoto *et al*., 1998). These results were confirmed by Barber *et al*. (1999a), who showed that the absence of MTL atrophy had a specificity of 100% and 88% for separating DLB from AD and vascular dementia respectively and a sensitivity of 38%. Sabattoli *et al.* (2008) described hippocampal loss in both pathologies in comparison to healthy control subjects, but the regions affected differed; while in DLB this loss involved CA2-3 and only the rostral part of CA1, in AD patients the areas that showed significant volumetric atrophy were located in CA1.

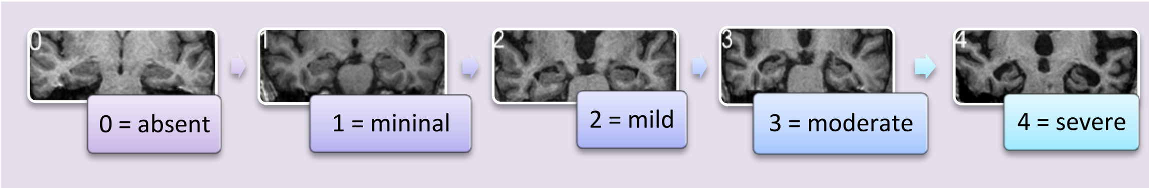


Figure 10. Example of coronal images of medial temporal lobe atrophy (Scheltens visual rating scale) showing increasing atrophy in PD, loss of height of the hippocampus, and widening of the temporal horn (Adapted from Tam *et al.,* 2005).

In PD, hippocampal volume reductions have been proposed as a risk factor for developing dementia (Tam *et al.,* 2005; Summerfield *et al.,* 2005; Junque *et al.,* 2005; Aybeck *et al.,* 2009). In fact, in a longitudinal study using serial MRI it was shown a greater annual brain volume loss in non-demented PD patients than in healthy controls (Hu *et al.*, 2001). Furthermore, Aybek *et al.* (2009) showed that hippocampal atrophy before subtalamic nucleus deep brain stimulation predicted conversion to dementia after surgery in PD patients. Moreover, Tam *et al.* (2005) using the Scheltens' scale, a standardized method to visually rate brain atrophy (see Figure 10), showed a progression of MTL atrophy in DLB, PDD, PD, AD and healthy elderly. In this study, AD patients were the most impaired, followed by DLB, PDD, PD and finally healthy control subjects (**control < PD ~ PDD ~ DLB < AD**). Later studies have given support to this finding (Summerfield *et al*., 2005; Junque *et al.*, 2005; Ibarretxe-Bilbao *et al.*, 2008; Kenny *et al.*, 2008). Only one study, using a manually-drawn ROI of the hippocampus, reported that hippocampal atrophy in PDD was even greater than in AD (Laakso *et al.*, 1996).

Concerning the amygdala, decreased volume has been reported in both DLB (Hashimoto *et al.,* 1998; Barber *et al.,* 2000a) and PDD patients (Junque *et al*., 2005; Bouchard *et al*., 2008) in comparison to healthy control subjects.

Almost all the studies that have explored MTL atrophy used manual segmentation to delimitate a ROI or used the Schelten's visual rating scale. However, a small percentage have also used VBM (Summerfield *et al.,* 2005; Junque *et al.,* 2005; Ibarretxe-Bilbao *et al.,* 2008) confirming the reduced volume of this region, in agreement with previous studies. Table 3 summarizes the main findings in the study of MTL in DLB and PDD patients.

Table 3. Summary of the studies showing MTL impairment in DLB and PDD

DLB studies of MTL

- Hashimoto et al., 1998; Barber et al., 1999; Barber et al., 2000; Barber et al., 2001 : hippocampal volume in DLB is relative preserved in comparison with AD
- Burton et al., 2002: DLB greater decrease of MTL related to CNT
- Tam et al., 2005: CNT > PD ~ PDD ~ DLB > AD
- Meyer et al., 2007: the Parkinson-Lewy body MCI is the prodromal of DLB. Has hippocampal atrophy but less than the present in MCI who converse to AD
- Sabattoli et al., 2008: 10-20% of hippocampal volume loss in DLB
- Burton et al., 2009: Braak stage and age at death were significant predictors of MTA.

PDD studies of MTL

- Laakso et al., 1996: PD greater hippocampal atrophy than AD
- Hu, et al. 2001: annual brain volume loss in non-demented PD respect to CNT
- Camicioli et al., 2003: in PD hippocampal atrophy correlated with impairment in episodic memory
- Tam et al., 2005: CNT > PD ~ PDD ~ DLB > AD
- Junque et al., 2005; Summerfield et al., 2005: CNT > PD > PDD
- Nagano-Saito et al., 2005: PDD had more atrophy of bilateral parahippocampus and right hippocampus than PD
- Beyer et al., 2007: PDD has decreased hippocampal and amygdala volumes than CNT
- Kenny et al, 2008: Entorhinal cortex reduction was 19.9% in DLB and 14.7% in PDD related to CNT
- Bouchard et al., 2008: PDD reduced hippocampal volume and PD reduced amygdala volume related to CNT
- Ibarretxe-Bilbao et al., 2008: PDD had hippocampal GM loss involving the whole hippocampus
- Jokinen et al., 2009: PD had hippocampal atrophy related to CNT, and that was related to memory
- Aysek et al., 2009: PD that developed dementia after STN-DBS had smaller preoperative hippocampal volumes than PD

Abbreviations: **DLB, Dementia with Lewy Bodies; PD, non-demented Parkinson's Disease patients, PDD: Parkinson Disease with Dementia; AD, Alzheimer's Disease; CNT, control subjects; MCI, mild cognitive impairment; STN-DBS, subtalamic nucleus deep brain stimulation; >, more atrophy.**

Basal ganglia

There are few studies that have explored the volume of the basal ganglia in PD or DLB (Barber *et al*., 2002; Almeida *et al*., 2003; Summerfield *et al.,* 2005). This may be due to the difficulty of studying these structures with automatic volumetric techniques because of their relatively small size and their proximity to the ventricles, which can be misclassified (Ashburner and Friston, 2000), even though being extensively studied with functional methods to measure striatal dopamine transporter binding. The caudate volume has been evaluated with a manually drawn ROI technique by Barber *et al.* (2002) in DLB and by Almeida *et al*. (2003) in PD and DLB. Thus, DLB patients presented decreased caudate volume with respect to healthy control subjects, but there were no differences between PD and DLB. Later on, Summerfield *et al.* (2005) used whole brain VBM to measure the gray matter volume of basal ganglia and found a decrease in putamen and accumbens volume in PDD compared with controls, but again they failed in finding significant differences between PD and PDD.

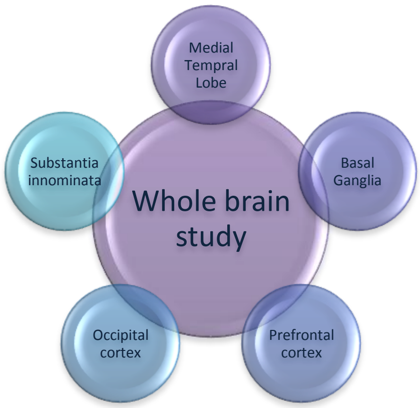
Substantia Innominata

The *substantia innominata* is a stratum which consists partly of gray and partly of white matter, and lies below the anterior part of the thalamus and lentiform nucleus. Two studies to date have evaluated the *substantia innominata* in DLB. In one of them, Whitwell *et al.* (2007b) found very little involvement in comparison with healthy control subjects, while Hanyu *et al.* (2005) reported decreased thickness of the *substantia innominata* compared with AD patients and control subjects. These findings support recent pathological studies showing an ascending pattern of LB progression from the brainstem to basal areas of the brain. Damage in this network of structures in DLB may affect different neurotransmitter systems which in turn may contribute to a number of the core clinical features of DLB (Whitwell *et al.*, 2007b).

White matter abnormalities

MRI can also detect changes in the homogeneity of white matter, visualized as high intensity lesions in proton density and T1-weighted scans. These white matter hyperintensities (WMH) can be divided into those immediately adjacent to the ventricles, periventricular hyperintensities (PVH), leukaraiosis (to use Hachinksy's terms), and those located in the deep white matter (DWMH). PVH and DWMHs probably result from different pathological processes and have been described in various conditions including normal aging, vascular dementia and AD (Barber *et al.*, 1999b). Although there is conflicting evidence, a number of studies have found a link between white matter lesions and cognitive impairment. In addition, white matter changes occurring in degenerative dementias may represent an important form of co-morbid vascular pathology, possibly interacting synergistically with other pathological processes (Barber *et al*., 2000b).

Some studies have assessed the WMH in DLB using the Schelten's visual rating scale or an equivalent scale (Barber *et al*., 1999b; Barber *et al.,* 2000b; Burton *et al.,* 2006; Sabattoli *et al.*, 2008). These studies have shown that WMH were greater in AD than in PDD and DLB and that age was correlated with total WMH and DWMH, showing a progression in 1-year follow-up (Burton *et al.*, 2006). PVH correlated with age, brain atrophy and vascular risk factors (Barber *et al.,* 2000b). Delusions and visual hallucinations were associated with absence of WMH in the occipital lobe, whereas frontal WMH were associated with higher depression scores (Barber *et al.*, 1999b).



In conclusion, as Figure 11 illustrates, the brain regions that have received most attention in the field of structural MRI in the case of PDD are: the MTL (hippocampus, amygdala, entorhinal cortex), striatum (caudate and putamen), prefrontal lobe and the occipital cortex; whereas in DLB the most studied regions are: the MTL, striatum, substantia innominata, the frontal lobe, occipital cortex, temporoparietal cortex, posterior cingulate, and white matter abnormalities.

Figure 11. Main target areas in the structural MRI study of DLB and PDD

1.1.3.3. Other approaches to the study of brain structure

A number of advanced MR techniques, namely spectroscopy, diffusion-weighted MRI, diffusion-tensor imaging, and magnetization transfer imaging, have been introduced as methods that allow detecting subtle changes in brain tissue and indirectly reflect microscopic aspects of the tissue damage which are believed to precede the final stage of tissue loss or atrophy. These techniques can be used to explore the brain-function correlations in more detail.

Studies of iron deposition

Very recently, the increasing availability of high field 3T MRI gave place to studies showing iron accumulation in the hippocampus of AD patients and in the *substantia nigra* of PD patients. Brar *et al.* (2009) explored whether patients with early AD accumulated iron in the *substantia nigra* as the disease progresses in association with the development of Parkinsonism. Iron deposits have been shown to shorten T2 relaxation times on T2-weighted MR images, so the fraction of voxels below a short T2 cut-off value will correspond to the amount of iron in that specific region of the brain. They found an iron increase in the *substantia nigra* but not in the hippocampus in PD patients without dementia and iron decreases in AD patients without parkinsonism (Brar *et al.,* 2009). Furthermore, as Figure 12 illustrates, patients who developed parkinsonism along with their existing dementia had significantly more iron in their *substantia nigra* than patients with AD only, proposing that iron accumulation may be a predictor of parkinsonism. In accordance, iron acumulation has been correlated with motor symptoms in PD patients (Wallis *et al.*, 2008).

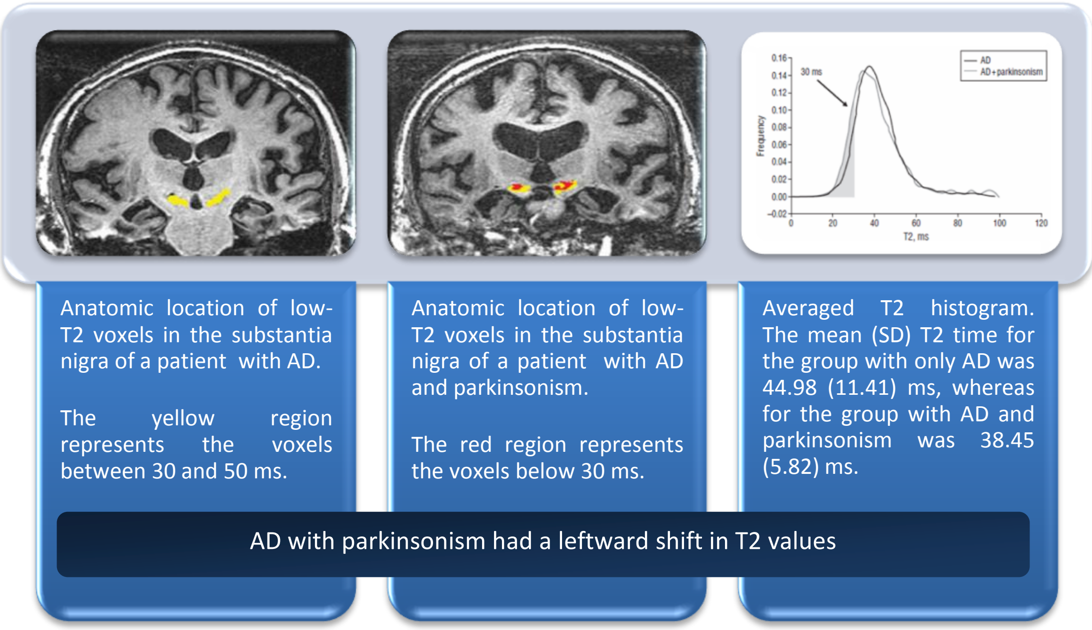


Figure 12. Iron content in the substantia nigra of AD and PD (Modified from Brar *et al.*, 2009)

<u>*Diffusion tensor imaging*</u>

Current conventional MRI techniques allow identifying gray matter, white matter and cerebrospinal fluid in the brain. However, white matter has a homogeneous appearance making difficult to observe and quantify the fiber tracts. With the development of diffusion tensor imaging, it is now possible to study anisotropic diffusion and white matter fiber tract directions in the brain (Le Bihan *et al*., 2001; Le Bihan and van Zijl, 2002; Mori and Zhang, 2006).

Diffusion tensor imaging (DTI) is a technique that allows measuring the diffusional motion of water molecules as a result of the interactions between tissue water and cellular structures and provides information about the size, shape, orientation and geometry of brain structures (Le Bihan *et al.*, 2001; Le Bihan and van Zijl, 2002). Because of the highly structured nature of axons, water tends to diffuse along the direction of white matter tracts rather than perpendicular to them. Pathological processes that modify tissue integrity can result in an altered diffusion coefficient. The diffusion coefficient is generally dependent upon the direction along which it is measured, that is anisotropic, that means it has a linear diffusion. This anisotropy reflects the underlying fiber structure (Le Bihan *et al.*, 2001; Le Bihan and van Zijl, 2002; Mori and Zhang, 2006). In DTI, a tensor that describes the diffusion of water in all spatial directions is calculated for each voxel. From the tensor it is possible to derive the mean diffusivity (MD), which reflects the average displacement of the molecules independently of any tissue directionality and is affected by cellular size and integrity; and fractional anisotropy (FA), which provides information about the shape of the diffusion tensor at each voxel, reflecting the degree of alignment of cellular structures with fiber tracts and their structural integrity (Basser *et al*., 1994; Basser and Pierpaoli, 1996). The FA depends on the relative diffusivity of water in different directions and varies from zero, where diffusion is equal in all directions, to 1, where diffusion occurs in a single direction. FA is high in regions of coherent white matter tracts (such as the corpus callosum) since the fibers all go in the same direction. DTI contains information about the principal direction of diffusion in a voxel that allows the delineation of white matter pathways of the brain by using tractography algorithms (Bozzali and Cherubini, 2007). Quantitative analyses are generally performed over a ROI or apply a more global approach based on histograms. Although it is superior to T1- and T2-weighted images for the assessment of the microstructural organization of white matter fibers, the main limitations of this technique are its highly sensitivity to motion, and the fact that it causes ghosting artifacts or signal loss, especially in patients with movement disorders. Besides, ROI analysis is easy to implement but time-consuming; furthermore, it is highly operator-dependent. In tractography, the ROIs are represented by fiber tracts that are automatically defined by tractography algorithms, making the analysis less operator dependent (Bozzali and Cherubini, 2007).

To date, four studies have analyzed brain structural characteristics in DLB using DTI. The first one, (Bozzali *et al.*, 2005) found reductions in FA and MD in almost all the white matter fibers studied (the corpus callosum and pericallosal areas, caudate, frontal, parietal, occipital and, less prominently, temporal white matter) in DLB patients respect to healthy control subjects, with specific abnormalities in the occipital lobes and basal ganglia. These microstructural cortico-subcortical changes were characteristic for DLB and completely different from what has been previously observed in AD patients (Zhang *et al.,* 2007). Moreover, in this study, parietal, frontal and occipital white matter integrity was related to neuropsychological measures. Lately, Firbank *et al.* (2007a; 2007b) showed that a decrease of FA in the bilateral posterior cingulate correlated with global atrophy in DLB patients. Figure 13 shows these results in comparison with previous ones of the same group showing also a hypometabolism in this region in the same group of patients (Firbank *et al.*, 2003). Recently, Ota *et al.* (2009) were able to show that DLB patients had lower FA in the inferior longitudinal fasciculus than healthy subjects and related this finding to visuospatial functions.

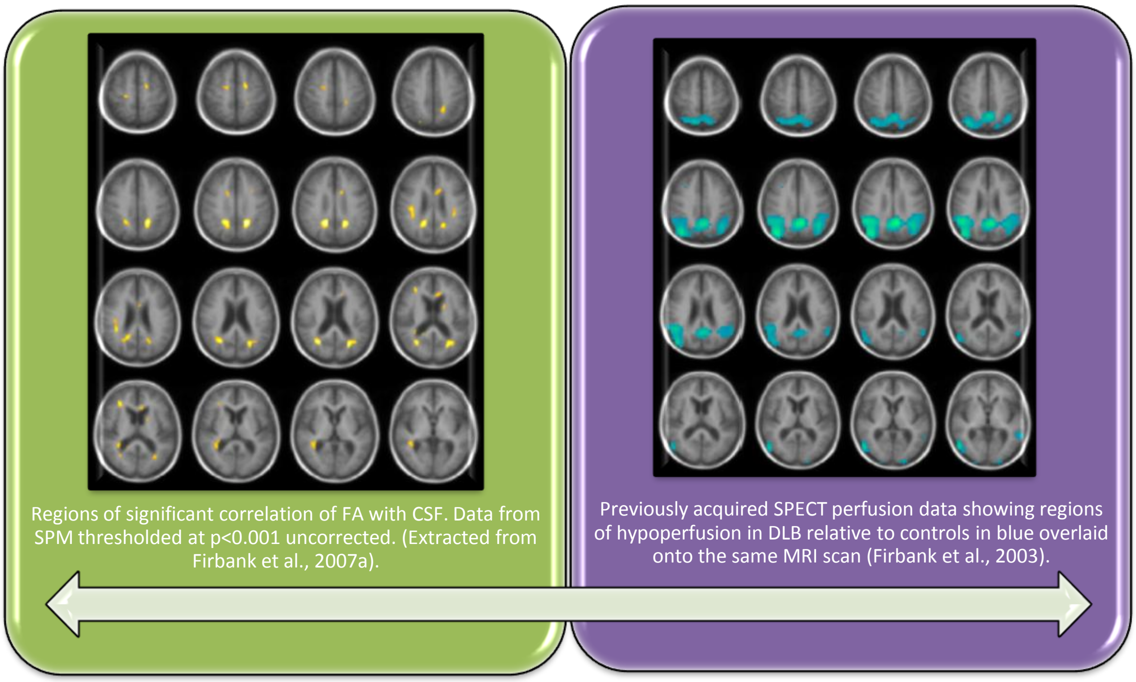


Figure 13. a) Correlation between bilateral posterior cingulate FA and global atrophy b) Hypometabolism in the same regions in DLB patients (*Source*: Firbank *et al.*, 2003; 2007b)

The only study that carried out a DTI analysis in a sample of PDD patients in comparison with non-demented PD and healthy control subjects found that both PD groups showed significant FA reductions in frontal, temporal and occipital white matter compared with controls. Moreover, the PDD group had lower FA in the bilateral posterior cingulate bundles than the PD group, even when controlling for the effect of the UPDRS-III scale. FA values in the left posterior cingulate bundle correlated with conceptualization and memory, the Hamilton Depression Scale and MMSE, whereas FA of the right cingulate only correlated with attention (Matsui *et al.*, 2007).

In conclusion, in DLB patients FA reductions have been described widespread in the white matter fibers, with a less impairment of the temporal ones in comparison with healthy control subjects, while in PD patients there is a reduction of the FA in fronto-temporo-occipital regions. Furthermore, the posterior cingulate FA is correlated with global brain atrophy in DLB and also reduced in PDD patients with respect to non-demented PD patients. Overall, DTI seems to be an adequate technique for evaluation of dementia *in vivo* in PD, specifically of the integrity of the posterior cingulate fibers. This new technique, combined with traditional volumetry, may be a valid MRI biomarker to predict cognitive decline in PD. However, further longitudinal studies are needed to confirm whether these markers are really sensitive to dementia progression. On the other hand, up to date there are no studies comparing the structure of white matter fibers in DLB and PDD patients; and the few available data show the same patterns of impairment in the two diseases.

Spectroscopy

In vivo Proton Magnetic Resonance Spectroscopy is a neurochemical technique used to investigate specific brain metabolites (van der Graaf, 2009). Some of the main metabolites of interest are N-accetylaspartate (NAA), choline (Cho) and creatine (Cr). NAA is an amino-acid found only in neurons in the adult central neurous system and it is used as a measure of neuronal viability, although NAA depletion is not always irreversible. However, the Cr peak refers to the sum of creatin and phosphocreatin. It is assumed that the Cr peak reflects energy use. It is thought to be relatively constant between individuals and to be present in most brain areas; therefore it is often used as an internal reference (van der Graaf, 2009).

To date, only two studies have used spectroscopy in the study of dementia associated with PD (Summerfield *et al.*, 2002; Griffith *et al.,* 2008). Compared with non-demented and control subjects Griffith *et al.* (2008) found that PDD patients have lower n-acetylaspartate/creatine ratios and Summerfield *et al.* (2002) found a reduction of N-acetylaspartate levels in the occipital lobe. N-acetylaspartate values correlated with neuropsychological performance but not with the severity of motor impairment (Summerfield *et al.,* 2002).

1.2. Parkinson's Disease with Dementia

Parkinson's disease (PD) is an age-related neurodegenerative disorder affecting about 1.6% of the elderly population in Europe (de Rijk et *al.,* 1997). PD is clinically characterized by rigidity, resting tremor, postural abnormalities, and bradykinesia. However, nowadays, it is recognized not only as a movement disorder, but as a multi-systemic disease affecting also cognitive functions, even in the early stages of the disease (Muslimovic *et al.,* 2007; Williams-Gray *et al.,* 2007; Caviness *et al.,* 2007; Aarsland *et al.,* 2008; Aarsland *et al.,* 2009). The prevalence rates of dementia in PD patients can range from 17 to 43% (Aarsland *et al.,* 2009) and increases up to 83% after 20-year follow-up (Hely *et al.,* 2008).

Dementia is a clinical state characterized by loss of function in multiple cognitive domains. The cognitive impairment must be severe enough to cause dysfunction in the patient's social and life functioning, and must represent a decline from a previously higher level of functioning. The most commonly used criteria for the diagnosis of dementia have been the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) (American Psychiatric Association, 2003) until in 2007 the diagnostic criteria for PDD were established (Emre *et al.,* 2007).

There is converging evidence that dementia has important clinical consequences for the patients such as increased disability, risk of psychosis, reduced quality of life and increased mortality. In addition, dementia increases the burden of caring for patients with PD, and increases the disease-related costs by increasing the risk for nursing home admission with important consequences for the patients, their caregivers, and the community (Emre *et al.,* 2007).

1.2.2. Neuropathological staging guidelines

PD is characterized by resting tremor, slowness of initial movement, rigidity, and general postural instability. These symptoms are mainly due to the loss of dopaminergic neurons in the *substantia* nigra *(SN) pars compacta* (Figure 15a), leading to reduced dopaminergic input to the striatum, and accompanied by adaptive responses in the internal and external globus pallidus, subthalamus, thalamus and *SN pars reticularis* (Ferrer, 2009). However, certain clinical symptoms might appear before the diagnosis and are a consequence of early degeneration of selected nuclei of the medulla oblongata (dorsal IX/X motor nucleus of the vagus nerve), pons, autonomic nervous system and olfactory structures. Other nuclei involved are the locus ceruleus and reticular nuclei of the brainstem and the basal nucleus of Meynert, the amygdala and the CA2 area of the hippocampus. LB inclusions and LN are found in all these locations (see Figure 14 (b-e)) (Ferrer, 2009). Based on the presence of Lewy inclusions, PD is considered the paradigm of Lewy body diseases (LBDs). In addition, triplication or duplication of the α-synuclein locus and mutations in other genes are associated with PD (Ferrer, 2009). These genes are the origin of familial and in some cases sporadic PD and include parkin (PARK2), DJ1 (PARK7), PINK1 (PARK6), LRRK2 (PARK8), HTRA2 (PARK13) and UCHL1 (PARK5).

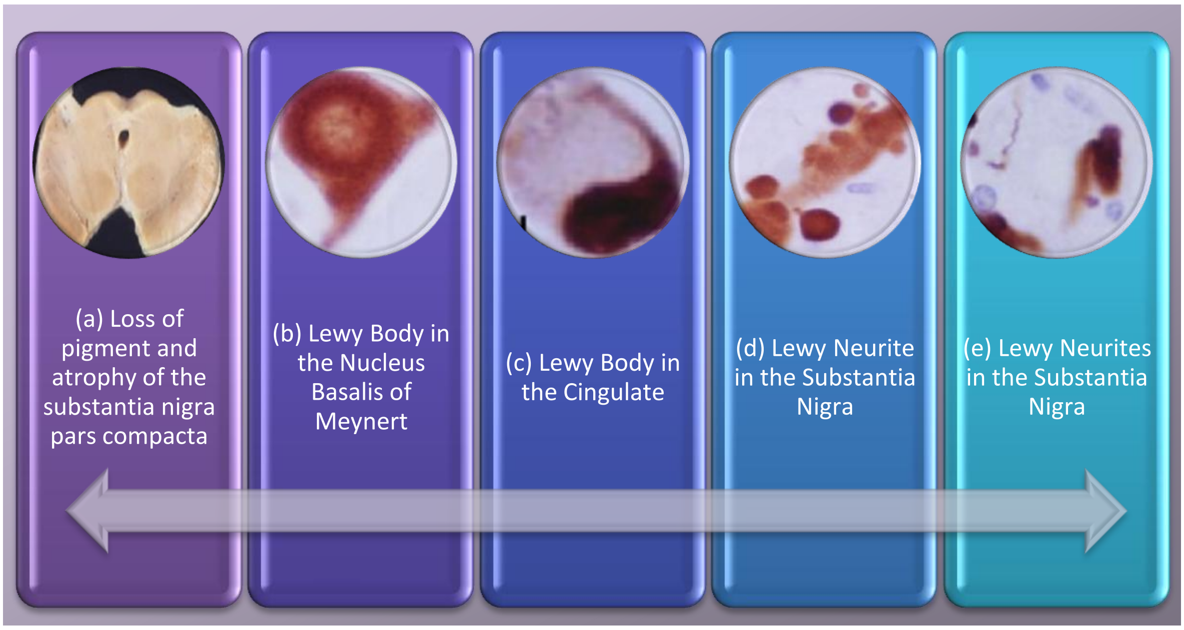


Figure 14. Typical lesions in Parkinson's disease. (a) Loss of pigment and atrophy of the substantia nigra pars compacta; (b-c) Lewy bodies; (d-e) aberrant neurites (Modified from Ferrer, 2009)

As reported in the first section of the introduction, Braak *et al.* (2003; 2006a) proposed a staging procedure to assess α-synuclein accumulations in the brain in relation to the clinical evolution of the disease (summarized in Table 4).

Braak *et al.* (2003; 2006a) propose that, at some point, some individuals arrive at and cross the threshold from a subclinical disease state to the symptomatic manifestation of disease. The symptoms can begin almost imperceptibly but increase in severity, and the clinical disease course appears to be reflected by a relatively uniform pathological process in the brain. They suggest that cognitive status significantly correlates with the proposed six neuropathological stages and the risk of dementia in PD becomes greater as the α-synuclein pathology in the brain progresses (*See section 1.1.2*). However, recent studies have not confirmed the correlation between LB pathology and cognitive impairment (Jellinger, 2009a; 2009b).

Table 4. Stages in the evolution of PD-related pathology (Modified from Braak *et al*. 2003, 2006)

STAGE 1	LN and LB in the **dorsal IX/X motor nucleus** of the vagus nerve and anterior **olfactory structures**.	**Early non-motor symptoms**	**PRESYMPTOMATIC PHASE**
STAGE 2	Pathology of stage 1 plus inclusion bodies in brainstem nuclei including portions of the raphe nuclei, gigantocellular reticular nucleus and LN within the noradrenergic **locus coeruleus**.		
STAGE 3 	Pathology of stage 2 plus midbrain lesions, in particular in the melanin-laden nerve cells in the pars compacta of the **substantia nigra** (even if there is no indication of macroscopically detectable depigmentation of the NS at this stage)). Neuronal damage in central subnucleus of the **amygdala** *(see figure)* and basal forebrain (including Meynert's nucleus).	**Clinical motor symptoms**	**SYMPTOMATIC PHASE**
STAGE 4 	After leading the amygdala, cortical LNs and LBs appear for the first time in a unique transition zone between the allocortex and neocortex: the **temporal mesocortex** *(*figure *arrow)*. LNs in the second sector of the allocortical Ammon's Horn also start to develop in this stage.		
STAGE 5 	The density of the lesions in the temporal mesocortex is more stricking and the disease process is present in the related insular and anterior cingulate mesocortex (figure *asterisks*). Pathology progresses into the high-order association fields of the **temporal and prefrontal neocortex**.	**Cognitive decline**	
STAGE 6 	Vulnerable sites within the substantia nigra appear nearly denuded of melanoneurons and are blanched upon macroscopic inspection (see *figure 14(a)*). Involvement of nearly **the entire neocortex**. Together with the insular and anterior cingulate impairment, the temporal mesocortex continues to show strong immunolabelling owing to the increasing severity of the inclusion bodies (figure *arrows*). Disease process affects even the **secondary and**, in very advanced cases, **primary** fields of the **neocortex**, as seen in the primary auditory field of Heschl's gyrus.		

Incidental Parkinson's Disease

Cases with LB pathology in the brainstem without parkinsonism are considered incidental PD (iPD) (Ferrer, 2009; Jellinger, 2009a; Jellinger, 2009b). Whether these cases constitute pre-symptomatic PD has been a matter of controversy for years. PD should not be considered as a disorder characterized only by parkinsonism, but a brain disease with disparate pre-motor manifestations such as olfactory dysfunction, dysautonomia, sleep fragmentation, rapid eye movement behavior disorder, mood and anxiety disorders and depression (Ferrer, 2009).

1.2.3. Clinical Diagnostic Criteria

As no criteria were operationalized to diagnose dementia associated with PD, the DSM-IV criteria were used until 2007 when the Movement Disorders' Society recruited a Task Force to define the clinical diagnostic criteria for PDD (in Table 6). Thus, Table 5 summarizes the main differences between the previously used DSM-IV criteria and the criteria of the Movement Disorders' Society, which are further described in Table 6. PDD is diagnosed when dementia occurs in the context of well-established PD (McKeith *et al.*, 2005).

Table 5. Comparison of DSM-IV criteria and criteria proposals for dementia in PD (*Source*: Verleden *et al.,* 2007)

DSM-VH (Kaufer *et al.*, 1997)

- Multiple cognitive deficits including
- memory impairment
  - one or more of the following
    - aphasia
    - apraxia
    - agnosia
    - executive dysfunction
- Impairment in social or occupational functioning
- Decline from a previous level of functioning
- Clinical/laboratory evidence relating the disturbance to a general medical condition
- Deficits do not occur exclusivey in the course of a delirium

Dubois and Pillon (Dubois *et al.*, 1997): reference to DSM-IV

- Progressive dysexecutive syndrome with memory deficits in the absence of aphasia, apraxia or agnosia
- Instrumental activities are rather preserved

Emre *et al.*, (2007): clinical features

- Dysexecutive syndrome with executive dysfunction as main feature
- Qualitatively the same type of deficits found in nondemented patients with PD but the impairments are more extensive and severe
  - Impaired attention, executive functions, memory and visuospatial functions
  - Language and praxis largely preserved
  - Personality changes and multiple behavioral symptoms

Table 6. Features of dementia associated with Parkinson's disease (Emre *et al*., 2007)

I. Core features

- Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
- A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
  - Impairment in more than one cognitive domain
  - Representing a decline from premorbid level
  - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

- Cognitive features:
  - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
  - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
  - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
  - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
  - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
- Behavioural features:
  - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
  - Changes in personality and mood including depressive features and anxiety
  - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
  - Excessive daytime sleepiness

III. Features which do not exclude PDD, but make the diagnosis uncertain

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

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

- Cognitive and behavioural symptoms appearing solely in the context of other conditions such as:
  - Acute confusion due to
    - Systemic diseases or abnormalities
    - Drug intoxication
  - Major Depression according to DSM IV
- Features compatible with Probable Vascular dementia criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits).

Probable PDD

A. Core features: Both must be present

B. Associated clinical features:

Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)

The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D

C. None of the group III features present

D. None of the group IV features present

Possible PDD

A. Core features: Both must be present

B. Associated clinical features:

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

Behavioural symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

1.2.4. Epidemiology

Point prevalence

In a recent review carried out by Aarsland *et al.* (2009), the prevalence rates of dementia in PD patients range from 17 to 43%. Previously, in a first review from the same group, employing strict methodological inclusion and exclusion criteria, they found a prevalence of 31.5%. In dementia populations, 3 to 4% of dementia cases were due to PDD. Furthermore, in the general population over 65, the estimated prevalence of PDD was between 0.2 to 0.5% and in PD patients between 16 to 48% (Aarsland *et al.,* 2005). Other studies have found prevalences between 22% and 48% of cases (Athey *et al.*, 2005; de Lau et al 2005; Hobson *et al.,* 2005).

Incidence

In community-based studies, Arsland *et al.* (2009) reported incidence rates between 9.5% and 11.2% per year, indicating that 10% of a PD population will develop dementia each year. The relative risk for developing dementia in PD compared to non-PD subjects ranged from 1.7 to 5.9.

Cumulative prevalence

Some studies have prospectively followed newly diagnosed PD patients to assess the frequency of dementia. After 3- and 5-year follow-up, 26 and 28% of patients respectively developed dementia (Reid *et al.,* 1996). In the same study, after 15 years, 48% had dementia, 36% mild cognitive impairment and only 15% remained without evidence of cognitive impairment. In an earlier study with 8-year follow-up, 80% of the patients had dementia (Aarsland *et al.,* 2003) and after a 20-year follow-up of newly diagnosed PD patients, 100 of 136 (74%) had died and dementia was present in 83% of 20-year survivors (Hely *et al.,* 2008). Furthermore, 75% of the patients who died were diagnosed with dementia before death. Figure 15 illustrates how dementia clearly correlates with increasing age in this sample.

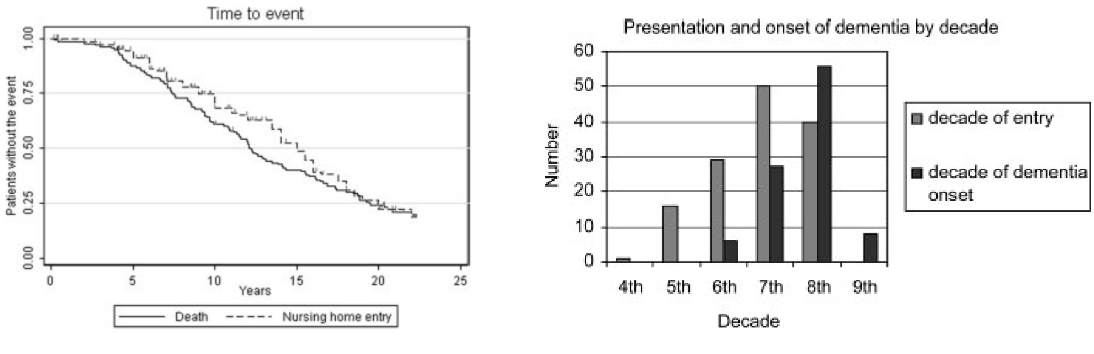


Figure 15. a) Kaplan–Meier plot of time to death and of nursing home placement; b) Decade of presentation to the study and of dementia. Age over 80 was an exclusion criteria of the study (*Source*: Hely *et al.,* 2008)

1.2.5. Risk factors for the development of Dementia in Parkinson's Disease

Many demographic and clinical features have been assessed as potential risk factors for dementia in PD. The most consistent risk factors in longitudinal studies were higher age, more severe parkinsonism (in particular rigidity, postural instability and gait disturbance) and mild cognitive impairment at baseline (Williams-Gray *et al.,* 2007; Emre *et al.,* 2007; Aarsland *et al.,* 2009). Visual hallucinations have been also related to the appearance of dementia (Emre *et al.,* 2007; Ravina *et al.,* 2007). Age and severity of motor symptoms seem to have a combined rather than additive effect on the risk of dementia (Emre *et al.,* 2007).

Recentlly, Muslimovic *et al.* (2009) reported that disease onset and axial impairment contributed to the cognitive decline of well-established PD patients, but not in newly diagnosed ones. Previously, the same group had reported that late onset of disease was an independent predictor of cognitive dysfunction in PD patients (Muslimovic *et al.,* 2005). Moreover, in a longitudinal study William-Gray *et al.* (2006) showed that the most important clinical predictors of global cognitive decline were the age, non-tremor dominant motor phenotype, poor semantic fluency and inaccurate pentagon copy.

Regarding to the neuropsychological assessment, Song *et al.* (2008) suggested that having also into account the cortical-type cognitive dysfunctions in early PD patients can help predict the development of dementia. Furthermore, alternating verbal fluency and delayed verbal memory independently differentiated the PD patients with MCI from the cognitively intact PD patients (Pagonabarraga *et al.,* 2008).

1.2.6. Cognitive profile of Parkinson's Disease with Dementia

According to the clinical criteria for the diagnosis of dementia associated with PD, a wide variety of cognitive disturbances have been reported in PD even early in the course of the disease (Emre *et al.,* 2007). These disturbances include memory impairment, visuospatial deficits, and executive dysfunction. There is some evidence of heterogeneity, with some patients expressing an amnestic profile, while others present a predominantly dysexecutive or mixed profile (Emre *et al.,* 2007).

In recent years, several studies have assessed the cognitive deficits related to PD in an attempt to identify prodromal stages of PDD. In this section, the main findings of these studies are going to be described *(for further details related to the articles, see Table 7 at the end of the section).*

Longitudinal studies in PD have shown that there is cognitive impairment since the early diagnosis and that evolution time and age are highly correlated with the development of dementia (Foltynie *et al.,* 2004; Williams-Gray *et al.*, 2007; Hely *et al.,* 2008; Muslimovic *et al.,* 2009; Elgh *et al.,* 2009). Following a cohort of 126 PD patients from 3 to 5 years, Williams-Gray *et al.* (2007) found that at baseline, 62% of the patients were already impaired on at least one neuropsychological test and at the follow-up 10% had developed dementia and 57% showed evidence of cognitive impairment with fronto-striatal deficits. Helly *et al.* (2008) reported that after 20-year follow-up, 74% of 136 newly diagnosed PD patients had died and dementia was present in 83% of the survivors. Similarly, very recently Muslimovic *et al.* (2009) described that the cognitive performance of 89 newly diagnosed PD patients decreased significantly over time, particularly on measures of psychomotor speed and attention, and to a lesser extent on memory, visuospatial skills and executive functions, 48% showed cognitive decline and 8.5% developed dementia after 3-year follow-up. Moreover, poor verbal fluency and inaccurate pentagon copy were related to the development of dementia (Santangelo *et al.,* 2007; Williams-Gray *et al.,* 2007).

Cognitive dysfunction is common in PD patients. Some studies have reported impairment even in newly-diagnosed patients in attention, executive functions (including category fluency), psychomotor speed, visuoconstructive skills and memory (Muslimovic *et al.*, 2005; Elgh *et al.*, 2009). Executive dysfunction in PD patients has been widely described (William-Gray *et al.,* 2007; Verleden *et al.,* 2007; Muslimovic *et al.,* 2009; Santangelo *et al.,* 2009) and has been associated with a failure to modelate frontal activation with increased task demands (Dirbenger *et al.,* 2005). As regards to memory function, Higginson *et al.* (2005) showed that non-demented PD patients exhibited deficits on cued recall and delayed recognition that were similar in magnitude to those on free recall. Furthermore, Wilkinson *et al.* (2009) reported that both implicit and explicit learning were significantly impaired in PD than in healthy control subjects. In comparison with AD patients, PD patients presented poorer verbal fluency in PD patients but better performances on the memory tests (Caltagirone *et al.,* 1989).

Following evidence of cognitive impairment in recently diagnosed PD patients, some studies have tried to delineate a prodromal MCI stage for the development of dementia (Foltynie *et al.,* 2004; Verleden *et al.,* 2007;Caviness *et al.,* 2007;

Pagonabarraga *et al.*, 2008; Song *et al.*, 2008; Aarsland *et al.*, 2009). Caviness *et al.* (2007), were the first to show MCI associated with PD, defined as impairment on at least one cognitive domain without the presence of dementia, in 21% of a group of 86 PD patients. Besides, 17% of the sample had dementia (see Figure 16). The most frequently impaired cognitive domain in PD-MCI was frontal/executive, followed by amnestic type. Single domain PD-MCI was more common than multiple domains.

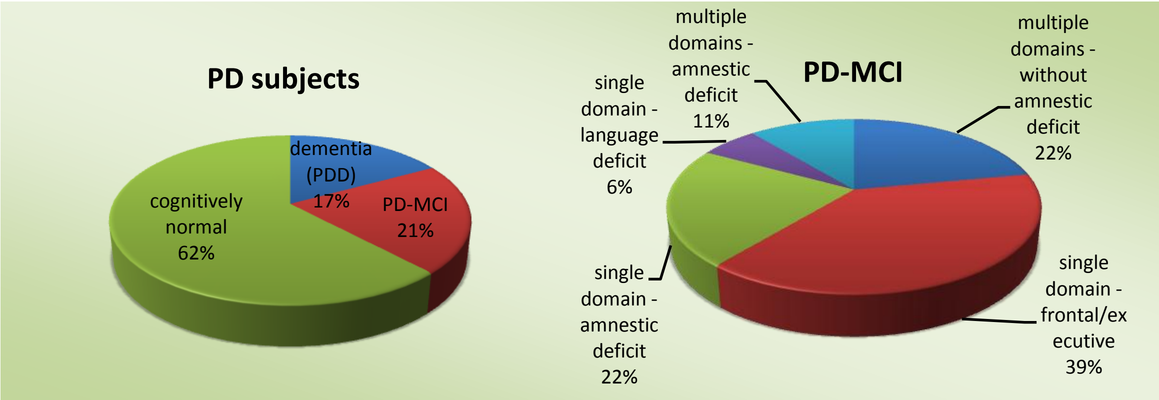


Figure 16. a) Pie chart showing the relative proportion of PD-cognitively normal, PD-MCI and PDD in the PD sample; b) the relative proportion of PD-MCI types by cognitive domain classification (Modified from Caviness *et al.*, 2008)

Similarly, Verleden *et al.* (2007) showed that 51% of a sample of 100 PD patients had impairment in one cognitive domain, most frequently executive/motor dysfunction (in 88% of the cases), 24% had below normal performance on two cognitive domains (in the 96% of the cases in executive/motor and memory/attention) and 7% had significant impairment on each cognitive domain. Depending on the criteria used for the assessment (DSM-IV or Emre *et al.*, 2007, *see Table 5*), 10 to 30% of the cohort will be categorized as PD with dementia. Very recently, Aarsland *et al.* (2009) studied a cohort of 196 naïve PD patients, showing that PD patients were more impaired in all neuropsychological tests than healthy control subjects; the largest effects were found in verbal memory and psychomotor speed. Of these, 18.9% were classified as MCI, with a relative risk for scoring below the cut-off of 2.1 in comparison with healthy control subjects. Two-thirds of the sample had a non-amnestic profile and one-third had amnestic MCI.

For this reason, some scales have been designed to assess the cognitive impairment in PD. Pagonabarraga *et al.* (2008) showed that alternating verbal fluency and delayed verbal memory independently differentiated MCI patients from healthy control subjects and cognitively intact PD patients. Likewise, Song *et al.* (2008) suggested that adding cognitive test of cortical type to the early cognitive assessment of PD-MCI can help to predict the development of dementia.

Moreover, the cognitive profile of PDD patients has also been studied (Pagonabarraga *et al.,* 2008; Llebaria *et al.,* 2008; Song *et al.,* 2008; Bronnick *et al.,* 2008; O'Brien *et al.,* 2009). In comparison with PD, PDD patients showed worse scores in confrontation naming (Pagonabarraga *et al.,* 2008) and greater impairment in attention, frontal/executive functions, verbal and non-verbal memory, language, calculation and visuospatial functions than non-cognitively impaired PD and MCI-PD patients *(Song et al.,* 2008; Llebarria *et al.,* 2008).

Attention and Executive functions

Attentional deficits have been shown in PDD, which tend to be as severe as in patients with DLB (Litvan *et al.,* 1991; Noe *et al.,* 2004, Ballard *et al.,* 2002). Clinically, 29% of PDD patients showed evidence of attentional fluctuation compared to 42% of those with DLB (Ballard *et al.,* 2002). Furthermore, Noe *et al.* (2004), reported that DLB patients made more omission errors in cancellation tasks compared to PDD. Mondon *et al.* (2007) as well refered more attentional deficits in maintained attention and the inhibitory control of attention in DLB patients, while other studies found a greater attentional impairment and more perseverative errors in PDD patients in comparison with DLB (Bronnick *et al.,* 2008; Filoteo *et al.,* 2009).

Executive dysfunction has also been described in PDD patients (Muslimovic *et al.,* 2005; Santangelo *et al.,* 2007; Song *et al.,* 2008; Muslimovic *et al.,* 2009; O'Brien *et al.,* 2009) and has been related with memory deficits (Higginson *et al.,* 2005; O'Brien *et al.,* 2009). Furthermore, deficits in phonetic and semantic verbal fluency are large in magnitude in PDD compared with PD (Henry and Crawford, 2004) and have been identified as predictive of later dementia progression (Santagelo *et al.,* 2007; William-Gray *et al.,* 2007).

Memory

Memory complaints were reported in 67% of patients with PDD, compared to 94% patients with DLB (Emre *et al.,* 2007). Patients with PDD have learning and immediate- and cued-recall impairment (Filoteo *et al.,* 2009). There is also growing evidence of recognition memory deficits in PDD for both verbal and non-verbal material tasks. Poor recognition appeared to be due to an elevated number of false positive and perseverative errors (Higginson *et al.,* 2005; Filoteo *et al.,* 2009). Furthermore, in these patients, the perfomance in executive measures predicted learning performance (Higginson *et al.,* 2005; O'Brien *et al.,* 2009).

Visuoperceptive, visuospatial and visuoconstructive functions

Visual perception (measured by tests of visual discrimination, space-motion, and object-form perception without needing manual responses) was globally more impaired in PDD than in non-demented controls, but did not differ from DLB patients (Levin *et al.,* 1991; Mosimann *et al.,* 2004). Compared to AD, PDD patients tended to perform worse in all perceptual scores (Levin *et al.,* 1991; Mosimann *et al.,* 2004). PDD patients were also impaired on motor-free visuospatial tasks with respect to controls and non-demented PD subjects (Janvin *et al.,* 2003; Mosimann *et al.,* 2004). The impairment in visuospatial functions was especially evident in more complex task requiring planning and sequencing of responses or self generation strategies (Levin *et al.,* 1991; Mosimann *et al.,* 2004). Furthermore, PDD patients exhibited deficits in assembling puzzles, formulating angular judgments and identifying embedded objects and geometric figures and at advanced stages of the disease, PDD patients showed impairment in all areas of visuospatial functioning (Levin *et al.,* 1991). Furthermore, all studies evaluating visuoconstruction in PDD patients using design copying tests showed an impairment of this function (Cormack *et al.,* 2004; William-Gray *et al.,* 2007) that has been suggested as a predictor of the development of dementia in PD (William-Gray *et al.,* 2007).

In conclusion, PD patients have cognitive impairment even in early stages of the disease. This impairment is progressive, developing to dementia as age increases and the disease progresses. The non-tremor phenotype and poor semantic fluency, visuoconstructive and delayed verbal memory deficits are risk factors for the progression of the disease. Impaired cognitive domains in PDD include attention, memory, and visuospatial, constructional and executive functions.

1.2.7. Neuroimaging studies

STRUCTURAL IMAGING TECHNIQUES

MRI allows an accurate identification of global and regional brain atrophy by visual inspection or by the more sophisticated techniques that perform statistical analysis of brain volume or shape described in *section 1.2.* In this section, the main findings using structural MRI in the study of the brain structure in PDD patients are going to be described *(For further details of the MRI studies in PDD, see Table 8 at the end of the section).*

The presence of cognitive impairment in PD is usually accompanied by brain atrophy. Volumetric studies have consistently demonstrated a reduction in hippocampal volume in PD compared with healthy control subjects (Laakso *et al.,* 1996; Camicioli *et al.,* 2003; Tam et al., 2005; Summerfield *et al.,* 2005; Junque *et al.,* 2005; Bouchard *et al.,* 2008; Jokinen *et al.,* 2009). Moreover, Camicioli *et al.* (2003) showed that this atrophy is even greater in PDD, suggesting a progressive hippocampal volume loss in PD, with the following pattern: healthy control subjects > PD > PDD > DLB. This pattern of atrophy has been confirmed by later studies (Ramirez-Ruiz *et al.,* 2005; Tam *et al.,* 2005; Summerfield *et al.,* 2005; Junque *et al.,* 2005; Nagano-Saito *et al.,* 2005; Kenny *et al.,* 2008). Furthermore, medial temporal lobe atrophy was related to age in PDD but not in PD (Tam *et al.,* 2005), and hippocampal volume in older (> 70 years) but not younger non-demented PD patients differed from healthy control subjects (Bouchard *et al.,* 2008). Moreover, hippocampal volume has been related to memory function in PD (Camicioli *et al.,* 2003; Junque *et al.,* 2005; Bouchard *et al.,* 2008; Kenny *et al.,* 2008; Aybek *et al.,* 2009; Jokinen *et al.,* 2009) and PDD (Laakso *et al.,* 1996; Camicioli *et al.*, 2003; Junque *et al.*, 2005; Kenny *et al.,* 2008). Effect sizes were 0.66 for PD and 1.22 for PDD compared with the healthy control subjects (Camicioli *et al.*, 2003) and the percentage of decrease was 11% in the amygdala and 10% in the hippocampus in PD, patients and 21% in the amygdala and 20% in the hippocampus in PDD patients (Junque *et al.,* 2005).

In addition to hippocampal atrophy, PD patients also show decreases in the prefrontal cortex (Burton *et al.,* 2004; Jokinen *et al.,* 2009), left anterior cingulate (Summerfield *et al*., 2005), right amygdala (Bouchard *et al.,* 2008) and superior temporal gyrus (Summerfield *et al.*, 2005; Beyer *et al.,* 2007a) in comparison with control subjects.

Furthermore, two studies to date assessed the brain changes related to mild cognitive impairment in PD and their relation to dementia progression (Meyer *et al.,* 2007; Beyer *et al.*, 2007a). Beyer *et al.* (2007a) found that PD with MCI had decreased volumes of the left middle frontal, precentral gyrus, left superior temporal and right inferior temporal gyri than non-cognitively impaired PD patients. However, these differences disappeared when age and sex were included as covariates in the analysis. Furthermore, by studying mild cognitive impaired patients that developed dementia, Meyer *et al.* (2007) described the characteristics of MCI secondary to PD and prodromal of PDD and DLB dementia. However, the pattern of brain atrophy did not differ from PDD and DLB patients. With respect to other types of MCI, PD-MCI displayed greater third ventricular enlargement, but less medial temporal lobe atrophy than prodromal MCI of AD and fewer vascular lesions than vascular MCI.

Furthermore, several studies have evaluated the pattern of atrophy of PDD patients compared to healthy subjects (Laakso *et al.,* 1996; Camicioli *et al.*, 2003; Burton *et al.*, 2004; Tam *et al.,* 2005; Summerfield *et al.,* 2005). The gray matter volume loss especially affects temporal, occipital and frontal areas and to a lesser extent the parietal lobe in PDD. The atrophic temporal areas include the superior, inferior and middle temporal lobes, insula, parahippocampal gyrus, hippocampus and amygdala. In the occipital lobe, Brodmann areas 18 and 19 are particularly involved. In the frontal lobe, the most affected areas are the middle and inferior frontal gyrus and anterior cingulate gyrus. Finally, subcortical structures such as the thalamus, substantia innominata, putamen and caudate nuclei, accumbens and hypothalamus are also reduced.

When compared with non-demented PD patients, PDD have shown greater gray matter loss in the hippocampus and entorhinal cortex as illustrates Figure 18 (Camicioli *et al.,* 2003; Summerfield *et al.*, 2005; Ibarretxe-Bilbao *et al.,* 2008; Kenny *et al.,* 2008) and in parahippocampus, superior temporal gyrus, temporo-polar region, anterior cingulate, medial and middle frontal gyri, parietal lobe, fusiform and lingual gyri, caudate nucleus and thalamus as shows Figure 17 (Burton *et al.,* 2004; Nagano-Saito *et al.,* 2005; Beyer *et al.,* 2007a). In a later study, Beyer and Aarsland (2008) found that PDD patients who develop dementia early had a greater decrease in the medial frontal gyrus, precuneus, inferior parietal lobe, and middle temporal gyrus compared to the ones that develop dementia late, but preserved the inferior frontal gyrus gray matter.

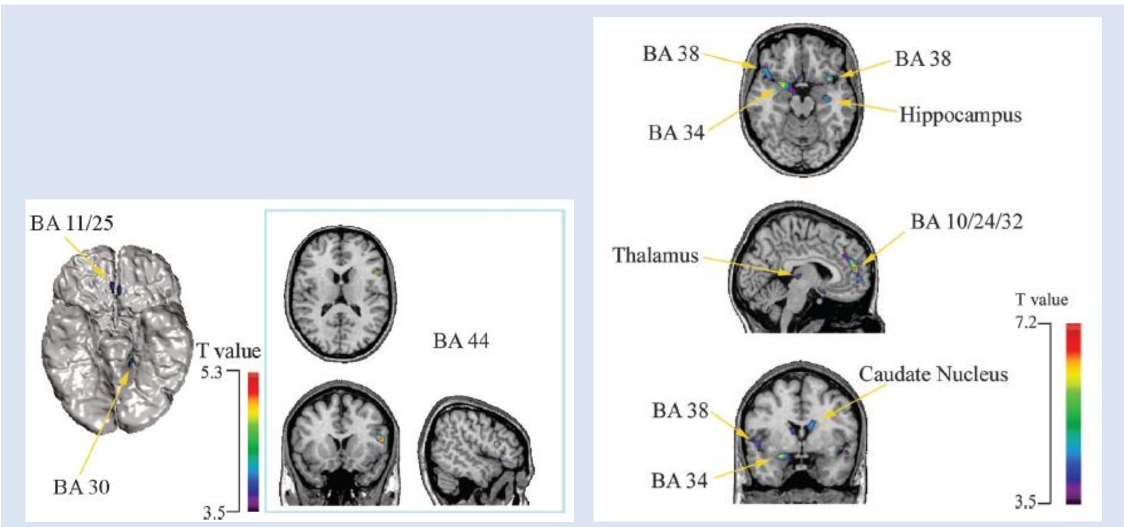


Figure 17. a) Regions showing significant differences between normal control subjects and non-demented patients with advanced PD. b) Regions with significant difference between advanced PD without dementia and PDD (*Source*: Nagano-Saito *et al.*, 2005).

Longitudinal studies have shown that the annual brain volume loss in non-demented PD patients was 10.35 ml/year, while in healthy control subjects was 0.49 ml/year (Hu *et al.*, 2001; Ramirez-Ruiz *et al.*, 2005). This ratio of volume loss correlated with cognitive decline measured through full IQ and performance IQ. Vocabulary on the WAIS and symptom duration also correlated with the percentage of brain loss (Hu *et al.,* 2001). Studying a group of PD and PDD patients, with an average of 25±5.2 months follow-up, Ramirez- Ruiz *et al.,* (2005) demonstrated that there was a progressive gray matter loss in non-demented PD patients in the anterior and posterior cingulate, hippocampus, insula, temporo-occipital region, hypothalamus and nucleus accumbens. In addition, gray matter loss over time in PDD patients was found in the fusiform gyrus, hippocampus, temporo-occipital region and medial temporal gyrus. After 1-year follow-up, Burton *et al.* (2005) found that the rate of atrophy did not correlate with age in PD/PDD patients nor with disease duration or cognitive symptoms. Furthermore, in PD patients who underwent surgery for subthalamic nucleus deep brain stimulation (STN-DBS), the pre-surgical hippocampal volume was a predictor of the conversion to dementia: Every 0.1 ml of decreased volume, corrected for MMSE and UPDRS-III, increased the likelihood to develop dementia by 24.6%, suggesting that the development of dementia after STN-DBS is related to the disease progression, rather than to the surgical procedure (Aybek *et al.,* 2009).

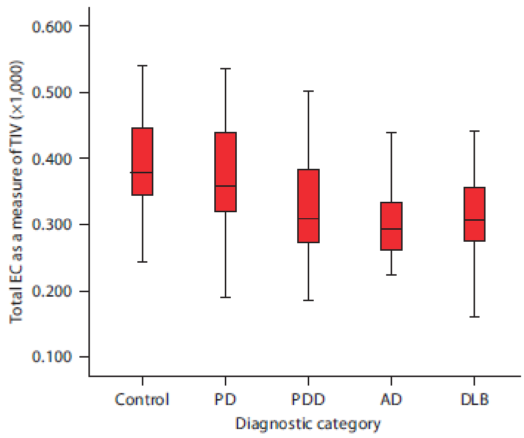


Figure 18. Box-and-whiskers plot of enthorhinal cortex volume by diagnostic group (*Source*: Kenny *et al.*, 2008)

Furthermore, volumetric techniques allow correlation of the brain volume of a particular region to cognitive and clinical functions. Specifically, relationships have been found between hippocampal volume reductions and memory impairment in PD and PDD (Laakso *et al.,* 1996; Camicioli *et al.,* 2003; Junque *et al.,* 2005; Bouchard *et al.,* 2008; Kenny *et al.,* 2008; Aybek *et al.,* 2009; Jokinen *et al.,* 2009) and between prefrontal cortex atrophy and prolonged reaction time in PD patients (Riekkinen *et al.,* 1998).

All together, there is evidence of a pattern of brain volume decrease associated with PD, which increases with development of dementia and correlates with cognitive dysfunction. Hippocampal gray matter loss is the more described characteristic of this brain deterioration, but atrophy extended later on to other temporal and frontal regions in PD patients and widespread throughout the neocortex, but in a lesser extent to the parietal lobe, in PDD patients.

DIFUSSION TENSOR IMAGING

Up to date, there is only one study exploring PDD patients with DTI (*for more details about the technique, see section 1.1.3.3*). This study found that PD and PDD patients showed a reduction in FA in the frontal, temporal and occipital white matter compared with healthy control subjects (Matsui *et al.,* 2007). In addition, the PDD group showed significant FA reduction in the bilateral posterior cingulate bundles compared with PD, even when UPDRS-III was included as a covariate. FA reductions in the left cingulate correlated with scores in conceptualization, memory, depression and MMSE, whereas the right cingulate related FA decreases correlated with attention performance. Previously, studying the diffusion pattern of PD Yoshikawa *et al.* (2004) found a decrease in the FA in the substantia nigra and, in advanced PD patients, in the subcortical white matter.

FUNCTIONAL IMAGING TECHNIQUES

Positron emission tomography (PET) and single-photon emission tomography (SPECT) allow visualizing and quantifying changes in cerebral blood flow, glucose metabolism and neurotransmitter function produced by parkinsonian disorders. Both PET and SPECT have become important tools in the differential diagnosis of these diseases and may have sufficient sensitivity to detect neuronal changes before the onset of clinical symptoms (Broderick *et al.,* 2005). PET studies of cerebral glucose metabolism have used the glucose analog [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), whereas the SPECT tracers ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) and ^{99m}Tc-ethylcysteinate dimmer (^{99m}Tc-ECD) are markers of cerebral blood flow and perfusion. Figure 19 summarizes all the studies to date performed by PET or SPECT and the radiotracers that were used. *For more information please check Table 9 at the end of this section.*

BRAIN PERFUSION: CEREBRAL BLOOD FLOW

- SPECT
  - Ceravolo et al., 2006: ^{99m}TC-ECD
  - Kasama et al., 2005: 123I-IMP
  - Mito et al., 2005: 123I-IMP
  - Osaki, 2005: 123I-IMP
  - Firbank et al., 2003: ^{99}TC HMPAO
  - Antonini et al., 2001: ^{99m}TC-ECD
  - Liu et al., 1992: ^{99m}TC-HMPAO
  - Kawabata et al., 1991: 123I-IMP
  - Spaminato et al., 1991: ^{99m}TC-HMPAO

GLUCOSE METABOLISM

- PET
  - Hokosai et al., 2009: [^{18}F]FDG
  - Lee et al., 2008: [^{18}F]FDG
  - Huang et al., 2007: [^{18}F]FDG

NEUROTRANSMITTER ABNORMALITIES

- PET
  - Jokinen et al., 2009: 6-[^{18}F] (FDOPA)
  - Shimada et al., 2009: [(11C)]MP4A
  - Bohnen et al., 2006: cortical AChE activity, [(11C)]PMP
  - Hilker et al., 2005: cortical AChE activity, [(11C)]MP4A and dopaminergic striatal uptake, 6-[^{18}F] (FDOPA)
  - Ito et al., 2002: Hilker et al., 2005: 6-[^{18}F] (FDOPA)

Abbreviations

AChE, Acetylcholinesterase; [18F]FDG, [18F]fluorodeoxyglucose; 123I-IMP, N-isopropyl-4-[123I]iodoamphetamine; 99mTc-HMPAO, 99mTc-hexamethylpropylene amine oxime; 99mTc-ECD, 99mTc-ethylcysteinate dimmer; 6-[18F] (FDOPA), 6-[18F]-fluorodopamine; [(11C)]MP4A, N-methyl-4-piperidin acetate; [(11C)]PMP, -[11c]methylpiperidin-4-yl propionate; Single photon emission computed tomography

Figure 19. Techniques and radiotracers used in the cerebral functional study of PDD

BRAIN PERFUSION AND CEREBRAL BLOOD FLOW STUDIES

SPECT imaging studies have shown differences in regional cerebral blood flow (rCBF) in PDD patients compared to PD patients and healthy controls in a variety of brain regions. Compared to healthy controls, PDD patients displayed hypoperfusion in several associative areas, in particular in lateral parietal, precuneus, temporal, posterior cingulate, occipital and frontal areas (Kawabata *et al.,* 1991; Liu *et al.*, 1992; Antonini *et al*., 2001; Firbank *et al.,* 2003; Kasama *et al.*, 2005; Mito *et al.*, 2005; Osaki *et al.*, 2005; Ceravolo *et al*., 2006). Firbank *et al.* (2003) showed hypometabolism in the mid-parietal and lateral occipitoparietal region (BA 7 and 39). In that study, blood flow did not correlate with scores in the CAMCOG battery. These results were supported by Kasama *et al.* (2005) who showed that PD patients had less blood flow in the bilateral parietal cortex, premotor area, cingulate nucleus and thalamus compared to healthy control subjects; and in PDD patients these reductions extended to frontal, posterior cingulate, temporal, occipital areas and precuneus. The rCBF of posterior regions (parietal, posterior cingulate and occipital cortex) was lower in PDD than PD patients. Mito *et al.* (2005) found a decrease in blood flow in anterior cingulate in PD compared with controls; that in PDD patients extended to posterior associative regions (temporo-parieto-occipital and precuneus). In a longitudinal study, Cercavolo *et al.* (2006) found a significant increase in cerebral blood flow in the anterior bilateral cingulate and superior, middle and inferior frontal gyri after 6 months of therapy with cholinesterase inhibitors with respect to baseline. Furthermore, Osaki *et al.* (2005) found a negative correlation between dementia and perfusion in the bilateral posterior cingulate, and between fluctuating cognition and parieto-occipital association areas perfusion.

All things considered, the differences observed between PD patients with and without dementia are not consistent but decreased rCBF has been reported in posterior cingulate gyrus, temporal, parietal, and occipital cortices in PDD related to PD (Kasama *et al.,* 2005; Mito *et al.,* 2005). However, an earlier study found parietal and parieto-occipital hypoperfusion in PD as well (Antonini *et al.,* 2001).

GLUCOSE METABOLISM STUDIES

PET studies of glucose metabolism have been performed with the glucose analog [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) in all the reviewed studies. Hosokai *et al.* (2009) found that PD patients had few areas of hypometabolism in the frontal lobe, namely the premotor, inferior and bilateral medial gyri, and occipital cortex, whereas PD with MCI had hypometabolism of the posterior cortical regions, including the temporo-parieto-occipital junction, medial parietal, inferior temporal cortices, occipital, and lateral and medial frontal cortex. When comparing both groups with PD, with and without MCI, greater reductions in temporal, parietal, and bilateral premotor cortices were found in the MCI group. This study suggests that posterior cortical dysfunction could be the primary neuroimaging feature at risk for dementia, but these results should be considered with care as PD without cognitive impairment had shorter disease duration and in consequence, lower UPDRS-III scores and levodopa dose may influence the results. Furthermore, a longitudinal study of the effect of cholinesterase inhibitor therapy (ChEI) (Lee *et al.,* 2008) reported increased cerebral metabolism after ChEI therapy in the left angular gyrus, extending to the supramarginal gyrus and superior and middle orbitofrontal gyrus and decreased metabolism in right fusiform gyrus. Besides, an improved MMSE score after ChEI was associated with increased cerebral metabolism in the left supramarginal, left orbitofrontal and left cingulate cortices. In addition, a longitudinal study assessing the PD motor- and cognitive-related FDG metabolic patterns after 2-year follow-up (Huang *et al.,* 2007) found that disease progression was associated with increasing metabolism in the subthalamic nucleus, internal globus pallidus, the dorsal pons and primary motor cortex. Advancing disease was also associated with declining metabolism in the prefrontal and inferior parietal regions. PD motor-related pattern expression was elevated at baseline compared with healthy control subjects, and increased progressively over time. PD-cognitive related activity also increased with time. However, these changes in network activity were slower than for the motor pattern, reaching abnormal levels only at the final time point. The motor- and cognitive-related patterns are represented in Figure 20.

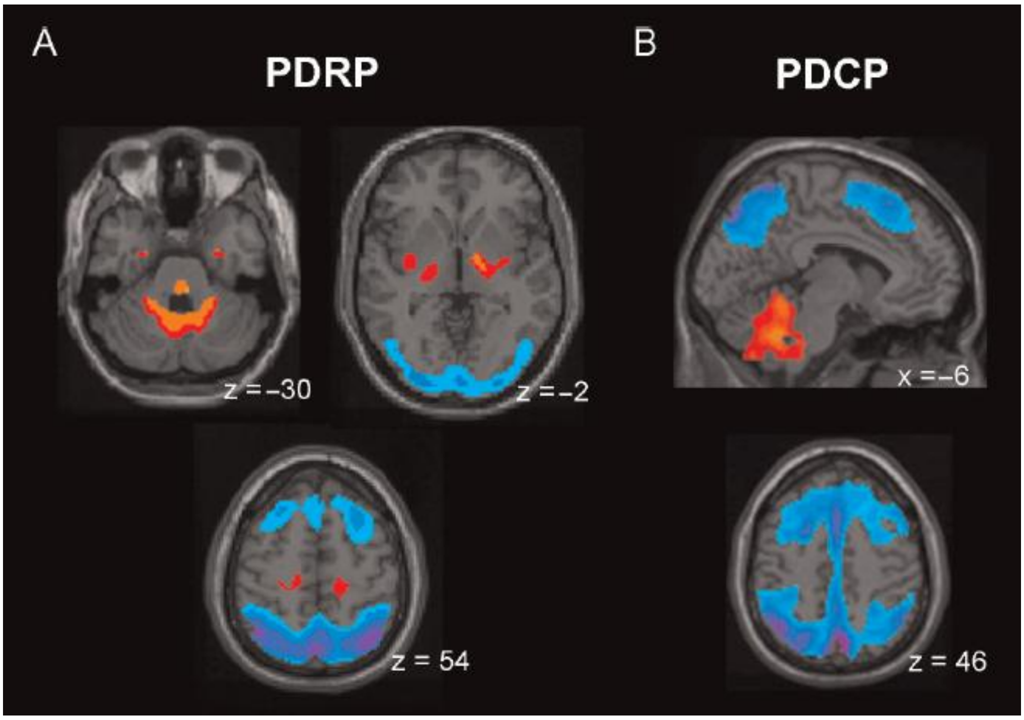


Figure 20. (A) Parkinson's Disease motor-related metabolic pattern. (B) Parkinson's Disease-Related Cognitive Pattern (PDCP).This patterns were identified in the network analysis of FDG PET scans.

In conclusion, the greater decrease of glucose metabolism in posterior regions may be related with cognitive impairment in PD. ChEI therapy increases the cerebral metabolism in these posterior regions and in the orbitofrontal cortex and these regional increases are related to an improvement in the MMSE score.

STUDIES OF NEUROTRANSMITTER FUNCTION

In general, the diagnostic accuracy of cerebral blood flow and glucose metabolism in differentiating neurodegenerative disorders is substantially poorer than direct imaging of the dopaminergic nigrostriatal pathway. PET studies of the nigrostriatal pathway used the uptake of 6-[^{18}F]fluorodopa (FDOPA) as a measure of the integrity of dopaminergic neurons. [^{18}F]fluorodopa measures changes in aromatic L-amino decarboxylase activity, which is dependent on the availability of striatal dopaminergic nerve terminals and is proportional to the number of dopamine neurons in the substantia nigra. PET and SPECT studies of radiotracer binding to postsynaptic dopamine receptors and presynaptic dopamine transporters have proved to be powerful techniques for quantifying the loss of dopaminergic neurons in PD (Broderick *et al.,* 2005). PET studies using the tracer 6-[^{18}F] have 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), indicating a consistent pattern of dopaminergic neuronal loss, usually with more pronounced deplection in the putamen rather than in the caudate.

There is frequently a marked asymmetry, particularly in the early stages of the disease, which progresses over time leading to further clinical deterioration (Colloby *et al.,* 2005) and a good correlation with symptom severity and illness duration (Broderick *et al.,* 2005). PET studies using FDOPA in PDD patients suggest a contribution of the basal ganglia to the cognitive deficits of PD. Nagano-Saito *et al.* (2004) described a relationship between frontal abnormalities and executive functions. In PD patients, Ito *et al.* (2002), demonstrated that [^{18}F] uptake was significantly lower in the striatum, midbrain and anterior cingulate than in normal controls. Similarly, Hilker *et al.* (2005) confirmed the decrease of striatal FDOPA uptake in PD and PDD compared with healthy control subjects. Compared with PD without dementia, PDD had a bilateral decline in the anterior cingulate area, ventral striatum and the right caudate nucleus. Later, Colloby *et al.* (2005) reported that lower scores in MMSE at baseline in PDD corresponded to a higher rate of decline in striatal (putamen) binding. Furthermore, Jokinen *et al.* (2009) found a positive correlation between caudate dopaminergic hypofunction and the impairment in verbal and visual memory. There were no correlations between prefrontal dopaminergic function and frontal cognitive functioning.

Besides, three studies evaluated the cholinergic activity in patients with PDD. Hilker *et al.* (2005) reported that global cortical 11C-MP4A binding, a marker of cortical acetylcholinesterase (AChE) activity, was severely reduced in PDD (29,7%) and moderately in PD patients (10.7%) with respect to healthy control subjects. PDD patients had lower left inferior parietal, left precentral and right posterior cingulate MP4A uptake rates than did patients with PD (Hilker *et al.,* 2005). Using [11C]PMP-PET, Bohnen *et al.* (2006) showed a lower mean cortical AChE hydrolysis rate in PD and PDD than in controls. Furthermore, the cortical AChE activity correlated with performance on the digit span test, but not with primary memory functions in PD/PDD; less significant correlations were found with line orientation, Stroop test and Trail Making Test B-A. Finally, Shimada *et al.* (2009) using 11C-MP4A, reported reduced AChE activity in the occipital lobe (BA 18) in early and advanced PD relative to controls. In comparison with non-cognitively impaired PD, PDD had reduced AChE activity in the inferior temporal gyrus (BA 20), supramarginal gyrus (BA 40) and the posterior cingulate (BA 31). Correlations between MMSE and cortical AChE values also were found, the strongest in the posterior cingulate gyrus.

All together, a pattern of dopaminergic neuronal loss has been described in PD, usually with greater depletion in the putamen than the caudate, and frequently asymmetric. This reduced uptake in basal ganglia has been correlated with cognitive deficits, giving evidence of the role of the basal ganglia in cognition. Furthermore, studies of cholinergic activity, showed reduced AChE activity in posterior regions, namely inferior temporal, parietal and posterior cingulate, in PDD in comparison with PD.

Table 7. Review of studies of cognitive functions in PDD

Study	Neuropsychological Assessment	Sample	Summary of main findings
Cognitive decline in Parkinson's disease: a prospective longitudinal study Muslimović et al., 2009	Psychomotor speed Attention Language Memory Executive Functions Visuospatial skills *3-year follow-up*	89 newly diagnosed PD 52 established PD (EPD) 70 CNT	✓ Cognitive performance of newly diagnosed patients decreased significantly over time, particularly on measures of psychomotor speed and attention and to a lesser extent on memory, visuospatial skills and EEFF. ✓ In the baseline, NDPD had impairment in comparison with normative data in attention, EEFF, visuoconstructive skills (clock drawing) and memory. After 3 years this deficits become more prevalent, including psychomotor speed. ✓ EPD had a deterioration performance in the follow-up in attention, psychomotor speed and constructive skills. ✓ 48% of the NDPD patients showed cognitive decline and 8,5% developed dementia in the follow-up; 50% of the EPD patients showed cognitive decline and 7% developed dementia in the follow-up ✓ None of the baseline features predicted cognitive impairment in newly diagnosed patients, whereas age at disease onset and axial impairment contributed to decline in EPD
The Contribution of Executive Control on Verbal-Learning Impairment in Patients with Parkinson's Disease with Dementia and Alzheimer's Disease O'Brien et al., 2009	EEFF (verbal fluency and CLOX) and CVLT, Raven matrices	25 PDD 25 AD	✓ Executive measures were predictive of list learning in the PDD group, but not in AD
Cognitive Dysfunctions and Pathological Gambling in Patients with Parkinson's Disease Santangelo et al., 2009	Frontal lobe/EEFF (FAB, cognitive flexibility WCST, spatial and verbal short-term and WM, logical abstract thinking, spatial planning, set-shifting TMT) Memory (visuospatial and verbal)	15 PD+PG 15 PD-PG	✓ PD+PG performed worse than PD-PG patients on cognitive tasks that evaluated visuo-spatial long-term memory and several frontal lobe functions 8FAB, phonological fluency task, TMT B-A ✓ Low scores on the FAB were the only independent predictor of PG. Frontal lobe dysfunctions in nondemented PD patients were associated with PD
Cognitive impairment in incident, untreated Parkinson disease Aarsland et al., 2008	Verbal memory Visuospatial Attentional-EEFF	196 non-demented drug-naive PD ↓ MCI 201 CNT	✓ PD was more impaired in all neuropsychological test than CNT. Largest effect size for verbal memory and psychomotor speed ✓ 18.9% of PD were classified as MCI, with a relative risk of 2.1 (1.2-3.6)in PD compared to the control group. 2/3 had a non-amnestic MCI subtype and 1/3 had an amnestic MCI ✓ PD patients with and without MCI did not differ significantly regarding demographic and motor features.
The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years Hely et al., 2008	MMSE, CDR, Boston Naming Test *20-year follow-up*	136 newly diagnosed PD	✓ 74% died after 20-year follow-up. The mortality rate fell in the first 3 years of treatment, then rose compared to the general population ✓ Dementia was present in 83% of the 20-year survivors. Dementia correlated with increasing age.
Early neuropsychological detection and the characteristics of Parkinson's disease associated	MMSE, CDR Attentional tests, language and	30 PDD 20 PD-MCI	✓ PDD had more severe impairments in attention, verbal and non-verbal memory, language and related functions, visuospatial functions and frontal EEFF than the

with mild dementia Song et al., 2008	related function test, visuospatial function test, verbal and non-verbal memory, frontal EEFF	33 CNT	other groups. The visual memory, visuospatial function, naming and the calculation test especially demonstrated more marked impairment ✓ PDD,PD-MCI<CNT: COWAT, fist-edge-palm and alternating hand movement, free and delayed recall, and repetition of language ✓ No significant differences between PD and PD-MCI ✓ Adding cognitive dysfunctions of cortical type to the early cognitive deficits of PD-MCI can help predict the development of dementia
Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease Pagonabarraga et al., 2008	Development of a new scale, the PD-CRS, that includes items assessing fronto-subcortical defects and items assessing cortical dysfunction	30 cognitively intact PD 30 MCI-PD 32 PDD 61 CNT	✓ Construct validity, test-retest and inter-rater reliability of PD-CRS total scores showed an intraclass correlation coefficient >0.70 ✓ Excellent test accuracy to diagnose PDD (sensitivity: 94%, specificity: 94%) ✓ The PD-CRS total scores and confrontation naming item (assessing cortical dysfunction), differentiated PDD from non-demented PD ✓ Alternating verbal fluency and delayed verbal memory independently differentiated the MCI group from both CNT and cognitively intact PD
Cut-Off Score of the Mattis Dementia Rating Scale for Screening Dementia in Parkinson's Disease Llebaria et al., 2008	MDRS	57 PD-ND 35 PDD	✓ Regression analysis showed MDRS total scores to differentiate PD-ND from PDD (mild, moderate and severe) ✓ Tukey post-hoc test found differences between mild PDD and moderate PDD, mild PDD and severe PDD, and moderate PDD and severe PDD ✓ Age and education did not predict the presence of dementia ✓ ROC curve analysis showed a cut-off score of ≤123 on the MDRS total scores to yield high sensitivity (92.65%), specificity (91.4%), positive and negative predictive values (PPV 83.3%, NPV 96.4%) ✓ A brief version of the MDRS obtained by memory, initiation/perseveration and conceptualization subscores yielded similar discriminant properties
Disturbance of automatic auditory change detection in dementia associated with Parkinson's disease: A mismatch negativity study Bronnick et al., 2008	Mismatch negativity event-related potential (MMN)	17 DLB 15 PDD 16 PD 16 AD 18 CNT	✓ PDD patients had reduced MMN area and amplitude compared to the DLB, PD and the CNT groups ✓ MMN area correlated significantly with number of missed target stimuli in the oddball-distractor task, and the PDD group missed targets significantly more often than the DLB group
Evolution of cognitive dysfunction in an incident Parkinson's Disease cohort Williams-Gray et al., 2007	MMSE, NART, verbal fluency, CANTAB, pattern and spatial recognition memory, Tower of London, pentagon copying *Between 3 and 5-year follow-up*	126 PD	✓ At baseline, 62% of patients were impaired on at least 1 neuropsychological test ✓ 10% of PD patients had dementia at the follow-up with a global pattern of cognitive deficits and 57% showed evidence of cognitive impairment, with frontostriatal deficits being the most common (spatial recognition memory, Tower of London) ✓ The most important clinical predictors of global cognitive decline were non-tremor dominant motor phenotype, poor semantic fluency and inaccurate pentagon copy
Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia Mondon et al., 2007	Orientation, Verbal episodic and Non-verbal memory, Attention, Language, Verbal fluency, Writing comprehension, Visuoconstructional	10 DLB 12 PDD	✓ DLB < PDD: orientation, TMT-A, reading of names of colours on the Stroop test, immediate and delayed recognition on the DMS-48 test

	Visuoperceptual skills, Logic and reasoning, EEFF		
Heterogeneity of Cognitive Dysfunction in Parkinson disease: A Cohort Study Verleden et al., 2007	Memory/attention, Visuospatial Executive/motor (COWAT, STROOP, WCST, PPT, RAVLT, VRT, road map test, VOSP)	100 PD	✓ 18% no impairment on either domain ✓ 51% impairment in one cognitive domain, most frequently in the executive/motor (88%) ✓ 24% performed below normal on two cognitive components, most often exectutive/motor and memory/attention deficits (96%) ✓ 7% had significant impairment on each cognitive component ✓ Depending on the criteria, 10-30% of the cohort will be categorized as PD patients with dementia (10% meet Emre criteria and 30% Dubois and Pillon)
Defining Mild Cognitive Impairment in Parkinson's Disease Caviness et al., 2007	RAVLT, Stroop, Benton visual retention test, COWAT,VOSP, Pugdue Pegboard Test, Road Map test	86 PD ↓ PD cognitively intact PD-MCI PDD	✓ PD-MCI defined as at least one cognitive domain impaired without dementia ✓ 62% of PD were cognitively normal, 21% met criteria for PD-MCI and 17% for PDD ✓ The mean duration of PD and MMSE scores of the PD-MCI group were intermediate and significantly different from both PD-cognitively intact and PDD ✓ The cognitive domain most frequently abnormal in PD-MCI was frontal/executive dysfunction followed by amnestic deficit. Single domain PD-MCI was more common than PD-MCI involving multiple domains
Cognitive profile of patients with newly diagnosed Parkinson disease Muslimovic et al., 2005	Psychomotor speed Attention, Language, Memory, EEFF, Visuospatial functions, Affective status	115 newly diagnosed PD 70 CNT	✓ PDD performed worse than CNT on 20 of the 28 neuropsychological measures ✓ Comparison with normative data showed that impairments were most frequent on measures of EEFF, memory and psychomotor speed ✓ 23.5% of PD displayed defective performance on at least three neuropsychological test and were classified as cognitively impaired ✓ Late onset of disease was independent predictor of cognitive dysfunction in PD
Recognition memory in Parkinson's disease with and without dementia: evidence inconsistent with the retrieval deficit hypothesis Higginson et al., 2005	CVLT	99 PD 99 CNT	✓ Non-demented PD exhibited deficits on cued recall and delayed recognition that were similar in magnitude to that of free recall ✓ This was also the case for the cued recall deficits exhibited by PDD; however, in this group recognition was worse than free recall ✓ In both groups poor recognition appeared due to an elevated number of false positive errors. *These results are inconsistent with the retrieval deficit hypothesis but support the notion that PD memory problems are secondary to prefrontal dysfunctio*
Neuropsychological profiles associated with subcortical white matter alterations and Parkinson's disease: implications for the diagnosis of dementia Libon et al., 2001	Finger Tapping Test, WMS-Mental Control, Boston Naming Test, Category Fluency, Clock Drawing, CVLT + Structural MRI	42 AD 34 VD 37 Mild WMA 39 signif. WMA 19 PDD	✓ Patients with mild WMA had better scores than patients with significant WMA ✓ No differences between patients with significant WMA and PD patients in mental control, verbal fluency and CVLT ✓ Drawing of significant WMA and PD patients was more impaired than the other groups
Differential aspects of cognitive impairment in patients suffering from Parkinson's and Alzheimer's disease: a neuropsychological evaluation. Caltagirone et al., 1989	Mental Deterioration Battery (MDB): memory, verbal, visuoconstructive and mental functions	67 AD 159 PD	✓ PD patients had better performances in the memory tests and worse on the verbal fluency test than AD, but differences were not significant

Abbreviations

AD, Alzheimer's Disease; CAMCOG, Cambridge Cognitive Examination; CDR, Clinical Dementia Rating; CNT, control subjects; COWAT, Controlled Oral Word Association test; CVLT, California Verbal Learning Test; DLB, Dementia with Lewy Bodies; DRS, Dementia Rating Scale; EEFF, Executive Functions; GDS, Global Deterioration Scale; LB, Lewy Bodies; MDRS, Mattis Dementia Rating Scale; MMN, Mismatch Negativity; MMSE, Minimental Status Evaluation; NPI, Neuropsychiatric Inventory; PD, Parkinson's Disease; PD, Parkinson's Disease; Prepulse inhibition; RAVLT, Rey auditory verbal learning test; TMT, Trail Making Test; VOSP, Visual Object and Space Perception battery; WAIS-R, Weschler Adult Intelligence Scale-revised; WM, Working Memory; WMA, white matter alterations; WMS-R, Weschler Memory Scale-reviewed; WRMT, Warrington Recognition memory test

This table is exclusively based on investigation works in the last ten years excluding revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; September 2009.

Table 8. Volumetric studies in PDD: Analysis of global and regional atrophy

Study	Methodology *(Tesla, sequence)*	Structures analyzed	Sample	Summary of main findings
Hippocampal atrophy predicts conversion to dementia after STN-DBS in Parkinson's disease Aybek et al., 2009	1.5T, 3D T1-weighted manual and automatic segmentation respectively *Longitudinal*	HPC Whole brain	14 PD 14 PDD	✓ PDD had smaller preoperative HPC volumes and EEFF than PD. ✓ Every 0.1 ml decrease of HPC volume increased the likelihood to develop dementia by 24.6%.
Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy Jokinen et al., 2009	1.5T, 3D FSPGR manually draw; Scheltens Scale	HPC PFC	12 PD 10 CNT	✓ atrophy in the hippocampus and the prefrontal cortex in PD ✓ hippocampal atrophy was related to impaired memory
Age and dementia-associated atrophy predominates in the hippocampal head and amygdala in Parkinson's disease Bouchard et al., 2008	1.5T, T1-weighted 3D MPRAGE manually segmented	Head, body and tail of HPC Amygdala	44 PD 13 PDD 44 CNT	✓ HPC volumes were smaller in PDD than CNT ✓ Right AG volumes were smaller in PD compared to CNT ✓ HPC volumes in older (>70) PD differed from younger PD and CNT ✓ Age and recall-scores correlated with HPC volume in PD-PDD
A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia Kenny et al., 2008	1.5T, 3D T1- weighted FSPGR manual segmentation technique (MIDAS) *Longitudinal*	Enthorrinal cortex volume	20 DLB 26 AD 30 PDD 31 PD 37 CNT	✓ EC volumes were significantly smaller in DLB, AD and PDD patients compared to CNT and PD. ✓ Volume reduction in EC volume in dementia groups relative to controls was 19.9% in DLB and 14.7% in PDD ✓ Correlations with memory scales in all subjects
Grey matter atrophy in early versus late dementia in Parkinson's disease Beyer et al., 2008	1.5T, T-1 weighted 3D FSPGR VBM (SPM2), 12mm Kernel, p<0.001 uncorrected. Customised template	VBM Whole brain	9 early PDD 6 late PDD	✓ Early<late: MODULATED: medial F gyrus bilaterally, right precuneus and left inf P lobe, sup F and middle T; UNMODULATED: right caudate, left putamen, left precentral gyrus, left middle T gyrus and right red nucleus ✓ Late<early: MODULATED: inferior F gyrus bilaterally; UNMODULATED: insula bilaterallly
Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies Beyer et al., 2007	1.5T, T-1 weighted 3D FSPGR VBM (SPM2), 12mm Kernel, p<0.001 uncorrected	VBM Whole brain	15 PDD 18 DLB 21 AD 20 CNT	✓ DLB<PDD: bilaterally in inferior P and precuneus; right insula, inf T gyrus and lentiform nucleus; left angular gyrus, cuneus, sup O gyrus
A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry Beyer et al., 2007	1.5T, T-1 weighted 3D FSPGR VBM (SPM2), 12mm Kernel, p<0.001 uncorrected. Customized templates	Whole brain	16 PDD 20 PD (12 cognit. normal, 8 MCI) 20 CNT	✓ PDD<CNT: amygdala, T bilaterally, frontal, cingulate, HPC, red nucleus in the left; right middle O. ✓ PDD<PD: frontal lobes, limbic, P and T bilaterally. Thalamus. ✓ PD<CNT: right sup T. ✓ PD-MCI<PD: left middle F, precentral gyrus, left sup T and right inf T.
MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias	1.5 T, T1- T2-weighted, FLAIR ROI manually Visual rating scale	Frontal Temporal Third ventricle HPC	52 CNT	✓ Converted 19 to AD, 17 to VaD and 15 to Parkinson-LBD ✓ There were no differences between PLB-MCI and PLBD subjects ✓ PLB-MCI (prodromal for PLBD): third ventricular enlargement greater

Meyer et al., 2007	*Longitudinal*	EC	30 AD-MCI 35 V-MCI 8 PLB-MCI	than N-MCI and V-MCI, less severe atrophy of medial temporal lobe than N-MCI and fewer vascular lesions than V-MCI.
Corpus callosum in neurodegenerative diseases: findings in Parkinson's disease Wiltshire et al., 2005	1.5T, T1 weighted images. ImageJ + Meta-analysis Manually segmentation	Corpus callosum	24 PD 25 PDD 16 AD 27 CNT	✓ PD and PDD did not show significant callosal atrophy compared to CNT or AD
Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging Burton et al., 2005	1.5T, T1-weighted 3D Semiautomated threshold-based procedure (MIDAS) *Longitudinal*	Whole brain	18 PD 13 PDD 24 CNT	✓ There was no association between rate of atrophy and age, duration of PD, duration of cognitive symptoms, baseline cognitive scores and changes in cognitive scores
Longitudinal evaluation of cerebral morphological changes in Parkinson's disease with and without dementia Ramírez-Ruiz et al., 2005	1.5T, 3D SPGR Opimized VBM (SPM2), p<0.001 uncorrected *Longitudinal*	Whole brain	30 PD 16 PDD follow up: 11 PD 8 PDD	✓ In PD, volume loss in right anterior and posterior cingulate, bilateral temporo-occipital region, bilateral insula, right hypothalamus, accumbens, left HPC ✓ In PDD, decrement in volume in right fusiform gyrus, right paraHPC and HPC, right T-O region and right medial anterior T gyrus
Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study Summerfield et al., Arch Neurol. 2005	1.5T, 3D SPGR Opimized VBM, ROIs by the Pick Atlas, SPM99, p<0.001 uncorrected	T lobes,Caudate Lentiform n. Cingulate Thalamus, Insula Amygdala HPC, paraHPC	16 PDD 13 PD 13 CNT	✓ PDD<CNT: putamen, accumbens, hippocampus, hypothalamus and anterior cingulate gyrus bilaterally, left side of the thalamus and parahippocampal region ✓ PD<CNT: right HPC, left anterior cingulate gyrus, left sup T gyrus ✓ PDD<PD: right HPC, L sup T gyrus
Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia Junqué et al., Mov Disord. 2005	1.5T, 3D T1-weighted SPGR Opimized VBM (SPM99), p<0.001 uncorrected. ROI with MRIcro	Amygdala HPC	16 PDD 16 PD 16 CNT	✓ PD<CNT: decreased volume in amygdala, 11% and hippocampus, 10% ✓ PDD<CNT: decreased volume in amygdala, 21% and hippocampus, 20% ✓ Verbal learning correlated with amygdala and HPC volumes
Cerebral atrophy and its relation to cognitive impairment in Parkinson disease Nagano-Saito et al., 2005	1.5T, 3D Field echo sequence VBM, p<0.001		9 PDD 39 advanced PD 31 CNT	✓ PDD<PD: bilateral ant cingulate, medial F gyrus (BA 10, 24, 32), bilateral paraHPC, bilateral sup T gyrus, temporo-polar region (BA 22, 38), right HPC, right middle F gyrus (BA 46), bilateral caudate nuclei, left thalamus
Temporal lobe atrophy on MRI in Parkinson disease with dementia. A comparison with Alzheimer disease and dementia with Lewy bodies Tam et al., Neurology 2005	1.5 T, T1-weighted 3D FSPGR Visual inspection		39 CNT 33 PD 31 PDD 25 DLB 31 AD	✓ MTA: CNT < PD ~ PDD ~ DLB < AD ✓ Age was related to MTA in PDD but not in PD ✓ No correlations between MTA and cognitive impairment in PD, PDD
Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's	1.5 T, T1-weighted 3D Optimized VBM (SPM99)		26 PDD 31 PD	✓ PDD < CNT: left O, T bilateral, right middle and inf F, left inf and sup P, right caudate tail and putamen, thalamus bilaterally

disease, dementia with Lewy bodies and controls Burton et al., 2004	p< 0.001. Customized template		28 AD 17 DLB 36 CNT	✓ PDD<CNT: sup, middle and inf F gyri on the right ✓ PDD<PD: bilaterally iform and lingual gyri
MRI study of caudate nucleus volume in Parkinson's disease with and without dementia with Lewy bodies and Alzheimer's disease Almeida et al., 2003	1.5T, T1-weighted 3D FSGR, manually drawn ROI (MIDAS)	Whole brain Caudate	28 PD 20 PD+DLB 27 AD 35 CNT	✓ AD had significantly reduced whole brain and caudate volume compared to CNT, PD (but not PD+DLB). Differences disappear after adjusting for total brain volume.
Parkinson's disease is associated with hippocampal atrophy Camicioli et al., 2003	1.5T, 3D Semiatomated recursive segmentation (REGION) and manual tracing (NIH image v.1.5)	HPC	10 PD 10 PDD 11 AD 12 CNT	✓ HPC volume showed a pattern (CNT > PD > PDD > AD). Effect sizes were: PD, 0.66; PDD, 1.22; and AD, 1.81. ✓ Among PD and PDD patients, recognition memory and MMSE scores correlated with left, but not right hippocampal volume.
Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline Hu et al., 2001	Serial volumetric T1 weighted *Longitudinal*		8 PD 10 CNT	✓ PD had significant reductions in annual brain volume loss when compared to CNT (year in PD and 0.49 in CNT). ✓ Correlations between brain volume loss and reductions in performance IQ and full scale IQ
Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: An MRI study Laakso et al., 1996	1.5T, T1-weighted MPRAGE Manually drawn and normalized to coronal intracranial area.	HPC	50 AD 9 VaD 8 PDD 34 CNT	✓ All patient groups had significantly smaller volumes of the HPC compared with CNT ✓ Correlation between HPC volume and memory in PDD but not in PD

Abbreviations

AD, Alzheimer's Disease; AG, amygdala; CAMCOG, Cambridge Cognitive Assessment; CNT, control subjects; cong., cognitively; DLB, Dementia with Lewy Bodies; EEFF, executive functions; EC, entorhinal cortex; F, frontal; FSPGR, Fast Spoiled Gradient Echo sequence; GM, gray matter; HPC, hippocampus; inf., inferior; MCI, mild cognitive impairment; MMSE, Mini-mental State Examination; MPRAGE, Magnetization Prepared Rapid Gradient Echo sequence; MTA, medial temporal atrophy; MTL, medial temporal lobe; O, occipital; P, parietal; PD, non-demented Parkinson's Disease; PDD, Parkinson's Disease with Dementia; PFC, Prefrontal cortex; PLBD, Parkinson-Lewy body dementias; ROI, Region of Interest; SI, substantia innominata; SPGR, Spoiled Gradient-Recalled Echo sequence; SPM, Statistical Parametric Mapping; STN-DBS, subtalamic nucleus deep brain stimulation; sup., superior; T, Tesla; T, temporal; UPDRS-III, Unified Parkinson's Disease Rating Scale III; VaD, vascular dementia; VBM, voxel-based morphometry; vs., versus; WM, white mater; WMH, white matter hyperintensities

This table is exclusively based on investigation works in the last ten years excluding revisions and case-studies. Source search: PubMed (www.pubmed.gov), language: English, last update; September 2009.

Table 9. Functional studies in PDD: Analysis of global and regional function

Study		Marker	Sample size	Summary of main findings
BRAIN PERFUSION: CEREBRAL BLOOD FLOW	**Brain perfusion effects of cholinesterase inhibitors in Parkinson's disease with dementia** Ceravolo et al., 2006 *Longitudinal*	^{99m}Tc-ECD SPECT	19 PDD	✓ Significant increase of rCBF in the anterior bilateral cingulate, subgyral and bilateral superior, middle and inferior frontal gyyri after ChEIs therapy with respect to baseline ✓ Cognitive improvement after 6-months
	Cerebral blood flow in Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease according to three-dimensional stereotactic surface projection imaging Kasama et al., 2005	123I-IMP SPECT	69 PD 16 DLB 15 AD 24 CNT	✓ PD patients revealed less flow in parietal bilaterally, premotor, cingulate and thalamic than CNT. In PDD, extended in P, F, posterior cingulate, T, O, precuneus ✓ PDD < PD: P, post cingulate and O ✓ DLB<CNT: P, F, T, O ✓ DLB<PDD: premotor area flow (including SMA) ✓ AD<DLB: lateral TP, m T regions ✓ DLB<AD: premotor cortical flow.
	Brain 3D-SSP SPECT analysis in dementia with Lewy bodies, Parkinson's disease with and without dementia, and Alzheimer's disease Mito et al., 2005	123I-IMP SPECT	30 PD	✓ DLB<CNT: lateral P, T, O association areas, anterior and post cingulate, precuneus, primary visual cortex, lateral frontal association ✓ PDD<CNT: anterior cingulate, lat P, T, O association and precuneus ✓ DLB<PDD: slightly decreased lat P, T association and post cingulate, precuneus (NS) ✓ PD< CNT: ant cingulate and primary visual cortex ✓ DLB<PD: lat P, T, O association, lateral occipital association, post cingulate and precuneus, primary visual cortex
	Three-dimensional stereotactic surface projection SPECT analysis in Parkinson's disease with and without dementia Osaki et al., 2005	123I-IMP SPECT	30 initially diagnosed PD 30 CNT	✓ PD<CNT: temporal, frontal and medial parietal lobes, visual cortices and parietal association areas ✓ Negative correlations between dementia and bilateral posterior cingulate, and among fluctuating cognition and bilateral medial parietal lobes, parietal association areas, and dorsal occipital lobes
	Regional cerebral blood flow in Parkinson's disease with and without dementia Firbank et al., 2003	Tc99 HMPAO SPECT	31 PD 34 PDD 37 CNT 32 AD 15 DLB	✓ PDD/DLB<CNT: mid-parietal and lateral occipitoparietal region (BA 7 and 39) ✓ PDD<AD: decrease blood flow in occipito-parietal region
	Perfusion ECD/SPECT in the characterization of cognitive deficits in Parkinson's disease Antonini et al., 2001	^{99m}TC-ECD	22 PD 22 PDD 21 CNT	✓ PDD patients showed significant perfusion decrements in all cortical areas, particularly temporal and parietal regions; in PD reductions were limited to the frontal lobe area
GLUCOSE METABOLISM	**Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment** Hosokai et al., 2009	CMRglc[18F]FDG-PET	13 PD-MCI 27 PD 13 CNT	✓ PD: hypometabolism in the F (right premotor, left inferior and bialateral medial) and O cortices ✓ PD-MCI: hypometabolism in the posterior cortical regions, including T-P-O junction, medial parietal and inf T cortices, O, lateral and medial F. ✓ PD-MCI<PD: greater reductions in T, P and bilateral premotor area, worse ADAScog

				recall ✓ PD: 11 anterior type, 11 posterior, 5 antero-post ✓ PD-MCI: antero-posterior pattern
	Changes in cerebral glucose metabolism in patients with Parkinson disease with dementia after cholinesterase inhibitor therapy Lee et al., 2008	[18F]FDG -PET	10 PDD	✓ Increased cerebral metabolism after ChEI therapy in the left angular gyrus, extending to the supramarginal gyrus and superior and middle an sup frontal gyri, middle OF gyrus ✓ decreased metabolism in right fusiform gyrus ✓ improved MMSE scores after ChEI treat were associated with increased cerebral metabolism in the left supramarginal, left OF and left cingulate cortices
	Changes in network activity with the progression of Parkinson's disease Huang et al., 2007	[18F]FDG -PET [^{18}F]- FP-CIT 2-year follow-up *Longitudinal*	15 early PD	✓ disease progression was associated with increasing metabolism in the STN, GPi, dorsal pons and primary motor cortex ✓ Advancing disease was associated with declining metabolism in the PFC and inferior parietal regions
NEUROTRANSMITTER ABNORMALITIES	**Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy** Jokinen et al., 2009	6-[^{18}F] (FDOPA)	12 PD 10 CNT	✓ Caudate Fdopa correlated with verbal (immediate and delayed) and visual memory. ✓ atrophy in the hippocampus and the prefrontal cortex ✓ hippocampal atrophy was related to impaired memory
	Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET Shimada et al., 2009	[(11C)]MP4A	18 PD (9 early, 9 advanced) 10 PDD 11 DLB 26 CNT	✓ Early and advanced PD<CNT: reduction of AChE in BA 18 ✓ DLB/PDD<CNT: reduced AChE in left lateral T lobe ✓ PDD/DLB<PD: reduced AChE in the inf T gyrus (BA 20), supramargina gyrus (BA 40), and the posterior cingulate gyrus (BA 31) ✓ PDD/DLB<CNT: blood flow reductions in almost all cortical areas, specially in O ✓ Correlations between MMSE and cortical AChE in PD and PDD/DLB, the strongest in posterior cingulate gyrus
	Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia Bohnen et al., 2006	[(11)C]PMP PET	11 PDD 13 PD 14 CNT	✓ PD/PDD<CNT: lower cortical AChE hydrolysis rate ✓ Cortical AChE activity correlated with performance on the digit span test, less significant correlation with line orientation, Stroop and TMT B-A
	Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways Hilker et al., 2005	[(11C)]MP4A 6-[^{18}F] (FDOPA)	17 PD 10 PDD 31 CNT	✓ Global cortical MP4A binding was severely reduced in PDD (29,7%) and moderately n PD (10.7%) vs controls ✓ PDD<CNT: lower left inf parietal, left precentral gyrus and right posterior cingulate MP4A uptake
	Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[18F]fluoro-L-dopa PET study Ito et al., 2002	6-[^{18}F] (FDOPA)	10 PD 10 PDD 15 CNT	✓ PD<CNT: decrease uptake in the putamen, the right caudate and the left ventral midbrain ✓ PDD<CNT: reduced uptake bilaterally in the striatum, midbrain and anterior cingulate ✓ PDD< PD: bilateral decline in the anterior cingulate and ventral striatum and in the right caudate nucleus

Abbreviations

AChE, Acetylcholinesterase; AD, Alzheimer's Disease; BA, Brodmann areas; ChEI, Choliniesterase inhibitors; CNT, control subjects; DLB, Dementia with Lewy Bodies; F, frontal; P, parietal; PD, Parkinson's Disease cognitively normal; PDD, Parkinson's Disease with Dementia; MCI, mild cognitive impairment; O, occipital; T, temporal; TMT, Trail making test; [18F]FDG, [18F]fluorodeoxyglucose; 123I-IMP, N-isopropyl-4-[123I]iodoamphetamine; 99mTc-HMPAO, 99mTc-hexamethylpropylene amine oxime; 99mTc-ECD, 99mTc-ethylcysteinate dimmer; 6-[18F] (FDOPA), 6-[18F]-fluorodopamine; [(11C)]MP4A, N-methyl-4-piperidin acetate; [(11C)]PMP, -[11c]methylpiperidin-4-yl propionate

This table is exclusively based on investigation works in the last ten years excluding revisions and case-report studies. Source search: PubMed (www.pubmed.gov), language: English, last update; September 2009.

1.3. Dementia with Lewy Bodies

The most widely studied neurodegenerative dementia in recent decades has been AD, that accounts for 50-60% of the cases of dementia in elderly patients. Vascular dementia used to be considered the cause of most remaining cases, until neuropathological autopsy studies reported the additional findings of LBs in the brainstem and cortex of 15 to 25% of elderly demented patients, constituting the largest pathological subgroup after pure AD (McKeith *et al.,* 1996).

In consequence, in 1996, the Consortium on Dementia with Lewy bodies (McKeith *et al.*, 1996) met to establish consensus guidelines for the clinical diagnosis of DLB and to determine a common framework for the assessment and characterization of pathologic lesions at autopsy. These criteria were reviewed in 2005 (McKeith *et al.*, 2005) incorporating new information about the core clinical features and suggesting improved methods to assess them. They emerged as an attempt to determine whether particular clinical symptoms are associated with LB pathology. The key symptoms suggestive of DLB are fluctuating cognitive impairment with episodic delirium, prominent psychiatric symptoms, especially visual hallucinations, and extrapyramidal features occurring either spontaneously or as part of an abnormal sensitivity to neuroleptic medication. In the revised criteria, REM sleep behavior disorder, severe neuroleptic sensitivity and reduced striatal dopamine transporter activity on functional MRI were given greater diagnostic weighting as features suggestive of a DLB diagnosis (see Table 12).

These diagnostic criteria are based on the assumption that DLB exists as a disorder with discernible pathological and clinical boundaries. The importance of accurate antemortem diagnosis of DLB is due to the characteristic and often rapidly progressive clinical syndrome, the need for particular caution with neuroleptic medication, and the possibility that DLB patients may be particularly responsive to cholinesterase inhibitors.

1.3.1. Neuropathological criteria

DLB is characterized by a variable burden of α-synuclein with cortical LBs and various degrees of AD-related pathology (Jellinger *et al.,* 2009). DLB exhibits a clinical phenotype that is apparently different from PD, but the morphology of LNs/LBs, the characteristics of the vulnerable neuronal types, and the distribution of the subcortical nuclei and cortical areas affected closely overlap with those of PD (Braak *et al.,* 2003; 2006).

As displayed in Table 10 and Figure 21, the *Consensus pathologic guidelines for the diagnosis of DLB* proposed a semiquantitative assessment of LB density based on α-synuclein immunohistochemistry in brainstem, basal forebrain and in five cortical regions.

Table 10. Consensus pathologic criteria for the diagnosis of DLB (*Source*: McKeith *et al.,* 2005)

Assignment of Lewy body type based upon pattern of Lewy-related pathology in brainstem, limbic, and neurocortical regions (McKeith *et al.,* 2005)

Lewy body type pathology	Brainstem regions			Basal forebrain/limbic regions				Neocortical regions		
	IX-X	LC	SN	nbM	Amygdala	Transentorhinal	Cingulate	Temporal	Frontal	Parietal
Brainstem-predominant	1-3	1-3	1-3	0-2	0-2	0-1	0-1	0	0	0
Limbic (transitional)	1-3	1-3	1-3	2-3	2-3	1-3	1-3	0-2	0-1	0
Diffuse neocortical	1-3	1-3	1-3	2-3	3-4	2-4	2-4	2-3	1-3	0-2

IX-X = 9^{th}-10^{th} cranial nerve nucleus; LC = locus ceruleus; SN = substantia nigra; nbM = nucleus basalis of Meynert
0 = none; 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Very severe

Revised consensus pathological guidelines for scoring cortical LB deposition

Cortical region	Brodmann area	Anatomy	Score		
Entorhinal cortex	29	Medial flank of collateral sulcus	0	1	2
Cingulate gyrus	24	Whole gyral cortex	0	1	2
Mid-frontal cortex	8/9	Lateral flank of superior frontal sulcus	0	1	2
Mid-temporal cortex	21	Inferior surface of superior temporal sulcus	0	1	2
Inferior parietal lobule	40	Lateral flank of parietal sulcus	0	1	2

Cortical Lewy body score: 0-2 Brainstem-predominant; 3-6 Limbic or transitional; 7-10 Neocortical

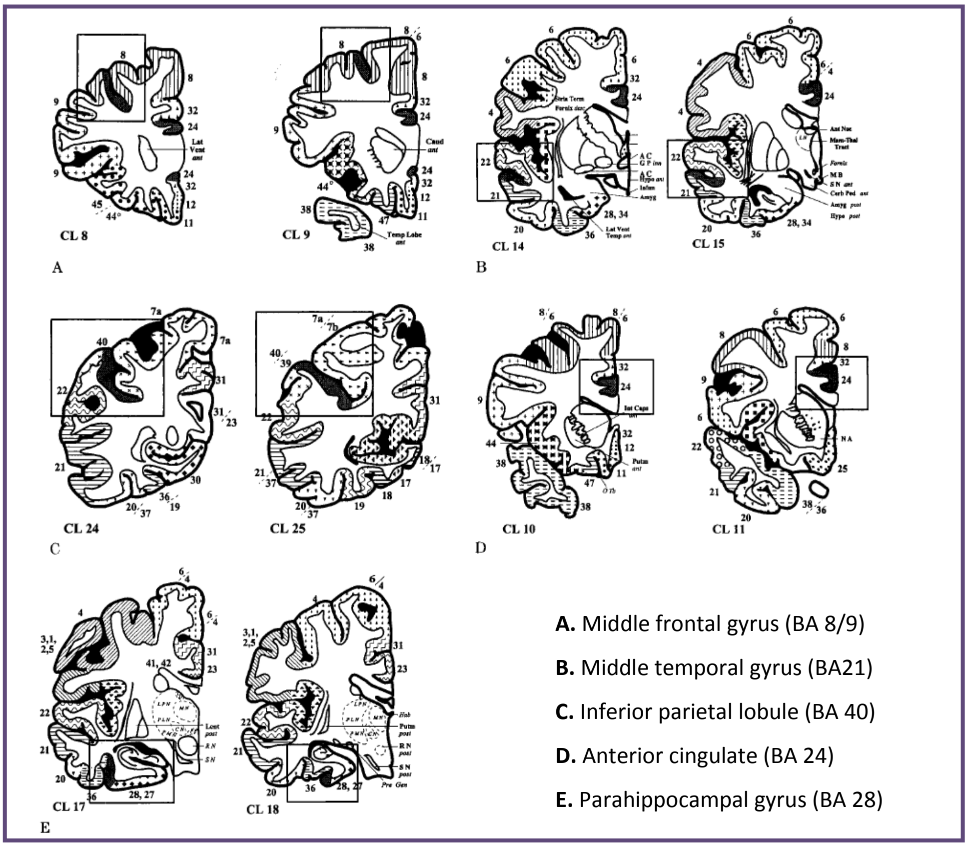


Figure 21. Cortical areas for LB assessment (*Source*: McKeith *et al.,* 2005)

Brainstem or cortical LBs are the only features considered essential for a pathological diagnosis of DLB, although Lewy-related neurites, AD pathology, and spongiform change may also be present (McKeith *et al.,* 2005). For this reason, AD-related pathology should be taken into account. The likelihood that the observed neuropathology explains the DLB clinical syndrome is directly related to the severity of Lewy-related pathology, and inversely related to the severity of concurrent AD-type pathology. Figure 22 illustrates the clinicopathological relations among AD, PD and LBD.

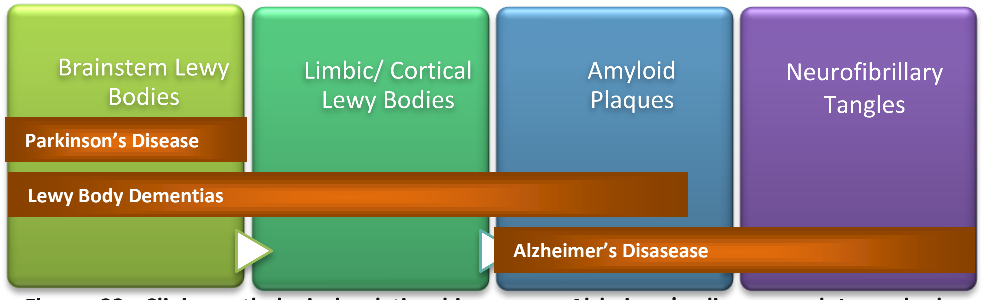


Figure 22. Clinico-pathological relationship among Alzheimer's disease and Lewy body disorders (Kaufer and Tröster, 2008)

However, Leverenz *et al.* (2008) found that 49% of LB-positive demented autopsy cases were not classifiable following the published Consensus criteria; they therefore proposed a modification of the criteria displayed in Table 11. The changes consisted of reducing the number of regions requiring examination, allowing more variability in Lewy-related pathology (LRP) severity scores within specific brain regions, and adding an amygdala predominant category. These modifications permitted the classification of 97% of LRP positive cases from a referral-based sample.

Table 11. Proposed modified criteria for categorization of Lewy-related pathology in patients with dementia: results from two autopsy series (Leverenz *et al.*, 2008)

Predominant region	LRP severity scoring with proposed criteria[a]				Results	
	SN or medulla[b]	Amygdala	Cingulate gyrus	Frontal cortex	LADRS, *n (%)*	ADPR, *n (%)*
Brainstem	1+ in either	0-2	0-1	0	5 (4)	20 (16)
Amygdala	0-1 in both	1+	0-1	0	23 (18)	24 (19)
Limbic	1+ in either	2+	1-3	0-1	26 (21)	22 (18)
Neocortical	1+ in either	2+	2+	2+	67 (54)	55 (44)
Mixed	*Cases not classifiable by modified criteria*				4 (3)	5 (4)

SN = substantia nigra; LADRS Lewy body-associated dementia research study; ADPR = Alzheimer's disease patients registry
[a] Severity of LRP was scored according to published consensus criteria as 0=none; 1=Mild; 2=Moderate; 3=Severe; 4=Very severe
[b] For medulla, the highest score in dorsal motor nucleus of the vagus nerve, raphe nuclei or lateral tegmentum was considered representative and 0 means no LRP in all three subregions of medulla

DLB occuring without or with scarce amyloid plaques is termed DLB pure form; whereas DLB with accompanying neurofibrillary tangles and senile plaques is called DLB common form. Among DLB cases, brains of the subtype showing severe AD pathology presented advanced Lewy pathology, suggesting that AD pathology exacerbates

Lewy pathology (Leverenz *et al.,* 2008; Ferrer, 2009). The reasons for AD and DLB potentiation are not fully known, but several studies have evidenced combined α-synuclein, hyper-phosphorylated tau and β-amyloid deposition in human α-synucleinopathies and taupathies, and in related animal models. Genetic studies have shown that DLB may be due to mutations in α-synuclein and LRRK2 (Ferrer, 2009).

1.3.2. Clinical diagnostic criteria

According to the consensus criteria, the main clinical features for the diagnosis of DLB are: 1) cognitive fluctuations with pronounced variations in attention and alertness; 2) spontaneous Parkinsonism and 3) well-formed visual hallucinations. Two of these core features are necessary for the diagnosis of probable DLB, and at least one for the diagnosis of possible DLB (McKeith *et al.,* 1996; McKeith *et al.,* 2005). DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism if it is present. If dementia occurs in the context of well-established Parkinson disease, the term PDD should be used (McKeith *et al.,* 1996; McKeith *et al.,* 2005). How relevant such a distinction is remains a matter of debate; most authorities consider that both syndromes represent the motor-onset or the cognitive-onset variants of the same disease continuum.

Additional features supporting the diagnosis are: auditory or olfactory hallucinations, delusions, repeated falls, syncopes, transient loss of consciousness and neuroleptic sensitivity. Other associated features are hypersomnia, major depression, REM sleep behavior disorder, abnormal EEG and urinary incontinence (see Table 12). These criteria have a high specificity (0.79-0.91), but their sensitivity is lower and more variable (0.22-0.95) (McKeith *et al.,* 1996; McKeith *et al.,* 2005). Diagnosis is therefore complex and the condition is sometimes confused with other dementias, such as AD and PDD, leading to underdiagnosis.

The distinction between DLB and PDD as two clinical phenotypes based solely on the temporal sequence of appearance of symptoms has been criticized by those who regard the different clinical presentations as simply representing different points on a common spectrum of LB disease, itself underpinned by abnormalities in alpha-synuclein metabolism.

Table 12. Revised criteria for the Clinical Diagnosis of Dementia with Lewy Bodies (McKeith *et al.,* 2005)

Central features (essential for the diagnosis)	✓ Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function ✓ Persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression ✓ Attention and executive deficits and visuospatial disability may be especially prominent
Core features (two core features for a diagnosis of probable DLB, one for possible DLB)	✓ Fluctuating cognition with pronounced variations in attention and alertness ✓ Recurrent visual hallucinations that are typically well formed and detailed ✓ Spontaneous features of parkinsonism
Suggestive features (Significantly more frequent that in other dementing disorders)	✓ REM sleep behavior disorder ✓ Severe neuroleptic sensitivity ✓ Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging
Supportive features (commonly present but not proven to have diagnostic specificity)	✓ Repeated falls and syncope ✓ Transient, unexplained loss of consciousness ✓ Severe autonomic dysfunction ✓ Hallucinations in other modalities ✓ Systematized delusions ✓ Depression ✓ Relative preservation of medial temporal lobe structures on CT/MRI scan ✓ Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity ✓ Abnormal MIBG myocardial scintigraphy ✓ Prominent slow wave activity on EEG with temporal lobe sharp waves
Diagnosis of DLB **less likely**	✓ In the presence of cerebrovascular disease ✓ In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture ✓ If parkinsonism only appears for the first time at a stage of severe dementia
Temporal sequence of symptoms	✓ DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease.

1.3.3. Epidemiology

Clinically, one study performed by Aarsland *et al.* (2008) reported a prevalence of 20% of DLB patients in a sample of 196 continuously-referred demented patients. Also recently, an Italian multicenter study showed that 14 of 1307 patients with parkinsonism had DLB (Colosimo *et al.,* 2009).

In autopsy studies, the brains of 33 of 139 normal subjects contained LB pathology in various regions. The most common regions involved were the medulla (26%), amygdala

(24%), pons (20%), and midbrain (20%) (Markesbery *et al.,* 2009). Prevalence rates of LB pathology from 15 to 28.4% in the brains of elderly demented patients have been also described (McKeith *et al.,* 1996; Wakisawa *et al.,* 2003).

Furthermore, a recent longitudinal study evaluated the risk factors related to PD and DLB in 235 subjects over 60 years old with medical and neuropathological records (Frigerio *et al.,* 2009), showing that the risk factors for PD were anxiety or depression, cancer, head injury or stroke, number of children, education and occupation as physician; and for DLB occupation as physician also increased the risk, and caffeine consumption reduced the risk as illustrates the Figure 23.

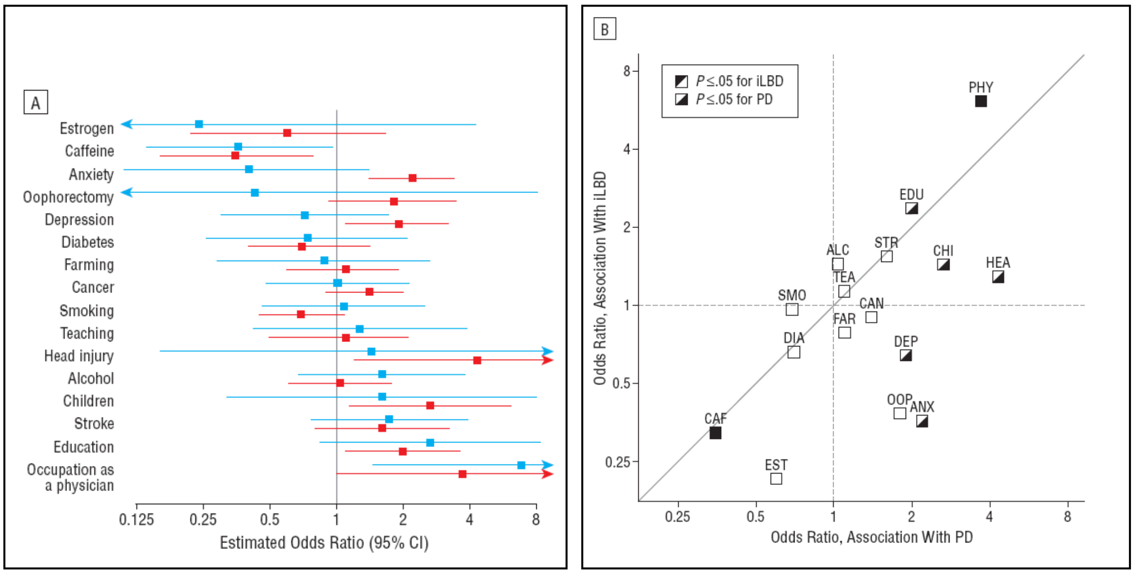


Figure 23. Association of risk factors with incidental LBD and PD in Olmsted County, Minnesota. A) Pooled data analysis (blue represents iLBD; red, PD). B) Scatterplot of odds ratios for risk factors observed for PD vs iLBD. ALC indicates alcohol; ANX, anxiety; CAF, caffeine; CAN, cancer; CHI, children; CI, confidence interval; DIA, diabetes; DEP, depression; EDU, education; EST, estrogen; FAR, farming; HEA, head injury; OOP, oophorectomy; PHY, physician as occupation; SMO, smoking; STR, stroke; and TEA, teaching (*Source*: Frigeiro *et al.,* 2009).

1.3.4. Cognitive profile of Dementia with Lewy Bodies

The Consensus Criteria for the Diagnosis of DLB (McKeith *et al.,* 2005) indicate that the central feature of DLB is a progressive cognitive impairment characterized by attentional impairment, with fluctuations in cognitive function and disproportionate problem solving as well as visuospatial difficulties.

Several studies have described the cognitive disturbances that differentiate between DLB and AD (Mori *et al.,* 2000; Horimoto *et al.,* 2003; Mosimann *et al.,* 2004; Cormack *et al.,* 2004; Johnson *et al.,* 2005; Kraybill *et al.,* 2005; Perriol *et al.,* 2005; Ferman *et al.,* 2006; Bradshaw *et al.,* 2006; Bronnick *et al.,* 2008; Hamilton *et al.,* 2008). Visuoperceptive and visuoconstructive deficits related to AD patients have been consistently described. Mori *et al.* (2000) found that DLB patients had more visuoperceptive deficits in comparison with AD. Later on, Cormack *et al.* (2004) showed that DLB patients have more difficulties in visuoconstructive tasks such as the pentagon copy (see Figure 24). Mosimann *et al.* (2004) confirmed the visuoperceptive and visuoconstructive deficits in DLB patients with respect to AD patients, while memory was less impaired in DLB. Other studies have confirmed this pattern of greater attentional, visuoperceptive and visuoconstructive dysfunction but better memory in DLB with respect to AD (Noe *et al.,* 2004; Johnson *et al*., 2005; Kraybill *et al.,* 2005; Ferman *et al.,* 2006; Bradshaw *et al.*, 2006; Hamilton *et al.,* 2008). Ferman *et al.* (2006) reported that worse attentional and visuoperceptive functions, but better naming and memory scores were suggestive of DLB but not AD, with a sensitivity of 83.3% and specificity of 91.4%, and that these deficits were progressive with the evolution of the disease (Johnson *et al.,* 2005). Greater fluctuations in attention have also been reported in DLB than in AD patients (Bradshaw *et al.,* 2006). Furthermore, the attentional deficit increased as greater demands were placed on attentional selectivity: the greater the executive control and visuospatial recruitment, the more pronounced the deficits. Finally, Hamilton *et al.* (2008) showed that poor baseline performance on visuospatial skills was strongly associated with a rapid rate of cognitive decline in DLB but not in AD. Moreover, DLB patients with poor visuospatial skills had fewer neurofibrillary tangles and were more likely to experience visual hallucinations than those with better visuospatial skills.

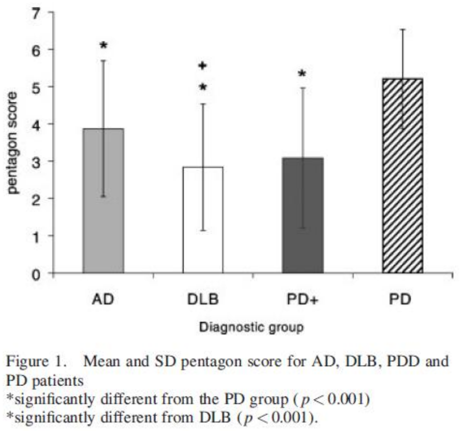


Figure 24. Differences between groups in the pentagon copy (*Source*: Cormack *et al.*, 2004)

Moreover, differences in the cognitive profile of DLB in comparison with PDD patients have also been studied, though the results are contradictory. Whereas some studies found no significant differences between groups in the cognitive profile (Horimoto *et al.*, 2003; Mosimann *et al.*, 2004; Noe *et al.*, 2004; Cormack *et al.,* 2004; Perriol *et al.,* 2005), others reported differences in attention, visual recognition memory and verbal memory (Mondon *et al.,* 2007; Bronnick *et al.,* 2008; Filoteo *et al.,* 2009). Mondon *et al.* (2007) showed that DLB subjects had better orientation, attention, reading of the names of colors in the Stroop test and immediate and delayed recognition memory than PDD patients, whereas Bronnick *et al.* (2008) suggested that the attentional impairment was greater in PDD. Finally, Filoteo *et al.* (2009) showed that DLB patients recalled less information than PDD patients on all but one of the recall measures and displayed a more rapid rate of forgetting, but similar results on recognition. On the other hand, PDD patients made more perseverative errors than DLB patients. Following these guidelines, they discriminated DLB from PDD with an accuracy rate of 81.3%.

In addition, two cross-sectional studies proposed an increase of the cognitive impairment between pathological groups. Downes *et al.* (1998) reported that DLB patients had greater impairment in arithmetic in DLB related to advanced PD and more frontal impairment following this pattern: control < early PD < advanced PD < DLB. Consistent with these findings, Perriol *et al.* (2005) found intermediate attentional deficits in PDD, between healthy control subjects and DLB, although these differences were not statistically significant.

Finally, in a cohort study Janvin et al. (2006) showed that 56% of PDD patients and 55% of DLB patients had a subcortical cognitive profile, compared with only 33% of AD subjects. Conversely, 30% of PDD and 26% of DLB had a cortical profile, compared with 67% of AD patients.

In conclusion, DLB patients have greater attentional, executive, visuoperceptive and visuoconstructive impairment than AD patients, but better memory and naming. This pattern of impairment is not that clear in comparison with PDD patients, though there is a least a trend. Furthermore, correlations with neuropathology showed that the severity of visuospatial deficits in DLB may identify those facing a particularly malignant disease course and may designate individuals whose clinical syndrome is impacted more by LB formation than AD pathology.

1.3.5. Neuroimaging studies

STRUCTURAL IMAGING TECHNIQUES

Neuroimage volumetric studies have demonstrated a reduction in hippocampal and amygdalar volume in DLB compared with healthy control subjects (Hashimoto *et al.*, 1998). The significant global hippocampal loss amounted to 10-20% and was mostly located in the anterior portion of the CA1 and along the longitudinal midline in the dorsal aspect of CA2-3. Furthermore, significant atrophy in other cerebral regions has been reported in other studies. Barber *et al.* (2002) showed a reduction in the left caudate volume that did not correlate with parkinsonism symptoms. Moreover, lower gray matter volumes in the temporal, parietal, frontal lobes, orbitofrontal cortex, insula, hippocampus, dorsal midbrain, substantia innominata, left putamen, caudate head and hypothalamus was reported in DLB compared with healthy control subjects (Burton *et al.,* 2002; Ballmaier *et al.,* 2004; Ishii *et al.,* 2007; Whitwell *et al.,* 2007b). A longitudinal study (O'Brien *et al.,* 2001), showed progressive brain atrophy in comparison with control subjects. The mean percentage of atrophy rate per year was 1.4 ± 1.1 and in controls 0.5 ± 0.7. The atrophy degree was related to the severity of cognitive impairment.

Furthermore, several studies have focused on the volumetric differences between DLB and AD patients, showing a consistent relative preservation of the MTL structures (hippocampus, parahippocampus and amydala) in the DLB patients in comparison with AD patients (Hashimoto *et al.,* 1998; Barber *et al.,* 1999a; Barber *et al.,* 2000a; Barber *et al.,* 2001; Ishii *et al.,* 2007; Firbank *et al.,* 2007a; Whitwell *et al.,* 2007b; Sabattoli *et al.,* 2008; Burton *et al.,* 2009). The absence of MTL atrophy had a specificity of 94-100% and sensitivity of 88-91% for separating DLB from AD (Barber *et al.,* 1999a; Burton *et al*., 2009). Moreover, reductions in the gray matter volume were also found in the putamen and caudate nuclei, substantia innominata, orbitofrontal cortex, inferior and medial frontal, the lateral and ventromedial temporal cortex and gyrus rectus (Cousins *et al.,* 2003; Ballmaier *et al.,* 2004; Ishii *et al.,* 2007). Putamen volume did not correlate with age, UPDRS-III or CAMCOG/MMSE scores (Cousins *et al.,* 2003).

Three studies have compared the pattern of brain atrophy between PDD and DLB and have presented contradictory results (Burton *et al.,* 2004; Tam *et al.,* 2005; Beyer *et al.,* 2007b). Using VBM, Burton *et al.* (2004) found no differences between groups; Beyer *et al.* (2007b), using the same technique and also on the basis of uncorrected results for multiple comparisons, found that DLB patients had greater atrophy bilaterally in the inferior parietal lobe and precuneus, the right insula, inferior temporal gyrus, lentiform nucleus, left angular gyrus, cuneus and superior occipital gyrus. However, the disease duration was longer in the DLB group and these differences may have influenced the results. Besides, Tam *et al.* (2005) performed a study on the MTL atrophy by visual inspection according to the Scheltens scale (see Figure 10), and found the following pattern of atrophy: control subjects < PD < PDD < DLB < AD, even though the differences PD < PDD and PDD < DLB were not statistically significant.

Memory impairment correlated with hippocampal volume loss in DLB as well as in PDD (Barber *et al.,* 1999a; Barber *et al.,* 2001). Furthermore, MTL volume has been related to age (Barber *et al.,* 2001; Burton *et al.,* 2009), age at death and Braak stage (Burton *et al*., 2009).

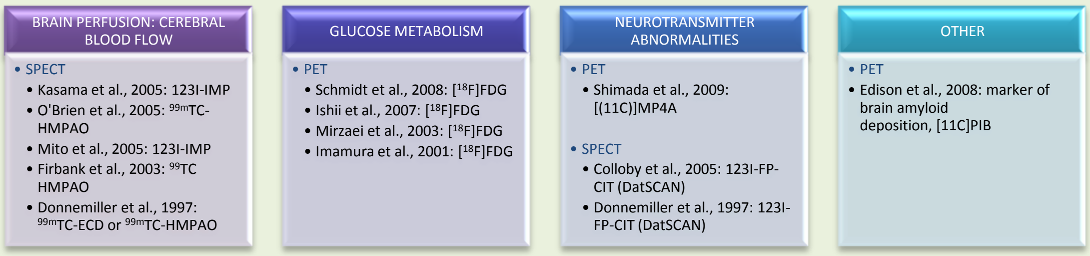
All things considered, a relative preservation of the MTL structures seems to be a marker to differentiate DLB from AD. However, the differences between DLB and PDD should be established, as the results are not consistent. More studies are required addressed to explore this subject in greater depth. *(For further details, see table 14 at the end of the section).*

DIFFUSION TENSOR IMAGING

To date, four studies have addressed the brain impairment related to DLB with DTI in comparison with healthy control subjects and AD patients *(see Table 15 at the end of the section)*. Compared with control subjects, DLB patients exhibited abnormalities in FA in the corpus callosum, pericallosal areas, caudate nucleus, frontal, parietal, occipital and temporal white matter (Bozzali *et al.,* 2005) and in the inferior longitudinal fasciculus (Ota *et al.,* 2009). However, no differences in FA were found between DLB and AD (Firbank *et al.,* 2007a; Firbank *et al.,* 2007b). Bilateral posterior cingulate FA correlated with global atrophy (Figure 13) (Firbank *et al.,* 2007a).

__FUNCTIONAL IMAGING TECHNIQUES__

Figure 25 describes the different studies and radiotracers used in the functional study of DLB patients. *These studies are summarized in Table 16 at the end of the section.*



Abbreviations
[18F]FDG, [18F]fluorodeoxyglucose; 123I-FP-CIT, [123I]beta-CIT (DatSCAN); N-isopropyl-4-[123I]iodoamphetamine; 123I-IMP, N-isopropyl-4-[123I]iodoamphetamine; 99mTc-HMPAO, 99mTc-hexamethylpropylene amine oxime; 99mTc-ECD, 99mTc-ethylcysteinate dimmer; [(11C)]MP4A, N-methyl-4-piperidin acetate; [(11C)]PMP, -[11c]methylpiperidin-4-yl propionate; [11C]PIB, 11C-labeled Pittsburgh Compound-B; PET, Positron Emission Tomography; SPECT, Single photon emission computed tomography

Figure 25 . Techniques and radiotracers used in the cerebral functional study of DLB

BRAIN PERFUSION AND CEREBRAL BLOOD FLOW STUDIES

SPECT studies of cerebral blood flow showed that DLB patients had hypoperfusion of temporo-parietal and occipital regions, anterior and posterior cingulate nucleus, precuneus, primary visual cortex, and frontal association areas compared with healthy control subjects (Donnemiller *et al.,* 1997; Firbank *et al.,* 2003; Kasama *et al.,* 2005; Mito *et al.,* 2005; Osaki *et al.,* 2005).

Furthermore, as figure 26 shows, similar degrees of perfusion have been found in PDD and DLB patients, affecting particularly parietal, occipital areas and temporal areas (Firbank *et al.,* 2003; Kasama *et al.,* 2005; Mito *et al.,* 2005). However, in the study by Firbank *et al.* (2003) DLB patients had a shorter disease duration than PDD (23 months versus 72 months) this difference may have influenced the findings. O'Brien *et al.* (2005) found correlations between the fluctuation of consciousness and increased thalamic and decreased inferior occipital perfusion, and between hallucinations severity and hypoperfusion in posterior cingulate, cuneus, precuneus and parietal regions.

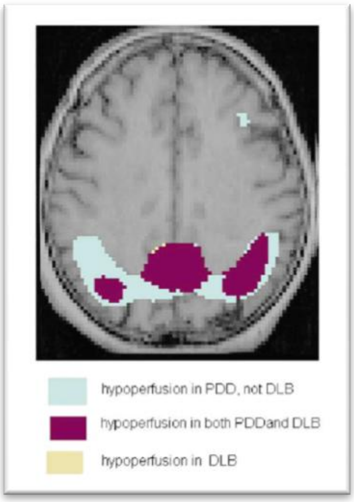


Figure 26. Hypoperfusion in PDD and DLB (*Source*: Firbank *et al.,* 2003)

GLUCOSE METABOLISM STUDIES

PET studies of glucose metabolism in patients with DLB performed with the glucose analog [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) showed reduced glucose metabolism in the medial and lateral occipital lobe in DLB patients without parkinsonism in comparison with AD patients (Imamura *et al.,* 2001). Furthermore, reduced metabolism has been reported in the entire cortex with relative sparing of the central region (Mirzaei *et al.*, 2003) and in the occipital, temporal and frontal lobe compared with control subjects (Ishii *et al.*, 2007). The occipital/hippocampal ratio of glucose uptake in the DLB group was significantly lower than in the control and AD groups (Ishii *et al.,* 2007).

STUDIES OF NEUROTRANSMITTER FUNCTION

Several tracers exist for imaging postsynaptic dopamine D2 receptors, using radioactively labeled dopamine receptor antagonists. The most widely used for SPECT is the 123I-FP-CIT, known as DatSCAN. Donnemiller *et al.* (1997) failed to find differences between AD, DLB and control subjects using this technique. However, in a longitudinal study, Colloby *et al.* (2005) reported significant differences in the dopamine uptake at 1-year follow-up in the DLB and PDD groups but not in PD or healthy control subjects. The changes in DLB patients were found in the anterior and posterior putamen, whereas the changes in PDD patients were in both caudate and putamen nuclei. With respect to control subjects, PD, PDD and DLB patients had lower caudate rates, but only PDD patients had a significant decline in anterior putamen. The percentage of uptake loss in the posterior putamen correlated with the rate of cognitive decline in the DLB group (Colloby *et al.,* 2005).

Furthermore, Shimada *et al.* (2009) studied the acetylcholinesterase (AChE) activity in DLB with the [(11C)]MP4A radiotracer, reporting that cortical values of AChE were reduced in PDD and DLB with respect to control subjects, most significantly in the left lateral temporal lobe. In comparison with PD, PDD and DLB had lower AChE values in the inferior frontal gyrus, the supramarginal gyrus and the posterior cingulate gyrus. There were no differences between PDD and DLB patients. Furthermore, blood flow was reduced in almost all the cortical areas in PDD and DLB in comparison with control subjects, especially in the occipital lobe.

OTHER MARKERS

Used [11C]PIB, a marker of brain amyloid deposition, Edison *et al.* (2008) found that 11 of 13 DLB patients had increased amyloid storage in one or more cortical regions compared with healthy control subjects. The areas of maximum increase were the anterior and posterior cingulate cortex, followed by the frontal, parietal, temporal and occipital regions. In contrast, 10 out of 12 PDD patients had normal uptake.

All things considered, DLB and PDD seem to have similar brain perfusion and glucose metabolism. However, in a longitudinal study, decreases in the DA uptake over time increased only in putamen in DLB, extending to caudate in PDD. On the other hand, amyloid deposition seems a useful marker for differentiating between PDD and DLB.

1.3.6. Clinicopathological associations

Harding *et al.* (2002c) showed that hippocampal atrophy in DLB correlated with atrophy and Lewy body formation in the frontal lobes, as well as with the severity of Lewy neurite formation in the CA2/3 subregions of the hippocampus. In DLB, neuronal loss was confined to the presubiculum and Lewy neuritis concentrated in the CA2-3 subregion compared with controls and cases with PD alone. Together with the CA2-3, the presubiculum accounts for 25% of hippocampal gray matter volume. The direct prefrontal-hippocampal connections are thought to coordinate working memory tasks, whereas the thalamic relays are important for memory consolidation and retrieval. This study suggests that DLB may disrupt working memory because of the considerable pyramidal cell loss in the direct hippocampal output to the dorsolateral prefrontal cortex. It would appear that the direct connections between the frontal lobe and hippocampus are significantly affected in DLB.

Table 13. Review of studies of cognitive functions in DLB

Study	Neuropsychological Assessment	Sample	Summary of main findings
Verbal learning and memory in patients with dementia with Lewy bodies or Parkinson's disease with dementia Filoteo et al., 2009	Verbal learning (CVLT), Mattis Dementia Rating Scale (MDRS) *Autopsy-confirmed*	24 DLB 24 PDD 24 CNT	✓ DLB patients recalled less information than PDD patients on all but one recall measure and displayed a more rapid rate of forgetting, but similar results on recognition ✓ PDD patients committed a greater percentage of perseveration errors than the DLB patients ✓ A discriminant function analysis differentiate DLB and PDD with 81.3% accuracy (sensitivity for diagnosis of PD was 75% and specificity 87.5%)
Disturbance of automatic auditory change detection in dementia associated with Parkinson's disease: A mismatch negativity study Bronnick et al., 2008	Mismatch negativity event-related potential (MMN)	17 DLB 15 PDD 16 PD 16 AD 18 CNT	✓ PDD patients had reduced MMN area and amplitude compared to the DLB, PD and the CNT groups ✓ MMN area correlated significantly with number of missed target stimuli in the oddball-distractor task, and the PDD group missed targets significantly more often than the DLB group
Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies Hamilton et al., 2008	DRS, Block Design Test, Clock Drawing Test-Copy, Boston Naming Test (30 items) *Neuropathologic diagnosed*	22 DLB 21 DLB+AD 44 pure AD	✓ Poor baseline performances on tests of visuospatial skills were strongly associated with a rapid rate of cognitive decline in DLB but not AD ✓ DLB patients with poor visuospatial skills had fewer neurofibrillary tangles and were more likely to experience visual hallucinations than those with better visuospatial skills
Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia Mondon et al., 2007	Orientation, Verbal episodic and Non-verbal memory, Attention, Language, Verbal fluency, Writing comprehension, EEFF, Logic and reasoning, Visuoconstructional, Visuoperceptual skills	10 DLB 12 PDD	✓ DLB < PDD: orientation, TMT-A, reading of names of colours on the Stroop test, immediate and delayed recognition on the DMS-48 test
Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease Ferman et al., 2006	GDS, TMT A-B, Rey-Osterrieth Complex Figure Copy, Benton Visual Form Discrimination, Boston Naming Test, COWAT, WMS-R, RAVLT, Block design *Some had neuropathology*	87 DLB 138 AD 103 CNT	✓ DLB>AD: Boston Naming Test and RAVLT percent retention ✓ DLB<AD: TMT-A and copy of the Rey-Osterrieth Figure (sensitivity of 83.3% and specificity of 91.4%)
Higher cortical deficits influence attentional processing in dementia with Lewy bodies, relative to patients with dementia of the Alzheimer's type and controls Bradshaw et al., 2006	Experimental computerized reaction time paradigm	20 DLB 19 AD 20 CNT	✓ DLB showed greater attentional impairment and fluctuations in attention relative to AD and CNT ✓ The attentional deficit was increased in magnitude as greater demands were place on attentional selectivity
Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's	Mattis Dementia Rating Scale (Attention, initiation and perseveration, construction,	50 PDD 39 AD 62 DLB	✓ 56% PDD and 55% DLB had a subcortical cognitive profile, but only 33% AD ✓ Conversely, 30% PDD and 26% DLB had cortical profile compared with 67% of AD

disease Janvin et al., 2006	conceptualization and memory); MMSE		
Verbal and visuospatial deficits in dementia with Lewy bodies Johnson et al., 2005	CDR, primary memory, WM, verbal fluency, visuospatial/constructive, motor speed *Longitudinal* *Neuropathology*	9 DLB 57 DLB/AD 66 pure AD	✓ Patients with AD pathology performed worse on the verbal memory dimension ✓ Patients with DLB performed worse on the visuospatial dimension ✓ Combined pathology affected visuospatial performance but not verbal memory ✓ DLB and DLB/AD had more visual and auditory hallucinations than AD ✓ Progressive cognitive impairment across visuospatial and memory domains in all groups
Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both Kraybill et al., 2005	DRS, WMS memory and visual reproduction, fuld object memory evaluation, WAIS-R digit span, comprehension, similarities, block design, proverbs, TMT, naming and MMSE	135 subjects ↓ Neuropathology 48 AD 65 DLB/AD 22 DLB	✓ AD patients performed worse than the DLB patients on memory measures and naming ✓ DLB patients were more impaired than AD on EEFF and attention ✓ Decline in MMSE and DRS scores over time were greatest in the patients with AD/DLB
Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia Noe et al., 2004	Orientation, Verbal and nonverbal memory, Reasoning, Naming, Verbal fluency, Auditory comprehension, Repetition, Attention, Visuoconstructional skills, Visuoperceptual skills	16 DLB 15 PDD 16 AD	✓ Psychoses associated with cognitive impairment at the beginning of the disease were more frequent in DLB patients (31.3%) than in AD and PDD ✓ DLB and PDD performed worse on attentional functions and better on memory than AD ✓ DLB also showed lower scores than AD subjects on visual memory, visuoperceptive and visuoconstructive tests ✓ No significant differences were found between PDD and DLB
Disturbance of sensory filtering in dementia with Lewy bodies: comparison with Parkinson's disease dementia and Alzheimer's disease Perriol et al., 2005	Prepulse inhibition (PPI) of the N1/P2, ability to filter out irrelevant sensory or cognitive information	10 DLB 10 AD 10 PDD 10 CNT	✓ PPI was significantly reduced in DLB compared to CNT and AD ✓ In the PDD group, the disturbance was of intermediate intensity ✓ No significant differences between DLB and PDD
Visual perception in Parkinson disease dementia and dementia with Lewy bodies Mosimann et al., 2004	CAMCOG, NPI, visuoconstruction, visual perception, visual discrimination	24 PDD 20 DLB 23 AD 24 PD 25 CNT	✓ Visual perception was more impaired in PDD than in PD and CNT, but was not different from DLB ✓ Visual perception of PDD/DLB patients with VH was worse than in patients without VH ✓ PD were similar to CNT and different from PDD in all but the abstract thinking score ✓ PDD/DLB vs. AD: less impaired in memory scores, but more impaired in visual construction, visuoperception and visual discrimination
Pentagon drawing and neuropsychological performance in Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease and Parkinson's disease with dementia Cormack et al., 2004	CAMCOG (Orientation, Language comprehension and expression, praxis, attention and calculation, recent memory, remote memory, visual memory, perception, abstract thinking), MMSE	100 AD 50 DLB 36 PDD 81 PD	✓ DLB draw worse pentagons than AD or PD, but not those with PDD
Cognitive conditions of pathologically confirmed	MMSE	19 DLB	✓ AD<DLB/PDD: MMSE, Hasegawa's Dementia Scale

dementia with Lewy bodies and Parkinson's disease with dementia Horimoto et al., 2003	Hasegawa's Dementia Scale *Neuropathologic diagnosis*	6 PDD 10 AD	✓ No significant differences between DLB and PDD ✓ DLB occur later than PDD and the disease diagnosis duration was significantly shorter
Visuoperceptual impairment in dementia with Lewy bodies Mori et al., 2000	Visuoperceptual function (object size discrimination, form discrimination, overlapping figure identification and visual counting)	24 DLB 48 AD	✓ DLB<AD in all the visuoperceptive tasks ✓ Patients with DLB and VH scored lower on the overlapping figure identification than those without them
Intellectual, mnemonic, and frontal functions in dementia with Lewy bodies: A comparison with early and advanced Parkinson's disease Downes et al., 1998	NART-R, MMSE, WAIS-R, logical memory and visual reproduction of WMS-R, WRMT, verbal fluency, Stroop test	10 DLB 10 early PD 10 advanced PD 10 CNT	✓ Verbal and performance IQ: E-PD matched to CNT, effect of PD severity ✓ Arithmetic: DLB worse than A-PD ✓ Memory: no differences between DLB and A-PD. In visual memory: effect of PD severity Face recognition was compromised early in the course in PD and increased with severity ✓ Frontal functions: impairment CNT<E-PD<A-PD<DLB

Abbreviations

AD, Alzheimer's Disease; CAMCOG, Cambridge Cognitive Examination; CDR, Clinical Dementia Rating; CNT, control subjects; COWAT, Controlled Oral Word Association test; CVLT, California Verbal Learning Test; DLB, Dementia with Lewy Bodies; DRS, Dementia Rating Scale; EEFF, Executive Functions; GDS, Global Deterioration Scale; LB, Lewy Bodies; MDRS, Mattis Dementia Rating Scale; MMN, Mismatch Negativity; MMSE, Minimental Status Evaluation; NPI, Neuropsychiatric Inventory; PD, Parkinson's Disease; PD, Parkinson's Disease; Prepulse inhibition; RAVLT, Rey auditory verbal learning test; TMT, Trail Making Test; VH, Visual Hallucinations; VOSP, Visual Object and Space Perception battery; WAIS-R, Weschler Adult Intelligence Scale-revised; WM, Working Memory; WMS-R, Weschler Memory Scale-reviewed; WRMT, Warrington Recognition memory test

This table is exclusively based on investigation works in the last ten years excluding revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; September 2009.

Table 14. Volumetric studies in DLB: Analysis of global and regional atrophy

Study	Methodology	Structures analyzed	Sample	Summary of main findings
Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Burton et al., 2009	1.0 T and 1.5T, T1-weighted 3D MPRAGE Neuropathology	Medial temporal lobe atrophy (MTA)	11 AD 23 DLB 12 VCI	✓ MTA was a highly accurate diagnostic marker for autopsy confirmed Alzheimer's disease (sensitivity of 91% and specificity of 94%) compared with DLB ✓ Total MTA correlated with age ✓ Braak stage (NFT pathol) and age at death were predictors of MTA
Hippocampal shape differences in dementia with Lewy bodies. Sabattoli et al., 2008	1.0 T scanner, 3D T1-weighted, FFE Radial atrophy mapping (SPM99)	HPC WM	14 DLB 28 CNT 28 AD	✓ In DLB, hippocampal loss (10–20%) mostly located in the anterior portion of the CA1 field on both sides, subiculum and presubiculum ✓ Different from the pattern characteristic of AD
A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia Kenny et al., 2008	1.5T, 3D T1- weighted FSPGR manual segmentation technique (MIDAS) *Longitudinal*	Enthorrinal cortex volume	20 DLB 26 AD 30 PDD 31 PD 37 CNT	✓ Total normalised EC volumes were significantly smaller in DLB, AD and PDD patients compared to controls/PD. ✓ The percentage reduction in EC volume was 19.9% in DLB and 14.7% in PDD relative to CNT ✓ MMSE, CAMCOG, recent memory and learning correlate with EC volume
Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies Beyer et al., 2007	1.5T, T-1 weighted 3D FSPGR VBM (SPM2), 12mm Kernel, p<0.001 uncorrected. Customised templates.	VBM Whole brain	15 PDD 18 DLB 21 AD 20 CNT	✓ DLB<PDD: bilaterally in inferior P and precuneus; right insula, inf T gyrus and lentiform nucleus; left angular gyrus, cuneus, sup O gyrus ✓ DLB<CNT:bilaterally in the insula and thalamus; right inf P, sup T and inf T; left red nucleus and middle O gyrus
Comparison of regional brain volume and glucose metabolism between patients with mild dementia with lewy bodies and those with mild Alzheimer's disease. Ishii et al., 2007	1.5-T Signa Horizon, 3D FSGE 18F-FDG PET images were obtained using a Headtome IV scanner	Whole brain	20 DLB 20 AD 20 CNT	✓ DLB had lower GM densities of the left putamen and caudate head than CNT (p<0.05 corrected) and reduced left caudate volume compared with AD (p<0.001 uncorrected) ✓ Absolute and relative striatal volumes (Str/TIV) in the DLB group were significantly smaller than those in the CNT and AD groups
Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease. Whitwell et al., 2007	1.5T, T1-weighted 3D, FSGE VBM (SPM2), p<0.05 ROI Manually drawn	Whole brain SI, midbrain Sensoriomotor, T-P cortex	72 DLB 72 AD 72 CNT	✓ DLB: very little cortical involvement in the dorsal midbrain, SI and hypothalamus, post HPC, insula, F, P lobes in comp with CNT ✓ T-P cortex correlated with MMSE and CDR in DLB
Rates of cerebral atrophy differ in different degenerative pathologies. Whitwell et al., 2007	1.5T , T1-weighted 3D, FSGE Semiautomated brain segmentation algorithm (JMP computer software) *Neuropathology* *follow-up (after 1-2 years)*	Changes in whole brain and ventricle volumes	9 DLB 13 AD/DLB 12 AD 12 FTLD 5 PSP 5 CBD 25 CNT	✓ CERAD, Braak and NIA Reagan criteria were higher in AD or AD/DLB groups than the others ✓ Age at baseline scan correlated with whole brain atrophy and ventricular expansion across all groups
MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias Meyer et al., 2007	1.5 T, T1- T2-weighted, FLAIR ROI manually Visual rating scale *Longitudinal*	Frontal Temporal Third ventricle HPC, EC	52 CNT 30 AD-MCI 35 V-MCI 8 PLB-MCI	✓ Converted: 19 to AD, 17 to VaD and 15 to Parkinson-LBD ✓ There were no differences between PLB-MCI and PLBD subjects ✓ <u>PLB-MCI</u>: third ventricular enlargement greater than N-MCI / V-MCI, less severe MTL atrophy than N-MCI and fewer vascular lesions than V-MCI.

Progression of white matter hyperintensities in Alzheimer disease, dementia with lewy bodies, and Parkinson disease dementia: a comparison with normal aging. Burton et al, 2006	1.5T, FLAIR, no 3D WMH volume was quantified using an automated technique but manually traced *1 year follow-up*	WMH Periventricular Hyperintensities	26 DLB 32 AD 31 PDD 39 CNT	✓ ✓ ✓ ✓	*Subjects at the follow-up:* 14 DLB, 23 AD, 13 PDD, 33 CNT Age was correlated with the total WMH and deep WMH WHM showed a signitficantly progression over 1 year Severity of baseline WMH was a predictor of lesion progression. Rate of WMH change had no association with change in cognitive performance
Differences in MR features of the substantia innominata between dementia with Lewy bodies and Alzheimer's disease. Hanyu et al., 2005	1.5-T ,T2-weighted FSE	Thickness of the SI	22 DLB 116 AD 26 CNT	✓ ✓	Thickness in DLB and AD decreased more significantly than control subjects (p<0.0001) DLB<AD: less thickness (p<0.05)
Temporal lobe atrophy on MRI in Parkinson disease with dementia. A comparison with Alzheimer disease and dementia with Lewy bodies Tam et al., 2005	1.5 T , T1- 3D FSE Visual inspection (Scheltens' Scale) SPSS	MTA	39 CNT 33 PD 31 PDD 25 DLB 31 AD	✓ ✓ ✓ ✓ ✓	MTA was greater on the left in all groups except the AD group MTA: CNT > PD ~ PDD ~ DLB > AD Differences PDD<PD and DLB<PDD were not significant Age was related to MTA in PPD and AD In DLB, language, orientation, memory and total CAMCOG correlated inversely with MTA
Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects Ballmaier et al., 2004	1.5 T, T1-weighted 3D FSPGR Cortical Pattern Matching and ROIs	Orbitofrontal Frontal dorsal Parietal Temporal	29 AD 16 DLB 38 CNT	✓ ✓ ✓	DLB<CNT: T ventral i lateral, P, OF, dèficits difusos T, P bilaterals DLB>AD: OF, T lateral i VM, F inf i medial, gir recte Female<Male (all groups); F dorsal dret i P esq.
Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls Burton et al., 2004	<u>1.5</u> T, <u>T1-weighted 3D</u> <u>Optimized VBM</u> (SPM99) p< 0.001	Whole brain	26 PDD 31 PD 28 AD 17 DLB 36 CNT	✓ ✓ ✓ ✓	PDD<CNT: O, T bilateral, right middle and inf F, left inf and sup P, right caudate and putamen, thalamus bilaterally PD<CNT: Sup, middle and inf F gyri on the right PDD<PD: bilaterally fusiform and lingual gyri AD<PDD: HPC, parahHPC bilaterally, inf T, claustrum and right uncus
Atrophy of the putamen in dementia with Lewy bodies but not Alzheimer's disease: an MRI study. Cousins et al., 2003	1.5T, T1-weighted 3D FSGR Manually traced (MIDAS) UPDRS-III, CAMCOG, MMSE	TIV Whole Brain Putamen volume	27 AD 14 DLB 37 CNT	✓ ✓	Patients with DLB had smaller putamen volumes than both CNT and AD Patients with AD did not differ from control
MRI study of caudate nucleus volume in Parkinson's disease with and without dementia with Lewy bodies and Alzheimer's disease Almeida et al., 2003	1.5T, T1-weighted 3D FSGR, manually drawn ROI (MIDAS)	Whole brain Caudate	28 PD 20 PD+DLB 27 AD 35 CNT	✓	AD had significantly reduced whole brain and caudate volume compared to CNT, PD (but not PD+DLB)
Patterns of Cerebral Atrophy in Dementia with Lewy Bodies Using Voxel-Based Morphometry Burton et al., 2002	1.0 T ,T1-weighted, 3D, p<0.001 VBM whole brain, ROI (SPM99) MMSE, CAMCOG, MADRS	Whole brain	25 DLB 30 AD 25 CNT	✓ ✓	DLB<CNT: Global: T, F, P and insular cortex bilaterally AD < DLB: medial temporal lobe, HPC, thalamus and amygdala bilaterally
Volumetric MRI study of the caudate nucleus in patients with dementia with Lewy bodies,	1.0T, T1 weighted 3D MPRAGE Manual drawn ROI (Analyze)	Caudate	26 DLB 21 AD	✓	Left caudate volume was reduced in AD and DLB compared with CNT

Alzheimer's disease, and vascular dementia. Barber et al., 2002	MMSE, CAMCOG		18 VaD 25 CNT	✓	Parkinsonian sympoms did not correlate with caudate nucleus volume
A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: MRI volumetric study Barber et al., 2001	1.0T, T1 weighted 3D MPRAGE Manual drawn ROI (Analyze)	MTL	26 DLB 22 AD 26 CNT	✓ ✓ ✓	AD>DLB: Hipocamp (cap, cos i cua), parahipocamp HPC asymmetry in CNT (R>L) but not in AD or DLB DLB: immediate memory CAMCOG correlate with HPC, paraHPC and inferior and medial T gyri
Progressive brain atrophy on serial MRI in dementia with Lewy bodies, AD, and vascular dementia O'Brien et al., 2001	1.0 T, T1 weighted 3D MPRAGE Manually segmentation (MIDAS) *Longitudinal*	Whole brain	10 DLB 9 AD 9 VaD 20 CNT	✓ ✓	Mean % ± SD atrophy rates/ year were: DLB, 1.4±1.1; AD, 2.0±0.9; VaD, 1.9± 1.1; controls, 0.5±0.7 Accelerating atrophy correlated with increasing severity of cognitive impairment
MRI volumetric study of dementia with Lewy bodies: A comparison with AD and vascular dementia Barber et al., 2000	1.0T, T1 weighted 3D, MPRAGE Manual ROI (Analyze) and semiautomated segmentation MMSE, CAMCOG	Whole brain Ventricular vol. F, T volume HPC, Amygdala	27 DLB 25 AD 24 VaD 26 CNT	✓ ✓ ✓	DLB<VaD: MMSE and CAMCOG DLB>AD: Hippocampus DLB>AD: amygdala bilaterally
MRI volumetric correlates of white matter lesions in dementia with Lewy bodies and Alzheimer's disease Barber et al., 2000	1.0T, T1, T2 weighted, proton density 3D, MPRAGE semiatomated segmentation Cogn function, depressive symptoms and psychotic features	WMH PVH Basal ganglia hyperintensities	27 DLB 25 AD	✓ ✓	PVH correlated with age DLB: correl between PVH and brain volume and lateral and 3rd ventricular volume
White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. Barber et al., 1999	1.0T, T1, T2 weighted, proton density 3D, MPRAGE semiatomated segmentation	WMH	27 DLB 28 AD 25 VaD 26 CNT	✓ ✓	All dementia groups had significantly higher total PVH scores compared with CNT There were no significant differences between DLB, VaD and AD subjects with respect to PVH and DWMH
Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. Barber et al., 1999	1.0T, T1 weighted 3D, MPRAGE Scheltens' Scale MMSE, CAMCOG	MTA	26 DLB 28 AD 24 VaD 26 CNT	✓	The absence of MTA had a specificity of 100% and 88% for separating DLB from AD and VaD respectively and a sensitivity of 38%
Medial temporal and whole-brain atrophy in dementia with Lewy bodies. Hashimoto et al., 1998	1,5T, 3D images	Whole brain HPC Amygdala	27 DLB 27 AD 27 CNT	✓ ✓	Hippocampal volume in DLB was larger than in AD but significantly smaller than in CNT DLB<CNT: amygdala and whole brain

Abbreviations

AD, Alzheimer's Disease; AG, amygdala; CAMCOG, Cambridge Cognitive Assessment; CNT, control subjects; cong., cognitively; DLB, Dementia with Lewy Bodies; EEFF, executive functions; EC, entorhinal cortex; F, frontal; FSPGR, Fast Spoiled Gradient Echo sequence; GM, gray matter; HPC, hippocampus; inf., inferior; MCI, mild cognitive impairment; MMSE, Mini-mental State Examination; MPRAGE, Magnetization Prepared Rapid Gradient Echo sequence; MTA, medial temporal atrophy; MTL, medial temporal lobe; O, occipital; P, parietal; PD, non-demented Parkinson's Disease; PDD, Parkinson's Disease with Dementia; PFC, Prefrontal cortex; PLBD, Parkinson-Lewy body dementias; ROI, Region of Interest; SI, substantia innominata; SPGR, Spoiled Gradient-Recalled Echo sequence; SPM, Statistical Parametric Mapping; STN-DBS, subtalamic nucleus deep brain stimulation; sup., superior; T, Tesla; T, temporal; UPDRS-III, Unified Parkinson's Disease Rating Scale III; VaD, vascular dementia; VBM, voxel-based morphometry; vs., versus; WM, white mater; WMH, white matter hyperintensities

This table is exclusively based on investigation works in the last ten years excluding revisions and case-studies. Source search: PubMed (www.pubmed.gov), language: English, last update; September 2009.

Table 15. Diffusion tensor imaging studies in DLB

Study	Methodology	Structures analyzed	Sample	Summary of main findings
Degeneration of dementia with Lewy bodies measured by diffusion tensor imaging Ota et al., 2009	1T, TRSE sequence 12 non-collinear directions, *b*=700s/mm^2	Inferior longitudinal fasciculus (ILF) Visual pathway Splenial fibres	14 DLB 13 CNT	✓ The FA of the ILF was significantly lower in DLB ✓ Mean diffusivity of ILF was at trend level
Atrophy is associated with posterior cingulate white matter disruption in dementia with Lewy bodies and Alzheimer's disease Firbank et al., 2007	1.5T, diffusion tensor imaging *b*=1000s/mm^2	HPC Posterior cingulate	15 AD 16 DLB 15 CNT	✓ Bilateral posterior cingulate FA correlated with global atrophy in structural MRI in the DLB group ✓ *Dementia disease progression as measured by global atrophy is associated with disruption of the white matter which connects posterior cingulate and lateral parietal regions*
Diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease Firbank et al., 2007	1.5T, diffusion tensor imaging *b*=1000 and 4000s/mm^2	Putamen Head of caudate Genu of CC Splenium of CC Anterior pericallosal area Posterior pericallosal area P, F, O, T WM Anterior internal capsule Posterior internal capsule Thalamus WM adjacent to Precuneus HPC	15 AD 16 DLB 15 CNT	✓ DLB<CNT: decreased FA in precuneus and in peri-callosal area ✓ DLB/AD<CNT: decreased FA in temporal and precuneus region ✓ No differences between DLB and AD in either FA or apparent diffusion coeficient
Brain tissue damage in dementia with Lewy bodies: an in vivo diffusion tensor MRI study Bozzali et al., 2005	1,5T PGSE EPI diffusion. 8 non-collinear directions, *b*=1044s/mm^2		15 DLB 10 CNT	✓ Abnormalities (MD and FA) in the corpus callosum, pericallosal areas, caudate nucleus, and frontal, parietal, occipital and, less prominently, temporal white matter in DLB ✓ Frontal WM integrity was related to dual performance test, phonemic and categorical fluency; Temporal WM to fragmented letter subtest from the VOSP; Parietal WM to Size discrimination test, shape discrimination and constructional praxis; Occipital WM to size discrimination test

Abbreviations

AD, Alzheimer's Disease; CNT, control subjects; DLB, Dementia with Lewy Bodies; DTI, Diffusion Tensor Imaging; FA, Fractional Anisotropy; FLAIR, Inversion Recovery sequence; HPC, hippocampus; ILF, Inferior Longitudinal Fasciculus; MPRAGE, Magnetization Prepared Rapid Gradient Echo sequence; MRI, Magnetic Resonance Imaging; PGSE EPI, pulsed-gradient spin-echo (PGSE) echo-planar (EPI) pulse sequence; T, Tesla; TRSE, Twice-refocused spin echo; TSE, Turbo Spin Echo; VOSP, Visual Object and Space Perception battery; WM, white matter

This table is exclusively based on investigation works in the last ten years excluding revisions. Source search: PubMed (www.pubmed.gov), language: English, last update; September 2009.

Table 16. Functional studies in DLB: Analysis of global and regional function

Study		**Marker**	**Sample size**	**Summary of main findings**
BRAIN PERFUSION: CEREBRAL BLOOD FLOW	**Cerebral blood flow in Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease according to three-dimensional stereotactic surface projection imaging** Kasama et al., 2005	123I-IMP SPECT	69 PD 16 DLB 15 AD 24 CNT	✓ PD<CNT: parietal bilaterally, premotor, cingulate and thalamic . In PDD, extended in P, F, post cingulate, T, O, precuneus. ✓ PDD<PD: P, post cingulate and O ✓ DLB<CNT: P, F, T, O. ✓ PDD<DLB: decreased premotor flow (including SMA) ✓ AD<DLB: lat TP, m T regions ✓ DLB<AD: premotor cortical flow.
	Change in perfusion, hallucinations and fluctuations in consciousness in dementia with Lewy bodies O'Brien et al., 2005	^{99m}TC-HMPAO SPECT *Longitudinal*	29 PD 14 DLB	✓ Correlation between decreased perfusion in midline P, posterior cingulate, precuneus and superior cuneus and hallucination severity ✓ Correlation between fluctuations of consciousness and increased thalamic and decreased inferior occipital perfusion
	Brain 3D-SSP SPECT analysis in dementia with Lewy bodies, Parkinson's disease with and without dementia, and Alzheimer's disease Mito et al., 2005	123I-IMP SPECT	30 PD	✓ DLB<CNT: lateral P, T, O association areas, anterior and post cingulate, precuneus, primary visual cortex, lateral frontal association ✓ PDD<CNT: ant cingulate, lat P, T, O association and precuneus ✓ DLB<PDD: not significant ✓ PD< CNT: ant cingulate and primary visual cortex ✓ DLB<PD: lat P, T, O association, lateral occipital association, post cingulate and precuneus, primary visual cortex
	Regional cerebral blood flow in Parkinson's disease with and without dementia Firbank et al., 2003	^{99m}TC-HMPAO SPECT	31 PD 34 PDD 37 CNT 32 AD 15 DLB	✓ PDD/DLB<CNT: mid-parietal and lateral occipitoparietal region (BA 7 and 39) ✓ PDD<AD: decrease blood flow in occipito-parietal region.
	Brain perfusion scintigraphy with 99mTc-HMPAO or 99mTc-ECD and 123I-beta-CIT single-photon emission tomography in dementia of the Alzheimer-type and diffuse Lewy body disease Donnemiller et al., 1997	^{99m}TC-ECD, ^{99m}TC-HMPAO SPECT	6 AD 7 DLB	✓ Bilateral T and P hypopefusion in all AD patients, additional F hypoperfusion in 2 patients and O hypoperfusion in 1 ✓ In DLB, in addition to TP hypoperfusion, there was O hypoperfusion resembling a horseshoe defect in 6 of 7 patients
GLUCOSE METABOLISM	**Value of combining activated brain FDG-PET and cardiac MIBG for the differential diagnosis of dementia: differentiation of dementia with Lewy bodies and Alzheimer disease when the diagnoses based on clinical and neuroimaging criteria are difficult** Schmidt et al., 2008	[18F]FDG –PET Cardiac MIBG	1 DLB 1 AD 1 CNT	✓ DLB had a marked reduction in cardiac MIBG accumulation. FDG-PET scan before and after activation with a visual attention task showed occipital cortex hypometabolism as compared with AD and a normal control.
	Comparison of regional brain volume and glucose metabolism between patients with mild dementia	[18F]FDG -PET	20 mild DLB	✓ DLB<CNT: significant glucose metabolic reductions in the temporal, parietal, and frontal areas, including in the occipital lobe

	with lewy bodies and those with mild Alzheimer's disease Ishii et al., 2007		20 mild AD 20 CNT	✓ AD<CNT: hippocampal glucose metabolism were significantly decreased, whereas the occipital volume and metabolism were preserved
	Assessment of diffuse Lewy body disease by 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) Mirzaei et al, 2003	[18F]FDG -PET	5 DLB 6 CNT	✓ DLB<CNT: Diffuse reduced glucose uptake in the entire cortex with relative sparing of the central
	Occipital glucose metabolism in dementia with lewy bodies with and without Parkinsonism: a study using positron emission tomography Imamura et al., 2001	[18F]FDG -PET	15 DLB with Pk 7 DLB without Pk 7 AD	✓ DLB with Pk<AD: lower medial and lateral O rCMRglc ✓ There were no significant differences in O metabolism btw DLB groups with/without Pk
NEUROTRANSMITTER ABNORMALITIES	**Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET** Shimada et al., 2009	[(11C)]MP4A-PET	18 PD (9 early and 9 advanced) 10 PDD 11 DLB 26 CNT	✓ Early and advanced PD had reduction of AChE levels in BA 18 relative to CNT. No differences between early and advanced PD. ✓ DLB/PDD<CNT: cortical AChE value reduced, the most significant in left lateral T lobe. No differences between DLB and PDD. ✓ PDD/DLB<PD: reduction of AChE in the inf T gyrus (BA 20), supramarginal gyrus (BA 40), and posterior cingulate gyrus (BA 31) ✓ No differences btw. younger and older DLB ✓ Correlations between MMSE and cortical AChE values in PD and PDD/DLB, the strongest in posterior cingulate gyrus ✓ PDD/DLB<CNT: blood flow reduced in almost all cortical areas, specially in O
	Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPEC. Colloby et al., 2005	123I-FP-CIT SPECT (DATSCAN) *Longitudinal*	20 DLB 20 PD 15 PDD	✓ Significant differences in uptake between baseline and follow-up in DLB and PDD but not in PD or CNT ✓ In DLB the changes were found in ant and post putamen; and in PDD in all regions ✓ PD/PDD/DLB<CNT: decline in caudate rates; only PDD had signif. decline in ant putamen ✓ Rates of decline were similar between DLB, PD and PDD ✓ In PDD, MMSE and age were predictors of mean annual % of change in caudate ✓ For constant age, low levels of cognition at baseline corresponded to higher rates of decline, while for constant MMSE, older subjects declined more rapidly than younger subjects ✓ Rate of cognitive decline correlated with greater uptake reduction in the posterior putamen in DLB
	Brain perfusion scintigraphy with 99mTc-HMPAO or 99mTc-ECD and 123I-beta-CIT single-photon emission tomography in dementia of the Alzheimer-type and diffuse Lewy body disease Donnemiller et al., 1997	123I-FP-CIT SPECT (DATSCAN)	6 AD 7 DLB	✓ 123I-b-CIT did not differe among the three groups (AD, DLB, 3 CNT)
OTHER	**Amyloid load in Parkinson's disease dementia and**	[11C]PIB	13 DLB	✓ 11/13 DLB had increased amyloid load in one or more cortical regions compared with

	Lewy body dementia measured with [11C]PIB positron emission tomography Edison et al., 2008	12 PDD 10 PD 41 CNT	CNT (maximum mean increases in ant or post cingulate, followed by F, P, T and O) ✓ 10/12 PDD had normal uptake, while 2 had a similar pattern than DLB (even if they do not differed clinically from the other PDD) ✓ None of the PD showed any significant increase

Abbreviations

AChE, Acetylcholinesterase; 18F]FDG, [18F]fluorodeoxyglucose; 123I-FP-CIT, [123I]beta-CIT (DatSCAN); N-isopropyl-4-[123I]iodoamphetamine; 123I-IMP, N-isopropyl-4-[123I]iodoamphetamine; 99mTc-HMPAO, 99mTc-hexamethylpropylene amine oxime; 99mTc-ECD, 99mTc-ethylcysteinate dimmer; [(11C)]MP4A, N-methyl-4-piperidin acetate; [(11C)]PMP, -[11c]methylpiperidin-4-yl propionate; [11C]PIB, 11C-labeled Pittsburgh Compound-B; F, frontal; O, occipital; P, parietal; PET, Positron Emission Tomography; SPECT, Single photon emission computed tomography; T, temporal

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1.4. Visual Hallucinations

The prelude to Daniel Dennett's book *Consciousness explained* (Dennet, 1991) is entitled 'How are hallucinations possible?' If one can be conscious of something that is not there, then the brain state underlying this mental state must be sufficient for a conscious perception, even in the absence of an external stimulus.

Figure 28. *Capricho* 43th: The dream of reason brings forth monsters (El sueño de la razón produce monstruos). (Francisco Goya, 1799)

Visual hallucinations (VH), together with fluctuation and parkinsonism, are core clinical features of DLB (McKeith *et al.,* 2005). According to the DSM IV-TR criteria (American Psychiatric Association, 2003), a hallucination is a sensory perception without external stimulation of the relevant sensory organ, distinguishing it from an illusion, in which an external stimulus is perceived but then misinterpreted.

1.4.1. Theories of Visual Hallucinations in Parkinson's Disease

Several theories have been proposed to explain the appearance of VH in PD (Barnes *et al.,* 2001; Collerton *et al.,* 2005; Diederich *et al.*, 2005; Diederich *et al.,* 2009).

The *Perception and Attention Deficit (PAD)* model of VH proposed by Collerton *et al.* (2005) suggests that a combination of deficits in attentional binding and object perception is essential to the occurrence of recurrent complex VH. On the other hand, the *Integrative model* proposed by Diederich *et al.* (2005; 2009) proposes that VH in PD may be related to a reduction of the capacities of the forebrain reality-controlling system, that means a difficulty in establishing the external or internal source of perceptions due to a deregulation of the gating and filtering of external perceptions and/or aberrant internal image production.

Furthermore, Barnes *et al.* (2001; 2003) suggested that the source-monitoring defects, together with visual perceptual disorders, were related to the development of VH in PD. Hallucinations in their patients were associated with a lax criterion for accepting and imaginary event as a real one, namely a reality-monitoring deficit. Source-monitoring deficits have been associated with temporal and frontal areas of the brain. They propose a multi-factorial model for the occurrence of hallucinations; the combination of degraded visual information about the environment, 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 details, provide the basis for VH (Barnes and David, 2001). Visual pathway lesions impair visual input and may result in hallucinations due to defective visual processing or an abnormal cortical release phenomenon. The failure to extract information from the stimuli, due to perceptual deficits and inadequacies of encoding, may trigger more complex and patterned activity in higher-level visual areas, which could lead to previously stored schema being played out in the form of internal images (Collerton *et al.,* 2005). More specifically, the fact that hallucinators may experience complex well-formed perceptual experiences when peripheral sensory input, provides degraded information about the world (f. e. formed auditory hallucinations are much more common following hearing impairment), is a persuasive argument that higher level processes in the perceptual processing hierarchy can at times dominate over lower level processes involved in the various domain-specific perceptual experiences (Barnes *et al.,* 2003). Sietz and Molholm (1947), proposed that hallucinations might be the result of abnormally vivid mental imagery, a theory developed further by Mintz and Alpert (1972), who argued that defective reality testing was also required for hallucinations to occur. Furthermore, it has been suggested that age-related deficits in some reality monitoring tasks result from reduced accessibility of source-specifying attributes in memory, such as perceptual detail, spatial and temporal information (Barnes *et al.,* 2003). One categorisation of VH is "simple" versus "complex". Complex VHs are characterized by visions that are clearly defined, have specific form, and may include animals, objects and humans (Barnes and David, 2001). These two types of VH tend to have localization value: simple, pointing to occipital pathology, or complex, presumed to involve the temporal cortex, either directly or indirectly through modulatory connections, as in peduncular hallucinosis (Barnes and David, 2001). The same authors pointed to three mechanisms which, alone or in combination, underlie complex VH: irritative processes acting on higher visual centers or pathways; defective visual processing (both peripheral and central); and brainstem modulation of thalamocortical connections.

1.4.2. Prevalence of VH in DLB and PDD

Estimates of the prevalence of psychotic symptoms vary widely: in PD from 25 to 50%, in PDD from 45 to 65% and in DLB from 60 to 80% (Emre *et al.,* 2007). Furthermore, Barnes *et* *al.* (2001; 2008) showed a prevalence of VH in PD between 8 and 40% and, more interestingly, that up to 33% of PD patients undergoing long-term anti-parkinsonian treatment will have VH during the course of their illness. However VH have been reported in PD patients before start taking medication (Barnes and David, 2001). In a community-based study of 235 patients with PD in Norway, Aarsland *et al.* (1999) found that 9.8% had hallucinations with retained insight, and another 6% had more severe VH and delusions. A cross-sectional study showed that VH were reported in 70% of patients with PD and dementia but only in 10% of patients without dementia.

Only two studies have compared psychiatric symptoms in DLB and PDD (Aarsland *et al.*, 2001; Mosimann *et al.*, 2006). Whereas Mosimann *et al.* (2006) found similar characteristics and frequency of VH in PDD and DLB, Aarsland *et al.* (2001) found them more common in DLB patients. Paranoid ideation and phantom boarder phenomenon were the most common delusional symptoms, and significant linear associations were found for both symptoms (DLB>PDD>PD). Recurrent VH are prevalent (60-80%) in PDD and DLB (Emre, 2003; McKeith and Mosimann, 2004).

1.4.3. Risk factors for the development of Visual Hallucinations in parkinsonism

Several studies have examined the clinical correlations of VH in PD and DLB. The results are consistent and show that higher age, disease and treatment duration, cognitive impairment, depression, PD motor severity, axial impairment, sleep disorders and visual disturbances are predictive factors of the development of VH (Klein *et al.*, 1997; Mori *et al.*, 2000; Aarsland *et al.*, 2001; Barnes and David, 2001; Holroyd *et al.*, 2001; Mosimann *et al.*, 2004; Grossi *et al.*, 2005; Diederich *et al.*, 2005; Matsui *et al.*, 2006b; Hamilton *et al.*, 2008; Diederich *et al.*, 2009). Many of these variables are also risk factors for dementia in PD. A cross-sectional study reported VH in 70% of PDD patients but only by 10% of PD patients without dementia (Aarsland *et al.*, 1999; Fenelon and Mahieux, 2004). Dementia in PD has been closely associated with VH and psychotic symptoms (Ravina *et al.*, 2007). In addition, some studies have suggested that certain types of medications such as dopamine agonists and anticholinergics are more likely to induce psychotic phenomena than levodopa; however, all treatments, including surgical interventions have been associated with cases of VH (Ravina *et al.*, 2007). In consequence, Ravina *et al.* (2007) proposed diagnostic criteria for PD associated with psychosis (see Table 17).

Table 17. Proposed diagnostic criteria for PD-associated psychosis (*Source*: Ravina *et al.*, 2007)

Characteristic symptoms
- Presence of at least one of the following symptoms
  - Illusions
  - False sense of presence
  - Hallucinations
  - Delusions

Primary Diagnosis
- UK brain bank criteria for PD

Chronology of the onset of symptoms of psychosis
- The symptoms in Criterion A occur after the onset of PD

Duration
- The symptom(s) in Criterion A are recurrent or continuos for 1 month

Exclusion of other causes
- The sympotmos in Criterion A are not better accounted for Lewy bodies, psychiatric disorder or mood disorder with psychotic features, or a general medical condition including delirium

Associated features (specify if associated)
- With/without insight
- With/without dementia
- With/without treatment for PD (specify drug, surgical, other)

The cognitive risk factors related to the appearance of VH have also been studied. Some studies reported that frontal dysfunction, characterized by poor phonological and semantic verbal fluency, executive dysfunction and impaired inhibitory control of attention, may predict the development of hallucinations or dementia over the course of PD (Nagano-Saito *et al.*, 2004; Grossi *et al.*, 2005; Santangelo *et al.*, 2007; Ramirez-Ruiz *et al.*, 2007a; Barnes and Boubert, 2008; Imamura *et al.*, 2008). In addition, visual perception in DLB/PDD with VH was worse than in DLB/PDD patients without VH (Mori *et al.*, 2000; Mosimann *et al.*, 2004). At the same time, DLB patients with poor visuospatial skills had fewer neurofibrillary tangles and were more likely to experience VH than those with better visuospatial skills (Hamilton *et al.*, 2008).

With regard to neuropathology underlying VH, Harding *et al.* (2002) showed that these phenomena were associated with LBs in the amygdala and parahippocampus, with early hallucinations related to higher LB densities in parahippocampal and inferior temporal cortices (Harding *et al.*, 2002a; Harding *et al.*, 2002c). Moreover, in another study of 788 autopsy cases of parkinsonism, the presence of VH was 92.9% specific for LB parkinsonism (Williams and Lees, 2005) and in another longitudinal study (Johnson *et al.*, 2005), patients with pure DLB or DLB+AD pathology had more visual and auditory hallucinations and more visuospatial deficits than patients with AD pathology alone.

Another hypothesis that has been proposed is that denervation hypersensitivity of mesolimbic and mesocortical dopaminergic receptors predisposes patients to a hypersensitivity response which manifests as psychosis. Other neurotransmitters, particularly serotonin and acetylcholine, may play a role too (Ravina *et al.,* 2007). There is consistent evidence for widespread cholinergic denervation in PD, and imbalances of serotonergic and cholinergic input, particularly in the temporal or parietal cortices, have been suggested as a possible explanation for psychosis and VH in DLB (Barnes and David, 2001; Ravina *et al.,* 2007). Consistently, Ballard *et al.* (2000) reported that patients with VH had lower ChAT levels in temporal visual association cortex (BA 36).

In conclusion, it seems that higher age, longer disease duration, dementia and cognitive impairment are strongly correlated with the appearance of VH in PD and DLB patients.

1.4.4. Characteristics of Visual Hallucinations

The few studies addressing hallucination phenomenology in DLB and PDD have reported well-formed complex VH of animals, objects, and humans (Barnes and David, 2001; Mosimann *et al.,* 2006). An investigation carried out by Barnes *et al.* (2001) indicated that the typical VH occurred while the patient was alert and with eyes open, generally in dim surroundings. They involved the sudden appearance of a blurry image without voluntary effort, filling an area of the visual field. The hallucination was present for a few seconds, typically moved while present, and then suddenly vanished. The VH most often reported were complex, containing animate or inanimate objects or persons, although more transient and less clearly perceptual phenomena also occurred. Usually they contained up to five images, which were sometimes meaningful to the patient. Most patients knew that they were hallucinating. The most common way of interacting with the hallucination was either by walking towards it or by trying to touch it. Patients with DLB showed more multimodal experiences and less insight than PDD.

1.4.5. Neuropsychological studies in DLB and PD with Hallucinations

Several studies have assessed the cognitive functions related to VH in PD. Roane *et al.* (1998) reported that delusional misidentification syndrome associated with parkinsonism results from a combination of dopaminergic psychosis and cognitive dysfunction involving the frontal lobe. Later on, Barnes *et al.* (2003) showed that PD patients with VH had more impairment in all the subtest of the Visual Object and Space Perception Battery (VOSP), a visuoperceptive and visuospatial test, especially in face recognition and silhouette identification and worse recognition memory and more intrusions than PD patients without VH. On the other hand, non-hallucinators were more successful at judging the source of an item than the hallucinators. Later studies have confirmed these deficits in verbal memory (learning, immediate recall or recognition), semantic and phonetic verbal fluency (Grossi *et al.,* 2005; Ramirez-Ruiz *et al.,* 2006; Santangelo *et al*., 2007; Ozer *et al.,* 2007; Ramirez-Ruiz *et al.,* 2007a), language (Ramirez-Ruiz *et al.,* 2006; 2007a), visuoperceptive functions (Ramirez-Ruiz *et al.,* 2006) and other frontal functions, such as inhibition control of attention, perseverations, false alarms and psychomotor speed (Santangelo *et al.,* 2007; Ozer *et al.,* 2007; Barnes and Boubert, 2008; Imamura *et al.,* 2008) in PD patients with VH in comparison with PD without VH.

In addition, two longitudinal studies have studied the cognitive correlations of VH in PD patients. Ramirez-Ruiz *et al.,* (2007a) reported a progressive decline affecting mainly visual memory for faces and visuoperceptive/visuospatial functions, whereas Santangelo *et al.,* (2007) showed that reduced phonological fluency at baseline was the only independent predictor of the onset of hallucinations after 2-year follow-up, whereas hallucinations and poor phonological fluency predicted development of cognitive impairment in the follow-up.

Two studies have described a greater visuoperceptive impairment in DLB patients with VH in comparison with DLB patients without them (Mori *et al.,* 2000; Mosimann *et al.,* 2004). One of these studies also included PDD patients in the sample. Moreover, Hamilton *et al.* (2008) reported that the severity of visuospatial deficits in DLB may identify those facing a particularly malignant disease course and may designate individuals whose clinical syndrome is impacted more by LB formation than AD pathology.

In conclusion, the cognitive impairment related to VH in PD patients is characterized by impairment in visuospatial and visuoperceptive functions, naming and frontal functions (specifically, verbal fluency). Only two studies have assessed the cognitive profile of DLB patients with VH, but they also seem to have greater visuoperceptive impairment than patients without VH.

1.4.6. Neuroimaging studies

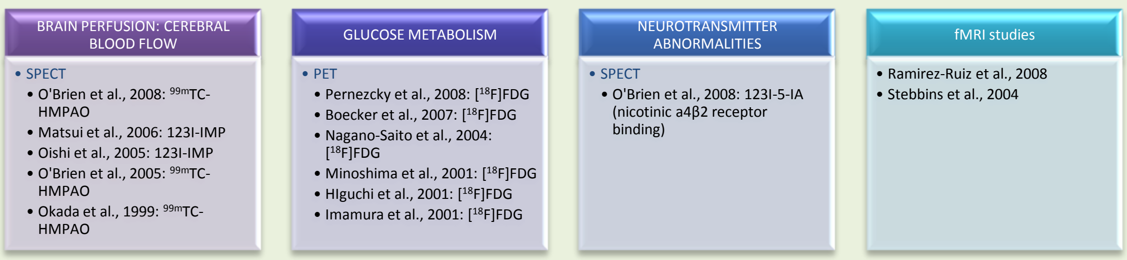
STRUCTURAL IMAGING TECHNIQUES

Three studies so far have assessed the correlations between VH and structural brain imaging in PD patients (Ramirez-Ruiz *et al.,* 2005; 2007b). The first of these was a longitudinal study by Ramirez-Ruiz *et al.* (2005), in which VH occurred in all demented patients but in none of the PD. However, the presence of VH did not correlate with gray matter volume in the temporo-occipital region, either at baseline or at the follow-up evaluation and they did not evaluate the possible relationship with other brain areas. Subsequently, the same group studied the cerebral pattern related to VH in PD patients without dementia, and found greater gray matter reductions in the lingual gyrus (BA 18) and the superior parietal lobe (BA 7) in PD patients with VH with respect to the ones without them. These areas are involved in higher visual processing (Ramirez-Ruiz *et al.,* 2007b). Later on, Ibarretxe-Bilbao et al., 2008 studied the hippocampal volume of PD patients with VH, showing that the atrophy was mainly confined to the hippocampus head.

To date, no study has evaluated through structural MRI the brain structures related to VH neither in a sample of DLB patients, nor in PDD extensively.

FUNCTIONAL IMAGING TECHNIQUES

Figure 28 illustrates the techniques used in the functional study of VH in PD, PDD and DLB patients.



Abbreviations

[18F]FDG, [18F]fluorodeoxyglucose; 123I-IMP, N-isopropyl-4-[123I]iodoamphetamine; 99mTc-HMPAO, 99mTc-hexamethylpropylene amine oxime; 123I-5-IA, 123I-5IA-8538; PET, Positron Emission Tomography; SPECT, Single photon emission computed tomography

Figure 28. Techniques used in different fMRI studies focused on VH PD, PDD and DLB patients

BRAIN PERFUSION STUDIES

Only one study (O'Brien *et al.,* 2005) has used SPECT with ^{99m}TC-HMPAO marker to assess the cerebral blood flow of DLB and PDD patients with VH, finding that the perfusion of the left posterior cingulate cortex and precuneus decreased with the worsening of VH in a mixed group with DLB and PDD. However, three different studies have assessed the brain perfusion of PD patients with VH in comparison with non-hallucinators. Using ^{99m}TC-HMPAO, Okada *et al.* (1999) showed that PD patients with medication induced VH had deficits in blood flow in the left temporal cortex and temporo-occipital regions than in patients without VH. In addition, using the radiotracer 123I-IMP, Oishi *et al.* (2005) found decreased blood flow in the right fusiform gyrus and increased flow in the right superior and middle temporal gyri in PD with VH with respect to PD without VH. Interestingly, Matsui *et al.* (2006a) found reduced perfusion in nearby regions, namely the inferior parietal lobe, inferior temporal gyrus, precuneus and occipital cortex.

GLUCOSE METABOLISM STUDIES

Seven studies have evaluated the pattern of glucose metabolism in patients with VH through 18F-FDG PET: three studies in PD patients (Minoshima *et al.,* 2001; Nagano-Saito *et al.,* 2004; Boecker *et al.,* 2007) and four studies in DLB (Imamura *et al.,* 1999; Higuchi *et al.,* 2000; Perneczky *et al.,* 2008a; Perneczky *et al.,* 2008b). In PD with VH, hypometabolism in the frontal lobe have been shown in comparison with PD without VH (Minoshima *et al.,* 2001), specifically in the left superior frontal gyrus (Nagano-Saito *et al.,* 2004). However, Boecker *et al.* (2007) found hypometabolism in occipito-temporo-parietal regions, such as the inferior and parietal lobe, middle temporal, posterior cingulate, parahippocampal and lingual gyri, in PD patients with VH with respect to non-hallucinationg PD patients (see Figure 29).

In addition, as the Figure 29 illustrates, hypometabolism in posterior temporal and parietal areas (Imamura *et al.,* 1999), in the occipito-temporal junction (BA 39) and middle frontal gyrus (BA 6) (Perneczky *et al.,* 2008a) have been reported in DLB patients with VH in comparison with those without VH. With respect to control subjects, the pattern of hypometabolism extended to anterior frontal areas (Perneczky *et al.,* 2008a). These frontal structures have also been related with delusions in DLB patients (Perneczky *et al.,* 2008b). Higuchi *et al.* (2000) suggested a correlation between neuropathological findings and hypometabolism in posterior cortical areas in patients with DLB and VH.

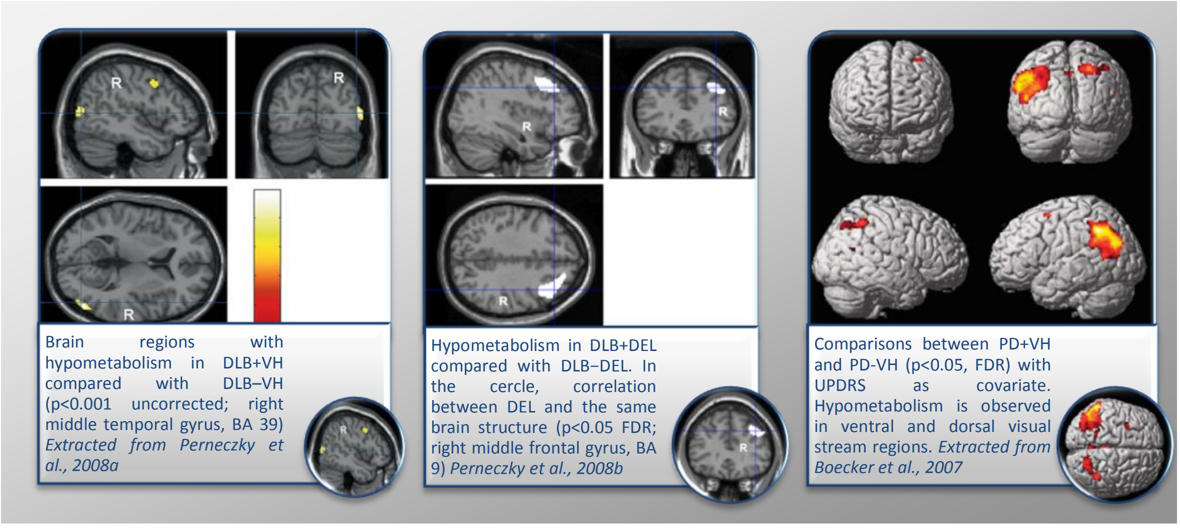


Figure 29. Brain regions with significant reductions of the rCMRglc in DLB or PD patients with VH and delusions in comparison with patients without them

STUDIES OF NEUROTRANSMITTER FUNCTION

The cholinergic system has been evaluated by binding of the nicotinic α4β2 receptor. In this study, DLB patients with VH showed increased uptake in the cuneus in comparison with DLB without VH; and reduced striatal and cingulate uptake with increases in the occipital lobe, cuneus and precuneus in comparison with control subjects (O'Brien et al., 2008).

FUNCTIONAL MRI STUDIES

A study by Stebbins *et al.* (2004) evaluated through a complex visual task the visual perception of PD patients with VH. They concluded that PD patients with VH had a shift in the visual circuitry from posterior to anterior regions associated with attentional processes, suggesting that altered network organization may play a role in the pathophysiology of VH in PD. However, Ramirez-Ruiz *et al.* (2008) showed that PD with VH had reduced activation during a face perception task in several right prefrontal areas (namely the Brodmann areas 6/8, 8, 10 and 47) and the anterior cingulate in comparison with non-hallucinating PD patients.

Taking these results together, it seems that prefrontal and visual associative areas play a role in the presence of VH in PD and DLB.

1.4.7. Clinicopathological associations

Ballard *et al.* (2000) showed that PD patients with VH had lower ChAT levels in the temporal visual association cortex than PD patients without VH. Papapetropoulos *et al.* (2006) reported higher LB burden across the amygdala, frontal, temporal and parietal cortical areas in PD patients with VH compared to those without. Accordingly, Halliday *et al.* (2008) reported an association between limbic and cortical Lewy Bodies and well-formed VH.

Furthermore, in neuropathologically diagnosed DLB patients, the secondary visual pathway revealed more severe LB pathology than the primary visual pathway, suggesting that the degeneration of the secondary visual pathway induces dysfunction in the recognition of objects, shapes and colors. Lewy pathologies in the secondary visual pathway and amygdala may cause the dysfunction of the visuo-amygdaloid pathway participating in visual misidentification in DLB (Yamamoto *et al.*, 2006).

APPROACH,
OBJECTIVES AND HYPOTHESIS

2. Approach, Objectives and Hypothesis of the thesis

2.1. STUDY I: Correlations between gray matter reductions and cognitive deficits in Dementia with Lewy Bodies and Parkinson's Disease with Dementia

2.1.1. Approach

LBD is a spectrum of disorders characterized pathologically by alpha-synuclein inclusions in the brainstem, subcortical nuclei, limbic and neocortical areas and clinically by attentional disturbance, parkinsonism, dementia and VH (McKeith *et al.,* 2005). Two clinical diagnoses within the LBD spectrum are DLB and PDD. Since the two syndromes present considerable clinical overlap, it has been argued that DLB and PDD may represent the same disease entity. DLB is diagnosed when dementia occurs before or concurrently with parkinsonism and PDD when dementia occurs in the context of well-established Parkinson's disease (McKeith *et al.,* 2005). Some studies compared cognitive function in PDD and DLB suggesting that DLB is characterized by specific declines in attention, executive function, visuospatial and constructional abilities and immediate and delayed recognition memory relative to PDD (Downes *et al.,* 1998; Aarsland *et al.,* 2003; Mondon *et al.,* 2007), whether other studies observed no differences between them (Ballard *et al.,* 2002; Horimoto *et al.,* 2003; Cormack *et al.,* 2004; Noe *et al.,* 2004; Janvin *et al.,* 2006;). Although there are two VBM studies comparing DLB and PDD (Burton *et al.,* 2004; Beyer *et al.,* 2007), showing contradictory results, there are no studies exploring the relationship between cognitive impairment and gray matter loss.

Thus, the purpose of the present study was to investigate the brain structure and neuropsychological functions of clinically diagnosed patients with DLB and PDD, and to explore their possible correlations.

2.1.2. Objectives

In summary, the main objectives of our study were:

<u>General objectives</u>

I. To examine the gray matter differences between DLB and PDD patients using VBM methods

II. To determine the differences in the cognitive pattern between DLB and PDD patients

Specific objectives

I. To evaluate the relationship between brain structures and cognitive functions in DLB and PDD
II. To assess if the pattern of brain-function correlations is different in both disorders
III. To determine MRI and neuropsychological biomarkers to differenciate DLB from PDD
IV. To compare the proportion of hippocampal atrophy in DLB and PDD

2.1.3. Hypothesis

We hypothesize that DLB patients will have greater decrease of gray matter than PDD subjects affecting associative neocortical areas and will present more cognitive deficits, specifically in prefrontal functions.

2.2. STUDY II: Frontal and associative visual areas related to Visual Hallucinations in Dementia with Lewy Bodies and Parkinson's Disease with Dementia

Visual Hallucinations are among the core features of DLB, but are also very frequent in PDD. The few studies addressing hallucination phenomenology in both disorders have reported well-formed complex VH of animals, objects, and humans in DLB and PDD (Aarsland *et al.,* 2001; Barnes and David, 2001; Mosimann *et al.,* 2006) with an estimated prevalence between 50-80% (Emre, 2003; McKeith and Mosimann, 2004; Diederich *et al.,* 2009). Neuroimaging techniques provide a direct means of identifying and characterizing *in vivo* the patterns of brain atrophy associated with VH in DLB and PDD. However, no studies to date have assessed structural differences between DLB and PDD with and without VH, or have tried to assess the relationship between gray matter changes and VH in DLB or PDD. Besides, there is only one study of cognitive functions in DLB patients with VH in comparison with DLB without hallucinations (Mori *et al.,* 2000), reporting that DLB patients with VH had greater visuoperceptual impairment.

Hence, the purpose of the present study was to investigate the pattern of gray matter and cognitive impairment underlying VH in DLB and PDD applying VBM and behavioral assessment.

2.2.1. Objectives

The main objectives of the study were:

General objectives

I. To evaluate *in vivo* structural brain changes associated with visual hallucinations in DLB and PDD patients
II. To determine the cognitive functions related to visual hallucinations in DLB and PDD patients

Specific objectives

I. To evaluate the differences in local gray matter between patients with DLB and PDD with VH
II. To assess the correlations between gray matter volume and the severity of visual hallucinations in DLB and PDD

III. To determine the correlations between cognitive function and the severity of visual hallucination in DLB and PDD

2.2.2. Hypothesis

We hypothesize that there will be more pronounced gray matter changes involving visual associative areas in patiens with VH than in patients without VH.

METHODS

2. Methods

The present thesis consists of two studies examining cognitive functions, visual hallucinations and structural brain characteristics in DLB and PDD patients using neuropsychological and MRI methods. The local ethics committee approved the studies and written informed consent was given by the patients and/or by the family if patients were not able, prior to the participation in the study. These studies were part of the same research project, so the sample and the MRI adquisition protocol were the same for both studies. A detailed description of the sample characteristics, methodological approaches, cognitive and/or behavioral tests and MRI analysis methods are detailed within each study.

4.1. Study sample

The evaluation of the sample was carried out in three steps. The sampling process and description of the excluded patients are displayed in Figure 30.

In the first phase, all subjects underwent a screening interview to be selected for the final sample according with the following inclusion and exclusion criteria:

- The <u>inclusion criteria</u> were: diagnosis of probable DLB (McKeith *et al*., 2005) and diagnosis of PDD (Daniel and Lees, 1993, DSM-IV-TR, 2002), MMSE < 24 and Geriatric Depression Scale (GDS) < 5.

- The <u>exclusion criteria</u> were: cases with psychiatric illness, traumatic brain injury, alcohol or drug abuse, presence of focal lesions in MRI and certain psychoactive drugs were excluded.

Initially, we evaluated 66 patients, recruited from Bellvitge University Hospital, Barcelona; from which only 21 DLB patients and 21 PDD patients fulfilled the criteria to participate in the study. The DLB diagnosis was therefore made using the Consensus Criteria (McKeith *et al.,* 2005). The diagnosis of PD was made according to the UK Brain Bank clinical (Daniel and Lees, 1993) and dementia due to PD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2003). Furthermore, 24 healthy control subjects were also asessessed.

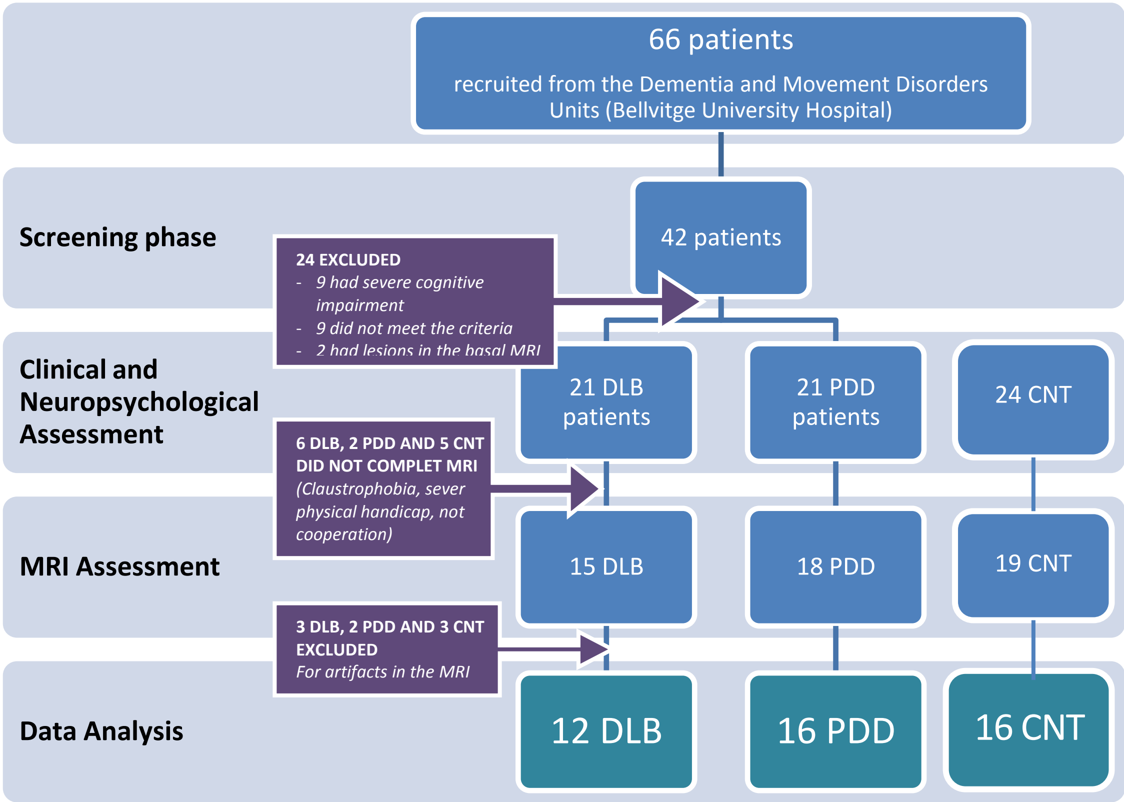


Figure 30. Flowchart of the sampling process

In the *second phase*, all subjects underwent a clinical and neuropsychological assessment and, in the *third phase*, the MRI assessment.

Some subjects were excluded from the studies afterwards during the data analysis because of artifacts and low quality of the images.

4.2. Cognitive and behavioural assessment

In this section, the clinical and neuropsychological assessments are described. *More detail on these assessments are included in the results section.*

- Structured interview assessing background, risk factors, and clinical criteria. MMSE was used as a general cognitive screening test, corrected according to age and education following published norms (Dufouil *et al.*, 2000) and GDS (Reisberg *et al.*, 1982) was used as a measure of cognitive decline. The severity of Parkinsonian symptoms was assessed through the subscale III of the Unified Parkinson's Disease Rating Scale (UPDRS-III)(Fahn, 1987) and disease stage was estimated using the Hoehn and Yahr Scale (Hoehn and Yahr, 1967). We calculated a levodopa equivalent dose (levodopa and dopaminergic agonists) using previously published methods (Vingerhoets et al., 2002). The hallucinations subscale of the Neuropsychiatric Inventory (NPI) (Cummings *et al.,* 1994) was used to quantify the severity and frequency of VH, defined as frequency per severity scores (range 0-12). We also assessed them qualitatively by Burnes Questionaire (Barnes and David, 2001).

- Neuropsychological assessment based on four cognitive domains: attention/executive functions, visuospatial/visuoperceptive functions, memory (visual and verbal) and constructional abilities. All tests were administered and scored in accordance with conventional procedures (Lezak, 2004):

    - Conner's Continuous Performance Test (CPT-II) (Conners, 1985)
    - Visual and verbal memory and the drawing copy tests of the CERAD battery (Welsh *et al.,* 1991)
    - Stroop test (Golden, 2001)
    - Verbal fluency: phonetic from the COWAT test (Sumerall *et al.,* 1997) and semantic from the Barcelona's Test (Peña *et al.,* 1991)
    - The Cortical Vision Screening test (CORVIST) (Merle James, 2001)

The statistical analysis of the neuropsychological and clinical data was conducted using SPSS (11.5, SPSS Inc.). Because of the sample size and the non-linear distribution of the variables, we used non-parametrical tests.

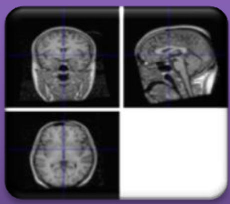
4.3. MRI protocol

Images were acquired in the Diagnostic Imaging Center from Bellvitge University Hospital. MRI data were acquired on a 1.5 T Philips Intera machine obtaining 110 overcontiguous slices (TR=40 ms; TE=1.79 ms; fa=35º; voxel size=0.98x0.98x1.3 mm). The statistical MRI analyses were carried out using Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, London, UK) (http://www.fil.ion.ucl.ac.uk/spm/) running under Matlab 6.5 (MathWorks, Natick, MA).

Analysis of the data: Voxel-based Morphometry

A VBM analysis was used to assess the pattern of gray matter changes according to previously described methods (Mechelli, 2005; Ashburner and Friston, 2005). The preprocessing steps included: **1)** spatial normalization of all subjects' images into the same stereotactic space by registering each of the images to the same template image. This normalization does not attempt to match every cortical feature exactly, but corrects for global brain shape differences (Crinion *et al.,* 2007); **2)** segmentation of the spatially normalized images into gray matter, white matter and cerebrospinal fluid based on a combination of *a priori* probability maps and a cluster analysis that identifies voxel intensity distributions of particular tissue types. As the segmentation is in part based on the voxel intensity, a correction for image intensity non-uniformity is also made (Acosta-Cabronero *et al.,* 2008; Ashburner and Friston, 2005); **3)** smoothing of the gray matter images by convolving with an isotropic Gaussian Kernel to: a) ensure that each voxel in the images contains the average amount of gray or white matter from around the voxel, b) make the data more normally distributed, c) compensate for the spatial normalization and d) reduce the effective number of statistical comparisons (Kiebel *et al.,* 1999); **4)** modulation of the images that aim to correct for volume change that occurred during the spatial normalization step and **5)** statistical analysis to localize and make inferences about group differences. The result is a statistical parametric map showing regions where gray matter or white matter concentrations differ between groups. This statistical parametric map comprises the results of many statistical tests, so it is necessary to correct for these multiple dependent comparisons (Ashburner and Friston, 2000). In SPM5 normalization and segmentation have been brought together (Ashburner and Friston, 2005). Tissue probability maps derived by a mixture of Gaussian models are used to assist the classification of the different tissues, but they include deformation of these maps, so they best match the images to segment. The probability that a voxel will belong to a tissue class has spatial dependencies. The pre-processing steps are summarized in Table 18.

Table 18. Steps for Voxel-based Morphometry (SPM5) (Based on Ashburner and Friston, 2005)



ORIGINAL IMAGE

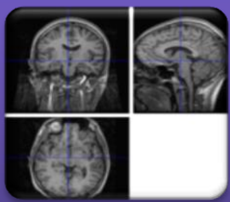
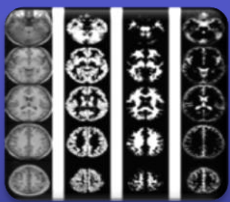
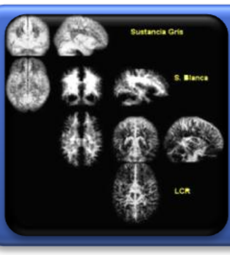


IMAGE REORIENTATION



SPATIAL NORMALIZATION AND SEGMENTATION

- Registering the brain volume to a standard space and automatically selecting voxels that have a high probability of belonging to each tissue class
- Classification of the different tissues according to they intensities by tissue probability maps
- Deformation of these maps, so they best match the images to segment
- The segmentation algorithm in SPM5 additionally warps the prior images to the data and tries to minimize the impact of the template and the prior images

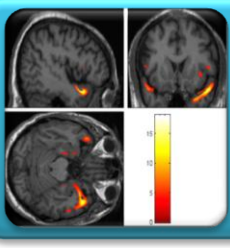


SMOOTHING the images to

- ensure that each voxel contains the average amount of gray or white matter from arround the voxel
- render the data more normally distrubuted
- compensate for spatial normalization
- reduce the effective numer of statistical comparisons

MODULATION

- to correct for volume chage that occured during the spatial normalization



STATISTICAL ANALYSIS -> statistical parametric map

RESULTS

4.1. STUDY I:

Correlations between gray matter reductions and cognitive deficits in Dementia with Lewy Bodies and Parkinson's Disease with Dementia

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Abstract

There is controversy regarding whether Dementia with Lewy Bodies (DLB) and Parkinson's disease with dementia (PDD) may or not be different manifestations of the same disorder. The purpose of the present study was to investigate possible correlations between brain structure and neuropsychological functions in clinically diagnosed patients with DLB and PDD.

The study sample consisted of 12 consecutively referred DLB patients, 16 PDD patients and 16 healthy control subjects recruited from an outpatient setting, who underwent MRI and neuropsychological assessment. Voxel-based morphometry results showed that DLB patients had greater gray matter atrophy in the right superior frontal gyrus, the right premotor area and the right inferior frontal lobe compared to PDD. Furthermore, the anterior cingulate and prefrontal volume correlated with performance on the Continuous Performance Test while the right hippocampus and amygdala volume correlated with Visual Memory Test in the DLB group. In conclusion, DLB patients had more fronto-temporal gray matter atrophy than PDD patients and these reductions correlated with neuropsychological impairment.

Key words: *Dementia, Parkinson's Disease, Lewy Body Disease, MRI, Neuropsychology.*

4.1.1. Introduction

LBD is a spectrum of disorders characterized pathologically by alpha-synuclein inclusions in the brainstem, subcortical nuclei, limbic and neocortical areas and clinically by attentional disturbance, parkinsonism, dementia and VH (McKeith *et al.,* 2005). Two clinical diagnoses within the LBD spectrum are DLB and PDD. Since the two syndromes present considerable clinical overlap, it has been argued that DLB and PDD may represent the same disease entity. DLB is diagnosed when dementia occurs before or concurrently with parkinsonism and PDD when dementia occurs in the context of well-established PD (McKeith *et al.,* 2005). Some studies compared cognitive function in PDD and DLB suggesting that DLB is characterized by specific declines in attention, executive function, visuospatial and constructional abilities and immediate and delayed recognition memory relative to PDD (Downes *et al.,* 1998; Aarsland *et al.,* 2003; Mondon *et al.,* 2007), whether other studies observed no differences between them (Ballard *et al.,* 2002; Horimoto *et al.,* 2003; Noe *et al.,* 2004; Cormack *et al.,* 2004; Janvin *et al.,* 2006). Although there are two VBM studies comparing DLB and PDD (Burton *et al.,* 2004; Beyer *et al.,* 2007b), there are no studies exploring the relationship between cognitive impairment and gray matter loss.

The aim of this study was to investigate the correlations between local gray matter volume and cognitive functioning in DLB and PDD. Given that several studies have shown that DLB patients present greater impairment in executive and attentional functions, we expected to find more pronounced gray matter changes affecting frontal areas in this group.

4.1.2. Methods

Subjects

12 patients with DLB, 16 patients with PDD and 16 control subjects were recruited from an outpatient movement disorders and dementia clinic (Department of Neurology, Bellvitge University Hospital, Barcelona, Spain). The local ethics committee approved the study and written informed consent was obtained from all the participants. Clinical diagnosis was made after comprehensive multidisciplinary assessment by a neurologist and a neuropsychologist. Thus, the DLB diagnosis was made according to the Consensus Criteria (McKeith *et al.,* 2005), the diagnosis of PD by using the UK Brain Bank criteria (Daniel and Lees, 1993) and the diagnosis of dementia due to PD according to the fourth edition of the DSM-IV-TR (American Psychiatric Association, 2003). The control

subjects were 2 spouses of the patients and 14 community volunteers without any history of psychiatric or neurological disorders who were matched with patients for age. The MMSE (Folstein *et al.,* 1983) was used as a general cognitive screening test, we corrected it according to age and education following published norms (Dufouil et al., 2000). Reisberg's Global Deterioration Scale (GDS) (Reisberg *et al.,* 1982) was used as a measure of cognitive decline. The severity of parkinsonian symptoms was assessed by subscale III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn, 1987) and disease stage was estimated using the Hoehn and Yahr Scale (Hoehn and Yahr, 1967). We calculated a levodopa equivalent dose (levodopa and dopaminergic agonists) using previously published methods (Vingerhoets *et al.,* 2002). Three subjects were treated with antipsychotic medication (risperidone). In the DLB group, one subject received a daily dosage of 1 mg and the other 0.5 mg. One subject in the PDD group received a daily dose of 1 mg. Demographic and clinical characteristics of the sample are shown in Table 19.

Table 19 Demographic and clinical characteristics of the sample

	PDD (n=16)	**DLB (n=12)**	**Control (n=16)**	**X^2/U**	***p*-value**
Sex (M:F)	11:5	8:4	8:8	1,38	NS†
Age	71.1 (7.2)	71.1 (10.8)	71.8 (7.6)	0,22[d]	NS††
Education	6.1 (6)	11 (6)	7.7 (6.5)	4,2[d]	0.05†† [b]
GDS	4.3 (0.9)	4.18 (1)	1.0	31,82[d]	0.001†† [c]
Corrected MMSE	21.8 (4.1)	19 (6.2)	28.6 (2)	22,79[d]	0.001†† [c]
UPDRS-III	35.5 (13.5)	27.3 (11)		41	0.02††[b]
Hoehn and Yahr	2.8 (0.8)	2.8 (0.6)		82	NS††
Duration parkinsonism (months)	52.8 (27.8)	32.6 (16.1)		58	NS††
Levodopa dose (mg)[a]	604.9 (281.7)	471.4 (439.5)		60,5	NS††

Values expressed as mean (SD). NS=not significant.†Pearson's Chi-square. ††U-Mann Whitney.
Abbreviations: PDD, Parkinson Disease with Dementia; DLB, Dementia with Lewy Bodies; GDS, Global Deterioration Scale; MMSE, Mini-mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]including dopamine agonists
[b]significant differences between DLB and PDD
[c]significant differences between controls and DLB, PDD
[d]value of the X^2-statistic (Kruskal-Wallis)

Brain imaging

MRI data were acquired on a 1.5 T Philips Intera machine obtaining 110 overcontiguous slices (TR=40 ms; TE=1.79 ms; fa=35°; voxel size=0.98x0.98x1.3 mm). The statistical MRI analyses were carried-out using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) running under Matlab 6.5 (MathWorks, Natick, MA). A standard VBM analysis was used to assess the pattern of gray matter changes according to previously described methods (Mechelli, 2005). The preprocessing steps included normalization of the images to a template, segmentation into tissue classes, modulation with Jacobian determinants and smoothing with an isotropic 8mm Gaussian kernel filter. The resulting smoothed and modulated images were used in the statistical analysis to assess gray matter volume changes.

Differences in whole-brain gray matter between groups were assessed using one-way ANCOVA analysis including years of education, UPDRS-III score and disease duration as covariates. To perform the comparisons, we defined gray matter regions of interest (ROIs) in prefrontal and sensorial associative areas (temporal, parietal and occipital) following the neuropathological data of Lewy Bodies Diseases that relate dementia progression to Lewy Bodies depositions in these areas (Braak *et al.*, 2003; McKeith *et al.,* 2005). The ROIs were anatomically defined using the Pick Atlas tool of the SPM package.

To control for the effect of education, UPDRS-III and parkinsonism duration in the correlation analyses, we used the full factorial design implemented in SPM5. There was one fix factor (clinical group) and one variable of interest (the neuropsychological function). For these analyses we defined the same ROIs as for the group comparison analyses.

For all the statistical analyses, the threshold was settled at voxel and cluster levels $p<0.05$ FWE corrected for multiple comparisons.

Neuropsychological assessment

All patients underwent a neuropsychological assessment based on three cognitive domains: attention, memory and constructional abilities, these being the main functions impaired in DLB in comparison with PDD. The battery consisted of Conner's Continuous

Performance Test (CPT-II) (Conners, 1985) and visual and verbal memory and the drawing copy tests of the CERAD battery (Welsh *et al.,* 1991). The CPT-II is a test to assess mantained attention and response inhibition. Single letters are presented consecutively in the center of a screen and the patient is required to press a button when any letter except the target letter “X” appears. To assess memory and constructional praxis, we used some subtests of the CERAD battery. The verbal learning task consist of an immediate free recall of 10-item word-list assessed over three separate learning trials. The subject is instructed to read aloud the 10 words each trial. Immediately, the subject is asked to recall the words. After a 5 to 8 minutes delayed period, the pacient should recall them. The number of words recalled on the last trial, the delayed recall and intrusion errors were recorded. In the constructional praxis task the subject is instructed to copy 4 geometrical figures and the delayed visual memory task consisted of the recall of these figures. All tests were administered and scored in accordance with conventional procedures (Lezak, 2004). The statistical analysis of neuropsychological data was conducted using SPSS (11.5, SPSS Inc.).

Because of the sample size and non-linear distribution of the variables, differences between groups were assessed using one-way Kruskal-Wallis test with a post-hoc Mann-Whitney U-test contrast. A X^2 test was used for qualitative variables.

4.1.3. Results

Group VBM analysis

The gray matter volume comparisons between groups including years of education, severity and duration of parkinsonian symptoms as covariates are shown in Table 20 and Figure 31. We did not find significant gray matter differences in the comparisons PDD<DLB, CNT<DLB, CNT<PDD.

When we performed a regression analysis between the covariables and brain gray matter, we found that the UPDRS-III score was related to gray matter volume in the middle and inferior frontal lobe bilaterally (Left BA 11,47 and right BA 10-11), while the other two covariables were no related to any of the studied areas.

Table 20. Stereotactic locations and Brodmann areas (BA) of significant differences in brain volume between DLB and PDD including education, disease duration and UPDRS-III as covariates

Region (BA)	Cluster size (mm^3)	Talairach coordinates (x,y,z)	T-value*
DBL < CONTROLS			
Right inferior frontal (45)	1346	59,20,21	5.02
Left posterior cingulate	303	-3,-36,45	4.38
Left superior temporal (38)	559	-48,14,-12	4.46
Left inferior parietal (39)	439	-55,-66,28	3.97
PDD < CONTROLS			
Right cuneus (18)	445	4,-95,15	4.19
Left inferior parietal (39)	275	-46,-70,37	4.27
DLB < PDD			
Right superior frontal (8)	176	6,40,52	4.17
Right premotor area (6)	368	48,17,48	5.20
Right inferior frontal (45)	196	56,22,20	4.00

**Significance threshold p<0.05 voxel-level corrected for multiple comparisons (FWE).*

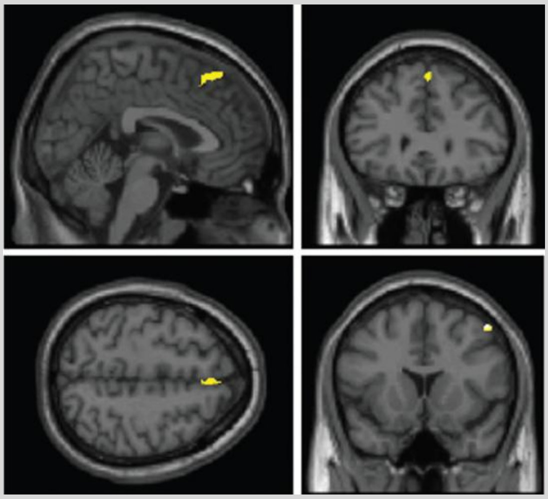

Figure 31. Stereotactic locations of significant clusters of gray matter volume loss in DLB patients compared with PDD in the right superior frontal lobe and the right premotor area. The results are overlapped in a T1 healthy control brain. The yellow colour shows the significant areas (p<0.05 FWE corrected).

Neuropsychological results

Mann-Whitney test comparisons (Table 21, Figure 32 and 33) indicated that DLB patients showed poorer performance in the vigilance variable in the CPT test. On the other hand, PDD patients made significantly more perseverations and became more erratic and less consistent during the performance of the CPT as well as committing more intrusions in the delayed verbal memory test.

Table 21. Neuropsychological results

	PDD (n=16)	DLB (n=12)	U	*p*-value
MEMORY – CERAD[a]				
Verbal learning	1.25 (2.1)	0.75 (0.96)	64,5	NS
Delayed verbal memory	1.31 (1.8)	0.5 (1.2)	66	NS
Intrusions in delayed verbal memory	0.88 (1.31)	0.17 (0.57)	62,5	0.05
Verbal recognition	14.75 (2.49)	12.50 (3.60)	56,5	0.06
Visual Memory (delayed)	1.5 (2)	1.83 (2.98)	86,5	NS
CONSTRUCTIONAL PRAXIS – CERAD	4.19 (2.97)	6.42 (3.39)	59	NS
ATTENTION – CPT[c]				
Omission errors	70 (40.4)	97.1 (68.3)	62	NS
Commission errors	23.9 (5.57)	20.3 (7.87)	49	NS
Detectability – attentiveness (d')	0.2 (0.29)	0.23 (0.48)	71	NS
Perseverations	60.4 (43.8)	22 (17)	33,5	0.02
Vigilance[b]	-0.06 (0.07)	0 (0.04)	38,5	0.02
Adjusting to presentation speed[b]	0.26 (0.09)	0.10 (0.16)	32,5	0.01

Group comparisons were performed by U-Mann Whitney. Values expressed as mean (SD). NS=not significant.
Abbreviations: PDD, Parkinson Disease with Dementia; DLB, Dementia with Lewy Bodies; CERAD, Consortium to establish a registry for Alzheimer Disease; CPT, Continuous Performance Test.
[a]values expressed as number of words
[b]values expressed as time
[c]higher scores indicate greater impairment

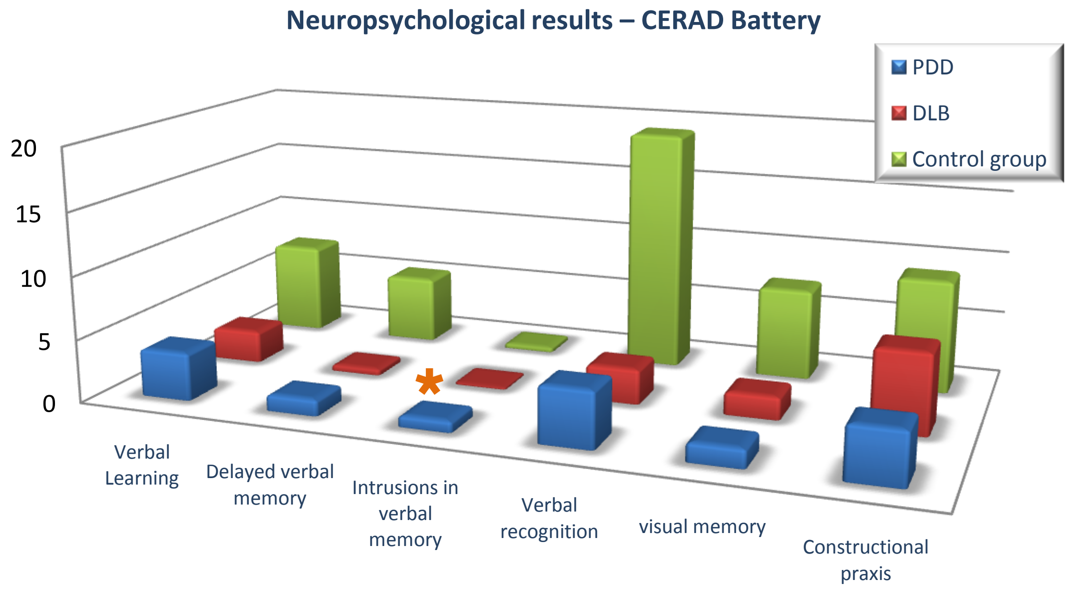

Figure 32. Histogram showing the differences in the performance in CERAD battery (only the items of memory and constructional praxis) in DLB in comparison with PDD. Control group has been included to make see the functioning of healthy people in the same task. Both pathological groups differed significantly from control subjects in all tasks.

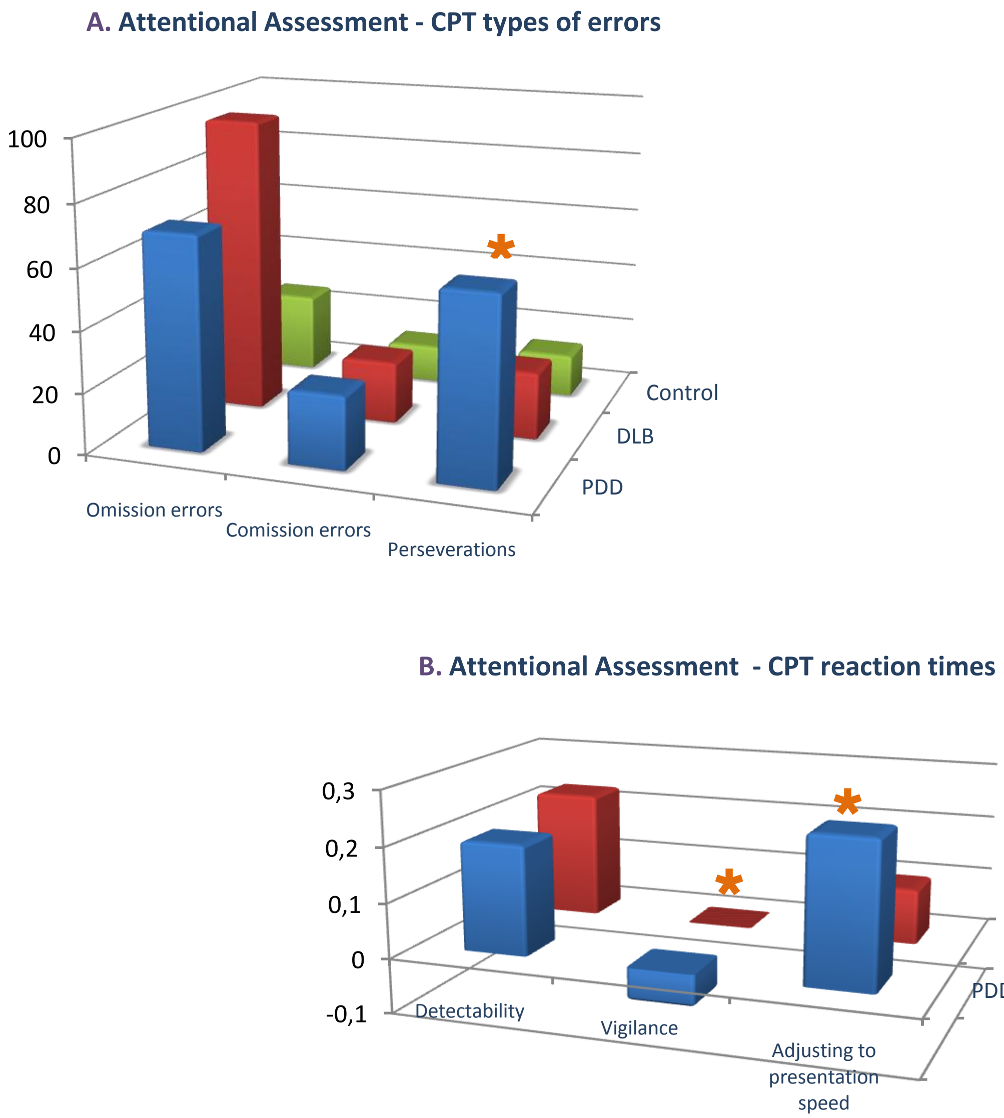

Figure 33. Histogram showing the differences in attentional performance in DLB in comparison with PDD. A) Type of errors. B) Reaction times. Control group has been included to make see the functioning of healthy people in the same task. Both pathological groups differed significantly from control subjects in all tasks. Higher punctutations indicate greater impairment.

Regional gray matter correlations with neuropsychological variables

The correlation analyses (Table 22, Figure 34a, b) showed significant correlations in the DLB group between the right hippocampus and amygdala volume and visual memory, and between the anterior cingulate and prefrontal areas (dorsolateral and inferior frontal cortex bilaterally) and performance on the CPT test (commission errors, detectability and perseverations). There were no significant correlations between the neuropsychological variables and the gray matter volume in the PDD group. However, in the control group, the right orbitofrontal volume was inversely related to the number of perseverations done in the CPT test.

Table 22. Correlations between neuropsychological data and brain regions in the DLB group including years of education, severity (UDPRS-III) and duration of parkinsonian symptoms as covariates ($p_{corrected}$<0.05 FWE)

Brain Area	Test	Cluster size	Correlation coefficients
DLB group			
R hippocampus	Visual memory	1668	0.83
R amygdala		366	0.81
L Anterior cingulate	CPT - detectability	369	0.84
	CPT - commission err.	351	0.84
L inferior frontal	CPT - detectability	586	0.86
L inferior frontal	CPT - commission err.	68	0.83
R inferior frontal		56	0.85
L dorsolateral		98	0.82
R dorsolateral		157	0.85
L inferior frontal	CPT - perseverations	386	0.83
L dorsolateral		334	0.87
R dorsolateral		339	0.86
Control group			
R orbitofrontal	CPT - perseverations	316	0.85

Abbreviations: CPT, Continuous Performance Test.

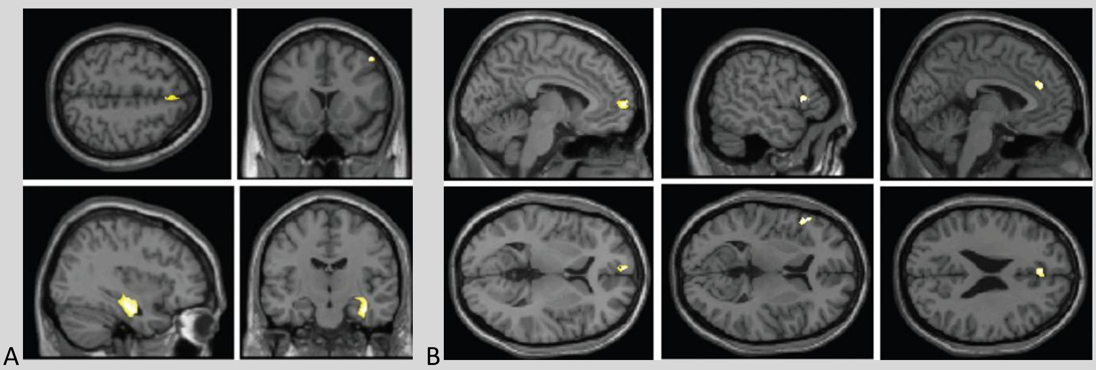

Figure 34. (A) Correlation between the Visual memory test and right hippocampus and amygdala in the DLB group. (B) Correlation between prefrontal areas and anterior cingulate and CPT results in the DLB group. The results are overlapped in a T1 healthy control brain. The yellow colour shows the significant areas (p<0.05 FWE corrected).

4.1.4. Discussion

To the best of our knowledge, this is the first study investigating the relationship between brain structural changes and cognitive performance in DLB and PDD. We found that DLB patients showed a consistent gray matter volume reduction involving the right superior frontal (BA 8), right premotor (BA 6) and right inferior frontal (BA 45) areas compared with PDD. Furthermore, the reduction of the gray matter volume of the inferior frontal lobe, the dorsolateral prefrontal cortex and the anterior cingulate in the DLB group was related to increased number of commission errors, perseverations and worse detectability on the CPT. These brain areas have been associated to response inhibition and executive attention (Lezak, 2004; Petrides, 2005; Fan *et al.*, 2005), and the Brodmann areas 6 and 8 have been involved in the circuitry of visual discrimination and attention (Petrides, 2005). Hence, we propose that the structural changes affecting these areas in DLB patients could lead to the visual attentional impairment considered as a core feature of DLB. These results are the first *in vivo* evidence showing the relationship between gray matter atrophic changes in prefrontal and premotor areas and attentional impairment in DLB. Moreover, in our DLB sample, right hippocampus and amygdala volumes were related to the visual memory performance.

With regard to the neuropsychological data, interestingly we found a different attentional profile: whereas DLB was characterized by distractibility during performance of the CPT (poorer vigilance and a trend for more omission errors); PDD patients showed more impulsivity on both the attentional and memory tasks (more perseverations and comission errors on the CPT and more intrusions during delayed recall). These results are in agreement with the Noe *et al.* study (2004), that reported more omission errors in cancellation tasks in DLB compared to PDD. In contrast, Bronnick *et al.* (2008) found more pronounced attentional disturbances in PDD compared to DLB. These discrepancies could be due to the sensorial modality assessed in the attentional tasks. These authors used auditory stimuli while we used visual stimuli. The attentional impairment observed in the DLB sample could be explained by our VBM results, where the anterior cingulate and prefrontal areas correlated with performance on the CPT. These findings are consistent with the model postulated by Posner and Rothbart, (2007) suggesting a role for the anterior cingulate in the executive control of attention to unpredictable events and inhibitory control.

We also found a different pattern of memory impairment: the DLB group tended to perform worse on free recall and overall recognition in agreement with previous studies (Mondon *et al.,* 2007), suggesting an encoding deficit more related to hippocampal structures. These deficits in memory could be associated with the observed atrophic changes involving prefrontal and hippocampal areas and the disruption therefore of the direct hippocampal output to the dorsolateral prefrontal cortex affected in DLB (Harding *et al.,* 2002b). Contrarily, the PDD group made more intrusion errors in delayed memory but better functioning in free recall and recognition. The presence of better recognition than free recall in PD patients has been extensively described (Savage, 1997). However, in a study with a large sample of PD patients addressed to test the retrieval deficit hypothesis, Higginson *et al.* (2005) showed that performance on measures of cued recall and delayed recognition were not significantly better than free recall performance. These results suggested that memory deficits in PD are not solely due to retrieval problems.

This investigation has some limitations. One of the limitations is the small sample size and the selection bias as the three groups regarding the sex distribution and the education. Furthermore, they showed a different distribution in clinical variables such as the duration of the parkinsonism and the degree of motor impairment. The difference in parkinsonism duration and degree of motor impairment are consequence of the inclusion criteria. To be diagnosed of PDD subjects should have a well-established parkinsonism for more than one year and this is not the case for DLB. To minimize the effect of these potential confounders, we included the years of education, UPDRS-III score and duration of parkinsonism as covariates of no-interest in all the performed analysis.

4.1.5. Conclusions

Our study revealed that DLB is characterized by a greater gray matter volume loss in prefrontal areas related to attentional impairment in comparison with PDD. Neuropsychologically, DLB patients had more distractibility and tended to perform worse on memory tasks, whereas PDD patients have more impulsive errors. Furthermore, in the DLB group the right hippocampus and amygdala volume were correlated with visual memory.

4.1.6. Complementary results

4.1.6.1. Individual analyses

In addition, to further characterize the individual patterns of hippocampal atrophy in DLB and PDD patients, we performed a single-case voxel-by-voxel analysis of the cortical gray matter distribution of each patient with those of the control group (Woermann *et al.,* 1999).

Methods

The MRI protocol and the MRI data pre-processing and analysis were exactly the same as in the previous analyses. However, for the statistical contrast, we performed a t-test comparison between one single pathological subject and the mean of the healthy control group. To perform the comparisons, we defined a region of interest comprising hippocampus bilaterally. The threshold was settled at voxel and cluster levels $p<0.05$ FWE corrected for multiple comparisons. Group comparisons were performed by Pearson's Chi-square.

Results

The single-case analysis of the gray matter distribution of each patient as compared with controls revealed a significant reduction in the right hippocampus in 50% of DLB patients, whereas only 6.3% of the PDD group showed such differences ($X^2=4.72$, $p=0.03$) (Table 23 and Figure 35). There was also a reduction in the left hippocampus in some patients (16.6% DLB and 18.8% PDD) but the differences between groups did not achieve statistical significance.

Table 23. Individual VBM analysis. Hippocampal gray matter reduction in DLB and PDD subjects.

Subject	Right Hippocampus	Left Hippocampus
DLB Group (n=12)		
1	Y	N
2	Y	N
3	N	N
4	N	N
5	Y	Y
6	N	N
7	Y	N
8	N	N
9	N	N
10	Y	N
11	Y	Y
12	N	N
Total	**6 (50%)** *	**2 (16.6%)**
PDD Group (n=16)		
1	N	N
2	N	N
3	N	N
4	Y	Y
5	N	N
6	N	N
7	N	N
8	N	N
9	N	N
10	N	N
11	N	Y
12	N	N
13	Y	Y
14	N	N
15	N	N
16	N	N
Total	**2 (12.5%)** *	**3 (18.8%)**

Abbreviations: Y, reduction; N, not reduction; PDD, Parkinson Disease with Dementia; DLB, Dementia with Lewy Bodies.

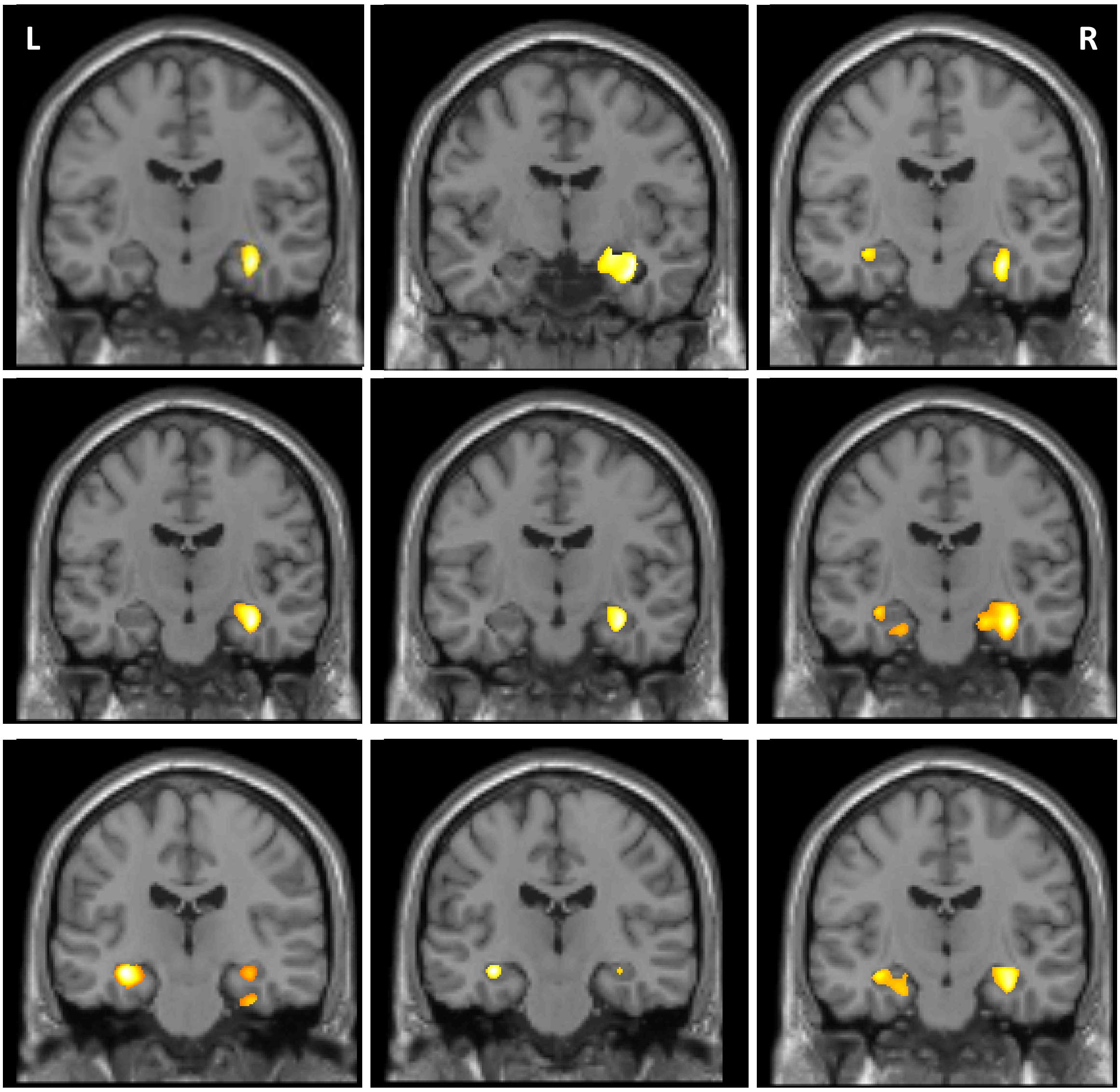

Figure 35. Hippocampal loss in DLB (two upper rows) and PDD patients (bottom row). The yellow colour shows the significant areas (L, left side; R, right side; p<0.05 FWE corrected).

4.1.6.2. Attentional profile: qualitative assessment

To further analyze qualitatively the attentional profile of DLB and PDD patients, we used the CPT test indicators of inattention, impulsivity and vigilance (Conners, 1985).

Methods

The CPT computerized test, offers a correction of the scores into a T score, adjusting for age and education. Furthermore, it clusters the impaired scores into three attentional impairment profiles (Conners, 1985): innatention, impulsivity and vigilance. Measures related to inattentiveness include omission errors, commission errors, slow mean reaction time, less consistent response, variability, attentiveness or poor discrimination, changes in reaction time over the three inter-stimulus intervals and adjusting to presentation speed (more erratic with the time between stimulus increase). The measures of impulsivity are commission errors, fast mean reaction time and perseverations. Vigilance is captured by the changes and inconsistency in reaction time over the 6 blocks of the test. Slower reaction times and less consistency as the test progresses indicate a loss of vigilance (Conners, 1985). In that context, we intended to peform a qualitative analysis of the attentional profiles of DLB and PDD patients to evaluate if there were differences between them.

The subjects with impairment of 6 or more scores in innatention profile (cluster of 8 scores) were defined as having *innatention*; as *impulsive*, the subjects with impairment in 2 or more scores of the impulsivity cluster (maximum 3) and as impaired in *vigilance* the subjects with 1 or more scores impaired in the vigilance cluster (maximum 2). Two subjects in the DLB group and 1 subject in the PDD group were excluded from the analysis because they obtained invalid scores in some of the items.

Results

Profile comparisons between groups are displayed in Table 24 and Figure 36. They indicate that PDD patients had a profile characterized by inattention and a trend to be more impulsive, while DLB subjects fitted more into a vigilance impairment profile (at a trend level, but significant in the quantitative analysis described in *section 4.1.3*) (Table 24 and Figure 36).

Table 24 Differences between the attentional profile between DLB and PDD.

	PDD (n = 15)	DLB (n = 10)	X^2	*p*-value
Inattention (score $\geq$ 6)	14 (93,3%)	6 (60%)	4.16	0.04* PDD < DLB
Impulsivity (score $\geq$ 2)	11 (73,3%)	4 (40%)	2.77	NS
Vigilance (score $\geq$ 1)	2 (13.3%)	4 (40%)	2.33	NS

Group comparison were performed by Pearson's Chi-square, *P<0.05. NS= not significant

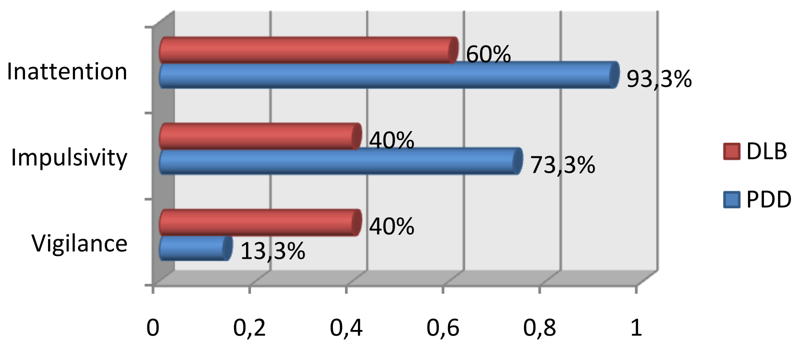

Figure 36. Comparison of the attentional profile in the CPT test between DLB and PDD patients (values are expressed as percentage of subjects with impairment as shows table 24).

4.2. STUDY II:

Frontal and associative visual areas related to Visual Hallucinations in Dementia with Lewy Bodies and Parkinson's Disease with Dementia

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Abstract

Visual Hallucinations (VH) are among the core features of Dementia with Lewy Bodies (DLB), but are also very frequent in demented patients with Parkinson's Disease (PDD). The purpose of the present study was to investigate the pattern of gray matter and cognitive impairment underlying VH in DLB and PDD. We applied voxel-based morphometry and behavioral assessment to 12 clinically diagnosed DLB patients and 15 PDD patients. Subjects with VH showed greater gray matter loss than non-hallucinators, specifically in the right inferior frontal gyrus (BA 45) in the DLB patients and in the left orbitofrontal lobe (BA 10) in the PDD patientsz. Comparing the two subgroups with VH, DLB patients had greater decrease of the bilateral premotor area (BA 6) than PDD patients. Furthermore, decreased volume in associative visual areas, namely left precuneus and inferior frontal lobe, correlated with visual hallucinations in the DLB but not in PDD patients. VH were related to impaired verbal fluency, inhibitory control of attention and visuoperception in the DLB group and to visual memory in the PDD group. In conclusion, DLB and PDD patients with VH had more frontal gray matter atrophy than non-hallucinators, the impairment being greater in the DLB group. The patterns of structural and functional correlations were different in both pathologies.

Key words: *visual hallucinations, Dementia, Lewy Body Disease, Parkinson's Disease, MRI, VBM.*

4.2.1. Introduction

LBD is a spectrum of disorders characterized pathologically by alpha-synuclein inclusions (Lewy bodies) in the brainstem, subcortical nuclei, limbic and neocortical areas and clinically by attentional disturbance, Parkinsonism, dementia and visual hallucinations (McKeith *et al.,* 2005). Disorders of a-synuclein aggregation are the second most common cause of neurodegenerative dementia after Alzheimer's disease (Daniel and Lees, 1993; McKeith *et al.,* 2005). Two clinical diagnoses within the LBD spectrum are DLB and PDD. DLB is diagnosed when dementia occurs before or concurrently with Parkinsonism. The term PDD is used to describe dementia that occurs in the context of well-established PD (McKeith *et al.,* 2005). The few studies addressing hallucination phenomenology in both disorders have reported well-formed complex VH of animals, objects, and humans in DLB and PDD (Aarsland *et al.,* 2001; Barnes and David, 2001; Mosimann *et al.,* 2006) with an estimated prevalence between 50-80% (Emre, 2003; McKeith and Mosimann, 2004; Diederich *et al.,* 2009).

Several theories have been proposed regarding the occurrence of VH in PD. The Perception and Attention Deficit (PAD) model (Collerton *et al.,* 2005) pointed to a combination of attentional and object perception deficits. Other studies supported the role of impaired inhibitory control of attention (Santangelo *et al.,* 2007; Barnes and Boubert, 2008) and frontal dysfunction in the development of VH (Nagano-Saito *et al.,* 2004; Grossi *et al.,* 2005; Santangelo *et al.,* 2007; Barnes and Boubert, 2008). The Integrative model (Diederich *et al.,* 2005; Diederich *et al.,* 2009) relates hallucinations to a deregulation of the gating and filtering of external perception and internal image production. The combination of degraded visual information about the environment, plus impaired source monitoring, together with failing memory which on occasion "fill in" for missing detail, provide the basis for VH (Barnes *et al.,* 2003).

Regarding the clinical correlations of VH, the results are consistent and show that patient's age, disease and treatment duration, cognitive impairment, depression, motor severity, sleep disturbances and visuoperceptual dysfunction are predictive factors of the appearance of VH (Klein *et al.,* 1997; Aarsland *et al.,* 2001; Barnes and David, 2001; Holroyd *et al.,* 2001; McKeith *et al.,* 2005; Grossi *et al.,* 2005; Diederich *et al.,* 2005; Mosimann *et al.,* 2006; Matsui *et al.,* 2006b; Diederich *et al.,* 2009). Furthermore, one study has shown that dementia and the severity of parkinsonism were related to the presence of VH in PD but not in DLB (Aarsland *et al.,* 2001).

To our knowledge, no studies to date have assessed structural differences between DLB and PDD with and without VH, or have tried to assess the relationship between gray matter changes and visual hallucinations in DLB or PDD. Only one single study assessed VBM characteristics in PD patients with and without hallucinations reporting larger gray matter reductions in areas involved in higher visual processing (Ramirez-Ruiz *et al.,* 2007b). The few metabolic studies in DLB patients with VH showed hypometabolism in visual association and frontal areas (O'Brien *et al.,* 2005; O'Brien *et al.,* 2008; Perneczky *et al.,* 2008a) when compared to non-VH DLB patients. None of these studies however explored structural or metabolic brain changes underlying VH in PDD alone. One study found a correlation between the hypometabolism in visual association areas and the amount of lewy pathology in the brain (Higuchi *et al.,* 2000).

The only study of cognitive functions in DLB patients with VH carried out to date (Mori *et al*., 2000) showed more visuoperceptual impairment than in DLB patients without hallucinations. However, some studies reported that frontal dysfunction, assessed by phonological and semantic verbal fluency tasks, may predict the development of hallucinations or dementia over the course of Parkinson's Disease (Santangelo *et al.,* 2007; Ramirez-Ruiz *et al.,* 2007a) suggesting that executive dysfunction may be considered a risk factor for the development of hallucinations in PD (Grossi *et al.,* 2005; Santangelo *et al.,* 2007; Barnes and Boubert, 2008; Imamura *et al.,* 2008).

An increased number of Lewy Bodies in the anterior frontal, temporal and parietal cortex, the cingulate, the amygdala and the insula (Harding *et al.,* 2002a; Papapetropoulos *et al.,* 2006) has been associated with the presence and onset of VH. Furthermore, the secondary visual pathway revealed severer Lewy pathology than the primary visual pathway (Yamamoto *et al.,* 2006) in VH patients.

Neuroimaging techniques provide a direct means of identifying and characterizing in vivo the patterns of brain atrophy associated with VH in DLB and PDD. In the present study, we used VBM and behavioural assessment to evaluate the differences in local gray matter and cognitive impairment between patients with DLB and PDD with and without VH, and to assess the correlations between the gray matter volume, the cognitive functioning and the severity of VH in these groups of patients. Given that several studies have shown VH to be related to frontal structures and areas involved in higher visual processing, and at the cognitive level, to frontal dysfunction and visuoperceptual impairment, we expected to find more pronounced gray matter changes affecting frontal and visual associative areas in the two subgroups with VH.

4.2.2. Methods

Subjects

Twelve consecutive patients with DLB and 15 patients with PDD recruited from an outpatient movement disorders and dementia clinic (Department of Neurology, Bellvitge University Hospital, Barcelona, Spain) participated in this study. Some of these patients have participated in a previous study (Sanchez-Castaneda *et al.,* 2009). The local ethics committee approved the study and written informed consent was obtained from all the participants. Clinical diagnosis was established after a comprehensive multidisciplinary assessment by a neurologist and a neuropsychologist based on structured interview assessing background, risk factors, and clinical criteria. The conditions were diagnosed as follows: DLB according to the Consensus Criteria (McKeith *et al.,* 2005), PD by using the UK Brain Bank criteria (Daniel and Lees, 1993) and dementia due to PD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)(American Psychiatric Association, 2003). The MMSE was used as a general cognitive screening test, corrected according to age and education following published norms (Dufouil *et al.,* 2000) and Reisberg's GDS (Reisberg *et al.,* 1982) was used as a measure of cognitive decline. Inclusion criteria were problable DLB or PDD diagnosis, MMSE<24 and GDS<5. Cases with psychiatric illness, traumatic brain injury, alcohol or drug abuse or presence of focal lesions in MRI were excluded. The severity of Parkinsonian symptoms was assessed by the UPDRS-III (Fahn, 1987) and disease stage was estimated using the Hoehn and Yahr Scale (Hoehn and Yahr, 1967). We calculated a levodopa equivalent dose (levodopa and dopaminergic agonists) using previously published methods (Vingerhoets *et al.,* 2002). Three subjects were treated with antipsychotic medication (risperidone): in the DLB-VH group, one subject received a daily dosage of 1 mg and another 0.5 mg, and in the PDD-VH group one subject received a daily dose of 1 mg. The hallucinations subscale of the Neuropsychiatric Inventory (NPI) (Cummings *et al.,* 1994) was used to quantify the severity of VH, defined as frequency per severity scores (range 0-12), obtained from the clinician interview with the main caregiver. We also assessed them qualitatively by Burnes Questionaire (Barnes and David, 2001). Formed VH were defined as "repetitive involuntary images of people, animals or objects that were experienced as real during the waking state but for which there was no objective reality" (Collerton *et al.,* 2005). According to their scores in the NPI hallucinations subscale, patients were divided into hallucinators (DLB-VH and PDD-VH) if scores (severity x frequency) were higher than 2 (from 2 to 12) and non-hallucinators (DLB-nVH and PDD-nVH) if NPI scores were 0-1. Visual acuity was measured with the visual acuity subscale of the CORVIST battery

(Merle James, 2001). Demographic and clinical characteristics of the sample are shown in Table 25.

Table 25. Demographic and clinical characteristics of the sample

	DLB-nVH (n=6)	DLB-VH (n=6)	PDD-nVH (n=7)	PDD-VH (n=8)	X^2/U	*p*-value
Sex (M:F)	4:2	4:2	4:3	6:2	0.5	NS†
Age	71 (10.7)	70.17 (12.4)	70.6 (7.1)	75.3 (4.9)	2.1	NS††
Education	10.4 (8.8)	11 (3.5)	8 (8.6)	5.9 (4)	3.6	NS††
GDS	3.6 (0.8)	4.6 (0.8)	3.8 (0.9)	4.3 (0.9)	3.9	NS††
Corrected MMSE	21.2 (8.1)	17.5 (5)	23.5 (4)	21.5 (3.5)	4.1	NS††
UPDRS-III	26.2 (13.9)	28.1 (9.2)	29.5 (14.1)	39.3 (9.6)	5.9	NS††
Hoehn and Yahr	3 (0.7)	2.6 (0.5)	2.6 (1)	2.8 (0.6)	0.6	NS††
Dementia duration (months)	30 (11.8)	32.8 (17.7)	31 (24.7)	20.2 (11.5)	3.0	NS††
Disease duration (months)	30 (11.8)	32.8 (17.7)	66 (24.8)	40.5 (16.8)	8.4	P<0.05††b
Levodopa dose (mg)[a]	710 (560.5)	233.3 (258.1)	634.33 (336.8)	676 (220.1)	5.1	NS††
Visual acuity scale (max. 36)	29.6 (1.3)	23.3 (7.5)	18.8 (12.1)	17.7 (6.5)	7.2	NS††
Visual hallucinations (NPI)		4.3 (1.9)		4.5 (3.2)	20	NS†††

Values expressed as mean (SD). NS=not significant. †Pearson's Chi-square. ††Kruskal-Wallis. †††U-Mann Whitney.
Abbreviations: PDD, Parkinson Disease with Dementia; DLB, Dementia with Lewy Bodies; VH, visual hallucinations; nVH, non-visual hallucinations; GDS, Global Deterioration Scale; MMSE, Mini-mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale.
[a] including dopamine agonists
[b] DLB-VH, DLB-nVH, PDD VH < PDD-nVH

Brain imaging

MRI data were acquired on a 1.5 T Philips Intera machine obtaining 110 overcontiguous slices (TR=40 ms; TE=1.79 ms; FA=35º; voxel size=0.98x0.98x1.3mm^3) (Sanchez-Castaneda *et al.,* 2009). The statistical MRI analyses were carried out using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) running under Matlab 6.5 (MathWorks, Natick, MA). A VBM analysis was used to assess the pattern of gray matter changes. The preprocessing steps included normalization of the images to a template, segmentation into tissue classes, modulation with Jacobian determinants and smoothing with an isotropic 8mm Gaussian kernel filter. The resulting smoothed and modulated images were used in the statistical analysis to assess gray matter volume changes.

Differences in gray matter between groups were assessed using the full factorial design implemented in SPM5 with two fixed factors (clinical group and presence of VH) including total intracranial volume as covariate. Since age and duration of dementia have been shown to be risk factors for developing VH and there are differences between groups in the disease duration, we included these variables into the analysis to control for their effect. To perform the comparisons, we selected the gray matter regions of interest (ROIs) that have previously been found to be related to visual hallucinations (Nagano-Saito *et al.,* 2004; Papapetropoulos *et al.,* 2006; Yamamoto *et al*., 2006; Boecker *et al.,* 2007; Ramirez-Ruiz *et al.,* 2007b; Ramirez-Ruiz *et al.,* 2008; O'Brien *et al.,* 2008; Perneczky *et al.,* 2008a; Perneczky *et al.,* 2008b). ROIs were located in 4 regions of the right and left hemispheres: frontal (BA 6, 8, 9, 10, 44, 45 and 47), occipital (BA 18, 19), parietal (BA 7, 39, 40) and temporal (20)) regions. The ROIs were automatically traced using the Pick Atlas tool version 2.4 from the SPM package. To perform the correlation analysis, we used the multiple regression design implemented in SPM5. For this analysis we defined the same ROIs as for the group comparison.

For all the statistical analyses, the threshold was settled at voxel and cluster levels $p<0.05$ FWE corrected for multiple comparisons.

Neuropsychological assessment

All patients underwent a neuropsychological assessment based on four cognitive domains related to visual hallucination in the literature: attention/executive functions, visuospatial/visuoperceptive functions, visual memory and constructional abilities. The battery consisted of the Stroop test, that evaluates selective attention and response inhibition. It is based on the fact that it takes longer to call out the color of the ink in which a color name is printed when the ink is of a different color than the color name (word). Verbal fluency tests measure speed and ease of verbal production, namely the number of words produced within a restricted category (in this case animals and word beginning with “p”) in one minute. The Cortical Vision Screening test (CORVIST) (Merle James, 2001) is designed to probe the higher visual areas of the brain and detect visual impairment in individuals with normal vision. To assess visual memory and constructional praxis, we used some subtests from the CERAD battery. In the constructional praxis task the subject is instructed to copy four geometrical figures; the delayed visual memory task consisted of the recall of these figures. All tests were administered and scored in accordance with conventional procedures (Lezak, 2004).

The statistical analysis of the neuropsychological data was conducted using SPSS (11.5, SPSS Inc.). Because of the sample size and the non-linear distribution of the variables, we used the Spearman test to assess the correlations between the presence of visual hallucinations and the cognitive variables including age, dementia duration and disease duration as covariates.

4.2.3. Results

Differences in brain volume between groups

The gray matter volume comparisons between groups are shown in Table 26 and Figure 37. The table presents the contrasts that achieved statistical significance at voxel and cluster level.

DLB patients with VH had reduced gray matter volume in the right inferior frontal gyrus (BA 45) compared with non-hallucinators. In turn, PDD patients with VH had reduced gray matter volume in the left orbitofrontal cortex (BA 10) compared with non-hallucinators. This difference disappeared when we entered the age as covariate, suggesting that age may be related to the developing of VH in PD with dementia.

Comparisons of the two subgroups with VH, covarying age, dementia duration and disease duration, showed that DLB patients had more atrophy in the premotor region bilaterally (BA 6) than PDD patients.

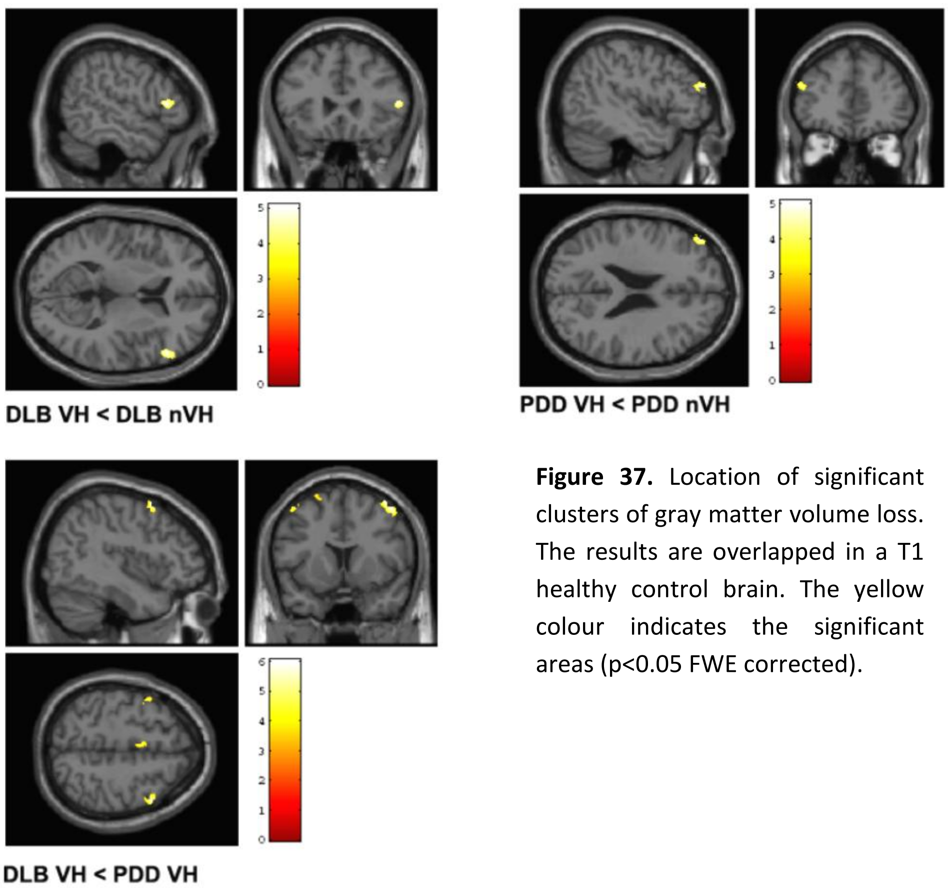


Figure 37. Location of significant clusters of gray matter volume loss. The results are overlapped in a T1 healthy control brain. The yellow colour indicates the significant areas (p<0.05 FWE corrected).

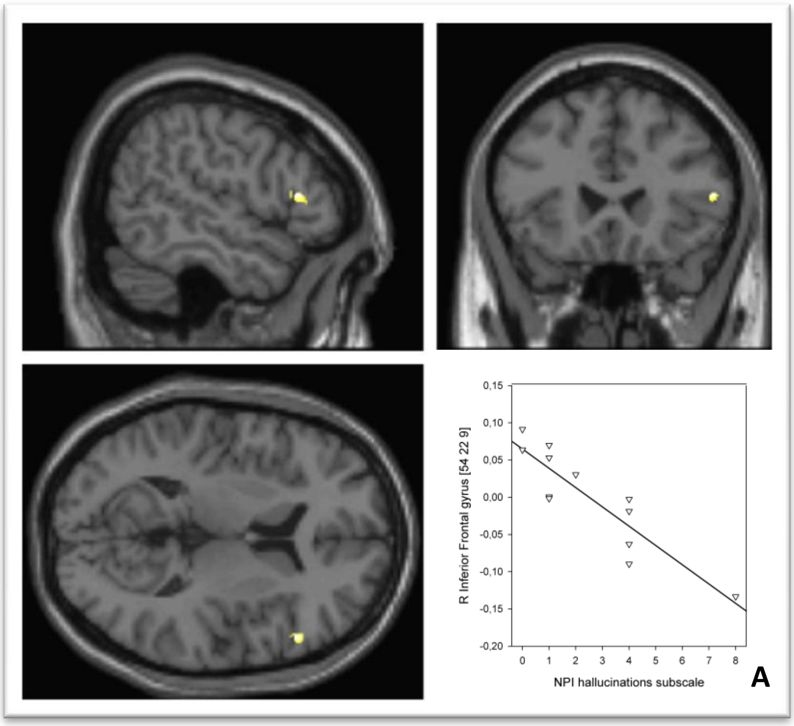
Table 26. Stereotactic locations and Brodmann areas (BA) of significant differences in brain volume between groups

Region (BA)	Cluster $p_{corrected}$	Cluster size (mm^3)	Talairach coordinates (x,y,z)	T-value*
Including TIV as covariate				
DLB VH < DLB nVH				
Right inferior frontal (45)	0.04	79	54,25,7	4.23
PDD VH < PDD nVH				
Left orbitofrontal (10)	0.01	351	-45,47,17	5.08
including TIV, dementia duration, disease duration and age as covariates				
DBL VH < DLB nVH				
Right inferior frontal (45)	0.001	524	54,27,7	5.11
DLB VH < PDD VH				
Right premotor area (6)	0.003	622	40,12,57	6.07
Left premotor area (6)	0.01	318	-45,-10,52	5.80

**Significance threshold p<0.05 voxel-level corrected for multiple comparisons (FWE).*
Abbreviations: PDD, Parkinson Disease with Dementia; DLB, Dementia with Lewy Bodies; VH, visual hallucinations; nVH, non-visual hallucinations

Correlation between visual hallucinations and gray matter volume

In the DLB group, we found significant correlations between severity of visual hallucinations and the gray matter volume reduction in the right inferior frontal gyrus (BA 45; r=0.89) and left precuneus (BA 7; r =0.95) (Figure 38). We did not find any significant correlation in the PDD group.



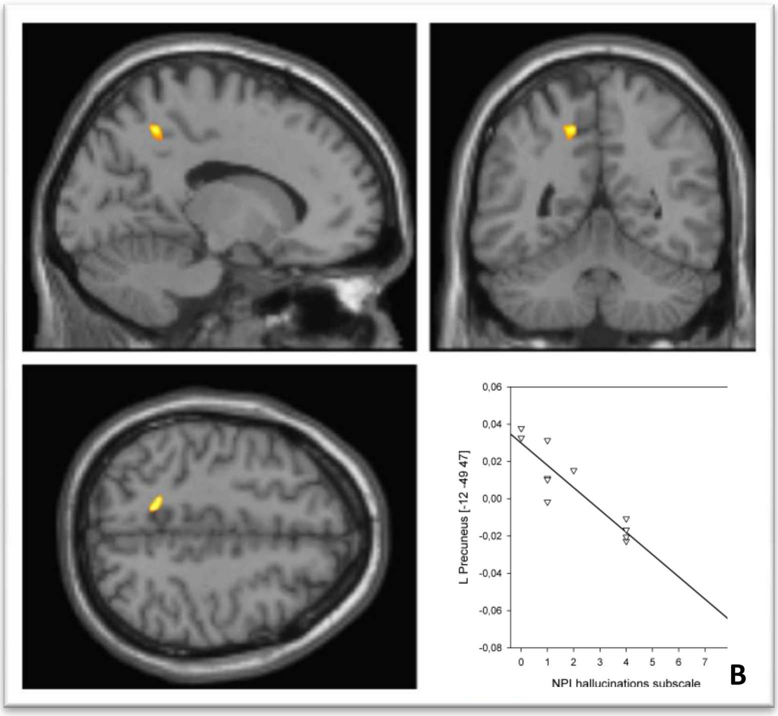


Figure 38. Relationship between volume decrease and severity of hallucinations. A) Right inferior frontal gyrus (BA 45; Talairach coordinates = 54, 22, 9; cluster size = 116; r=0.89; p=0.01); B) Left precuneus (BA 7; Talairach coordinates = -12, -49, 47; cluster size = 267; r=0.95; p=0.004) in DLB patients (N=12). Significance threshold p<0.05 voxel and cluster level corrected for multiple comparisons (FWE). DLB-nVH (scores 0-1); DLB- VH (scores 2-8).

Correlation between visual hallucinations and cognitive performance

Significant correlations between cognitive functions and severity of VH are shown in Table 27. There were significant correlations between the severity of visual hallucinations and impairment in semantic verbal fluency (p=0.006), inhibitory control of attention (Stroop WC) (p=0.004) and visuoperception (Hue discrimination) (p=0.03) in the DLB group and between visual hallucinations and visual memory (p=0.02) in the PDD group. Controlling for the effect of age, dementia duration and disease duration, only the correlations between semantic verbal fluency and inhibitory control of attention in the DLB group remained significant (p= 0.02 and 0.04 respectively).

Table 27. Correlation between the severity of visual hallucination (NPI) and cognitive impairment

Cognitive test	Correlation Coefficient	p-value
DLB group		
Semantic verbal fluency	-0,74	0.006*
Phonetic verbal fluency	-0,55	0.06
Inhibition control of attention (Stroop WC)	-0,78	0.004*
Visuoperception (Hue Discrimination - CORVIST)	-0,63	0.03
PDD group		
Visual memory (CERAD)	-0,59	0.023

*STROOP WC, Stroop Word-color; CORVIST, Cortical Vision Screening test; CERAD, Consortium to establish a registry for Alzheimer Disease. * p<0.05 after including age, disease duration and dementia duration as covariates.*

4.2.4. Discussion

In the present study we aimed to describe the regional distribution of gray matter atrophy and cognitive functions underlying VH in a sample of DLB and PDD patients by using VBM and a behavioral assessment. To our knowledge, our study is the first to investigate brain structure and cognitive changes associated with VH in DLB and PDD patients. Our findings support the hypothesis that VH in Lewy Body Diseases are indeed related to changes in brain morphology.

We found that patients with VH had greater atrophy in specific cortical regions than non-hallucinators. In particular, DLB patients with VH had greater gray matter reductions in the right inferior frontal lobe (BA 45) and PDD patients with VH in the left orbitofrontal area (BA 10). These results were confirmed by the correlation analysis, where we found a correlation between the severity of VH and the right BA 45 gray matter decrease in the DLB group. Furthermore, comparing the two groups with VH, DLB patients had greater gray matter loss in the premotor area (BA 6) bilaterally than PDD patients. These results demonstrate the involvement of frontal lobes in the presence of visual hallucinations in DLB and PDD and thus lend support to both the PAD and Integrative models of VH (Collerton *et al.,* 2005; Diederich *et al.,* 2005). A previous study in PD patients showed structural changes in more posterior regions (Ramirez-Ruiz *et al.,* 2007b). A possible explanation for these different findings may be that in the initial stages of the disease the main gray matter loss is posterior extending to frontal structures in the later stages when dementia progresses. Metabolic studies in DLB and PD with VH have shown both anterior and posterior patterns (Higuchi *et al.,* 2000; Nagano-Saito *et al.,* 2004; Stebbins *et al.,* 2004; O'Brien *et al.,* 2005; Matsui *et al.,* 2006a; Boecker *et al.,* 2007; O'Brien *et al.,* 2008; Perneczky *et al.,* 2008a) of impairment. We suggest there might be two different mechanism at the basis of VH, 1) the impairment of posterior visual associative areas that triggers visual hallucination as means of a defective visual perception in line with the Attention and Perception model (Collerton *et al*., 2005), and 2) a frontal impairment related to the insight and consciousness of the hallucinations according to the Integrative model (Diederich *et al.,* 2005). This latter model indeed relates hallucinations to a difficulty in establishing the external or internal source of perceptions due to a deregulation of the gating and filtering of external perceptions and/or aberrant internal image production. Moreover, a previous longitudinal study (Ramirez-Ruiz *et al.*, 2005) failed to find correlations between the presence of VH and the temporo-occipital gray matter volume in a group of 8 hallucinating PDD patients neither at baseline nor at the follow-up evaluation. Furthermore, Stebbins et al. (2004) already proposed that a shifting visual circuitry from posterior to anterior regions associated with attentional processes may play a role in the pathophisiology of VH in PD. Superior frontal regions, specifically the frontal-eye-fields (BA 6), receive inputs from the striatum and form reciprocal connections with the parietal lobe and the prefrontal cortex and may further mediate visual attention (Goldberg and Goldberg, 2000).

We also found a relationship between left precuneus (BA 7) and right inferior frontal lobe (BA 45) gray matter decrease and severity of visual hallucinations in the DLB group. These results supports the role of the associative visual areas in VH in DLB patients in agreement with those reported by Pernezcky et al. using 18F-FDG PET (Perneczky *et al.,* 2008a; Perneczky *et al.,* 2008b), who suggested that hypometabolism in visual association and frontal areas, namely the right middle frontal gyrus and right BA 6, 9 and 45, was related to VH and delusions in DLB patients. Furthermore, there is neuropathological evidence of LB burden in fronto-parietal areas (Papapetropoulos *et al.,* 2006; Yamamoto *et al.,* 2006) and functional neuroimaging studies showing abnormalities in frontal regions and visual pathways (Nagano-Saito *et al.,* 2004; Stebbins *et al.*, 2004; Boecker *et al.,* 2007; Ramirez-Ruiz *et al.,* 2008) in the brains of PD patients with VH suggesting that a degeneration of the secondary visual areas underlies the presence and onset of visual hallucinations inducing dysfunction in the recognition of objects, shape and colors (Yamamoto *et al.,* 2006). Structurally, the superior parietal lobe has been related to VH in PD (Ramirez-Ruiz *et al.,* 2007b).

These brain areas have been associated with response inhibition, visual discrimination, executive attention (Nagano-Saito *et al.,* 2004; Lezak, 2004; Picton *et al.*, 2007; Sanchez-Castaneda *et al.*, 2009) and internal attributions of events (Blackwood *et al.,* 2000). Areas 6 and 45 are specifically involved in response inhibition and in the monitoring of performance (Picton *et al.,* 2007; Sanchez-Castaneda *et al.*, 2009), the impairment of them would give support to the PAD (Collerton *et al.,* 2005) and the Integrative (Stebbins *et al.,* 2004; Diederich *et al.,* 2005; Diederich *et al.,* 2009) models of VH. Furthermore, have been shown that PD Patients with VH respond to visual stimuli with increased frontal activity and decreased visual cortical activation (Stebbins *et al.*, 2004). So, the structural changes affecting these areas in our DLB patients could lead to the visual attentional impairment and inhibitory control deficit associated with VH.

With regard to the neuropsychological data, we found that the severity of visual hallucinations was correlated with impairment in semantic verbal fluency, inhibitory control of attention and visuoperceptive deficits in the DLB group and with visual memory in the PDD group. These results support the PAD hypothesis (Collerton *et al.*,

2005) that relates VH to an inhibition control deficit of attention and defective visual perception and are in agreement with the longitudinal studies describing frontal dysfunction, specifically verbal fluency, as a predictor of the development of hallucinations in Parkinson's Disease (Santangelo *et al.,* 2007; Ramirez-Ruiz *et al.*, 2007a). Following this hypothesis, it could be that in the DLB group a deficit of the inhibitory control of attention allows the intrusion of a hallucinated object into a scene perception, whereas in PDD hallucinations may be related to a memory deficit that fills in for missing details (Barnes *et al.,* 2003).

All together, in the present study DLB and PDD patients have different patterns of gray matter and cognitive correlations. Whereas in DLB, VH are related to a fronto-parietal gray matter reduction and to frontal and visuoperceptive cognitive impairment, in PDD are related to frontal structures in a lesser extent and to visual memory deficits. It seems that a combination of deficits is needed to develop visual hallucinations as suggested by the Integrative and the PAD models of VH (Collerton *et al.,* 2005; Diederich *et al.,* 2005; Diederich *et al.,* 2009).

However, a limitation of the present study is that the sample size limits a generalization of the results to wider PDD and DLB populations. In addition, the groups differed on several features that may have influenced our findings. That for, it may not be possible to conclude that the two pathologies have different patterns of atrophy related to hallucinations. Further studies on bigger populations are needed to confirm these preliminary observations.

4.2.5. Complementary results

<u>Differences in Behavioral Scales</u>

Fluctuation Scales

To date, two scales have been develop to assess the fluctuations in cognition characteristics of DLB, the One Day Fluctuation Assessment Scale (ODFAS) and the Clinician Assessment of Fluctuations (CAF) (Walker *et al.,* 2000). All patients underwent those scales together with the NPI scale.

The CAF scale is divided in two sub-items, one assessing the frequency of the fluctuations, and the second one assessing the duration of fluctuations. However, the ODFAS scale goes deeper in qualitative details of the cognitive fluctuations.

Results

Regarding the cognitive fluctuations we found that DLB patients had greater scores in all scales, but the differences were only significant for the first scale of the CAF test, assessing the frequency of the fluctuations (see Table 28).

Table 28 Differences in fluctuations in cognition between groups.

	PDD (n = 16)	DLB (n = 12)	*t*	*p*-value
CAF (scale 1)	2.69 (1.19)	3.5 (0.52)	-2.2	0.037* PDD < DLB
CAF (scale 2)	2 (1.46)	3 (1.2)	-1.9	0.06
ODFAS	6.63 (3.98)	6.75 (4.39)	-0.07	NS

Values expressed as mean (SD). Group comparison were performed by Student t-test, *P<0.05. NS= not significant

GENERAL DISCUSSION

5. General Discussion

Lewy Body Disease is a relatively recent entity that was first described from the pathological point of view as being characterized for LB inclusions. The most representative diseases within this pathological group are DLB and PDD. There is some controversy in the literature as to whether they should be considered as two separate disorders or as two different phenotypes of the same disease continuum. Additionally, to the best of our knowledge, non study to date has investigated the brain structural changes related to cognitive performance and VH in DLB and PDD patients. This uncertainty highlights the need for a prospective study addressed to identify the clinical, cognitive and behavioral characteristics of DLB and PDD in relation to the brain changes in MRI.

Therefore, in the first study, we aimed to characterize the pattern of gray matter loss accompanying DLB and PDD, and its relationship with cognitive impairment. In the second study we intended to determine the brain changes and cognitive impairment underlying visual hallucinations in this sample.

We found that DLB patients had a consistent gray matter volume reduction in the right inferior frontal gyrus (BA 45), left posterior cingulate, left superior temporal (BA 38) and left inferior parietal (BA 39) gyri related to healthy control subjects, whereas PDD patients had gray matter loss in the right cuneus (BA18) and left inferior parietal gyrus (39). Though we found different patterns of impairment in both diseases, frontal and parieto-temporal in DLB patients, and more posterior, embracing only parietal and occipital areas, in PDD patients, the gray matter loss was limited to associative areas, in agreement with neuropathological studies that indicated LB accumulations in the neocortex of DLB and PDD patients in frontal and high order associative areas (Braak *et al.,* 2006b; Papetropoulos *et al.,* 2006).

Moreover, we found that DLB patients had decreased frontal volume in comparison with PDD patients, specifically in the right superior frontal (BA 8), right premotor (BA 6) and right inferior frontal (BA 45) areas. Interestingly, these areas were also related with VH in DLB patients in our sample: DLB patients with VH had decreased gray matter in the right inferior frontal gyrus (BA 45) than DLB patients without VH, and in the premotor area bilaterally in comparison with hallucinating PDD patients. However, PDD patients with VH had less orbitofrontal lobe (BA 10) volume compared with PDD patients without VH, though these differences disappeared when corrected for the effect of age. These results support the hypotheses that DLB patients present greater gray matter loss in frontal regions than PDD patients, and that VH in LBDs are indeed related to changes in brain morphology, restricted also to the frontal lobe. Still, these results were confirmed by the correlation analysis, where we found a correlation between the severity of VH and the right BA 45 gray matter decrease in the DLB group. Previous studies have also shown decreased volumes of fronto-parietal areas in DLB patients compared with control subjects (Burton *et al.,* 2002; Ballmaier *et al.,* 2004; Whitwell *et al.,* 2007b) and in PDD patients compared with PD patients (Burton *et al.*, 2004; Nagano-Saito *et al.*, 2005; Beyer *et al.,* 2007a; Beyer and Aarsland, 2008). However, only one study to date has found cerebral structural differences between DLB and PDD patients (Beyer *et al.,* 2007b) in temporal, parietal (including precuneus) and occipital areas, while Burton *et al.* (2004) found no differences between groups.

Additionally, the single-case analysis revealed a gray matter volume loss involving hippocampus bilaterally in DLB and PDD patients in comparison with control subjects. The frequency of hippocampal decrease was similar in both disorders for the left side, but significantly more frequent in the right side in DLB patients. MRI and neuropathological studies have already described a hippocampal asymmetry that is even present in utero, with the right hippocampus being larger than the left (Xu *et al.,* 2008); however, some developmental, pathological and dementing diseases are associated with alteration and reversal of this normal anatomical asymmetry (Geroldi *et al*., 2000; Barber *et al.,* 2001). Barber *et al.* (2001) showed how this asymmetry disappeared in DLB patients. This evidence is consistent with our finding of a greater prevalence of atrophy in the right hippocampus in DLB compared to PDD, reversing the regular anatomical pattern, whereas we found no significant differences in the frequency of impairment in the left hippocampus. Neuropathological studies have found that the medial temporal lobe is sensitive to the accumulation of Lewy Bodies (Harding *et al.,* 2002b), specifically in CA2/3 hippcampal areas (Jellinger, 2006). MRI studies have also consistently described hippocampal atrophy in DLB (Hashimoto *et al.,* 98; Burton *et al.,* 2002; Tam *et al.,* 2005; Sabatoli *et al.,* 2008; Burton *et al.,* 2009) and PDD patients (Tam *et al.,* 2005; Summerfield *et al.,* 2005; Junque *et al.,* 2005; Ibarretxe-Bilbao *et al.,* 2008; Aybeck *et al.,* 2009).

When exploring the brain-behavior relationship in the DLB group, reduced volumes of the inferior frontal lobe (BA 45), dorsolateral prefrontal cortex (BA 9/46) and anterior cingulate were related to the attentional impairment, expressed by an increased number of commission errors, perseverations and worse detectability on the CPT test. In addition, in the same group a decrease in left precuneus (BA 7) and right inferior frontal

(BA 45) volume was related to the presence and severity of VH. However, we did not find any significant correlation in the PDD group. These results support the role of the frontal lobe in attentional function, which, together with the associative visual areas, contribute to the appearance of VH in DLB patients. These frontal areas (inferior frontal, dorsolateral frontal and anterior cingulate) have been associated to response inhibition, executive attention and internal attributions of events (Nagano-Saito *et al.,* 2004; Lezak, 2004; Petrides, 2005; Fan *et al.,* 2005; Picton *et al.,* 2007; Blackwood *et al.,* 2000). Brodmann areas 6 and 8 have also been implicated in the circuitry of visual discrimination and attention (Petrides, 2005), and areas 6 and 45 are specifically involved in response inhibition and in the monitoring of performance (Picton *et al.,* 2007). Superior frontal regions, specifically the frontal-eye-fields (BA 6), receive inputs from the striatum and form reciprocal connections with the parietal lobe and the prefrontal cortex and may further mediate visual attention (Goldberg and Goldberg, 2000). This fronto-parietal network have been related to orienting attention in healthy subjects (Shulman *et al.,* 2009). Using 18F-FDG PET, Perneczky *et al.* (2008a; 2008b) reported that hypometabolism in visual association and frontal areas, namely the right middle frontal gyrus and right BA 6, 9 and 45, was related to VH and delusions in DLB patients. Furthermore, functional neuroimaging studies have shown abnormalities in frontal and visual associative areas in the brains of PD patients with VH (Nagano-Saito *et al.,* 2004; Stebbins *et al.,* 2004; Boecker *et al.,* 2007; Ramirez-Ruiz *et al.,* 2008; Meppelink *et al.,* 2009) suggesting that the degeneration of the secondary visual areas is related to the presence and onset of visual hallucinations, inducing dysfunction in the recognition of objects, shape and colors (Yamamoto *et al.,* 2006). Structurally, the superior parietal lobe has been related to VH in PD (Ramirez-Ruiz *et al.,* 2007b). Evidence of LB burden in fronto-parietal areas has also been shown in PD patients with VH (Papapetropoulos *et al.,* 2006; Yamamoto *et al.,* 2006) and metabolic studies in DLB and PD with VH have shown both an anterior and posterior pattern of cortical involvement (Higuchi *et al.,* 2000; Nagano-Saito *et al.,* 2004; Stebbins *et al.,* 2004; O'Brien *et al.,* 2005; Matsui *et al.,* 2006a; Boecker *et al.,* 2007; O'Brien *et al.,* 2008; Perneczky *et al*., 2008a).

Therefore, we propose that the structural changes affecting these areas in DLB patients may lead to the visual attentional impairment considered as a core feature of DLB, and to an inhibitory control deficit that may trigger the appearance of VH. Thus, the impairment of these regions would lend support to both the Perception and Attention Deficit (PAD) and Integrative models of VH (Collerton *et al.,* 2005; Diederich *et al.,* 2005) which hypothesize that a combination of deficits is needed for VH to develop. The first suggests that a combination of attentional and visuoperceptive deficits is essential to the occurrence of VH, whereas the second stresses an impairment of the forebrain's reality-control system, which causes a difficulty in establishing the external or internal source of perceptions due to a dysregulation of the gating and filtering of external perceptions and/or aberrant internal image production. We suggest that there might be two different mechanisms underlying VH: 1) the impairment of posterior visual associative areas which triggers visual hallucination as means of a defective visual perception in line with the Attention and Perception model (Collerton *et al.,* 2005), and 2) a frontal impairment related to the insight and consciousness of the hallucinations according to the Integrative model (Diederich *et al.,* 2005). A recent study from Meppelink *et al.* (2009) also confirmed the hypoactivation of frontal and parieto-occipital structures in the visual perception of PD patients with VH.

Moreover, in our DLB sample, the gray matter decrease of right medial temporal lobe structures (hippocampus and amygdala) correlated to the visual memory performance. However, we found no relationship between verbal memory and brain structure in the DLB group as there was not enough within-group variability in the delayed memory task, which was severely impaired (83.3% of subjects were not able to remember any words after a delayed period). These findings provide support to the classical theories that relate hippocampal volume to memory impairment (Riekkinen *et al*., 1998; Barber *et al.,* 2001; Camicioli *et al.,* 2003; Lezak, 2004; Junque *et al.*, 2005; Bouchard *et al.*, 2008; Kenny *et al.,* 2008; Aybeck *et al.,* 2009; Jokinen *et al.,* 2009).

With regard to the neuropsychological data, interestingly we found a different attentional profile: whereas DLB was characterized by distractibility during performance of the CPT (patients presented poorer vigilance, and therefore slower reaction times as the task progressed); PDD patients showed more impulsivity on both the attentional and memory tasks (more perseverations on the CPT test and more intrusions during delayed recall. Furthermore, they were more erratic as the time between stimulus increased, related to their impulsivity). Likewise, in the qualitative analysis of the attentional profile, we observed that PDD patients were more frequently inattentive and impulsive than DLB patients, even though the differences in impulsivity were not significant, whereas DLB subjects tended to be less vigilant than PDD (at a trend level, but significant in the quantitative analysis). All PDD patients but one had high scores in inattention, which may have been influenced by the motor impairment present in these patients as these scores are influenced by slow reaction times.

These results are in agreement with other studies reporting impairment in attentional tasks both in DLB (Noe *et al.,* 2004; Kraybill *et al.,* 2005; Bradshaw *et al.,* 2006; Mondon *et* *al.,* 2007) and PDD patients (Caviness *et al.,* 2007; Song *et al.,* 2008; O'Brien *et al.,* 2009; Filoteo *et al.,* 2009). Noe *et al.* (2004), reported difficulty in processing visuospatial information among DLB subjects, who tended to commit more omission errors in cancellation tasks than PDD; and Mondon *et al.* (2007) also showed more attentional deficits in DLB patients in measures of orientation, sustained attention and inhibitory control of attention (Stroop test). In contrast, other studies found more pronounced attentional disturbances and greater percentage of perseverations in PDD patients than in DLB patients (Bronnick *et al.,* 2008; Filoteo *et al.,* 2009). These discrepancies could be due to the sensorial modality and the aspects of attention studied through the different tasks: Bronnick *et al.* (2008) used auditory stimuli, while the others used visual stimuli. In addition the different tasks used measured different components of attention. Moreover, Bradshaw *et al.* (2006) showed that the attentional deficits in DLB patients were more pronounced in tasks that required more executive control and visuospatial cognitive processes. These finding are in harmony with our results, that reported attentional deficits in both DLB and PDD patients, but the attentional profile is different in both diseases.

The attentional impairment observed in the DLB sample could be explained by our VBM results, in which the anterior cingulate and prefrontal volume correlated with performance on the CPT test. These findings are consistent with the model postulated by Posner and Rothbart, (2007) suggesting a role for the anterior cingulate in the executive control of attention to unpredictable events and inhibitory control. LB pathology is usually localized in frontal, cingulate and infero-medial temporal lobes, areas which are related to attention, executive function and visual object recognition performance (Fan *et al.,* 2002).

We also found a different pattern of memory impairment: the DLB group tended to perform worse on free recall and overall recognition suggesting an encoding deficit that is more related to hippocampal structures. However, our PDD group made more intrusion errors in delayed memory but presented better functioning in free recall and recognition. Previous studies have shown worse immediate and delayed recall and more rapid rate of forgetting but similar recognition in DLB patients than in PDD patients (Mondon *et al.,* 2007; Filoteo *et al.,* 2009). These findings support the results of Higginson *et al.* (2005) who described false positive errors in cued recall and recognition in patients with PD associated with frontal dysfunction and reduced inhibition. Executive functions have been shown to be predictive of list learning in PDD patients (O'Brien *et al.,* 2009). These deficits in memory could be associated with the atrophic changes observed involving prefrontal and hippocampal areas and the disruption therefore of the direct hippocampal output to the dorsolateral prefrontal cortex which is affected in DLB (Harding *et al.,* 2002b).

We found that the severity of visual hallucinations was correlated with impairment in semantic verbal fluency, inhibitory control of attention and visuoperceptive deficits in the DLB group and with visual memory in the PDD group. These results support the *PAD* hypothesis (Collerton *et al.,* 2005) which relates VH to an inhibition control deficit in attention and defective visual perception and are in agreement with the longitudinal studies that identify frontal dysfunction, specifically verbal fluency, as a predictor of the development of hallucinations in PD (Santangelo *et al.,* 2007; Ramirez-Ruiz *et al.,* 2007a). Following this hypothesis, it could be that in the DLB group a deficit in the inhibitory control of attention allows the intrusion of a hallucinated object into a scene perception, whereas in PDD hallucinations may be related to a memory deficit that fills in for missing details (Barnes *et al.,* 2003).

Taken together, this thesis provides evidence of the presence of different patterns of gray matter and behavioral correlations in DLB and PDD patients. In the first study, we showed that in DLB there is an impairment of the frontal, temporal and parietal regions related to attention and visual memory impairment; whereas PDD patients have a larger decrease of parieto-occipital gray matter and are cognitively characterized by greater impulsivity. In DLB patients, visual hallucinations are related to fronto-parietal gray matter reduction and to frontal and visuoperceptive cognitive impairment, while in PDD they are related to frontal structures to a lesser extent and to visual memory deficits. This thesis gives support to the hypothesis that a combination of deficits is needed to develop visual hallucinations in DLB and PDD patients, as suggested by the *Integrative* and the *PAD* models of VH (Collerton *et al.,* 2005; Diederich *et al.,* 2005; Diederich *et al.*, 2009).

This investigation has some limitations. One of the limitations is the small sample size and the selection bias (depending on the study) regarding sex distribution, age and education in the different groups. Furthermore, they showed a different distribution in clinical variables such as the duration of parkinsonism and the degree of motor impairment. The difference in parkinsonism duration and degree of motor impairment are a consequence of the inclusion and diagnostic criteria: to be diagnosed of PDD subjects had to have a well-established parkinsonism of more than one year's duration but this requirement was not made in DLB. To minimize the effect of these potential confounders, we included them as covariates in the analyses performed (when convenient). Furthermore, a new sample is being recruited with a 3 Tesla scanner and a more complete MRI protocol including structural imaging, diffusion tensor imaging and functional MRI is being acquired to further characterize the neuroanatomical basis of those disorders.

CONCLUSIONS

6. Conclusions

The main conclusions of this thesis, derived from study I and II can be summarized as follows:

I. PDD and DLB patients have different patterns of regional atrophy. Compared to controls, PDD have gray matter reductions in parieto-occipital regions and DLB patients in frontal, temporal and parietal regions. Moreover, DLB patients have greater gray matter loss than PDD in several frontal areas, namely the right inferior frontal, right superior frontal and right premotor areas.

II. In the individual analyses, both PDD and DLB patients present bilateral hippocampal gray matter loss, but the frequency of right hippocampus gray matter reduction is higher in DLB than in PDD.

III. The presence of visual hallucinations (VH) is related to gray matter decrease in frontal regions in both groups, but in different areas. In DLB patients the decrease is located in the inferior frontal lobe and in PDD in the orbitofrontal region. In addition, the severity and frequency of VH correlate negatively with the inferior frontal lobe and precuneus regions in the DLB group.

IV. In the attentional profile, DLB patients have more distractibility, characterized by a poorer vigilance, while PDD patients show more impulsivity, reflected by perseverative and intrusive errors.

V. In the DLB group, the visual memory impairment is related to right medial temporal lobe gray matter decrease (hippocampus and amygdala), and attention deficits correlate with the anterior cingulate, inferior frontal and dorsolateral prefrontal cortex.

VI. In DLB patients, the presence and severity of visual hallucinations are related to impairment in semantic verbal fluency, the inhibitory control of attention and visuoperception, while in PDD patients they are related to visual memory deficits.

In both dementia groups, there are a different pattern of cortical gray matter loss and a different cognitive profile. Furthermore, each disease has a distinctive pattern of gray matter and behavioral correlations.

SUMMARY OF THE THESIS

RESUM DE LA TESI

7. Sumary of the thesis / *Resum de la tesi*

CANVIS EN L'ESTRUCTURA CEREBRAL, DÈFICITS COGNITIUS I AL·LUCINACIONS VISUALS EN LA DEMÈNCIA AMB COSSOS DE LEWY I LA MALALTIA DE PARKINSON AMB DEMÈNCIA

Introducció

Les malalties amb cossos de Lewy, són un conjunt de malalties caracteritzades neuropatològicament per la presència d'inclusions intracitoplasmàtiques que contenen α-sinucleïna en les neurones del tronc encefàlic, els nuclis subcorticals i àrees límbiques i neocorticals (McKeith *et al.,* 1996; 2005). S'anomena proteïnopaties a les malalties que es caracteritzen per una alteració estructural de diverses proteïnes. En aquest context, les sinucleïnopaties són malalties que es caracteritzen per una alteració del metabolisme de l'α-sinucleïna, que porta a la formació d'agregats proteics anomenats cossos de Lewy (Braak *et al.,* 2003; Cummings, 2003; Ferrer, 2009). L'agregament de proteïnes mutades s'ha descrit en un 70% de les demències i més del 90% de les malalties neurodegeneratives (Cummings, 2003). Tanmateix, els desordres de l'α-synucleïna representen entre un 10 i un 28,4% de les demències (Wakisaka *et al.,* 2003; McKeith *et al.,* 2005). Dues de les sinucleïnopaties més comuns són la Malaltia de Parkinson (MP) i la demència am cossos de Lewy (DCL). Donat que la MP cursa amb demència a mesura que evoluciona la malaltia (Williams-Gray *et al.,* 2007; Hely *et al.,* 2008; Aarsland *et al.,* 2009), i ambdues malalties, la MP amb demència (MPD) i la DCL presenten una clínica similar, hi ha controvèrsia respecte a si formen part del mateix espectre patològic o si són dues malalties diferents.

S'han descrit estadiatges neuropatològics per les dues malalties basats en la valoració semiquantitativa del patró de distribució i progressió de la patologia relacionada amb l'α-synucleïna (els cossos i els cabdells de Lewy). Ambdós estadiatges, l'estadiatge de Braak i Braak per la MP (Braak *et al.,* 2003; 2006) i els criteris de Consens per la DCL (McKeith *et al.,* 1996; 2005), es basen en l'assumpció de que la patologia amb cossos de Lewy es un *continuum* patològic, que afecta en primer terme a estructures del tronc encefàlic, progressant a estructures mesencefàliques, límbiques i finalment neocorticals, començant per les estructures de primer ordre associatives, i finalment afectant a tota l'escorça cerebral, incloent àrees sensorials i motores primàries (Braak *et al.,* 2003; 2006; McKeith *et al.,* 1996; 2005). Les inclusions a nivell de tronc cerebral es relacionen amb la simptomatologia motora extrapiramidal, mentre que l'aparició de trastorns cognitius i/o demència s'ha relacionat amb la presència de cossos de Lewy a àrees límbiques i neocorticals (Braak *et al.,* 2003; 2006b; Lippa *et al.,* 2007; Jellinger *et al.,* 2009a; 2009b).

Degut a la similaritat de la simptomatologia que presenten, resulta difícil la diferenciació clínica entre MPD i DCL. L'estudi neuropatològic és útil en ocasions però només es pot realitzar postmortem. Per aquest motiu, les tècniques de neuroimatge cerebral representen una tècnica efectiva per avaluar *in vivo* el teixit cerebral amb una bona resolució anatòmica. Comparar els biomarcadors de neuroimatge en la MPD i la DCL pot ajudar a determinar si efectivament existeixen diferències morfomètriques entre les dues malalties.

La MP és un trastorn neurodegeneratiu que afecta a un 1.6% de la població d'edat avançada a Europa (de Rijk *et al.,* 1997). Clàssicament es caracteritzava per rigidesa, tremolor, anomalies posturals i bradicinèsia. Actualment, però és reconegut com un trastorn multisistèmic que afecta també a nivell cognitiu, fins i tot en estadiatges temprans de la malaltia (Williams-Gray *et al.,* 2007; Aarsland *et al.,* 2009). La prevalença de demència en la MP oscil·la entre el 17 i el 43% i la incidència anual és entre 4 i 6 vegades més alta respecte a la població sana (Aarsland *et al.,* 2009). De tota manera, hi ha variacions considerables, i alguns pacients desenvolupen demència de manera temprana. L'inici temprà de la demència es relaciona amb més canvis a nivell estructural cerebral (Burton *et al.,* 2004; Beyer *et al.,* 2007). Els predictors més importants de demència en la MP són una edat avaçada, la severitat de la simptomatologia motora, trastorn de la marxa i fenotip no tremorígen de la malaltia (Williams-Gray *et al.,* 2007), així com la presència de trastorn cognitiu lleu i d'al·lucinacions visuals (Emre *et al*., 2007).

D'altra banda, segons els criteris de consens, la DCL és una malaltia que es caracteritza clínicament per: 1) presència de fluctuacions cognitives amb pronunciades variacions en atenció i alerta; 2) parkinsonisme espontani; 3) al·lucinacions visuals ben formades. Dos d'aquests criteris són necessaris pel diagnòstic de DCL probable i al menys un pel diagnòstic de DCL possible (McKeith *et al.,* 1996;McKeith *et al.*, 2005). La DCL es diagnostica quan la demència apareix abans o paralel·lament al parkinsonisme (en el cas de que aquest es presenti). Si la demència apareix en el context d'una MP ben establerta, s'hauria de fer servir el terme malaltia de Parkison amb demència (MPD) (McKeith *et al.,* 1996; McKeith *et al.,* 2005). Aquesta distinció continua sent tema de debat, moltes autoritats consideren que les dues síndromes representen dues variants (motora i cognitiva) del mateix *continuum* patològic.

El perfil cognitiu de les dues malalties és similar, provocant principalment alteració atencional, disfunció executiva, dèficits visuoperceptius, visuoespaials i visuoconstructius, i trastorn de la memòria (Mori *et al.,* 2000; Horimoto *et al.,* 2003; Mosimann *et al.,* 2004; Noe *et al.,* 2004; Cormack *et al.,* 2004; Higginson *et al.,* 2005; Johnson *et al.,* 2005; Kraybill *et al.,* 2005; Perriol *et al.,* 2005; Ferman *et al.,* 2006; Bradshaw *et al.,* 2006; Verleden *et al.,* 2007; Caviness *et al.,* 2007; Song *et al.,* 2008; Bronnick *et al.,* 2008; Hamilton *et al.,* 2008; Filoteo *et al.,* 2009).

Tanmateix, hi ha evidència d'un patró de pèrdua de substància grisa cerebral associat a la MP, que incrementa en la MPD i correlaciona amb la disfunció cognitiva (Laakso *et al.,* 1996; Camicioli *et al.,* 2003; Tam *et al.,* 2005; Summerfield *et al.,* 2005; Junque *et al*., 2005; Bouchard *et al.,* 2008; Jokinen *et al.,* 2009). La pèrdua de substància grisa hipocampal es la característica més descrita (Camicioli *et al.,* 2003; Summerfield *et al.,* 2005; Ibarretxe-Bilbao *et al.,* 2008; Kenny *et al.,* 2008), però el deteriorament s'estén posteriorment a altres àrees temporals i frontals en els pacients amb MP (Burton *et al.,* 2004; Summerfield *et al.,* 2005; Jokinen *et al.,* 2009) i més àmpliament, afectant gairebé tota l'escorça cerebral amb relativa preservació de les regions parietals, en la MPD (Burton *et al.,* 2004; Nagano-Saito *et al.*, 2005; Beyer *et al.,* 2007a; Beyer *et al.,* 2008). D'altra banda, en la DCL, s'ha demostrat una relativa preservació d'estructures temporals respecte a la malaltia d'Alzheimer (MA); no obstant, les diferències entre DCL i MPD a nivell volumètric cerebral encara no són clares. Els dos estudis portats a terme fins al moment han trobat resultats contradictoris: mentre Burton *et al.* (2004) no va trobar diferències entre les dues malalties, Beyer *et al.* (2007b) van mostrar un major decrement en la substància grisa cerebral en els pacients amb DCL en la circumvolució parietal inferior i el precuneus bilateralment, la insula dreta, la circumvolució temporal inferior, el nucli lentiforme, la circumvolució angular esquerra, el cuneus i la circumvolució occipital superior. De tota manera, la durada de la malaltia era major en el grup amb DCL, fet que pot haver influenciat els resultats.

Cap estudi fins al moment, ha estudiat la correlació entre substància grisa cerebral, el funcionament cognitiu, i les al·lucinacions visuals en aquests dos grups de pacients.

Les al·lucinacions visuals (AV) són un dels símptomes principals de la DCL, però també molt freqüents en la MPD. La prevalença d'AV en aquestes malalties es troba entre el 60 i el 80% (Emre, 2003; McKeith and Mosimann, 2004), i els principals factors de risc per desenvolupar AV són avançada edat, demència i/o trastorn cognitiu i major durada de la malaltia (Klein *et al.,* 1997; Mori *et al.,* 2000; Aarsland *et al.,* 2001; Barnes and David, 2001; Holroyd *et al.,* 2001; Mosimann *et al.,* 2004; Grossi *et al.,* 2005; Diederich *et al.,* 2005; Matsui *et al.,* 2006b; Hamilton *et al.,* 2008; Diederich *et al.,* 2009). Les funcions cognitives que s'han relacionat amb el desenvolupament i l'aparició d'AV són les funcions executives, la fluència verbal i el control inhibitori de l'atenció (Nagano-Saito *et al.,* 2004; Grossi *et al.,* 2005; Santangelo *et al.,* 2007; Ramirez-Ruiz *et al.,* 2007a; Barnes and Boubert, 2008; Imamura *et al.,* 2008). Les AV s'han relacionat en pacients amb MP amb trastorns visuoespaials i visuoperceptius, denominació i funcions frontals, específicament la fluència verbal (Grossi *et al.,* 2005; Ramirez-Ruiz *et al.,* 2006; Santangelo *et al.,* 2007; Ozer *et al.,* 2007; Ramirez-Ruiz *et al.,* 2007a; Barnes and Boubert, 2008; Imamura *et al.,* 2008). Només dos estudis han avaluat les funcions cognitives relacionades amb les AV en DCL, mostrant també alteracions visuoperceptives (Mori *et al.*, 2000; Mosimann *et al.,* 2004). Els estudis de neuroimatge tanmateix han mostrat implicació de les àrees cerebrals frontals i associatives visuals en les al·lucinacions visuals tant en pacients amb MP com en pacients amb DCL (Nagano-Saito *et al.,* 2004; Stebbins *et al.,* 2004; Boecker *et al.,* 2007; Ramirez-Ruiz *et al.,* 2008; Perneczky *et al.,* 2008a; Perneczky *et al.,* 2008b).

Objectius de la tesi

L'interès general d'aquest projecte de tesi doctoral es centra en l'estudi de les bases neuroanatòmiques, mesurades mitjançant el patró d'alteració de la substància grisa cerebral, relacionades amb el rendiment cognitiu i les al·lucinacions visuals que presenten el pacients amb DCL i MPD. Amb aquest propòsit s'han fet servir tècniques de volumetria cerebral basades en imatges obtingudes amb RM i avaluacions cognitives i conductuals realitzades a dues mostres de pacients amb DCL i MPD, en comparació a subjectes controls sans aparellats per edat i escolaritat. Aquesta tesi doctoral consta de dos estudis, els objectius dels quals es detallen a continuació.

Estudi I. Correlacions entre les reduccions en substància grisa cerebral i els dèficits cognitius en la demència amb cossos de Lewy i la malaltia de Parkinson amb demència

Alguns estudis han comparat el funcionament cognitiu de pacients amb DCL i MPD, suggerint que la DCL es caracteritza per una major alteració atencional, de funcions executives, memòria de reconeixement immediata i diferida, i habilitats visuoespaials i visuoconstructives respecte a pacients amb MPD (Downes *et al.,* 1998; Aarsland *et al.,* 2003; Mondon *et al.,* 2007), mentre que altres estudis no han trobat diferències entre els dos grups (Ballard *et al.,* 2002; Horimoto *et al.,* 2003; Cormack *et al.,* 2004; Noe *et al.,* 2004; Janvin *et al.,* 2006;). Tot i que hi ha dos estudis que han comparat amb tècniques volumètriques cerebrals (Voxel-based Morphometry, VBM) la DCL i la MPD (Burton *et al.,* 2004; Beyer *et al.,* 2007), no hi ha cap estudi que hagi explorat les possibles correlacions entre la pèrdua en substància grisa cerebral i les alteracions cognitives en aquestes malalties.

Per aquest motiu, el propòsit del present estudi va ser investigar les possible correlacions entre l'estructura cerebral i les funcions neuropsicològiques en pacients clínicament diagnosticats de DCL i MPD.

En síntesi, els objectius del primer estudi d'aquesta tesi doctoral van ser:

<u>Objectius generals</u>

I. Examinar i quantificar els canvis en substància grisa cerebral en pacients am DCL i MPD mitjançant l'anàlisi vòxel a vòxel del cervell (VBM)
II. Establir les diferències en el patró cognitiu de pacients amb DCL i MPD

<u>Objectius específics</u>

I. Avaluar la relació entre les estructures cerebrals i les funcions cognitives en la DCL i la MPD
II. Analitzar si el patró de correlacions entre estructura cerebral i funció és diferent en les dues malalties
III. Determinar els marcadors de neuroimatge i neuropsicològics que serveixin per diferenciar la DCL de la MPD
IV. Comparar la proporció d'atròfia hipocampal en la DCL i la MPD

<u>Hipòtesi de treball</u>

Hipotetitzem que els pacients amb DCL tindran major alteració de la substància grisa cerebral que els subjectes amb MPD, afectant a àrees associatives neocorticals, així com presentaran més alteracions cognitives, especialment en funcions prefrontals.

Estudi II. Les àrees frontals i associatives visuals es relacionen amb les al·lucinacions visuals en la demència amb cossos de Lewy i la malaltia de Parkinson amb demència

Les AV són un dels símptomes principals de la DCL, però també molt freqüents en la MPD. Els pocs estudis adreçats a caracteritzar la fenomenologia de les al·lucinacions en les dues malalties han referit AV ben formades d'animals, objectes i humans tant en la DCL com en la MPD (Aarsland *et al.,* 2001; Barnes and David, 2001; Mosimann *et al.,* 2006) amb una prevalença estimada d'entre un 50 i un 80% (Emre, 2003; McKeith and Mosimann, 2004; Diederich *et al.,* 2009). Segons el nostre coneixement, cap estudi fins al moment ha estudiat els canvis estructurals cerebrals en pacients amb DCL i MPD amb i sense AV, ni s'han avaluat els canvis en substància grisa cerebral relacionats amb les AV en aquest grup de pacients. Tanmateix, tan sols un estudi va avaluar les funcions cognitives relacionades amb les AV en un grup de pacients amb diagnòstic de DCL, amb i sense AV, demostrant que els pacients amb al·lucinacions tenien més alteracions visuoperceptives (Mori *et al.,* 2000).

Les tècniques de neuroimatge proporcionen un mitjà directe per identificar i caracteritzar *in vivo* el patró de decrement de substància grisa cerebral associat a les AV en una cohort de pacients amb diagnòstic de DCL i MPD.

Per tant, l'objectiu del present estudi va ser investigar el patró de substància grisa cerebral i el perfil cognitiu subjacent a les AV en pacients amb DCL i MPD mitjançat VBM i una avaluació conductual.

En síntesi, els objectius del segon estudi van ser:

<u>Objectius generals</u>

I. Avaluar *in vivo* els canvis estructurals en substància grisa cerebral relacionats amb les al·lucinacions visuals en pacients amb DCL i MPD
II. Determinar les funcions cognitives relacionades amb les al·lucinacions visuals en pacients amb DCL i MPD

<u>Objectius específics</u>

I. Avaluar les diferències en substància grisa local en pacients amb DCL i MPD amb al·lucinacions visuals
II. Estudiar les correlacions entre el volum de substància grisa cerebral i la severitat de les al·lucionacions visuals en la DCL i MPD

III. Determinar les correlacions entre funcions cognitives i la severitat de les al·lucinacions visuals en la DCL i la MPD

Hipòtesi de treball

Hipotetitzem que hi haurà una major afectació de la susbstància grisa cortical en àrees associatives visuals en els pacients que presenten AV que en els pacients sense AV.

Metodologia

La present tesis consisteix en dos estudis que examinen les bases neuroanatòmiques relacionades amb les funcions cognitives i les al·lucinacions visuals en pacients que presenten DCL i MPD. Per això, s'han estudiat dues mostres de subjectes independents i s'han fet servir una aproximació de volumetria de teixit cerebral, així com avaluacions del rendiment cognitiu i dels trastorns conductuals de la mostra a estudi.

Ambdós estudis van ser aprovats pel Comitè Ètic de l'Hospital Universitari de Bellvitge, i tots els pacients i/o familiars van donar el consentiment informat prèviament a la seva participació. Cada estudi conté una descripció detallada de les mostres, la metodologia d'anàlisis de les imatges per RM i de les avaluacions cognitives i conductuals emprades.

L'avaluació de la mostra es va portar a terme en tres fases: en la *primera fase*, es va realitzar una entrevista de *screening* a tot els subjectes derivats per valorar els criteris d'inclusió i exclusió. Els criteris d'inclusió van ser: diagnòstic clínic de DCL probable segons els criteris de consens (McKeith *et al.,* 2005) i diagnòstic de MP segons els criteris de Daniels and Lees (1993) i de demència segons els criteris DSM-IV (2002); així com presentar un MMSE menor de 24 i un GDS menor de 5. Dels 66 pacients avaluats en aquesta primera fase, 21 DCL i 21 MPD van complir criteris per formar part en el estudi. Tanmateix, 24 voluntaris sans aparellats per edat i sexe van formar també part de l'estudi. En la *segona fase*, es va realitzar l'exploració neuropsicològica i conductual a tots els subjectes de l'estudi. L'exploració incloïa una entrevista estructurada avaluant els antecedents, exploració neurològica i les següents escales per tal de caracteritzar la mostra: MMSE (Folstein *et al.,* 1983), *Reisberg's Global Deterioration Scale* (GDS) (Reisberg *et al.,* 1982), *l'Unified Parkinson's Disease Rating Scale* (UPDRS-III) (Fahn, 1987) i l'escala de Hoehn i Yahr (Hoehn and Yahr, 1967). Les al·lucinacions visuals es van avaluar quantitativament mitjançat l'Inventari Neuropsiquiàtric (NPI) (Cummings *et al.,* 1994) i qualitativament mitjançant el qüestionari de canvis visuals de Burnes i David (2001). L'exploració neuropsicològica es va centrar en quatre dominis cognitius:

funcions executives/atenció, funcions visuoespaials/visuoperceptives, memòria (visual i verbal) i habilitats visuoconstructives. Per tal de portar a terme l'exploració es van fer servir les següents proves: el test d'atenció contínua de Conner's (CPT-II) (Conners, 1985); la memòria verbal, memòria visual i la còpia de figures geomètriques de la bateria CERAD (Welsh *et al.,* 1991), el test de Stroop (Golden, 2001), fluència verbal fonètica de l'escala COWAT (Sumerall *et al.,* 1997), fluència verbal semàntica del test Barcelona (Peña *et al.,* 1991) i el *Cortical Vision Screening test* (CORVIST) (Merle James, 2001). L'anàlisi estadística de les dades demogràfiques, neuropsicològiques i conductuals es van dur a terme emprant el programa SPSS (11.5, SPSS Inc.).

A la *tercera fase*, es va realitzar l'exploració per RM. Les imatges de RM es van adquirir al servei de Diagnòstic per la Imatge de l'Hospital Universitari de Bellvitge, les imatges es van adquirir amb un escàner Philips Intera de 1.5 Tesla. Es van obtindre 110 talls continus en un protocol de les següents característiques: TR=40 ms; TE=1.79 ms; fa=35º; voxel size=0.98x0.98x1.3 mm.

La tècnica de neuroimatge emprada per avaluar les diferències cerebrals en substància grisa entre els tres grups va ser la VBM (Ashburner and Friston, 2000; 2001; 2005). El preprocessament de les dades i l'anàlisi estadística de les imatges es va portar a terme fent servir el programa *Statistical Parametric Mapping* (SPM5, Wellcome Department of Imaging Neuroscience, London, UK) (http://www.fil.ion.ucl.ac.uk/spm/) implementat en Matlab 6.5 (MathWorks, Natick, MA). Les fases del preprocessament són les següents: *1)* normalització espaial de totes les imatges respecte a una imatge mitjana *(template)* (Crinion *et al.,* 2007); *2)* segmentació de les imatges en substància grisa, substància blanca i líquid cefaloraquidi en base a una combinació de mapes de probabilitat *a priori* i un *cluster* anàlisi basat en la intensitat dels voxels (Acosta-Cabronero *et al.,* 2008; Ashburner and Friston, 2005); *3)* suavitzat de les imatges de substància grisa aplicant un Kernel Gaussià (Kiebel *et al.,* 1999); *4)* modulació de les imatges; i finalment 5) anàlisi estadística (Ashburner and Friston, 2000). El llindar de significació es va establir en $p<0.05$ FWE corretgit per comparacions múltiples.

Resultats

Estudi I. Correlacions entre les reduccions en substància grisa cerebral i els dèficits cognitius en la demència amb cossos de Lewy i la malaltia de Parkinson amb demència

Anàlisi VBM grupal

Les comparacions de substància grisa cerebral entre grups, incloent l'escolaritat, severitat i durada de la simptomatologia extrapiramidal com a covariables, mostren un decrement de la substància grisa cerebral en els pacients amb DCL respecte a subjectes control en la circumvolució frontal dreta, el cingulat posterior, i les circumvolucions parietal inferior i temporal superior esquerres; mentre que els pacients amb MPD presentaven una reducció de la substància grisa cerebral respecte a controls al cuneus i al lòbul parietal inferior drets. Tanmateix, en la comparació entre els dos grups patològics, els pacients amb DCL presentaven una major alteració de la substància grisa en àrees frontals dretes respecte als pacients amb MPD, concretament en les circumvolucions frontals superior i inferior, i en l'àrea premotora.

Anàlisi de VBM individual

L'anàlisi individual de la distribució de substància grisa cerebral en cada pacient en comparació amb els subjectes control, va mostrar una reducció significativa de la substància grisa a l'hipocamp dret en un 50% dels pacients amb DCL i només en un 6.3% dels pacients amb MPD (X^2=4.72, p=0.03). Tanmateix, una reducció de la substància grisa a l'hipocamp esquerre es va trobar a un 16,6% dels pacients amb DCL i un 18.8% dels pacients amb MPD, però aquestes diferències no eren significatives.

Resultats neuropsicològics

El test de Mann-Whitney va mostrar que els pacients amb DCL presentaven una major alteració de la vigilància en el CPT test (un test computeritzat que mesura atenció mantinguda i inhibició). D'altra banda, els pacients amb MPD, presentaven més errors perseveratius i les seves respostes eren menys consistents i més erràtiques a mesura que avançava la prova, així com cometien més errors intrusius en la prova de memòria.

Correlació entre la substància grisa regional i les variables neuropsicològiques

L'anàlisi de regressió va mostrar una correlació significativa en els pacients amb DCL entre l'alteració en estructures temporals medials dretes (hipocamp i amigdala) i el dèficit en memòria visual; i entre la disminució en substància grisa en el cingulat anterior i àrees prefrontals (prefrontal dorsolateral i inferior frontal bilaterals) i la alteració atencional (errors de comissió, perseveratius i un baix índex de detecció d'estímuls en el CPT test). Tanmateix, no es van trobar correlacions significatives entre les variables neuropsicològiques i el volum de substància grisa cerebral en els pacients amb MPD, mentre que en el grup control, l'alteració orbitofrontal dreta es va relacionar amb el nombre d'errors perseveratius realitzats en el CPT test.

Estudi II. Les àrees frontals i associatives visuals es relacionen amb les al·lucinacions visuals en la demència amb cossos de Lewy i la malaltia de Parkinson amb demència

Diferències en volum cerebral entre grups

Les comparacions de la substància grisa regional entre grups va mostrar que els pacients amb DCL i AV presentaven una major reducció de la substància grisa cerebral a la circumvolució frontal inferior dreta (BA 45) en comparació amb els pacients amb DCL sense AV. D'altra banda, els pacients amb MPD i AV presentaven una major alteració de la substància grisa cerebral a l'escorça orbitofrontal esquerra (BA 10) en comparació amb els pacients sense al·lucinacions. Les diferències en aquest grup desapareixien quan s'incloïa l'edat com a covariable, suggerint que l'edat pot estar relacionada amb l'aparició de les AV en els pacients amb MP i demència.

Comparant els dos subgrups amb AV, i covariant per edat, durada de la demència i durada de la malaltia, els pacients amb DCL presentaven una major alteració de la substància grisa a l'àrea premotora bilateral (BA 6) respecte als pacients amb MPD.

Correlacions entre al·lucinacions visuals i substància grisa regional

En el grup amb DCL, es va trobar una correlació significativa entre la severitat de les AV i la reducció en substància grisa a la circumvolució frontal dreta (BA 45; r=0.89) i al precuneus esquerre (BA 7; r =0.95). Per el contrari, no es va trobar cap correlació significativa entre substància grisa cerebral i AV en el grup amb MPD.

Correlacions entre al·lucinacions visuals i funcionament cognitiu

Es van trobar correlacions significatives entre la severitat de les AV i una alteració en la fluència verbal semàntica (p=0.006), en control inhibitori de l'atenció (Stroop PC) (p=0.004) i les habilitats visuoperceptives (discriminació de tons) (p=0.03) en el grup amb DCL, i entre les AV i la memòria visual (p=0.02) en el grup amb MPD. Controlant l'efecte de l'edat, la durada de la demència i la durada de la malaltia, només les correlacions entre fluència verbal semàntica i control inhibitori de l'atenció en el grup amb DCL romanien significatives (p= 0.02 and 0.04 respectivament).

Discussió

La DCL i la MPD són les dues sinucleïnopatíes més comunes. Hi ha controvèrsia a la literatura sobre si considerar-les dues malalties diverses o dos fenotips diferents dintre del mateix *continuum* patològic. Segons el nostre coneixement, no hi ha estudis que hagin estudiat els canvis estructurals cerebrals relacionats amb les alteracions cognitives i les al·lucinacions visuals en pacients amb DCL i MPD. Aquest fet fa palesa la necessitat d'estudis prospectius adreçats a clarificar les característiques clíniques, cognitives i conductuals de pacients amb DCL i MPD en relació als canvis en l'estructura cerebral mesurats mitjançant ressonància magnètica (RM).

Per aquest motiu, en el primer estudi que composa aquesta tesi doctoral, vam pretendre estudiar el patró de decrement en substància grisa cerebral associat a la DCL i MPD, així com la seva relació amb en funcionament cognitiu en aquesta mostra. Complementàriament, en el segon estudi, teníem per objectiu establir les diferències en estructura cerebral i funcionament cognitiu subjacents a les al·lucinacions visuals en aquests pacients.

Així, els nostres estudis van proporcionar evidència de la reducció en volum de substància grisa cerebral en pacients amb DCL en la circumvolució frontal inferior (BA 45), el cingulat posterior, així com en àrees temporals superiors (BA 38) i parietals inferiors (BA 39) en comparació amb subjectes control sans, mentre que els pacients amb MPD van presentar una pèrdua de substància grisa cerebral en la circumvolució parietal inferior (BA 39) i el cuneus. Tot i que el patró d'afectació cortical en les dues malalties és diferent, frontal i parieto-temporal en els pacients amb DCL i més posterior, afectant només a estructures parieto-occipitals en MPD; la pèrdua de substància grisa es trobava restringida a àrees associatives en ambdós casos. Aquests resultats són consistents amb estudis neuropatològics que demostren inclusions en l'escorça cerebral de pacients amb DCL i PDD a àrees associatives neocorticals, evolucionant en els darrers estadiatges de la malaltia a una afectació més global del cervell incloent àrees sensorials i motores primàries (Braak *et al.,* 2006b; Lippa *et al.,* 2007; Jellinger, 2009a; 2009b; Ferrer, 2009).

Tanmateix, vam trobar que els pacients amb DCL presenten una major alteració de la substància grisa a estructures frontals respecte a pacients amb MPD, concretament a les circunvolucions frontal inferior i superior dretes (BA 8, 45) i a l'àrea premotora dreta (BA 6). Aquestes àrees, s'han relacionat també amb les al·lucinacions visuals en els pacients amb DCL en la nostra mostra. En aquest sentit, els pacients amb DCL que cursen amb AV presenten un decrement de la substància grisa cerebral en la circumvolució frontal inferior dreta (BA 45) en comparació amb els pacients amb DCL sense AV, i en l'àrea premotora bilateral en comparació amb els pacients amb MPD i AV. D'altra banda, els pacients amb MPD amb VH presenten un decrement de la substància grisa cerebral en el lòbul orbitofrontal (BA 10) en comparació als pacients amb MPD sense AV, tot i que aquestes diferències desapareixen quan s'inclou l'edat com a covariable en l'anàlisi. Aquests resultats donen suport a les hipòtesis que argumenten que els pacients amb DCL presenten major pèrdua de substància grisa en regions frontal que els pacients amb MPD, i a l'hora, que les AV en les malalties que cursen amb cossos de Lewy estan efectivament relacionades amb canvis morfològics, circumscrits al lòbul frontal. Tanmateix, l'anàlisi de les correlacions confirma aquesta implicació del lòbul frontal en les AV. En aquest sentit, els nostres resultats proporcionen evidència de la correlació entre l'àrea de Brodmann 45 i les al·lucinacions visuals en el grup amb DCL. Els nostres resultats són consistents amb altres investigacions que mostren un decrement del volum de les àrees fronto-parietals en DCL respecte a subjectes controls (Burton *et al.,* 2002; Ballmaier *et al.,* 2004; Whitwell *et al.,* 2007b) i en la MPD respecte a pacients amb MP sense demència (Burton *et al.,* 2004; Nagano-Saito *et al.,* 2005; Beyer *et al.,* 2007a; Beyer and Aarsland, 2008). No obstant, només un estudi fins al moment ha trobat diferències a nivell estructural cerebral entre pacients amb DCL i MPD (Beyer *et al.,* 2007b) en àrees temporals, parietals (incloent el precuneus) i occipitals, mentre que Burton *et al.,* (2004) no van trobar diferències entre els dos grups.

Les anàlisis complementàries individuals van mostrar una pèrdua de substància grisa hipocampal tant en la DCL com en la MPD, però els pacients amb DCL presentaven una pèrdua de substància grisa hipocampal dreta amb més freqüència que els MPD, mentre que no es van trobar diferències a nivell de l'hipocamp esquerre. Aquests resultats suggereixen que en el grup amb MPD l'atròfia hipocampal és menys prominent i més uniforme als dos hemisferis cerebrals, mentre que en el grup amb DCL es més pronunciada a l'hemisferi dret. Diversos estudis de neuroimatge i neuropatològics han descrit una asimetria hipocampal, que es troba ja present en l'úter, caracteritzada per un major volum de l'hipocamp dret respecte a l'esquerre (Xu *et al.,* 2008); tanmateix, alguns trastorns del neurodesenvolupament, processos patològics i neurodegeneratius s'associen amb alteracions i inversió d'aquesta asimetria anatòmica normal (Geroldi *et al.*, 2000; Barber *et al.,* 2001). Barber *et al.* (2001) va demostrar com aquesta asimetria desapareixia en els pacients amb DCL. Aquesta evidència és consistent amb la nostra troballa d'una major prevalença d'atròfia hipocampal dreta a la DCL en comparació amb la MPD, invertint el patró anatòmic normal; mentre que no es van trobar diferències significatives en la freqüència de deteriorament de l'hipocamp esquerre. Estudis neuropatològics han descrit la sensibilitat de la circumvolució temporal medial a l'acomulació de cossos de Lewy (Harding *et al.,* 2002b), específicament a àrees CA2/3 hipocampals (Jellinger, 2006). Diversos estudis de neuroimatge també han confirmat la presència d'atròfia hipocampal en la DCL (Hashimoto *et al.,* 1998; Burton *et al.,* 2002; Tam *et al.,* 2005; Sabatoli *et al.,* 2008; Burton *et al.,* 2009) i en la MPD (Tam *et al.,* 2005; Summerfield *et al.,* 2005; Junque *et al.,* 2005; Ibarretxe-Bilbao *et al.,* 2008; Aybeck *et al.,* 2009).

L'anàlisi de les correlacions entre estructura cerebral i conducta en el grup amb DCL van mostrar que la reducció del volum del lòbul frontal inferior (BA 45), l'escorça prefrontal dorsolateral (BA 9/46) i del cingulat anterior estaven relacionades amb l'alteració atencional, expressada per un major número d'errors de comissió, perseveracions i pitjor capacitat de detecció dels estímuls en les tasques atencionals. A més, en el mateix grup, un decrement en el volum del precuneus esquerre (BA 7) i del frontal inferior dret (BA 45) es van relacionar amb la presència i severitat de les AV. No es va trobar cap correlació significativa entre estructura cerebral i funció cognitiva en el grup amb MPD. En conjunt, aquests resultats donen suport al ja conegut paper dels lòbuls frontals en el funcionament atencional, i junt amb les àrees associatives visuals, contribueixen a l'aparició de les AV en els pacients amb DCL. Aquestes estructures fronto-parietals han estat relacionades amb la orientació de l'atenció en subjectes sans (Goldberg and Golberg, 2000; Shulman *et al.,* 2009). Tanmateix, el frontal dorsolateral i cingulat anterior s'han relacionat amb la inhibició de les respostes, l'atenció executiva i l'atribució interna dels fets (Nagano-Saito *et al.,* 2004; Lezak, 2004; Petrides, 2005; Fan *et al.,* 2005; Picton *et al.,* 2007; Blackwood *et al.,* 2000). Les àrees 6 i 8 de Brodmann també han estat involucrades en el circuit de la discriminació visual i l'atenció (Petrides, 2005), i les àrees 6 i 45 es troben específicament implicades en l'inhibició de la resposta i la monitorització de la conducta (Picton *et al.,* 2007). L'hipometabolisme en aquestes àrees frontals i en àrees associatives visuals, s'ha relacionat amb les AV i deliris en pacients amb DCL (Pernezcky *et al.,* 2008a; 2008b). Tanmateix, els estudis de neuroimatge funcional han mostrat alteracions en àrees frontals i visuals associatives cerebrals en pacients amb PD amb AV (Nagano-Saito *et al*., 2004; Stebbins *et al.,* 2004; Boecker *et al.,* 2007; Ramirez-Ruiz *et al.,* 2008; Meppelink *et al.,* 2009) suggerint que la neurodegeneració de les àrees visuals secundaries es troba relacionada amb la presència i aparició de AV, provocant disfunció en el reconeixement d'objectes, formes i colors (Yamamoto *et al.,* 2006). A nivell estructural, la circumvolució parietal superior s'ha relacionat amb les AV en pacients amb MP (Ramirez-Ruiz *et al.,* 2007b). Diversos estudis han aportat també evidència d'inclusions amb cossos de lewy en àrees fronto-parietals en pacients amb MP i AV (Papapetropoulos *et al.,* 2006; Yamamoto *et al.,* 2006), així com estudis metabòlics en DCL i PD amb AV han demostrat un patró d'afectació cortical tant en estructures anteriors com posteriors (Higuchi *et al.,* 2000; Nagano-Saito *et al.,* 2004; Stebbins *et al.,* 2004; O'Brien *et al.,* 2005; Matsui *et al.,* 2006a; Boecker *et al.,* 2007; O'Brien *et al.,* 2008; Perneczky *et al.,* 2008a).

Per tant, aquests estudis mostren evidència de que els canvis estructurals en aquestes àrees presents en els pacients amb DCL poden portar al trastorn d'atenció visual considerat com un símptoma central d'aquesta malaltia, i a un dèficit de control inhibitori que pot provocar l'aparició de les AV, també central de la malaltia. En aquest sentint, l'alteració d'aquestes regions cerebrals donaria suport a dues de les teories sobre l'aparició de les al·lucinacions visuals, el model del *Dèficit Perceptiu i Atencional (DPA)* i el model *Integratiu* (Collerton *et al.,* 2005; Diederich *et al.,* 2005) que hipotetitzen que una combinació de diversos dèficits és necessària per l'aparició de les AV. El primer model fa èmfasi en la combinació de dèficits atencionals i visuoperceptius com a desencadenant de les AV; mentre que el segon model, accentua el paper d'una dificultat per atribuir la font de les percepcions (interna o externa) degut a una desregulació del filtre atencional de les percepcions externes i d'una producció aberrant d'imatges internes.

Tanmateix, en el grup amb DCL, la disminució de la substància grisa en estructures temporal medial dretes (hipocamp i amígdala) correlaciona amb l'alteració de la memòria visual. Aquests resultats són consistents amb la ja ben coneguda funció de l'hipocamp en la memòria i l'aprenentatge (Riekkinen *et al.,* 1998; Barber *et al.,* 2001; Camicioli *et al.,* 2003; Lezak, 2004; Junque *et al.,* 2005; Bouchard *et al.,* 2008; Kenny *et al.*, 2008; Aybeck *et al.,* 2009; Jokinen *et al.,* 2009).

La comparació a nivell neuropsicològic va mostrar un patró atencional diferent en els dos grups patològics: mentre que els pacients amb DCL es caracteritzaven per major distractibilitat durant l'execució de la prova atencional (presentaven una alteració de la vigilància, en el sentit de temps de reacció més lents conforme avança la prova); mentre que els pacients amb MPD presenten major impulsivitat tant en tasques atencionals com en les proves de memòria (més perseveracions en la prova atencional i més intrusions en el record diferit. Tanmateix, cometien més errors quan l'interval entre estímuls augmentava, relacionat amb la seva impulsivitat).

Aquests resultats són consistents amb estudis previs que mostren alteració atencional en pacients amb DCL (Noe *et al.,* 2004; Kraybill *et al.,* 2005; Bradshaw *et al.,* 2006; Mondon *et al.,* 2007) i MPD (Caviness *et al.,* 2007; Song *et al.,* 2008; O'Brien *et al.,* 2009; Filoteo *et al.,* 2009). Noe *et al.* (2004), va descriure una dificultat en el processament d'informació visuoespaial en pacients amb DCL, que cometien més errors d'omissió en tests de cancelació que els pacients amb MPD. També Mondon *et al.* (2007) va descriure més dèficits atencionals en pacients amb DCL en orientació, atenció mantinguda i control inhibitori de l'atenció. Per contra, altres estudis han trobat més alteracions atencionals i errrors perseveratius en pacients amb MPD en comparació amb DCL (Bronnick *et al.,* 2008; Filoteo *et al.,* 2009). Aquestes discrepàncies poden ser degudes a la modalitat sensorial i als aspectes de l'atenció estudiats en els diversos estudis. Bronnick *et al.* (2008) van fer servir estímuls auditius, mentre que els altres feien servir estímuls visuals. A més, les diferents tasques emprades en els diversos estudis mesuren diferents components de l'atenció. Bradshaw *et al.* (2006) van demostrar que els dèficits atencionals en DCL es trobaven més accentuats en les tasques que requerien més control executiu i funcions visuoespaials. Aquests resultats es troben en la mateixa línia dels nostres resultats, que mostren alteració atencional tant en DCL com en MPD però amb diferents perfils.

La disfunció atencional observada en els pacients amb DCL pot explicar-se pels nostres resultats de VBM, on el volum del cingulat anterior i les regions prefrontals correlacionen amb l'execució en la prova atencional. Aquestes troballes són consistents amb el model postulat per Posner and Rothbart, (2007) en que descriu el paper del cingulat anterior en el control executiu de l'atenció i el control inhibitori. Des del punt de vista de la neuropatologia, els cossos de Lewy es concentren en els lòbuls frontals, infero-medial i el cingulat anterior, àrees relacionades amb les funcions executives i el reconeixement visual (Fan *et al.,* 2002).

En la mateixa línia, també vam trobar un patró diferent de memòria entre els dos grups: els pacients amb DCL tendien a tenir pitjors puntuacions en evocació espontània i en el reconeixement, suggerint una alteració en la codificació de la informació relacionat amb estructures hipocampals; mentre que els pacients amb MPD presentaven més errors intrusius en el record diferit però una tendència a presentar un millor funcionament en evocació espontània i reconeixement. Estudis previs han descrit una major alteració de l'evocació immediata i diferida en pacients amb DCL respecte a MPD (Mondon *et al.,* 2007; Filoteo *et al.,* 2009), així com una tassa més elevada d'oblit (Filoteo *et al.,* 2009). Higginson *et al.* (2005) van descriure falsos positius en el reconeixement i evocació amb claus en pacients amb PD associats a una disfunció frontal i una alteració de la inhibició. En aquest sentit, O'Brien *et al.* (2009) van demostrar com les funcions executives eren predictives del rendiment en proves d'aprenentatge en pacients amb MPD. Aquests dèficits mnèsics poden estar associats als canvis en substància grisa observats en àrees prefrontals i hipocampals i a la disrupció per tant de les connexions hipocampo-prefrontals dorsolaterals, que es troven afectades a la DCL (Harding *et al.*, 2002b).

En relació a les AV, vam trobar que la severitat de les AV estava correlacionada amb l'alteració de la fluència verbal semàntica, el control inhibitori de l'atenció i els dèficits visuoperceptius en el grup amb DCL i amb la memòria visual en el grup amb MPD. Aquests resultats donen suport a la hipòtesi del *DPA* (Collerton *et al.,* 2005) que relaciona les AV amb un dèficit del control inhibitori de l'atenció i una percepció visual deficitària; així com són consistents amb estudis longitudinals previs que descriuen una disfunció prefrontal, específicament de la fluència verbal, com a predictors del desenvolupament de les AV en la MP (Santangelo *et al.*, 2007; Ramirez-Ruiz *et al.,* 2007a). Seguint aquesta hipòtesi, podem suggerir que en els pacients amb DCL el dèficit en control inhibitori atencional permet la intrusió d'un objecte no real (al·lucinatori) en l'escena perceptiva, mentre que en els pacients amb MPD, les AV podrien ser la conseqüència de confabulacions per completar els oblits provocats per un dèficit mnèsic (Barnes *et al.*, 2003).

En conclusió, el present projecte de recerca dona evidència de que els pacients amb DCL i MPD presenten diferents patrons de pèrdua de substància grisa cerebral, i que aquesta correlaciona de manera diferent amb el funcionament cognitiu i les al·lucinacions visuals. En el primer estudi, es va demostrar que els pacients amb DCL presenten una alteració en estructures cerebrals frontals, temporals i parietals, relacionades amb l'alteració atencional i de la memòria visual; mentre que els pacients amb MPD presenten una major alteració de les regions parieto-occipitals, i cognitivament, es caracteritzen per major impulsivitat. En relació a les AV, en pacients amb DCL, es troben relacionades amb un decrement de la substància grisa fronto-parietal i alteracions cognitives frontals i visuoperceptives; mentre que en els pacients amb MPD es relacionen amb estructures frontals, i cognitivament, amb dèficits en memòria visual. Aquests resultats donen suport a la hipòtesi de que una combinació de dèficits és necessària per donar lloc a les AV en aquestes malalties (Collerton *et al.,* 2005; Diederich *et al.,* 2005; Diederich *et al.,* 2009).

Conclusions

I. Els pacients amb MPD i DCL presenten un patró diferent d'atròfia regional. En comparació amb els subjectes control, els pacients amb MPD presenten una major reducció de la substància grisa cerebral en regions parieto-occipitals i en pacients amb DCL en regions frontals, temporals i parietals. Tanmateix, els pacients amb DCL tenen una major pèrdua de substància grisa cerebral que els pacients amb MPD en diverses àrees frontals, específicament en les circumvolucions inferior i superior frontal dretes i l'àrea premotora dreta.

II. En l'anàlisi individual, hi ha una pèrdua de substància grisa hipocampal tant en pacients amb MPD com en pacients amb DCL, però la freqüència de la reducció de substància grisa en l'hipocamp dret és major en la DCL que en la MPD.

III. La presència d'al·lucinacions visuals (AV) es relaciona amb un decrement en la substància grisa cerebral en àrees frontals en tots dos grups patològics, però a diferents regions. En els pacients amb DCL el decrement es troba a la regió prefrontal lateral, mentre que en pacients amb MPD es troba a la regió orbitofrontal. A més, la severitat i la freqüència de les AV correlaciona negativament amb la reducció en substància grisa cerebral en la circumvolució frontal inferior i el precuneus en el grup amb DCL.

IV. En el perfil atencional, els pacients amb DCL presenten més distractibilitat, caracteritzada per una pobre vigilància, mentre que els pacients amb MPD presenten major impulsivitat reflexada per errors perseveratius i intrusius.

V. En el grup amb DCL, l'alteració en memòria visual es relaciona amb un decrement de la substància grisa cerebral en el lòbul temporal medial dret (hipocamp i amígdala) i els dèficits atencionals correlacionen amb el deteriorament del cingulat anterior, la circumvolució frontal inferior i l'escorça prefrontal dorsolateral.

VI. En els pacients amb DCL, la presència i severitat de les al·lucinacions visuals correlaciona amb una alteració de la fluència verbal semàntica, el control inhibitori de l'atenció i de l'habilitat visuoperceptiva, mentre que en els pacients amb MPD es correlaciona amb dèficits en memòria visual.

En els dos grups amb demència, hi ha un patró diferent de pèrdua de substància grisa cerebral i de perfil cognitiu. Tanmateix, cada malaltia té un patró diferent de correlacions entre substància grisa i conducta.

REFERENCES

8. References

Aarsland, D., K. Andersen, J. P. Larsen, A. Lolk, and P. Kragh-Sorensen, 2003, Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study: Arch.Neurol., v. 60, no. 3, p. 387-392.

Aarsland, D., C. Ballard, J. P. Larsen, and I. McKeith, 2001, A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia: Int.J.Geriatr.Psychiatry, v. 16, no. 5, p. 528-536.

Aarsland, D., K. Bronnick, J. P. Larsen, O. B. Tysnes, and G. Alves, 2009, Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study: Neurology, v. 72, no. 13, p. 1121-1126.

Aarsland, D., J. P. Larsen, J. L. Cummins, and K. Laake, 1999, Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study: Arch.Neurol., v. 56, no. 5, p. 595-601.

Aarsland, D., A. Rongve, S. P. Nore, R. Skogseth, S. Skulstad, U. Ehrt, D. Hoprekstad, and C. Ballard, 2008, Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria: Dement.Geriatr.Cogn Disord., v. 26, no. 5, p. 445-452.

Acosta-Cabronero J, Williams GB, Pereira JM, Pengas G, Nestor PJ, 2008, The impact of skull-stripping and radio-frequency bias correction on grey-matter segmentation for voxel-based morphometry. Neuroimage, v. 15;39(4):1654-65.

Almeida, O. P., E. J. Burton, I. McKeith, A. Gholkar, D. Burn, and J. T. O'Brien, 2003, MRI study of caudate nucleus volume in Parkinson's disease with and without dementia with Lewy bodies and Alzheimer's disease: Dement.Geriatr.Cogn Disord., v. 16, no. 2, p. 57-63.

American Psychiatric Association., 2003,American Psychiatric Association. *Manual diagnostico y estadistico de los trastornos mentales, Cuarta edición revisada, DSM-IV-TR*.: Barcelona, Masson.

Antonini, A., N. R. De, R. Benti, G. D. De, and G. Pezzoli, 2001, Perfusion ECD/SPECT in the characterization of cognitive deficits in Parkinson's disease: Neurol.Sci., v. 22, no. 1, p. 45-46.

Ashburner, J., and K. J. Friston, 2000, Voxel-based morphometry--the methods: Neuroimage., v. 11, no. 6 Pt 1, p. 805-821.

Ashburner, J and K. J. Friston, 2001, Why voxel-based morphometry should be used. Neuroimage, v. 14, no. 6, p. 1238-1243.

Ashburner, J., and K. J. Friston, 2005, Unified segmentation: Neuroimage., v. 26, no. 3, p. 839-851.

Aybek, S., F. Lazeyras, A. Gronchi-Perrin, P. R. Burkhard, J. G. Villemure, and F. J. Vingerhoets, 2009, Hippocampal atrophy predicts conversion to dementia after STN-DBS in Parkinson's disease: Parkinsonism.Relat Disord., v. 15, no. 7, p. 521-524.

Ballard, C. et al., 2000, Delusions associated with elevated muscarinic binding in dementia with Lewy bodies: Ann.Neurol., v. 48, no. 6, p. 868-876.

Ballard, C. G. et al., 2002, Fluctuations in attention: PD dementia vs DLB with parkinsonism: Neurology, v. 59, no. 11, p. 1714-1720.

Ballmaier, M., J. T. O'Brien, E. J. Burton, P. M. Thompson, D. E. Rex, K. L. Narr, I. G. McKeith, H. DeLuca, and A. W. Toga, 2004, Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects: Neuroimage., v. 23, no. 1, p. 325-335.

Barber, R., C. Ballard, I. G. McKeith, A. Gholkar, and J. T. O'Brien, 2000a, MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia: Neurology, v. 54, no. 6, p. 1304-1309.

Barber, R., A. Gholkar, P. Scheltens, C. Ballard, I. G. McKeith, and J. T. O'Brien, 2000b, MRI volumetric correlates of white matter lesions in dementia with Lewy bodies and Alzheimer's disease: Int.J.Geriatr.Psychiatry, v. 15, no. 10, p. 911-916.

Barber, R., A. Gholkar, P. Scheltens, C. Ballard, I. G. McKeith, and J. T. O'Brien, 1999a, Medial temporal lobe atrophy on MRI in dementia with Lewy bodies: Neurology, v. 52, no. 6, p. 1153-1158.

Barber, R., I. McKeith, C. Ballard, and J. O'Brien, 2002, Volumetric MRI study of the caudate nucleus in patients with dementia with Lewy bodies, Alzheimer's disease, and vascular dementia: J.Neurol.Neurosurg.Psychiatry, v. 72, no. 3, p. 406-407.

Barber, R., I. G. McKeith, C. Ballard, A. Gholkar, and J. T. O'Brien, 2001, A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: magnetic resonance imaging volumetric study: Dement.Geriatr.Cogn Disord., v. 12, no. 3, p. 198-205.

Barber, R., P. Scheltens, A. Gholkar, C. Ballard, I. McKeith, P. Ince, R. Perry, and J. O'Brien, 1999b, White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging: J.Neurol.Neurosurg.Psychiatry, v. 67, no. 1, p. 66-72.

Barnes, J., and L. Boubert, 2008, Executive functions are impaired in patients with Parkinson's disease with visual hallucinations: J.Neurol.Neurosurg.Psychiatry, v. 79, no. 2, p. 190-192.

Barnes, J., L. Boubert, J. Harris, A. Lee, and A. S. David, 2003, Reality monitoring and visual hallucinations in Parkinson's disease: Neuropsychologia, v. 41, no. 5, p. 565-574.

Barnes, J., and A. S. David, 2001, Visual hallucinations in Parkinson's disease: a review and phenomenological survey: J.Neurol.Neurosurg.Psychiatry, v. 70, no. 6, p. 727-733.

Basser, P. J., J. Mattiello, and D. LeBihan, 1994, Estimation of the effective self-diffusion tensor from the NMR spin echo: J.Magn Reson.B, v. 103, no. 3, p. 247-254.

Basser, P. J., and C. Pierpaoli, 1996, Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI: J.Magn Reson.B, v. 111, no. 3, p. 209-219.

Batelli S, Albani D, Rametta R, Polito L, Prato F, Pesaresi M, Negro A, Forloni G, 2008, DJ-1 modulates alpha-synuclein aggregation state in a cellular model of oxidative stress: relevance for Parkinson's disease and involvement of HSP70. PLoS One., v. 3, no. 4, p. e1884.

Beyer, M. K., and D. Aarsland, 2008, Grey matter atrophy in early versus late dementia in Parkinson's disease: Parkinsonism.Relat Disord., v. 14, no. 8, p. 620-625.

Beyer, M. K., C. C. Janvin, J. P. Larsen, and D. Aarsland, 2007a, A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry: J.Neurol.Neurosurg.Psychiatry, v. 78, no. 3, p. 254-259.

Beyer, M. K., J. P. Larsen, and D. Aarsland, 2007b, Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies: Neurology, v. 69, no. 8, p. 747-754.

Blackwood, N. J., R. J. Howard, D. H. ffytche, A. Simmons, R. P. Bentall, and R. M. Murray, 2000, Imaging attentional and attributional bias: an fMRI approach to the paranoid delusion: Psychol.Med., v. 30, no. 4, p. 873-883.

Boecker, H., A. O. Ceballos-Baumann, D. Volk, B. Conrad, H. Forstl, and P. Haussermann, 2007, Metabolic alterations in patients with Parkinson disease and visual hallucinations: Arch.Neurol., v. 64, no. 7, p. 984-988.

Bohnen, N. I. et al., 2006, Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia: J.Neurol., v. 253, no. 2, p. 242-247.

Bouchard, T. P., N. Malykhin, W. R. Martin, C. C. Hanstock, D. J. Emery, N. J. Fisher, and R. M. Camicioli, 2008, Age and dementia-associated atrophy predominates in the hippocampal head and amygdala in Parkinson's disease: Neurobiol.Aging, v. 29, no. 7, p. 1027-1039.

Bozzali, M., and A. Cherubini, 2007, Diffusion tensor MRI to investigate dementias: a brief review: Magn Reson.Imaging, v. 25, no. 6, p. 969-977.

Bozzali, M. et al., 2005, Brain tissue damage in dementia with Lewy bodies: an in vivo diffusion tensor MRI study: Brain, v. 128, no. Pt 7, p. 1595-1604.

Braak, H., J. R. Bohl, C. M. Muller, U. Rub, R. A. de Vos, and T. K. Del, 2006a, Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered: Mov Disord., v. 21, no. 12, p. 2042-2051.

Braak, H., T. K. Del, U. Rub, R. A. de Vos, E. N. Jansen Steur, and E. Braak, 2003, Staging of brain pathology related to sporadic Parkinson's disease: Neurobiol.Aging, v. 24, no. 2, p. 197-211.

Braak, H., U. Rub, and T. K. Del, 2006b, Cognitive decline correlates with neuropathological stage in Parkinson's disease: J.Neurol.Sci., v. 248, no. 1-2, p. 255-258.

Bradshaw, J. M., M. Saling, V. Anderson, M. Hopwood, and A. Brodtmann, 2006, Higher cortical deficits influence attentional processing in dementia with Lewy bodies, relative to patients with dementia of the Alzheimer's type and controls: J.Neurol.Neurosurg.Psychiatry, v. 77, no. 10, p. 1129-1135.

Brar, S., D. Henderson, J. Schenck, and E. A. Zimmerman, 2009, Iron accumulation in the substantia nigra of patients with Alzheimer disease and parkinsonism: Arch.Neurol., v. 66, no. 3, p. 371-374.

Broderick, P. A., D. N. Rahni, and E. H. Kolodny, 2005,Broderick, P. A., D. N. Rahni, and E. H. Kolodny Bioimaging in Neurodegeneration: NJ, Humana Press.

Bronnick, K. S., H. Nordby, J. P. Larsen, and D. Aarsland, 2008, Disturbance of automatic auditory change detection in dementia associated with Parkinson's disease: A mismatch negativity study: Neurobiol.Aging.

Burton, E. J., R. Barber, E. B. Mukaetova-Ladinska, J. Robson, R. H. Perry, E. Jaros, R. N. Kalaria, and J. T. O'Brien, 2009, Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis: Brain, v. 132, no. Pt 1, p. 195-203.

Burton, E. J. et al., 2002, Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry: Neuroimage., v. 17, no. 2, p. 618-630.

Burton, E. J., I. G. McKeith, D. J. Burn, M. J. Firbank, and J. T. O'Brien, 2006, Progression of white matter hyperintensities in Alzheimer disease, dementia with lewy bodies, and Parkinson disease dementia: a comparison with normal aging: Am.J.Geriatr.Psychiatry, v. 14, no. 10, p. 842-849.

Burton, E. J., I. G. McKeith, D. J. Burn, and J. T. O'Brien, 2005, Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging: Mov Disord., v. 20, no. 12, p. 1571-1576.

Burton, E. J., I. G. McKeith, D. J. Burn, E. D. Williams, and J. T. O'Brien, 2004, Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls: Brain, v. 127, no. Pt 4, p. 791-800.

Caltagirone, C., A. Carlesimo, U. Nocentini, and S. Vicari, 1989, Differential aspects of cognitive impairment in patients suffering from Parkinson's and Alzheimer's disease: a neuropsychological evaluation: Int.J.Neurosci., v. 44, no. 1-2, p. 1-7.

Camicioli, R., M. M. Moore, A. Kinney, E. Corbridge, K. Glassberg, and J. A. Kaye, 2003, Parkinson's disease is associated with hippocampal atrophy: Mov Disord., v. 18, no. 7, p. 784-790.

Caviness, J. N., E. Driver-Dunckley, D. J. Connor, M. N. Sabbagh, J. G. Hentz, B. Noble, V. G. Evidente, H. A. Shill, and C. H. Adler, 2007, Defining mild cognitive impairment in Parkinson's disease: Mov Disord., v. 22, no. 9, p. 1272-1277.

Ceravolo, R. et al., 2006, Brain perfusion effects of cholinesterase inhibitors in Parkinson's disease with dementia: J.Neural Transm., v. 113, no. 11, p. 1787-1790.

Collerton, D., E. Perry, and I. McKeith, 2005, Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations: Behav.Brain Sci., v. 28, no. 6, p. 737-757.

Colloby, S. J., E. D. Williams, D. J. Burn, J. J. Lloyd, I. G. McKeith, and J. T. O'Brien, 2005, Progression of dopaminergic degeneration in dementia with Lewy bodies and Parkinson's disease with and without dementia assessed using 123I-FP-CIT SPECT: Eur.J.Nucl.Med Mol.Imaging, v. 32, no. 10, p. 1176-1185.

Colosimo, C. et al., 2009, Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study: J.Neurol..

Conners, C. K., 1985, The computerized continuous performance test: Psychopharmacol.Bull., v. 21, no. 4, p. 891-892.

Cormack, F., D. Aarsland, C. Ballard, and M. J. Tovee, 2004, Pentagon drawing and neuropsychological performance in Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease and Parkinson's disease with dementia: Int.J.Geriatr.Psychiatry, v. 19, no. 4, p. 371-377.

Cousins, D. A., E. J. Burton, D. Burn, A. Gholkar, I. G. McKeith, and J. T. O'Brien, 2003, Atrophy of the putamen in dementia with Lewy bodies but not Alzheimer's disease: an MRI study: Neurology, v. 61, no. 9, p. 1191-1195.

Crinion J, Ashburner J, Leff A, Brett M, Price CJ, Friston KJ, 2007, Spatial normalization of lesioned brains: Performance evaluation and impact on fMRI analyses. *Neuroimage*, v. 37, no. 3:866-875.

Cummings, J. L., 2003, Toward a molecular neuropsychiatry of neurodegenerative diseases: Ann.Neurol., v. 54, no. 2, p. 147-154.

Cummings, J. L., M. Mega, K. Gray, S. Rosenberg-Thompson, D. A. Carusi, and J. Gornbein, 1994, The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia: Neurology, v. 44, no. 12, p. 2308-2314.

Daniel, S. E., and A. J. Lees, 1993, Parkinson's Disease Society Brain Bank, London: overview and research: J.Neural Transm.Suppl, v. 39, p. 165-172.

Dauer, W., and S. Przedborski, 2003, Parkinson's disease: mechanisms and models: Neuron, v. 39, no. 6, p. 889-909.

de Rijk, M. C., C. Tzourio, M. M. Breteler, J. F. Dartigues, L. Amaducci, S. Lopez-Pousa, J. M. Manubens-Bertran, A. Alperovitch, and W. A. Rocca, 1997, Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease: J.Neurol.Neurosurg.Psychiatry, v. 62, no. 1, p. 10-15.

Dennet, D., 1991,Dennet, D. Consciousness explained: The Penguin Press.

Diederich, N. J., G. Fenelon, G. Stebbins, and C. G. Goetz, 2009, Hallucinations in Parkinson disease: Nat.Rev Neurol., v. 5, no. 6, p. 331-342.

Diederich, N. J., C. G. Goetz, and G. T. Stebbins, 2005, Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perceptions: focused review and a new integrative model: Mov Disord., v. 20, no. 2, p. 130-140.

Dirnberger G, Frith CD, Jahanshahi M, 2005, Executive dysfunction in Parkinson's disease is associated with altered pallidal-frontal processing, Neuroimage, v. 25, no. 2, p. 588-99

Donnemiller, E., J. Heilmann, G. K. Wenning, W. Berger, C. Decristoforo, R. Moncayo, W. Poewe, and G. Ransmayr, 1997, Brain perfusion scintigraphy with 99mTc-HMPAO or 99mTc-ECD and 123I-beta-CIT single-photon emission tomography in dementia of the Alzheimer-type and diffuse Lewy body disease: Eur.J.Nucl.Med, v. 24, no. 3, p. 320-325.

Downes, J. J., N. M. Priestley, M. Doran, J. Ferran, E. Ghadiali, and P. Cooper, 1998, Intellectual, mnemonic, and frontal functions in dementia with Lewy bodies: A comparison with early and advanced Parkinson's disease: Behav.Neurol., v. 11, no. 3, p. 173-183.

Dubois B, Pillon B, 1997, Cognitive deficits in Parkinson’s disease. J Neurol, 244: 2–8.

Dufouil, C. et al., 2000, Population norms for the MMSE in the very old: estimates based on longitudinal data. Mini-Mental State Examination: Neurology, v. 55, no. 11, p. 1609-1613.

Emre, M., 2003, Dementia associated with Parkinson's disease: Lancet Neurol., v. 2, no. 4, p. 229-237.

Emre, M. et al., 2007, Clinical diagnostic criteria for dementia associated with Parkinson's disease: Mov Disord., v. 22, no. 12, p. 1689-1707.

Fahn S, 1987, Unified Idiopathic Parkinson's disease Rating Scale., in Fahn S ed., Florham Park, NJ., Macmillan Health Care Information, Recent Developments in Parkinson's Disease, Vol 2., p. 153-164.

Fan J., et al, 2002, Testing the efficiency and independence of attentional networks. Cogn Neurosc, v. 14, no. 3, 340-347.

Fan, J., B. D. McCandliss, J. Fossella, J. I. Flombaum, and M. I. Posner, 2005, The activation of attentional networks: Neuroimage., v. 26, no. 2, p. 471-479.

Fenelon, G., and F. Mahieux, 2004, [Hallucinations and dementia. Prevalence, clinical presentation and pathophysiology]: Rev Neurol.(Paris), v. 160, no. 4 Pt 2, p. S31-S43.

Ferman, T. J. et al., 2006, Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease: Clin.Neuropsychol., v. 20, no. 4, p. 623-636.

Ferrer, I., 2009, Early involvement of the cerebral cortex in Parkinson's disease: convergence of multiple metabolic defects: Prog.Neurobiol., v. 88, no. 2, p. 89-103.

Filoteo, J. V., D. P. Salmon, D. M. Schiehser, A. E. Kane, J. M. Hamilton, L. M. Rilling, J. A. Lucas, V. Zizak, and D. R. Galasko, 2009, Verbal learning and memory in patients with dementia with Lewy bodies or Parkinson's disease with dementia: J.Clin.Exp.Neuropsychol., p. 1-12.

Firbank, M. J., A. M. Blamire, M. S. Krishnan, A. Teodorczuk, P. English, A. Gholkar, R. Harrison, and J. T. O'Brien, 2007a, Atrophy is associated with posterior cingulate white matter disruption in dementia with Lewy bodies and Alzheimer's disease: Neuroimage., v. 36, no. 1, p. 1-7.

Firbank, M. J., A. M. Blamire, M. S. Krishnan, A. Teodorczuk, P. English, A. Gholkar, R. M. Harrison, and J. T. O'Brien, 2007b, Diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease: Psychiatry Res., v. 155, no. 2, p. 135-145.

Firbank, M. J., S. J. Colloby, D. J. Burn, I. G. McKeith, and J. T. O'Brien, 2003, Regional cerebral blood flow in Parkinson's disease with and without dementia: Neuroimage., v. 20, no. 2, p. 1309-1319.

Foltynie T, Brayne CE, Robbins TW, Barker RA, 2004, The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study, Brain, 2004 v. 127, no. 3, p. 550-60.

Folstein, M. F., L. N. Robins, and J. E. Helzer, 1983, The Mini-Mental State Examination: Arch.Gen.Psychiatry, v. 40, no. 7, p. 812.

Forno, L.S., 1969, Concentric hyalin intraneuronal inclusions of Lewy type in the brains of elderly persons (50 incidental cases): relationship to parkinsonism, J. Am. Geriatr. Soc., v. 17, p. 557–575.

Frigerio, R. et al., 2009, Comparison of risk factor profiles in incidental Lewy body disease and Parkinson disease: Arch.Neurol., v. 66, no. 9, p. 1114-1119.

Galvin, J. E., J. Pollack, and J. C. Morris, 2006, Clinical phenotype of Parkinson disease dementia: Neurology, v. 67, no. 9, p. 1605-1611.

Geroldi, C., N. M. Akkawi, S. Galluzzi, M. Ubezio, G. Binetti, O. Zanetti, M. Trabucchi, and G. B. Frisoni, 2000, Temporal lobe asymmetry in patients with Alzheimer's disease with delusions: J.Neurol.Neurosurg.Psychiatry, v. 69, no. 2, p. 187-191.

Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M, 2008, Second consensus statement on the diagnosis of multiple system atrophy. Neurology, Aug 26;71(9):670-6.

Goldberg, K. B., and R. E. Goldberg, 2000, Is seeing believing? Visual hallucinations in age-related macular degeneration and Charles Bonnet: J.Ophthalmic Nurs.Technol., v. 19, no. 1, p. 39-42.

Golden, C., 2001, Stroop Test.

Griffith, H. R., J. A. den Hollander, O. C. Okonkwo, T. O'Brien, R. L. Watts, and D. C. Marson, 2008, Brain N-acetylaspartate is reduced in Parkinson disease with dementia: Alzheimer Dis.Assoc.Disord., v. 22, no. 1, p. 54-60.

Grossi, D., L. Trojano, M. T. Pellecchia, M. Amboni, N. A. Fragassi, and P. Barone, 2005, Frontal dysfunction contributes to the genesis of hallucinations in non-demented Parkinsonian patients: Int.J.Geriatr.Psychiatry, v. 20, no. 7, p. 668-673.

Halliday, G. M., and H. McCann, 2008, Human-based studies on alpha-synuclein deposition and relationship to Parkinson's disease symptoms: Exp.Neurol., v. 209, no. 1, p. 12-21.

Halliday et al., 2008b, The progression of pathology in longitudinally followed patients with Parkinson’s disease Acta Neuropathol, v. 115, p. 409–415

Hamilton, J. M., D. P. Salmon, D. Galasko, R. Raman, J. Emond, L. A. Hansen, E. Masliah, and L. J. Thal, 2008, Visuospatial deficits predict rate of cognitive decline in autopsy-verified dementia with Lewy bodies: Neuropsychology., v. 22, no. 6, p. 729-737.

Hanyu, H., Y. Tanaka, S. Shimizu, H. Sakurai, T. Iwamoto, and K. Abe, 2005, Differences in MR features of the substantia innominata between dementia with Lewy bodies and Alzheimer's disease: J.Neurol., v. 252, no. 4, p. 482-484.

Harding, A. J., G. A. Broe, and G. M. Halliday, 2002a, Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe: Brain, v. 125, no. Pt 2, p. 391-403.

Harding, A. J., and G. M. Halliday, 2001, Cortical Lewy body pathology in the diagnosis of dementia: Acta Neuropathol., v. 102, no. 4, p. 355-363.

Harding, A. J., B. Lakay, and G. M. Halliday, 2002b, Selective hippocampal neuron loss in dementia with Lewy bodies: Ann.Neurol., v. 51, no. 1, p. 125-128.

Harding, A. J., E. Stimson, J. M. Henderson, and G. M. Halliday, 2002c, Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease: Brain, v. 125, no. Pt 11, p. 2431-2445.

Hashimoto, M., H. Kitagaki, T. Imamura, N. Hirono, T. Shimomura, H. Kazui, S. Tanimukai, T. Hanihara, and E. Mori, 1998, Medial temporal and whole-brain atrophy in dementia with Lewy bodies: a volumetric MRI study: Neurology, v. 51, no. 2, p. 357-362.

Hassler R, 1938, Zur pathologie der paralysis agitans und des postenzephalitischen Parkinsonismus. J Psychologie Neurologie 48:387-476.

Hely, M. A., W. G. Reid, M. A. Adena, G. M. Halliday, and J. G. Morris, 2008, The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years: Mov Disord., v. 23, no. 6, p. 837-844.

Henry JD, Crawford JR, 2004, Verbal fluency deficits in Parkinson's disease: a meta-analysis, J Int Neuropsychol Soc, v. 10, no. 4, p.608-22.

Higginson, C. I., V. L. Wheelock, K. E. Carroll, and K. A. Sigvardt, 2005, Recognition memory in Parkinson's disease with and without dementia: evidence inconsistent with the retrieval deficit hypothesis: J.Clin.Exp.Neuropsychol., v. 27, no. 4, p. 516-528.

Higuchi, M. et al., 2000, Glucose hypometabolism and neuropathological correlates in brains of dementia with Lewy bodies: Exp.Neurol., v. 162, no. 2, p. 247-256.

Hilker, R., A. V. Thomas, J. C. Klein, S. Weisenbach, E. Kalbe, L. Burghaus, A. H. Jacobs, K. Herholz, and W. D. Heiss, 2005, Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways: Neurology, v. 65, no. 11, p. 1716-1722.

Hoehn, M. M., and M. D. Yahr, 1967, Parkinsonism: onset, progression and mortality: Neurology, v. 17, no. 5, p. 427-442.

Holroyd, S., L. Currie, and G. F. Wooten, 2001, Prospective study of hallucinations and delusions in Parkinson's disease: J.Neurol.Neurosurg.Psychiatry, v. 70, no. 6, p. 734-738.

Horimoto, Y., M. Matsumoto, H. Nakazawa, H. Yuasa, M. Morishita, H. Akatsu, H. Ikari, T. Yamamoto, and K. Kosaka, 2003, Cognitive conditions of pathologically confirmed dementia with Lewy bodies and Parkinson's disease with dementia: J.Neurol.Sci., v. 216, no. 1, p. 105-108.

Hosokai, Y. et al., 2009, Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment: Mov Disord., v. 24, no. 6, p. 854-862.

Hu, M. T., S. J. White, K. R. Chaudhuri, R. G. Morris, G. M. Bydder, and D. J. Brooks, 2001, Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline: J.Neural Transm., v. 108, no. 5, p. 571-580.

Huang, C., C. Tang, A. Feigin, M. Lesser, Y. Ma, M. Pourfar, V. Dhawan, and D. Eidelberg, 2007, Changes in network activity with the progression of Parkinson's disease: Brain, v. 130, no. Pt 7, p. 1834-1846.

Hurtig, H. I. et al., 2000, Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease: Neurology, v. 54, no. 10, p. 1916-1921.

Ibarretxe-Bilbao, N., B. Ramirez-Ruiz, E. Tolosa, M. J. Marti, F. Valldeoriola, N. Bargallo, and C. Junque, 2008, Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia: J.Neurol., v. 255, no. 9, p. 1324-1331.

Imamura, K., K. Wada-Isoe, M. Kitayama, and K. Nakashima, 2008, Executive dysfunction in non-demented Parkinson's disease patients with hallucinations: Acta Neurol.Scand., v. 117, no. 4, p. 255-259.

Imamura, T., N. Hirono, M. Hashimoto, T. Shimomura, S. Tanimukai, H. Kazui, T. Hanihara, and E. Mori, 1999, Clinical diagnosis of dementia with Lewy bodies in a Japanese dementia registry: Dement.Geriatr.Cogn Disord., v. 10, no. 3, p. 210-216.

Imamura, T., K. Ishii, N. Hirono, M. Hashimoto, S. Tanimukai, H. Kazui, T. Hanihara, M. Sasaki, and E. Mori, 2001, Occipital glucose metabolism in dementia with lewy bodies with and without Parkinsonism: a study using positron emission tomography: Dement.Geriatr.Cogn Disord., v. 12, no. 3, p. 194-197.

Ishii, K., T. Soma, A. K. Kono, K. Sofue, N. Miyamoto, T. Yoshikawa, E. Mori, and K. Murase, 2007, Comparison of regional brain volume and glucose metabolism between patients with mild dementia with lewy bodies and those with mild Alzheimer's disease: J.Nucl.Med, v. 48, no. 5, p. 704-711.

Ito, K. et al., 2002, Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[18F]fluoro-L-dopa PET study: Brain, v. 125, no. Pt 6, p. 1358-1365.

Jahanshahi M Jenkins HI Brown RG Marsden CD Passingham RE Brooks CD, 1995, Self-initiated versus externally-triggered movements: I. An investigation using regional cerebral blood flow and movement-related potentials in normals and in patients with Parkinson's disease. Brain, v. 118, p. 913-33

Jahanshahi M, Jones CRG, Dirnberger G, Frith CD, 2006, The substantia nigra pars compacta and temporal processing. J Neuroscience, v. 26, p. 12266-73

Janvin, C. C., J. P. Larsen, D. P. Salmon, D. Galasko, K. Hugdahl, and D. Aarsland, 2006, Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's disease: Mov Disord., v. 21, no. 3, p. 337-342.

Jellinger, K.A., 2004, Lewy body-related alpha-synucleinopathy in the aged human brain, J. Neural Transm., V. 111, p.1219–1235.

Jellinger, K. A., 2006, The morphological basis of mental dysfunction in Parkinson's disease: J.Neurol.Sci., v. 248, no. 1-2, p. 167-172.

Jellinger, K. A., 2009a, A critical evaluation of current staging of alpha-synuclein pathology in Lewy body disorders: Biochim.Biophys.Acta, v. 1792, no. 7, p. 730-740.

Jellinger, K. A., 2009b, Significance of brain lesions in Parkinson disease dementia and Lewy body dementia: Front Neurol.Neurosci., v. 24, p. 114-125.

Johnson, D. K., J. C. Morris, and J. E. Galvin, 2005, Verbal and visuospatial deficits in dementia with Lewy bodies: Neurology, v. 65, no. 8, p. 1232-1238.

Jokinen, P., A. Bruck, S. Aalto, S. Forsback, R. Parkkola, and J. O. Rinne, 2009, Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy: Parkinsonism.Relat Disord., v. 15, no. 2, p. 88-93.

Junque, C., B. Ramirez-Ruiz, E. Tolosa, C. Summerfield, M. J. Marti, P. Pastor, B. Gomez-Anson, and J. M. Mercader, 2005, Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia: Mov Disord., v. 20, no. 5, p. 540-544.

Kasama, S., H. Tachibana, K. Kawabata, and H. Yoshikawa, 2005, Cerebral blood flow in Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease according to three-dimensional stereotactic surface projection imaging: Dement.Geriatr.Cogn Disord., v. 19, no. 5-6, p. 266-275.

Kaufer DI, Cummings JL, 1997, Dementia and delirium: an overview; in Feinberg TE, Farah MJ (eds): Behavioral Neurology and Neuropsychology. New York, McGraw-Hill, pp 499–520.

Kawabata, K., H. Tachibana, and M. Sugita, 1991, Cerebral blood flow and dementia in Parkinson's disease: J.Geriatr.Psychiatry Neurol., v. 4, no. 4, p. 194-203.

Kenny, E. R., E. J. Burton, and J. T. O'Brien, 2008, A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia: Dement.Geriatr.Cogn Disord., v. 26, no. 3, p. 218-225.

Kiebel SJ, Poline JB, Friston KJ, Holmes AP, and Worsley KJ, 1999, Robust Smoothness Estimation in Statistical Parametric Maps Using Standardized Residuals from the General Linear Model. Neuroimage, v. 10:756-766.

Klein, C., D. Kompf, U. Pulkowski, A. Moser, and P. Vieregge, 1997, A study of visual hallucinations in patients with Parkinson's disease: J.Neurol., v. 244, no. 6, p. 371-377.

Kovari, E., G. Gold, F. R. Herrmann, A. Canuto, P. R. Hof, C. Bouras, and P. Giannakopoulos, 2003, Lewy body densities in the entorhinal and anterior cingulate cortex predict cognitive deficits in Parkinson's disease: Acta Neuropathol., v. 106, no. 1, p. 83-88.

Kraybill, M. L., E. B. Larson, D. W. Tsuang, L. Teri, W. C. McCormick, J. D. Bowen, W. A. Kukull, J. B. Leverenz, and M. M. Cherrier, 2005, Cognitive differences in dementia patients with autopsy-verified AD, Lewy body pathology, or both: Neurology, v. 64, no. 12, p. 2069-2073.

Krishnan S, Chi EY, Wood SJ, Kendrick BS, Li C, Garzon-Rodriguez W, Wypych J, Randolph TW, Narhi LO, Biere AL, Citron M, Carpenter JF, 2003, Oxidative dimer formation is the critical rate-limiting step for Parkinson's disease alpha-synuclein fibrillogenesis. Biochemistry., v. 42, no. 3, p. 829-37.

Laakso, M. P., K. Partanen, P. Riekkinen, M. Lehtovirta, E. L. Helkala, M. Hallikainen, T. Hanninen, P. Vainio, and H. Soininen, 1996, Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: An MRI study: Neurology, v. 46, no. 3, p. 678-681.

Le, B. D., 1991, Molecular diffusion nuclear magnetic resonance imaging: Magn Reson.Q., v. 7, no. 1, p. 1-30.

Le, B. D., J. F. Mangin, C. Poupon, C. A. Clark, S. Pappata, N. Molko, and H. Chabriat, 2001, Diffusion tensor imaging: concepts and applications: J.Magn Reson.Imaging, v. 13, no. 4, p. 534-546.

Le, B. D., and Z. P. van, 2002, From the diffusion coefficient to the diffusion tensor: NMR Biomed., v. 15, no. 7-8, p. 431-434.

Lee, P. H., S. W. Yong, and Y. S. An, 2008, Changes in cerebral glucose metabolism in patients with Parkinson disease with dementia after cholinesterase inhibitor therapy: J.Nucl.Med, v. 49, no. 12, p. 2006-2011.

Leverenz, J. B. et al., 2008, Empiric refinement of the pathologic assessment of Lewy-related pathology in the dementia patient: Brain Pathol., v. 18, no. 2, p. 220-224.

Lezak MD, 2004, Neuropsychological Assessment: New York, Oxford University Press.

Lippa, C. F. et al., 2007, DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers: Neurology, v. 68, no. 11, p. 812-819.

Litvan I, Mohr E, Williams J, Gomez C, Chase TN, 1991, Differential memory and executive functions in demented patients with Parkinson's and Alzheimer's disease, J Neurol Neurosurg Psychiatry, v. 54, no. 1, p. 25-9.

Liu, R., Lin, S., Wang, D. Shan, J.L. Fuh, S.H. Yeh, and H.C. Liu, 1992, Cognition and 99Tcm-HMPAO SPECT in Parkinson's disease: Nucl.Med Commun., v. 13, no. 10, p. 744-748.

Llebaria, G., J. Pagonabarraga, J. Kulisevsky, C. Garcia-Sanchez, B. Pascual-Sedano, A. Gironell, and M. Martinez-Corral, 2008, Cut-off score of the Mattis Dementia Rating Scale for screening dementia in Parkinson's disease: Mov Disord., v. 23, no. 11, p. 1546-1550.

Markesbery, W. R., G. A. Jicha, H. Liu, and F. A. Schmitt, 2009, Lewy body pathology in normal elderly subjects: J.Neuropathol.Exp.Neurol., v. 68, no. 7, p. 816-822.

Matilla, A. et al., 1998, Mice lacking ataxin-1 display learning deficits and decreased hippocampal paired-pulse facilitation: J.Neurosci., v. 18, no. 14, p. 5508-5516.

Matsui, H., K. Nishinaka, M. Oda, N. Hara, K. Komatsu, T. Kubori, and F. Udaka, 2006a, Hypoperfusion of the visual pathway in parkinsonian patients with visual hallucinations: Mov Disord., v. 21, no. 12, p. 2140-2144.

Matsui, H., K. Nishinaka, M. Oda, H. Niikawa, T. Kubori, and F. Udaka, 2007, Dementia in Parkinson's disease: diffusion tensor imaging: Acta Neurol.Scand., v. 116, no. 3, p. 177-181.

Matsui, H., F. Udaka, A. Tamura, M. Oda, T. Kubori, K. Nishinaka, and M. Kameyama, 2006b, Impaired visual acuity as a risk factor for visual hallucinations in Parkinson's disease: J.Geriatr.Psychiatry Neurol., v. 19, no. 1, p. 36-40.

McKeith, I. G. et al., 2005, Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium: Neurology, v. 65, no. 12, p. 1863-1872.

McKeith, I. G. et al., 1996, Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop: Neurology, v. 47, no. 5, p. 1113-1124.

McKeith, I. G., and U. P. Mosimann, 2004, Dementia with Lewy bodies and Parkinson's disease: Parkinsonism.Relat Disord., v. 10 Suppl 1, p. S15-S18.

Mechelli A, 2005, Voxel-Based Morphometry of the Human Brain: Methods and Applications.: Curr Med Imaging Rev, v. 1, p. 1.

Meppelink, A. M., B. M. de Jong, R. Renken, K. L. Leenders, F. W. Cornelissen, and L. T. van, 2009, Impaired visual processing preceding image recognition in Parkinson's disease patients with visual hallucinations: Brain.

Merle James,G, 2001, Cortical Vision Screening Test (CORVIST). Pearson Education Ltd.

Meyer, J. S., J. Huang, and M. H. Chowdhury, 2007, MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias: J.Neurol.Sci., v. 257, no. 1-2, p. 97-104.

Minoshima, S., N. L. Foster, A. A. Sima, K. A. Frey, R. L. Albin, and D. E. Kuhl, 2001, Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation: Ann.Neurol., v. 50, no. 3, p. 358-365.

Mirzaei, S., P. Knoll, H. Koehn, and T. Bruecke, 2003, Assessment of diffuse Lewy body disease by 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET): BMC.Nucl.Med, v. 3, no. 1, p. 1.

Mito, Y., K. Yoshida, I. Yabe, K. Makino, M. Hirotani, K. Tashiro, S. Kikuchi, and H. Sasaki, 2005, Brain 3D-SSP SPECT analysis in dementia with Lewy bodies, Parkinson's disease with and without dementia, and Alzheimer's disease: Clin.Neurol.Neurosurg., v. 107, no. 5, p. 396-403.

Mondon, K. et al., 2007, Visual recognition memory differentiates dementia with Lewy bodies and Parkinson's disease dementia: J.Neurol.Neurosurg.Psychiatry, v. 78, no. 7, p. 738-741.

Monti B, Polazzi E, Batti L, Crochemore C, Virgili M, Contestabile A.J, 2007, Alpha-synuclein protects cerebellar granule neurons against 6-hydroxydopamine-induced death. Neurochem., v. 103, no. 2, p. 518-30.

Mori, E., T. Shimomura, M. Fujimori, N. Hirono, T. Imamura, M. Hashimoto, S. Tanimukai, H. Kazui, and T. Hanihara, 2000, Visuoperceptual impairment in dementia with Lewy bodies: Arch.Neurol., v. 57, no. 4, p. 489-493.

Mori, S., and J. Zhang, 2006, Principles of diffusion tensor imaging and its applications to basic neuroscience research: Neuron, v. 51, no. 5, p. 527-539.

Mosimann, U. P., G. Mather, K. A. Wesnes, J. T. O'Brien, D. J. Burn, and I. G. McKeith, 2004, Visual perception in Parkinson disease dementia and dementia with Lewy bodies: Neurology, v. 63, no. 11, p. 2091-2096.

Mosimann, U. P., E. N. Rowan, C. E. Partington, D. Collerton, E. Littlewood, J. T. O'Brien, D. J. Burn, and I. G. McKeith, 2006, Characteristics of visual hallucinations in Parkinson disease dementia and dementia with lewy bodies: Am.J.Geriatr.Psychiatry, v. 14, no. 2, p. 153-160.

Muslimovic, D., B. Post, J. D. Speelman, R. J. De Haan, and B. Schmand, 2009, Cognitive decline in Parkinson's disease: a prospective longitudinal study: J.Int.Neuropsychol.Soc., v. 15, no. 3, p. 426-437.

Muslimovic, D., B. Post, J. D. Speelman, and B. Schmand, 2005, Cognitive profile of patients with newly diagnosed Parkinson disease: Neurology, v. 65, no. 8, p. 1239-1245.

Muslimovic, D., B. Schmand, J. D. Speelman, and R. J. De Haan, 2007, Course of cognitive decline in Parkinson's disease: a meta-analysis: J.Int.Neuropsychol.Soc., v. 13, no. 6, p. 920-932.

Nagano-Saito, A. et al., 2004, Visual hallucination in Parkinson's disease with FDG PET: Mov Disord., v. 19, no. 7, p. 801-806.

Nagano-Saito, A., Y. Washimi, Y. Arahata, T. Kachi, J. P. Lerch, A. C. Evans, A. Dagher, and K. Ito, 2005, Cerebral atrophy and its relation to cognitive impairment in Parkinson disease: Neurology, v. 64, no. 2, p. 224-229.

Noe, E., K. Marder, K. L. Bell, D. M. Jacobs, J. J. Manly, and Y. Stern, 2004, Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia: Mov Disord., v. 19, no. 1, p. 60-67.

O'Brien, J. T., S. J. Colloby, S. Pakrasi, E. K. Perry, S. L. Pimlott, D. J. Wyper, I. G. McKeith, and E. D. Williams, 2008, Nicotinic alpha4beta2 receptor binding in dementia with Lewy bodies using 123I-5IA-85380 SPECT demonstrates a link between occipital changes and visual hallucinations: Neuroimage., v. 40, no. 3, p. 1056-1063.

O'Brien, J. T., M. J. Firbank, U. P. Mosimann, D. J. Burn, and I. G. McKeith, 2005, Change in perfusion, hallucinations and fluctuations in consciousness in dementia with Lewy bodies: Psychiatry Res., v. 139, no. 2, p. 79-88.

O'Brien, J. T. et al., 2001, Progressive brain atrophy on serial MRI in dementia with Lewy bodies, AD, and vascular dementia: Neurology, v. 56, no. 10, p. 1386-1388.

O'Brien, T. J., V. Wadley, A. P. Nicholas, N. P. Stover, R. Watts, and H. R. Griffith, 2009, The contribution of executive control on verbal-learning impairment in patients with Parkinson's disease with dementia and Alzheimer's disease: Arch.Clin.Neuropsychol., v. 24, no. 3, p. 237-244.

Oishi, N., F. Udaka, M. Kameyama, N. Sawamoto, K. Hashikawa, and H. Fukuyama, 2005, Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations: Neurology, v. 65, no. 11, p. 1708-1715.

Okada, K., N. Suyama, H. Oguro, S. Yamaguchi, and S. Kobayashi, 1999, Medication-induced hallucination and cerebral blood flow in Parkinson's disease: J.Neurol., v. 246, no. 5, p. 365-368.

Okazaki, H., L. E. Lipkin, and S. M. Aronson, 1961, Diffuse intracytoplasmic ganglionic inclusions (Lewy type) associated with progressive dementia and quadriparesis in flexion: J. Neuropathol. Exp. Neurol., v. 20, p. 237-244.

Osaki, Y., Y. Morita, M. Fukumoto, N. Akagi, S. Yoshida, and Y. Doi, 2005, Three-dimensional stereotactic surface projection SPECT analysis in Parkinson's disease with and without dementia: Mov Disord., v. 20, no. 8, p. 999-1005.

Ota, M., N. Sato, M. Ogawa, M. Murata, S. Kuno, J. Kida, and T. Asada, 2009, Degeneration of dementia with Lewy bodies measured by diffusion tensor imaging: NMR Biomed., v. 22, no. 3, p. 280-284.

Ozer, F., H. Meral, L. Hanoglu, O. Ozturk, T. Aydemir, S. Cetin, B. Atmaca, and R. Tiras, 2007, Cognitive impairment patterns in Parkinson's disease with visual hallucinations: J.Clin.Neurosci., v. 14, no. 8, p. 742-746.

Pagonabarraga, J., J. Kulisevsky, G. Llebaria, C. Garcia-Sanchez, B. Pascual-Sedano, and A. Gironell, 2008, Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease: Mov Disord., v. 23, no. 7, p. 998-1005.

Papapetropoulos, S., D. S. McCorquodale, J. Gonzalez, L. Jean-Gilles, and D. C. Mash, 2006, Cortical and amygdalar Lewy body burden in Parkinson's disease patients with visual hallucinations: Parkinsonism.Relat Disord., v. 12, no. 4, p. 253-256.

Parkkinen L., T. Pirttila, I. Alafuzoff, 2008, Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance, Acta Neuropathol., v. 115, p. 399–407.

Perneczky, R., A. Drzezga, H. Boecker, H. Forstl, A. Kurz, and P. Haussermann, 2008a, Cerebral metabolic dysfunction in patients with dementia with Lewy bodies and visual hallucinations: Dement.Geriatr.Cogn Disord., v. 25, no. 6, p. 531-538.

Perneczky, R., A. Drzezga, H. Boecker, S. Wagenpfeil, H. Forstl, A. Kurz, and P. Haussermann, 2008b, Right prefrontal hypometabolism predicts delusions in dementia with Lewy bodies: Neurobiol.Aging.

Perriol, M. P., K. Dujardin, P. Derambure, A. Marcq, J. L. Bourriez, E. Laureau, F. Pasquier, L. Defebvre, and A. Destee, 2005, Disturbance of sensory filtering in dementia with Lewy bodies: comparison with Parkinson's disease dementia and Alzheimer's disease: J.Neurol.Neurosurg.Psychiatry, v. 76, no. 1, p. 106-108.

Petrides, M., 2005, Lateral prefrontal cortex: architectonic and functional organization: Philos.Trans.R.Soc.Lond B Biol.Sci., v. 360, no. 1456, p. 781-795.

Picton, T. W., D. T. Stuss, M. P. Alexander, T. Shallice, M. A. Binns, and S. Gillingham, 2007, Effects of focal frontal lesions on response inhibition: Cereb.Cortex, v. 17, no. 4, p. 826-838.

Posner, M. I., and M. K. Rothbart, 2007, Research on attention networks as a model for the integration of psychological science: Annu.Rev Psychol., v. 58, p. 1-23.

Ramirez-Ruiz, B., C. Junque, M. J. Marti, F. Valldeoriola, and E. Tolosa, 2006, Neuropsychological deficits in Parkinson's disease patients with visual hallucinations: Mov Disord., v. 21, no. 9, p. 1483-1487.

Ramirez-Ruiz, B., C. Junque, M. J. Marti, F. Valldeoriola, and E. Tolosa, 2007a, Cognitive changes in Parkinson's disease patients with visual hallucinations: Dement.Geriatr.Cogn Disord., v. 23, no. 5, p. 281-288.

Ramirez-Ruiz, B., M. J. Marti, E. Tolosa, D. Bartres-Faz, C. Summerfield, P. Salgado-Pineda, B. Gomez-Anson, and C. Junque, 2005, Longitudinal evaluation of cerebral morphological changes in Parkinson's disease with and without dementia: J.Neurol., v. 252, no. 11, p. 1345-1352.

Ramirez-Ruiz, B., M. J. Marti, E. Tolosa, C. Falcon, N. Bargallo, F. Valldeoriola, and C. Junque, 2008, Brain response to complex visual stimuli in Parkinson's patients with hallucinations: a functional magnetic resonance imaging study: Mov Disord., v. 23, no. 16, p. 2335-2343.

Ramirez-Ruiz, B., M. J. Marti, E. Tolosa, M. Gimenez, N. Bargallo, F. Valldeoriola, and C. Junque, 2007b, Cerebral atrophy in Parkinson's disease patients with visual hallucinations: Eur.J.Neurol., v. 14, no. 7, p. 750-756.

Ravina, B. et al., 2007, Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group: Mov Disord., v. 22, no. 8, p. 1061-1068.

Reid, W. G., M. A. Hely, J. G. Morris, G. A. Broe, M. Adena, D. J. Sullivan, and P. M. Williamson, 1996, A longitudinal of Parkinson's disease: clinical and neuropsychological correlates of dementia: J.Clin.Neurosci., v. 3, no. 4, p. 327-333.

Reisberg, B., S. H. Ferris, M. J. de Leon, and T. Crook, 1982, The Global Deterioration Scale for assessment of primary degenerative dementia: Am.J.Psychiatry, v. 139, no. 9, p. 1136-1139.

Riekkinen, P., Jr., K. Kejonen, M. P. Laakso, H. Soininen, K. Partanen, and M. Riekkinen, 1998, Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients: Neuroreport, v. 9, no. 7, p. 1507-1511.

Roane, D. M., J. D. Rogers, J. H. Robinson, and T. E. Feinberg, 1998, Delusional misidentification in association with parkinsonism: J.Neuropsychiatry Clin.Neurosci., v. 10, no. 2, p. 194-198.

Sabattoli, F., M. Boccardi, S. Galluzzi, A. Treves, P. M. Thompson, and G. B. Frisoni, 2008, Hippocampal shape differences in dementia with Lewy bodies: Neuroimage., v. 41, no. 3, p. 699-705.

Sanchez-Castaneda, C. et al., 2009, Correlations between gray matter reductions and cognitive deficits in dementia with Lewy Bodies and Parkinson's disease with dementia: Mov Disord., v. 24, no. 12, p. 1740-1746.

Santangelo, G., L. Trojano, C. Vitale, M. Ianniciello, M. Amboni, D. Grossi, and P. Barone, 2007, A neuropsychological longitudinal study in Parkinson's patients with and without hallucinations: Mov Disord., v. 22, no. 16, p. 2418-2425.

Savage, C. R., 1997, Neuropsychology of subcortical dementias: Psychiatr.Clin.North Am., v. 20, no. 4, p. 911-931.

Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ, 2009, A clinico-pathological study of subtypes in Parkinson's disease.

Shimada, H. et al., 2009, Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET: Neurology, v. 73, no. 4, p. 273-278.

Shulman, G. L., S. V. Astafiev, D. Franke, D. L. Pope, A. Z. Snyder, M. P. McAvoy, and M. Corbetta, 2009, Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks: J.Neurosci., v. 29, no. 14, p. 4392-4407.

Song, I. U., J. S. Kim, D. S. Jeong, H. J. Song, and K. S. Lee, 2008, Early neuropsychological detection and the characteristics of Parkinson's disease associated with mild dementia: Parkinsonism.Relat Disord., v. 14, no. 7, p. 558-562.

Stebbins, G. T., C. G. Goetz, M. C. Carrillo, K. J. Bangen, D. A. Turner, G. H. Glover, and J. D. Gabrieli, 2004, Altered cortical visual processing in PD with hallucinations: an fMRI study: Neurology, v. 63, no. 8, p. 1409-1416.

Sumerall, S. W., P. L. Timmons, A. L. James, M. J. Ewing, and M. E. Oehlert, 1997, Expanded norms for the Controlled Oral Word Association Test: J.Clin.Psychol., v. 53, no. 5, p. 517-521.

Summerfield, C., B. Gomez-Anson, E. Tolosa, J. M. Mercader, M. J. Marti, P. Pastor, and C. Junque, 2002, Dementia in Parkinson disease: a proton magnetic resonance spectroscopy study: Arch.Neurol., v. 59, no. 9, p. 1415-1420.

Summerfield, C., C. Junque, E. Tolosa, P. Salgado-Pineda, B. Gomez-Anson, M. J. Marti, P. Pastor, B. Ramirez-Ruiz, and J. Mercader, 2005, Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study: Arch.Neurol., v. 62, no. 2, p. 281-285.

Tam, C. W., E. J. Burton, I. G. McKeith, D. J. Burn, and J. T. O'Brien, 2005, Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies: Neurology, v. 64, no. 5, p. 861-865.

van der, G. M., 2009, In vivo magnetic resonance spectroscopy: basic methodology and clinical applications: Eur.Biophys.J.

Verleden, S., G. Vingerhoets, and P. Santens, 2007, Heterogeneity of cognitive dysfunction in Parkinson's disease: a cohort study: Eur.Neurol., v. 58, no. 1, p. 34-40.

Vingerhoets, F. J., J. G. Villemure, P. Temperli, C. Pollo, E. Pralong, and J. Ghika, 2002, Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up: Neurology, v. 58, no. 3, p. 396-401.

Wakisaka Y, Furuta A, Tanizaki Y, Kiyohara Y, Iida M, Iwaki T, 2003, Age-associated prevalence and risk factors of Lewy body pathology in a general population: the Hisayama study. Acta Neuropathol., v. 106, no. 4, p. 374-82.

Walker, M. P., G. A. Ayre, J. L. Cummings, K. Wesnes, I. G. McKeith, J. T. O'Brien, and C. G. Ballard, 2000, The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale. Two methods to assess fluctuating confusion in dementia: Br.J.Psychiatry, v. 177, p. 252-256.

Wallis, L. I., M. N. Paley, J. M. Graham, R. A. Grunewald, E. L. Wignall, H. M. Joy, and P. D. Griffiths, 2008, MRI assessment of basal ganglia iron deposition in Parkinson's disease: J.Magn Reson.Imaging, v. 28, no. 5, p. 1061-1067.

Welsh, K., N. Butters, J. Hughes, R. Mohs, and A. Heyman, 1991, Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures: Arch.Neurol., v. 48, no. 3, p. 278-281.

Whitwell, J. L., C. R. Jack, Jr., J. E. Parisi, D. S. Knopman, B. F. Boeve, R. C. Petersen, T. J. Ferman, D. W. Dickson, and K. A. Josephs, 2007a, Rates of cerebral atrophy differ in different degenerative pathologies: Brain, v. 130, no. Pt 4, p. 1148-1158.

Whitwell, J. L. et al., 2007b, Focal atrophy in dementia with Lewy bodies on MRI: a distinct pattern from Alzheimer's disease: Brain, v. 130, no. Pt 3, p. 708-719.

Wilkinson L, Khan Z, Jahanshahi M, 2009, The role of the basal ganglia and its cortical connections in sequence learning: Evidence from implicit and explicit sequence learning in Parkinson’s disease. Neuropsychologia, v. 47, p. 2564-73

Williams, D. R., and A. J. Lees, 2005, Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study: Lancet Neurol., v. 4, no. 10, p. 605-610.

Williams-Gray, C. H., T. Foltynie, C. E. Brayne, T. W. Robbins, and R. A. Barker, 2007, Evolution of cognitive dysfunction in an incident Parkinson's disease cohort: Brain, v. 130, no. Pt 7, p. 1787-1798.

Williams-Gray, C. H., T. Foltynie, S. J. Lewis, and R. A. Barker, 2006, Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options: CNS.Drugs, v. 20, no. 6, p. 477-505.

Windisch M, Wolf HJ, Hutter-Paier B, Hofmeister A, Wronski R, 2007, Is alpha-synuclein pathology a target for treatment of neurodegenerative disorders? Curr Alzheimer Res. V. 4, no. 4, p. 446-57.

Woermann, F. G., S. L. Free, M. J. Koepp, S. M. Sisodiya, and J. S. Duncan, 1999, Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI: Brain, v. 122, no. 11, p. 2101-2108.

Xu, Y., D. J. Valentino, A. I. Scher, I. Dinov, L. R. White, P. M. Thompson, L. J. Launer, and A. W. Toga, 2008, Age effects on hippocampal structural changes in old men: the HAAS: Neuroimage., v. 40, no. 3, p. 1003-1015.

Yamamoto, R. et al., 2006, Investigation of Lewy pathology in the visual pathway of brains of dementia with Lewy bodies: J.Neurol.Sci., v. 246, no. 1-2, p. 95-101.

Yoshikawa, K., Y. Nakata, K. Yamada, and M. Nakagawa, 2004, Early pathological changes in the parkinsonian brain demonstrated by diffusion tensor MRI: J.Neurol.Neurosurg.Psychiatry, v. 75, no. 3, p. 481-484.

Zhang Y, Schuff N, Jahng GH, Bayne W, Mori S, Schad L, Mueller S, Du AT, Kramer JH, Yaffe K, Chui H, Jagust WJ, Miller BL, Weiner MW, 2007, Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. Neurology, v. 68, no. 1, p. 13-9.

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Correlations Between Gray Matter Reductions and Cognitive Deficits in Dementia with Lewy Bodies and Parkinson's Disease with Dementia

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Abstract: There is controversy regarding whether Dementia with Lewy Bodies (DLB) and Parkinson's disease with dementia (PDD) may or not be different manifestations of the same disorder. The purpose of the present study was to investigate possible correlations between brain structure and neuropsychological functions in clinically diagnosed patients with DLB and PDD. The study sample consisted of 12 consecutively referred DLB patients, 16 PDD patients, and 16 healthy control subjects recruited from an outpatient setting, who underwent MRI and neuropsychological assessment. Voxel-based morphometry results showed that DLB patients had greater gray matter atrophy in the right superior frontal gyrus, the right premotor area and the right inferior frontal lobe compared to PDD. Furthermore, the anterior cingulate and prefrontal volume correlated with performance on the Continuous Performance Test while the right hippocampus and amygdala volume correlated with Visual Memory Test in the DLB group. In conclusion, DLB patients had more fronto-temporal gray matter atrophy than PDD patients and these reductions correlated with neuropsychological impairment. © 2009 Movement Disorder Society

Key words: dementia; Parkinson's disease; Lewy body disease; MRI; neuropsychology

Lewy body disease (LBD) is a spectrum of disorders characterized pathologically by alpha-synuclein inclusions in the brainstem, subcortical nuclei, limbic and neocortical areas, and clinically by attentional disturbance, Parkinsonism, dementia, and visual hallucinations.[1] Two clinical diagnoses within the LBD spectrum are Dementia with Lewy Bodies (DLB) and Parkinson's disease with Dementia (PDD). Since the two syndromes present considerable clinical overlap, it has been argued that DLB and PDD may represent the same disease entity. DLB is diagnosed when dementia occurs before or concurrently with Parkinsonism and PDD when dementia occurs in the context of well-established Parkinson's disease.[1] Some studies compared cognitive function in PDD and DLB suggesting that DLB is characterized by specific declines in attention, executive function, visuospatial, and constructional abilities and immediate and delayed recognition memory relative to PDD,[2–4] whether other studies observed no differences between them.[5–9] Although there are two voxel-based morphometry (VBM) studies comparing DLB and PDD,[10,11] there are no studies exploring the relationship between cognitive impairment and gray matter loss.

The aim of this study was to investigate the correlations between local gray matter volume and cognitive functioning in DLB and PDD. Given that several stud-

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ies have shown that DLB patients present greater impairment in executive and attentional functions, we expected to find more pronounced gray matter changes affecting frontal areas in this group.

SUBJECTS AND METHODS

Subjects

Twelve patients with DLB, 16 patients with PDD, and 16 control subjects were recruited from an outpatient movement disorders and dementia clinic (Department of Neurology, Bellvitge University Hospital, Barcelona, Spain). The local ethics committee approved the study and written informed consent was obtained from all the participants. Clinical diagnosis was made after comprehensive multidisciplinary assessment by a neurologist and a neuropsychologist. Thus, the DLB diagnosis was made according to the Consensus Criteria,[1] the diagnosis of PD by using the UK Brain Bank criteria[12] and the diagnosis of dementia due to PD according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).[13] The control subjects were two spouses of the patients and 14 community volunteers without any history of psychiatric or neurological disorders who were matched with patients for age. The Mini Mental State Examination (MMSE)[14] was used as a general cognitive screening test, we corrected it according to age and education following published norms.[15] Reisberg's Global Deterioration Scale (GDS)[16] was used as a measure of cognitive decline. The severity of parkinsonian symptoms was assessed by subscale III of the Unified Parkinson's Disease Rating Scale (UPDRS-III)[17] and disease stage was estimated using the Hoehn and Yahr Scale.[18] We calculated a levodopa equivalent dose (levodopa and dopaminergic agonists) using previously published methods.[19] Three subjects were treated with antipsychotic medication (risperidone). In the DLB group, one subject received a daily dosage of 1 mg and the other 0.5 mg. One subject in the PDD group received a daily dose of 1 mg. Demographic and clinical characteristics of the sample are shown in Table 1.

Brain Imaging

MRI data were acquired on a 1.5 T Philips Intera machine obtaining 110 overcontiguous slices (TR = 40 milliseconds; TE = 1.79 milliseconds; fa = 35°; voxel size = $0.98 \times 0.98 \times 1.3$ mm^3). The statistical MRI analyses were carried-out using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK) running under Matlab 6.5 (MathWorks, Natick, MA). A standard VBM analysis was used to assess the pattern of gray matter changes according to previously described methods.[20] The preprocessing steps included normalization of the images to a template, segmentation into tissue classes, and modulation with Jacobian determinants and smoothing with an isotropic 8 mm Gaussian kernel filter. The resulting smoothed and modulated images were used in the statistical analysis to assess gray matter volume changes.

Differences in whole-brain gray matter between groups were assessed using one-way ANCOVA analysis including years of education, UPDRS-III score and disease duration as covariates. To perform the comparisons,

TABLE 1. *Demographic and clinical characteristics of the sample*

	PDD (n = 16)	DLB (n = 12)	Control (n = 16)	X^2/U	*P*
Sex (M:F)	11:5	8:4	8:8	1,38	NS[a]
Age	71.1 (7.2)	71.1 (10.8)	71.8 (7.6)	0,22[b]	NS[c]
Education	6.1 (6)	11 (6)	7.7 (6.5)	4,2[b]	0.05[c,d]
GDS	4.3 (0.9)	4.18 (1)	1.0	31,82[b]	0.001[c,e]
Corrected MMSE	21.8 (4.1)	19 (6.2)	28.6 (2)	22,79[b]	0.001[c,e]
UPDRS-III	35.5 (13.5)	27.3 (11)		41	0.02[c,d]
Hoehn and Yahr	2.8 (0.8)	2.8 (0.6)		82	NS[c]
Duration Parkinsonism (mo)	52.8 (27.8)	32.6 (16.1)		58	NS[c]
Levodopa dose (mg)[f]	604.9 (281.7)	471.4 (439.5)		60,5	NS[c]

The values are expressed as mean (SD).
[a]Pearson's Chi-square.
[b]Value of the X^2-statistic (Kruskal-Wallis).
[c]U-Mann Whitney.
[d]Significant differences between DLB and PDD.
[e]Significant differences between controls and DLB, PDD.
[f]Including dopamine agonists.
PDD, Parkinson disease with dementia; DLB, dementia with Lewy bodies; GDS, Global Deterioration Scale; MMSE, Mini-mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; NS, not significant.

we defined gray matter regions of interest (ROIs) in prefrontal and sensorial associative areas (temporal, parietal and occipital) following the neuropathological data of Lewy Bodies Diseases that relate dementia progression to Lewy Bodies depositions in these areas.[1,20,21] The ROIs were anatomically defined using the Pick Atlas tool of the SPM package.

To control for the effect of education, UPDRS-III and Parkinsonism duration in the correlation analyses, we used the full factorial design implemented in SPM5. There was one fix factor (clinical group) and one variable of interest (the neuropsychological function). For these analyses, we defined the same ROIs as for the group comparison analyses.

For all the statistical analyses, the threshold was settled at voxel and cluster levels $P < 0.05$ FWE corrected for multiple comparisons.

Neuropsychological Assessment

All patients underwent a neuropsychological assessment based on three cognitive domains: attention, memory, and constructional abilities, these being the main functions impaired in DLB in comparison with PDD. The battery consisted of Conner's Continuous Performance Test (CPT-II)[22] and visual and verbal memory and the drawing copy tests of the CERAD battery.[23] The CPT-II is a test to assess mantained attention and response inhibition. Single letters are presented consecutively in the center of a screen and the patient is required to press a button when any letter except the target letter "X" appears. To assess memory and constructional praxis, we used some subtests of the CERAD battery. The verbal learning task consist of an immediate free recall of 10-item word-list assessed over three separate learning trials. The subject is instructed to read aloud the 10 words each trial. Immediately, the subject is asked to recall the words. After a 5 to 8 minutes delayed period, the patient should recall them. The number of words recalled on the last trial, the delayed recall and intrusion errors were recorded. In the constructional praxis task, the subject is instructed to copy four geometrical figures and the delayed visual memory task consisted of the recall of these figures. All tests were administered and scored in accordance with conventional procedures.[24] The statistical analysis of neuropsychological data was conducted using SPSS (11.5, SPSS Inc.).

Because of the sample size and non-linear distribution of the variables, differences between groups were assessed using one-way Kruskal-Wallis test with a post-hoc Mann-Whitney U-test contrast. A X^2 test was used for qualitative variables.

RESULTS

Group VBM Analysis

The gray matter volume comparisons between groups including years of education, severity and duration of parkinsonian symptoms as covariates are shown in Table 2 and Figure 1a. We did not find significant gray matter differences in the comparisons PDD<DLB, CNT<DLB, CNT<PDD.

When we performed a regression analysis between the covariables and brain gray matter, we found that the UPDRS-III score was related to gray matter volume in the middle and inferior frontal lobe bilaterally (Left BA 11,47 and right BA 10-11), while the other two covariables were no related to any of the studied areas.

Neuropsychological Results

Mann-Whitney test comparisons (Table 3) indicated that DLB patients showed poorer performance in the vigilance variable in the CPT test. On the other hand, PDD patients made significantly more perseverations and became more erratic and less consistent during the performance of the CPT as well as committing more intrusions in the delayed verbal memory test.

TABLE 2. *Stereotactic locations and Brodmann areas (BA) of significant differences in brain volume between DLB and PDD including education, disease duration and UPDRS-III as covariates*

Region (BA)	Cluster size (mm^3)	Talairach coordinates (*x*, *y*, *z*)	*T*-value*
DBL < Controls			
Right inferior frontal (45)	1346	59, 20, 21	5.02
Left posterior cingulate	303	−3, −36, 45	4.38
Left superior temporal (38)	559	−48, 14, −12	4.46
Left inferior parietal (39)	439	−55, −66, 28	3.97
PDD < Controls			
Right cuneus (18)	445	4, −95, 15	4.19
Left inferior parietal (39)	275	−46, −70, 37	4.27
DLB < PDD			
Right superior frontal (8)	176	6, 40, 52	4.17
Right premotor area (6)	368	48, 17, 48	5.20
Right inferior frontal (45)	196	56, 22, 20	4.00

*Significance threshold $P < 0.05$ voxel-level corrected for multiple comparisons (FWE).

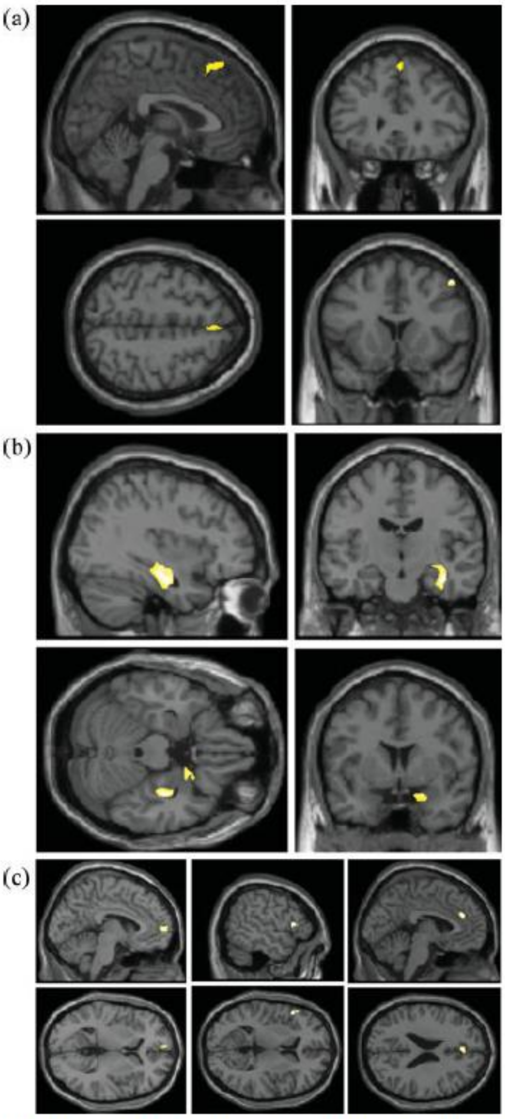

FIG. 1. A: Stereotactic locations of significant clusters of gray matter volume loss in DLB patients compared with PDD in the right superior frontal lobe and the right premotor area. **B**: Correlation between the visual memory test and right hippocampus and amigdala in the DLB group. **C**: Correlation between prefrontal areas and anterior cingulate and CPT results in the DLB group. The results are overlapped in a T1 healthy control brain. The yellow colour shows the significant areas ($P < 0.05$ FWE corrected).

Regional Gray Matter Correlations with Neuropsychological Variables

The correlation analyses (Table 4, Fig. 1b,c) showed significant correlations in the DLB group between the right hippocampus and amygdala volume and visual memory, and between the anterior cingulate and prefrontal areas (dorsolateral and inferior frontal cortex bilaterally) and performance on the CPT test (commission errors, detectability and perseverations). There were no significant correlations between the neuropsychological variables and the gray matter volume in the PDD group. However, in the control group, the right orbitofrontal volume was inversely related to the number of perseverations done in the CPT test.

DISCUSSION

To the best of our knowledge, this is the first study investigating the relationship between brain structural changes and cognitive performance in DLB and PDD. We found that DLB patients showed a consistent gray matter volume reduction involving the right superior frontal (BA 8), right premotor (BA 6) and right inferior frontal (BA 45) areas compared with PDD. Furthermore, the reduction of the gray matter volume of the inferior frontal lobe, the dorsolateral prefrontal cortex and the anterior cingulate in the DLB group was related to increased number of commission errors, perseverations and worse detectability on the CPT. These brain areas have been associated to response inhibition and executive attention,[24–26] and the Brodmann areas 6 and 8 have been involved in the circuitry of visual discrimination and attention.[25] Hence, we propose that the structural changes affecting these areas in DLB patients could lead to the visual attentional impairment considered as a core feature of DLB. These results are the first *in vivo* evidence showing the relationship between gray matter atrophic changes in prefrontal and premotor areas and attentional impairment in DLB. Moreover, in our DLB sample, right hippocampus and amygdala volumes were related to the visual memory performance.

With regard to the neuropsychological data, interestingly we found a different attentional profile: whereas DLB was characterized by distractibility during performance of the CPT (poorer vigilance and a trend for more omission errors); PDD patients showed more impulsivity on both the attentional and memory tasks (more perseverations and comission errors on the CPT and more intrusions during delayed recall).

TABLE 3. *Neuropsychological results*

	PDD (n = 16)	DLB (n = 12)	U	*P*-value
Memory: CERAD[a]				
Verbal learning	1.25 (2.1)	0.75 (0.96)	64,5	NS
Delayed verbal memory	1.31 (1.8)	0.5 (1.2)	66	NS
Intrusions in delayed verbal memory	0.88 (1.31)	0.17 (0.57)	62,5	0.05
Verbal recognition	14.75 (2.49)	12.50 (3.60)	56,5	0.06
Visual memory (delayed)	1.5 (2)	1.83 (2.98)	86,5	NS
Constructional Praxis: CERAD	4.19 (2.97)	6.42 (3.39)	59	NS
Attention: CPT[b]				
Omission errors	70 (40.4)	97.1 (68.3)	62	NS
Commission errors	23.9 (5.57)	20.3 (7.87)	49	NS
Detectability: attentiveness (d′)	0.2 (0.29)	0.23 (0.48)	71	NS
Perseverations	60.4 (43.8)	22 (17)	33,5	0.02
Vigilance[c]	−0.06 (0.07)	0 (0.04)	38,5	0.02
Adjusting to presentation speed[c]	0.26 (0.09)	0.10 (0.16)	32,5	0.01

Group comparisons were performed by U-Mann Whitney. The values are expressed as mean (SD).
[a]Values expressed as number of words.
[b]Higher punctuations indicate greater impairment.
[c]Values expressed as time.
PDD, Parkinson disease with dementia; DLB, dementia with Lewy bodies; CERAD, Consortium to establish a registry for Alzheimer Disease; CPT, Continuous Performance Test; NS, not significant.

These results are in agreement with the Noe et al.[5] study, that reported more omission errors in cancellation tasks in DLB compared to PDD. In contrast, Bronnick et al.,[27] found more pronounced attentional disturbances in PDD compared to DLB. These discrepancies could be due to the sensorial modality assesed in the attentional tasks. These authors used auditory stimuli while we used visual stimuli. The attentional impairment observed in the DLB sample could be explained by our VBM results, where the anterior cingulate and prefrontal areas correlated with performance on the CPT. These findings are consistent with the model postulated by Posner and Rothbart[28] suggesting a role for the anterior cingulate in the executive control of attention to unpredictable events and inhibitory control.

We also found a different pattern of memory impairment: the DLB group tended to perform worse on free recall and overall recognition in agreement with previous studies,[2] suggesting an encoding deficit more related to hippocampal structures. These deficits in memory could be associated with the observed atrophic changes involving prefrontal and hippocampal areas and the disruption therefore of the direct hippocampal output to the dorsolateral prefrontal cortex affected in DLB.[29] Contrarily, the PDD group made more intrusion errors in delayed memory but better functioning in free recall and recognition. The presence of better recognition than free recall in PD patients has been extensively described.[30] However, in a study with a large sample of PD patients addressed to test the retrieval deficit hypothesis, Higginson et al.[31] showed that performance on measures of cued recall and delayed recognition were not significantly better than free recall performance. These results suggested that memory deficits in PD are not solely due to retrieval problems.

This investigation has some limitations. One of the limitations is the small sample size and the selection bias of the three groups regarding the sex distribution

TABLE 4. *Correlations between neuropsychological data and brain regions in the DLB group including years of education, severity (UDPRS-III) and duration of Parkinsonian symptoms as covariates ($p_{corrected}$ < 0.05 FWE)*

Brain area	Test	Cluster size	Correlation coefficients
DLB group			
R hippocampus	Visual memory	1668	0.83
R amygdala		366	0.81
L Anterior cingulate	CPT: detectability	369	0.84
	CPT: commission err.	351	0.84
L inferior frontal	CPT: detectability	586	0.86
L inferior frontal	CPT: commission err.	68	0.83
R inferior frontal		56	0.85
L dorsolateral		98	0.82
R dorsolateral		157	0.85
L inferior frontal	CPT: perseverations	386	0.83
L dorsolateral		334	0.87
R dorsolateral		339	0.86
Control group			
R orbitofrontal	CPT: perseverations	316	0.85

CPT, continuous performance test.

and the education. Furthermore, they showed a different distribution in clinical variables such as the duration of the Parkinsonism and the degree of motor impairment. The difference in Parkinsonism duration and degree of motor impairment are consequence of the inclusion criteria. To be diagnosed of PDD subjects should have a well-established Parkinsonism for more than 1 year and this is not the case for DLB. To minimize the effect of these potential confounders, we included the years of education, UPDRS-III score and duration of Parkinsonism as covariates of no-interest in all the performed analysis.

CONCLUSIONS

Our study revealed that DLB is characterized by a greater gray matter volume loss in prefrontal areas related to attentional impairment in comparison with PDD. Neuropsychologically, DLB patients had more distractibility and tended to perform worse on memory tasks, whereas PDD patients have more impulsive errors. Furthermore, in the DLB group the right hippocampus and amygdala volume were correlated with visual memory.

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REFERENCES

1. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.
2. Mondon K, Gochard A, Marqué A, et al. Visual recognition memory differenciates dementia with Lewy bodies and Parkinson's disease with dementia. J Neurol Neurosurg Psychiatry 2007;78:738–741.
3. Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003;74:1215–1220.
4. Downes JJ, Priestley NM, Doran M, Ferran J, Ghadiali E, Cooper P. Intellectual, mnemonic, and frontal functions in dementia with Lewy bodies: a comparison with early and advanced Parkinson's disease. Behav Neurol 1998;11:173–183.
5. Noe E, Marder K, Bell KL, Jacobs DM, Manly JJ, Stern Y. Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. Mov Disord 2004;19:60–67.
6. Janvin CC, Larsen JP, Salmon DP, Galasko D, Hugdahl K, Aarsland D. Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's disease. Mov Disord 2006;21:337–342.
7. Ballard CG, Aarsland D, McKeith I, et al. Fluctuations in attention. PD dementia vs DLB with Parkinsonism. Neurology 2002;59:1714–1720.
8. Horimoto Y, Matsumoto M, Nakazawa H, et al. Cognitive conditions of pathologically confirmed dementia with Lewy bodies and Parkinson's disease with dementia. J Neurol Sci 2003;216:105–108.
9. Cormack F, Aarsland D, Ballard C, Tovée M. Pentagon drawing and neuropsychological performance in Dementia with Lewy Bodies, Alzheimer's disease, Parkinson's disease and Parkinson's disease with dementia. Int J Geriatr Psychiatry 2004;19:371–377.
10. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004;127:791–800.
11. Beyer MK, Larsen JP, Aarsland D. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies. Neurology 2007;69:747–754.
12. Daniel SE, Lees AJ. Parkinson's disease society brain bank, London: overview and research. J Neural Transm Sup 1993;39:165–172.
13. American Psychiatric Association. Manual diagnostico y estadistico de los trastornos mentales, Cuarta edición revisada, DSM-IV-TR. Barcelona: Masson; 2003.
14. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
15. Dufouil C, Clayton D, Brayne C, et al. Population norms for the MMSE in the very old. Neurology 2000;55:1609–1613.
16. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136–1139.
17. Fahn S, Elton RL,UPDRS program members. Unified idiopathic Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent developments in Parkinson's disease, Vol. 2. Florham Park, NJ: Macmillan Health Care Information; 1987. p 153–164.
18. Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.
19. Vingerhoets FJ, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J. Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 2002;58:396–401.
20. Mechelli A, Price CJ, Friston KJ, Ashburner J. Voxel-based morphometry of the human brain: methods and applications. Curr Med Imaging Rev 2005;1:1–9.
21. Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's Disease. Neurobiol Aging 2003;24:197–211.
22. Conners CK. The computerized continuous performance test. Psychopharmacol Bull 1985;21:891–892.

23. Welsh K, Butters N, Hughes JP, et al. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol 1991;48: 278–281.
24. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological assessment, 4th ed. New York: Oxford University Press; 2004.
25. Petrides M. Lateral prefrontal cortex: architectonic and functional organization. Philos Trans R Soc Lond B Biol Sci 2005;360: 781–795.
26. Fan J, McCandliss BD, Fossella J, Flombaum JI, Posner MI. The activation of attentional networks. Neuroimage 2005;26:471–479.
27. Bronnick K, Nordby H, Larsen JP, Aarsland D. Disturbances of auditory change detection in dementia associated with Parkinson's disease: a mismatch negativity study. Neurobiol Aging 2008 (Epub ahead of print).
28. Posner NI, Rothbart MK. Research on attention networks as a model for the integration of spychological science. Annu Rev Psychol 2007;58:1–23
29. Harding AJ, Broe GA, Halliday GM. Selective hippocampal neuron loss in dementia with Lewy bodies. Ann Neurol 2002;51: 125–128.
30. Savage CR. Neuropsychology of subcortical dementias. Psychiatr Clin North Am 1997;20:911–931.
31. Higginson CI, Wheelock VL, Carroll KE, Sigvardt KA. Recognition memory in Parkinson's disease with and without dementia: evidence inconsistent with the retrieval deficit hypothesis. J Clin Exp Neuropsych 2005;27:516–528.

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Enviado: sábado, 10 de octubre de 2009 8:00:14
Para: c.sanchez@idibell.org

10-Oct-2009

Dear Ms. Sanchez-Castaneda:

Thank you for submitting your revised manuscript entitled "Frontal and associative visual areas related to Visual Hallucinations in Dementia with Lewy Bodies and Parkinson's Disease with Dementia" to the Movement Disorders. It is a pleasure to accept your manuscript in its current form for publication.

A signed copyright transfer agreement is needed for publication. You can access the copyright transfer agreement at http://www3.interscience.wiley.com/homepages/76507419/CTA-Consent.pdf

Thank you for your contribution.

Sincerely,

Prof. G. Deuschl
Editor-in-Chief
Movement Disorders