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Neural and cognitive correlates of visual hallucinations in Lewy Body Disease and other degenerative dementias

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Abstract

Visual hallucinations (VH) are severe and disabling symptoms frequently experienced in dementia with Lewy bodies (DLB) and Parkinson's disease (PD), two forms of Lewy body disease (LBD), and less commonly in Alzheimer's disease (AD). The neural mechanisms underpinning VH are still unclear, specifically regarding disease and symptom-specific neurocognitive processes across conditions and their relationship with the presence of different types of dementia. The aim of this thesis was to explore the neurocognitive, structural and functional brain features associated with VH across different diagnoses, namely DLB, PD and AD.

Findings revealed that deficits in visual attention and visuoconstruction were associated with VH in DLB. Grey matter (GM) loss was found in DLB patients with VH in frontal and striatal areas, the latter being significantly associated with visual attention deficits. Structural and functional connectivity analyses also suggested an involvement of top-down and bottom-up impairments, as well as alterations in the brain default mode network in hallucinating DLB patients. Moreover, in DLB, the only significant predictor of the development of VH at follow-up was the presence of more severe verbal memory deficits at baseline. PD patients with VH presented more severe executive dysfunctions, and striatal GM loss, which correlated with both attention and executive deficits. Meta-analytic results on PD revealed occipital GM atrophy and more severe verbal memory impairments in patients with VH. Finally, AD patients with VH had more severe deficits in visuoconstructive abilities, more pronounced occipital hypometabolism and GM loss.

These findings suggest a complex combination of cognitive and neural dysfunctions related to VH across conditions, mediated by deficits in verbal memory, visual attention and visual perception, and disruption in the underpinning neural circuits. The role of specific top-down control functions might be slightly different across conditions, and seemed to involve more severe executive dysfunctions in PD, and visual attention deficits in DLB.

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AAL: Automated Anatomical Labeling; **AD:** Alzheimer's disease; **ADNI:** Alzheimer's Disease Neuroimaging Initiative; **ANCOVA:** analysis of covariance; **ANOVA:** analysis of variance; **AROMA:** Automatic Removal of Motion Artifacts; **ASL:** arterial spin labelling; **BA:** Brodmann area; **BET:** Brain Extraction Tool; **BOLD:** blood oxygen-level dependent; **BPP:** bistable percept paradigm; **CDR:** Clinical Dementia Rating; **ChEI:** cholinesterase inhibitor; **CI:** confidence interval; **CIS:** cingulate island sign; **CN:** cognitively normal; **CSF:** cerebrospinal fluid; **DAN:** dorsal attention network; **DARTEL:** Diffeomorphic Anatomical Registration using Exponentiated Lie algebra; **DAT:** dopamine transporter; **DLB:** dementia with Lewy bodies; **DMN:** default mode network; **DTI:** diffusion tensor imaging; **FA:** fractional anisotropy; **FAB:** Frontal Assessment Battery; **FDG:** fluorodeoxyglucose; **FDT:** FMRIB's Diffusion Toolbox; **fMRI:** functional magnetic resonance imaging; **FSL:** FMRIB software library; **FWE:** family-wise error; **GBA:** glucocerebrosidase; **GM:** grey matter; **H&Y:** Hoehn and Yahr scale; **HC:** healthy controls; **ICA:** independent component analysis; **ICBM:** International Consortium for Brain Mapping; **IDA:** Image Data Archive; **IFOF:** inferior fronto-occipital fasciculus; **ILF:** inferior longitudinal fasciculus; **LB:** Lewy body; **LBD:** Lewy body disease; **LRRK2:** leucine-rich repeat kinase 2; **MCI:** mild cognitive impairment; **MD:** mean diffusivity; **MDS:** Movement Disorders Society; **MMSE:** Mini-Mental State Examination; **MNI:** Montreal Neurological Institute; **MRI:** magnetic resonance imaging; **MTL:** medial temporal lobe; **NEVHI:** North-East Visual Hallucinations Interview; **NPI:** Neuropsychiatric Inventory; **NVH:** no visual hallucinations; **NVH-FU:** NVH follow-up; **OR:** odds ratio; **PAD:** Perception and Attention deficit; **PD:** Parkinson's disease; **PDD:** Parkinson's disease dementia; **PET:** positron emission tomography; **RAVLT:** Rey Auditory Verbal Learning Test; **RBD:** sleep behaviour disorder; **REM:** rapid eye movement; **REST:** Resting-State fMRI Data Analysis Toolkit; **ROI:** region of interest; **SDM:** Seed-based d Mapping; **SLF:** superior longitudinal fasciculus; **SNCA:** Synuclein Alpha; **SPECT:** single photon emission computed tomography; **SPM:** Statistical Parametric Mapping; **SPM:** Statistical Parametric Mapping; **SPSS:** Statistical Package for the Social Sciences; **TBSS:** tract-based spatial statistics; **TDP-43:** TAR DNA binding protein 43; **TFCE:** Threshold-Free Cluster Enhancement; **TIV:** total intracranial volume; **TMT:** Trail Making Test; **UPDRS:** Unified Parkinson's Disease Rating Scale; **VAN:** ventral attention network; **VBM:** voxel-based morphometry; **VH:** visual hallucinations; **VH-FU:** VH follow-up; **VOSP:** Visual and Object Space Perception; **WM:** white matter.

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To Pandi and Mimosa

Chapter 1. Lewy body disease

1.1 Historical background and general overview

The term Lewy body disease (LBD) indicates a spectrum of disorders characterised by the inclusion of pathologic α-synuclein aggregates called Lewy bodies (LBs) (Dickson et al., 2009, Lippa et al., 2007). Clinical manifestations of LB pathology include dementia with Lewy bodies (DLB), Parkinson's disease (PD), and Parkinson's disease dementia (PDD).

The clinical symptoms of PD were described for the first time in 1817 by James Parkinson, syndrome that was named after him by Jean-Martin Charcot over 50 years later (Goetz, 2011). Its neuropathology, however, remained unknown untill 1912, when Fritz Heinrich Lewy discovered the cellular inclusions that were subsequently called "Lewy bodies" in the brains of PD patients (Kosaka, 2014). LBs were found mainly in subcortical areas. Cortical Lewy bodies were first described in 1976 in a case of progressive dementia and parkinsonism that could not be classified with any of the clinical diagnostic criteria available at that time (Kosaka et al., 1976). Today, we know that widespread cortical LBs, along with the subcortical ones, are a characteristic feature of both DLB and PDD (Goedert et al., 2013, Jellinger, 2018). DLB was described as a separate clinical and pathological entity in 1996, when the first consensus guidelines for its diagnosis were published (McKeith et al., 1996). On the other hand, specific clinical criteria for the diagnosis of dementia associated with PD were established only in 2007 (Emre et al., 2007). Despite the nosological separation between DLB and PDD, whether they are distinct entities or different clinical phenotypes on a spectrum of LBD disorders is still matter of debate (Jellinger, 2018, McKeith, 2009). The term Lewy body dementia (LB dementia) usually refers to patients with DLB and PDD, and it will be used throughout this thesis with reference to both (Lippa et al., 2007).

The main biochemical component of LBs in PD and DLB was identified as α-synuclein only in 1997 (Spillantini and Goedert, 2016, Spillantini et al., 1997). Today, PD, DLB and PDD are known as α-synucleinopathies, forming part of a clinical and neuropathological spectrum of disorders. Clinically, they share a number of symptoms, among which parkinsonism, visual hallucinations (VH), sleep disorders, and cognitive impairment (Aarsland, 2016). The characterization of the symptomatology and its temporal progression may also reflect the distribution of LB pathology throughout the brain (Goedert et al., 2013, Wakabayashi et al., 2013). Besides, clinical and

neuropathological overlapping features are also observed between LB dementia and Alzheimer's disease (AD), resulting in difficulties in differential diagnosis. In fact, DLB remains largely unidentified, with a high proportion of cases misdiagnosed with other conditions (Vann Jones and O'Brien, 2014). The correct identification of each disorder is crucial for an adequate management and for the implementation of treatments targeted to specific symptomatology. Despite the impact that LBD has on patients, families and the overall related social costs as the world's population ages, the aetiology remains largely unknown and there is currently no cure. Thus, there is an urgent need of a more accurate understanding of disease and symptom-specific neurobiological mechanisms to clarify the pathophysiology of these severe conditions.

1.2 Prevalence and incidence

PD is the second most common neurodegenerative disease, and synucleinopathies the second most common neurodegenerative cause of dementia after AD (de Lau and Breteler, 2006, Outeiro et al., 2019). Several studies have investigated the prevalence and incidence of PD. However, results from different studies are not always directly comparable, mainly due to methodological differences (de Lau and Breteler, 2006, Tysnes and Storstein, 2017). For example, the use of more homogeneous diagnostic criteria would improve the quality of the epidemiological findings (de Lau and Breteler, 2006, Pringsheim et al., 2014, Tysnes and Storstein, 2017). Moreover, record-based and clinical studies may underestimate indices of prevalence and incidence, compared to door-to-door surveys (de Lau and Breteler, 2006). Overall, the occurrence of PD increases with age, and the onset rarely happens in people with less than 50 years old (de Lau and Breteler, 2006, Tysnes and Storstein, 2017). Estimated prevalence ranges between 0.1 and 0.3% in the European general population, increasing to 1% in people with 60 years old and above (von Campenhausen et al., 2005). Incidence rates were also found to increase with age, being between 11 and 19 per 100,000 people per year, up to 346 per 100,000 in people over the age of 60 (von Campenhausen et al., 2005). Similarly, more recent meta-analyses have reported increases with age in both indices, reaching a prevalence of 2% in individuals with 80 years old and above (Hirsch et al., 2016, Pringsheim et al., 2014).

Studies have shown that patients with PD have an increased risk of developing dementia than healthy people (de Lau and Breteler, 2006). Point prevalence of dementia in PD was estimated as approximately 30%, with up to 70% of patients with

more than 10-year history of PD eventually developing dementia (Aarsland and Kurz, 2010). A systematic review showed that the prevalence of PDD in the general population was roughly 0.03%, and 0.2 to 0.5% in people over 65 years old (Aarsland et al., 2005). Similarly, Vann Jones and O'Brien (2014) reported that the population prevalence of DLB in people over 65 was around 0.4%, even though a wide range from zero to 21.9% was found among the reviewed studies. In the same study, annual incidence rates showed that a diagnosis of DLB was made in around 4% of new dementia cases (Vann Jones and O'Brien, 2014). Among patients with dementia, different studies reported similar percentages of population prevalence for DLB (Vann Jones and O'Brien, 2014) and PDD (Aarsland et al., 2005), reaching roughly 4% for each condition. However, it is worth highlighting that a study published in 2008 found that the frequency of DLB in specialist outpatient clinics was 25% higher when using the 2005 diagnostic criteria as opposed to the 1996 ones (Aarsland et al., 2008b). This finding suggests that the use of the more recent and revised criteria may modify further current figures on the prevalence and incidence of this disorder. Moreover, as mentioned by Aarsland et al. (2005), the clinical overlap between DLB and PDD, along with the nosological issue around the two might lead to estimation inaccuracies. Several studies failed to report the exact timing of the presentation of motor and cognitive symptoms, which is crucial for the diagnostic classification of the two conditions (Aarsland et al., 2005). Hence, in some cases, PDD might have been misdiagnosed as DLB and vice versa.

Other findings suggest the underestimation of DLB cases in the clinical setting, which would affect prevalence and incidence estimations. In fact, neuropathological studies suggest that LB pathology may be found in 15 to 20% cases at autopsy, which is inconsistent with the results shown by the population prevalence studies described above for both DLB and PDD (Kane et al., 2018, Outeiro et al., 2019). On the other hand, it has been reported that around 50% of cases with LB pathology did not present with the DLB typical clinical profile during life, and showed higher levels of concomitant AD pathology at autopsy (Outeiro et al., 2019). Improving the diagnostic accuracy for each condition, along with a better understanding of the relationship between neuropathological and clinical features may improve future epidemiological studies.

1.3 Risk factors

Even though the aetiology of LBD remains largely unknown, over the last years genetic and environmental risk factors that may play a role in the pathogenesis of the LB disorders have been identified (Jellinger, 2015, Outeiro et al., 2019, Tysnes and Storstein, 2017, Walker et al., 2015). Sporadic cases, resulting from complex interactions between susceptible genes and environment, represent the majority of the cases (de Lau and Breteler, 2006). Monogenetic causes were described only in 5 to 10% PD patients, which may manifest differently from sporadic PD, both clinically and pathologically (de Lau and Breteler, 2006, Tysnes and Storstein, 2017, Walker et al., 2015).

The substantial genetic overlap along the LBD spectrum, as well as AD, is in line with the multifaceted pattern of clinical and neuropathological manifestations, making the identification of disease-specific mutations more complex (Outeiro et al., 2019, Vergouw et al., 2017, Walker et al., 2015). Moreover, research on the genetics of DLB have focused primarily on genes already associated with PD and AD, which might have complicated further the discovery of mutations specific for DLB (Vergouw et al., 2017). Defects in the alpha-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), and glucocerebrosidase (GBA) genes have been linked to PD, as well as LB dementia (Aarsland and Kurz, 2010, Tysnes and Storstein, 2017, Walker et al., 2015). The most common monogenetic forms of PD are mutations in LRRK2 and Parkin, autosomal dominant and recessive, respectively, while mutations in the GBA its most robust genetic risk factor (Kalia and Lang, 2015). With regard to DLB, research has shown that GBA mutations and the presence of the APOE ε4 allele were the strongest genetic risk factors (Outeiro et al., 2019, Walker et al., 2015). APOE ε4 carriers seem to have a higher risk of developing AD, mixed AD and LB pathology, but also more severe LB pathology in cases with lower AD pathology (Aarsland and Kurz, 2010, Outeiro et al., 2019, Vergouw et al., 2017). On the other hand, no association appeared between the APOE ε4 allele and PD without dementia (Outeiro et al., 2019). These findings, taken together, suggest that carrying the APOE ε4 allele may represent a risk factor for the development of dementia with underlying LB pathology with or without concomitant AD (Outeiro et al., 2019, Vergouw et al., 2017).

Among the environmental risk factors, positive associations were found between PD and pesticides exposure, previous head injury, rural living, beta-blocker use, agricultural occupation and well water drinking (Kalia and Lang, 2015, Noyce et al., 2012). On the other hand, a decreased risk was shown in association with use of

tobacco, coffee, alcohol, non-steroidal anti-inflammatory drugs and calcium channel blockers, and hypertension (Kalia and Lang, 2015, Noyce et al., 2012). Risk factors in DLB have received less attention, and are mainly related to age and having a family history of dementia (Boot et al., 2013, Woodruff et al., 2006). A case-control study published by Boot et al. (2013) found that the factors associated with the likelihood of receiving a diagnosis of DLB were having a history of depression, anxiety, stroke, a family history of PD, and the presence of the APOE ε4 allele. In addition, patients with idiopathic rapid eye movement (REM) sleep behaviour disorder (RBD), autonomic dysfunction and frequent delirium were more likely to develop DLB (Walker et al., 2015). The most frequently reported risk factors for dementia in PD were mainly age, more severe parkinsonism and mild cognitive impairment (Aarsland and Kurz, 2010). Duration of PD was not associated with conversion to PDD, probably because age is the most widely recognised risk factor for dementia (Goldmann Gross et al., 2008).

1.4 Symptomatology and clinical diagnosis

1.4.1 Clinical presentations and diagnostic issues

A certain diagnosis of Lewy body disease can be made only post-mortem, with the detection of LB pathology at autopsy. Even though there is no definitive diagnostic test during life, widely recognised criteria are available for each disorder. However, the problem of an early and differential diagnosis remains unsolved for both PD and DLB, having a number of patients still being misdiagnosed with other conditions. Accurately diagnosing these disorders is of critical importance in order to offer an accurate prognosis and direct patients to the appropriate form of treatment. This is emphasized by the presence of different reactions to pharmacological interventions. For example, DLB patients present good responsiveness to cholinesterase inhibitors, but severe sensitivity to antipsychotic medication (Zupancic et al., 2011). Hence, it is important not to administer antipsychotics to patients with all types of dementia, being severe reactions more likely to happen in DLB compared to other conditions (Aarsland et al., 2008a).

Different criteria have been proposed for the clinical diagnosis of PD (Gelb et al., 1999, Gibb and Lees, 1988, Litvan et al., 2003, Postuma et al., 2015). Among these, the UK PD brain bank criteria are some of the most commonly used (Gibb and Lees, 1988, Hughes et al., 1992, Jankovic, 2008). Recently, the movement disorder society (MDS) clinical diagnostic criteria for PD were developed, taking into account previously published criteria. The MDS-PD criteria were mainly designed for research purposes,

but may also be used as guidance in clinical settings (Postuma et al., 2015). Nevertheless, a number of patients are still misdiagnosed with other neurodegenerative disorders, among which multiple system atrophy, progressive supranuclear palsy and DLB (Postuma et al., 2015, Rizzo et al., 2016). Notably, diagnostic accuracy was found to be higher when relying on expert movement disorders clinicians, rather than formal diagnostic criteria alone, highlighting the need to improve the latter (Postuma et al., 2015, Rizzo et al., 2016).

The central feature for a diagnosis of PD is represented by motor symptoms, namely bradykinesia, muscular rigidity, rest tremor, and postural instability. Bradykinesia and at least one of the other abovementioned motor symptoms are essential for a clinical diagnosis (Hughes et al., 1992, Postuma et al., 2015). A number of other features are considered supportive of the diagnosis, among which unilateral onset, persistent asymmetry, excellent response to dopaminergic treatment and levodopa induced dyskinesia (Hughes et al., 1992, Jankovic, 2008, Postuma et al., 2015). PD should be ruled out when the symptomatology is due to other causes, such as history of repeated strokes, head injury, encephalitis, supranuclear gaze palsy, cerebellar signs and early severe dementia (Hughes et al., 1992, Jankovic, 2008). Following the available diagnostic criteria, it was found that 75 to 95% of patients with a clinical diagnosis of PD were confirmed at autopsy (Postuma et al., 2015).

Patients with PD also frequently show cognitive impairment, neuropsychiatric symptoms and sleep disorders (Aarsland et al., 2009, Fields, 2017). Even though these symptoms are not essential for the diagnosis, their clinical relevance clearly emerges in relation to functional outcomes and treatment trajectories. Indeed, they may have a detrimental effect on activities of daily living, quality of life of the patients and their caregivers, and have been linked to increased rates of hospitalization (Aarsland et al., 2000, Fields, 2017, Goldmann Gross et al., 2008). In spite of this, they are still underdiagnosed and often remain untreated, highlighting the need for these symptoms to receive more attention (Chaudhuri and Schapira, 2009).

Progressive cognitive decline represents the central feature of the DLB symptomatology, which is essential for clinical diagnosis (McKeith et al., 2017, McKeith et al., 2005). The core symptoms of DLB include cognitive fluctuations, recurrent VH, and one or more features of parkinsonism (bradykinesia, rest tremor or rigidity) (McKeith et al., 2017, McKeith et al., 2005). RBD was included as a core symptom only in 2017 (McKeith et al., 2017), while it was just a suggestive characteristic in previous criteria (McKeith et al., 2005). Other supportive clinical features commonly present, but lacking diagnostic specificity, include severe

sensitivity to antipsychotic medications, hyposmia, hypersomnia and other neuropsychiatric symptoms. Indicative biomarkers are also used to aid the diagnosis, such as reduced dopamine transporter uptake in the basal ganglia detected by functional neuroimaging. Other biomarkers include a low uptake of metaiodobenzylguanidine myocardial scintigraphy and polysomnographic confirmation of REM sleep without atonia. A diagnosis of probable DLB is made when two or more core features are present, or one core feature with one or more biomarkers (McKeith et al., 2017).

DLB is a largely underdiagnosed condition, with up to 50% missed cases (Vann Jones and O'Brien, 2014). Results on the diagnostic accuracy of DLB have shown low sensitivity (around 32%), but high specificity (over 95%), meaning that clinically diagnosed patients are usually confirmed at autopsy, while a proportion of autopsy-confirmed cases are misdiagnosed during life (McKeith et al., 2005, Nelson et al., 2010). Hence, it remains crucial to improve the diagnostic accuracy of DLB. To this end, the DLB consortium reported revised diagnostic criteria in 2017, improving those previously used (McKeith et al., 2017, McKeith et al., 2005, McKeith et al., 1996). The most common misdiagnosis of DLB is with other types of dementia such as AD due to overlapping clinical, cognitive and neuropathological characteristics (McKeith et al., 2017, Morra and Donovick, 2014). The issue is complicated further by the presence of patients with concomitant LB and AD pathology, for whom the DLB symptomatology may be less distinctive (Aarsland et al., 2004).

DLB may also be difficult to distinguish from PDD, especially when patients present motor symptoms (Dickson et al., 2009). In fact, DLB shares several characteristics with PDD, including cognitive, neuropsychiatric and extrapyramidal features, neuroleptic sensitivity and responsiveness to cholinesterase inhibitors (McKeith et al., 2005, Morra and Donovick, 2014). Some differences in the clinical presentation have also been reported between the two conditions, but they are often small and inconsistent between studies (Goldmann Gross et al., 2008). Despite the differentiation between DLB and PDD as distinct diagnostic labels, it is still a matter of debate whether they are separate entities or different phenotypes on a continuum of cognitive, motor and neuropsychiatric symptoms (Aarsland et al., 2004, Goldmann Gross et al., 2008, Lippa et al., 2007, McKeith, 2009). The clinical presentation of patients within each diagnostic label may be very different. For example, a patient with well-established PD and dementia is not clinically comparable to a patient diagnosed with DLB with cognitive fluctuations and visual hallucinations (McKeith, 2009). At the same time, it may be more difficult for other patients to fall into one

diagnostic label or the other due to overlapping early symptomatology. This might be the case for DLB patients with parkinsonism and PD patients with an early manifestation of cognitive impairment (Aarsland, 2016, Lippa et al., 2007, McKeith, 2009). At present, the differentiation between DLB and PDD is conventionally based on the temporal expression of the symptoms, following the one-year rule. DLB is diagnosed when dementia precedes or occurs within one year of the onset of motor symptoms (Emre et al., 2007, McKeith et al., 2005). On the other hand, a clinical diagnosis of PDD is made when dementia occurs in patients already diagnosed with PD (Emre et al., 2007).

As noted above, a substantial overlap in clinical symptomatology may be seen across patients with DLB, PDD and PD. In this sense, the three conditions might be conceptualised as a continuum of disorders with different clinical manifestations and temporal exhibition of the core features, which may also reflect the underlying neuropathological distribution. Moreover, a considerable overlap of prodromal symptoms has been shown in DLB and PD that mainly include autonomic and sleep disturbances (McKeith et al., 2016). In the following sections, the main overlapping symptoms are described in more detail with respect to the different manifestations presented by each LBD condition.

1.4.2 Dementia, cognitive deficits and fluctuations

Dementia represents the essential feature to diagnose clinically both DLB and PDD (Emre et al., 2007, McKeith et al., 2017). This means that patients with LB dementia are characterized by progressive cognitive decline significantly affecting their usual daily activities, social and occupational functioning (Emre et al., 2007, McKeith et al., 2005). As mentioned in previous sections, often DLB is misdiagnosed with other types of dementia, namely AD and PDD. Understanding better the specific cognitive deficits typical of each condition represents an important aid to the clinical diagnosis, especially at the early stages. In this respect, neuropsychological assessment represents a helpful tool to quantify the degree of impairment within each cognitive domain and to monitor its progression. Hence, the development of neuropsychological tests able to identify different and overlapping deficits between conditions may help in reaching a more accurate differential diagnosis (Metzler-Baddeley, 2007). Neuropsychological evaluation has been widely used to aid the early and differential diagnosis between DLB and AD. For example, in DLB, performance on visuospatial, visuoconstructive and visuoperceptive tasks has been

found to be particularly impaired. Within this framework, the use of neuropsychological tests commonly used in clinical practice may be extremely useful. Caffarra et al. (2013) validated a qualitative scoring method for the pentagons copy test of the Mini-Mental State Examination (MMSE), a widely used screening test for global cognitive functioning. This qualitative scoring method comprises different drawing aspects, including number of angles, distance/intersection, closure/opening, rotation and closing-in, with DLB patients scoring less than AD in most of them (Caffarra et al., 2013). Notably, Mitolo et al. (2014) found consistent results in autopsy-confirmed patients, especially in the number of angles, suggesting further the potential of this scoring method in the differential diagnosis of DLB.

A factor that complicates further the diagnosis of DLB as well as PDD may be the presence of fluctuating cognition, which manifests mainly with spontaneous alterations in attention, arousal, behaviour and functional abilities, confusion and disorientation (Goldmann Gross et al., 2008, McKeith et al., 2017, Varanese et al., 2010). This symptom is among the core features for the diagnosis of DLB; however, it is one of the most difficult to identify and evaluate in clinical practice (McKeith et al., 2005, Lee et al., 2012a). Other types of dementia may also have cognitive fluctuations, especially at more advanced stages, and therefore may be of more diagnostic utility when detected early in the progression of the disease (McKeith et al., 2017). Asking questions about the presence of cognitive fluctuation directly to the caregivers may not be sufficient to distinguish DLB and AD (McKeith et al., 2017, McKeith et al., 2005). In fact, in order to support the diagnosis, fluctuating cognition should be detected through dedicated and more detailed measures of assessment (McKeith et al., 2017, McKeith et al., 2005). Nevertheless, among the core features of DLB, cognitive fluctuations are less likely to occur at the prodromal stages (Donaghy and McKeith, 2014, Donaghy et al., 2015). They are more common later in the progression of the disease, at the same time or following the development of dementia (Donaghy and McKeith, 2014, Donaghy et al., 2015). Moreover, fluctuating attention was found to be comparable between PDD and DLB, but it was not observed in PD without dementia (Ballard et al., 2002).

DLB and PDD, may be defined as visuoperceptive, attentional and executive dementias, as opposed to the more severe memory deficits observed in AD (Collerton et al., 2003, Goldmann Gross et al., 2008). A comparable pattern of cognitive impairment between PDD and DLB has been largely recognised, even though some studies showed worse performance in DLB in tasks assessing, for example, visuospatial abilities, verbal and visual memory (Aarsland et al., 2003b, Fields, 2017,

Filoteo et al., 2009, Goldmann Gross et al., 2008, Lee et al., 2010b, Mondon et al., 2007, Mosimann et al., 2004, Noe et al., 2004).

A meta-analysis of 24 studies showed that patients with DLB performed worst in attentional, executive, visuoconstructive and visuoperceptive tasks when compared with both healthy controls (HC) and patients with AD (Collerton et al., 2003). These findings have also been confirmed by more recent studies that have shown deficits in different neuropsychological tests using visual stimuli, among which drawing, copying (Cagnin et al., 2015b, Cormack et al., 2004a, Noe et al., 2004), and object and space perception tasks (Cagnin et al., 2013, Mosimann et al., 2004, Wood et al., 2013a, Wood et al., 2013b). Notably, Tiraboschi et al. (2006) reported that lack of early visuospatial dysfunctions predicted the absence of LB pathology at autopsy, suggesting that these deficits may be helpful in differentiating DLB from AD even at the early stages of the disease. Studies also showed that visuospatial impairments were associated with higher rates of cognitive decline and with the development of VH (Hamilton et al., 2012, Hamilton et al., 2008). On the other hand, performance on tasks requiring drawing from memory was found to be similarly impaired in DLB and AD (Cagnin et al., 2013, Calderon et al., 2001). Differences in performance between copying and drawing from memory tasks may be explained by the more severe perceptive deficits in DLB patients that may affect their performance on visual memory tasks. Conversely, in AD it may reflect memory impairment typical of the disease (Metzler-Baddeley, 2007). Regarding the performance on episodic memory tests, patients with LB dementia presented less severe impairments than AD in tasks requiring verbal recall, although the performance was significantly worse than healthy controls (Cagnin et al., 2013, Calderon et al., 2001, Crowell et al., 2007, Emre et al., 2007, Guidi et al., 2006).

Along with the abovementioned visuoperceptive impairment, other cognitive domains that tend to be more severely impaired in LB dementias compared to AD include attention, mainly in tasks using visual stimuli, and executive functioning (Cagnin et al., 2013, Calderon et al., 2001, Collerton et al., 2003, Crowell et al., 2007, Guidi et al., 2006, Noe et al., 2004, Park et al., 2011). Deficits were reported in a range of different tasks, among which visual search, selective, sustained and divided attention, response inhibition and phonemic fluency (Cagnin et al., 2015a, Calderon et al., 2001, Collerton et al., 2003, Cormack et al., 2004b, Crowell et al., 2007, Guidi et al., 2006, Metzler-Baddeley, 2007, Noe et al., 2004). Some of these deficits were observed already at the prodromal stage and were better associated with progression to DLB rather than AD (Cagnin et al., 2015a, Ferman et al., 2013). On the other hand, other

studies showed similar performance between DLB and AD on these tasks (Metzler-Baddeley, 2007, Noe et al., 2004). Discrepancies might reflect different disease stages between studies, but also the more frequently shown fluctuating attention in LB dementia, which complicates further the assessment of these cognitive domains.

Cognitive deficits are common also in patients with PD without dementia, which may manifest even in the early stages, even at time of diagnosis (Dirnberger and Jahanshahi, 2013, Litvan et al., 2011). The term mild cognitive impairment (MCI) refers to cognitive decline not simply attributable to age, which it is not sufficiently severe to impair daily living activities (Fields, 2017, Litvan et al., 2011). MCI was reported in approximately 27% of non-demented PD patients, and these patients were shown to have a higher risk of developing dementia subsequently (Dirnberger and Jahanshahi, 2013, Litvan et al., 2012). In a longitudinal study, Aarsland et al. (2003a) found that 78% of PD patients developed dementia over an 8-year period, indicating that the majority of patients with PD will eventually develop dementia. Age is the risk factor that was shown to be the best predictor of future cognitive decline in PD (Goldmann Gross et al., 2008). Other risk factors include disease severity, hallucinations, depression and more severe motor symptoms (Aarsland, 2016, Fields, 2017, Xu et al., 2016).

The cognitive profile of patients with MCI in PD is heterogeneous and includes deficits that have been defined as subcortical, such as impairments in executive functions, and cortical, like memory and visuospatial impairments (Goldman et al., 2018). Executive dysfunction may be present since the early stages of PD, and it has been shown to worsen with the progression of the disease (Dirnberger and Jahanshahi, 2013). There is extensive evidence showing lower performance in a number of neuropsychological tests assessing different aspects of executive functioning, such as attention control, response inhibition, set-shifting, planning, decision-making and phonemic fluency (Dirnberger and Jahanshahi, 2013, Henry and Crawford, 2004). Dopaminergic dysfunction due to disrupted fronto-striatal circuits reflecting nigrostriatal dopaminergic depletion is thought to underlie, at least in part, these deficits (Kehagia et al., 2010, Lewis et al., 2003). In support of this view, it was shown that dopaminergic medication benefited cognition with improvements in tasks involving response inhibition, set-shifting and working memory (Kehagia et al., 2010). Moreover, in contrast with non-cognitively impaired patients, those with executive dysfunctions presented reduced activity in fronto-striatal regions in response to a working memory task as shown by functional magnetic resonance imaging (fMRI) (Lewis et al., 2003). Deficits in other cognitive functions were also reported in early

PD. A meta-analysis of verbal fluency in PD reported evidence of semantic memory impairment (Henry and Crawford, 2004). Although lower performance in PD patients was found in both phonemic and semantic fluency, the degree of impairment was larger in the latter, suggesting a role of temporal lobe pathology (Henry and Crawford, 2004). On the other hand, phonemic fluency abilities rely more on frontal functions, which might reflect the fronto-striatal disruption typical of PD patients. Notably, a longitudinal study on a cohort of 126 PD patients reported that deficits in semantic fluency and visuoconstructive abilities were the best predictors of cognitive decline, while executive dysfunction was found as the most common cognitive deficit in non-demented patients (Williams-Gray et al., 2007). In contrast to these findings, other studies showed an association between executive dysfunction in PD-MCI patients and subsequent dementia (Kehagia et al., 2010). These findings suggest a heterogeneous pattern of early cognitive impairments and features predicting conversion to dementia in PD.

Memory deficits may also be detected at the early stages, especially in encoding and free recall, while recognition memory may remain relatively intact (Fields, 2017, Goldman and Litvan, 2011). These findings suggest that, at least at the early stages of the disease, the memory impairment observed in PD may be due to difficulties in retrieving information secondary to an executive dysfunction, rather than deficits in encoding new information. Other findings, however, provide evidence towards the hypothesis of a storing and learning impairment as well. For example, recently Chiaravalloti et al. (2014) showed that PD patients needed a significantly higher amount of trials to be successful in the learning process in comparison with healthy controls. Once controlling for these discrepancies, however, there was no performance difference between groups in retrieving information (Chiaravalloti et al., 2014). Therefore, memory impairments in PD might be secondary to both an executive dysfunction and medial temporal lobe related damage that may be associated with deficits in information retrieval and storing, respectively (Aarsland, 2016).

DLB may also be preceded by a state of mild cognitive impairment, with 5 to 25% of all MCI cases subsequently developing DLB (Donaghy and McKeith, 2014). The amnestic subtype of MCI is characterised by a more prominent memory problem, and has been consistently associated with progression to AD (Ferman et al., 2013, Gauthier et al., 2006). On the other hand, a non-amnestic type of MCI, with deficits in multiple cognitive domains, more often precedes DLB (Ferman et al., 2013, Gauthier et al., 2006). Specifically, attention, visuospatial and executive functions may be

particularly impaired in people with DLB-MCI, therefore reflecting a pattern of deficits similar to the one presented by patients already diagnosed with probable and possible DLB (Donaghy et al., 2015, Donaghy et al., 2018, Ferman et al., 2013).

1.4.3 Motor symptoms

The presence of motor symptoms is necessary for the diagnosis of PD, particularly bradykinesia and at least one among muscular rigidity, rest tremor and postural instability (Hughes et al., 1992, Postuma et al., 2015). Bradykinesia is described as slowness of movement and decline of speed or amplitude once the movement continues, and primarily occurs as limb bradykinesia (Postuma et al., 2015). It may also manifest as lack of spontaneous movements and facial expressions, slowness while performing daily activities, slowness of voice, gait, and in tasks requiring fine motor control (Jankovic, 2008, Postuma et al., 2015). Tremor is one of the most common motor features typical of PD, it occurs at rest at a frequency between 4 and 6 Hz, and disappears once the movement is initiated and during sleep (Jankovic, 2008, Postuma et al., 2015). It most likely appears in the limbs, especially with hand tremors, but may also be present in other parts of the body. However, it rarely occurs as head tremor, symptom that is more characteristic of other conditions, such as essential tremor or cervical dystonia (Jankovic, 2008, Postuma et al., 2015). Other core motor symptoms include muscular rigidity and postural instability. Rigidity is identified as resistance to passive movements of the limbs, but it may also occur as neck and trunk rigidity, resulting in postural deformities (Jankovic, 2008, Postuma et al., 2015). Postural instability is also common, especially at later stages of the disease and it is often cause of falls and risk of hip fractures (Jankovic, 2008).

As opposed to PD, features of parkinsonism are not essential for the diagnosis of DLB, but represent a core clinical feature, with up to 85% of cases eventually experiencing at least one of these symptoms (McKeith et al., 2017). Moreover, gait problems and tremor were identified as presenting symptoms in approximately 25% of DLB patients (Auning et al., 2011). The temporal manifestation of extrapyramidal features, along with cognitive decline, represents the current conventionally recognised approach to distinguish DLB from PDD. Indeed, motor symptoms occurring within one year from the presentation of dementia lead to the diagnosis of PDD (Emre et al., 2007).

Differences and similarities were shown between DLB and PD in respect to the manifestation of motor symptoms. Specifically, a study found similar posture and tremor at rest, while action tremor, body bradykinesia, gait and rigidity were more

severe in DLB (Aarsland et al., 2001b). In this study, however, DLB patients were older at both assessment and disease onset and most likely included more severe cases, being recruited from a tertiary clinical service. On the other hand, the PD sample was composed of mild to severe cases and included only patients with good response to antiparkinsonian medications (Aarsland et al., 2001b). In another study, patients were divided into postural-instability gait or tremor dominant (Burn et al., 2003). The two subgroups were equally distributed in PD, while the postural-instability subtype was more common in the LB dementias. Moreover, motor symptoms were more severe in PDD compared to the other disorders, finding that were not associated with the longer disease duration observed (Burn et al., 2003). Finally, DLB patients are often less responsive to dopaminergic medications, suggesting that a proportion of motor symptoms in DLB may not be due to a dopaminergic dysfunction (Aarsland et al., 2001b, McKeith et al., 2017, McKeith et al., 2005).

1.4.4 Neuropsychiatric symptoms and sleep disturbances

Neuropsychiatric symptoms are frequent in LBD; they affect a large proportion of patients during the course of the disease, worsen their quality of life and are associated with increased risk of hospitalisation and burden for caregivers (Aarsland et al., 2009, Mueller et al., 2017). Studies have shown that the vast majority of PDD patients, around 90%, presented at least one neuropsychiatric symptom, and almost 80% had two or more (Aarsland et al., 2007, Lee et al., 2012b). The most common neuropsychiatric features are depression, anxiety, apathy and psychosis (Aarsland et al., 2007, Aarsland et al., 2009). Neuropsychiatric features were consistently associated with the presence of cognitive deficits in PD, especially in executive functions (Alzahrani and Venneri, 2015). Psychotic symptoms, including delusions, hallucinations and illusions, are common in PD (Ffytche et al., 2017). In DLB, the presence of VH is among the core features for its clinical diagnosis, making their accurate identification particularly important (McKeith et al., 2017). The presence of neuropsychiatric symptoms other than VH, including delusions, is common and aids the diagnosis, even though they are not specific to DLB (McKeith et al., 2017). In fact, they were observed frequently also in other types of neurodegenerative conditions, such as AD and frontotemporal dementia (Engelborghs et al., 2005). Nevertheless, the proportion of neuropsychiatric symptoms seems to be higher in the LB dementias as opposed to AD (Aarsland et al., 2007, Fritze et al., 2011).

As described previously, DLB may be preceded by an MCI stage, mainly non-amnestic with more prominent deficits in visual perception and attention abilities. In addition to this, other prodromal subtypes were described in the literature, including DLB with psychiatric onset (McKeith et al., 2016). Particularly, it may occur as a late-onset affective disorder, mainly depression, or psychosis (Donaghy et al., 2015, McKeith et al., 2016). Similarly, depressive symptoms are common at the early stages of PD, and may precede the onset of extrapyramidal symptoms of many years (Aarsland et al., 2007, Aarsland et al., 2009). Depression is one of the most common neuropsychiatric symptoms in PD, which was described in around 30-40% of non-demented patients and in up to 60% of those with LB dementia (Aarsland et al., 2007, Aarsland et al., 2009, Borroni et al., 2008). Anxiety often coexists with depression, it was detected in approximately 40% of patients with PD, and it mainly manifests as panic attacks, generalised anxiety disorder and social phobia (Aarsland et al., 2009, Chaudhuri and Schapira, 2009). It has been shown that depression and anxiety have an impact on other symptoms, such as motor features and cognitive impairment, and are associated with younger disease onset, longer duration and greater severity of the disease (Sagna et al., 2014). Apathy also frequently occurs in LBD, often in comorbidity with other neuropsychiatric features, particularly depression (Aarsland et al., 2009, Alzahrani and Venneri, 2015, Borroni et al., 2008). Studies have shown an association between cognitive decline and apathy, with apathetic patients being significantly more impaired (Alzahrani and Venneri, 2015, Dujardin et al., 2009). Apathy was also shown to be a predictive factor of dementia in PD (Dujardin et al., 2009).

Evidence reported approximately 80% of patients with LB dementia experiencing sleep problems, percentage that was significantly higher than in AD patients (McKeith et al., 2017, Rongve et al., 2010). In patients with dementia, the presence of sleep disturbances has been associated with psychiatric symptoms, mainly depression and anxiety (Rongve et al., 2010). The most common sleep disorder in LBD is RBD, which represents a relevant clinical aid to the diagnosis of DLB (McKeith et al., 2017, Rongve et al., 2010). The loss of the muscular atonia characteristic of REM sleep is the main feature of RBD, resulting in abnormal physical behaviours and enactment of dreams (Gagnon et al., 2006, McKeith et al., 2017). RBD is a parasomnia frequently observed in different α-synucleinopathies (PD, PDD, DLB and multiple system atrophy) and often precedes the onset of dementia or motor symptoms of many years (Claassen et al., 2010, McKeith et al., 2005, Ferini-Strambi et al., 2014). Studies reported that the risk of developing a neurodegenerative disorder is significantly

higher in patients with idiopathic RBD, especially a LB disorder, with up to 60% eventually developing LB dementia (Claassen et al., 2010, Iranzo et al., 2013, Postuma et al., 2009).

1.5 Treatment

Even though disease-modifying therapies for LB disorders are under investigation, no cure is currently available (Connolly and Lang, 2014, Hershey and Coleman-Jackson, 2019, O'Brien et al., 2017). The pharmacological management is therefore symptomatic, and aims to address different combinations of symptoms requiring treatment, while balancing the complex relationship between drug-induced benefits and side effects.

The dopamine precursor levodopa is the gold standard treatment for the motor symptoms typical of PD. Dopamine agonists are also effective, and the combined use of different medications is chosen in many cases (Connolly and Lang, 2014). Dopamine agonists are usually preferred as initial treatment for patients with early onset, as motor fluctuations and dyskinesia have been associated with prolonged use of levodopa (Connolly and Lang, 2014, Rizek et al., 2016). However, the advantages linked to the use of dopamine agonists over levodopa often diminish over a 10-year period (Connolly and Lang, 2014). Levodopa was found to be a risk factor for psychosis in PD, which may trigger hallucinations, even though findings on this relationship are controversial (Connolly and Fox, 2014, Ffytche et al., 2017). The presence of VH was reported also in unmedicated patients, supporting the view that this symptom is also a feature of the disease itself (Connolly and Lang, 2014, Ffytche et al., 2017). Levodopa is used for the treatment of motor symptoms also in DLB, although lower doses are preferable to avoid the exacerbation of psychotic symptoms, agitation and daytime somnolence (Hershey and Coleman-Jackson, 2019). Dopamine agonists tend to be avoided in DLB, as their use has been linked to a higher risk of developing hallucinations and sleepiness (Hershey and Coleman-Jackson, 2019).

The LB dementias are characterised by an early and more severe cholinergic deficit compared with both AD and PD without dementia, and respond to cholinesterase inhibitors (ChEI) better than AD (Grothe et al., 2014, Hall et al., 2014, Swanberg and Cummings, 2002, Tiraboschi et al., 2002). ChEI have been shown to be beneficial in LB dementia, showing positive effects on cognitive deficits, psychotic and neuropsychiatric symptoms, and daily living activities (Connolly and Fox, 2014,

Hershey and Coleman-Jackson, 2019, O'Brien et al., 2017, Rolinski et al., 2012). Moreover, a recent study has reported decreased incidence and severity of hallucinations in DLB treated with ChEI (Hershey and Coleman-Jackson, 2019). On the other hand, antipsychotics should be considered very carefully for the treatment of psychosis in LBD as they may worsen, for example, motor symptoms (Connolly and Fox, 2014). Importantly, severe antipsychotic sensitivity is a supportive clinical feature for the diagnosis of DLB, and may include the development of extrapyramidal signs and neuroleptic malignant syndrome (McKeith et al., 2017, McKeith et al., 2005, Swanberg and Cummings, 2002).

1.6 Neuropathology

The main neuropathological feature of PD and DLB is represented by the neural inclusion of LBs and Lewy neurites (LNs), with α-synuclein being the major biochemical component. There are two types of LBs: brainstem and cortical LBs, which are both made of filamentous structures (Wakabayashi et al., 2013). The brainstem LBs are spherical or elongated eosinophilic inclusions with a core and a peripheral halo, and are found in the cytoplasm of the neurons (Goedert et al., 2013, Jellinger, 2009, Wakabayashi et al., 2013). The cortical ones are also eosinophilic, but less well defined in shape and structure and often lack a marked halo (Goedert et al., 2013, Jellinger, 2009, Wakabayashi et al., 2013). Along with the LBs, there are the LNs which may eventually become LBs and share with them the principal biochemical features, among which the α-synuclein protein (Jellinger, 2009). Despite being the main neuropathological characteristics of LBD, the nature of the relationship between α-synuclein aggregations and neurodegeneration is still unclear. It was shown that the proportion of LBs in the substantia nigra remains stable over the progression of the disease (Greffard et al., 2010, Parkkinen et al., 2011). This observation brought to the hypothesis that the LBs are destroyed along with the containing neurons death, suggesting a direct link between LBs formation and neurodegeneration (Greffard et al., 2010). On the other hand, others suggested that α-synuclein may be associated with neuroprotective mechanisms (Lee et al., 2006, Quilty et al., 2006, Wakabayashi et al., 2013). Whether α-synuclein aggregations play a neuroprotective or neurotoxic role is still matter of debate (Goedert et al., 2013, Wakabayashi et al., 2013).

Different classification systems are used for the assessment of LB pathology in PD (Braak et al., 2003, Braak et al., 2004, Braak et al., 2006) and DLB (McKeith et al.,

2017, McKeith et al., 2005). However, the majority of the current knowledge on LB pathology comes from research on PD, though leaving a proportion of unclassified cases (Jellinger, 2012). Braak and colleagues proposed a pattern of neuropathological progression in PD that was later replicated by several studies (Braak et al., 2003, Braak et al., 2004, Braak et al., 2006, Goedert et al., 2013). According to the Braak staging system, the α-synuclein deposition in PD occurs in a predictable way (Braak et al., 2003, Braak et al., 2004, Braak et al., 2006). The pathology normally starts in anterior olfactory structures (stage 1), medulla oblongata nuclei (stages 1 and 2), and pontine tegmentum (stage 2). These first stages are usually asymptomatic, while the first typical motor symptoms of PD manifest when the pathology extends to the midbrain, especially in the substantia nigra pars compacta (stage 3). Then, the α-synuclein deposition expands to the basal prosencephalon, the mesocortex (stage 4) and finally, the neocortex (stages 5 and 6). These latter stages (5 and 6) have frequently been associated with cognitive decline (Jellinger, 2012). However, there are cases where the Braak system is violated, suggesting that the initiation of the pathological process may also be multifocal (Frigerio et al., 2011). Moreover, most DLB cases have LB pathology reflecting an advanced Braak stage with cortical LBs, suggesting that different trajectories may be taken in terms of LBs progression and distribution (Donaghy and McKeith, 2014, Walker et al., 2015).

Beach et al. (2009) proposed a unified staging system to classify subjects with LB pathology, including those with DLB, asymptomatic cases, known as incidental LBD, and AD with sparse LBs, mainly limbic, as well as PD. According to this system, the first stage includes patients with pathology only in the olfactory bulb (stage 1). The second stage may then follow two separate pathways, one predominantly involving the brainstem (stage 2a) and the other the limbic system (stage 2b). In stage 3, LB pathology in the brainstem and limbic areas is approximately the same, converging in one single brainstem and limbic stage. Then, LB pathology spreads to the neocortex (stage 4). According to this system, most PD and DLB patients may be classified as stage 3 (brainstem and limbic) or 4 (neocortical). The temporal progression of the stages within each diagnostic group can only be speculative, since DLB and PD patients frequently present LB pathology in all the regions taken into account (Beach et al., 2009). Nevertheless, it was hypothesised that PD patients may come from a brainstem predominant stage, and PDD patients were more likely to progress to the neocortical stage than those without dementia (Beach et al., 2009). A high quantity of widespread LB pathology in the neocortex is less common in PD patients without cognitive decline (Lippa et al., 2007). In DLB, LBs are mainly found in the brainstem,

limbic system, and neocortex (McKeith et al., 2005), with most patients at autopsy being already in the neocortical stage, making more difficult to speculate on the temporal sequence of the stages (Beach et al., 2009). Differences between DLB and PDD include a higher LB load in temporal and parietal areas in DLB, while they share other pathological features (Jellinger, 2012, Jellinger, 2018).

AD pathology, including β-amyloid and tau deposition, may be found also in patients with a diagnosis of DLB, further highlighting the neuropathological overlap between the two disorders (McKeith et al., 2005, Morra and Donovick, 2014). A neuropathological diagnosis of DLB is made assessing the degree of LBs and AD pathology and the likelihood that these features may explain the clinical syndrome (McKeith et al., 2017, McKeith et al., 2005). The latest diagnostic criteria, recently published by McKeith et al. (2017), identify five phenotypes associated with the likelihood to present the typical clinical features of DLB taking into account concomitant AD pathology. LBs distribution may be diffuse neocortical, limbic (transitional), brainstem predominant, amygdala predominant and olfactory bulb only (McKeith et al., 2017). The last three are associated with a low likelihood to present a DLB clinical syndrome, while diffuse neocortical LBs are associated with high or intermediate likelihood (McKeith et al., 2017). Depending on the degree of AD pathology, the presence of limbic LBs may lead to high to low likelihood to be associated with the clinical presentation of DLB (McKeith et al., 2017). AD pathology may also be identified in PDD, even though higher β-amyloid load in the cortex and in the striatum is found in DLB (Jellinger, 2012, Jellinger, 2018). A proportion of autopsy-confirmed DLB cases also presented concomitant vascular pathology, even though its role and pathogenesis is still unclear (Outeiro et al., 2019). There is no consensus regarding the specific neuropathological substrates of cognitive decline in LBD that may be related to LB pathology only or in combination with AD and cardiovascular pathology (Jellinger, 2012, Jellinger, 2018).

The presence of LBs itself may not necessarily reflect the characteristic LBD symptomatology, as LBs may be detected also in incidental LBD and AD (Jellinger, 2012, McKeith et al., 2005). According to Beach et al. (2009), AD with LBs was mainly characterised by olfactory bulb only or limbic LB pathology, while most incidental LBD cases were in the brainstem predominant stage. Neuropathological studies suggest that 8 to 17% of people with no neurological conditions present LB pathology at autopsy, which may represent pre-symptomatic LBD (Frigerio et al., 2011). Frigerio et al. (2011) proposed that some incidental LBD cases eventually progress to PD, mainly those with isolated brainstem α-synuclein pathology, and others to DLB. The

latter may reflect incidental cases with LBs in cortical areas, though to a lesser extent than clinically diagnosed patients (Frigerio et al., 2011). Studies observed that nearly 50% of patients with LB pathology did not show the typical clinical profile of DLB, but that of AD (Outeiro et al., 2019). Among the clinical features, the presence of VH was found to be associated with LB pathology in AD (Outeiro et al., 2019).

Along with LB pathology, neuropathological criteria for the diagnosis of PD include neuronal loss within the pars compacta of the substantia nigra (Dickson et al., 2009). Neurodegeneration involves mainly the dopaminergic neurons of its ventrolateral region projecting to the striatum, which is usually associated with motor symptoms (Dickson et al., 2009). This results in a striatal dopamine loss that correlates with the degeneration of nigral dopaminergic neurons (Jellinger, 2012). Nigrostriatal dopaminergic dysfunction is a characteristic of all three conditions, namely PD, PDD and DLB. In DLB, however, the less severe neuronal loss in the substantia nigra seems to affect mostly dorsolateral cell groups (Jellinger, 2018). Neural loss in the substantia nigra have been associated with the motor features typical of PD, mainly bradykinesia and rigidity (Kalia and Lang, 2015), and the severity of this neurodegeneration is used to classify the likelihood to present motor symptoms in DLB (McKeith et al., 2017). Nigral degeneration represents one of the main neuropathological differences between DLB and PDD, being more severe in the latter (Jellinger, 2012, Lippa et al., 2007).

Patients with LB dementia are also characterised by a cholinergic dysfunction that has been linked to cognitive impairment and visual hallucinations (Francis and Perry, 2007, Siderowf et al., 2018). Loss of cholinergic neurons and choline acetyltransferase activity were greater in the LB dementias than both AD and PD (Francis and Perry, 2007, Siderowf et al., 2018). Neurodegeneration of cholinergic neurons in the basal forebrain was found in DLB, along with the subsequent reduction of cortical cholinergic activity (Fujishiro et al., 2006, Grothe et al., 2014, Lippa et al., 1999). The earlier and more severe cholinergic deficit may be linked to the better response to ChEI compared to AD (Grothe et al., 2014, Hall et al., 2014, Swanberg and Cummings, 2002, Tiraboschi et al., 2002).

1.7 Biomarkers

One of the issues related to the clinical diagnosis of the LB disorders is the lack of *in vivo* direct indicators of LB pathology. In fact, as outlined above, a certain diagnosis can be made only post-mortem, with the detection of LBs and LNs at autopsy. The

identification of biomarkers able to measure the neurobiological mechanisms underpinning the disorders represents an urgent area of investigation. Such biomarkers may be of great value to aid clinical diagnosis, and may help to achieve a better understanding of the different expressions of the disease and the biological processes that are distinguishable from other disorders with similar symptomatic manifestations. Biomarkers may also be valuable tools to reach a more accurate early diagnosis, to monitor the progression of the disease and to assess treatment efficacy (Schapira, 2013). A multimodal approach, aiming to combine findings from different methodologies may be the key to develop disease and symptom-specific biomarkers, which would also inform on the underlying pathophysiological processes. For this purpose, neuroimaging techniques represent valuable tools in detecting the features that characterise these disorders.

At present, a number of methods is available to support the correct identification of LBD clinically, which are useful to reach a more accurate differential diagnosis between disorders, and to overcome the unsolved problem of underdiagnosing conditions like DLB. Some of them are currently included as indicative or supportive features among the DLB diagnostic criteria, and may be used and developed to differentiate PD from other PD-like syndromes with no parkinsonism (McKeith et al., 2017, Postuma et al., 2015). Differences were also detected between the LB disorders that may reflect the complex variety of clinical phenotypes and neuropathological substrates. In the following sections, evidence regarding the main biomarkers is summarised, with special focus on findings from neuroimaging studies.

1.7.1 Structural brain imaging

1.7.1.1 Structural magnetic resonance imaging

Structural magnetic resonance imaging (MRI) has been extensively used to investigate regional brain volumes in a wide range of neurological, psychiatric and neurodegenerative, including those causing dementia. Over the years, consistent findings differentiating the LB dementias from AD suggested that structural MRI may be a useful tool for differential diagnosis. Currently, the relative preservation of medial temporal lobe (MTL) regions, detected on MRI or computed tomography scans, is among the biomarkers that support the diagnosis of DLB (McKeith et al., 2017). On the other hand, less conclusive results are available in relation to the macrostructural characteristics of PD. Although grey matter (GM) alterations were reported in cortical and subcortical areas, other studies found no differences between PD patients without

dementia and healthy participants (Burton et al., 2004, Nagano-Saito et al., 2005, Pyatigorskaya et al., 2014, Summerfield et al., 2005). Inconsistencies between studies may be in part explained by differences in methodology, sample size, age, disease duration and severity, and other clinical features. Overall, PDD is characterised by widespread cortical and subcortical atrophy that is more severe than in cognitively normal PD (Siderowf et al., 2018).

The pattern of GM loss detected in PDD substantially overlaps with DLB and includes cortical and subcortical regions. Most studies reported no differences between these two clinical conditions (Borroni et al., 2015, Burton et al., 2004, Hattori et al., 2012, Janzen et al., 2012, Kenny et al., 2008), although others found more pronounced GM loss in DLB (Beyer et al., 2007, Lee et al., 2010a, Sanchez-Castaneda et al., 2009). DLB is characterised by widespread cortical atrophy, including frontal, temporal and parietal regions, even though generally to a lesser extent than AD (Ballmaier et al., 2004, Beyer et al., 2007, Sanchez-Castaneda et al., 2009, Sinha et al., 2012, Hattori et al., 2012, Whitwell et al., 2007). Although occipital hypometabolism and hypoperfusion has been repeatedly highlighted as typical of DLB (Ishii et al., 1999, Lobotesis et al., 2001), evidence demonstrating a pronounced atrophy in this area is lacking. Only some studies have reported occipital GM loss compared to controls (Hattori et al., 2012, Lee et al., 2010a), while others have found no differences (Burton et al., 2002, Ishii et al., 2007, Middelkoop et al., 2001, Peraza et al., 2015a). Nevertheless, white matter (WM) microstructural alterations have been found in the inferior longitudinal fasciculus (ILF), a bundle of associative fibres that connects the occipital and temporal lobes (Catani and Thiebaut de Schotten, 2008, Hattori et al., 2012, Kantarci et al., 2010, Kiuchi et al., 2011, Ota et al., 2009). This WM tract has been related to visual memory and perception (Catani and Thiebaut de Schotten, 2008). These findings suggest that the pronounced perceptual deficits in DLB may be more related to functional alterations and disrupted connections, rather than selective structural impairment of occipital GM.

One of the most consistent findings in the literature is represented by reduced GM volume in MTL structures in AD relative to LB dementia (Barber et al., 2001, Burton et al., 2002, Inui et al., 2014, Watson et al., 2009), which is not surprising given the less severe memory deficits in LBD. Specifically, less pronounced GM loss compared to AD was found in the hippocampus, amygdala, entorhinal cortex, and parahippocampus (Barber et al., 2000, Barber et al., 2001, Beyer et al., 2007, Burton et al., 2002, Grothe et al., 2014, Hayashi et al., 2012, Inui et al., 2014, Mak et al., 2015, Takahashi et al., 2010). Hippocampal atrophy may also be detected in PD

without dementia when compared with controls, even though to a lesser extent than both AD and PDD (Camicioli et al., 2003). Interestingly, an AD pattern of GM loss, mostly MTL and parietal areas, was predictive of cognitive performance in PD, and was associated with the progression of cognitive decline (Weintraub et al., 2012). Whether these brain changes are due to AD, LB or mixed pathology remains unknown, although they may result from a combination of factors (Weintraub et al., 2012). Nedelska et al. (2015) investigated brain atrophy rates in autopsy-confirmed patients with DLB, AD and mixed AD/DLB. Patients with high likelihood DLB had significantly reduced atrophy rates in temporal structures compared to both other groups, while mixed AD/DLB cases showed a pattern of alterations similar to AD (Nedelska et al., 2015). These findings suggest that the presence of mixed pathology in clinically diagnosed patients may lead to a differential pattern of structural brain alterations, which might partially account for some of the inconsistencies detected across studies. Although neurodegeneration of the substantia nigra is well-established finding, results from MRI studies have reported contrasting results, ranging from normal, decreased and increased volumes in PD, which may be in part due to methodological differences between studies (Al-Radaideh and Rababah, 2016, Dickson et al., 2009, Pyatigorskaya et al., 2014). On the other hand, striatal atrophy was found in LBD, especially in patients with LB dementia, and was more severe than in AD (Cousins et al., 2003, Goto et al., 2010, Watson et al., 2009).

Basal forebrain structures were also found to be involved in LBD, having been associated with cholinergic neuronal loss, and related reduction of cortical cholinergic activity (Fujishiro et al., 2006, Grothe et al., 2014, Lippa et al., 1999). Structural MRI findings reported evidence of GM atrophy in the basal forebrain in DLB, as well as AD (Brenneis et al., 2004, Grothe et al., 2014). Similarly, studies focusing on the substantia innominata consistently showed reduced volume/thickness in the LB dementias compared with both AD and healthy subjects (Hanyu et al., 2007, Hanyu et al., 2005, Kim et al., 2011). The volume of the substantia innominata was also associated with general cognitive functioning in DLB, PDD and PD MCI, but not in AD (Kim et al., 2011).

1.7.1.2 Diffusion tensor imaging

Diffusion tensor imaging (DTI) has been widely used to assess WM microstructural integrity and structural connectivity *in vivo*. This imaging technique has allowed the mapping of the architecture of the major WM tracts, showing a good level of

consistency with post-mortem studies (Wakana et al., 2004). Even though it has been applied mainly to WM, DTI has also been used to study GM microstructure, but with higher uncertainty about fibres orientation (Atkinson-Clement et al., 2017, Jones, 2008). DTI measures the orientation properties of the diffusion of water molecules within biological tissues, reflecting the interaction with membranes and other obstacles (Suri et al., 2014, Wakana et al., 2004). The main principle is that water diffusion along WM matter tracts is anisotropic, meaning that it is oriented in one main axis, depending on the direction of the fibres (Mori and Zhang, 2006). The main metrics deriving from DTI are fractional anisotropy (FA) and mean diffusivity (MD). The latter quantifies the overall water diffusion, while FA is a measure of diffusion anisotropy (O'Donovan et al., 2014, Suri et al., 2014). Lower FA and higher MD values are usually conceptualised as indicative of WM damage. For example, FA varies from 0 (equal diffusion in all directions) and 1 (anisotropic diffusion, i.e. diffusion in one direction) (O'Donovan et al., 2014).

DTI has been applied to a number of studies investigating WM microstructure in several neurological and psychiatric disorders, including different types of dementia (Burgel et al., 2006, Suri et al., 2014). The most consistent result that has emerged from DTI studies in DLB is the alteration of the ILF, specifically showing both decreased FA and increased MD compared with controls (Hattori et al., 2012, Kantarci et al., 2010, Kiuchi et al., 2011, Ota et al., 2009). Hattori et al. (2012) used a multimodal approach to investigate grey and white matter alterations, and cerebral perfusion in patients with DLB, PD, PD-MCI and PDD. Tract-based spatial statistics (TBSS) analyses were carried out to investigate WM integrity and differences among groups. In addition to ILF abnormalities, decreased FA was found in the superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus, and cingulum in DLB, PD-MCI and PDD in comparison with healthy controls (Hattori et al., 2012). Hattori et al. (2012) reported no differences between DLB and PDD, while other findings showed decreased FA in DLB in posterior temporal, posterior cingulate, and occipital areas (Lee et al., 2010b). WM abnormalities, especially in the ILF, are less common in PD without dementia, suggesting that these alterations may be related to the progression of cognitive decline (Haghshomar et al., 2018).

In a tractography-based study, Kiuchi et al. (2011) investigated differences in FA mean values in pre-defined WM tracts between patients with DLB, AD and normal controls. Although they did not find differences between patients groups, a differential pattern of abnormalities was detected when they were both compared with controls.

In fact, DLB patients presented reduced FA in the IFOF and ILF, while the only tract involved in both disorders was the uncinate fasciculus (Kiuchi et al., 2011). The IFOF and the ILF contain fibres connecting occipital areas with orbitofrontal and temporal regions, respectively (Catani and Thiebaut de Schotten, 2008) that may be implicated in the more pronounced visual perceptive deficits observed in DLB. Notably, increased MD was found in the ILF in patients with VH in DLB compared to those without (Kantarci et al., 2010). Other studies comparing DLB and AD showed reduced FA in the precuneus (Firbank et al., 2007), pons and thalamus (Watson et al., 2012), but no differences in the uncinate fasciculus (Serra et al., 2012).

One of the most consistent findings resulting from DTI studies in PD is represented by decreased FA in the substantia nigra that was found to correlate with disease severity (Atkinson-Clement et al., 2017, Cochrane and Ebmeier, 2013, Schwarz et al., 2013). Other meta-analytic results included altered FA and MD in the corpus callosum, cingulate and temporal cortices compared with controls (Atkinson-Clement et al., 2017).

1.7.2 Functional and molecular brain imaging

1.7.2.1 Resting-state functional magnetic resonance imaging

Brain functional connectivity can be investigated by means of resting-state fMRI and has been explored in several neuropsychiatric disorders, including AD, schizophrenia and depression (Greicius, 2008). This approach allows the investigation of the brain intrinsic functional organisation, and over the years has led to the identification of independent brain networks (Damoiseaux et al., 2006, Kalcher et al., 2012, Raichle, 2015, Rosazza and Minati, 2011). Spatial maps of brain regions showing temporally coherent patterns of spontaneous low frequency blood oxygen-level dependent (BOLD) signal fluctuations (below 0.1 Hz) constitute the so-called resting-state networks, namely spatially separate brain regions that are functionally connected (Greicius, 2008, Raichle, 2015, Rosazza and Minati, 2011).

The default mode network (DMN) is a resting-state network which is mainly activated during rest and deactivated during goal-related activities, and it includes regions such as the posterior cingulate, precuneus, inferior parietal lobule, medial prefrontal cortex, and temporal areas (Buckner et al., 2008, Greicius et al., 2003, Raichle et al., 2001, Rosazza and Minati, 2011, Utevsky et al., 2014). Reduced DMN connectivity has been reported by numerous studies in AD (Badhwar et al., 2017, Hafkemeijer et al., 2012), while less evidence is available for DLB. Studies so far have shown spared

connectivity within the DMN in DLB (Franciotti et al., 2013, Peraza et al., 2014). Nevertheless, a recent meta-analysis of resting-state fMRI studies in PD with cognitive decline reported evidence of decreased connectivity of regions within the DMN compared with HC (Wolters et al., 2018). Reduced DMN connectivity was also detected in comparison with cognitively normal PD patients, suggesting that such alterations may be related to cognitive decline (Wolters et al., 2018).

When compared with AD, DMN activity was found to be lower in AD than DLB, and the posterior cingulate cortex activity discriminated between the two groups with a specificity of 0.89 (Franciotti et al., 2013). Conversely, Lowther et al. (2014) found decreased functional connectivity in the DMN in DLB compared to AD. Differences in the functional connectivity of the precuneus, a functional hub of the DMN, was also shown between DLB and AD (Galvin et al., 2011). Moreover, as opposed to AD, hippocampal disconnections were not detected in DLB (Kenny et al., 2012, Mak et al., 2014). The differential pattern of functional connectivity shown between the two types of dementia suggests that resting-state fMRI may be useful in the identification of new disease-specific biomarkers, even though the limited studies available highlight the need for further investigation.

In another study, Peraza et al. (2015a) used a seed-based approach to investigate differences in the connectivity of cortical and subcortical regions between DLB, PDD and HC. No differences were found between DLB and PDD, which showed a similar pattern of disconnections of DMN-related seeds in comparison with controls (Peraza et al., 2015a). Reduced functional connectivity of seeds related to the fronto-parietal network was also detected in both disorders, but to a lesser extent in PDD (Peraza et al., 2015a). Meta-analytic evidence confirmed the presence of reduced connectivity within the right fronto-parietal network in PD with cognitive decline in comparison with controls (Wolters et al., 2018). Moreover, as for functional connectivity in PD, several studies have shown altered motor networks, including corticostrial networks (Weingarten et al., 2015).

1.7.2.2 Brain glucose metabolism and cerebral blood flow

Brain glucose metabolism and cerebral blood flow have been extensively studied in LBD by means of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and single photon emission computed tomography (SPECT), respectively. Overall, DLB and PDD show a similar pattern of alteration on FDG-PET and SPECT, characterised by parietal, precuneal and occipital hypometabolism and perfusion, with

only minor differences, if any are present (Jellinger, 2018). Brain perfusion has also been studied by arterial spin labelling (ASL) MRI studies, which showed hypoperfusion in frontal, insular, and temporal cortices in both LB dementias (Jellinger, 2018). Hypometabolism in parietal, premotor and supplementary motor areas has been observed in PD by FGD-PET studies, while preserved metabolism in the basal ganglia may distinguish this disorder from other parkinsonian syndromes, such as multiple system atrophy and progressive supranuclear palsy (Saeed et al., 2017).

The latest diagnostic criteria for DLB included occipital hypometabolism and hypoperfusion, as well as the relative preservation of posterior/midcingulate metabolism, known as the cingulate island sign, as supportive biomarkers of DLB (McKeith et al., 2017). AD, instead, is characterised by more prominent parietotemporal and posterior cingulate hypometabolism (Sinha et al., 2012). These features seem to be distinctive of DLB and aid differential diagnosis with AD (Imabayashi et al., 2016, Iizuka et al., 2017, Mak et al., 2014, McKeith et al., 2017, Sinha et al., 2012). In an autopsy confirmed study, Minoshima et al. (2001) reported that both AD and DLB patients presented hypometabolic regions in parietotemporal, frontal and posterior cingulate cortices. In addition, DLB patients showed occipital hypometabolism that was a differentiating feature between the two conditions with 90% sensitivity and 80% specificity (Minoshima et al., 2001). More recently, O'Brien et al. (2014) investigated brain glucose metabolism and blood flow in a sample of clinically diagnosed patients with AD (n=38), DLB (n=30) and controls (n=30). They found that FDG-PET better distinguished DLB from AD, recommending this technique for differential diagnosis (O'Brien et al., 2014).

1.7.2.3 Neurotransmitter imaging

Although to different extent, each LB disorder is characterised by nigrostriatal dopaminergic dysfunction, characterised by neuronal loss in the substantia nigra compacta, corresponding to a loss of dopaminergic neurons and terminals within the striatum (Jellinger, 2012). Neuroimaging techniques have been developed to measure the dopamine transporter (DAT) uptake in the striatum, indicating that integrity of the nigrostriatal dopaminergic terminals correlates with severity and duration of motor symptoms (Siderowf et al., 2018, Jellinger, 2012). Specifically, integrity of these terminals can be assess by means of either ^{123}I-β-CIT SPECT or ^{18}fluorodopa PET (Jellinger, 2018). Several studies have shown reduced DAT uptake in the striatum in DLB compared to AD, suggesting that it may be a useful tool to

differentiate these two clinical conditions (Jellinger, 2018, McKeith et al., 2017). In fact, it has been included as an indicative biomarker for DLB among the latest diagnostic criteria, showing a sensitivity of 78% and a specificity of 90% (McKeith et al., 2017). However, a normal DAT scan was among the findings in autopsy confirmed DLB patients that may be indicative of minimal brainstem involvement in those cases (Jellinger, 2018, McKeith et al., 2017). Therefore, an unimpaired DAT scan does not exclude a diagnosis of DLB, with 3-9% of patients not presenting nigrostriatal pathology (Walker et al., 2015). On the other hand, a normal DAT scan excludes a diagnosis of PD and PDD, although may not be useful to distinguish it from other parkinsonian conditions, such as atypical parkinsonian syndromes (Postuma et al., 2015, Schapira, 2013). However, it may be used to differentiate PD from other PD-like syndromes with no parkinsonism like essential tremor (Postuma et al., 2015). Similar striatal DAT uptake has been shown in DLB, PDD and PD, while it has been found to be normal in AD (Brooks, 2016).

PET may also be used to evaluate the degree of brain cholinergic dysfunction *in vivo*, by means of acetylcholinesterase activity measures (Sinha et al., 2012). Patients with LB dementia are characterised by a widespread cortical cholinergic deficit (Grothe et al., 2014, Sinha et al., 2012). Compared to AD, patients with both LB dementias presented decreased cortical acetylcholinesterase activity, especially in the medial occipital cortex (Sinha et al., 2012). PET imaging studies showed that patients with PD without dementia also presented with cortical cholinergic dysfunctions that were, however, less severe than PDD and DLB (Hilker et al., 2005, Shimada et al., 2009).

1.7.3 Other biomarkers

In addition to those outlined in the sections above, other biomarkers have been included as indicative or supportive biomarkers for the diagnosis of DLB, including reduced [^{123}I]Metaiodobenzylguanidine (^{123}I-MIBG) uptake detected on myocardial scintigraphy, REM sleep without atonia confirmed at polysomnography, and prominent posterior slow wave activity on electroencephalography (McKeith et al., 2017). Currently, there is no proven cerebrospinal fluid (CSF) a-synuclein biomarker, even though different CSF markers have been studied (McKeith et al., 2017, Schapira, 2013). Aβ, tau, and phospho-tau detection may be used to identify concomitant AD pathology, and as an indicator of cognitive decline in LBD (McKeith et al., 2017, Schapira, 2013).

Aβ deposition, detected with ^{11C}PIB-PET was found in more than 50% of patients with DLB, and is less frequently observed in PDD (Jellinger, 2018, McKeith et al., 2017). Given the high frequency of Aβ accumulation in DLB, its detection with PET represents a less useful tool for differential diagnosis with AD. On the other hand, Tau PET imaging may have an important role in detecting mixed AD/LB pathology, along with MTL atrophy (Jellinger, 2018, McKeith et al., 2017). Tau ^{18F}AV-145 uptake has been found mainly in the inferior temporal gyrus and precuneus, and is less commonly observed in PDD and PD without dementia (Jellinger, 2018).

Chapter 2. Visual hallucinations in Lewy body disease

2.1 Introduction to visual hallucinations in Lewy body disease

Visual hallucinations represent a common symptom experienced by patients within the LBD spectrum, they were identified as the clinical feature better differentiating DLB from AD in the early stages of the disease course, and they are among the core symptoms leading to a clinical diagnosis of DLB (McKeith et al., 2005, Tiraboschi et al., 2006). Even though they may occur in all sensory modalities, VH are the most common (Aarsland et al., 2009, McKeith et al., 2017). Recurrent and complex VH are repetitive, involuntary and well-formed images perceived in the absence of real stimuli, therefore they may be conceptualised as perceptions inconsistent with objective reality (Collerton et al., 2005). The most common VH include people, animals and inanimate objects, and show similarities between conditions, especially DLB and PDD (Collerton et al., 2005, Mosimann et al., 2006, Onofrj et al., 2013). Other related visuo-perceptual phenomena, including sensations of presence, sideway passages and visual illusions, may also be present, and may be shown in conjunction with VH (Aarsland et al., 2009, McKeith et al., 2017, Onofrj et al., 2013).

Approximately 60-80% of DLB, 45-65% of PDD and 25-40% of PD patients present VH (Aarsland et al., 2001a, Emre et al., 2007, Williams and Lees, 2005). They tend to be more frequent, complex and severe in LBD patients with dementia, who are often unaware of the unreal nature of their experience (Aarsland et al., 2001a, Emre et al., 2007, Onofrj et al., 2013, Williams and Lees, 2005). VH are often present since the early stages of DLB, and are considered an important hallmark of the disorder (McKeith et al., 2005). On the other hand, they tend to occur later in the progression of PD, with longer disease duration identified as independent predictor of VH (Fenelon and Alves, 2010, Gallagher et al., 2011). Other variables associated with VH are greater severity of the disease, older age, poor vision, and presence of sleep disorders, particularly RBD (Collerton et al., 2005, Fenelon and Alves, 2010, Gallagher et al., 2011). VH have also been linked with the occurrence of other neuropsychiatric symptoms, which contribute, along with the more severe cognitive decline, in worsening significantly the overall quality of life of both patients and their caregivers (Onofrj et al., 2013). This emphasises the importance of clarifying the mechanisms underlying this severe symptomatology that still remain not well understood.

Historically, VH in PD were considered as drug-induced symptoms, especially following treatment with levodopa (Ffytche et al., 2017, Onofrj et al., 2013). However, subsequent studies found that antiparkinsonian medications do not increase the risk of developing VH, and that these symptoms also occur in unmedicated patients (Ffytche et al., 2017, Onofrj et al., 2013). Therefore, VH appear to be an intrinsic feature of PD and are associated with specific neuropathological breakdowns, rather than being a drug-induced phenomenon (Onofrj et al., 2013). In fact, VH may be considered a marker of LB pathology, being a strong predictor of LBs accumulation in the brain (Emre et al., 2007, Onofrj et al., 2013, Tiraboschi et al., 2006). In patients with VH, high proportions of LBs have been found mainly in frontal and temporal areas, especially in the amygdala, (Gallagher et al., 2011, Harding et al., 2002a, Harding et al., 2002b, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006), but not in the occipital lobe (Kalaitzakis et al., 2009). Interestingly, Toledo et al. (2013) found that hallucinations were a strong predictor of concomitant LB pathology also in AD, although the sensory modality in which hallucinations were experienced was not specified in this study.

2.2 Multifactorial models of visual hallucinations

In an attempt to understand the mechanisms underlying recurrent complex VH in different disorders, a number of multidimensional, integrative models has been proposed (Collerton et al., 2005, Diederich et al., 2005, Diederich et al., 2015, Shine et al., 2011). These models suggest that VH are the result of different biological and cognitive vulnerabilities involving both top-down and bottom-up processes that, interacting with each other, foster the development of these disabling symptoms.

One of the leading models is represented by the Perception and Attention deficit (PAD) model proposed by Collerton et al. (2005). The authors suggest that recurrent, complex VH result from the combination of impaired top-down and bottom-up processes, specifically coexisting deficits in attention and visual perception. The conceptualisation of the model was guided by the high prevalence of VH in DLB, but it aimed to be generalizable to other neurodegenerative and non-degenerative disorders (Collerton et al., 2005). The neurocognitive and pathological features of DLB, along with the fact that VH normally manifest at the attentional focus of an otherwise unaltered scene, played a central role in devising the model (Collerton et al., 2005).

A core concept of the PAD model is represented by proto-objects, consisting in object templates that compete with each other for further processing (Diederich et al., 2015, Muller et al., 2014). In normal perception, proto-objects remain unconscious until one of them reaches conscious awareness, thus being actually perceived. Top-down and bottom up mechanisms influence this process. Specifically, salient physical properties of the stimuli, such as colour, brightness and contrast, create bottom-up biases. Top-down factors, instead, include representations of similar visual scenes stored in long-term memory, individual expectations, and goal-directed attention that bias sensory processing (Collerton et al., 2005, Diederich et al., 2015). Attentional binding plays a key role in influencing the process by which proto-objects are selected and reach awareness. According to the model, VH would be generated when an incorrect proto-object is processed and bound in the attentional focus of the scene, being, therefore, perceived as a real object in an otherwise relatively unaltered scene (Collerton et al., 2005). Impaired visual perception and attention would both be necessary to experience VH. Therefore, isolated deficits in either of the two would be insufficient for the development of this symptom. These deficits would be supported by impaired activity in the lateral frontal cortex, and the ventral visual stream, regions involved in object-based attention and object perception, respectively (Collerton et al., 2005).

Another recent model proposed by Shine et al. (2011) highlights the importance of dysfunctional attentional mechanisms in the development of VH. Even though initially proposed to explain misperceptions and hallucinations in PD, it was later applied to other disorders characterised by attention deficits and hallucinations (Shine et al., 2011, Shine et al., 2014b). The authors suggest that hallucinations arise from a disrupted engagement of brain networks regulating attention, specifically the DMN, the dorsal attention network (DAN), and the ventral attention network (VAN).

The DMN is a network of brain regions activated at rest and deactivated during goal-related tasks. It has been associated with internal self-referential thoughts, and the retrieval and manipulation of episodic memories (Shine et al., 2011). The VAN enables rapid engagement of attention towards salient stimuli, triggered by bottom-up stimulus-related information. The processing of bottom-up information by the VAN often requires top-down processing by the DAN that is involved in task-related orienting of attention, therefore linked to the behavioural significance of stimuli (Lewis et al., 2015). When directing attention to goal-directed stimuli, the task-independent DMN is deactivated, while the DAN is usually recruited. The VAN, triggered by bottom-up stimulus-related information, is thought to modulate and coordinate activity between the other two networks. Shine et al. (2011) suggested that false images may

originate from the emergence of previously recorded percepts in the DMN. In this context, a relative inability to recruit the DAN, and a simultaneous overactivity of the DMN and the VAN would generate hallucinations, especially in the presence of ambiguous stimuli and impaired visual processing (Shine et al., 2011, Shine et al., 2014b).

Another relevant model was proposed by Diederich et al. (2005), who applied the Hobson's Activation-Input-Modulation model for the states of consciousness to the understanding of VH (Diederich et al., 2005, Hobson et al., 2000). According to the model developed by Hobson, the first dimension, *activation*, involves the ability to process information. It is particularly high when subjects are alert, and low in non-REM sleep, and it is thought to be regulated by the reticulo-thalamo-cortical system (Diederich et al., 2005). The second dimension, *input*, relates to the ability to exchange information with the external world, and to create internally generated information, by balancing internal and external perceptions. Internal stimuli formation is controlled by the ponto-geniculo-occipital system that also induces the associative visual cortex to trigger generation of endogenous perception (Diederich et al., 2005). The last dimension, *modulation*, integrates the other dimensions over time, and it is supported by aminergic and cholinergic brainstem systems. The nucleus peduncolopontinus is a major cholinergic centre, also involved in REM sleep (Diederich et al., 2005). According to Diederich et al. (2005), impaired visual activation processes, along with the release of internally generated images would result in VH, fostered by the inability to regulate the gating and filtering of external stimuli and internally formed images. In this context, a dysfunctional ponto-geniculo-occipital system may generate REM sleep related intrusions into wakefulness (Diederich et al., 2005).

2.3 Neuropsychology of visual hallucinations in Lewy body disease

One of the approaches used to investigate VH aims to identify the cognitive processes underlying this symptomatology and its neural basis. A very close relationship with cognitive deficits has been reported consistently, both in LBD with and without dementia. Patients with cognitive decline tend to develop more severe and complex VH that are found more commonly in LB dementia than cognitively preserved PD patients (Aarsland et al., 2001a, Emre et al., 2007, Onofrj et al., 2013, Williams and Lees, 2005). Several studies identified cognitive impairment and dementia as

independent risk factors for hallucinations (Fenelon and Alves, 2010). Similarly, an increased risk of developing dementia in PD characterised by early hallucinations was reported, further highlighting the close relationship between this symptom and cognitive decline (Aarsland et al., 2003a). More severe progressive cognitive decline has also been detected in patients with VH compared with those with no VH (NVH) (Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2007a). A number of studies has reported differences between LBD patients with and without VH in specific cognitive domains, among which visual perception (Barnes and Boubert, 2011, Koerts et al., 2010, Mosimann et al., 2004), attention (Bronnick et al., 2011, Cagnin et al., 2013), executive functioning (Barnes and Boubert, 2008, Grossi et al., 2005, Ozer et al., 2007, Santangelo et al., 2007) and long-term memory (Grossi et al., 2005, Hepp et al., 2013, Santangelo et al., 2007). Despite the high rate of VH in DLB, their cognitive correlates in this disorder have not been studied extensively, while more evidence is available for PD. Findings for each cognitive domain are outlined in the following sections.

2.3.1 Visual perception and visuoconstruction

Significantly worse performance was found in tests assessing visual perception in patients with VH, in both LB dementia (Mori et al., 2000, Mosimann et al., 2004), and PD (Barnes et al., 2003, Ibarretxe-Bilbao et al., 2010, Koerts et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a). One of the most used tests to explore visual perception abilities is the Visual and Object Space Perception (VOSP) battery, assessing object and space perception (Lezak et al., 2012, Rapport et al., 1998, Warrington and James, 1991). Studies focusing on PD have shown worse performance in patients with hallucinations in a number of subtests of the VOSP, mainly the object decision and silhouettes subtests (Barnes and Boubert, 2011, Barnes et al., 2003, Koerts et al., 2010). Notably, to rule out the influence of the executive dysfunction commonly observed in PD, Koerts et al. (2010) matched the subgroups of patients for their executive functioning, evaluated with the Frontal Assessment Battery (FAB); visuoperceptive impairment remained, however. Face recognition has also been studied in PD with VH using the Benton facial recognition task; the results were contrasting, with some showing significant differences (Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2006), while others did not (Ozer et al., 2007). As for LB dementia, no significant differences in any of the VOSP subtests were found between DLB VH (n=45) and NVH (n=36) (Cagnin et al., 2013).

However, cognitive performance in a visual perception task was found to be associated with the severity of VH in patients with DLB, but not PDD (Sanchez-Castaneda et al., 2010). Moreover, two studies reported more severe deficits in other visual perception tasks in hallucinating patients with LB dementia (Mori et al., 2000, Mosimann et al., 2004). However, the sample sizes of these studies were quite small, and no significant differences were reported in some perceptual tasks (Mori et al., 2000, Mosimann et al., 2004). Therefore, due to the limited number of available studies, further evidence is needed to understand better the role of visual perception in the development of VH in LBD, especially in patients with dementia. Overall, the impaired performance outlined in the abovementioned studies might be due to brain alterations in visual associative areas, namely in the occipito-temporal cortex, which is in line with the atrophy and reduced cerebral blood flow detected in these regions, mainly in non-demented PD with VH (Oishi et al., 2005, Ramirez-Ruiz et al., 2007b).

Other tasks relying on visual perception abilities include those testing visuoconstruction. Although some studies outlined above reported no differences in visual perception between patients with and without VH in PD and DLB, the same studies showed significantly lower scores on the clock drawing test in hallucinating patients, indicating poorer visuospatial and visuoconstructional abilities (Cagnin et al., 2013, Ozer et al., 2007). In addition, more severe visuospatial and visuocontructional impairments were found to predict significantly the likelihood of presenting VH in autopsy-confirmed DLB patients, suggesting that these deficits may play a role in the development of this symptom (Hamilton et al., 2012, Hamilton et al., 2008). However, performance on the copy of the Rey complex figure was found to be similar between DLB patients with and without VH by some studies (Cagnin et al., 2013, Heitz et al., 2015). The inconsistencies reported may reflect differences in the cognitive tests used to investigate visuoconstructive abilities, which may involve additional cognitive functions (e.g. executive functioning in the clock drawing test). Less inconsistent findings are reported in PD, with findings showing that, overall, lower scores on the Rey figure copy were found in VH patients (Chang et al., 2016, Manganelli et al., 2009, Shin et al., 2012), and one study only reporting comparable performance (Hepp et al., 2013). Thus, differences between VH and NVH patients may become less evident in patients with cognitive decline, due to the severe visuoperceptive and visuoconstructive deficits exhibited also by patients without VH. In fact, these symptoms are considered distinctive features of both LB dementias (Collerton et al., 2003, Goldmann Gross et al., 2008). Therefore, the more severe deficits in visual perception and visuoconstruction in hallucinating patients may be more subtle when

comparing patients with dementia, and may be more easily detectable in cognitively normal PD. Moreover, some tests may be more sensitive than others in differentiating the subgroups, as they have all been designed to assess cognition in general, rather than VH-related cognitive impairments. The small sample sizes investigated in some studies might also explain subthreshold results, at least in part.

2.3.2 Attention

Even though different models of VH have proposed an involvement of attention deficits in the development of VH, visual attention has not been studied extensively by neuropsychological studies. One of the most used tests was the Trail Making Test part A (TMT-A), evaluating visual attention, visuomotor and scanning abilities. Studies have explored differences between VH and NVH patients using this test in PD, and have reported contrasting results (Chang et al., 2016, Gasca-Salas et al., 2016, Hepp et al., 2013). In a study investigating the cognitive features associated with VH in PD without dementia, Hepp et al. (2013) found that scores on the TMT-A and Rey Auditory Verbal Learning Test (RAVLT), assessing verbal memory, were the only variables differentiating VH (n=31) from NVH (n=31) patients, with hallucinating patients performing worst. In this study, the two groups of patients were matched for age, gender, duration and severity of the disease, motor symptoms, education and global cognitive impairment. Importantly, differences on the TMT-A remained significant after controlling for motor symptoms (Hepp et al., 2013). Similarly, Chang et al. (2016) found that patients with VH (n=12) took significantly longer time to complete the TMT-A than NVH (n=23). Since there were group differences in disease duration and severity, motor symptoms, and duration of levodopa use, these variables were added as covariates of no-interest in the analysis (Chang et al., 2016). On the contrary, another study on PD (Gasca-Salas et al., 2016), and two on DLB (Cagnin et al., 2013, Heitz et al., 2015) found no between-group differences in the TMT-A. Cagnin et al. (2013) included another measure of visual attention, specifically visual search, namely the digit cancellation test, with VH patients (n=45) scoring worse than NVH (n=36). Among all comparisons of tests in neuropsychological testing, the only difference that was significant after correcting for multiple comparisons was that between scores achieved on the digit cancellation test ($p<0.005$) (Cagnin et al., 2013). In this study, however, VH patients were older and with a later disease onset, while disease duration was similar between groups (Cagnin et al., 2013). Moreover, they obtained lower scores on the MMSE, although this difference was only marginally

significant (p=0.05) (Cagnin et al., 2013). Hallucinating patients performed poorer on the digit cancellation test also in PD without dementia (Manganelli et al., 2009). Bronnick et al. (2011) examined the cognitive correlates of VH in PDD. They carried out a stepwise logistic regression analysis, including measures of attention, visuoconstruction, working memory, verbal fluency and language. In addition, disease duration and motor symptoms were entered as control variables. Choice reaction time, as a measure of attention, was the only significant independent predictor of VH (Bronnick et al., 2011). Finally, hallucinating patients were found to perform similarly to non-hallucinating ones on the digit span forward, a measure of auditory attention and short-term memory, both in PD (Barnes and Boubert, 2008, Chang et al., 2016, Hepp et al., 2013, Shin et al., 2012) and DLB (Heitz et al., 2015). Cagnin et al. (2013), instead, reported poorer performance on the digit span forward in DLB patients with VH compared with those without.

2.3.3 Executive functioning

The studies that have focused on the investigation of executive functioning have reported findings that lack consistency and are mainly related to PD. The term executive functioning refers to a number of cognitive abilities, including response inhibition, working memory, cognitive flexibility, and interference control (Diamond, 2013). The most used tests have been phonemic fluency, TMT part B (TMT-B), Wisconsin card sorting test, Stroop test, go-no/go tasks and FAB.

Phonemic fluency, measuring cognitive flexibility and executive control abilities, has been used in several studies on PD, yielding contrasting results. Some have found lower scores in VH patients (Grossi et al., 2005, Manganelli et al., 2009, Santangelo et al., 2007), while others have reported no differences (Gasca-Salas et al., 2016, Hepp et al., 2013, Ramirez-Ruiz et al., 2006, Shin et al., 2012). Moreover, scores on phonemic fluency predicted the development of VH at a 2-year follow-up in PD (Santangelo et al., 2007), and VH patients showed more severe progressive decline in phonemic fluency compared to NVH (Ramirez-Ruiz et al., 2007a). In LB dementia, hallucinating patients were found to perform similarly to non-hallucinating patients (Bronnick et al., 2011, Cagnin et al., 2013, Heitz et al., 2015).

Inhibitory control of attention was investigated in PD with hallucinations, mainly using the Stroop test, with some studies reporting more severe deficits (Barnes and Boubert, 2008, Imamura et al., 2008), but not others (Gasca-Salas et al., 2016, Hepp et al., 2013, Manganelli et al., 2009). Response inhibition was also assessed with no-no/go

tasks, providing evidence of impaired inhibitory control in PD, using both a computerised task (Barnes and Boubert, 2008) and the FAB go-no/go subtest (Santangelo et al., 2007). The Wisconsin Card Sorting Test, assessing set shifting and abstract reasoning, was also used to evaluate executive dysfunction in PD with and without VH, however yielding no significant results (Chang et al., 2016, Manganelli et al., 2009, Ozer et al., 2007). In addition to the findings on the TMT-A outlined in the previous section, some studies also used the TMT-B that is a test designed to evaluate executive functioning, mainly cognitive flexibility and task switching. No significant results were found in PD (Chang et al., 2016, Gasca-Salas et al., 2016) and DLB (Heitz et al., 2015). Another aspect of executive functioning is represented by working memory abilities, evaluated in LBD with VH by means of the digit span backward test (Cagnin et al., 2013, Heitz et al., 2015, Shin et al., 2012), a 2-back task (Barnes and Boubert, 2008), and the serial 7s task from the MMSE (Bronnick et al., 2011). Overall, no differences were found between VH and NVH patients, in PD (Shin et al., 2012), PDD (Bronnick et al., 2011) and DLB (Cagnin et al., 2013, Heitz et al., 2015). The only significant difference appeared in the percentage of false alarm responses in the 2-back task, which was higher in PD VH compared to both NVH and controls (Barnes and Boubert, 2008). However, the percentage of hits and the corrected hit rate score did not differ between PD subgroups (Barnes and Boubert, 2008). In the same study, a reading span test was also performed, in which patients had to repeat the last words of two sentences for each of five sets. Although both PD groups performed poorly compared with controls, no differences were detected between VH and NVH patients (Barnes and Boubert, 2008). Finally, other studies have used the FAB, originally designed to assess frontal lobe functions in neurological conditions, which comprises subtests evaluating different aspects of executive functioning (Appollonio et al., 2005, Dubois et al., 2000). Some studies reporting the overall FAB score indicated lower performance in patients with VH in PD (Wang et al., 2010), but other studies found no differences neither in PD (Santangelo et al., 2007) nor in DLB (Heitz et al., 2015).

2.3.4 Verbal, visual and semantic memory

Several studies involving PD patients with VH have reported more severe deficits in verbal long-term memory (Grossi et al., 2005, Hepp et al., 2013, Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a, Santangelo et al., 2007). In patients with VH, these deficits were characterised by faster cognitive

decline compared with patients without VH (Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2007a). The most used test was the RAVLT, which involves immediate and delayed recall, and a recognition test of a list of words. All studies (Grossi et al., 2005, Hepp et al., 2013, Ramirez-Ruiz et al., 2006) but one (Manganelli et al., 2009) showed differences between PD subgroups in the immediate recall section, but not in the delayed recall (Grossi et al., 2005, Hepp et al., 2013, Manganelli et al., 2009) or in the RAVLT recognition sections (Hepp et al., 2013, Ramirez-Ruiz et al., 2006). Verbal memory was also studied with other neuropsychological tests in PD, mostly word-list recall and recognition tests (Barnes et al., 2003, Bronnick et al., 2011, Chang et al., 2016, Gasca-Salas et al., 2016, Ozer et al., 2007, Shin et al., 2012). Ozer et al. (2007) reported poorer performance in patients with VH on the delayed recall of a verbal learning test involving a list of words. Overall, no other differences between hallucinating and non-hallucinating patients were detected (Barnes et al., 2003, Bronnick et al., 2011, Chang et al., 2016, Gasca-Salas et al., 2016, Shin et al., 2012). In addition to these findings, Barnes et al. (2003) found impaired source monitoring in hallucinating patients. Specifically, they were more likely to report imagined stimuli as real percepts, originally presented as words at the encoding phase, suggesting that they have more difficulties in recalling and allocating the appropriate modality source than non-hallucinating patients.

In PD, visual memory was mainly assessed with the delayed recall of a complex figure, such as the Rey-Osterrieth Complex Figure, and recognition memory tests for faces. Lower scores on the Rey figure recall was found by Shin et al. (2012), but not by other studies (Chang et al., 2016, Hepp et al., 2013). Contrasting findings were reported with respect to recognition memory for faces, with some studies reporting significant difference between VH and NVH PD patients (Barnes et al., 2003) while others reporting non-significant differences (Ramirez-Ruiz et al., 2006).

PD with VH was also found associated with semantic memory deficits, mainly assessed with the category fluency test (Barnes and Boubert, 2008, Grossi et al., 2005, Ozer et al., 2007). A higher percentage of perseverations was also found by some authors (Barnes and Boubert, 2008). Other studies, however, have found no differences between PD subgroups (Hepp et al., 2013, Ramirez-Ruiz et al., 2006, Shin et al., 2012)

Fewer neuropsychological investigations of VH have been undertaken in DLB, and the available studies have shown no differences between subgroups with and without VH in verbal (Cagnin et al., 2013, Heitz et al., 2015), visual (Cagnin et al., 2013) and semantic memory (Heitz et al., 2015).

2.4 Structural and functional neuroimaging of visual hallucinations in Lewy body disease: a systematic literature review

The systematic literature review reported in this section represents an update of the review published in 2017 by the same author of the present thesis (Pezzoli et al., 2017). The originally published article is reported in Appendix 1, and can be accessed online at https://www.mdpi.com/2076-3425/7/7/84. The authors of the original article retain the copyright of the published material, and all provided consent to reuse it for the purpose of the present thesis, as reported in Appendix 2 (copyright details available at https://www.mdpi.com/authors/rights).

Aim. The purpose was to summarise the current literature on structural and functional brain abnormalities associated with VH in LBD, namely PD and DLB. Specifically, findings from structural MRI, DTI, fMRI, PET, and SPECT studies were critically reviewed.

Method. Articles were identified through a systematic literature search, initially carried out in January 2017 by using the PubMed and Web of Science databases with no time limit. An updated search was subsequently undertaken in March 2019. The following key words were used: “visual hallucinations”, “visual hallucination”, "Lewy body", "dementia with Lewy bodies", "Parkinson's disease", “magnetic resonance imaging”, “MRI”, “voxel-based morphometry”, “VBM”, “fMRI”, "resting-state", “diffusion tensor imaging”, “DTI”, “positron emission tomography”, and “PET”, “single photon emission computed tomography”, “SPECT”. An additional manual search of references was also performed. Studies were excluded according to the following exclusion criteria: (1) pathologies other than DLB, PD or PDD, (2) neuroimaging analysis not related to VH, (3) patients with medication-induced VH, (4) studies not using MRI, fMRI, DTI, PET, SPECT, (5) PET and studies not investigating glucose metabolism and regional cerebral blood flow, (6) MRI studies using visual rating, (7) magnetic resonance spectroscopic imaging, (8) pharmacological studies, (9) case studies (except for fMRI during VH), (10) review and theoretical articles, (11) non-English articles, (12) non-peer reviewed articles. The search strategy followed the PRISMA guidelines (Moher et al., 2009). The articles included were assessed for scientific suitability to the aim of the present review by using a set of 14 criteria adapted from Welton et al. (2015). These criteria can be found in the supplementary

materials of the published article (Pezzoli et al., 2017), and are reported in Appendix 1.

Results. The systematic search retrieved 770 titles, among which 443 were duplicate publications that were excluded. Three studies were identified through manual search. A total number of 327 titles and abstracts were assessed, of which 118 full-text articles were retrieved and screened for eligibility. The final review included 68 studies investigating the structural and functional brain correlates of VH in LBD by using structural and functional MRI, DTI, PET, and SPECT. Among the 68 articles reviewed, 12 (Barrell et al., 2018, Bejr-Kasem et al., 2019, Chabran et al., 2018, Colloby et al., 2017, Firbank et al., 2018, Hepp et al., 2017, Iaccarino et al., 2018, Lenka et al., 2018, Morbelli et al., 2019, Nishio et al., 2018, Nishio et al., 2017, Schumacher et al., 2018) were found following the second systematic search, thus they were not included in the published article (Pezzoli et al., 2017). A flow chart describing the selection process of the studies included in the final review is shown in Figure 2.1, adapted from Moher et al. (2009).

Studies investigating VH in LBD using more than one approach or imaging technique were included in more than one section of the review and the findings for each technique reported separately in the relevant section. There were 11 studies combining different techniques, specifically structural and functional MRI (Bejr-Kasem et al., 2019, Franciotti et al., 2015, Yao et al., 2014), structural MRI and PET (Iizuka and Kameyama, 2016, Kantarci et al., 2012, Nishio et al., 2017), structural MRI and DTI (Hepp et al., 2017, Lee et al., 2016, Lee et al., 2017), structural MRI, DTI and fMRI (Firbank et al., 2018, Yao et al., 2016), fMRI and ASL-MRI (Taylor et al., 2012). Moreover, in two structural MRI studies, different methods were used to investigate regional brain volumes (Meppelink et al., 2011, Shin et al., 2012).

Overall, among the main limitations of the studies, we found lack of a priori hypotheses on VH (n=33 studies), sample sizes with less than 15 participants per group (n=42 studies), and absence of correlational analyses with VH indices (n=39 studies) and cognitive measures (n=58 studies).

In the following sections, findings for each imaging technique are summarised and critically reviewed.

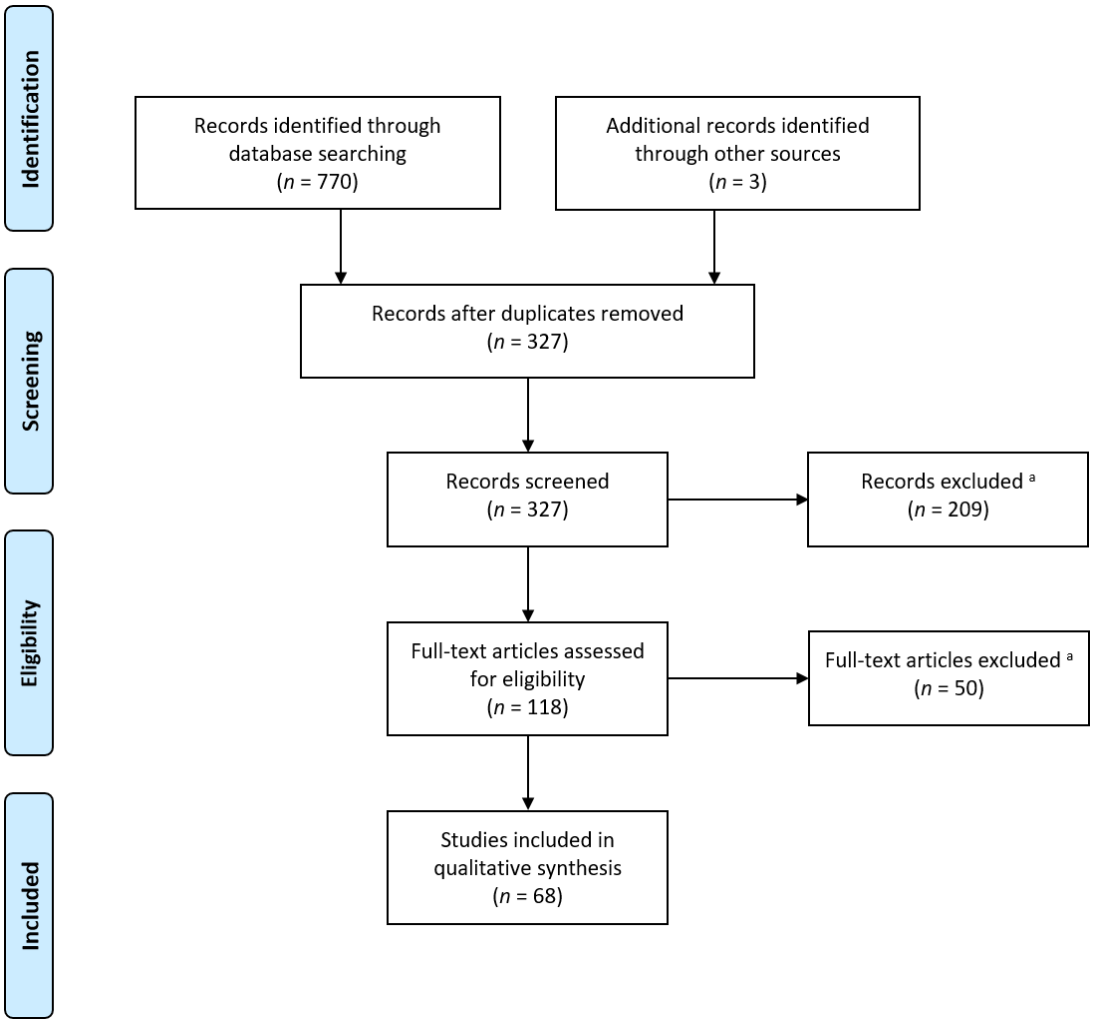

Figure 2.1 Flow chart describing the selection process of the studies included, adapted from Moher et al. (2009). [a] Exclusion criteria: (1) pathologies other than DLB, PD or PDD, (2) neuroimaging analysis not related to VH, (3) patients with medication-induced VH, (4) studies not using MRI, fMRI, DTI, PET, SPECT, (5) PET and SPECT studies not investigating glucose metabolism and regional cerebral blood flow, (6) MRI studies using visual rating, (7) magnetic resonance spectroscopic imaging, (8) pharmacological studies, (9) case studies (except for fMRI during VH), (10) review and theoretical articles, (11) non-English articles, (12) non-peer reviewed articles.

2.4.1 Structural brain imaging

The brain structural changes associated with VH in LBD, detected with MRI, were investigated by 31 studies. The findings are summarised according to the analytic approach used, namely voxel-based morphometry (VBM), other methods to investigate brain morphology, namely regional volumes, shape and cortical thickness, and DTI.

2.4.1.1 Voxel-based morphometry

A total of 16 VBM studies were identified. Eleven studies focused on regional volumetric brain differences between LBD patients with and without VH, including eleven studies that used whole brain analyses and three voxel-based analyses restricted to predefined regions of interest (ROIs). Five studies also included results on the association between grey matter loss and VH or other cognitive variables (Colloby et al., 2017, Goldman et al., 2014, Ibarretxe-Bilbao et al., 2010, Ibarretxe-Bilbao et al., 2008, Sanchez-Castaneda et al., 2010). Moreover, one study included only the comparison between PD subgroups and controls (Gama et al., 2014), and another investigated progression of brain atrophy (Ibarretxe-Bilbao et al., 2010). The VBM methodology implemented was largely consistent between studies. All used the Statistical Parametric Mapping (SPM) software for imaging analysis, and nine used the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) algorithm to create a study-specific template. A threshold corrected for multiple comparisons was applied in five whole brain (Bejr-Kasem et al., 2019, Ibarretxe-Bilbao et al., 2010, Meppelink et al., 2011, Ramirez-Ruiz et al., 2007b, Shin et al., 2012), and four ROI (Gama et al., 2014, Ibarretxe-Bilbao et al., 2008, Janzen et al., 2012, Sanchez-Castaneda et al., 2010) studies. The results of those studies which used uncorrected thresholds (Blanc et al., 2016, Goldman et al., 2014, Janzen et al., 2012, Lee et al., 2017, Shin et al., 2012, Watanabe et al., 2013) should be interpreted more cautiously, since analyses using uncorrected threshold may generate a higher number of false positives. Clinical and demographic features, including severity of cognitive impairment, disease duration, age, and years of education varied between studies. Some of these studies reported no differences in global cognitive impairment between patients with and without VH (Goldman et al., 2014, Janzen et al., 2012, Lee et al., 2017, Meppelink et al., 2011, Sanchez-Castaneda et al., 2010, Shin et al., 2012, Watanabe et al., 2013), while others showed more severe cognitive decline in hallucinating patients (Gama et al., 2014, Ibarretxe-Bilbao et al., 2010, Ibarretxe-Bilbao et al., 2008, Ramirez-Ruiz et al., 2007b). Furthermore, some studies on PD reported more advanced disease stage (Hoehn and Yahr stage) in patients with VH than in those without (Ibarretxe-Bilbao et al., 2010, Janzen et al., 2012, Lee et al., 2017, Ramirez-Ruiz et al., 2007b).

Ibarretxe-Bilbao et al. (2010) investigated the progression of brain atrophy in PD patients with and without VH. Hallucinating patients presented more extensive grey matter loss over time, accompanied by faster cognitive decline. Progressive grey matter reduction from baseline to follow-up extended to parietal, temporal, frontal,

thalamic, and limbic areas in patients with VH, whereas only small clusters in frontal, and cerebellar regions showed reductions in those without. Cognitive impairment and disease severity at baseline, however, were greater in patients with VH than in those without, but MMSE scores were included in the analysis as covariate of no interest (Ibarretxe-Bilbao et al., 2010). Additionally, significant associations between grey matter loss and cognitive functions were detected in patients with VH, specifically in measures of learning (left hippocampus, r=0.88), delayed recall (left prefrontal cortex, r=0.95), semantic fluency (left thalamus, r=0.95), and language comprehension (left amygdala, r=0.89).

In a whole brain VBM study, Ramirez-Ruiz et al. (2007b) found grey matter volumetric reductions in the left lingual gyrus, and bilateral superior parietal lobe in PD patients with VH when compared with those without ($p<0.05$ corrected at the cluster level). In this study, PD patients were matched with healthy controls. In this article no information about the age of the included cohorts was given, and in the comparison between hallucinating and non-hallucinating patients the authors do not appear to have controlled for age in their analysis. Furthermore, patients with VH had more severe impairments in global cognitive status, as measured by the MMSE (Folstein et al., 1975), more advanced PD stage, rated with the Hoehn and Yahr scale (H&Y) (Hoehn and Yahr, 2001a), and more severe depression, measured by the Hamilton depression rating scale (Hamilton, 1960). These variables were included as covariates in the VBM statistical analyses (Ramirez-Ruiz et al., 2007b). Consistently with these findings, other studies reported less grey matter volume in PD patients with VH than in those without in occipito-temporal regions, namely in the lingual and fusiform gyri, bilaterally (Goldman et al., 2014, Watanabe et al., 2013). Goldman et al. (2014) reported positive associations between VH severity and grey matter volume of the left parietal lobule and cuneus, and of the right lingual gyrus ($p < 0.01$ uncorrected). Nishio et al. (2017) explored the relationship between clinical and cognitive variables (grouped through factor analysis), and brain structure (structural MRI) and function (FDG-PET) using a partial least-squares correlation analysis. Minor hallucinations and illusions were grouped in one factor, and visual hallucinations in another one along with delusions, depression and cognitive fluctuations. Minor hallucinations were associated with posterior cortical atrophy and hypometabolism, including temporo-occipital, occipito-parietal, and primary visual cortices, while the psychosis/dysphoria factor with atrophy and hypometabolism mainly in the upper brainstem and thalamus (Nishio et al., 2017). Bejr-Kasem et al. (2019) investigated the neural substrate of mild hallucinatory phenomena in a multimodal VBM and

resting-state fMRI study. They compared 18 PD patients with minor hallucinations with 14 PD NVH patients similar for education, disease severity, levodopa use, and global cognitive function. Hallucinating patients were older (70.4±5.5) than NVH patients (65.8±7.8), although this difference did not reach statistical significance (p=0.06). Whole brain analysis showed GM loss in patients with minor VH in the right posterior cingulate using a cluster-level family-wise error (FWE) corrected threshold (Bejr-Kasem et al., 2019). When small volume correction (FWE corrected) was applied to regions related to VH, they found GM reductions in the fusiform/parahippocampal gyrus and precuneus in the right hemisphere, and in the middle occipital, supramarginal and angular gyri in the left hemisphere (Bejr-Kasem et al., 2019).

In addition to the findings described above, GM reductions were reported in widespread brain areas, which were mainly located in the inferior parietal lobes (Goldman et al., 2014, Lee et al., 2017), cingulate cortex (Goldman et al., 2014, Watanabe et al., 2013), frontal (Shin et al., 2012, Watanabe et al., 2013), temporal (Shin et al., 2012, Watanabe et al., 2013), and occipital (Goldman et al., 2014, Watanabe et al., 2013) areas bilaterally, and in the right supramarginal gyrus (Lee et al., 2017, Watanabe et al., 2013). Another whole brain VBM study reported differences between PD patients with and without mild VH (presence and passage hallucinations), both decreases, mainly in the right vermis and precuneus, and increases, mainly in the posterior lobe of the cerebellum and in the left inferior frontal cortex, were detected in patients with mild VH (Pagonabarraga et al., 2014). These VBM studies, however, used thresholds uncorrected for multiple comparisons (Goldman et al., 2014, Lee et al., 2017, Pagonabarraga et al., 2014, Shin et al., 2012, Watanabe et al., 2013). Differently from the studies above, Meppelink et al. (2011) did not detect a difference between non-demented PD patients with and without VH, which may have been due to the more conservative threshold of $p<0.05$ cluster-level corrected for multiple comparisons being used in this study. These apparently contrasting findings could, therefore, be a simple reflection of the application of a less rigours statistical thresholding approach by the studies reviewed above.

In addition to the whole brain studies described above, two VBM studies investigated volumetric brain differences between hallucinating and non-hallucinating PD patients by using an ROI approach (Ibarretxe-Bilbao et al., 2008, Janzen et al., 2012). Specifically, Janzen et al. (2012) investigated the grey matter volume of the pedunculopontine nucleus due to its cholinergic function thought to be involved in the development of VH, and the thalamus as one of its projection areas. The authors

found reduced grey matter in the left and right pedunculopontine nucleus between non-demented PD patients with and without VH, but not in the thalamus by using a threshold corrected for multiple comparisons. Hallucinating patients had significantly longer disease duration (VH: 11.5±5.2 years; no VH 3.1±3.6 years), were at a more severe Hoehn and Yahr stage (VH: 2.5±0.3; no VH: 2.1±0.5) and were taking higher levodopa equivalent doses. Furthermore, when hallucinating PD patients with and without dementia were combined and compared with non-demented patients without VH, the reduction in volume extended to the thalamus bilaterally (Janzen et al., 2012). In another voxel-based ROI study, the analyses were restricted to the hippocampus, due to its link with dementia development (Ibarretxe-Bilbao et al., 2008). This region was chosen since the presence of VH is thought to be a risk factor for dementia and, therefore, VH patients might exhibit the same pattern of atrophy shown by patients with dementia. The authors reported no differences in the direct comparison of non-demented PD patients with and without VH. When the two PD groups were independently compared with healthy controls, only hallucinating patients showed reduced grey matter in the anterior hippocampus bilaterally ($p<0.05$ corrected); hippocampal volume also correlated with the learning scores achieved on a verbal memory test (Ibarretxe-Bilbao et al., 2008). Overall, however, the PD patients with VH had more severe cognitive impairment, as shown by their lower MMSE scores and poorer scores on a verbal memory test (Ibarretxe-Bilbao et al., 2008). Temporal lobe abnormalities were also confirmed by a whole brain VBM study, specifically in the right anterior temporal lobe in PD VH when compared with NVH, extending to the hippocampus and amygdala when compared with controls (Firbank et al., 2018). Negative findings were reported by another VBM study, which found no differences in the hippocampus in any PD group, when compared with controls (Gama et al., 2014). These contrasting findings might be due to differences in clinical and demographic variables, such as cognitive performance, disease duration, and age, and methodological differences in the analyses (i.e. standard VBM vs. DARTEL). In Gama et al. (2014), when PD patients with and without VH were compared separately with healthy controls, using an ROI approach with ROIs in temporal, and frontal areas, reduced grey matter was found in the left superior frontal gyrus in both PD groups, while reduction in grey matter in the left frontal operculum was detected only in hallucinating patients. The two PD groups, however, differed from each other in some clinical variables, including global cognitive level (measured with the MMSE), motor symptoms, evaluated with the Unified Parkinson's Disease Rating Scale motor score subsection, UPDRS III (Fahn and Elton, 1987), and depression, assessed with the

Beck Depression Inventory (Beck and Steer, 1984), with the hallucinating group being more severe in all these measures (Gama et al., 2014).

Only two studies used VBM to investigate differences between hallucinating and non-hallucinating patients with DLB (Blanc et al., 2016, Sanchez-Castaneda et al., 2010). Despite the small sample size (6 DLB with VH, 6 without VH), Sanchez-Castaneda et al. (2010) found a reduction of grey matter volume in the right inferior frontal gyrus in hallucinating patients ($p<0.05$ corrected) using a voxel-based ROI approach. In the same study, patients with PDD presented grey matter volumetric reductions in the left orbitofrontal cortex, which was no longer significant when controlling for age (Sanchez-Castaneda et al., 2010). In the hallucinating DLB subgroup, VH severity was strongly associated with reduction in the volume of the right inferior frontal gyrus ($r=0.89$), and left precuneus ($r=0.95$), while no significant correlations were found in the PDD subgroup. Another VBM study in DLB identified volumetric grey matter reductions posteriorly, in the left cuneus, by using a whole brain approach (Blanc et al., 2016). These findings, however, should be taken with caution as the threshold used in this study was not corrected for multiple comparisons. Moreover, demographic and clinical comparisons between patients with and without VH were not reported, probably due to the exploratory nature of the analysis on VH (the main aim of the study was to compare DLB with AD patients and with controls) (Blanc et al., 2016). Finally, Colloby et al. (2017), in a DARTEL VBM study focusing on the substantia innominate, found no significant association between this structure and Neuropsychiatric Inventory (NPI) hallucination scores. This study, however, did not focus on VH, but the primary aim was to investigate differences between DLB and AD (Colloby et al., 2017).

2.4.1.2 Other structural MRI studies

In addition to the VBM studies described above, other studies have investigated brain morphological features of predefined ROIs, especially their overall volume (Delli Pizzi et al., 2016, Iizuka and Kameyama, 2016, Kantarci et al., 2012, Lee et al., 2016, Meppelink et al., 2011, Pereira et al., 2013, Yao et al., 2016), and shape (Yao et al., 2016) in LBD. Four studies examined group differences in cortical thickness or volume using the Freesurfer software package (Barrell et al., 2018, Delli Pizzi et al., 2014a, Franciotti et al., 2015, Yao et al., 2014). Seven studies investigated volumetric (Lee et al., 2016, Lenka et al., 2018, Meppelink et al., 2011, Pereira et al., 2013, Shin et al., 2012, Yao et al., 2016), or cortical thickness (Franciotti et al., 2015, Yao et al.,

2014) differences between PD patients with and without VH. Other studies focused on the comparison between DLB and AD patients, and reported an association with VH indices (Delli Pizzi et al., 2016, Delli Pizzi et al., 2014a, Iizuka and Kameyama, 2016, Kantarci et al., 2012).

MTL structures, especially the hippocampus, were investigated by six studies (Delli Pizzi et al., 2016, Iizuka and Kameyama, 2016, Kantarci et al., 2012, Lenka et al., 2018, Pereira et al., 2013, Yao et al., 2016). Three of them focused on PD, and argued for an involvement of the hippocampus in the formation of VH mainly based on its role in memory, and evidence suggesting the presence of a high burden of LB pathology in this region (Lenka et al., 2018, Pereira et al., 2013, Yao et al., 2016). Yao et al. (2016) used a multimodal MRI approach to investigate hippocampal volume, shape, MD, and functional connectivity. The authors found no differences between groups (PD with and without VH, and controls) in hippocampal volume and shape (MD and functional connectivity results are described in subsequent sections). Another MRI study reported significant volumetric reduction in hippocampal substructures, namely CA2-3 and CA4-DG, in PD patients with VH compared with those without (Pereira et al., 2013). Nevertheless, differences in the hippocampus as a whole were reported only when hallucinating patients were compared with healthy controls. The more severe cognitive impairment in patients with VH, however, might have affected the results (Pereira et al., 2013). The value of the findings of these studies is limited by the relatively small size of the samples included in both studies (Pereira et al., 2013, Yao et al., 2016). In another recent study, Lenka et al. (2018) investigated hippocampal subfield volumes in PD, showing enlarged hippocampal fissure in patients with VH or minor VH. In addition, VH severity was inversely associated with the left CA3 volume (Lenka et al., 2018). Three MRI studies investigated the association between VH indices in DLB, and MTL (Iizuka and Kameyama, 2016), hippocampus (Kantarci et al., 2012), and hippocampal substructures volumes (Delli Pizzi et al., 2016). A negative correlation was reported between severity of VH and volumetric measures in MTL (entorhinal cortex, hippocampus, and amygdala) (Iizuka and Kameyama, 2016). However, these three studies failed to report *a priori* hypotheses based on the involvement of MTL regions in the development of VH, probably because VH were not the primary objective of investigation.

Lee et al. (2016) selected five ROIs within the visual pathway to investigate differences between hallucinating and non-hallucinating PD patients in the optic chiasm area, lateral geniculate nucleus, and V1 volumes and white matter microstructure features in the optic nerve and optic radiation (the latter are described

in the following section). These regions were selected to examine the neural bases of VH in relation to their role in processing visual information. Volumetric reductions in VH patients were reported only in the lateral geniculate nucleus (Lee et al., 2016). In addition to the whole brain analysis described in the previous section, Meppelink et al. (2011) focused on an ROI in the left fusiform gyrus, detecting no differences between PD with and without VH. Basal forebrain structures, mainly the substantia innominata, were also investigated due to their role in the cholinergic system. A structural MRI study carried out an ROI analysis by delineating the left and right substantia innominata boundaries (in addition to the VBM analysis reported above) and identified a smaller volume of this structure in hallucinating PD patients (46 PD with VH, 64 PD without VH) (Shin et al., 2012). Furthermore, the volume of this region correlated with scores on verbal memory, semantic fluency, and go/no-go tests (Shin et al., 2012). On the other hand, Hepp et al. (2017) found no volumetric differences in the nucleus basalis of Meynert in PD patients with VH, but they showed microstructural alterations assessed with DTI.

Studies investigating cortical thickness or volume did not detect any differences between PD patients with and without VH (Barrell et al., 2018, Franciotti et al., 2015, Yao et al., 2014). However, when hallucinating PD patients were compared with non-hallucinating patients at a less advanced disease stage (H&Y; PD with VH: 3.0±0.5; no VH: 2.1±0.4), and controls, reduced cortical thickness was reported in frontal and parietal regions (Franciotti et al., 2015). In the latter study, the analysis was restricted to regions within the DMN (Franciotti et al., 2015). On the other hand, Yao et al. (2014) found no differences between PD subgroups and controls in the analysis of the whole cortical surface. Barrell et al. (2018) found widespread cortical volume loss, especially in parietal and cerebellar hemisphere, however using a non-corrected threshold. Finally, Delli Pizzi et al. (2014a) found a significant association between the NPI hallucination score (Cummings et al., 1994), and cortical thickness in right lateralised parietal regions, namely the precuneus, and superior parietal gyrus in DLB patients ($p<0.05$ corrected).

2.4.1.3 Diffusion tensor imaging

Six DTI studies were found, four on PD (Firbank et al., 2018, Hepp et al., 2017, Lee et al., 2016, Lee et al., 2017), and two on DLB (Delli Pizzi et al., 2014b, Kantarci et al., 2010). Four studies investigated predefined ROIs of grey or white matter (Delli Pizzi et al., 2014b, Hepp et al., 2017, Kantarci et al., 2010, Lee et al., 2016), while two

used a whole brain approach, namely TBSS (Firbank et al., 2018, Lee et al., 2017). Most of the studies used the FMRIB software library (FLS) for DTI analysis (Delli Pizzi et al., 2014b, Firbank et al., 2018, Hepp et al., 2017, Lee et al., 2016, Lee et al., 2017). One study did not include a sample of LBD patients without VH, and hallucinating patients where compared to controls, and AD (Delli Pizzi et al., 2014b).

Lee et al. (2016) reported disrupted white matter integrity in the right optic nerve, and in the left optic radiation by using an ROI approach. In another multimodal study (VBM analysis reviewed above), Lee et al. (2017) performed voxelwise analysis of FA and MD by using TBSS. No differences were found between non-demented PD subgroups with and without VH, and a similar pattern of abnormalities was reported when independently compared with age-matched healthy subjects, specifically in fronto-temporo-parietal, and brainstem regions (Lee et al., 2017). In these two studies, PD with and without VH did not differ for age, disease duration, MMSE score, and motor symptoms (Lee et al., 2016, Lee et al., 2017), but in one of these studies hallucinating patients were at a more advanced disease stage than non-hallucinating patients (Lee et al., 2017). From the articles, however, it could not be established whether some of the patients investigated in the latter two references were the same in both studies (Lee et al., 2017, Lee et al., 2016). In another TBSS study, Firbank et al. (2018) showed widespread differences in both FA and MD in PD patients with VH and controls. Basal forebrain structures were also investigated by means of DTI, specifically Hepp et al. (2017) explored the integrity of WM microstructure of regional tracts of the nucleus basalis of Meynert, and others connecting this nucleus to the cerebral cortex in PD with VH (n=15), PD without VH (n=40) and age matched controls (n=15). They have shown higher MD in patients with VH in parietal and occipital tracts.

Although DTI is mainly used to investigate microstructural white matter abnormalities, two studies focused on grey matter (Delli Pizzi et al., 2014b, Yao et al., 2016). Yao et al. (2016) reported increased MD in the right hippocampus in hallucinating PD patients. Moreover, Delli Pizzi et al. (2014b) investigated grey matter MD differences between DLB patients with VH and healthy controls by using a tractography-based subdivision of the thalami. The authors found increased MD in thalamic sub-regions projecting to prefrontal, parieto-occipital cortices (bilaterally), amygdala (right lateralised), and motor cortices (left lateralised). Moreover, MD in the right thalamic sub-region projecting to parietal and occipital cortices was associated with severity of VH (Delli Pizzi et al., 2014b). Finally, among the studies that focused on DLB, Kantarci et al. (2010) showed increased MD in the ILF in patients with VH compared with those without. Demographic and clinical differences between these groups of patients were

not reported, however, probably because the main purpose was to differentiate DLB and AD patients (Kantarci et al., 2010).

2.4.2 Functional brain imaging

A total of 45 studies undertook functional imaging focusing on VH in LBD, including studies using task-based and resting-state fMRI, PET, and SPECT.

2.4.2.1 Task-based fMRI

Eleven studies used fMRI to identify brain activation patterns in response to simple visual stimuli (Erskine et al., 2015, Firbank et al., 2018, Holroyd and Wooten, 2006, Lefebvre et al., 2016, Stebbins et al., 2004, Taylor et al., 2012), perception recognition tasks (Meppelink et al., 2009, Ramirez-Ruiz et al., 2008, Shine et al., 2015b), and two single cases during VH (Goetz et al., 2014, Howard et al., 1997). The majority of them was on PD (Firbank et al., 2018, Goetz et al., 2014, Holroyd and Wooten, 2006, Lefebvre et al., 2016, Meppelink et al., 2009, Ramirez-Ruiz et al., 2008, Shine et al., 2015b, Stebbins et al., 2004), while only three included patients with DLB (Erskine et al., 2015, Howard et al., 1997, Taylor et al., 2012). Two studies performed different analyses on the same sample of DLB patients who had performed a visual task in the scanner (Erskine et al., 2015, Taylor et al., 2012). Methodology and fMRI paradigm differed between studies, which may partly account for some inconsistencies in the findings. Other differences between studies include the threshold used to report the results, age, cognitive impairment, and duration of the disease. One study described in this section included PD patients experiencing minor VH, including sensation of passage, presence or misperceptions (Lefebvre et al., 2016).

Five studies examined BOLD signal in response to simple visual stimuli (Erskine et al., 2015, Holroyd and Wooten, 2006, Lefebvre et al., 2016, Stebbins et al., 2004, Taylor et al., 2012). Specifically, they investigated the perception of moving stimuli (Erskine et al., 2015, Firbank et al., 2018, Holroyd and Wooten, 2006, Taylor et al., 2012), apparent motion (Stebbins et al., 2004), circular gratings (Lefebvre et al., 2016), checkboards, objects (Erskine et al., 2015), and stroboscopic stimulation (Stebbins et al., 2004). Regions of both increased and decreased activation were found in hallucinating PD patients, compared with the non-hallucinating ones (Holroyd and Wooten, 2006, Lefebvre et al., 2016, Stebbins et al., 2004). The most consistent finding was decreased activity in occipital and temporal regions (Holroyd and Wooten, 2006, Lefebvre et al., 2016, Stebbins et al., 2004), even though increases in occipital

(Lefebvre et al., 2016), and temporal (Holroyd and Wooten, 2006) areas were also reported. One of these studies, however, had a very small sample size (3 PD with VH, 3 PD without VH) (Holroyd and Wooten, 2006). In addition, reduced activity was found in the parietal and cingulate cortices (Stebbins et al., 2004). On the other hand, increased activity was reported mainly in the frontal lobe (Lefebvre et al., 2016, Stebbins et al., 2004). Two studies focusing on DLB reported no correlation between BOLD signal and VH indices, but no comparison with patients without VH was performed (Erskine et al., 2015, Taylor et al., 2012). One of the latter studies reported a negative association between the NPI hallucination score and perfusion in V4, detected by using ASL-MRI (Taylor et al., 2012). In addition, Firbank et al. (2018) used magnetic resonance spectroscopy to explore occipital GABA levels, showing lower GABA+ levels in hallucinating PD patients in comparison with those without, but no between-groups differences were detected using task-based fMRI.

Three studies on PD focused on perceptual recognition of complex visual stimuli (Meppelink et al., 2009, Ramirez-Ruiz et al., 2008, Shine et al., 2015b). In comparison with non-hallucinating patients, those with VH presented decreased activity in the right superior frontal gyrus ($p<0.05$ cluster-level corrected) during perceptual recognition of faces (Ramirez-Ruiz et al., 2008), animals, and objects (Meppelink et al., 2009). In addition to these regions, decreased activation was found in the right inferior frontal (face recognition) (Ramirez-Ruiz et al., 2008), left lingual, and bilateral fusiform gyri (animal/object recognition) (Meppelink et al., 2009). In one of these studies (Ramirez-Ruiz et al., 2008), however, patients with VH had more severe cognitive impairment and behavioural performance (fMRI task) than those without, which might have partially affected the results. Shine et al. (2015b) identified dysfunctional connectivity in and between attention networks and the DMN during the bistable percept paradigm (BPP) in PD patients with VH. During this task, patients were asked to discriminate between images containing only one perceptual interpretation (stable, e.g. a candlestick) and images containing more than one perceptual interpretation (bistable, e.g. two faces and a candlestick) (Shine et al., 2015b). In this study, PD patients were divided into two groups according to the percentage of misperceptions at the BPP. Patients performing above a previously established cut-off score (Shine et al., 2012) also presented clinically assessed VH, while those performing below did not (Shine et al., 2015b).

Two fMRI studies recorded brain activity during the occurrence of visual hallucinations in single cases (Goetz et al., 2014, Howard et al., 1997). Both patients experienced complex VH, namely seeing animals (Goetz et al., 2014, Howard et al., 1997) and

people (Goetz et al., 2014) in the MRI scanner. Howard et al. (1997) scanned a DLB patient in the hallucination-free state (the patient was taking risperidone), and a second time whilst he was hallucinating (7 days after risperidone was stopped). They found decreased activation in V1 and V2 in response to photic stimulation while the patient was hallucinating compared with the hallucination-free scan (Howard et al., 1997). Goetz et al. (2014) performed an event-related design in order to compare hallucinating, and non-hallucinating events in a patient with PD. While the patient was experiencing VH, decreased activity was reported mainly in occipito-temporal areas, but activity increased in the anterior and posterior cingulate cortex (Goetz et al., 2014).

2.4.2.2 Resting-state fMRI

Nine studies (Bejr-Kasem et al., 2019, Chabran et al., 2018, Franciotti et al., 2015, Peraza et al., 2014, Peraza et al., 2015b, Shine et al., 2015a, Yao et al., 2016, Yao et al., 2015, Yao et al., 2014) carried out resting-state fMRI analysis, including five statistical comparisons between patients with and without VH in PD (Bejr-Kasem et al., 2019, Franciotti et al., 2015, Shine et al., 2015a, Yao et al., 2016, Yao et al., 2015, Yao et al., 2014). Only three studies included a sample of hallucinating DLB patients, and adopted correlational analyses (Chabran et al., 2018, Peraza et al., 2014, Peraza et al., 2015b). Heterogeneity in methodology was found between studies. Specifically, independent component analysis (ICA) (Franciotti et al., 2015, Yao et al., 2014), ROI and seed-based analyses (Bejr-Kasem et al., 2019, Franciotti et al., 2015, Yao et al., 2016, Yao et al., 2015) of functional connectivity, amplitude of low-frequency fluctuation (Franciotti et al., 2015, Yao et al., 2015), and graph analysis (Peraza et al., 2015b) were used. Moreover, between-study differences were detected for age, disease duration, motor symptoms, and global cognitive impairment, even though patients with and without VH were usually well matched within single studies. In addition, overall sample sizes were relatively small.

Two resting-state fMRI studies investigated differences between PD patients with and without VH in the functional connectivity of the DMN (Franciotti et al., 2015, Yao et al., 2014). In both studies, the DMN was identified by performing ICA. The methodology implemented to investigate group differences in functional connectivity, however, was different. Specifically, in Franciotti et al. (2015) pairwise ROIs centred on the DMN were compared between groups. Yao et al. (2014) more broadly investigated the differences in the spatial map of the DMN. Both studies reported increased functional connectivity in hallucinating patients in comparison with the non-

hallucinating ones, mainly in fronto-parietal regions. Specifically, Franciotti et al. (2015) detected increased connectivity between the superior frontal sulcus bilaterally with ipsilateral and contralateral parietal regions, and also between contralateral parietal regions. Yao et al. (2014) found increased activity in the right superior middle frontal lobe, and bilateral precuneus and posterior cingulate gyrus within the DMN ($p<0.05$ corrected). Both PD patients with and without VH presented a pattern of decreased functional connectivity when independently compared to healthy controls (Franciotti et al., 2015, Yao et al., 2014). In a seed-based resting-state fMRI and VBM study (described above), Bejr-Kasem et al. (2019) explored the functional connectivity of the posterior cingulate cortex, a core hub of the DMN, and that is inversely correlated with attentional networks. They found increased functional connectivity in PD patients with minor VH (n=18) compared with NVH (n=14) between this region and the following: bilateral middle temporal gyrus and superior parietal lobes with a cluster-level FWE corrected threshold (Bejr-Kasem et al., 2019). Moreover, when applying small volume correction (FWE corrected), higher connectivity was found with the right precentral gyrus, middle cingulate cortex, and middle occipital gyrus, including the V5/MT area (Bejr-Kasem et al., 2019). Results from another resting-state fMRI study (Shine et al., 2015a) were consistent with an association between VH and disrupted activity of the DMN, and other attention networks. The authors performed regression analyses to investigate the association between misperceptions at the BPP (the paradigm described above in section 2.4.2.1) (Shine et al., 2012) and resting-state networks connectivity. All patients performing below a predefined BPP cut-off were also clinically classified as hallucinating. BPP error scores predicted connectivity between the VAN and the DAN, and increased connectivity within the DMN and the VAN (Shine et al., 2015a).

In addition to the functional connectivity analyses reviewed above, Franciotti et al. (2015) also investigated the fractional amplitude of low-frequency fluctuation on DMN centred ROIs. Compared with non-hallucinating patients, PD with VH presented higher spectral power in fronto-parietal areas bilaterally (Franciotti et al., 2015). Yao et al. (2015) performed spectral analysis on the same sample in a previous study (Yao et al., 2014), reviewed above. They found increased amplitude of low-frequency fluctuation in VH patients in areas located in the cerebellum, temporal, and parietal lobes. Decreased amplitude of low-frequency fluctuation was reported in occipital regions, namely in the lingual gyrus and cuneus bilaterally. These latter results were used to perform seed-based functional connectivity analysis. Compared with controls, both PD groups showed decreased functional connectivity, but in VH patients it was

increased when compared with non-hallucinating patients (Yao et al., 2015). In a multimodal MRI study, Yao et al. (2016) reported both increased and decreased functional connectivity of the hippocampus in patients with VH compared with those without, using a seed-based approach. Specifically, increased connectivity was found with fronto-parietal regions, while it was decreased with occipito-temporal areas (Yao et al., 2016). When compared to controls, however, both PD subgroups presented decreased connectivity of the hippocampus, bilaterally (Yao et al., 2016). These latter studies performed different analyses on the same cohort of patients, and this needs to be taken into account when interpreting the results (Yao et al., 2014, Yao et al., 2015, Yao et al., 2016).

Yao et al. (2016) also performed correlational analyses between cognitive measures and the regions of differential connectivity between PD groups. Specifically, the functional connectivity of the right hippocampus with right occipital, and medial temporal areas was negatively associated with visuospatial memory performance, which was in turn associated with VH severity (Yao et al., 2016). On the other hand, other studies found no association between measures of VH and functional connectivity of regions of the DMN in PD (Yao et al., 2014) and DLB (Bejr-Kasem et al., 2019, Chabran et al., 2018), and anterior cingulate, insular (Bejr-Kasem et al., 2019), temporal networks (Peraza et al., 2014) and visuoperceptual ROI (Chabran et al., 2018) in DLB. Peraza et al. (2015b) explored functional connectivity in DLB by using a graph theory approach. They found no significant correlation between the NPI hallucination score and integrated global network measures (Peraza et al., 2015b). However, they found an association with local network measures of node degree (negative for the left postcentral gyrus and positive for the putamen), and nodal betweenness centrality (negative for the right intracalcarine cortex and positive for the fusiform cortex) (Peraza et al., 2015b). In another study, Peraza et al. (2014) performed secondary analyses on VH in DLB, which showed an association between the NPI hallucination score and the left fronto-parietal, and sensory-motor networks. It is not clear whether for two of the latter studies a subsample of the patients was from the same cohort of patients or not (Peraza et al., 2014, Peraza et al., 2015b).

2.4.2.3 Positron emission tomography

We identified 15 studies investigating regional cerebral glucose metabolism using PET. Among them, six focused on the differences between patients with and without VH, four in PD (Boecker et al., 2007, Gasca-Salas et al., 2016, Nagano-Saito et al.,

2004, Park et al., 2013), and two in DLB (Imamura et al., 1999, Perneczky et al., 2008). Other studies examined associations between glucose metabolism and VH indices, including severity and frequency (Firbank et al., 2016, Iaccarino et al., 2018, Iizuka and Kameyama, 2016, Kantarci et al., 2012, Nishio et al., 2018, Nishio et al., 2017, Park et al., 2013, Uchiyama et al., 2015). In addition, Iaccarino et al. (2018) undertook FDG-PET metabolic connectivity analyses in DLB with and without VH.

PD patients with VH presented hypometabolism mainly in posterior regions, especially in the parietal and temporal lobes (Boecker et al., 2007, Gasca-Salas et al., 2016, Park et al., 2013). The bilateral precuneus and lingual gyrus were particularly affected (Boecker et al., 2007, Gasca-Salas et al., 2016). Gasca-Salas et al. (2016) also reported two smaller clusters in the right occipital lobe, while Boecker et al. (2007) reported frontal hypometabolism in VH patients. In contrast, Nagano-Saito et al. (2004) found frontal hypermetabolism, specifically in the left superior frontal gyrus. Discrepancies might be partially explained by differences in demographic and clinical features between studies, including age, disease duration, and global cognitive impairment. Moreover, in Boecker et al. (2007), hallucinating patients were at a more advanced disease stage, and had more severe motor symptoms than non-hallucinating patients. However, UPDRS III scores were included as covariate of no interest in the statistical analysis (Boecker et al., 2007). Only two studies compared DLB subgroups and reported contrasting findings. In a whole brain analysis, Perneczky et al. (2008) showed hypometabolism in right lateralised temporo-occipital and frontal regions. Although results from the latter study were not corrected for multiple comparisons, differences were only expected in regions found to be hypometabolic when compared with controls (occipital, temporo-parietal, and frontal areas) (Perneczky et al., 2008). In contrast, Imamura et al. (1999) reported increased regional cerebral glucose metabolic rate in temporal and parietal regions. In the latter study, however, patient groups significantly differed in MMSE scores (DLB with VH: 19.5±3.9; no VH: 15.0±3.0; AD: 19.7±3.5) (Imamura et al., 1999). Moreover, different methods were used, namely whole brain voxel-wise comparisons (Perneczky et al., 2008) and ROI analyses (Imamura et al., 1999). In addition to these findings, a PET study divided DLB patients into two subgroups, based on the hypermetabolism of peri-motor areas, cerebellum, and basal ganglia. The group with more regions of hypermetabolism also experienced more frequent VH (Miyazawa et al., 2010).

Studies investigating correlations between glucose metabolism and VH indices mainly reported negative associations with posterior regions (Firbank et al., 2016, Iaccarino et al., 2018, Iizuka and Kameyama, 2016, Kantarci et al., 2012, Park et al., 2013,

Uchiyama et al., 2015). Specifically, occipital hypometabolism has been related to severity (Firbank et al., 2016) and frequency (Firbank et al., 2016, Kantarci et al., 2012) of VH. A negative correlation with VH has also been found with the posterior cingulate, dorsolateral frontal (Morbelli et al., 2019), parietal (Morbelli et al., 2019, Uchiyama et al., 2015), and temporal regions (Park et al., 2013). On the other hand, positive correlation was detected with MTL, orbitofrontal cortex, cerebellum, brainstem and basal ganglia (Morbelli et al., 2019). Iizuka and Kameyama (2016) found a negative association with the standardized uptake value ratio in the precuneus/cuneus ($r=-0.62$, $p<0.01$), and a positive association with the cingulate island sign ratio on FDG-PET ($r=0.44$, $p<0.05$). Nishio et al. (2017) found a differential pattern of hypometabolism related to two distinct factors, one including minor hallucinations and illusions, and the other VH and delusions (described above in the VBM studies section). However, no differences were found between patients with minor hallucinations and VH, and patients with VH only (Nishio et al., 2017). In another study, Nishio et al. (2018) investigated the relationship between brain glucose metabolism and clinical variables, among which VH, kinetopsia and object misidentification illusions in PD. All these variables were related with temporo-parietal hypometabolism, and object misentification illusions were also associated with occipital hypometabolism (Nishio et al., 2018). In this study, however, patients with VH had lower MMSE scores (Nishio et al., 2018).

Finally, Iaccarino et al. (2018) undertook metabolic correlation and connectivity analyses in DLB VH (n=19), NVH (n=19) and controls (n=38). Right occipito-temporal hypometabolism negatively correlated with the NPI VH score, specifically in the right middle occipital gyrus, extending to the inferior temporal gyrus ($p<0.05$ FWE corrected threshold) (Iaccarino et al., 2018). The occipito-temporal cluster resulted from these analyses was then used to investigate metabolic connectivity, revealing decreased connectivity with the right fusiform gyrus and hippocampus in VH patients compared with NVH ($p<0.05$ FWE corrected threshold) (Iaccarino et al., 2018).

2.4.2.4 Single photon emission computed tomography

Regional cerebral blood flow in LBD patients with VH has been investigated by nine SPECT studies, four on PD (Matsui et al., 2006, Oishi et al., 2005, Osaki et al., 2005), five on DLB (Heitz et al., 2015, Lobotesis et al., 2001, Nagahama et al., 2010, Pasquier et al., 2002), one on PDD and DLB combined (O'Brien et al., 2005), and a single case on PDD (Kataoka et al., 2008). Six studies examined the differences

between hallucinating and non-hallucinating patients, three whole brain analyses (Heitz et al., 2015, Matsui et al., 2006, Oishi et al., 2005) and three ROI analyses (Lobotesis et al., 2001, Osaki et al., 2005, Pasquier et al., 2002). Different tracers were used to investigate cerebral blood flow using SPECT, including N-isopropyl-p-[^{123}I]iodoamphetamine, [^{99m}Tc]ethyl cysteinate dimer, and ^{99m}Tc-HMPAO. Three studies investigated areas of association between perfusion and VH indices (Heitz et al., 2015, Nagahama et al., 2010, O'Brien et al., 2005), and one study performed a SPECT scan during VH (Kataoka et al., 2008). Overall, hallucinating patients showed regions of reduced brain perfusion compared with non-hallucinating patients. Only two studies reported no differences between groups (Lobotesis et al., 2001, Osaki et al., 2005).

Occipital hypoperfusion has been reported in both hallucinating PD (Matsui et al., 2006) and DLB (Heitz et al., 2015, Pasquier et al., 2002) patients, even though these studies presented some limitations. For example, one only reported demographic and clinical characteristics of DLB and AD, without differentiating between patients with (n=26) and without (n=4) VH (Pasquier et al., 2002). Moreover, Heitz et al. (2015) performed whole brain analyses without correcting the results for multiple comparisons. Other ROI SPECT studies found no differences in occipital perfusion (Lobotesis et al., 2001, Osaki et al., 2005). In another whole brain SPECT study, Oishi et al. (2005) compared PD patients with (n=24) and without (n=41) VH. The authors found reduced cerebral blood flow in the right fusiform gyrus, which remained significant when correcting for multiple comparisons. Other temporal and parietal regions were found to be different between groups by using an uncorrected threshold (Oishi et al., 2005). In another whole brain study, O'Brien et al. (2005) investigated the relationship between changes in brain perfusion and hallucinations over one year in a combined group of patients with DLB and PDD. They found a negative association with left parietal regions, namely the posterior cingulate gyrus and the precuneus ($p<0.05$ cluster-level corrected) (O'Brien et al., 2005). Another SPECT study performed factor analysis in order to investigate associations between regional cerebral blood flow and psychotic symptoms in DLB (Nagahama et al., 2010). The authors showed a relationship between parietal and occipital hypoperfusion, and the sense of presence and hallucinations of people, but not of animals, insects and objects (Nagahama et al., 2010). Finally, Kataoka et al. (2008) described a patient with PDD having VH during a SPECT scan, showing increased regional cerebral blood flow in the temporal lobe bilaterally, and in the left inferior frontal gyrus.

2.4.3 Discussion

The aim of the present review was to provide an overview of the neuroimaging findings from studies that have investigated the neural bases of VH in LBD, by critically reviewing the current literature in the field. What emerged is that LBD patients with VH are characterized by widespread structural and functional brain abnormalities in cortical, but also subcortical regions. Given the more limited evidence in DLB and PDD than PD without dementia, it is difficult to infer disease-specific mechanisms within the LBD spectrum. A summary of the most consistent neuroimaging findings associated with VH in LBD patients is shown in Table 2.1.

Table 2.1 Summary of the most consistent findings associated with VH in LBD, from Pezzoli et al. (2017).

Brain regions	GM volume	Functional connectivity	Task-related BOLD activation	Glucose metabolism	Brain perfusion
Frontal	↓	↑	↑↓	↓↑	
Parietal	↓	↑		↓↑	
Temporal				↓↑	
Occipito- temporal	↓		↓↑	↓	
Occipital			↓↑		↓

BOLD: blood-oxygenation level-dependent; GM: grey matter; LBD: Lewy body disease; VH: visual hallucinations; ↓: decrease; ↑: increase.

Overall, the most consistent finding among structural MRI studies of VH in LBD is grey matter loss in frontal areas, mainly in patients with dementia (Sanchez-Castaneda et al., 2010), and parietal and occipito-temporal regions (Ramirez-Ruiz et al., 2007b) in non-demented PD patients. The presence of frontal and parietal impairment is consistent with results reported by neuropsychological studies showing more severe deficits in executive functions and visual attention in patients with VH (Cagnin et al., 2013, Grossi et al., 2005, Hepp et al., 2013, Santangelo et al., 2007). This is in line with multifactorial models of VH proposing a role of visual attention deficits and disrupted engagement of attention networks in the development of VH (Collerton et al., 2005, Shine et al., 2011).

Notably, cholinergic treatment has been shown to decrease VH and improve cognitive functioning, especially attention (Burghaus et al., 2012), corroborating the hypothesis of an involvement of attention dysfunction in the development of VH. Collerton et al. (2005) proposed the PAD model, and suggested that VH result from the combination of impaired top-down and bottom-up processes, specifically coexisting deficits in attention and visual perception. These deficits would be supported by impaired activity

in the lateral frontal cortex, and the ventral visual stream, respectively (Collerton et al., 2005). Surprisingly, given the established deficits in visual perception in LBD patients with VH (Ibarretxe-Bilbao et al., 2010, Koerts et al., 2010, Mori et al., 2000, Mosimann et al., 2004), evidence of structural grey matter differences in the occipital lobe is limited. However, occipito-temporal and parietal grey matter loss, and reduction of cerebral blood flow were present mainly in PD (Oishi et al., 2005, Ramirez-Ruiz et al., 2007b). Moreover, occipital and occipito-temporal hypometabolism was associated with VH indices (Firbank et al., 2016, Iaccarino et al., 2018, Kantarci et al., 2012). Occipital hypoperfusion detected by SPECT has been found (Heitz et al., 2015, Matsui et al., 2006, Pasquier et al., 2002), even though negative findings were also reported (Lobotesis et al., 2001, Osaki et al., 2005). Discrepancies were reported in resting-state FDG-PET studies. The most consistent finding is parietal and temporal glucose hypometabolism in PD with VH, even though inconsistencies were shown in frontal areas. The findings of these studies were both decreased and increased metabolism in the same regions in DLB, which might reflect demographic, clinical, and methodological differences between studies. In summary, resting-state functional studies point towards hypometabolism/reduced blood flow in occipito-temporal and parietal regions in LBD patients with VH. This dysfunction in visual association regions might play a role in the genesis of VH in LBD. This finding is further supported by the demonstration of disrupted white matter integrity in hallucinating DLB patients in the ILF (Kantarci et al., 2010), a bundle of associative fibres that has been related to visual memory and perception (Catani and Thiebaut de Schotten, 2008).

To date, only a few studies have investigated how resting-state networks are disrupted in VH, and these studies have focused mainly on PD. Overall, increased functional connectivity in the DMN has been shown in hallucinating patients compared with those without hallucinations, while reduction in functional connectivity was a consistent finding in both PD subgroups when compared with healthy controls. Therefore, dysfunctional increased connectivity might play a significant role in the genesis of VH, especially within the DMN and fronto-parietal regions (Franciotti et al., 2015, Yao et al., 2014). A speculative interpretation can be put forward, suggesting that a dysfunctional compensatory mechanism, resulting in increased functional connectivity in hallucinating patients, may foster the emergence of these symptoms. Functional abnormalities in frontal, temporo-occipital, and occipital areas have been reported by task-based fMRI studies. The direction of such alterations in the BOLD

signal activity is still unclear, however. This might be due to differences in the behavioural tasks and in the stimuli used in the different studies.

Overall, discrepancies in findings between studies using different imaging modalities or MRI sequences might simply indicate the differential ability of each of these techniques to capture a qualitatively different level of dysfunction. Volumetric analysis does not capture alterations of neuronal function at the cellular level, but can only detect neuronal loss or shrinkage. Quantification of brain volume, therefore, would not detect any difference in regions where cellular alterations do not cause cell loss. In contrast, methods that are sensitive to functional changes are more readily able to detect alterations (whether increases or decreases in connectivity, or metabolic or blood flow variations) even in the absence of a substantial volumetric change, and even minor structural changes could generate a robust functional compensatory response. On this basis, the inconsistency of findings across imaging modalities or MRI sequences would be easy to explain.

Taken together, the results of imaging studies in LBD patients with VH are scarce for DLB but more frequent for PD. There is a mismatch between a more prominent involvement of primary and association visual regions in brain metabolism and blood flow studies and a more prominent involvement of more frontal regions when studying GM volume or cortical thickness, although occipito-temporal atrophy has been reported mainly in cognitively normal PD. None of these findings appears to be associated with a different burden of neuropathological changes. In fact, despite the association between LB pathology and VH in MTL areas (Harding et al., 2002a, Harding et al., 2002b, Papapetropoulos et al., 2006), substantial structural alterations in these regions have not emerged from this review. Neuropathological findings have shown a negative association between LB pathology and regional brain atrophy, specifically in the frontal lobe, but conflicting evidence has been reported for the amygdala (Burton et al., 2012, Cordato et al., 2000) and no associations have been found with occipital lobe dysfunction. Neither the macrostructural alterations observed with MRI nor the functional PET/SPECT findings, therefore, appear directly informative about the different underlying cellular events and neuropathology (Zatorre et al., 2012). We can, therefore, speculate that VH in LBD emerge only in the presence of a double hit, i.e. concomitant alterations of large functional and structural attentional networks, of which frontal lobe atrophy may be a surrogate marker, and dysfunction of visual information processing, of which occipital-temporal and parietal hypometabolism is the functional hallmark. Large attentional networks may be impaired by diffuse cortical deposition of synuclein, and even amyloid. The cause of

reduction in metabolism in posterior brain regions, i.e. which crucial cortical or subcortical projections are deafferenting the occipital cortex, remains still unexplained.

Visual hallucinations in LBD have been consistently associated with cognitive impairment. Firstly, their prevalence was found to be significantly higher in patients with dementia, and cognitive decline has been shown to be a significant predictor of VH (Fenelon and Alves, 2010, Fenelon et al., 2000). In addition, there is an increased risk of developing dementia in PD patients with early hallucinations (Aarsland et al., 2003a). LBD patients with VH have more severe deficits in a number of cognitive domains, especially visual perception and visual attention in both DLB (Cagnin et al., 2013, Mori et al., 2000, Mosimann et al., 2004) and PD (Barnes et al., 2003, Hepp et al., 2013, Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a), and executive functioning (Barnes and Boubert, 2008, Grossi et al., 2005, Ozer et al., 2007, Santangelo et al., 2007) and long-term memory (Grossi et al., 2005, Hepp et al., 2013, Santangelo et al., 2007) in PD. Therefore, an important future development of research in this field may be the study of the association between cognitive functions and brain regions and networks specifically altered in LBD patients with VH.

A limitation of the current literature in the field is that there have been only a few studies investigating structural brain alterations related to VH in DLB. In particular, only three studies compared patients with and without VH directly (Blanc et al., 2016, Kantarci et al., 2010, Sanchez-Castaneda et al., 2010), and only one used a whole brain VBM approach (Blanc et al., 2016). The neuroanatomical correlates of this symptom were assessed more extensively in PD. Further research is, therefore, needed to clarify better how these structural changes are related to cognitive functioning and connectivity between brain regions. This clarification may be achieved by integrating studies using different imaging techniques, specifically resting-state fMRI and DTI, for the simultaneous study of functional and structural connectivity respectively. Although some resting-state fMRI studies were conducted in PD, none is available in which DLB patients with and without VH have been directly compared. Similarly, lack of DTI studies examining white matter integrity emerged from this literature review. Future studies may benefit from the investigation of functional and structural networks associated with those cognitive functions impaired in patients with VH. To our knowledge, only a few studies have explored the relationship between cognitive functioning and brain abnormalities in hallucinating LBD patients (Ibarretxe-Bilbao et al., 2010, Ibarretxe-Bilbao et al., 2008, Shin et al., 2012, Yao et al., 2016).

Other studies performed correlational analysis using clinical variables, especially VH severity and frequency, which have been mainly associated with parietal regions by both structural (Delli Pizzi et al., 2014a, Goldman et al., 2014, Sanchez-Castaneda et al., 2010) and functional studies (Iizuka and Kameyama, 2016, O'Brien et al., 2005, Peraza et al., 2014, Uchiyama et al., 2015), but other correlational studies showed no relationship with any brain region (Delli Pizzi et al., 2016, Erskine et al., 2015, Kantarci et al., 2010, Kantarci et al., 2012, Peraza et al., 2015b, Yao et al., 2014).

Finally, the present review itself presents some limitations. Even though negative results were reported by some studies, publication bias cannot be completely ruled out. In addition, we tried to reduce selection bias by undertaking an extensive literature search in two different databases with no time limit. Despite this, the possibility of having missed suitable studies cannot be fully excluded. We reviewed neuroimaging studies that had analysed VH in LBD that met the inclusion criteria. However, not all the studies had VH as their primary focus of investigation (e.g. analysis on VH in studies assessing differences between different types of dementia), and several studies failed to report clearly stated a priori hypotheses on the mechanisms underlying VH. Moreover, studies performing whole brain analyses were included even when results were not corrected for multiple comparisons, which may increase the occurrence of false positives. These factors, together with the inclusion of small sample sizes and other methodological limitations (e.g. statistical analyses not including covariates of no interest) might contribute in lowering the overall quality of the records included.

VH are severe and disabling symptoms frequently observed in patients with LBD. The present review provides an up to date summary of current knowledge about the neural bases of VH in LBD. Overall, the findings suggest the involvement of structural and functional alterations in several brain areas in frontal, parietal, and occipito-temporal cortex. The mechanisms underlying VH in LBD, especially in patients with dementia, and how these differ between conditions remain still unclear, however. Future research might benefit from a combined investigation of structural *and* functional connectivity, as well as its association with neuropsychological measures. This multimodality and multidomain approach might aid the understanding of the pathophysiology underlying VH in LBD and its relationship with cognitive decline. Neuroimaging techniques might help in the detection of symptom-specific biomarkers, which might be used to assess efficacy of treatments in the future, and as targets for new interventions.

Chapter 3. Aims and Objectives

Visual hallucinations are commonly experienced by people with DLB and PD, but may also occur in other neurodegenerative conditions, such as AD. They have been shown to worsen significantly the quality of life of patients and their caregivers, and have been associated with more severe and rapid cognitive decline, higher rates of neuropsychiatric symptoms and earlier institutionalisation (Aarsland et al., 2000, Onofrj et al., 2013, Swann and O'Brien, 2018). Nevertheless, there is currently no treatment specifically targeted for VH, and the neural mechanisms underpinning these disabling symptoms are not well understood. The detection of symptom-specific biomarkers, and a wider knowledge of the underlying pathophysiology, might also aid current research on the treatment of VH, by developing new targets and assessing the efficacy of existing interventions. Neuroimaging methods, and neuropsychological measures represent valuable tools that may provide a better understanding of the neural substrates, and cognitive deficits associated with VH in neurodegeneration. This may also help in detecting patients who are more likely to experience this symptom, and might allow, in the future, the implementation of preventative treatments.

Different models have been proposed to explain the neurocognitive processes leading to VH, suggesting a combination of top-down and bottom-up mechanisms, mainly visual perception and attention deficits, and underlying disrupted neural circuits (Collerton et al., 2005, Shine et al., 2011). However, current findings in the literature are often contradictory (reviewed in Chapter 2), and do not cover exhaustively the complexity of the neurocognitive and biological processes linked to VH in different neurodegenerative conditions. Moreover, within the VH-related literature, patients with dementia due to LBD and AD have been included by a few studies only, making it difficult to infer symptom and disease-specific features associated with VH across neurodegenerative conditions, especially in relation to the presence of different types of dementia.

The overall purpose of the present thesis was to investigate the cognitive, structural and functional brain characteristics underlying VH in different LBD diagnoses, namely DLB and PD, as well as AD. In more detail, the research aims and objectives were as follows:

1. To investigate the neuroanatomical and cognitive correlates of VH in LBD patients with and without dementia, specifically in DLB and PD.

Whole brain VBM and ROI analyses on structural MRI scans, and neuropsychological testing were performed on clinically diagnosed patients with DLB and PD without dementia. In order to assess differences in GM volumes and cognitive performance, hallucinating patients for each group were compared with corresponding non-hallucinating ones. Specifically, we aimed to test whether there was an interplay between visual attention and visual perception/construction deficits, and related neuroanatomical alterations in the expression of VH in LBD patients with and without dementia. Moreover, correlational analyses were undertaken to identify regional GM volumes associated with visual attention and visual perception/construction. The results of this study are reported in Chapter 4, Experiment 1.

2. To explore patterns of brain functional connectivity related to VH in DLB.

Resting-state fMRI was used to investigate differences in functional connectivity between DLB patients with and without VH using two approaches. Firstly, we performed seed-based analyses to explore the functional connectivity of predefined ROIs in fronto-parietal, subcortical and occipito-temporal regions. Then, we undertook ICA analyses to investigate differences between patients with and without VH in intrinsic resting-state functional brain networks. Findings are presented in Chapter 4, Experiment 2.

3. To investigate white matter microstructural alterations associated with VH in DLB.

TBSS analyses were performed on DTI data to explore differences between DLB patients with and without VH in WM microstructure, with a specific interest in tracts involved in visual attention and visual perception. Results are presented in Chapter 4, Experiment 3.

4. To replicate the cognitive findings of Experiment 1 in a completely independent dataset of DLB patients with and without VH, and to assess baseline neuropsychological features predicting the development of VH at follow-up in DLB patients.

Firstly, we aimed to replicate the results obtained in Experiment 1 concerning the cognitive differences between patients with and without VH in DLB. Then, in a subsample of non-hallucinating DLB patients, we investigated the baseline cognitive features that predicted the development of VH at follow-up. Results are presented in Chapter 5, Experiment 4.

5. To perform a meta-analysis of VBM studies on VH in PD and DLB combining peak coordinate data and T-maps.

A meta-analysis of VBM studies investigating volumetric GM differences between LBD patients with and without VH was undertaken combining peak coordinates and statistical maps of the whole brain, with the aim to reconcile findings of VBM studies available in the literature. Results are presented in Chapter 6, Experiment 5.

6. To combine statistically findings from neuropsychological studies comparing LBD patients with and without hallucinations.

A neuropsychological meta-analysis of VH in PD, DLB and PDD was performed, which comprised a wide range of cognitive measures. The aim was to reconcile findings of neuropsychological studies of VH in LBD. The results of this study are reported in Chapter 6, Experiment 6.

7. To investigate cognitive, neuroanatomical and metabolic brain features associated with VH in people with MCI and dementia due to AD.

People with MCI or dementia due to AD with and without VH and cognitively normal matched controls were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to explore the cognitive, macrostructural and metabolic brain features associated with VH in AD. Analyses were performed on neuropsychological measures, structural MRI (whole brain VBM) and FDG-PET scans. The findings of this study are reported in Chapter 7, Experiment 7.

Chapter 4. Structural and functional brain correlates of visual hallucinations in Lewy body disease

The rapid advancement of neuroimaging techniques over the last decades has allowed the study of different aspects of brain function and structure, both in the healthy brain, and in various neuropsychiatric and neurological conditions. Combining different imaging methods, specifically structural MRI, fMRI and DTI, enables the investigation of grey and white matter structural damage, but also how brain regions are interconnected, both functionally and structurally.

Studies integrating different imaging techniques may be very helpful to shed light on the mechanisms involved in the development of VH. Notably, following our systematic literature review, we found only 11 studies out of 68 on VH in LBD that used a multimodal imaging approach (details are reported in Chapter 2). Among these, only two, both on PD, combined more than two different imaging methods (Firbank et al., 2018, Yao et al., 2016). For example, Yao et al. (2016) investigated hippocampal volume, shape, MD, and functional connectivity. They found no differences between VH and NVH patients in hippocampal volume and shape, but reported alterations in MD values and functional connectivity. In this study, however, WM structural connectivity was not explored. In another study, Firbank et al. (2018) hypothesised that poor visual input in LBD may lead to reduced GABAergic inhibition to optimise visual object recognition, which would predispose patients to hallucinate. Accordingly, using magnetic resonance spectroscopy, they found lower occipital GABA+ levels in hallucinating patients in comparison with those without and controls (Firbank et al., 2018). In addition, the authors used task-based fMRI to study visual perception of simple stimuli, and VBM to explore regional brain volumes, showing medial temporal atrophy, but no functional differences. They also performed TBSS to investigate WM integrity, but widespread differences were only reported in comparison with controls (Firbank et al., 2018).

Other studies combined structural and functional MRI (Bejr-Kasem et al., 2019, Franciotti et al., 2015, Yao et al., 2014), structural MRI and PET (Iizuka and Kameyama, 2016, Kantarci et al., 2012, Nishio et al., 2017), structural MRI and DTI (Hepp et al., 2017, Lee et al., 2016, Lee et al., 2017), fMRI and ASL-MRI (Taylor et al., 2012). Of these studies, only three were on DLB, however, none of these investigated between-group differences between hallucinating and non-hallucinating patients (Iizuka and Kameyama, 2016, Kantarci et al., 2012, Taylor et al., 2012).

The present chapter comprises three experiments investigating cognitive, brain structural and functional differences between LBD patients with and without VH. Firstly, we investigated GM alterations related to VH in DLB and PD. Then, we explored functional and structural connectivity in subsamples of hallucinating and non-hallucinating DLB patients. To our knowledge, this is the first multimodal study on VH in DLB integrating structural MRI, resting-state fMRI, and DTI.

4.1 Experiment 1: Regional grey and white matter volumes in patients with visual hallucinations in Lewy body disease

4.1.1 Introduction

As outlined in previous chapters, structural MRI has been widely used to explore brain anatomical features related to disease and symptom-specific alterations in LBD. To this purpose, a number of VBM studies has investigated regional volumetric differences between patients with and without VH in LBD using a whole brain approach (see Chapter 2 for a critical review). As an alternative procedure to ROI studies, whole brain VBM allows the investigation of areas that may not be explored by studies that restrict the analysis to pre-defined brain regions (Giuliani et al., 2005, Mechelli et al., 2005).

Using whole brain VBM, Ramirez-Ruiz et al. (2007b) investigated GM volumetric differences between 18 PD patients with VH, and 20 without. The authors found that VH patients were characterised by reduced GM in occipito-temporal and parietal regions (left lingual gyrus and bilateral superior parietal lobe), concluding that these findings may be related to visual processing, and attention abilities, respectively (Ramirez-Ruiz et al., 2007b). Other studies confirmed these findings, some identifying also a positive association between VH severity and occipito-temporal and parietal GM (Goldman et al., 2014, Watanabe et al., 2013). In a more recent VBM study, Bejr-Kasem et al. (2019) found that mild hallucinatory phenomena were associated with GM atrophy in the right posterior cingulate, by comparing PD patients with (n=18) and without (n=14) minor VH. When applying small volume correction, they also reported GM atrophy in occipito-temporal, parietal and occipital areas (Bejr-Kasem et al., 2019). Conversely, Meppelink et al. (2011) identified no differences between hallucinating and non-hallucinating PD patients using neither whole brain VBM, nor ROI analysis in the left fusiform gyrus. Among VBM studies of VH in LBD, however, only a few presented cluster-level corrected results (Bejr-Kasem et al., 2019, Meppelink et al.,

2011, Ramirez-Ruiz et al., 2007b), while others used a more liberal statistical threshold (Blanc et al., 2016, Goldman et al., 2014, Lee et al., 2017, Watanabe et al., 2013), therefore being more difficult to interpret. Overall, GM loss in occipito-temporal regions represents one of the most consistent findings characterising PD with VH (Bejr-Kasem et al., 2019, Goldman et al., 2014, Ramirez-Ruiz et al., 2007b, Watanabe et al., 2013). On the other hand, little evidence is reported for DLB. Only two VBM studies were identified that compared patients with and without VH (Blanc et al., 2016, Sanchez-Castaneda et al., 2010). In one of these, Sanchez-Castaneda et al. (2010) applied a voxel-based ROI approach in two separate samples of patients with DLB and PDD. They found decreased GM volume in the right inferior frontal gyrus in DLB VH, and in the left orbitofrontal cortex in PDD VH compared with the corresponding non-hallucinating groups. Moreover, decreased GM in the right inferior frontal gyrus, and left precuneus correlated with VH severity in DLB, but not in PDD. The presence of frontal lobe atrophy was interpreted in the light of integrative models of VH (Collerton et al., 2005, Diederich et al., 2005), especially in relation to dysfunctional regulation of the gating and filtering of external perception and internally generated images (Diederich et al., 2005, Sanchez-Castaneda et al., 2010). In another study, Blanc et al. (2016) found reduced GM volume in the left cuneus in prodromal DLB with VH compared with those without. To our knowledge, the latter study is the only whole brain VBM investigation of VH in LB dementia. However, the primary aim was to distinguish DLB from AD, thus the authors did not formulate any *a priori* hypothesis on VH, and the results were not corrected for multiple comparisons (Blanc et al., 2016). Some findings have also been confirmed by FDG-PET and SPECT studies that identified reduced glucose metabolism/perfusion in occipito-temporal, occipital, and parietal regions in hallucinating LBD patients with and without dementia (Boecker et al., 2007, Gasca-Salas et al., 2016, Heitz et al., 2015, Pasquier et al., 2002), but less evidence is available concerning frontal hypometabolism (Perneczky et al., 2008). Moreover, high concentration of LBs has been found in hallucinating patients by neuropathological studies (Gallagher et al., 2011, Papapetropoulos et al., 2006).

Visuoperceptive and visuoconstructive deficits have been found in hallucinating patients by neuropsychological studies in PD (Barnes et al., 2003, Chang et al., 2016, Ibarretxe-Bilbao et al., 2010, Manganelli et al., 2009, Koerts et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a, Shin et al., 2012), and LB dementia (Mori et al., 2000, Mosimann et al., 2004). Regarding visual attention, known to be supported by fronto-parietal brain regions, contrasting findings are available, some showing poorer performance in PD (Chang et al., 2016, Hepp et al., 2013, Manganelli

et al., 2009) and DLB with VH (Cagnin et al., 2013), but not others (Gasca-Salas et al., 2016, Heitz et al., 2015). Some studies explored visual attention and perception/construction in the same neuropsychological investigation both in PD (Chang et al., 2016, Gasca-Salas et al., 2016, Hepp et al., 2013, Manganelli et al., 2009), and DLB (Cagnin et al., 2013, Heitz et al., 2015) with VH. However, to our knowledge, no study so far has taken into account the interaction between these deficits in relation to the presence of VH in LBD.

In the PAD model, Collerton et al. (2005) proposed that VH may generate from a combined deficit in visual attention and perception. The abovementioned results, overall, suggest that deficient visual information processing related to VH may be associated with damaged visual association areas (e.g. occipito-temporal), rather than primary visual cortices. This, in conjunction with impaired fronto-parietal attention networks, may facilitate the development of VH in LBD. Nevertheless, due to the limited amount of findings, sometimes contrasting, this hypothesis needs to be explored further by both neuroimaging and neuropsychological investigations. Moreover, VH in LB dementia have been studied by a few studies only, making it difficult to infer if and how neuroanatomical and neurocognitive features associated with VH differ across the LBD spectrum, especially in relation to the presence of dementia. In this regard, studies that involved samples of hallucinating PD patients with and without dementia, however, did not include a sample of matched patients with dementia and no VH (Janzen et al., 2012, Lee et al., 2017). On the other hand, Sanchez-Castaneda et al. (2010) explored VH in both DLB and PDD, by comparing VH patients with separate samples of non-hallucinating ones within each diagnostic group (Sanchez-Castaneda et al., 2010). However, this study did not include patients without dementia (Sanchez-Castaneda et al., 2010). Therefore, no conclusions can be drawn in relation to the presence/absence of dementia in hallucinating patients, and how it relates to VH occurrence. Moreover, the sample size was quite small (DLB VH, n=6; DLB NVH, n=6; PDD VH, n=8; PDD NVH, n=7) (Sanchez-Castaneda et al., 2010), further emphasizing the need to explore the neural correlates of VH across different LB disorders, with and without dementia. Another poorly studied area of investigation emerged from the literature is the association between cognitive impairments and brain regions and networks specifically altered in LBD patients with VH. Only a few structural MRI studies correlated GM atrophy and deficits in specific cognitive functions, all using an ROI approach (Ibarretxe-Bilbao et al., 2008, Lenka et al., 2018, Pereira et al., 2013), while no whole brain VBM correlation analysis has been carried out.

Top-down modulation refers to the goal-based neural modulation of cortical sensory areas in order to prioritise the processing of task-relevant information discarding the others (Gazzaley and Nobre, 2012). Different integrative models of VH proposed that top-down processes may play a crucial role in the development of these symptoms (Collerton et al., 2005, Diederich et al., 2005, Diederich et al., 2015, Shine et al., 2011). The neural mechanism underlying the top-down control of spatial attention has been shown to rely on a fronto-parietal network of brain regions, directly interconnected to each other, and indirectly through subcortical hubs located in the striatum, and the pulvinar nucleus of the thalamus (Gazzaley and Nobre, 2012, Nobre and Mesulam, 2014). As proposed by Shine et al. (2011), the ventral striatum, especially the head of the caudate, is involved in the voluntary orienting of attention supported by the DAN network that, if dysfunctional, may facilitate the development of VH, along with a concomitant dysregulation of other attention networks (VAN and DMN). The pulvinar has also been suggested to be implicated in VH in DLB, due to its role in visual and attention processes (Delli Pizzi et al., 2014b, Erskine et al., 2019). In fact, it is part of a visual pathway projecting from the retina to the superior colliculus, then innervating the pulvinar (Erskine et al., 2019). Moreover, Erskine et al. (2017), in a neuropathological study, detected LB pathology in the pulvinar in DLB with VH, and more severe neuronal loss compared with AD (Erskine et al., 2017). The role that these subcortical nuclei play in top-down attentional control suggests that their alteration may also constitute a vulnerability to VH, although the specific mechanisms involved are not clear. In a DTI study, Delli Pizzi et al. (2014b) investigated differences in grey matter mean diffusivity between DLB with VH and AD using a tractography-based subdivision of the thalami. The authors found microstructural differences between the two groups in thalamic sub-regions, including the pulvinar, projecting to parietal and occipital cortices. However, to our knowledge, the investigation of the structural volumetric characteristics of the pulvinar and the striatum, detected *in vivo,* has not yet been targeted by structural MRI studies of VH LBD, specifically in the comparison between DLB with and without VH.

Aims and hypotheses

In the light of the findings outlined above, the primary aim of the present study was to investigate the neuropsychological and neuroanatomical correlates of VH in LBD, particularly in patients with and without dementia.

In particular, the present neuropsychological investigation tried to reconcile findings in the current literature by testing whether there was an interplay between deficits in top-down (visual attention) and bottom-up (visual perception) mechanisms in the

expression of VH. Specifically, we investigated whether deficits in visual attention persisted even controlling for visuoperceptive/visuoconstructive abilities, and vice versa. We hypothesised that the presence of VH will be accounted by visual attention/perception deficits even after controlling for the parallel variable.

In terms of structural brain features, a whole brain VBM approach was used to detect brain volumetric differences between VH and NVH patients within each diagnostic group. We hypothesised decreased GM volume in patients with VH in regions consistent with the cognitive deficits proposed. Specifically, GM loss was expected in fronto-parietal regions and subcortical nuclei (pulvinar and striatum), sustaining attention deficits, and occipito-temporal areas, related to perception deficits.

Finally, whole brain voxel-based correlational analyses were undertaken to identify regional brain volumes associated with visual attention and visual perception/construction. We hypothesised that performance in neuropsychological tests evaluating attention would correlate with frontal, parietal and subcortical nuclei GM loss, and those assessing visual perception would be associated with GM loss in occipital, temporal and parietal areas.

Multifactorial models have proposed unified underlying mechanisms for hallucinations in different neurological and psychiatric disorders (Collerton et al., 2005, Shine et al., 2011, Shine et al., 2014b). In line with this view, we expected consistent findings in both patients with DLB and PD without dementia, and therefore visual attention/perception deficits and underlying neuroanatomical substrates. However, in line with studies in the field, we propose that hallucinating patients with LB dementia may be characterised by a more prominent frontal GM loss, exacerbated by the presence of dementia itself. In this context, frontal atrophy may represent a marker of a dysfunctional large-scale attention network that may not yet be detectable in relatively cognitively preserved PD patients. Disrupted fronto-striatal circuits are among the mechanisms believed to underlie cognitive deficits in PD (Flannery et al., 2018, Kehagia et al., 2010, Lewis et al., 2003), and might contribute to the dysfunctional brain mechanisms involved in VH. In this context, structural abnormalities may be subtle in cognitively unimpaired PD patients, while functional/behavioural impairments, possibly linked to fronto-striatal circuits, might be more pronounced and therefore detectable at earlier stages.

4.1.2 Methods

4.1.2.1 Participants

The present study involved 28 clinically diagnosed patients with DLB, and 24 patients with idiopathic PD, who were recruited and studied retrospectively from outpatient memory and neurology Parkinson clinics. In order to assess further structural brain abnormalities in PD with and without VH, 15 healthy controls were also included in the neuroimaging section of the study. This study was approved by the ethical committee of the research institute IRCCS San Camillo, Venice, Italy, where data collection took place for this study. Informed consent was obtained from each participant. Ethical approval is reported in Appendix 3.

Clinical diagnosis of DLB was based on the consensus criteria proposed by the DLB consortium (McKeith et al., 2005). The diagnostic criteria published in 2005 (McKeith et al., 2005) were used in the present study since all the data were collected before the publication of the latest criteria (McKeith et al., 2017). A diagnosis of probable DLB was made in the presence of two core features (VH, cognitive fluctuations, parkinsonism), or if one or more suggestive features (RDB, severe neuroleptic sensitivity, low DAT uptake) were present in the presence of one or more core features (McKeith et al., 2005). Possible DLB was diagnosed in the presence of one core feature, or in the presence of one or more suggestive features (McKeith et al., 2005). Twenty-one patients were diagnosed with probable DLB, including 10 with VH and 11 without VH, while 7 had possible DLB, one with VH and 6 without VH. The DLB sample included 11 DLB patients with VH (mean age: 75.09, SD=5.03; 4 males and 7 females) and 17 without VH (mean age: 73.65, SD=6.47; 9 males and 8 females). DLB patients were included in the study if they presented mild to moderate cognitive decline, as assessed using a MMSE test score cut-off of 18 or above. None of the patients presented severe cerebrovascular disease, assessed by brain computed tomography or MRI scan, history of psychiatric disorders, and severe eye pathology impairing visual acuity. Medications used included: cholinesterase inhibitors, benzodiazepines, psychotropic medications. Neuroleptic drugs were taken by 45% of patients with VH and one without VH. ChEIs were taken by 82% of patients with VH and 53% of patients without VH. Two patients, one with VH and one without, were treated with levodopa. Pramipexole was taken by one patient with VH. Only patients on a stable dose of cholinesterase inhibitors and/or levodopa for at least 3 months were included in the analyses.

Diagnosis of PD was based on the UK PD Brain Bank Criteria (Hughes et al., 1992). Patients with moderate and severe cognitive decline were excluded from the study, using a MMSE cut-off of 24. According to the Hoehn and Yahr staging system, all patients were in the mild stage of the disease (between stage 1 and 3) (Hoehn and Yahr, 2001b). The PD group involved 9 patients with VH (mean age: 67.00, SD=10.56; 5 males and 4 females), and 15 without VH (mean age: 67.33, SD=8.05; 10 males and 5 females). Patients had no previous history of psychiatric or other neurological disorders, except for one patient with VH who had a history of depressive symptoms. All PD patients were treated with levodopa and 75% of them with dopamine agonists. Besides levodopa, dopaminergic therapy included pramipexole (n=13), pergolide (n=1) and ropinirole (n=4). Levodopa equivalent dose in mg/d was calculated for each antiparkinsonian medication as described by Moller et al. (2005).

Other medications used were: monoamine oxidase inhibitors, antidepressants and benzodiazepines. The healthy control sample included 15 participants with a mean age of 67.27 (SD=8.99), comprising 10 males and 5 females, with no previous history of psychiatric or neurological diseases.

Missing data are due to the retrospective nature of the study, as shown in the results section.

4.1.2.2 Clinical assessment

Behavioural disorders were evaluated with the NPI questionnaire, consisting in a well-validated structured interview with a caregiver (Cummings, 1997). This instrument assesses 12 different neuropsychiatric features, namely delusions, hallucinations, depression/dysphoria, agitation/aggression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep, appetite and eating disorders. For each variable, scores for frequency and severity range from 1 to 4 and 1 to 3, respectively. The overall score is obtained by multiplying scores of frequency and severity for each symptom. Presence, severity and frequency of VH were explored with the NPI subsection for hallucinations. Only patients with recurrent, complex VH were included in the study. The sensory modality of hallucinatory phenomena was ascertained with qualitative assessments of reported patients' experiences.

In DLB, extrapyramidal symptoms were investigated with the Unified Parkinson's Disease Rating Scale motor score subsection III (UPDRS-III) (Fahn and Elton, 1987). The presence of cognitive fluctuations and RDB symptoms in DLB was determined by using the Mayo Fluctuations Questionnaire (Ferman et al., 2004), and the Mayo

Sleep Questionnaire (Boeve et al., 2011), respectively. Disease severity for patients with PD was measured using the H&Y scale (Hoehn and Yahr, 2001b).

4.1.2.3 Neuropsychological assessment

Each patient underwent a comprehensive neuropsychological assessment using the Italian version of each test. Global cognitive functioning was evaluated with the MMSE, a screening test assessing orientation, memory, attention and calculation, naming, repetition, comprehension and praxis (Folstein et al., 1975). The total score range is 0-30 with lower scores indicating poorer performance. The following neuropsychological tests were used to assess specific cognitive domains.

Digit cancellation test. The purpose of this test is to measure visual attention, specifically visual search, and processing speed (Spinnler and Tognoni, 1987). In this test, participants are asked to cancel numbers as fast as they can on three different matrices within a time limit (45 seconds per matrix). Targets consist of one, two and three numbers respectively for each trial. Scores are calculated by summing all targets correctly crossed out within each matrix. Digits cancelled beyond the time limit are not included within the corrected responses.

Trail Making Test (TMT). The TMT is divided into two parts, A and B. The purpose is to assess visual attention, visuomotor and scanning abilities (part A and B), and executive functioning, particularly cognitive flexibility and task switching (part B). In part A participants are asked to draw a line connecting 25 numbered circles in ascending numerical order, while part B consists in alternating two sequences, numbered circles (1 through 13) and lettered circles (A through L) by connecting the circles alternating between the two (e.g. 1 to A, A to 2, 2 to B, etc.) (Lezak et al., 2012). Subjects are instructed not to raise the pencil from the sheet, and to connect the circles as fast as they can using straight lines. Time is recorded and constitutes the final score of the test, one for each part (A and B). Number of errors and omissions are also recorded. Outcome of interest for the present study consisted in the time needed to complete part A.

Stroop colour-word test. This task was used to measure the ability to inhibit cognitive interference, as well as other functions, such as attention and processing speed (Scarpina and Tagini, 2017). A short version of this test widely adopted in clinical practice for the assessment of patients with dementia was used for the purpose of this study (Caffarra et al., 2002b). The test is composed of three parts in which

participants are asked to 1) read words printed in black ink, 2) name the colour of a series of circles, 3) name the colour ink of printed incongruent colour names. The interference effect is calculated by subtracting the average time of the first two parts from the third one. The same procedure applies to the error scores (Caffarra et al., 2002b).

Phonemic fluency test. The present test was used to assess executive control abilities, including mental flexibility, inhibition of irrelevant responses, and systematic memory search (Lezak et al., 2012, Shao et al., 2014). Participants are given the instruction to produce as many words as possible beginning with a certain letter. The test is composed of three trials using the letters P, L and F, allowing a time limit of 60 seconds each. The final score is represented by the total number of words produced.

Frontal Assessment Battery (FAB). This test was designed to evaluate frontal lobe functions, especially for the identification of dysexecutive syndromes in neurological conditions (Appollonio et al., 2005, Dubois et al., 2000). The FAB is composed of six subtests assessing different aspects of executive functions: conceptualisation (similarities), mental flexibility (phonemic fluency), motor programming (Luria's motor series), sensitivity to interference (conflicting instructions), inhibitory control (go-no go), and environmental autonomy (prehension behaviour) (Dubois et al., 2000). A final composite score is calculated to assess the severity of the dysexecutive syndrome.

Digit span forward and backward. In both tests, participants are asked to recall a list of numbers of progressively increasing length (up to nine), immediately after presentation (Lezak et al., 2012, Orsini et al., 1987). Digits have to be repeated exactly in the same order as presented in the digit forward, while in reversed order for the digit backward. They both involve auditory attention and short-term memory, as well as working memory abilities for the digit span backward (Lezak et al., 2012).

Prose memory test. This test evaluates the ability to retain information in verbal long-term memory (Novelli et al., 1986). Participants are asked to recall a short story immediately after presentation (immediate recall), and another time after 10 minutes (delayed recall), during which participants undertake a non-verbal task. Final scores reflect the number of elements recalled within each trial. The story recall test version for this study was the one developed by Novelli et al. (1986).

Rey Auditory Verbal Learning Test (RAVLT). The purpose of this test is to assess verbal long-term memory and learning abilities (Lezak et al., 2012). The test includes five immediate recall trials of 15 unrelated words, and a 30-minute delayed recall trial.

Patients are asked to repeat as many words they can remember following each trial. The immediate recall score reflects the total number of words recalled after the first five trials (out of 75), while the delayed recall score is the number of words repeated after 15 minutes delay (out of 15). A final recognition test (yes/no) may also be performed, with the original 15 words and other 15 distracting words.

Rey-Osterrieth Complex Figure. This test comprises two parts, the first one consisting in the copy of a complex figure, and the second one in the reproduction from long-term memory after a 10-minute delay. The cognitive functions involved include visuospatial, visuoperceptive and visuoconstructive abilities (copy), and visual memory (delayed recall) (Caffarra et al., 2002a).

Clock drawing test. The present test involves a number of cognitive skills, ranging from visuospatial, visuoperceptive and constructional abilities to more executive functions, such as planning and spatial organisation (Caffarra et al., 2011, Lezak et al., 2012). There are different scoring methods and versions of the test (e.g. free-drawn or pre-drawn conditions) (Caffarra et al., 2011, Lezak et al., 2012). In the present study, a pre-drawn circular contour was provided. Patients were asked to insert all numbers in the correct disposition, and hands indicating a specific time (Mondini et al., 2003).

Visual and Object Space Perception (VOSP) Battery. This battery was used to assess different aspects of visual perception, namely object and space perception (Lezak et al., 2012, Rapport et al., 1998, Warrington and James, 1991). Object perception subtests: *1) Incomplete letters* presents a number of degraded letters at 70% that patients need to identify. *2) Silhouettes* includes black shapes of common objects shown in atypical perspectives. *3) Object decision* requires the identification of a real object among black shapes. *4) Progressive silhouettes* presents a series of cards with a progressively identifiable object (Lezak et al., 2012, Rapport et al., 1998). Space perception subtests: *5) Dot counting* includes arrays containing black dots that have to be counted. *6) Position discrimination* presents two identical squares both containing a black dot, one centred and the other slightly off-centred; patients have to identify which square contains the centred dot. *7) Number location* includes two squares, one with randomly spaced numbers, and the other with a black dot; subjects have to indicate the number located in the same position as the black dot. *8) Cube analysis* requires the identification of the number of 3D cubes presented in 2D space (Lezak et al., 2012, Rapport et al., 1998).

The following tests were administered to DLB patients only: digit cancellation, clock drawing test and VOSP; while the following just to PD patients: RAVLT, Stroop test and FAB. Scores for all the remaining tests were available for both groups.

4.1.2.4 Statistical analyses

IBM SPSS (Statistical Package for the Social Sciences) Statistics 22 was used to assess differences in demographic, clinical and neuropsychological characteristics within each diagnostic group. For the DLB group, differences between patients with and without VH were investigated using the following statistics: independent sample t-test and Mann-Whitney U test for normally and non-normally distributed numerical variables respectively; Fisher's Exact Test was used for categorical variables. Differences in demographics between PD subgroups and healthy controls were assessed using one-way ANOVA (analysis of variance) and Kruskal-Wallis tests for normally and non-normally distributed numerical variables respectively. Categorical variables were analysed with the Pearson Chi-Square test. Statistical analyses of neuropsychological tests were conducted as for DLB patients. Non-parametric correlations (Spearman's rho test) were run between VH severity and frequency, and attention and visuospatial tests within each diagnostic group. Bonferroni correction was applied to account for multiple comparisons, by which statistical significance is reached with a p value $< \alpha/n$, where α is equal to the p value for each comparison ($p=0.05$) and n the number of comparisons.

A general linear model was used to assess attentional deficits in patients with VH controlling for visuoperceptive or visuoconstructive deficits, separately for each patient group. Specifically, ANCOVA (analysis of covariance) analyses were performed by entering performance on a relevant attention test as the dependent variable, performance on a visuoperceptive (or visuoconstructive) test as a covariate of no interest, and the presence of VH as a fixed factor. Moreover, in order to investigate changes in visuoperceptive (or visuoconstructive) deficits accounting for visual attention deficits, an ANCOVA design was used with a visuoperceptive (or visuoconstructive) test as the dependent variable, an attention test as covariate of no interest, and the presence of VH as a fixed factor.

In addition, two separate forward stepwise (likelihood ratio) logistic regression models were performed in order to explore what variables independently predicted VH in DLB and PD. For each model, all neuropsychological variables were entered as predictor variables with presence of VH as dependent variable.

4.1.2.5 Structural MRI analyses

4.1.2.5.1 MRI acquisition

Three dimensional T1 weighted structural scans were acquired with a 1.5 Tesla Philips Achieva MRI scanner. The following acquisition parameters were applied: TR=7.4 ms, TE=3.4 ms, field of view (FOV): 220 mm for DLB and 230 for PD, flip angle: 8°, 160 slices, voxel dimension 1.04x1.04x0.66 mm.

4.1.2.5.2 VBM pre-processing

VBM is a whole-brain, unbiased objective technique that uses structural MRI scans to identify differences in regional grey and white matter volume between groups of subjects, allowing a voxel by voxel comparison of the entire brain (Mechelli et al., 2005). VBM consists of several pre-processing steps including spatial normalization, segmentation, modulation, smoothing, and finally voxel-wise statistical analysis. The output is a statistical parametric map, which is thresholded to show significant between-group differences in regional brain tissue (Ashburner and Friston, 2000, Mechelli et al., 2005).

Whole brain VBM was carried out using the Statistical Parametric Mapping (SPM) 12 software (Wellcome Centre for Human Neuroimaging, London, UK), running on MATLAB R2014a, version 8.3 (The MathWorks, Icn, Natick, Massachussetts), including pre-processing and statistical analyses. First, structural MRI data were manually reoriented to the Anterior Commissure-Posterior Commissure line, and then segmented into GM, WM and CSF. The next step was spatial normalisation, which consists in the transformation of the MRI data in order to align each image to the same stereotactic space, namely the Montreal Neurological Institute (MNI) space (Ashburner and Friston, 2000). Each image was registered to the same standard template, the ICBM152 brain (International Consortium for Brain Mapping), available on SPM, which is the result of the coregistration of 152 T1 weighted MRI brain scans. The resulting images were then modulated to preserve absolute volumes. In a modulated image, the intensity of a voxel represents the true volume of that voxel. Images were, then, smoothed using a FWHM 8mm isotropic Gaussian kernel. In the smoothed images, each contains the average amount of GM of the surrounding voxels (Ashburner and Friston, 2000). Total GM, WM, and CSF volumes were determined using the MATLAB “get_totals” script (available at http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) from each image in native space. Total intracranial volume (TIV) was calculated for each patient by summing

GM, WM and CSF total volumes. Differences between groups in total GM, WM, CSF volumes and TIV were examined using SPSS (v22).

4.1.2.5.3 VBM statistical analyses

A general linear model with TIV and age as covariates of no interest was used to determine differences between groups in GM and WM volumes. TIV was included in the model to account for individual global differences, while investigating regional changes. Within each diagnostic group, the following contrasts were performed: VH < NVH and VH > NVH. Each PD subgroup was further compared to a group of healthy controls. In addition, to account for global cognitive impairment in DLB, the analyses were repeated by adding MMSE within the model as covariate of no interest. Analyses within the PD sample were also performed including no covariates.

The same procedure was performed for whole brain correlation analyses, undertaken to assess the association between regional GM volumes, cognitive functions and VH severity and frequency.

To exclude voxels outside the brain, relative threshold masking of 0.2 and 0.8 were applied for GM and WM analyses, respectively. Significance level was set at $p<0.001$ uncorrected for multiple comparisons (set-level). A cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons was chosen to report significant results in all the analyses.

Montreal Neurological Institute (MNI) coordinates were converted into Talairach coordinates using GingerALE, v2.3.6 (available at http://www.brainmap.org/ale/). Then, the Talairach Client, v2.4.3 (available at http://www.talairach.org/client.html) was used to determine brain region labels for each significant cluster. White matter regions were determined using the following atlases: the JHU white-matter tractography and ICBM-DTI-81 white-matter labels atlases, available on FSL (Mori et al., 2008, Hua et al., 2008, Wakana et al., 2007).

4.1.2.5.4 Post hoc region of interest analyses

To assess our *a priori* hypothesis of an involvement of the pulvinar and the striatum in the mechanisms underlying VH, ROIs were placed *post-hoc* in the left and right pulvinar, putamen and caudate nucleus, and other control regions, namely the left and right lateral geniculate body, hippocampus and primary motor cortex. The lateral geniculate body was selected as control nucleus of the thalamus. It is part of the central visual pathway, specifically involved in the transmission of information from the retina to the primary visual cortex (Johns, 2014). The hippocampus was chosen

as control region involved in cognitive processes other than visual attention and perception, and the primary motor cortex as control region not involved in high cognitive processing. ROIs were created with the WFU PickAtlas toolbox, version 3.0.5 (Maldjian et al., 2004, Maldjian et al., 2003), specifically using the Brodmann Area atlas based on the Talairach Daemon database (Lancaster et al., 1997, Lancaster et al., 2000). In order to investigate whether the VBM results were associated with cognitive performance, ROI masks were generated *post hoc* based on the significant clusters from the VBM analysis. Further *post hoc* analyses were undertaken within the PD sample to assess group differences in line with our *a priori* hypotheses. The ROIs were chosen in frontal, parietal, occipital and occipito-temporal regions. Specifically, differences between PD patients with and without VH were investigate in the following ROIs: left and right frontal eye field (BA 8), superior parietal lobule (BA 7), primary visual cortex, secondary visual cortex (BA 18), visual associative cortex (BA 19), inferior temporal area (BA 20), and occipitotemporal area (BA 37). The frontal eye field and the superior parietal lobule were chosen for their role in goal-directed visual attention (Asplund et al., 2010, Nobre and Mesulam, 2014, Squire et al., 2013). On the other hand, the formation of objects visual representations is sustained by a ventral visual pathway, identified in an occipito-temporal network of regions lying between primary visual cortices and other specialised areas involved in memory and learning, which form representations with stable elements of the visual information (Kravitz et al., 2013). Key regions in this process include primary, associative visual, and occipito-temporal cortices, and inferior temporal areas (DiCarlo et al., 2012, Kravitz et al., 2013).

GM volumes in these regions were extracted from each patient's smoothed, segmented, normalised, and modulated image by using the MarsBar toolbox for SPM (http://marsbar.sourceforge.net). Then, volumetric differences between hallucinating and non-hallucinating patients within each diagnostic group were, then, assessed performing ANCOVA analyses with TIV and age as covariates of no interest. Volumes were also correlated with the scores achieved on relevant cognitive tests using the same covariates (partial correlations). Non-parametric correlations (Spearman's rho) were also performed to investigate the relationship with VH severity and frequency. Given that not all cognitive scores were recorded for all patients, the number of participants used for these analyses varied, as reported in the result section. Statistical analyses were undertaken using SPSS (v22). Results are shown in the following sections.

4.1.3 Results

4.1.3.1 Demographic and clinical features

Demographics and clinical characteristics of DLB and PD patients are reported in Table 4.1 and Table 4.2. The two groups of DLB patients did not significantly differ in age, gender, years of education, age of onset, duration of disease, presence of cognitive fluctuations, and UPDRS scores (Table 4.1). Patients with DLB with VH presented higher percentage of RBD symptoms (p=0.04) and had higher NPI scores (p=0.004). However, subtracting the NPI scores for VH from the NPI total scores, the two groups did not differ in other neuropsychiatric symptoms (p=0.17). Mean NPI subscores related to VH were 1.70 (0.82) for severity and 2.30 (1.25) for frequency.

Table 4.1 Demographic and clinical characteristics for DLB patients with and without VH. Mean and SD are reported for each variable unless otherwise specified.

Characteristic	DLB VH (n=11)	DLB NVH (n=17)	p value
Age	75.09 (5.03)	73.65 (6.47)	0.54 [a]
Gender M:F	4:7	9:8	0.46 [b]
Years of education	6.09 (3.24)	8 (4.90)	0.30 [c]
Disease duration (years)	2.64 (1.21)	2.06 (1.30)	0.17 [c]
MMSE	22.45 (3.45)	25.00 (3.50)	0.07 [a]
UPDRS III	8.00 (11.86)	4.59 (5.92)	0.83 [c]
ChEIs	82%	53%	0.23 [b]
RBD [d]	91%	47%	0.04 [b]
Cognitive fluctuation	73%	88%	0.35 [b]
Motor symptoms	64%	65%	1.00 [b]
NPI total score	15.82 (9.64)	5.53 (3.7)	<0.01 [c]
NPI^{hall}	4.60 (4.00)	-	-
NPI tot - NPI^{hall} [g]	11.64 (9.51)	5.53 (3.71)	0.17 [c]

ChEIs: cholinesterase inhibitors; DLB: dementia with Lewy bodies; F: female; M: male; MMSE: Mini-Mental State Examination; NPI: neuropsychiatric inventory; NVH: no visual hallucinations; RBD: REM sleep behaviour disorder; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; VH: visual hallucinations. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Mann-Whitney U test; [d] Missing data for a VH patient; [e] NPI total score minus NPI hallucinations.

PD patients with and without VH and healthy controls did not differ significantly in age, gender and years of education. No differences were detected between PD subgroups in disease duration, H&Y scores and presence of sleep disturbances. The most common sleep disturbance was repeated awakening. Only one patient with VH presented RBD. PD patients with VH had higher NPI total scores (p=0.01); this difference remained significant also after subtracting the NPI hallucination subscore

(p=0.03). Mean NPI subscores related to VH were 1.89 (0.60) for severity and 2.33 (1.00) for frequency. Details and statistical tests are reported in Table 4.2.

DLB patients with VH were significantly older (p=0.04) and less educated (p=0.01) than those with PD and VH. Moreover, they had later disease onset (p<0.001), lower disease duration (p<0.001), and lower scores in the MMSE (p=0.03). On the other hand, total NPI score (p=0.08), NPI total minus VH subscore (p=0.07), VH severity (p=0.48) and frequency (p=0.93) were not significantly different between the two groups.

Table 4.2 Demographic and clinical characteristics for PD patients with and without VH and healthy controls. Mean and SD are reported for each variable unless otherwise specified.

Characteristic	PD VH (n=9)	PD NVH (n=15)	Controls (n=15)	p value
Age	67.00 (10.56)	67.33 (8.05)	67.27 (8.99)	1.00 [a]
Gender M:F	5:4	10:5	10:5	0.83 [b]
Years of education	11.33 (5.27)	11.33 (4.24)	11.47 (4.21)	0.97 [c]
Disease duration (years)	9.89 (5.68)	10 (4.23)	-	0.76 [d]
MMSE	26.22 (2.05)	27.60 (1.68)	29.27 (0.88)	0.001 [c]
H&Y [f]	2 (1.00)	2.29 (0.95)	-	0.60 [d]
LED mg/d	608.33 (247.18)	546.27 (204.35)	-	0.51 [e]
Sleep disturbances	89%	67%	-	0.22 [b]
NPI total score	32.67 (25.45)	9.00 (9.89)	-	0.01 [d]
NPI^{hall}	4.67 (2.40)	-	-	-
NPI tot - NPI^{hall} [g]	28.00 (24.60)	9.00 (9.89)	-	0.03 [d]

F: female; H&Y: Hoehn and Yahr scale; LED: Levodopa equivalent dose; M: male; MMSE: Mini-Mental State Examination; NPI: neuropsychiatric inventory; NVH: no visual hallucinations; PD: Parkinson's disease; SD: standard deviation; VH: visual hallucinations. [a] One-way ANOVA; [b] Pearson Chi-Square; [c] Kruskal-Wallis Test; [d] Mann-Whitney Test; [e] Independent-sample t-test; [f] Missing data for 4 VH patients and 8 without VH; [g] NPI total minus NPI hallucinations.

4.1.3.2 Neuropsychological findings

4.1.3.2.1 Dementia with Lewy bodies

Patients with VH had similar performance in global cognitive functioning, compared with patients without, as assessed with the MMSE (p=0.07).

To test the hypothesis of an involvement of visual attention and visual perception/construction in the development of VH, the following tests were taken into account: digit cancellation test, TMT-A, VOSP subtest silhouettes, copy of the Rey figure. The results from the comparison between patients with and without VH in these tests are reported in Table 4.3. Patients with VH had poorer performance in the digit cancellation test only (p=0.01, Figure 4.1). Differences in the digit cancellation test

were significant even when controlling for global cognitive functioning assessed with the MMSE (ANCOVA analysis, p=0.049). Even though statistically not significant, patients with VH presented worst performance on the copy of the Rey figure (Figure 4.2), with 4 patients out of 9 scoring 0 (as opposed to 1 patients out of 14 in the non-hallucinating group) (Fisher's Exact Test, p=0.06). Difference in the TMT-A was marginally significant, even when controlling for MMSE (ANCOVA analysis, p=0.046). In addition to visual attention abilities, the TMT-A and the digit cancellation tests involve visuomotor skills (Lezak et al., 2012). To rule out the influence of motor symptoms on the performance on these tests, between-group differences were assessed controlling for scores on the UPDRS III. Differences on the digit cancellation (ANCOVA analysis, p=0.02), but not on the TMT-A (ANCOVA analysis, p=0.16), remained significant even after controlling for motor symptoms.

Table 4.3 Differences in neuropsychological tests assessing visual attention, visual perception and visuoconstruction between DLB patients with and without VH.

Test	DLB VH			DLB NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit cancellation	10	24.40 (8.90)	25.0 (12.0)	16	34.81 (9.90)	37.50 (16.0)	**0.01** [a]
TMT-A (seconds)	8	184.0 (94.0)	139.5 (152)	14	123.64 (73.04)	96.50 (61.0)	0.05 [b]
Rey figure Copy	9	11.94 (15.0)	2.0 (28.5)	14	20.68 (10.86)	22.0 (19.13)	0.16 [b]
VOSP Silhouettes	11	9.45 (5.37)	10.0 (7.0)	16	12.44 (3.76)	13.0 (5.25)	0.10 [a]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no visual hallucinations; SD: standard deviation; TMT-A: Trail Making Test A; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.

Attention deficits, assessed with the digit cancellation test, persisted even when controlling for visuoperceptive and visuoconstructive abilities as evaluated with the VOSP subtest silhouettes (ANCOVA analysis, p=0.04), and the copy of the Rey figure (ANCOVA analysis, p=0.03), respectively. No differences were found in VOSP silhouettes (ANCOVA analysis, p=0.56) and copy of the Rey figure (ANCOVA analysis, p=0.71) when controlling for digit cancellation scores.

Non-parametric correlation analyses (Spearman's rho test) showed no significant association between severity and frequency of VH and performance on the digit cancellation (VH severity, p=0.36; VH frequency, p=0.17), VOSP silhouettes (severity, p=0.60; frequency, p=0.98) and copy of the Rey figure (severity, p=0.16). Scores on

the Rey figure copy significantly correlated with VH frequency (p=0.03) even though not surviving correction for multiple comparisons (p<0.005). When considering the NPI hallucination score as a whole (frequency x severity), performance on the TMT-A (p=0.003) and Rey figure copy (p=0.03) was found to correlate significantly, but not on the digit cancellation test (p=0.23) and the VOSP silhouettes (p=0.74).

Results from the comparison between DLB patients with and without VH on the other neuropsychological tests are summarised in Table 4.4. Hallucinating patients presented greater impairment in neuropsychological tests assessing verbal working memory (digit span backward, p=0.04), and visuoconstructive long-term memory (delayed recall of Rey figure, p=0.03). When accounting for MMSE scores, differences in the digit span backward (ANCOVA analysis, p=0.23) and Rey figure delayed recall (ANCOVA analysis, p=0.16) were no longer significant. However, none of these significant differences survived correction for multiple comparisons (p<0.003). Comparable scores between groups were found in the following tests: digit span forward, prose memory (immediate and delayed recall), phonemic fluency, clock drawing, copy of the Rey figure, and all the VOSP subtests.

When all tests were included in a stepwise logistic regression model, it revealed that the only significant predictor of VH was the performance on the digit cancellation test (OR=0.82, p=0.02). Only patients who had scores on all neuropsychological tests were included in the model (8 DLB VH, 10 DLB NVH). It should be noted that multicollinearity among predictor variables might influence the results. Multicollinearity occurs when one or more predictors are highly correlated, and may cause unstable estimates and inaccurate variances (Midi et al., 2010). To safeguard against any effect of multicollinearity, additional analyses were run. Firstly, we run correlation analyses in order to check the degree of correlation between the independent variables. A correlation coefficient greater then 0.8 was considered a concern for multicollinearity (Midi et al., 2010). The following variables resulted highly correlated (Pearson correlation coefficient greater than 0.8): digit span forward and backward (p<0.001), prose memory immediate and delayed recall (p<0.001), Rey figure copy and delayed recall (p<0.001), Rey figure copy and VOSP incomplete letters (p<0.001). The logistic regression analysis was repeated excluding all but one of the highly correlated variables. To avoid the inclusion of redundant variables, only one measure of visual perception/construction was included (Rey figure copy). Therefore, the stepwise logistic regression model was run including the following neuropsychological measures: digit cancellation, TMT-A, digit span backward, prose memory immediate recall, phonemic fluency, clock drawing and copy of the Rey figure. Collinearity

diagnostic statistics revealed a tolerance greater than 0.1 for all the variables, thus ruling out a potential collinearity problem (Midi et al., 2010). Results of this final stepwise logistic regression model are reported in Table 4.5.

Table 4.4 Exploratory analyses on other neuropsychological tests in the comparison between DLB patients with and without VH.

Test	DLB VH			DLB NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit span:							
Forward	10	3.70 (1.57)	4.0 (1.25)	16	4.75 (1.06)	4.50 (1.75)	0.07 [b]
Backward	9	2.00 (0.82)	2.0 (0.25)	15	2.81 (1.17)	3.00 (1.75)	**0.04** [b]
Prose memory:							
Immediate recall	11	7.36 (5.57)	6.0 (5.00)	17	7.24 (3.98)	6.00 (3.50)	0.87 [b]
Delayed recall	11	8.09 (4.97)	7.0 (7.00)	17	7.94 (5.06)	7.00 (6.50)	0.89 [b]
Phonemic fluency	10	14.5 (10.5)	11.50 (8.50)	14	17.07 (11.6)	14.0 (19.25)	0.84 [b]
Clock drawing	10	3.80 (3.22)	4.0 (5.50)	17	4.80 (3.46)	6.00 (6.25)	0.47 [a]
Rey figure recall	9	2.94 (4.35)	0.0 (6.25)	14	8.00 (5.97)	7.75 (10.00)	**0.03** [b]
VOSP:							
Screening test	11	18.73 (2.2)	20.0 (1.0)	16	19.38 (0.72)	19.50 (1.00)	0.96 [b]
Incomplete letters	11	9.27 (6.25)	8.0 (10.0)	16	12.38 (7.32)	15.0 (12.25)	0.24 [b]
Object decision	11	8.90 (4.97)	11.0 (7.0)	15	11.07 (3.82)	12.00 (6.00)	0.28 [b]
Progressive silhouettes	11	9.55 (6.88)	13.0 (16.0)	15	11.60 (3.85)	11.00 (4.00)	0.74 [b]
Dot counting	11	8.45 (2.30)	9.0 (2.0)	16	9.44 (1.50)	10.00 (0.75)	0.10 [b]
Position discrimination	11	15.18 (7.4)	19.0 (5.0)	16	17.44 (3.67)	19.50 (6.75)	0.37 [b]
Number location	11	6.09 (4.25)	7.0 (7.0)	16	6.06 (2.46)	7.00 (4.00)	0.98 [a]
Cube analysis	11	4.09 (3.08)	5.0 (6.0)	16	5.69 (3.24)	5.00 (5.50)	0.21 [a]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no visual hallucinations; SD: standard deviation; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.

Table 4.5 Final stepwise logistic regression model in DLB. Variables not in the equation: TMT-A, digit span backward, prose memory immediate recall, phonemic fluency, clock drawing, Rey figure copy.

Predictor	B coefficient	SE	OR	OR 95% CI	p value
Digit cancellation	-0.21	0.09	0.82	0.68 to 0.97	0.02

CI: confidence interval; OR: odds ratio; SE: standard error. Nagelkerke R^2=0.52; Model p=0.003; Classification percentage: 77.8%.

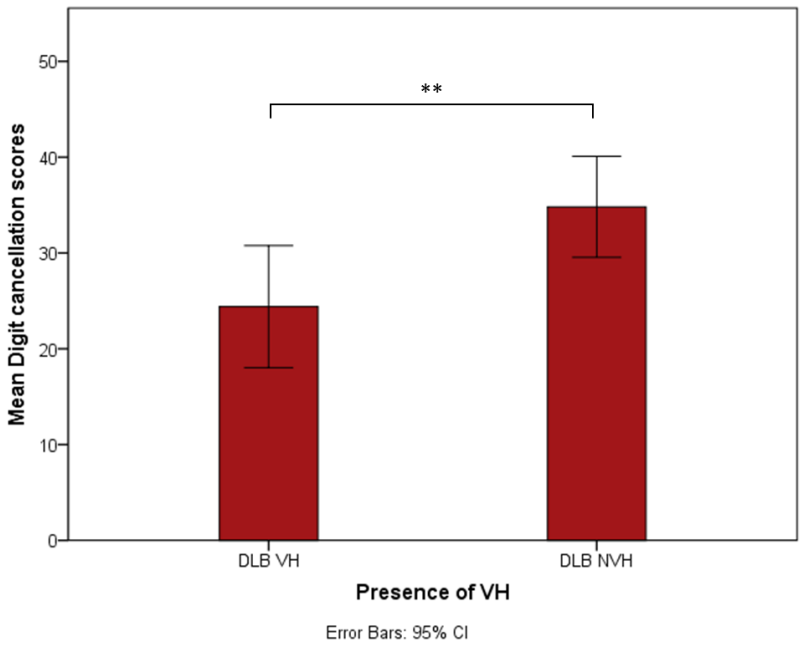

Figure 4.1 Significantly lower scores in the digit cancellation in DLB VH compared with NVH. ** p<0.01.

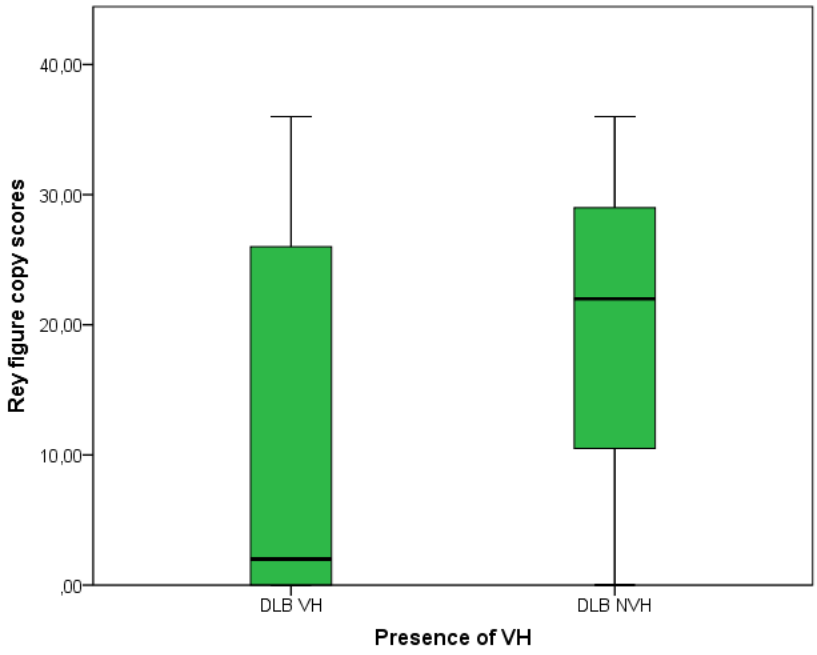

Figure 4.2 Boxplot showing differences between DLB VH and NVH in the copy of the Rey figure, although non-significant.

4.1.3.2.2 Parkinson's disease

PD patients with and without VH did not differ significantly in global cognitive performance (MMSE, Post-hoc Dunn's pairwise test, p=0.52), but MMSE scores were

significantly lower than controls (Post-hoc Dunn's pairwise test, VH vs. controls: p=0.001; NVH vs. controls: p=0.03).

No differences between patients with and without VH were detected in tests assessing visual attention (TMT-A, p=0.45) and visuoconstruction (Rey figure copy, p=0.92). Results are reported in Table 4.6. An additional analysis on the TMT-A data controlling for motor impairment severity according to H&Y stages showed unaltered results (ANCOVA analysis, p=0.89). ANCOVA analyses revealed no significant differences in visual attention when accounting for visuospatial abilities (TMT-A controlling for the copy of the Rey figure, p=0.49); and no differences in visuoconstructive abilities when accounting for visual attention (Rey figure copy controlling for the TMT-A, p=0.76). Non-parametric correlations (Spearman's rho) showed no significant association between TMT-A and VH severity (p=0.38) and frequency (p=0.41), and copy of the Rey figure and VH severity (p=0.75) and frequency (p=0.70). When the NPI hallucination score was taken as a whole (frequency x severity), the correlations were still not significant (TMT-A, p=0.41; Rey figure copy, p=0.7)

Table 4.6 Differences in neuropsychological tests assessing visual attention and visuoconstruction between PD patients with and without VH.

Test	PD VH			PD NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
TMT-A (s)	7	71.43 (23.75)	64.00 (38.0)	15	61.20 (31.0)	58.00 (39)	0.45 [a]
Rey figure copy	8	28.06 (2.47)	28.50 (4.30)	14	27.86 (7.15)	29.0 (12.9)	0.92 [a]

IQR: interquartile range; NVH: no visual hallucinations; PD: Parkinson's disease; s: seconds; SD: standard deviation; TMT-A: Trail Making Test A; VH: visual hallucinations. [a] Independent-sample t-test.

Scores on other neuropsychological tests of PD patients with and without VH are reported in Table 4.7. Patients with VH presented greater impairment compared with those without in tests assessing long-term memory (RAVLT immediate recall, p=0.03), and executive functioning (FAB, p=0.006). The scores on the phonemic fluency test were marginally significant (p=0.05) between VH and NVH groups. None of the differences survived correction for multiple comparisons (p<0.006). In the comparison between patients with and without VH, differences in FAB remained significant (ANCOVA analysis, p=0.02) after controlling for the NPI total score minus the NPI hallucination subscore, but those in RAVLT immediate recall (ANCOVA analysis, p=0.08), and phonemic fluency (ANCOVA analysis, p=0.31) did not. No differences were found in the performance in the following tests: digit span forward and backward,

RAVLT (delayed recall), Rey figure delayed recall, and Stroop test. *Post-hoc* correlation analyses on the tests that resulted significantly different between VH and NVH patients revealed significant correlations (Spearman's rho) between the NPI hallucination score and performance on the FAB (p=0.001), and RAVLT immediate recall (p=0.03), but not phonemic fluency (p=0.08). The total NPI score minus NPI hallucination also correlated with performance on the FAB (p=0.02), and phonemic fluency (p=0.03), but not on the RAVLT (p=0.15).

Table 4.7 Exploratory analyses on other neuropsychological tests in the comparison between PD patients with and without VH.

Test	PD VH			PD NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit span:							
Forward	5	6.00 (1.23)	6.0 (2.0)	8	6.38 (0.92)	6.0 (1.0)	0.54 [a]
Backward	5	3.60 (0.89)	3.0 (2.0)	8	3.63 (0.74)	3.50 (1.0)	0.87 [b]
RAVLT:							
Immediate	6	26.33 (6.47)	26.0 (11.0)	11	38.73 (11.33)	34.0 (21.0)	**0.03** [a]
Delayed	6	5.17 (2.32)	5.50 (5.0)	11	7.73 (3.50)	9.0 (7.0)	0.17 [b]
Phonemic fluency	8	24.25 (4.92)	25.0 (8.0)	15	31.6 (9.47)	31.0 (16.0)	0.05 [a]
Rey figure recall	8	11.31 (4.87)	12.25 (9.10)	14	12.73 (5.85)	13.50 (5.30)	0.57 [a]
Stroop test (s)	6	64.67 (77.5)	36.50 (56.0)	15	32.83 (17.82)	28.50 (29.0)	0.48 [b]
Stroop test (errors)	6	5.00 (5.97)	3.0 (6.0)	15	3.30 (5.11)	2.0 (5.0)	0.31 [b]
FAB	6	11.83 (2.40)	12.0 (3.0)	7	16.14 (1.57)	17.0 (2.0)	**0.01** [b]

FAB: Frontal Assessment Battery; IQR: interquartile range; RAVLT: Rey Auditory Verbal Learning Test; MMSE: Mini-Mental State Examination; NVH: no VH; PD: Parkinson's disease; s: seconds; SD: standard deviation; VH: visual hallucinations. [a] Independent-sample t-test; [b] Mann-Whitney U test

A stepwise logistic regression model showed that the only predictor of VH was the performance on the FAB (OR=0.38, p=0.08), although this prediction did not reach significance level. Only patients who had scores for all neuropsychological tests were included in the model (4 VH, 6 NVH). The following variables resulted highly correlated (Pearson correlation coefficient greater than 0.8): phonemic fluency and TMT-A (p<0.001); phonemic fluency and RAVLT delayed recall (p=0.003). Phonemic fluency was, therefore, excluded from the final regression model. Collinearity diagnostic statistics revealed a tolerance greater than 0.1 for all the variables, a part from a tolerance of 0.1 for the TMT-A. Thus, the interpretation of the results should

take into account potential multicollinearity problems. Results of the final stepwise logistic regression model are reported in Table 4.8.

Table 4.8 Final stepwise logistic regression model in PD. Variables not in the equation: TMT-A, digit span forward and backward, RAVLT immediate and delayed recall, Rey figure copy and delayed recall, Stroop test seconds.

Predictor	B coefficient	SE	OR	OR 95% CI	p value
FAB	-0.97	0.55	0.38	0.13 to 1.11	0.08

CI: confidence interval; OR: odds ratio; SE: standard error. Nagelkerke R^2=0.64; Model p=0.01; Classification percentage: 80.0%.

4.1.3.3 Whole brain VBM findings

4.1.3.3.1 Dementia with Lewy bodies

No differences between DLB subgroups were found in TIV, total GM, WM and CSF volumes within each diagnostic group (Table 4.9). As for regional volumetric changes, reduced GM in DLB patients with VH in comparison with those without was found in three clusters located in frontal and subcortical areas. Specifically, peak coordinates were shown in the right superior frontal gyrus, putamen and medial frontal gyrus, with TIV and age included as covariate of no interest (Table 4.10 and Figure 4.3). All clusters were significant at a cluster-level threshold of p<0.05 FWE corrected for multiple comparisons. When the analysis were repeated including MMSE as covariate of no interest (in addition to TIV and age), only one cluster survived cluster-level correction for multiple comparisons. Peak coordinates were found in the right superior frontal gyrus, BA 10 (MNI coordinates: x=9, y=62, z=-12; cluster size: k=703 voxels; T score: 6.09; Z score: 4.65; p=0.01). Sub-peaks were located in the right superior frontal (BA 10; MNI coordinates: x=21, y=62, z=4; T score: 5.01; Z score: 4.08) and middle frontal gyri (MNI coordinates: x=34, y=54, z=-9; T score: 4.74; Z score: 3.92).

Table 4.9 Total volumes in brain tissues in DLB patients with VH compared to those without (independent-sample t-tests). Mean and standard deviation are reported for each variable.

Volume (ml)	DLB VH (n=11)	DLB NVH (n=17)	p value
Total GM volume	479.20 (51.83)	493.39 (30.86)	0.37
Total WM volume	441.79 (65.81)	447.31 (59.50)	0.82
Total CSF volume	525.06 (81.66)	479.73 (82.30)	0.17
Total intracranial volume	1446.04 (134.09)	1420.43 (140.75)	0.64

CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; GM: grey matter; SD: standard deviation; NVH: no VH; VH: visual hallucinations; WM: white matter.

Table 4.10 Regions of reduced GM volume in DLB patients with VH compared to those without (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Superior frontal gyrus (BA 10)	R	1328	9	62	-12	6.28	4.79	<0.001
Superior frontal gyrus (BA 10)	R		21	62	4	5.41	4.33	
Middle frontal gyrus	R		34	54	-9	5.06	4.14	
Putamen	R	625	26	20	-4	5.50	4.38	0.02
Insula (BA 13)	R		38	26	4	4.44	3.76	
Caudate head	R		14	20	-2	3.83	3.35	
Medial frontal gyrus (BA 11)	R	576	3	45	-27	4.57	3.84	0.03
Medial frontal gyrus (BA 11)	R		6	32	-26	4.44	3.76	

BA: Brodmann area; DLB: dementia with Lewy bodies; FWE: family-wise error; GM: grey matter; R: right; TIV: total intracranial volume; VH: visual hallucinations.

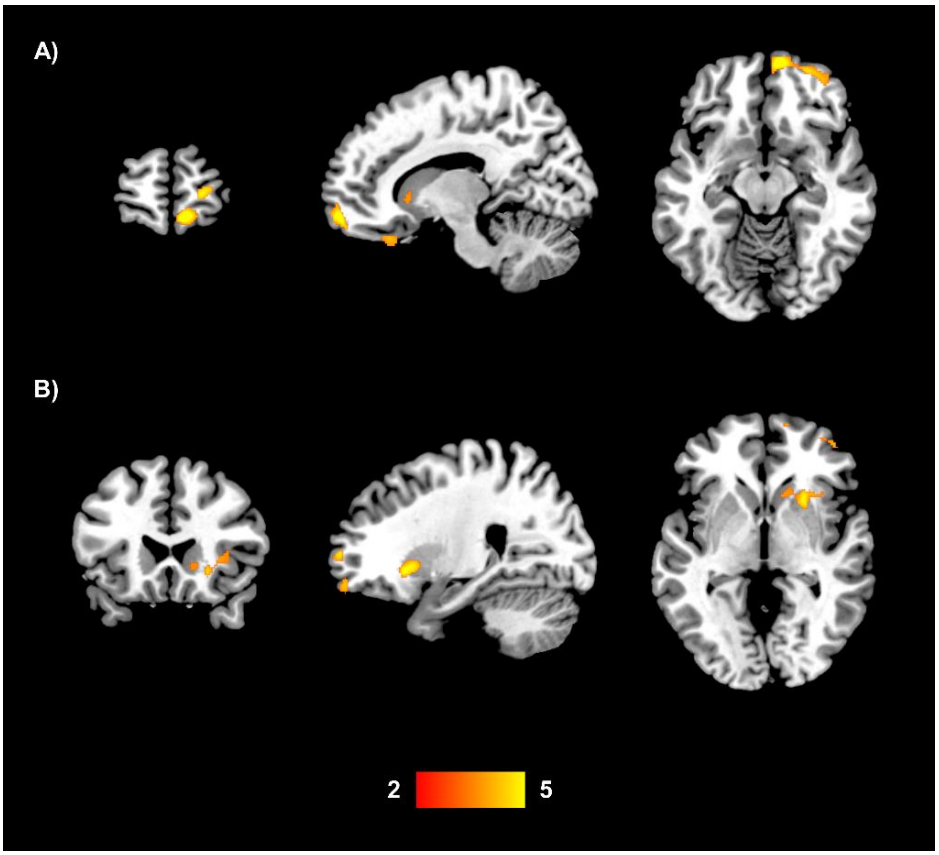

Figure 4.3 Regions of reduced GM volume in DLB patients with VH compared to those without: A) right superior, middle and medial frontal gyri, and B) right putamen, insula and caudate nucleus. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons, with TIV and age as covariates of no interest.

Whole brain analysis on WM revealed one cluster of reduced volume in the forceps minor / genu of corpus callosum (Table 4.11 and Figure 4.4), which disappeared when adding MMSE scores in the model as covariate of no interest.

Table 4.11 Regions of reduced WM volume in DLB patients with VH compared to those without (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure	Cluster size	MNI coordinates			T score	Z score	p value
Forceps minor / Genu of corpus callosum	1043	9	30	0	4.55	3.83	<0.001
Body of corpus callosum		16	15	24	4.38	3.72	
Right anterior thalamic radiation / Genu of corpus callosum		20	24	21	4.36	3.71	

DLB: dementia with Lewy bodies; FWE: family-wise error; TIV: total intracranial volume; VH: visual hallucinations; WM: white matter.

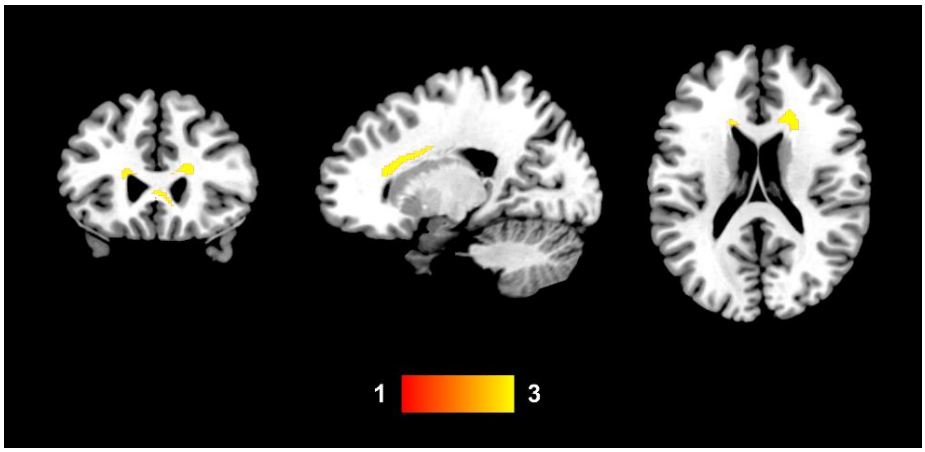

Figure 4.4 Regions of reduced WM volume in DLB patients with VH compared to those without. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons, with TIV and age as covariates of no interest.

Whole brain correlation analyses showed positive associations between a) the digit cancellation test and the right putamen and left caudate nucleus, and b) the VOSP silhouettes subtest and the right inferior temporal gyrus (Table 4.12 and Figure 4.5). No regions of GM volume were associated with scores at the copy of the Rey figure, VH severity and frequency.

Table 4.12 Whole brain voxel-based positive correlations between GM volumes and digit cancellation and VOSP silhouette (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Digit cancellation								
Putamen	R	599	22	14	3	5.59	4.37	0.02
Caudate body	R		15	-3	20	4.51	3.76	
Caudate body	R		18	-12	21	4.32	3.63	
Caudate body	L	482	-15	-4	24	5.47	4.30	0.05
Caudate body	L		-20	10	18	5.18	4.14	
Caudate body	L		-9	-2	14	3.67	3.21	
VOSP silhouettes								
Inferior temporal gyrus (BA 20)	R	1059	60	-36	-20	5.32	4.25	0.002
Middle temporal gyrus (BA 21)	R		66	-28	-14	5.29	4.23	
Middle temporal gyrus (BA 21)	R		64	-22	-20	4.87	4.00	

BA: Brodmann area; DLB: dementia with Lewy bodies; FWE: family-wise error; GM: grey matter; R: right; TIV: total intracranial volume; VH: visual hallucinations; VOSP: Visual Object and Space Perception Battery.

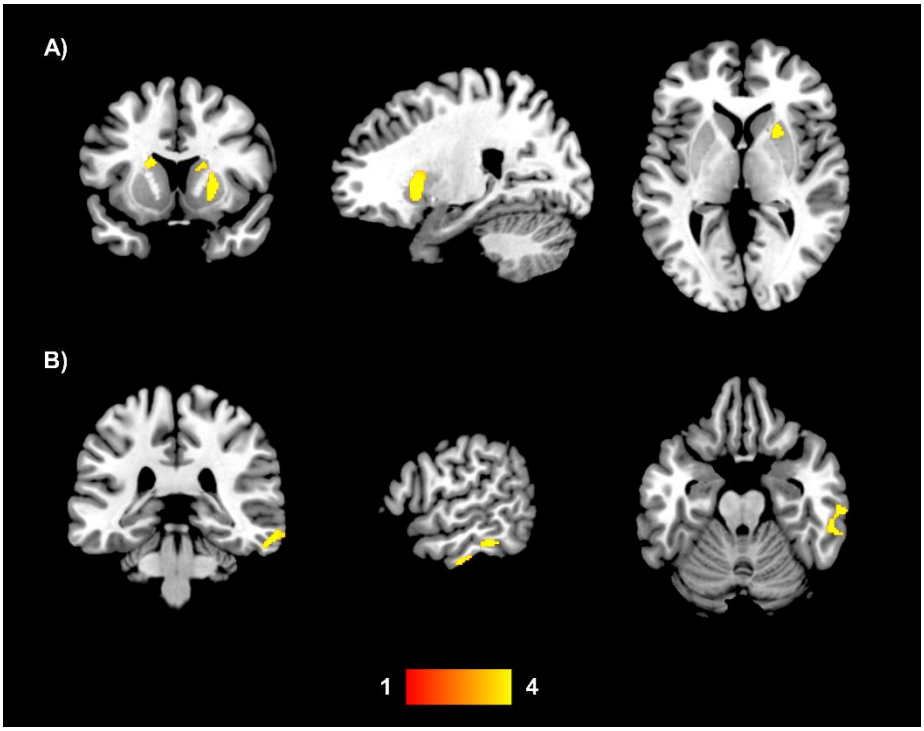

Figure 4.5 Results from whole brain voxel-based positive correlation between grey matter volumes and A) digit cancellation and B) VOSP silhouettes scores. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest.

4.1.3.3.2 Parkinson's disease

The same analyses in PD patients yielded no between group differences in regional GM and WM volumes using a cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons. No differences were found between each PD subgroup and a group of healthy controls. The analyses were repeated with no covariates of no interest, but no results reached statistical significance. No significant differences were found between the three groups (PD with and without VH and healthy controls) in total GM, WM, CSF volumes, and TIV (Table 4.13).

Table 4.13 Total volumes in brain tissues in PD patients with VH compared to those without (One-way ANOVA). Mean and standard deviation are reported for each variable.

Volume (ml)	PD VH (n=9)	PD NVH (n=15)	Controls (n=15)	p value
Total GM volume	561.69 (71.52)	613.79 (64.86)	604.25 (59.94)	0.16
Total WM volume	458.48 (58.26)	498.09 (64.64)	460.21 (49.37)	0.14
Total CSF volume	393.29 (93.24)	376.86 (87.48)	378.03 (86.31)	0.89
Total intracranial volume	1413.46 (159.90)	1488.74 (146.13)	1442.48 (105.78)	0.40

CSF: cerebrospinal fluid; GM: grey matter; PD: Parkinson's disease; SD: standard deviation; NVH: no visual hallucinations; VH: visual hallucinations; WM: white matter.

4.1.3.4 Post hoc region of interest findings

4.1.3.4.1 Dementia with Lewy bodies

ROI analyses reported statistically significant differences in the left ($p=0.0004$) and right caudate nucleus ($p=0.002$), left putamen ($p=0.04$), left ($p=0.02$) and right hippocampus ($p=0.01$), using an ANCOVA design with TIV and age as covariates of no interest. Adding MMSE as covariate to the design, the left ($p=0.002$) and right caudate nucleus ($p=0.02$), the left putamen ($p=0.04$), and the left hippocampus remained significant ($p=0.03$), while the right hippocampus was only marginally significant ($p=0.05$). The only differences that survived correction for multiple comparisons ($p<0.004$) were in the left and right caudate nucleus. No significant differences were found in the other ROIs (Table 4.14).

Table 4.14 Differences between DLB patients with VH compared to those without in ROIs volumes (ANCOVA analysis with TIV and age as covariates of no interest). Mean and standard deviation of the MRI signal are reported for each ROI.

Volume (MRI signal)	Side	DLB VH (n=11)	DLB NVH (n=17)	p value
Caudate	L	0.16 (0.35)	0.22 (0.35)	**0.0004**
	R	0.17 (0.41)	0.22 (0.37)	**0.002**
Putamen	L	0.27 (0.31)	0.29 (0.31)	**0.04**
	R	0.26 (0.28)	0.27 (0.30)	0.10
Pulvinar	L	0.24 (0.04)	0.25 (0.03)	0.12
	R	0.23 (0.04)	0.25 (0.03)	0.31
Lateral geniculate body	L	0.06 (0.01)	0.07 (0.01)	0.05
	R	0.08 (0.01)	0.07 (0.01)	0.53
Hippocampus	L	0.35 (0.06)	0.41 (0.65)	**0.02**
	R	0.35 (0.08)	0.42 (0.05)	**0.01**
Primary motor cortex (BA 4)	L	0.19 (0.04)	0.18 (0.02)	0.26
	R	0.19 (0.04)	0.18 (0.02)	0.71

BA: Brodmann area; DLB: dementia with Lewy bodies; L: left; NVH: no visual hallucinations; R: right; ROI: region of interest; TIV: total intracranial volume; VH: visual hallucinations.

In order to investigate whether regions of reduced GM were associated with cognitive deficits, volumes within the clusters that were found to be significantly different between DLB subgroups were extracted and correlated with performance on the digit cancellation test and the TMT-A (assessing visual attention) within the whole DLB group. Partial correlational analyses (controlling for TIV and age) showed a statistically significant positive association between scores on the digit cancellation and the subcortical ROI (within the putamen, insula and caudate nucleus; n=26, R=0.58, p=0.003; Figure 4.6). No other significant correlation was found with the ROIs based on the VBM results. Partial correlations were also run between the digit cancellation and TMT-A scores and the left and right pulvinar, in line with our hypothesis, which showed no significant results. None of the ROIs was associated with severity and frequency of VH (Spearman's rho correlations).

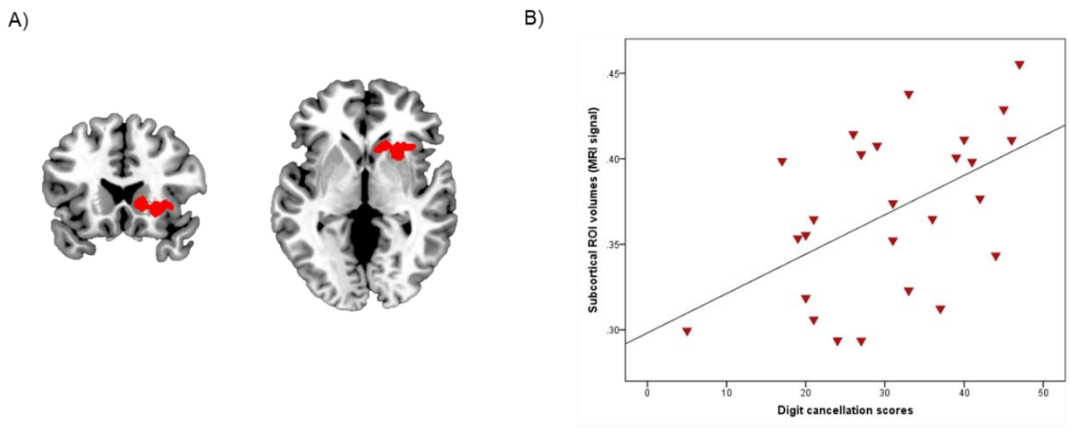

Figure 4.6 A) Subcortical ROI of decreased grey matter volume as resulted from VBM analysis (ROI regions: right putamen, insula and caudate). B) Scatterplot showing the significant correlation between the digit cancellation test scores and the ROI volumes (MRI signal).

4.1.3.4.2 Parkinson's disease

ROI analyses were performed to investigate differences between patients with and without VH in PD, based on *a priori* hypotheses (covariates: TIV, age). Even though not surviving correction for multiple comparisons ($p<0.002$), significant differences were found in the left ($p=0.008$) and right caudate nucleus ($p=0.005$; Table 4.15). These results remained significant even when adding MMSE to the model. As shown in Figure 4.7, these regions significantly correlated with scores on the FAB (n= 13) and the TMT-A (n=22). Specifically, partial correlations (TIV, age and MMSE as covariates) revealed significant positive associations between FAB scores and the left ($r=0.70$, $p=0.03$) and right ($r=0.68$, $p=0.03$) caudate nucleus, and negative associations between the TMT-A and the caudate nucleus, in the left ($r=-0.48$, $p=0.04$) and right ($r=-0.48$, $p=0.04$) hemispheres. Negative correlations, as assessed with the Spearman's rho test, were also reported with VH frequency (left caudate, $r=-0.46$, $p=0.03$; right caudate, $r=-0.46$, $p=0.03$) and VH severity (left caudate, $r=-0.48$, $p=0.02$; right caudate, $r=-0.47$, $p=0.02$).

Table 4.15 Differences between PD patients with VH compared to those without in ROIs volumes (ANCOVA analysis with TIV and age as covariates of no interest). Mean and standard deviation of the MRI signal are reported for each ROI.

Volume (MRI signal)	Side	PD VH (n=9)	PD NVH (n=15)	p value
DLB VBM results ROIs				
Orbitofrontal cortex ROI	R	0.36 (0.05)	0.41 (0.05)	0.08
Subcortical ROI	R	0.41 (0.05)	0.46 (0.03)	**0.02**
Gyrus rectus ROI	R	0.33 (0.05)	0.37 (0.06)	0.23
ROIs based on *a priori* hypotheses				
Pulvinar	L	0.33 (0.06)	0.34 (0.03)	0.91
	R	0.34 (0.05)	0.36 (0.03)	0.37
Lateral geniculate body	L	0.09 (0.02)	0.09 (0.01)	0.35
	R	0.11 (0.03)	0.12 (0.02)	0.85
Caudate nucleus	L	0.24 (0.06)	0.29 (0.04)	**0.008**
	R	0.24 (0.05)	0.29 (0.04)	**0.005**
Putamen	L	0.34 (0.04)	0.37 (0.03)	0.10
	R	0.30 (0.04)	0.34 (0.03)	**0.03**
Frontal eye field (BA 8)	L	0.24 (0.04)	0.28 (0.04)	**0.03**
	R	0.25 (0.04)	0.29 (0.04)	**0.047**
Superior parietal lobule (BA 7)	L	0.32 (0.04)	0.34 (0.03)	0.24
	R	0.31 (0.05)	0.33 (0.03)	0.33
Primary visual cortex (BA 17)	L	0.29 (0.04)	0.31 (0.05)	0.66
	R	0.27 (0.03)	0.30 (0.05)	0.19
Secondary visual cortex (BA 18)	L	0.27 (0.03)	0.30 (0.05)	0.16
	R	0.25 (0.03)	0.28 (0.04)	0.08
Visual associative cortex (BA 19)	L	0.29 (0.03)	0.32 (0.04)	0.06
	R	0.26 (0.03)	0.29 (0.04)	0.15
Inferior temporal area (BA 20)	L	0.42 (0.05)	0.45 (0.05)	0.24
	R	0.43 (0.05)	0.46 (0.05)	0.20
Occipitotemporal area (BA 37)	L	0.42 (0.05)	0.45 (0.05)	0.13
	R	0.40 (0.05)	0.44 (0.05)	0.09
Hippocampus	L	0.48 (0.06)	0.51 (0.05)	0.20
	R	0.50 (0.06)	0.54 (0.05)	0.09
Primary motor cortex (BA 4)	L	0.23 (0.04)	0.26 (0.03)	0.21
	R	0.24 (0.04)	0.25 (0.03)	0.44

BA: Brodmann area; L: left; NVH: no VH; PD: Parkinson's disease; R: right; ROI: region of interest; TIV: total intracranial volume; VH: visual hallucinations.

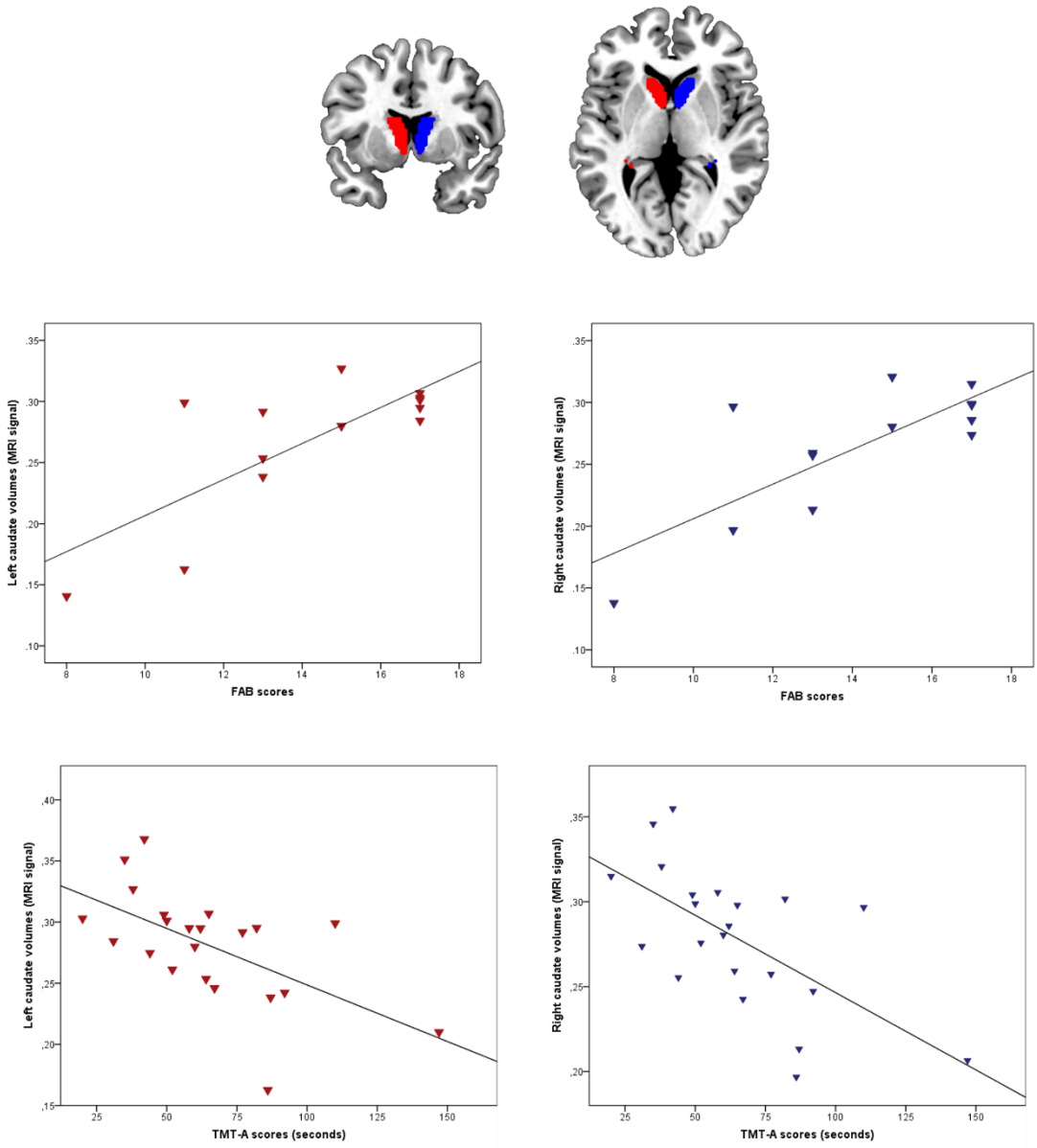

Figure 4.7 ROIs: left (in red) and right (in blue) caudate nucleus. B) Scatterplot showing the significant correlation between the ROIs volumes (MRI signal) and the FAB and TMT-A (seconds) scores.

4.1.4 Discussion

The present study provides evidence of the presence of frontal and subcortical GM loss, and visual attention deficits in DLB patients with VH compared with those without, confirming in part our *a priori* hypotheses. Specifically, GM atrophy was found in the right superior, middle and medial frontal gyri, and in a subcortical cluster comprising the right putamen, caudate nucleus and insula. Interestingly, GM volumes in the putamen and caudate was significantly associated with performance on a visual attention test, as shown by whole brain correlational analyses. Even though no

differences were detected between PD subgroups using whole brain VBM, GM loss in the bilateral caudate nucleus was found when restricting the analyses to predefined ROIs, suggesting an involvement of this structure also in hallucinating PD patients without dementia. Table 4.16 summarises the main findings.

Table 4.16 Summary of the main findings from Experiment 1.

	DLB with VH	PD with VH
Cognitive deficits	Visual attention deficit (digit cancellation test) Correlations with VH: - Visual attention (TMT-A) - Visuoconstruction (Rey figure copy)	Executive dysfunction (FAB) Verbal long-term memory deficit (RAVLT immediate recall)
Cortical atrophy	Right superior, middle and medial frontal gyri (whole brain VBM)	None
Subcortical atrophy	Right putamen, caudate, insula (whole brain VBM) Correlations with visual attention (digit cancellation test): - Right putamen - Caudate bilaterally	Caudate bilaterally (ROI analyses) Correlations with executive functioning (FAB): - Caudate bilaterally Correlations with visual attention (TMT-A): - Left caudate Correlations with VH severity and frequency: - Caudate bilaterally

DLB: dementia with Lewy bodies; FAB: Frontal Assessment Battery; PD: Parkinson's disease; RAVLT: Rey Auditory Verbal Learning Test; ROI: region of interest; TMT-A: Trail Making Test A; VH: visual hallucinations; VBM: voxel-based morphometry.

The present study aimed at testing whether there was an interplay between deficits in visual attention, and visuoperceptive/visuoconstructive abilities in LBD patients with VH, compared to those without. Firstly, hallucinating DLB patients presented with more severe deficits in visual attention, assessed with the digit cancellation test, which remained significant even after accounting for visuoperceptive and visuoconstructive abilities, investigated using the VOSP silhouettes subtest, and the copy of the Rey figure, respectively. Moreover, as shown by a logistic regression model, performance on the digit cancellation test was the only significant predictor of the presence of VH. DLB patients with VH also presented a marginally significant difference in the TMT-A,

which disappeared when visual perception deficits were controlled for. However, a relatively high number of missing data was reported for the TMT-A (3 DLB VH and 3 DLB NVH), suggesting that some patients may have encountered difficulties in completing the task. This might have an impact on the results, which refer only to a subsample of patients that was able to complete the test. Studies have reported attention deficits in patients with both DLB and PD with VH (Cagnin et al., 2013, Hepp et al., 2013). The present study adds additional insight about the interaction between attention and visual perception deficits in hallucinating patients. Specifically, the attention deficits shown by hallucinating DLB patients do not seem to rely on disrupted visual perception. Neuropsychological investigations reported evidence of deficits in visual perception in hallucinating patients with LB dementia (Mori et al., 2000, Mosimann et al., 2004), and PD (Barnes et al., 2003, Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a). In this study, however, we found no changes in visuoperceptive and visuoconstructive abilities in DLB and PD patients with VH. In spite of this, a non-significant trend indicating worst performance in hallucinating DLB was observed in the copy of the Rey figure (displayed in Figure 4.1). Moreover, four patients out of 9 scored 0, as opposed to 1 patients out of 14 in the non-hallucinating group. The small sample size of the present investigation may partially explain this subthreshold result. Moreover, visuoperceptive and visuoconstructive deficits represent disease-specific symptoms of DLB (Collerton et al., 2003), regardless of the presence of VH. Therefore, it may be that differences between VH and NVH patients in these cognitive functions may be subtle, due to the pronounced deficits presented also by non-hallucinating patients. We also found significant correlations between indices of VH and visual attention (TMT-A) and visuoconstructive performance (Rey figure copy). In this context, visual perception deficits, in conjunction with visual attention impairments, may be both necessary to generate VH, as proposed by Collerton et al. (2005).

In contrast, PD patients with and without VH presented comparable performance in both attention and visuoconstruction. These contrasting results may be due, at least in part, to some differences in the neuropsychological tests used to assess attention and visual perception/construction abilities in the two conditions. In fact, the digit cancellation test and the VOSP subtests were administered only in DLB, while the TMT-A and the Rey figure copy in both DLB and PD. None of these tests were specifically designed to evaluate the cognitive correlates of VH in neurodegeneration, but cognition in general. Thus, some neuropsychological tests may be more sensitive than others in detecting such differences, which may be more subtle in LBD patients

without dementia. Even though not surviving correction for multiple comparisons, exploratory analyses on other cognitive tests revealed more severe executive dysfunction and verbal memory deficits in PD with VH, in line with previous research (Hepp et al., 2013, Ramirez-Ruiz et al., 2006, Wang et al., 2010). Studies argued that memory deficits, in combination with executive dysfunctions, might be interpreted as source-monitoring deficiencies, relying on alterations in temporal and frontal areas (Grossi et al., 2005, Ozer et al., 2007). Accordingly, Barnes et al. (2003) found that PD patients with VH had more severe deficits in a reality monitoring task, specifically in source identification.

The cognitive mechanisms underlying VH might be slightly different between DLB and PD, especially concerning top-down control mechanisms. They may be more related to attention deficits in DLB, and executive dysfunctions in PD without dementia. This might be independent of VH severity and frequency, which we found to be comparable between the two diseases. Notably, a higher index of neuropsychiatric symptoms, different from VH, was observed in both PD and DLB patients with VH, compared to corresponding patients without VH, although differences were significant only for the PD cohort. Higher rates of neuropsychiatric symptoms may be linked to the greater executive dysfunctions observed in PD with hallucinations. In support of this view, a recent systematic review reported more severe executive deficits in PD patients with neuropsychiatric symptoms, including depression, apathy, impulse control disorders, and psychosis (Alzahrani and Venneri, 2015). Nevertheless, the present experiment showed significantly lower scores in the FAB in PD with VH patients even after controlling for neuropsychiatric symptoms. Executive deficits have been previously associated with VH in PD without dementia by using different neuropsychological tests, such as phonemic, Stroop test, FAB, and go/no-go test (Barnes and Boubert, 2008, Grossi et al., 2005, Imamura et al., 2008, Manganelli et al., 2009, Santangelo et al., 2007). On the other hand, a notable lack of studies investigating this cognitive aspect concerns DLB. Even from the present investigation, it is difficult to infer whether a substantial executive dysfunction is present also in DLB with VH. In fact, the FAB, resulted significantly different between PD subgroups, was not available for the DLB group. Despite this, phonemic fluency, a measure of cognitive flexibility, was marginally significant in PD, but not DLB. Therefore, these findings suggest that executive dysfunction may be more characteristic of PD with VH, rather than DLB. Executive functioning comprises different cognitive abilities, among which response inhibition, working memory, cognitive flexibility, and interference control, which is closely linked to selective attention (Diamond, 2013). Executive dysfunction is

typically observed in PD, regardless of the presence of dementia, and it has been shown to worsen as the disease progresses (Dirnberger and Jahanshahi, 2013, Goldman et al., 2018). Further research is needed to understand better whether there are specific executive domains, and/or top-down attention mechanisms selectively impaired in hallucinating LBD patients with and without dementia. In this context, future studies would be very informative if including a sample of PDD patients, but also VH/NVH subgroups matched for other neuropsychiatric features. This would clarify whether the executive dysfunctions observed are related to the occurrence of VH, or represent disorder-specific features (PD vs. DLB), maybe exacerbated by the presence of comorbid neuropsychiatric symptoms. A further development of the present study may be the use of factor analysis to combine the original neuropsychological measures into factors, thus grouping interrelated measures, which would reduce the dimensionality of the data set (Nagahama et al., 2010, Santos et al., 2015).

Another possible explanation for the presence of differential cognitive deficits between the two disorders may lie in the phenomenology of VH. In fact, they tend to be more complex and severe in patients with dementia, and false sensation of presence are also common in PD (Onofrj et al., 2013). However, the phenomenology of VH could not be studied in this experiment due to the limitations related to the NPI, which is not specific for the assessment of VH in LBD.

In the present study, DLB patients with VH presented higher rates of RBD than those without. Only one hallucinating patient with PD, however, presented this disorder. RBD is a parasomnia frequently observed in α-synucleinopathies, including both PD and DLB, and often precedes the onset of dementia or motor symptoms of many years (McKeith et al., 2005, Ferini-Strambi et al., 2014). It has been suggested that hallucinations might be REM sleep related intrusions into wakefulness, even though there is currently insufficient evidence to support this view (Diederich et al., 2005, Waters et al., 2016). Moreover, DLB patients with VH had lower scores on the MMSE, although not significant, than patients without VH. In this context, poorer performance in tests assessing specific cognitive functions might drive the more severe global cognitive impairment observed in patients with VH. In LBD, the very close relationship between VH and the presence of dementia complicates the investigation of specific cognitive impairments underlying hallucinations. Within this framework, DLB patients with VH may represent more severe phenotypes of the disease, which may also explain the presence of higher rates of neuropsychiatric symptoms, RBD, as well as

more severe global cognitive impairment, which may be driven by more severe attention deficits.

Although VH have been historically related to the use of levodopa in PD, these symptoms have been shown to occur also in unmedicated patients, confirming that VH are an intrinsic feature of PD (Ffytche et al., 2017, Onofrj et al., 2013). However, the relationship between the use of dopaminergic treatment and development of VH is still not clear, with some studies reporting that LED increases the risk of developing these symptoms, but not others (Ffytche et al., 2017, Onofrj et al., 2013). However, in the present study, there was no significant difference in LED between patients with and without VH in PD, and only three DLB patients, two with VH and one without, were taking dopaminergic drugs at the time of the assessment, thus suggesting that the results may not be affected by the use of medications in the present cohorts.

DLB patients with and without VH presented GM volumetric differences in three big clusters located in the right hemisphere, specifically in the superior/middle and medial frontal gyri, and subcortical areas, including the putamen, caudate nucleus and insula. All clusters survived a cluster-level threshold of $p<0.05$ corrected for multiple comparisons. Similarly, Sanchez-Castaneda et al. (2010) found GM loss in frontal areas in hallucinating patients with both DLB and PDD, which was strongly associated with VH severity in the DLB group. Superior frontal areas have been found to be involved in both spatial and object-based attention (Corbetta and Shulman, 2002, Serences et al., 2004), which may explain the involvement of frontal regions in the development of VH in DLB. Notably, we found areas of frontal grey matter loss lateralised to the right hemisphere. Although both hemispheres have been found to control the orienting of spatial attention to the contralateral space, a right hemisphere dominance has been reported by both clinical and imaging studies (Nobre and Mesulam, 2014), which might account for the right lateralised frontal GM loss reported in DLB patients with VH. In contrast, frontal GM atrophy has not been consistently reported in hallucinating PD patients without dementia. Nevertheless, higher LB density in frontal areas, especially in the middle frontal gyrus, has been associated with VH in autopsy confirmed PD patients (Gallagher et al., 2011, Papapetropoulos et al., 2006). These findings suggest that frontal LB accumulation in hallucinating patients may occur earlier in the progression of PD, which may result in macrostructural alterations and attention deficits only later, mainly in patients with concomitant dementia.

In addition to frontal atrophy, DLB patients with VH also showed GM loss in the striatum, both in the caudate and putamen. Due to the involvement of the striatum in

attention processes (Nobre and Mesulam, 2014), we propose that its macrostructural alterations may underlie dysfunctional pathophysiological mechanisms resulting in attention impairments, and ultimately VH. Interestingly, our whole brain correlation analyses showed an association between volumes in these regions and scores in a visual attention test (digit cancellation), further corroborating this hypothesis. No significant results were detected between PD patients with and without VH using whole brain VBM. However, when restricting the analyses to predefined ROIs, we observed GM loss in subcortical nuclei, especially in the caudate. In turn, regional volumes in the left and right caudate significantly correlated with executive dysfunction, attention deficits, and VH severity. Disrupted fronto-striatal circuits are among the mechanisms believed to underlie the executive dysfunction typical of PD (Kehagia et al., 2010, Lewis et al., 2003). Thus, striatal atrophy observed in our cohort of PD patients may represent a macrostructural hallmark of dysfunctional brain mechanisms ultimately resulting in executive and attention deficits, as well as VH.

Contrary to our hypothesis, no pulvinar GM abnormalities were detected in association with VH, neither in PD, nor in DLB, suggesting that the attention deficits observed in DLB may rely more on other structures of a large-scale attention network, namely frontal and striatal areas. No significant differences were found not even in occipito-temporal regions, in contrast with other previous studies in PD with VH (Bejr-Kasem et al., 2019, Ramirez-Ruiz et al., 2007b). Reduced glucose metabolism/cerebral blood flow have been previously detected in occipito-temporal, occipital, and parietal regions in hallucinating LBD patients (Boecker et al., 2007, Gasca-Salas et al., 2016, Heitz et al., 2015, Pasquier et al., 2002). Therefore, it may be that occipito-temporal and parietal hypometabolism represent a functional hallmark of impaired visual processes underpinning VH, which may not necessarily result in GM atrophy.

The subcortical cluster resulted from the VBM analysis also included a sub-peak in the right insula. It has been hypothesised that its involvement in discriminating between internally generated and external information may foster the development of hallucinations in schizophrenia (Wylie and Tregellas, 2010). Insular reduced GM volume has also been associated with hallucinations in other conditions, such as bipolar disorder (Neves Mde et al., 2016) and AD (Blanc et al., 2014). The insula, along with the anterior cingulate cortex, represent central hubs of the salience network, involved in generating appropriate behaviour to salient stimuli by detecting and integrating internal and external events (Menon, 2011, Menon and Uddin, 2010). These structures are also central in the model for VH proposed by Shine et al. (2014b),

as part of the VAN, for the modulation and coordination of the activity between the DAN and the DMN. Therefore, the GM loss that we observed in the insula may underlie disrupted functional networks fostering the development of VH.

The present study also provided evidence of macrostructural WM alterations in hallucinating DLB patients, mainly detected in the genu of the corpus callosum. As the corpus callosum interconnects corresponding cortical regions, such as the prefrontal and orbitofrontal cortices, it is implicated in different cognitive, sensory and motor functions (Catani and Thiebaut de Schotten, 2008). Thus, in addition to GM abnormalities, corpus callosum alterations may partially contribute to the cognitive deficits outlined above.

A number of limitations should be taken into account when interpreting the results of the present study. Firstly, the sample size was reasonably small. Future studies with larger sample sizes may elucidate further the role of specific cognitive functions and GM abnormalities linked to VH in LBD. Moreover, some clinical and neuropsychological data were not available, due to the retrospective nature of the study. Thus, analyses on cognitive measures included slightly different sample sizes, depending on the variables taken into account. Furthermore, cognitive results obtained for the DLB and PD groups were not fully comparable, due to slight differences in the neuropsychological testing. The tests used were not specifically designed to assess cognitive deficits related to VH. However, these tests are widely used in clinical settings, suggesting that the results from the present study may be, in the future, more easily transferable to clinical practice. Another limitation concerns the NPI as a tool to evaluate VH, which is not specific for the assessment of VH in LBD.

To our knowledge, this is the first whole brain VBM study investigating grey and white matter volumes, and cognitive impairments associated with VH in LBD that included samples of patients with and without dementia, namely DLB and PD, in comparison with corresponding non-hallucinating patients. VBM, as a whole brain automated technique, is very sensitive to the detection of volumetric differences of grey and white matter. The opportunity to assess the whole brain for detecting regional volume changes represents an advantage of VBM over other ROI approaches. Furthermore, VBM, as an objective technique, allows the reduction of biases linked to manual tracing techniques. Moreover, we only reported results significant at a cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons, which decreases the probability of type I error. Other brain properties may be explored while studying the structural brain features associated with VH, allowing the investigation of other aspects of brain morphology, such as the quantification of its cortical thickness. The

use of VBM, however, allows the investigation of the whole brain, including regional GM differences in subcortical structures, which was one of the aims of the present study. Future studies may combine whole brain VBM and cortical thickness analyses to investigate different brain morphometric features in the same sample of patients.
In conclusion, findings from the present study suggest that frontal and striatal areas may contribute significantly to the emergence of VH in DLB, which may be fostered by the more severe attention deficits. In PD without dementia, instead, striatal GM loss and executive dysfunction appeared to play a predominant role.

4.2 Experiment 2: Functional connectivity of visual hallucinations in dementia with Lewy bodies

4.2.1 Introduction

Complex behaviour has been increasingly conceptualised as resulting from the coordinated activity of distinct brain areas, often spatially remote, but interconnected (Nobre and Mesulam, 2014, Rosazza et al., 2012). The functional connectivity of brain regions relies on the temporal coherence of their neural activity (Rosazza et al., 2012, Sporns, 2013). Studies have demonstrated a significant overlap between functional connectivity and underlying structural projections, although many other functional networks are connected by indirect pathways with intermediate stops (Sporns, 2013). The intrinsic functional connectivity between brain regions can be investigated using a variety of techniques, including resting-state fMRI. Among the most used approaches available there are seed-based and network-based analyses. The first one allows the investigation of functional connectivity of pre-defined ROIs and other voxels throughout the whole brain, and it is usually used to explore *a priori* hypotheses regarding dysfunctional connections of specific brain regions (Tahmasian et al., 2015). It is performed by correlating the averaged signal time courses of a specific region with all other brain voxels (Rosazza et al., 2012). On the other hand, a network-based approach refers to the study of intrinsic functional networks, and the most common method is represented by ICA (Tahmasian et al., 2015). ICA allows the identification of independent components of BOLD signal reflecting neural networks (Calhoun et al., 2001, Rosazza et al., 2012, Tahmasian et al., 2015). Specifically, ICA is a technique that identifies statistically independent spatial maps of brain regions and associated time courses (Beckmann et al., 2005, Rosazza et al., 2012). Several

studies have consistently reported the identification of independent resting networks across individuals, scanning sessions, and research centres (Damoiseaux et al., 2006, Kalcher et al., 2012, Sporns, 2013).

Even though it has been proposed that VH generate from a disrupted organisation of functional brain networks (Shine et al., 2014a, Shine et al., 2011), there is still insufficient evidence fully corroborating this hypothesis. As for other imaging modalities, resting-state studies of VH have been performed mainly in PD, and less in LB dementia. In a multimodal neuroimaging study, Franciotti et al. (2015) focused on the role of the DMN in explaining the occurrence of VH in PD. They tested the hypothesis proposed by previous theoretical articles based on the intrusion of self-referential images into misperceptions due to a dysfunctional DMN (Muller et al., 2014, Onofrj et al., 2013, Shine et al., 2014b). ICA analysis revealed increased connectivity in VH patients compared with those without between the superior frontal sulcus bilaterally and parietal regions, and also between contralateral parietal regions. The authors also examined the fractional amplitude of low-frequency fluctuation on DMN centred ROIs, showing higher spectral power in fronto-parietal areas (Franciotti et al., 2015). Consistently, in another study, Yao et al. (2014) reported increased activity in hallucinating PD patients within the DMN, specifically in fronto-parietal regions. Interestingly, in both studies, patients with and without VH had reduced connectivity when compared with control subjects (Franciotti et al., 2015, Yao et al., 2014), suggesting that increased functional connectivity observed in VH patients, compared with non-hallucinating ones, may reflect dysfunctional compensatory mechanisms that, in turn, may foster the development of VH. These findings have also been confirmed by a recent seed-based resting-state fMRI study on minor hallucinations in PD (Bejr-Kasem et al., 2019). The authors focused on the posterior cingulate, a central hub of the DMN, showing increased connectivity between this region and temporal and parietal areas. In another study, Yao et al. (2016) investigated the connectivity of the hippocampus, showing increased connectivity with fronto-parietal areas, and decreased connectivity with occipito-temporal regions.

Generally, the most consistent finding is represented by increased connectivity of DMN-related regions in hallucinating patients with PD, especially with frontal and parietal areas. However, due to the limited amount of investigations available, the overall picture of the brain functional connectivity related to VH is not clear. In addition, no study so far has undertaken a group-comparison between hallucinating and non-hallucinating patients in DLB, showing a literature gap that needs to be tackled. In fact, to our knowledge, the few resting-state fMRI studies including a sample of DLB

patients with VH carried out correlational analyses with VH indices only (Chabran et al., 2018, Peraza et al., 2014, Peraza et al., 2015b). As the primary aim was not related to VH, a clear lack of *a priori* hypotheses on the mechanisms underlying these symptoms appeared from these studies (Chabran et al., 2018, Peraza et al., 2014, Peraza et al., 2015b).

Aims and hypotheses

To date, evidence showing if and how resting-state networks are altered in LBD patients with VH is limited, and the few studies available focused mainly on PD without dementia. Therefore, the aim of the present experiment was to explore brain functional connectivity in DLB patients with VH in comparison with a matched sample of non-hallucinating DLB patients. In order to achieve this, two different approaches were adopted to conduct the analysis.

Firstly, we undertook seed-based analyses to investigate the functional connectivity of ROIs consistent with the hypothesis of an involvement of fronto-parietal and subcortical regions, underlying attention deficits, and occipital/occipito-temporal areas, leading to impaired visual perception. Specifically, we looked at the functional connectivity of the following ROIs: left and right pulvinar, caudate nucleus, putamen, frontal eye field, superior parietal lobule, primary visual cortex, secondary visual cortex, visual associative cortex, inferior temporal area, and occipitotemporal area. As outlined in section 4.1.2.5.4, the choice of these ROIs was based on their involvement in attention and visual processes.

Then, we performed ICA analysis to identify intrinsic resting-state functional brain networks, and whether they differed between VH and NVH patients in DLB. We aimed to investigate the functional connectivity of the DMN, lateralised fronto-parietal components and visual cortical areas (Beckmann et al., 2005, Menon, 2011, Rosazza and Minati, 2011).

4.2.2 Methods

4.2.2.1 Participants

The present experiment consisted of a subgroup of DLB patients of the VBM study reported previously in the present chapter (for a detailed description of the sample see section 4.1.2). From the whole DLB sample, resting-state fMRI scans were excluded for 5 patients (4 with VH and 1 without) due to poor quality of the images, specifically movement and signal artefacts. Final resting-state analysis involved 23

DLB patients, 7 with VH (mean age: 75.29, SD: 5.09; 2 males and 5 females) and 16 without VH (mean age: 73.50, SD: 6.65; 9 males and 7 females).

A detailed description of the clinical and neuropsychological assessment can be found in sections 4.1.2.2 and 4.1.2.3 of the present chapter. The neuropsychological tests taken into account were as follows: digit cancellation, TMT-A, digit span forward and backward, prose memory immediate and delayed recall, phonemic fluency, clock drawing, Rey figure copy and delayed recall, all VOSP subtests. Differences between groups were assessed using independent sample t-test and Mann-Whitney U test for normally and non-normally distributed numerical variables, respectively, and Fisher's Exact Test for categorical variables. Statistical analyses on neuropsychological tests were undertaken for a descriptive purpose of the sub-sample of DLB patients.

4.2.2.2 Resting-state fMRI analysis

4.2.2.2.1 fMRI acquisition

Echo planar T2* weighted MRI images were acquired on a 1.5 Tesla Philips Achieva MRI scanner using the following parameters: repetition time=2.02s, echo delay time=50ms, acquisition time=2.1s, flip angle 90°, voxel dimensions 1.80x1.80x6.00mm, field of view 220 mm. Images were acquired in a single run including 250 volumes, with interleaved slice acquisition (21 axial slices per volume).

4.2.2.2.2 Resting-state fMRI pre-processing

Firstly, all images were visually inspected to rule out excessive movement and signal artefacts. Following this, 5 out of 28 scans of DLB patients were excluded from the analyses due to susceptibility artefacts observed in the frontal lobe.

Resting-state fMRI pre-processing and statistical analyses were undertaken using SPM 12 running on MATLAB R2014a, version 8.3. Pre-processing steps included slice timing, realignment to account for head movement, smoothing and normalisation to the same stereotactic space. First, all scans were slice-timed by using a middle slice as reference (consistent between subjects). This step was undertaken to homogenise the different time points at which each slice was acquired within the repetition time. Then, all images were realigned in space by registering them to the mean of all images in order to account for spatial displacement between volumes. Within this step, the 4th Degree B-Spline Interpolation option was used. Linear and rotational parameters of head motion were estimated, plotted and inspected to identify excessive head motion (exceeding 1.5mm and 3° for linear and rotational movement

respectively). The following step consisted in normalising the images to the SPM echo-planar template in the MNI space. Voxel size was also re-dimensioned to 2.0x2.0x2.0mm. The REST (Resting-State fMRI Data Analysis Toolkit) toolbox (www.restfmri.net) was used to apply a band-pass temporal filter (Song et al., 2011). Low and high-pass filters were applied to 0.008 and 0.1 Hz respectively. Finally, filtered volumes were smoothed with a full-width at half maximum isotropic Gaussian kernel of 6mm to maximise the signal-to-noise ratio.

Functional connectivity refers to spatial patterns of temporally coherent low-frequency (<0.1 Hz) fluctuations in the BOLD signal of distinct brain areas, and it is commonly explored using seed-based and independent component analyses (Kalcher et al., 2012, Rosazza et al., 2012). For the purpose of this study, slice-timed, realigned, normalised, filtered and smoothed images were used for both types of functional connectivity analysis.

4.2.2.2.3 Seed-based analyses

Seed-based analyses were undertaken in order to explore the functional connectivity of ROIs based on our *a priori* hypotheses. The ROIs were the following: left and right pulvinar, lateral geniculate body, caudate nucleus, putamen, frontal eye field (BA 8), superior parietal lobule (BA 7), primary visual cortex (BA 17), secondary visual cortex (BA 18), visual associative cortex (BA 19), inferior temporal area (BA 20), occipitotemporal area (BA 37). These areas were chosen as involved in attention and visuoperceptive abilities. In addition, the left and right hippocampus and primary motor cortex were chosen as control regions. Two masks based on the WM and CSF maps were also created. All seed regions were identified using the Brodmann Area atlas based on the Talairach Daemon database (Lancaster et al., 1997, Lancaster et al., 2000) within the WFU PickAtlas toolbox, version 3.0.5 (Maldjian et al., 2004, Maldjian et al., 2003). Then, the MarsBar toolbox for SPM (http://marsbar.sourceforge.net) was used to extract signal time-courses of all seeds for each subject. First and second level seed-based analyses were performed with SPM 12. First, individual maps of seed-based connectivity were computed accounting for the signal extracted from WM and CSF maps and movement vectors (created in the realignment pre-processing step).

Subsequently, second-level analyses were carried out in order to identify differences between groups for each seed-based connectivity, controlling for TIV and age. TIV was preferred over other global measures as it has been found to reflect total premorbid brain size/volume in neurodegenerative conditions, and might be a

confounding factor in volumetric and structural connectivity analyses (Edland et al., 2002, Malone et al., 2015). In these analyses, TIV was used for consistency across experiments throughout this thesis. An uncorrected threshold of $p<0.001$ was set to display significant results. Only peaks surviving a cluster-level threshold of $p<0.05$ FWE corrected for multiple comparisons were reported in the results section. In addition, in order to account for the number of ROIs considered, significant results (cluster-level corrected) were also explored using an uncorrected threshold of $p<0.000038$ at the set-level.

Labels of brain regions were identified as previously described (section 4.1.2.5.3), using the GingerALE and Talairach Client software. In case of uncertain identification of coordinates labels, some peaks and sub-peaks were further checked manually on the 1988 Talairach atlas (Talairach and Tournoux, 1988).

4.2.2.2.4 Independent component analysis

Functional networks of brain regions were identified by means of ICA. Slice-timed, realigned, normalised, filtered and smoothed images were used for first-level ICA, performed with the GIFT toolbox (v1.3i; mialab.mrn.org/software/gift). The Infomax algorithm was used and the number of components set at 20. Following visual inspection of all estimated components, six were identified as functional brain networks, specifically the salience, occipital, sensory-motor, cerebellar, DMN and fronto-parietal networks. Three-dimensional maps of z scores for each network were extracted for each subject and used for inferential models, aiming at investigating between-group differences. Second-level modelling and statistical analyses for each component were performed with SPM12 and followed the same methodology described for seed-based analyses (section 4.2.2.2.3).

4.2.3 Results

4.2.3.1 Demographic, clinical and neuropsychological features

Results on demographic, clinical and neuropsychological features are reported in Table 4.17 and Table 4.18. Briefly, patients with and without VH did not differ for all demographic, clinical and neuropsychological characteristics, a part from NPI total score ($p=0.01$) and presence of RBD, which was marginally significant ($p=0.05$).

Table 4.17 Demographic and clinical characteristics for DLB patients with and without VH (subsample for resting-state fMRI analysis). Mean and SD are reported for each variable unless otherwise specified.

Characteristic	DLB VH (n=7)	DLB NVH (n=16)	p value
Age	75.29 (5.09)	73.50 (6.65)	0.54 [a]
Gender M:F	2:5	9:7	0.37 [b]
Years of education	6.00 (3.11)	8.19 (5.00)	0.39 [c]
Disease duration (years)	2.57 (1.40)	2.13 (1.31)	0.42 [c]
MMSE	22.71 (3.20)	24.81 (3.53)	0.19 [a]
UPDRS III	5.57 (11.80)	4.75 (6.07)	0.46 [c]
RBD [d]	100%	44%	0.05 [b]
Cognitive fluctuation	57%	88%	0.14 [b]
NPI total score	17.71 (9.39)	5.50 (3.83)	0.01 [c]
NPI tot - NPI^{hall} [e]	12.71 (10.52)	5.50 (3.83)	0.15 [c]

DLB: dementia with Lewy bodies; F: female; M: male; MMSE: Mini-Mental State Examination; NPI: neuropsychiatric inventory; NVH: no VH; RBD: REM sleep behaviour disorder; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; VH: visual hallucinations. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Independent-sample Mann-Whitney U test; [d] Missing data for a VH patient; [e] NPI total score minus NPI hallucinations.

4.2.3.2 Seed-based analysis

Seed based analyses yielded regions of significantly decreased and increased connectivity in DLB VH patients as opposed to patients without hallucinations (Table 4.19, Figure 4.8 and Figure 4.9). In particular, the seed located in the left geniculate nucleus showed decreased connectivity with the left anterior cingulate gyrus, and increased with the left fusiform gyrus. The left visual associative cortex also presented regions of decreased (with the right anterior cingulate), and increased (with the left precuneus) connectivity. Differences in the functional connectivity of other seeds were also found, decreased (left and right superior parietal lobule with the right anterior cingulate), and increased (right putamen and left primary visual cortex with the right cingulate gyrus).

Using a set-level uncorrected threshold of $p<0.000038$, findings that survived cluster-level correction for multiple comparisons ($p<0.05$) represented increased functional connectivity in DLB with VH between 1) left geniculate nucleus with the left fusiform gyrus (MNI coordinates: x=-38, y=-60, z=-12; cluster size: k=31 voxels; T score: 7.89; Z score: 5.19; p=0.005); 2) left visual associative cortex with the left precuneus (MNI coordinates: x=-28, y=-62, z=38; cluster size: k=24 voxels; T score: 7.29; Z score: 4.98; p=0.016); 3) right putamen with the right cingulate gyrus (MNI coordinates: x=14, y=-42, z=38; cluster size: k=21 voxels; T score: 6.21; Z score: 4.54; p=0.026).

Table 4.18 Differences in neuropsychological tests between DLB patients with and without VH (subsample for resting-state fMRI analysis).

Test	DLB VH			DLB NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit cancellation	6	27.33 (6.65)	26.50 (13.0)	15	34.20 (9.92)	36.0 (15.0)	0.14 [a]
TMT-A (s)	6	166.8 (74.3)	139.50 (148)	13	128.0 (74.10)	101.0 (65.0)	0.13 [b]
Digit span:							
Forward	6	4.17 (0.98)	4.0 (0.75)	15	4.80 (1.08)	5.00 (2.0)	0.24 [b]
Backward	6	2.33 (0.52)	2.0 (1.0)	15	2.87 (1.19)	3.00 (2.0)	0.21 [b]
Prose memory:							
Immediate	7	6.29 (2.21)	6.0 (4.0)	16	6.94 (3.91)	6.00 (3.0)	0.97 [b]
Delayed	7	6.71 (3.95)	7.0 (3.0)	16	7.50 (4.87)	7.00 (6.0)	0.77 [b]
Phonemic fluency	6	17.17 (12.0)	11.5 (18.5)	13	16.62 (11.92)	11.00 (21.5)	0.70 [b]
Clock drawing	6	5.17 (2.86)	4.0 (4.25)	16	4.66 (3.52)	5.75 (6.38)	0.76 [a]
Rey figure Copy	6	12.75 (15.2)	7.25 (28.5)	13	20.19 (11.14)	22.0 (19.75)	0.32 [b]
Rey figure Delayed	6	2.58 (3.69)	1.50 (4.63)	13	7.27 (5.52)	7.00 (9.75)	0.09 [b]
VOSP:							
Screening test	7	18.29 (2.63)	20.0 (5.0)	15	19.33 (0.72)	19.00 (1.0)	0.95 [b]
Incomplete letters	7	8.57 (6.48)	8.0 (11.0)	15	12.20 (7.54)	15.00 (13.0)	0.30 [b]
Silhouettes	7	8.29 (6.24)	9.0 (11.0)	15	12.33 (3.87)	13.00 (6.0)	0.08 [a]
Object decision	7	7.29 (5.71)	9.00 (12.00)	14	11.14 (3.96)	12.00 (6.25)	0.09 [a]
Progressive silhouettes	7	8.29 (6.50)	8.00 (14.00)	14	11.36 (3.88)	11.00 (3.50)	0.19 [a]
Dot counting	7	9.43 (0.79)	10.00 (1.00)	15	9.40 (1.55)	10.00 (1.00)	0.58 [b]
Position discrimination	7	15.43 (7.04)	19.00 (4.00)	15	17.27 (3.73)	19.00 (8.00)	0.41 [b]
Number location	7	6.14 (4.67)	7.00 (8.00)	15	6.07 (2.55)	7.00 (4.00)	0.97 [a]
Cube analysis	7	4.57 (3.10)	5.00 (5.00)	15	5.53 (3.29)	5.00 (6.00)	0.52 [a]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no VH; s: seconds; SD: standard deviation; TMT-A: Trail Making Test A; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test, [b] Mann-Whitney U test.

4.2.3.3 Independent component analysis

From the 20 components estimated by the ICA, six were identified as functional brain networks, namely the salience, occipital, sensory-motor, cerebellar, DMN and fronto-parietal networks. Only the statistical analysis on the DMN yielded regions of significant decreased and increased functional connectivity. The DMN was identified as showing BOLD signal in the following regions: posterior cingulate, inferior parietal

lobule, lateral middle temporal areas, precuneus, medial prefrontal cortex and midline cerebellar areas (Buckner et al., 2008, Habas et al., 2009, Utevsky et al., 2014). Patients with VH showed a cluster of decreased connectivity with the DMN, which was located in the left insula. Increased connectivity was found with parietal regions, namely the left inferior parietal lobule and supramarginal gyrus (Table 4.20 and Figure 4.10).

Table 4.19 Regions of decreased and increased functional connectivity in DLB patients with VH compared to those without resulted from seed-based analyses (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
DLB VH < DLB NVH								
Left lateral geniculate nucleus seed								
Anterior cingulate gyrus (BA 32)	L	175	-6	52	0	5.15	4.03	0.001
Medial frontal gyrus (BA 10)	L		-4	46	-18	4.41	3.61	
Anterior cingulate (BA 32)	L		-6	44	-4	4.28	3.54	
Left superior parietal lobule (BA 7) seed								
Cingulate gyrus (BA 32)	R	89	18	32	24	4.82	3.85	0.051
Anterior cingulate (BA 32)	R		22	34	16	4.59	3.72	
Right superior parietal lobule (BA 7) seed								
Anterior cingulate (BA 32)	R	110	16	30	22	5.52	4.21	0.021
Left visual associative cortex (BA 19) seed								
Anterior cingulate (BA 24)	R	150	6	28	-12	4.92	3.90	0.005
Lentiform nucleus (putamen)	R		24	22	0	4.47	3.65	
DLB VH > DLB NVH								
Left lateral geniculate nucleus seed								
Fusiform gyrus (BA 37)	L	91	-38	-60	-12	7.89	5.19	0.04
Declive (cerebellar vermis)	L		-30	-70	-12	4.43	3.63	
Right putamen seed								
Cingulate gyrus (BA 31)	R	249	14	-42	38	6.21	4.54	<0.001
Cingulate gyrus (BA 31)	R		26	-42	40	5.75	4.33	
Left primary visual cortex (BA 17) seed								
Cingulate gyrus (BA 32)	R	89	10	32	24	5.62	4.26	0.039
Anterior cingulate (BA 24)	R		8	24	18	5.09	3.99	
Left visual associative cortex (BA 19) seed								
Precuneus (BA 7)	L	111	-28	-62	38	7.29	4.98	0.048

BA: Brodmann area; DLB: dementia with Lewy bodies; FWE: family-wise error; L: left; NVH: no VH; R: right; TIV: total intracranial volume; VH: visual hallucinations.

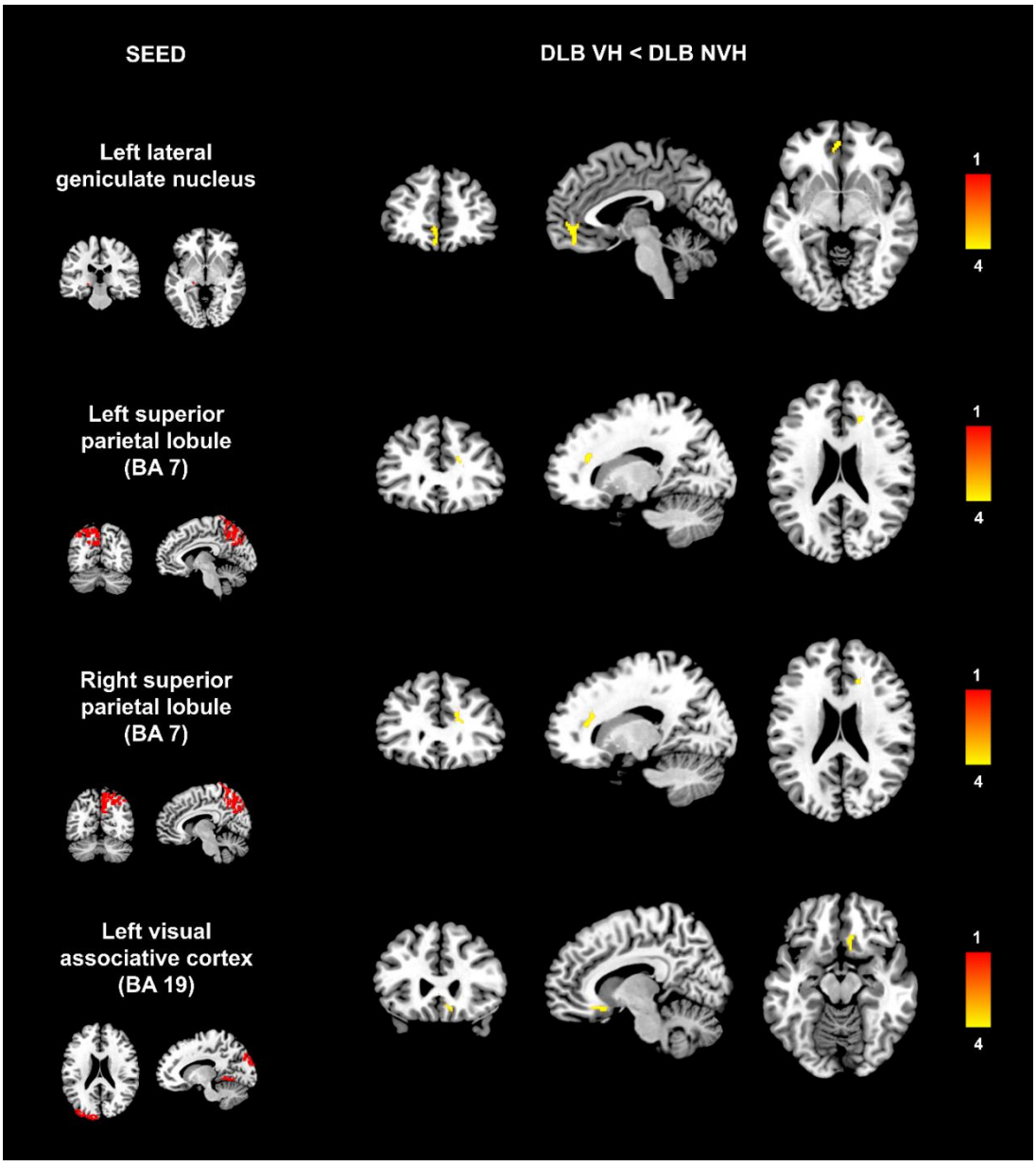

Figure 4.8 Regions of decreased connectivity in DLB patients with VH compared to those without VH that resulted from seed-based analyses. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest.

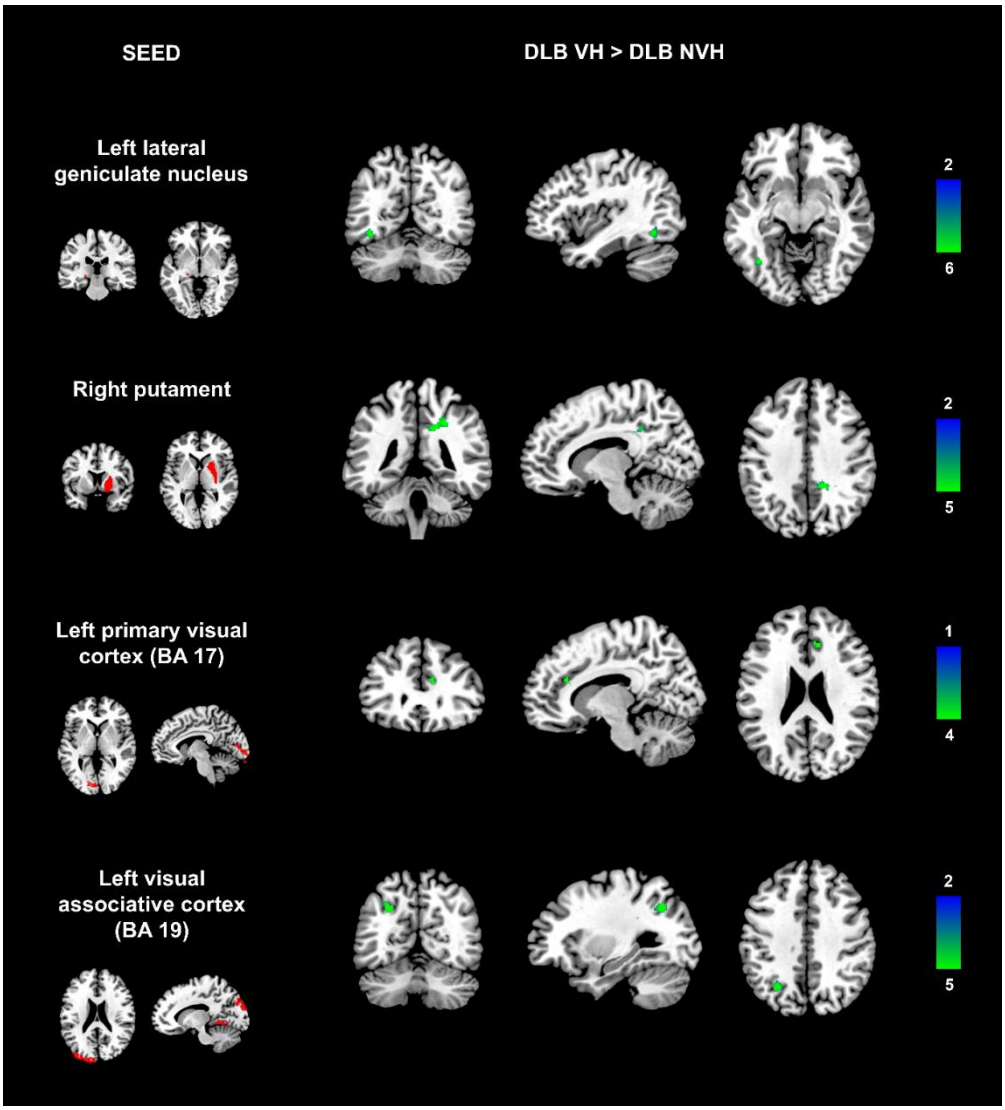

Figure 4.9 Regions of increased connectivity in DLB patients with VH compared to those without VH resulted from seed-based analyses. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest.

Table 4.20 Regions of decreased and increased connectivity of the DMN in DLB patients with VH compared to those without resulted from independent component analysis (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Decreased connectivity								
Insula (BA 13)	L	180	-30	6	20	7.34	5.00	<0.001
Increased connectivity								
Inferior parietal lobule (BA 40)	L	136	-54	-46	44	5.74	4.32	0.003
Inferior parietal lobule (BA 40)	L		-48	-54	48	5.35	4.13	
Supramarginal gyrus (BA 40)	L		-54	-56	42	5.14	4.02	

BA: Brodmann area; DLB: dementia with Lewy bodies; DMN: default mode network; FWE: family-wise error; L: left; TIV: total intracranial volume; VH: visual hallucinations.

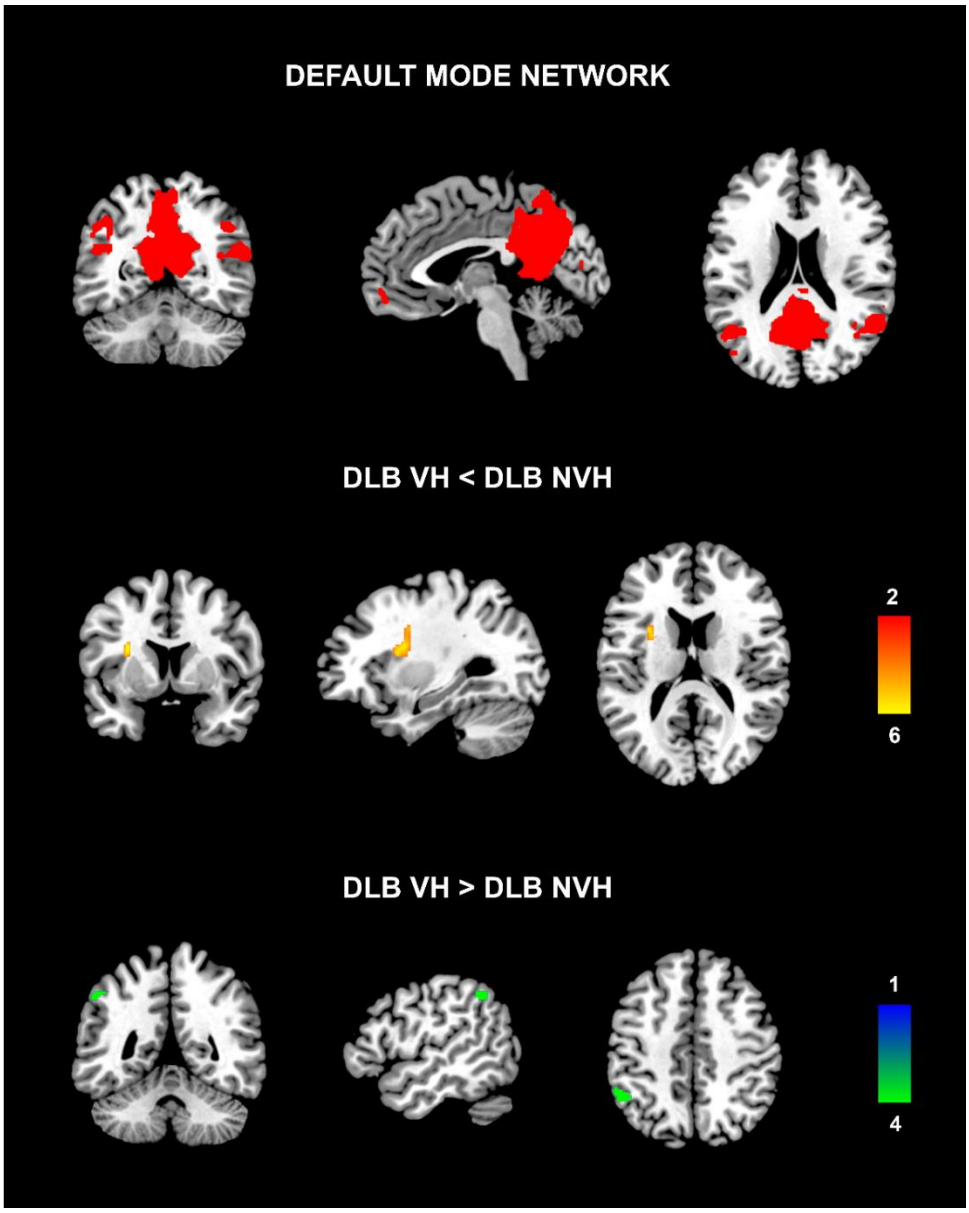

Figure 4.10 Regions of decreased and increased connectivity in DLB patients with VH compared to those without resulted from ICA. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest.

4.2.4 Discussion

The present experiment provides evidence of both increased and decreased functional connectivity in DLB patients with VH, as shown by seed-based and ICA analyses.

Seed-based analyses revealed decreased connectivity in hallucinating DLB patients between visuoperceptive areas (left geniculate nucleus and visual associative cortex) and the anterior cingulate cortex. The same regions also showed increased connectivity with the left fusiform gyrus (lateral geniculate nucleus) and the left

precuneus (visual associative cortex). Moreover, lower connectivity was identified between the bilateral superior parietal lobule and the right anterior cingulate cortex. Finally, significantly increased co-activation was found in hallucinating patients between the right putamen and the left primary visual cortex with the right anterior cingulate.

Notably, all the ROIs taken into account showed decreased connectivity in the DLB VH group in the anterior cingulate, both visual areas (geniculate nucleus and visual associative cortex), and attentional regions (superior parietal lobule). High density of LB pathology has been reported in the anterior cingulate in PD patients with VH, and has been found to differentiate PD patients with and without dementia with high sensitivity and specificity (Gallagher et al., 2011, Kalaitzakis et al., 2009). Moreover, alterations of the cholinergic receptors within the anterior cingulate have been related to VH in DLB (Teaktong et al., 2005). Cholinergic dysfunction has been proposed to foster the development of VH (Diederich et al., 2005), and its treatment has been shown to ameliorate this symptom, as well as attention deficits (Burghaus et al., 2012). This might be linked to the impaired connectivity we found in this region, which may be modulated by cholinergic dysregulation.

The anterior cingulate is a complex region involved in different emotional and top-down cognitive processes, including attention, response inhibition, and goal-directed behaviour (Gasquoine, 2013). Lewis et al. (2012) showed that the neuronal integrity of the anterior cingulate in PD patients was significantly associated with poorer performance on attentional set-shifting and response inhibition tasks, as well as VH, suggesting an important role of this structure in the pathophysiology of these symptoms. We propose that the reduced connectivity that we observed with the geniculate nucleus, visual associative cortex, and superior parietal lobule, along with the increased connectivity with the putamen, might reflect dysfunctional top-down mechanisms of the anterior cingulate over visual and other attention areas. Shine et al. (2011) proposed that VH may be the result of a disrupted engagement of attention networks, specifically an overactivity of the DMN and the VAN, and an impropriate engagement of the DAN. The authors suggested that the VAN coordinates the activity between the other two networks, and it allows the rapid engagement of attention towards salient stimuli (Shine et al., 2011, Shine et al., 2014b). It comprises two major hubs located in the anterior cingulate and the insula. In accordance with this view, it may be that increased connectivity between the anterior cingulate and the primary visual cortex might reflect a dysfunctional overactivity of the VAN. This, along with the altered top-down mechanisms described above, and an increased connectivity

between visual areas (lateral geniculate nucleus and fusiform gyrus), might ultimately result in VH. Thus, an increased co-activation of visuoperceptive areas might reflect dysfunctional compensatory mechanisms in response to impaired visual processing. This speculative interpretation, however, demands further investigation to shed light on the mechanisms behind this pattern of higher and lower functional connectivity. We propose that VH may generate from dysfunctional top-down control mechanisms of the anterior cingulate over visual areas that might foster the generation of false images arising from an increased activity of the DMN. ICA revealed differences between hallucinating and non-hallucinating patients only in the DMN. Specifically, higher connectivity was detected in hallucinating patients with the right inferior parietal lobule, while it was lower with the left insula. The inferior parietal lobule is a core region of the DMN (Buckner et al., 2008, Rosazza et al., 2012). Therefore, an overactivity of this network might reflect excessive self-referential internal processing, that may form the basis for the emergence of false images (Shine et al., 2011). The insula, on the other hand, is a central hub of the VAN, which has been proposed to coordinate the activity of the DMN and the goal-directed DAN network (Shine et al., 2011). The present findings partially contradict the model proposed by Shine and colleagues, according to which hallucinations would develop from the simultaneous overactivity of the VAN and the DMN, together with the inability to recruit appropriately the DAN and impaired visual processing (Shine et al., 2011, Shine et al., 2014b). In an fMRI study, Shine et al. (2015b) reported significantly lower activity during visual misperceptions in the DAN in patients with hallucinations, while it was higher in the VAN and DAN, suggesting an over-reliance on endogenous attention networks. Similarly, in another study, visual misperceptions were associated with higher connectivity within the VAN and the DMN, as well as lower connectivity between the DAN and VAN, and between visual networks and the VAN and the DAN (Shine et al., 2015a). Thus, the lower connectivity between the DMN and the insula reported by the present study appears to be in contrast with these findings. In this context, the role of the VAN in the development of VH and the direction of its impaired functional connectivity in relation to other attention networks require further investigation.

The present experiment presents some limitations linked to features of the sample, as described in section 4.1.4. Moreover, from the original sample of 28 DLB patients, 5 were excluded from the resting-state analyses due to susceptibility artefacts. Excessive head motion was excluded for each subject included in the analyses after estimation and inspection of head motion parameters. Second level analyses were computed accounting for movement vectors, which were obtained in the realignment

pre-processing step. However, no additional motion correction was performed. ICA-based strategies may be performed to account for head motion, such as the ICA-based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA), which has been shown to reduce fMRI motion-induced signal variations (Pruim et al., 2015).
Other weaknesses and advantages are related to the techniques used. ICA can be carried out as exploratory investigation and allows the separation of coherent brain networks and other sources of signal due to, for example, head movement, imaging artefacts and other physiological variables (i.e. cardiac or respiratory activity) (Damoiseaux et al., 2006, Rosazza et al., 2012, Tahmasian et al., 2015). However, it may introduce biases related to the identification of physiological noise and actual cortical networks (Rosazza et al., 2012). On the other hand, seed-based analyses need *a priori* hypotheses on the functional connectivity of specific brain regions, and it is less susceptible to interpretative issues, but the presence of non-neural variables might bias the detection of BOLD fluctuations (Rosazza et al., 2012, Tahmasian et al., 2015).

4.3 Experiment 3: Structural connectivity of visual hallucinations in dementia with Lewy bodies

4.3.1 Introduction

Structural connectivity refers to the anatomical WM projections linking different brain regions, and can be studied *in vivo* by means of DTI, which provides structural maps of WM organisation that have shown consistency with post-mortem investigations (Sporns, 2013, Wakana et al., 2004). DTI has been widely used to map the architecture of WM tracts of the healthy brain, but also to study its microstructural integrity in a wide range of psychiatric and neurological conditions, such as schizophrenia, AD, and also LBD (Burgel et al., 2006, Sporns, 2013, Suri et al., 2014). While disease-specific features have been studied more widely, only a few studies explored WM microstructural alterations related to VH in PD (Firbank et al., 2018, Hepp et al., 2017, Lee et al., 2016, Lee et al., 2017) and DLB (Kantarci et al., 2010). For example, Lee et al. (2016) used an ROI approach to explore WM microstructural integrity along visual pathways, from the optic nerve to the primary visual cortex. They found that hallucinating PD patients had WM alterations in the right optic nerve, and in the left optic radiation compared with non-hallucinating ones. In another study, Hepp et al. (2017) hypothesised that damaged WM tracts connecting the nucleus

basalis of Meynert and the cerebral cortex may be linked to VH in PD, being this nucleus involved in the cholinergic innervation of the cortex. Significantly higher MD was found in parietal and occipital tracts in hallucinating patients compared to non-hallucinating ones (Hepp et al., 2017). Both studies used an ROI approach to investigate WM microstructural changes (Hepp et al., 2017, Lee et al., 2016). As an alternative procedure, TBSS is a fully automated technique based on the estimation of a group mean FA skeleton including sample-specific fibre bundles, and thus it does not require the specification of predefined tracts of interest for group-comparisons (Smith et al., 2006). Only two studies on PD used this technique to investigate WM microstructure linked to the presence of VH, but no differences have been reported when directly comparing hallucinating and non-hallucinating patients (Firbank et al., 2018, Lee et al., 2017).

Only one study explored WM integrity related to VH in DLB using an ROI approach (Kantarci et al., 2010), but no study used a whole brain automated technique. The authors have found increased MD in DLB with VH compared with those without in the ILF (Kantarci et al., 2010), a bundle of associative fibres that connects the occipital and temporal lobes that has been associated with visuoperceptive abilities (Catani and Thiebaut de Schotten, 2008). However, the primary aim of the study was to differentiate DLB and AD patients, and no a priori hypothesis about VH was formulated (Kantarci et al., 2010). Moreover, demographic and clinical features were not reported separately for the two subgroups of DLB patients. Therefore, other unknown variables might have contributed to the results.

Aims and hypotheses

Overall, the integrity of WM microstructure in relation to VH in LBD has been examined by a few studies only. The majority has focused on PD, while evidence on DLB is still lacking. Thus, the aim of the present experiment was to use TBSS to investigate differences between DLB patients with and without VH in WM microstructure, specifically using FA and MD indices.

In line with the hypothesis of an involvement of attention and visual perception deficits in the development of VH, we expected alterations in hallucinating DLB patients in WM tracts sustaining these cognitive functions. In particular, we hypothesised that hallucinating DLB patients would present WM abnormalities in the following tracts: ILF, SFL and IFOF. The ILF is composed of long and short fibres connecting occipital and temporal regions, specifically visual areas with the amygdala and the hippocampus (Catani and Thiebaut de Schotten, 2008). Studies have reported its involvement in a number of functions, including visual perception, face recognition,

visual memory, reading and language-related abilities (Catani and Thiebaut de Schotten, 2008). The SLF is a bundle of association fibres that connects frontal and parietal regions of the attention network (Nobre and Mesulam, 2014). Studies have shown that damaged SLF is related to the occurrence of neglect-related symptoms, highlighting its involvement in spatial and attentional processes (Doricchi et al., 2008). The IFOF is the only direct link between frontal and occipital areas that has been found in humans, specifically connecting the ventral occipital lobe with the orbitofrontal cortex, passing through temporal and parietal areas (Catani and Thiebaut de Schotten, 2008, Doricchi et al., 2008). It has been associated with attention, reading, and visual processing (Catani and Thiebaut de Schotten, 2008, Wu et al., 2016).

4.3.2 Methods

4.3.2.1 Participants

DTI data were only available for a subsample of patients from Experiment 1 of the present chapter (section 4.1), comprising 22 DLB patients, 8 with VH (mean age: 75.50, SD: 5.32; 3 males and 5 females) and 14 without VH (mean age: 74.07, SD: 7.00; 7 males and 7 females). Statistical analyses on demographic, clinical and cognitive measures were performed as described previously (section 4.2.2.1).

4.3.2.2 Diffusion tensor imaging analysis

4.3.2.2.1 Image acquisition

Images were acquired using a 1.5 Tesla Philips Achieva MRI scanner using a protocol consisting of axial diffusion-weighted echo planar images with the following acquisition details: TR=11114ms, TE=80ms, diffusion-encoding gradients b=0 and 800 s/mm^2, directions=32, slices=65-70, acquisition matrix 112x110, reconstructed matrix 128x128, slice thickness=2mm field of view=224mm, acquisition voxel=2x2mm, reconstructed voxel=1.75x1.75x2mm, acquisition time: 12.24 minutes.

4.3.2.2.2 Tract-Based Spatial Statistics and statistical analyses

Pre-processing, TBSS and voxel-wise statistical analysis were undertaken using the FMRIB Software Library v5.0.8 (http://www.fmrib.ox.ac.uk/fsl). Standard TBSS procedure guidelines (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide) were applied (Smith et al., 2006).

Firstly, all images were corrected for eddy current distortions and head movements using the FMRIB's Diffusion Toolbox (FDT). Corrected images were then brain extracted with the Brain Extraction Tool (BET) in order to remove non-brain tissue voxels applying a fractional intensity threshold of 0.5. The FDT was used to fit the diffusion tensor model, and to compute voxel-wise maps of FA and MD. A target image was chosen by aligning each image to every other one and identifying the most representative subject of the sample. Nonlinear registration was then used to align all FA maps to the target image and affine-transformed into MNI space. After this, the resulting FA images were averaged to generate a mean FA image, which was used to create a mean FA skeleton (Smith et al., 2006). The skeleton was thresholded at 0.2 to exclude GM and CSF voxels from subsequent analysis, resulting in a binary skeleton mask (Smith et al., 2006). Each individual FA map was then projected into the skeleton (to maintain only voxels within the identified WM tracts), resulting in one single 4D skeletonised FA image containing all skeletonised FA maps. For MD analysis, the FA images were used to perform the nonlinear registration and skeletonisation stages (including the estimation of the projection vectors). The original nonlinear registration was applied to the MD data, which were merged into a 4D file and projected into the initial FA skeleton.

Voxel-wise between-group comparisons of FA and MD data were undertaken using a permutation-based nonparametric approach (Nichols and Holmes, 2002) by means of the FSL randomise tool, performing 5000 permutations for each model (Smith et al., 2006). Multiple comparisons were taken into account by employing the Threshold-Free Cluster Enhancement (TFCE) correction ($p<0.05$) (Smith and Nichols, 2009), with TIV and age as covariate of no interest. Multiple regression analyses were also carried out to explore the association between FA and MD, and cognitive variables using the same parameters. WM tracts of significant coordinate voxels, in MNI space, were identified using the JHU white-matter tractography and ICBM-DTI-81 white-matter labels atlases, available on FSL (Mori et al., 2008, Hua et al., 2008, Wakana et al., 2007).

4.3.3 Results

4.3.3.1 Demographic, clinical and neuropsychological features

Results obtained from between-group statistical analyses on demographic, clinical and cognitive features are reported in Table 4.21 and Table 4.22. VH patients showed

a higher percentage of RBD and higher NPI total scores. No significant differences were detected in all other variables.

Table 4.21 Demographic and clinical characteristics for DLB patients with and without VH. Mean and SD are reported for each variable unless otherwise specified.

Characteristic	DLB VH (n=8)	DLB NVH (n=14)	p value
Age	75.50 (5.32)	74.07 (7.00)	0.62 [a]
Gender M:F	3:5	7:7	0.68 [b]
Years of education	6.75 (3.58)	8.64 (5.20)	0.46 [c]
Disease duration (years)	2.88 (1.25)	2.14 (1.35)	0.16 [c]
MMSE	23.75 (3.11)	25.57 (3.44)	0.23 [a]
UPDRS III	6.88 (11.18)	3.57 (5.57)	0.70 [c]
RBD [d]	100%	43%	**0.02** [b]
Cognitive fluctuation	75%	86%	0.60 [b]
NPI total score	13.63 (9.13)	5.29 (3.38)	**0.02** [c]
NPI tot - NPI^{hall} [e]	8.75 (8.35)	5.29 (3.38)	0.56 [c]

DLB: dementia with Lewy bodies; F: female; M: male; MMSE: Mini-Mental State Examination; NPI: neuropsychiatric inventory; NVH: no VH; RBD: REM sleep behaviour disorder; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale; VH: visual hallucinations. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Independent-sample Mann-Whitney U test; [d] Missing data for a VH patient; [e] NPI total score minus NPI hallucinations.

4.3.3.2 Tract-Based Spatial Statistics

TBSS analyses yielded significant between-group differences in MD, but not in FA. Specifically, increased MD was found in VH patients WM tracts: bilateral superior longitudinal fasciculus, and inferior fronto-occipital fasciculus, forceps minor and major, right inferior longitudinal fasciculus, and posterior limb of the internal capsule. No significant association was found between FA and MD, and the following neuropsychological tests: digit cancellation, VOSP silhouette, copy of the Rey figure, and also VH severity and frequency. Results are reported in Table 4.23 and Figure 4.11.

Table 4.22 Differences in neuropsychological tests between DLB patients with and without VH (subsample for DTI analysis).

Test	DLB VH			DLB NVH			p value
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
Digit cancellation	7	28.29 (5.77)	27.00 (9.0)	14	35.14 (9.16)	37.50 (14.0)	0.09 [a]
TMT-A (s)	7	174.7 (97.5)	136.0 (159)	12	127.0 (78.6)	96.50 (89.0)	0.12 [b]
Digit span:							
Forward	7	3.57 (1.81)	4.00 (1.00)	14	4.86 (1.10)	5.00 (2.0)	0.06 [a]
Backward	7	2.00 (1.00)	2.00 (1.00)	14	3.00 (0.96)	3.00 (2.0)	0.06 [b]
Prose memory:							
Immediate recall	8	8.25 (5.47)	6.50 (4.00)	14	7.36 (4.03)	6.00 (3.25)	0.75 [b]
Delayed recall	8	9.13 (4.58)	7.50 (7.25)	14	8.14 (5.36)	7.50 (6.0)	0.67 [a]
Phonemic fluency	7	15.43 (12.65)	12.00 (19.0)	12	17.33 (12.0)	14.0 (23.25)	0.75 [a]
Clock drawing	7	4.71 (3.30)	4.00 (5.00)	14	5.21 (3.33)	6.0 (5.50)	0.75 [a]
Rey figure:							
Copy	7	15.36 (15.5)	12.50 (31.0)	13	20.77 (11.3)	22.0 (19.75)	0.38 [a]
Delayed recall	8	3.79 (4.64)	3.00 (9.50)	14	7.96 (6.21)	7.00 (10.50)	0.56 [b]
VOSP:							
Screening test	8	19.13 (2.10)	20.00 (0.75)	13	19.46 (0.78)	20.00 (1.00)	0.63 [b]
Incomplete letters	8	11.38 (5.80)	11.0 (11.25)	13	13.62 (7.14)	16.00 (9.00)	0.36 [b]
Silhouettes	8	10.75 (5.12)	11.50 (7.75)	13	12.54 (4.05)	13.00 (5.50)	0.39 [a]
Object decision	8	9.38 (4.66)	11.50 (6.00)	12	11.25 (3.08)	12.00 (5.25)	0.29 [a]
Progressive silhouettes	8	11.13 (5.72)	13.50 (8.25)	12	12.00 (3.19)	12.00 (3.50)	0.67 [a]
Dot counting	8	9.00 (2.07)	10.00 (1.00)	13	9.38 (1.66)	10.00 (0.50)	0.49 [b]
Position discrimination	8	18.50 (1.93)	19.00 (3.25)	13	17.46 (3.64)	19.00 (5.50)	0.92 [b]
Number location	8	5.88 (3.68)	7.50 (6.50)	13	6.15 (2.19)	7.00 (4.00)	0.83 [a]
Cube analysis	8	4.63 (3.34)	5.50 (6.25)	13	5.77 (3.49)	5.00 (6.50)	0.47 [a]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no visual hallucinations; s:seconds; SD: standard deviation; TMT-A: Trail Making Test A; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.

Table 4.23 Regions of increased mean diffusivity in DLB patients with VH compared to those without (p<0.05 TFCE corrected for multiple comparisons, k>10 voxels, covariates of no interest: TIV, age).

White matter tract		Cluster size	MNI coordinates			T score	p value
Superior longitudinal fasciculus	L	10870	-36	-19	25	6.68	0.021
Inferior fronto-occipital fasciculus	L		-25	19	4	6.26	
Forceps minor / Genu of corpus callosum			16	29	16	6.07	
Superior corona radiata	L		-19	8	30	5.87	
Superior corona radiata	L		-19	14	28	5.85	
Cingulum	L		-7	13	24	5.63	
Forceps major		1213	20	-55	18	5.29	0.040
Forceps major			17	-81	27	4.67	
Forceps major / Splenium of corpus callosum			26	-51	20	4.52	
Inferior fronto-occipital fasciculus	R		27	-49	22	4.48	
Forceps major			28	-69	14	4.46	
Forceps major / Inferior fronto-occipital fasciculus	R		27	-53	20	4.36	
Inferior fronto-occipital fasciculus	R	247	38	-36	-1	5.59	0.047
Inferior longitudinal fasciculus	R		39	-33	6	4.17	
Inferior fronto-occipital fasciculus	R		35	-39	11	3.77	
Inferior longitudinal fasciculus	R		37	-37	6	3.74	
Inferior fronto-occipital fasciculus	R		32	-28	2	3.69	
Inferior longitudinal fasciculus	R		29	-25	-2	3.62	
Superior longitudinal fasciculus	R	166	46	-3	21	4.73	0.048
Superior longitudinal fasciculus	R		44	-3	26	4.66	
Superior longitudinal fasciculus	R		45	-4	24	4.30	
Superior longitudinal fasciculus	R		53	2	12	4.25	
Superior longitudinal fasciculus	R		47	-1	19	4.08	
Superior longitudinal fasciculus	R		51	0	22	3.72	
Superior longitudinal fasciculus	R	25	44	12	12	7.65	0.048
Superior longitudinal fasciculus	R		46	12	9	3.03	
Corticospinal tract / Posterior limb of internal capsule	R	19	23	-12	5	4.39	0.049
Corticospinal tract /	R		24	-12	9	3.94	
Posterior limb of internal capsule							

DLB: dementia with Lewy bodies; L: left; R: right; TIV: total intracranial volume; TFCE: Threshold-Free Cluster Enhancement; VH: visual hallucinations.

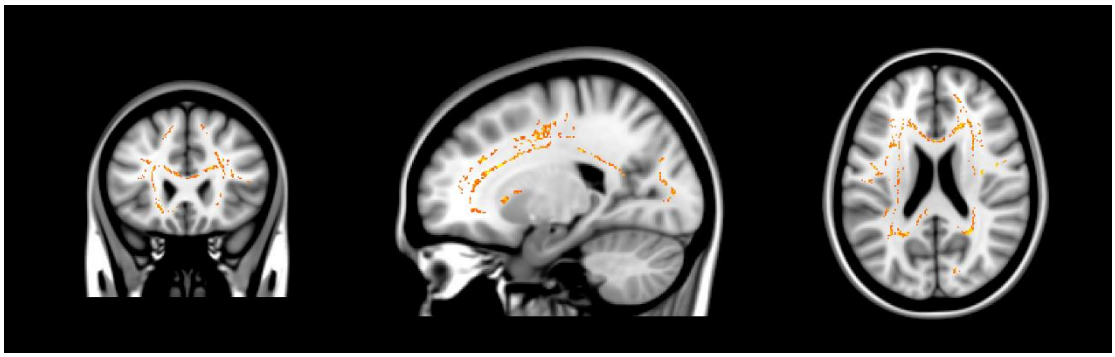

Figure 4.11 Clusters of higher mean diffusivity in DLB patients with VH compared to those without VH.

4.3.4 Discussion

To our knowledge, this is the first whole brain investigation of WM integrity related to VH in DLB. We found that hallucinating patients had significantly higher MD compared with non-hallucinating ones in tracts located in both hemispheres. On the other hand, no differences were detected in FA. MD and FA both represent valuable indices of WM integrity, specifically measuring diffusion anisotropy and the overall water diffusion, respectively. Higher MD, as well as lower FA values usually refer to WM damage. The present study provides evidence of WM microstructural damage in tracts consistent with our *a priori* hypothesis, specifically we found increased MD in hallucinating patients in the SLF and IFOF bilaterally, and the right ILF.

The ILF was the only WM tract that has already been associated with VH in DLB by Kantarci et al. (2010). Interestingly, the ILF is the WM tract found to be more consistently impaired in DLB, regardless of the presence of VH (Hattori et al., 2012, Kantarci et al., 2010, Kiuchi et al., 2011, Ota et al., 2009). Similarly, DTI studies have reported WM damage in DLB in the IFOF (Hattori et al., 2012, Kiuchi et al., 2011) and the SLF (Hattori et al., 2012). The ILF and the IFOF contains fibres connecting occipital regions with temporal and orbitofrontal areas, respectively, and they have both been implicated in visual processing (Catani and Thiebaut de Schotten, 2008). Damage to these WM tracts may be implicated in the significant visuoperceptive deficits characteristic of DLB syndrome, and may be exacerbated in patients with VH. Evidence has also reported an involvement of the ILF, the IFOF and the SLF in attention abilities (Catani and Thiebaut de Schotten, 2008, Doricchi et al., 2008). Specifically, structural damage to these tracts has been shown to contribute significantly to neglect-related symptoms (Doricchi et al., 2008). Moreover, the integrity of the SLF, ILF and corpus callosum, predicted the performance on a visual search task in both younger and older people (Bennett et al., 2012).

The internal capsule consists of projection fibres comprising ascending fibres from subcortical nuclei to the cortex, and descending fibres, from the fronto-parietal cortex to subcortical nuclei and spinal cord (Catani and Thiebaut de Schotten, 2008, Johns, 2014). Therefore, our finding of increased MD in hallucinating patients in this tract may support the hypothesis of disrupted connections between fronto-parietal and striatal areas, fostering the cognitive features observed in DLB patients with VH, particularly visual attention deficits. Finally, we found WM abnormalities in the corpus callosum, which is implicated in different cognitive functions, interconnecting corresponding cortical regions (Catani and Thiebaut de Schotten, 2008), and thus may contribute to the attention and perception impairments outlined above.

These findings, together, are in line with the PAD model for VH (Collerton et al., 2005), and provide further evidence of structural damage that may sustain both attention and perception deficits in DLB, and ultimately VH. However, we found no significant correlation between WM integrity and performance on attention and perception tests, and not even VH indices, probably due to the small sample size of the present experiment. Future studies with bigger sample sizes may elucidate further on the relationship between cognitive performance and WM microstructural features, and how it is linked to the occurrence of VH.

We acknowledge the presence of some limitations. As mentioned, the sample size was small. However, other studies on PD also had small sample size, with the hallucinating group with 10 to 20 patients only (Firbank et al., 2018, Hepp et al., 2017, Lee et al., 2016, Lee et al., 2017). Other limitations related to the sample are outlined in section 4.1.4.

To our knowledge, this is the first whole brain investigation of WM integrity in DLB with VH, and aids further insight on the complex mechanisms that underlie this severe symptom. When TBSS was initially developed, Smith et al. (2006) aimed to improve the sensitivity and objectivity of the analysis of DTI data. First, as for the VBM analysis described in previous sections, it allows the investigation of the whole brain in a fully automated way, and it does not require the specification of predefined tract of interest. Moreover, since it uses a study-specific FA skeleton, each voxel takes the value of the nearest relevant tract (Smith et al., 2006).

4.4 General discussion

The present study adds further knowledge about the presence of structural and functional brain abnormalities, and cognitive deficits in LBD patients with VH, and

differences and similarities between conditions. Our findings suggest that attention deficits, and their neural substrates, may play a significant role in the development of VH, in line with integrative models (Collerton et al., 2005, Shine et al., 2011). Specifically, Collerton et al. (2005) proposed that VH might be the result of the combination of attentional and perceptual deficits. We found that DLB patients with VH had more severe deficits in visual attention, compared to patients without, which seemed to be independent from deficits in visual perception/construction. In turn, visuoconstructive deficits correlated with VH indices, but no between-group differences were detected. We suggest, therefore, that top-down attention mechanisms might have a predominant role in the development of VH, especially in patients with dementia. This is consistent with the pattern of GM atrophy we found in these patients, given the important role played by fronto-parietal regions and the striatum in the top-down control of attention (Gazzaley and Nobre, 2012, Nobre and Mesulam, 2014). On the other hand, GM atrophy was identified in the striatum in PD without dementia only when restricting the analyses to predefined ROIs. We speculate that prefrontal macrostructural alterations might be more pronounced in hallucinating LBD patients with dementia. Cognitive changes and striatal GM atrophy, instead, may be detectable also in cognitively normal PD, and may represent behavioural and structural brain hallmarks of more severely disrupted fronto-striatal circuits. However, the relationship between attention and executive deficits in PD in the development of VH still needs to be clarified.

Interestingly, we found microstructural damage in DLB with VH in WM tracts connecting frontal areas with parietal (SLF), and temporal, parietal and occipital regions (IFOF). Both the SLF and the IFOF have also been related to attention deficits (Doricchi et al., 2008). These findings are in line with our VBM results, showing reduced GM in frontal areas in DLB patients with VH. Notably, we found increased MD in hallucinating DLB patients in the internal capsule, a bundle of fibres connecting fronto-parietal and subcortical nuclei, which may be linked with the striatal atrophy detected through structural MRI. Thus, the more severe attention deficits observed may be sustained by both macrostructural GM, and microstructural WM damage to brain regions and tracts that may also foster the development of VH in LBD. On the other hand, the ILF and the IFOF, found to be impaired in DLB with VH, have been found to be implicated in visual processing (Catani and Thiebaut de Schotten, 2008), and may be interpreted as reflecting disrupted bottom-up mechanisms.

Analyses of functional connectivity also corroborate the hypothesis of an involvement of attention and perception as key cognitive deficits implicated in VH. We found

decreased connectivity of visual (geniculate nucleus and visual associative cortex) and attentional (superior parietal lobule) areas with the anterior cingulate cortex. This may be interpreted as reflecting top-down attentional control impairment that, in conjunction with increased co-activation of visual perception areas, may lead to the unsuccessful inhibition of internally generated images, which may be due to dysfunctional compensatory mechanisms in response to impaired visual processing. This view was also confirmed by ICA analyses that revealed increased connectivity within the DMN that may lead to an excessive self-referential processing, ultimately generating false visual images. Instead, reduced connectivity of this network with the insula, a central hub of the VAN, may reflect impaired bottom-up attention processes. In the light of the findings described in this chapter, we speculate that VH in LBD, especially DLB, may generate from concomitant alterations of large-scale functional and structural top-down and bottom-up brain networks. Within these processes, frontal and striatal atrophy might represent a structural marker of dysfunctional attention networks, which might be impaired by LB pathology. On the other hand, structural and functional connectivity of visuoperceptive areas might be hallmarks of impaired visual processing.

Chapter 5. Neuropsychology of visual hallucinations in dementia with Lewy bodies

5.1 Experiment 4. Cognitive correlates and baseline predictors of development of visual hallucinations at follow-up in dementia with Lewy bodies

5.1.1 Introduction

VH are a complex phenomenon and are most likely the result of dysfunctions of different brain regions and neural connections that, together, contribute to the development of these symptoms. VH have been studied using different methods to explore the neuropathological characteristics of hallucinating patients *post mortem*, but also brain structure and function *in vivo*, by means of brain imaging. Another area of investigation is represented by the study of the cognitive mechanisms, the disruption of which is associated with these symptoms, including visual perception, attention, executive functioning and memory. In fact, a close relationship between VH and cognitive functioning has been reported consistently. For example, LBD patients with cognitive impairment usually present more severe and complex VH, and those with PD are more likely to develop dementia if hallucinating (Fenelon and Alves, 2010, Onofrj et al., 2013). In this context, the investigation of the cognitive processes underlying VH may aid our knowledge of the related neural mechanisms, as well as the specific cognitive deficits that may predispose some patients to hallucinate. Neuropsychological assessment has been widely used to identify disease-specific cognitive characteristics in several neurodegenerative disorders as an important aid to clinical diagnosis. It represents an important tool in both research and clinical settings for the investigation and understanding of behavioural features that are manifestations of underlying neuropathology (Lezak et al., 2012). Neuropsychological assessment has also been increasingly applied to the investigation of symptom-specific processes, including VH, aiding the understanding of the contributing cognitive impairments. Worse performance in hallucinating LBD patients has been shown in neuropsychological tests assessing different cognitive functions, including, for example, deficits in visual perception, visuoconstruction, attention, executive functions and memory. Although DLB is the disorder with the highest prevalence of

VH, the neurocognitive features linked to VH have been understudied in DLB, while the majority of the currently available evidence is on PD (see Chapter 2 for review).

Visuoperceptive and visuoconstructive deficits are typical features of DLB symptomatology, and have been shown to be helpful in distinguishing this type of dementia from AD at the early stages (Collerton et al., 2003, Tiraboschi et al., 2006). Mori et al. (2000) assessed visual perception in 24 DLB patients (18 VH and 6 NVH) and 48 AD. They found that patients with DLB performed worse than those with AD in visuoperceptive tasks including on tasks of size and form discrimination, overlapping figure identification, and visual counting. In the comparison between hallucinating and non-hallucinating DLB patients, those with VH presented poorer performance only on the overlapping figure identification (Mori et al., 2000). This test requires more complex visuoperceptive abilities, specifically object recognition. On the other hand, no differences were detected between DLB subgroups in simple visual tasks, such as size discrimination, suggesting that VH may be more linked to impaired visual association areas, rather than primary visual areas (Mori et al., 2000). In addition, Mosimann et al. (2004) found more severe impairment in hallucinating patients with LB dementia in visual perception, especially in visual discrimination. In these studies, however, no other cognitive function was taken into account. In another study, Cagnin et al. (2013) performed a comprehensive neuropsychological assessment in a sample of patients with DLB (n=81) and AD (n=45), and detected greater impairment in DLB patients in visual perception and attention abilities, while AD patients had more severe verbal memory impairment. DLB patients with VH (n=45) presented more severe visual attention deficits in comparison with those without (n=36), but no differences were detected in any of the VOSP subtests, assessing visual perception. The authors suggested that visuoperceptive deficits might be a necessary but not sufficient condition for the development of VH, while visual attention may be a marker of the symptom (Cagnin et al., 2013). On the other hand, Heitz et al. (2015) found no differences between DLB with and without VH in cognitive performance, but hypoperfusion was identified in hallucinating patients in prefrontal, anterior cingulate and occipital cortices, suggesting a role of both visual and inhibitory control regions.

Other studies have investigated the relationship between progressive cognitive decline and VH in PD. For example, Ramirez-Ruiz et al. (2007a) found that hallucinating patients with VH (n=20) presented significantly greater cognitive decline over time (one-year follow-up) compared to non-hallucinating ones (n=20) in a number of functions, including language, verbal and visual memory, visual perception

and executive functioning. Twenty-six of these patients (12 VH and 14 NVH) were also included in another study with follow-up assessment at 30 months, confirming the same pattern of more severe progressive cognitive decline (Ibarretxe-Bilbao et al., 2010). In the same study, VH patients presented significantly greater decline in global cognitive impairment, with 75% of hallucinating patients developing dementia at follow-up, accompanied by more extensive GM loss over time compared to non-hallucinating patients (Ibarretxe-Bilbao et al., 2010). Instead, none of the patients without VH developed dementia subsequently, although they showed better cognitive performance at baseline as opposed to those with VH (Ibarretxe-Bilbao et al., 2010). A relationship between visual hallucinations and faster cognitive decline over one year was also found by Creese et al. (2018), which was specifically driven by executive dysfunction.

The abovementioned studies, together, highlight further the close relationship between VH, cognitive decline and dementia in PD. However, evidence on the neuropsychological features predicting the future development of VH is still limited. Muller et al. (2017) explored the baseline neuropsychological profile of PD patients that developed VH at follow-up (n=18) in comparison with those that did not progress to VH (n=15). They found that patients with VH at follow-up had significantly worse baseline performance on tests assessing visual attention and processing speed (Muller et al., 2017). In another study, Santangelo et al. (2007) found that the only significant predictor of VH at follow-up in PD was performance on the phonemic fluency test, assessing executive functioning. In these studies, however, visuoperceptive/visuoconstructional abilities were not evaluated (Muller et al., 2017, Santangelo et al., 2007). This, along with the substantial lack of evidence on patients with LB dementia, highlights the need to carry out studies investigating the cognitive characteristics predicting the development of VH in LBD more extensively, especially in patients with dementia. To our knowledge, the only follow-up assessment of VH in DLB is the abovementioned study carried out by Cagnin et al. (2013), who also performed an analysis of the cognitive features predicting the subsequent development of VH. Attention deficit at baseline was the only significant predictor of VH at 12-month follow-up. The sample, however, was small, with only six patients out of 36 eventually developing the symptom (Cagnin et al., 2013).

The presence of VH is the strongest predictor of LB pathology (Onofrj et al., 2013). The identification of patients that will eventually develop VH is, therefore, an important area of investigation that may inform not only on the dysfunctions involved, but also has the potential to aid clinical practice and the formulation of a more accurate disease

prognosis. An early detection of patients that are more likely to experience VH may allow the implementation of preventative treatments, such as cognitive training specifically targeted to the cognitive processes playing a significant role.

Aims and hypotheses

Current evidence on the cognitive mechanisms underlying VH in DLB is limited and the role of visual perception and attention deficits is still not very well understood. We previously reported evidence of more severe attention deficits, independent from visuoperceptive abilities, in DLB with VH compared with those without (Experiment 1, section 4.1). Therefore, the first aim of the present study was to replicate these findings in a completely independent dataset (Experiment 4.1), pursuing the hypothesis of a predominant role of visual attention difficulties in the expression of VH in DLB. The second aim was to investigate the neuropsychological features that predict the development of VH at follow-up in a subsample of DLB patients (Experiment 4.2). The third aim of the present study was to investigate *post-hoc* the role of the thalamus in the development of VH (Experiment 4.3), by using the sample of patients described in Experiment 1. The thalamus has been found to be involved in memory processing, mainly due to its connections with MTL structures and prefrontal areas (Carlesimo et al., 2015, Jankowski et al., 2013, Mitchell and Chakraborty, 2013). We hypothesised an involvement of thalamic nuclei in the development of VH in DLB, which might be related to impairments in memory functioning. This hypothesis was based on the results obtained in Experiment 4.2 and explored *post-hoc* in a separate sample of patients.

5.1.2 Methods

5.1.2.1 Study sample, clinical and neuropsychological assessment

Patients with a diagnosis of DLB were retrospectively selected from the clinical records of the outpatient memory clinic of the Department of Neurosciences at the University of Padua, Italy. The search yielded the identification of 152 patients with a diagnosis of probable or possible DLB. To avoid missing data and overlapping samples, only patients with a full neuropsychological battery that were not involved in previous studies were considered for the purpose of the present study. In addition, exclusion criteria included the following: severe cognitive decline (MMSE cut-off below 18), comorbid neurological conditions, and previous history of psychiatric disorders. Allowed medications included ChEIs, benzodiazepines, neuroleptics,

levodopa and dopamine agonists. Each patient had been diagnosed by experienced neurologists at the time of their initial assessment. Subsequently diagnosis was retrospectively confirmed using the consensus criteria developed by the DLB consortium (McKeith et al., 2005). The final sample consisted of 67 patients with DLB. Ethical approval is reported in Appendix 4.

Clinical records for each patient were screened for follow-up visits, specifically for information regarding the presence of VH. Time at follow-up was calculated in days, by recording the time interval between baseline assessment, and either the first visit when patients presented VH, or the last visit available confirming their non-hallucinating status. Follow-up visits were accessible for 34 patients. Of the 67 patients included in the present study, 18 had VH at the time of their initial assessment (DLB VH), 32 did not (DLB NVH), and 17 had no VH at baseline and experienced VH at a later timepoint at follow-up (DLB VH-FU). Among the NVH patients, 17 had no VH at follow-up (DLB NVH-FU), while no recorded follow-up information for the presence of VH was available for 15 patients. All the 34 patients for whom follow-up visits were available had no VH at the time of their initial assessment, and only their clinical and neuropsychological measures at baseline were considered for the purpose of the present study. Details on the selection strategy of this study sample, and number of participants for each experiment performed are displayed in Figure 5.1.

For all patients, the following demographic and clinical information at the time of their initial assessment were recorded including: age, gender, years of education, disease duration, MMSE, presence of RBD, cognitive fluctuations, parkinsonism, hypertension and other comorbidities, and medication used (ChEIs, benzodiazepines, neuroleptics, levodopa and dopamine agonists). All DLB core and suggestive features, including VH, were diagnosed clinically. Comorbidities were assessed by means of the Charlson Comorbidity Index (Charlson et al., 1987), excluding the dementia condition from the scoring. The neuropsychological battery included the following tests: digit cancellation, digit span forward and backward, prose memory immediate and delayed recall, phonemic fluency, Rey figure copy and delayed recall. All tests were administered as described previously (section 4.1.2.3).

The first experiment (Experiment 4.1) involved 50 patients, 18 DLB with VH (mean age: 75.72, SD: 6.55; 7 males and 11 females) and 32 NVH (mean age 72.84, SD= 5.31; 22 males and 10 females). Mean disease duration was 2.72 (SD=2.92) years in patients with VH and 2.09 (SD=2.05) in those without. Cognitive fluctuations were observed in 25 patients, 11 VH and 14 NVH; parkinsonism was present in 32 patients, 13 VH and 19 NVH; and RBD was recorded in 28 patients, 10 VH and 18 NVH. DLB

VH-FU patients were excluded from the first experiment as the subsequent development of VH might have influenced the results.
For the purpose of the second experiment (Experiment 4.2), only patients with follow-up visits were considered, specifically 17 DLB VH-FU (mean age 74.47, SD= 5.80; 11 males and 6 females; mean disease duration: 1.31, SD=1.77) and NVH-FU (mean age 72.12, SD=5.67; 11 males and 6 females; mean disease duration: 2.32, SD=2.67). Nineteen patients presented cognitive fluctuations (10 VH-FU, 9 NVH-FU), 20 RBD (12 VH-FU, 8 NVH-FU), and 22 parkinsonism (11 VH-FU, 11 VH-FU).

5.1.2.2 Statistical analyses

Statistical analyses on demographic, clinical and neuropsychological features were undertaken with SPSS (v22). Firstly, differences between DLB VH and NVH were explored by means of independent sample t-test and Mann-Whitney U test for normally and non-normally distributed numerical variables, respectively, and Fisher's Exact Test for categorical variables. Bonferroni correction for multiple comparisons was applied (p value < α/n, where α is the p value for each comparison and n the number of comparisons), therefore $p < (0.05/8) = 0.006$. The same analyses were performed to investigate the differences between VH-FU and NVH-FU on all demographic, clinical and neuropsychological variables at baseline.
Then, the same analyses performed in Chapter 4 (section 4.1.2.4) were undertaken to test whether there was an interplay between attention and visuoconstructive deficits in the presentation of VH at baseline. Specifically, an ANCOVA design was used to assess differences in attention deficits (digit cancellation test) controlling for visuoconstruction (Rey figure copy), and differences in visuoconstructive deficits controlling for visual attention.
Finally, two separate forward stepwise (likelihood ratio) logistic regression models were carried out to investigate what variables independently predicted: 1) the presence of VH at baseline, and 2) the development of VH at follow-up. In the first model, all the neuropsychological tests were included as predictor variables, and the presence of VH was entered as dependent variable. The second logistic regression model included presence of VH at follow-up as dependent variable, and scores on all neuropsychological tests at baseline as predictors. In order to account for different follow-up time points, time to follow-up (days) was also entered as predictor variable in the latter model.

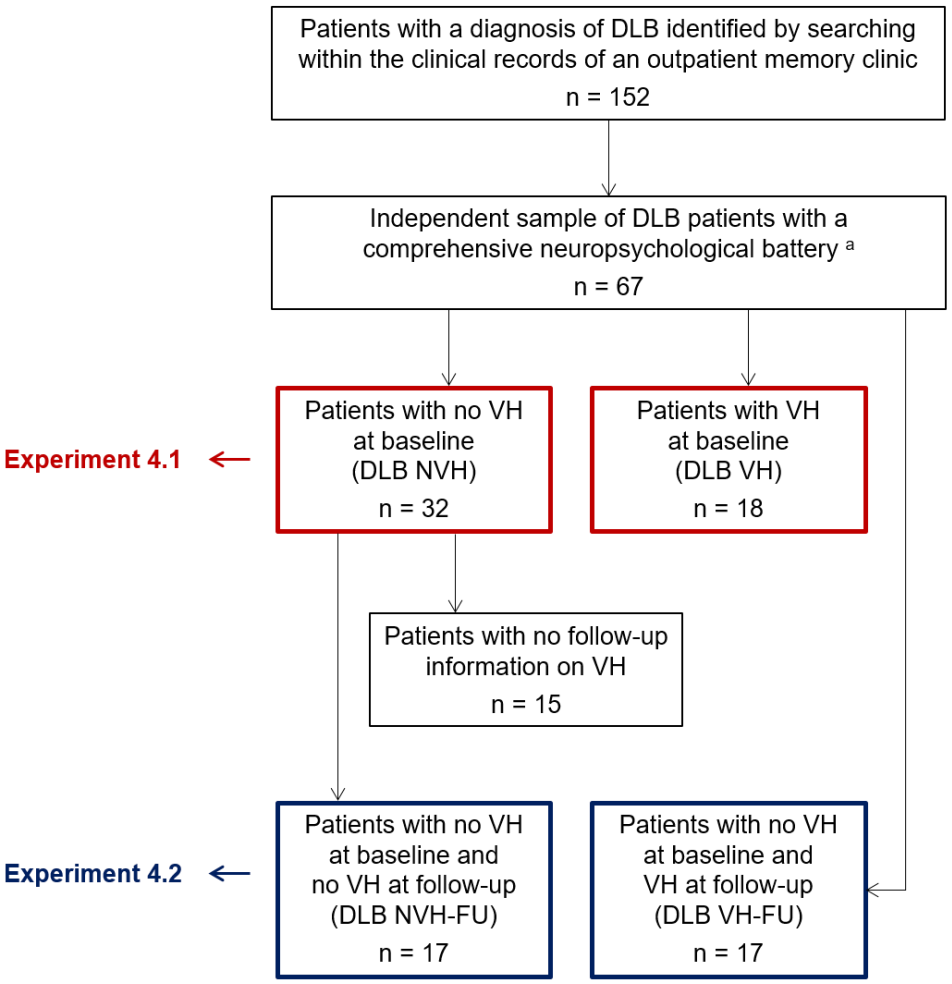

Figure 5.1 Flow chart describing the selection process of DLB patients for experiments 4.1 and 4.2. [a] Neuropsychological tests included: digit cancellation, digit span forward and backward, prose memory immediate and delayed recall, phonemic fluency, Rey figure copy and delayed recall.

5.1.2.3 Post hoc voxel-based region of interest analyses

Based on the results of Experiment 4.2, the present *post hoc* investigation (Experiment 4.3) aimed to explore in more detail the role of the thalamus in the development of VH in DLB, which might be mediated by dysfunctional memory abilities. The thalamus is a complex subcortical structure involved in first-order sensory functions, but also high-order cognitive processes, including memory and learning, attention, language and set-shifting, sustained by cortico-thalamo-cortical pathways (Carlesimo et al., 2015, Saalmann, 2014, Saalmann and Kastner, 2015). The role of the thalamus in memory functioning has been linked to its connections with MTL structures, especially the hippocampal formation, passing through the mammillary bodies via the mammillo-thalamic tract, but also connections between thalamic nuclei and prefrontal areas (Carlesimo et al., 2015, Jankowski et al., 2013,

Mitchell and Chakraborty, 2013). In particular, anterior and mediodorsal thalamic nuclei have been found to play a role in memory processes (Jankowski et al., 2013, Mitchell and Chakraborty, 2013).

In Experiment 4.3, we explored structural GM differences between DLB patients with and without VH by restricting the analyses to the thalamus bilaterally. In order to do so, we used the sample of DLB patients described in Experiment 1. Characterisation of the sample, MRI acquisition and VBM pre-processing are reported in detail in section 4.1.2.

An ROI was placed *post hoc* in the thalamus bilaterally, and this was created using the WFU PickAtlas toolbox, version 3.0.5 (Maldjian et al., 2004, Maldjian et al., 2003). Voxel-based ROI analyses were then performed to test differences between DLB patients with and without VH. Statistical analyses were performed as described in section 4.1.2.5.3, and were restricted to the thalamus.

5.1.3 Results

Experiment 4.1. There were no between group differences in age, gender, disease duration, MMSE, and other clinical variables, namely presence of RBD, cognitive fluctuations, parkinsonism (Table 5.1). Patients with VH were less educated, even though the difference was only marginally significant ($p=0.05$). The two groups of patients did not differ for the presence of hypertension, Charlson comorbidity index, and use of ChEIs, benzodiazepines, neuroleptics, levodopa and dopamine agonists. Information on some clinical variables, and medication used was missing for a few patients (see Table 5.1 for details).

The comparison between patients with and without VH yielded significant results in the Rey figure copy ($p=0.001$, Figure 5.2), and delayed recall ($p=0.01$). However, when correcting for multiple comparisons, the only significant difference was in the copy of the Rey figure ($p<0.006$). To account for the marginally significant differences in years of education between the groups, the analyses were repeated adding years of education as covariate of no interest. Significant differences remained (ANCOVA analysis, $p=0.005$). No differences were detected for all other neuropsychological measures (Table 5.2).

Table 5.1 Demographic and clinical characteristics for DLB patients with and without VH.

Characteristic	n	DLB VH	n	DLB NVH	p value
Age, mean (SD)	18	75.72 (6.55)	32	72.84 (5.31)	0.10 [a]
Gender M:F	18	7:11	32	22:10	0.07 [b]
Education (years), mean (SD)	18	6.78 (3.14)	32	9.56 (4.91)	0.05 [c]
Disease duration (years), mean (SD)	18	2.72 (2.92)	32	2.09 (2.05)	0.39 [c]
MMSE, mean (SD)	18	24.50 (3.15)	32	25.03 (2.86)	0.56 [c]
RBD, n (%)	17	10 (58.82%)	32	18 (56.25%)	1.00 [b]
Cognitive fluctuation, n (%)	17	11 (64.60%)	31	14 (45.16%)	0.24 [b]
Parkinsonisms, n (%)	18	13 (72.22%)	32	19 (59.38%)	0.54 [b]
Hypertension, n (%)	17	10 (58.82%)	31	16 (51.61%)	0.77 [b]
Charlson comorbidity index, mean (SD)	16	1.44 (0.81)	32	1.28 (1.02)	0.48 [c]
ChEIs, n (%)	18	2 (11.11%)	31	1 (3.23%)	0.55 [b]
Benzodiazepines, n (%)	18	8 (44.44%)	31	5 (16.13%)	0.05 [b]
Neuroleptics, n (%)	18	2 (11.11%)	31	1 (3.23%)	0.55 [b]
Levodopa, n (%)	17	2 (11.76%)	31	1 (3.23%)	0.28 [b]
Dopamine agonists, n (%)	17	0 (0.00%)	31	2 (6.45%)	0.53 [b]

DLB: dementia with Lewy bodies; ChEIs: cholinesterase inhibitors; F: female; M: male; MMSE: Mini-Mental State Examination; NVH: no visual hallucinations; RBD: REM sleep behaviour disorder; SD: standard deviation; VH: visual hallucinations. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Independent-sample Mann-Whitney U test.

Table 5.2 Differences in neuropsychological tests between DLB patients with and without VH.

Test	DLB VH (n=18)		DLB NVH (n=32)		p value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Digit cancellation	35.16 (12.71)	38.50 (23.50)	42.25 (9.94)	42.00 (11.00)	0.10 [a]
Digit span forward	4.44 (0.86)	4.00 (1.00)	4.91 (0.93)	5.00 (2.00)	0.05 [a]
Digit span backward	2.89 (0.83)	3.00 (1.00)	3.25 (0.84)	3.00 (1.00)	0.12 [a]
Prose memory:					
Immediate recall	7.33 (3.38)	8.00 (5.00)	8.88 (4.32)	8.50 (7.80)	0.20 [b]
Delayed recall	9.06 (4.76)	8.50 (7.30)	10.25 (5.41)	10.00 (8.50)	0.44 [b]
Phonemic fluency	19.00 (7.91)	19.00 (9.00)	22.09 (8.82)	23.50 (10.00)	0.22 [b]
Rey figure:					
Copy	16.11 (9.41)	18.00 (15.90)	24.83 (8.31)	26.00 (10.90)	**0.001** [b]
Delayed recall	5.28 (4.29)	5.25 (5.40)	9.33 (6.44)	8.00 (10.10)	**0.01** [b]

DLB: dementia with Lewy bodies; IQR: interquartile range; NVH: no visual hallucinations; SD: standard deviation; TMT-A: Trail Making Test A; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample Mann-Whitney U test. [b] Independent-sample t-test.

The more severe deficits in visuoconstruction (Rey figure copy) were significant even when accounting for visual attention, as assessed with the digit cancellation test (ANCOVA analysis, p=0.02). On the other hand, differences in the digit cancellation test were not significant when controlling for the scores on the Rey figure copy

(ANCOVA analysis, p=0.77). Finally, stepwise logistic regression revealed that the only significant predictor of the presence of VH was the copy of the Rey figure (OR=0.90, p=0.004; see Table 5.3 for details). There was no evidence of collinearity, as resulted from multicollinearity diagnostic statistics (tolerance above 0.1).

Table 5.3 Final stepwise logistic regression model. Variables not in the equation: digit cancellation, prose memory immediate and delayed recall, digit span forward and backward, phonemic fluency and Rey figure delayed recall.

Predictor	B coefficient	SE	OR	OR 95% CI	p value
Rey figure copy	-0.11	0.04	0.90	0.84 to 0.97	**0.004**
Constant	1.64	0.83	5.16	-	0.05

CI: confidence interval; OR: odds ratio; SE: standard error. Nagelkerke R^2=0.25; Model p=0.002; Classification percentage: 74%.

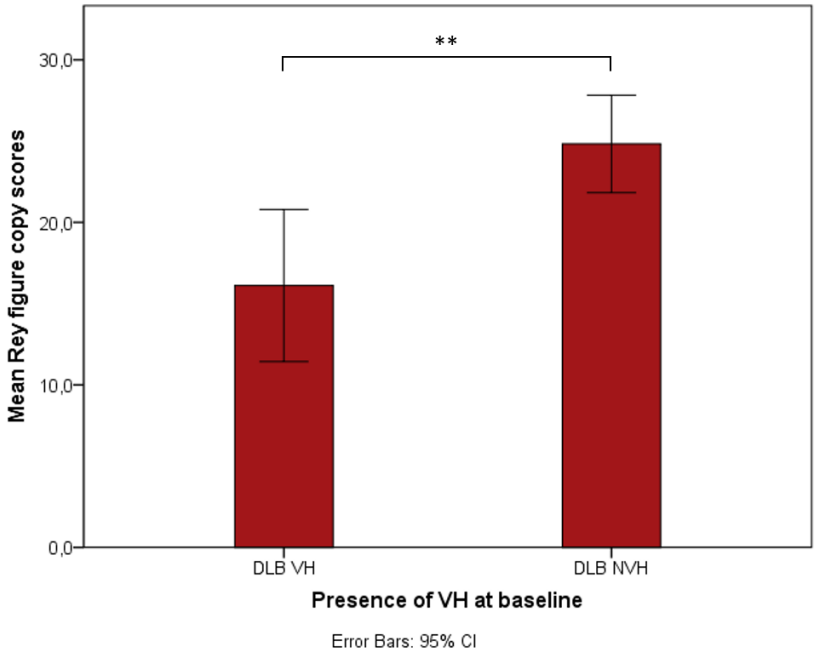

Figure 5.2 Significantly lower scores in the copy of the Rey figure in DLB patients with VH compared with NVH. ** p<0.01.

Experiment 4.2. Patients with and without VH at follow-up di not differ in age, gender, years of education, disease duration, MMSE and presence of other clinical variables (RBD, cognitive fluctuations and parkinsonism) at baseline. No differences were found in the presence of hypertension, Charlson comorbidity index, and medication use. Information on medications was missing for a patient with no VH at follow-up. Time at follow-up, measured in days, was comparable between groups. The results

of the comparison between DLB VH-FU and NVH-FU in demographic and clinical characteristics are summarised in Table 5.4.

As for differences between groups in neuropsychological measures, patients developing VH at follow-up showed significantly lower scores in prose memory immediate recall at baseline (p=0.02, Table 5.5 and Figure 5.3). Marginally significant differences were detected in prose memory delayed recall (p=0.05). None of these results, however, survived correction for multiple comparisons (p<0.006).

Table 5.4 Demographic and clinical characteristics for DLB patients with and without VH at follow-up.

Characteristic	DLB VH-FU (n=17)	DLB NVH-FU (n=17)	p value
Age, mean (SD)	74.47 (5.80)	72.12 (5.67)	0.24 [a]
Gender M:F	11:6	11:6	1.00 [b]
Education (years), mean (SD)	8.53 (4.98)	10.24 (5.04)	0.29 [c]
Disease duration (years), mean (SD)	1.31 (1.77)	2.32 (2.67)	0.10 [c]
MMSE, mean (SD)	24.29 (4.55)	25.59 (2.94)	0.47 [c]
RBD, n (%)	12 (70.59%)	8 (47.06%)	0.30 [b]
Cognitive fluctuation, n (%)	10 (58.82%)	9 (52.94%)	1.00 [b]
Parkinsonisms, n (%)	11 (64.71%)	11 (64.71%)	1.00 [b]
Hypertension, n (%)	8 (47.06%)	11 (64.71%)	0.49 [b]
Charlson comorbidity index, mean (SD)	1.12 (1.05)	1.00 (0.06)	0.18 [c]
ChEIs, n (%) [d]	5 (29.41%)	1 (6.25%)	0.18 [b]
Benzodiazepines, n (%) [d]	2 (11.76%)	3 (18.75%)	0.66 [b]
Neuroleptics, n (%) [d]	2 (11.76%)	0 (0.00%)	0.49 [b]
Levodopa, n (%) [d]	1 (5.88%)	1 (6.25%)	1.00 [b]
Dopamine agonists, n (%) [d]	1 (5.88%)	2 (12.5%)	0.60 [b]
Time at follow-up (days), mean (SD)	842.41 (469.89)	850.82 (646.36)	0.63 [c]

DLB: dementia with Lewy bodies; ChEIs: cholinesterase inhibitors; F: female; M: male; FU: follow-up; MMSE: Mini-Mental State Examination; NVH: no visual hallucinations; RBD: REM sleep behaviour disorder; SD: standard deviation; VH: visual hallucinations. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Independent-sample Mann-Whitney U test; [d] Missing information for one DLB NVH patient.

Table 5.5 Differences in neuropsychological tests between DLB patients with and without VH at follow-up.

Test	DLB VH-FU (n=17)		DLB NVH-FU (n=17)		p value
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Digit cancellation	35.00 (11.06)	38.00 (15.50)	41.35 (10.01)	42.00 (10.50)	0.09 [a]
Digit span:					
Forward	5.12 (0.93)	5.00 (2.00)	4.88 (0.99)	5.00 (2.00)	0.66 [b]
Backward	3.12 (1.45)	3.00 (1.00)	3.29 (0.99)	3.00 (2.00)	0.29 [b]
Prose memory:					
Immediate recall	6.12 (4.48)	5.00 (6.50)	10.06 (4.55)	10.00 (7.50)	**0.02** [a]
Delayed recall	7.91 (5.48)	8.00 (9.50)	11.77 (5.76)	11.00 (7.50)	0.05 [a]
Phonemic fluency	26.41 (12.08)	26.00 (21.00)	23.24 (9.05)	24.00 (11.00)	0.39 [a]
Rey figure:					
Copy	20.29 (10.85)	21.00 (20.80)	24.09 (9.48)	24.00 (33.50)	0.39 [b]
Delayed recall	7.06 (5.64)	5.50 (9.00)	10.06 (7.15)	8.00 (12.30)	0.18 [a]

DLB: dementia with Lewy bodies; FU: follow-up; IQR: interquartile range; NVH: no visual hallucinations; SD: standard deviation; TMT-A: Trail Making Test A; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery. [a] Independent-sample t-test; [b] Independent-sample Mann-Whitney U test.

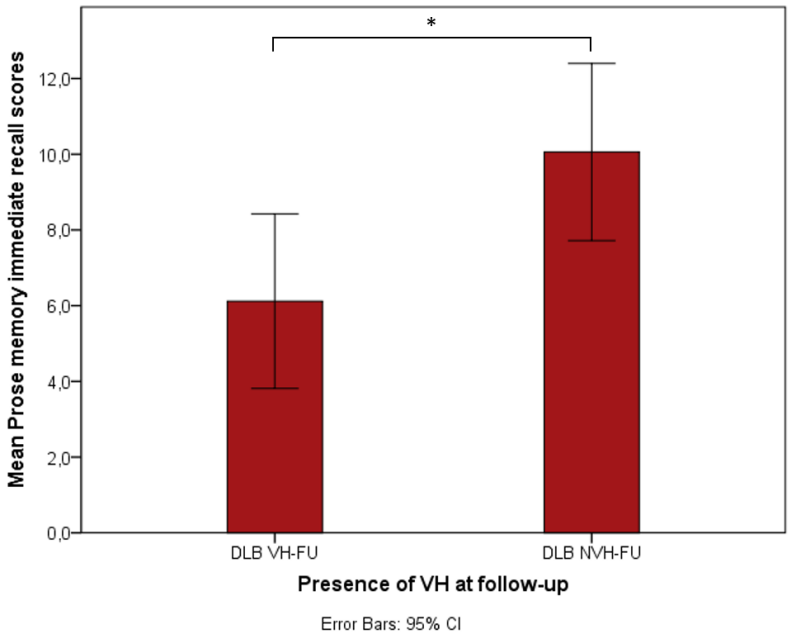

Figure 5.3 Significantly lower scores in prose memory immediate recall in DLB VH-FU compared with NVH-FU. * p<0.05.

The final stepwise logistic regression model retained only one significant predictor of the development of VH at follow-up, namely performance on the prose memory immediate recall test (OR=0.82, p=0.03, Table 5.6). The coefficient was negative (B=-0.19), indicating that a lower score on this test at baseline (poorer performance) was

suggestive of higher probability of developing VH at follow-up. No other significant predictors were found. The other variables entered in the original model, including all the other neuropsychological tests and time at follow-up, were therefore excluded from the final logistic regression model. The overall model was statistically significant (χ^2=6.08, p=0.01), and accurately predicted 64.7% of the cases. There was no evidence of collinearity, as resulted from multicollinearity diagnostic statistics (tolerance above 0.1).

Table 5.6 Final stepwise logistic regression model predicting the development of VH at follow-up. Variables not in the equation: time at follow-up, digit cancellation, prose memory delayed recall, digit span forward and backward, phonemic fluency, Rey figure copy and delayed recall.

Predictor	B coefficient	SE	OR	OR 95% CI	p value
Prose memory immediate recall	-0.19	0.09	0.82	0.70 to 0.98	**0.03**
Constant	1.56	0.78	4.74	-	0.05

CI: confidence interval; OR: odds ratio; SE: standard error. Nagelkerke R^2=0.22; Model p=0.01; Classification percentage: 64.7%.

Experiment 4.3. Reduced GM volume was found in the left medial dorsal nucleus of the thalamus, using a cluster-level threshold of p<0.05 FWE corrected for multiple comparisons (Table 5.7 and Figure 5.4). Ten voxels of the same cluster (MNI coordinates: x=-8, y=-14, z=8) survived a set-level threshold of p<0.05 FWE corrected.

Table 5.7 Thalamic regions of reduced grey matter volume in DLB patients with VH compared to those without using a region of interest voxel-based approach (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Medial dorsal nucleus, thalamus	L	73	-8	-14	8	4.55	3.82	<0.05

DLB: dementia with Lewy bodies; FWE: family-wise error; L: left; TIV: total intracranial volume; VH: visual hallucinations.

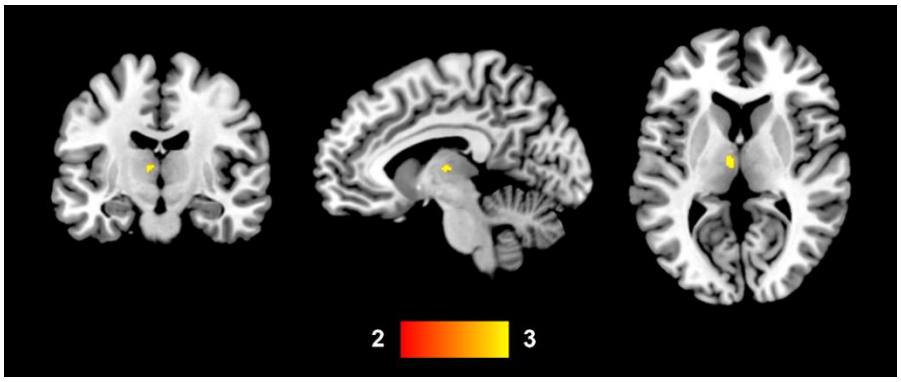

Figure 5.4 Thalamic regions of reduced GM volume in DLB patients with VH compared to those without: left medial dorsal nucleus. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons, with TIV and age as covariates of no interest.

5.1.4 Discussion

In the current study, we have described the presence of cognitive differences between DLB patients with and without VH. Specifically, we found that hallucinating patients presented worse performance on a visuoconstructive test, the copy of the Rey figure, which was independent of visual attention abilities, assessed with the digit cancellation test. Then, we investigated baseline neuropsychological features predicting the subsequent development of VH, showing verbal memory performance as the only significant predictor of VH at follow-up. To our knowledge, this is the larger longitudinal study investigating the neuropsychological features predicting VH in DLB. With the present experiment, we aimed to replicate, in an independent sample of DLB patients, the findings described in the first chapter of the present thesis. We previously showed that DLB patients with VH had more severe visual attention deficits compared with those without, which persisted even when controlling for visual perception/construction (Experiment 1, section 4.1). Cagnin et al. (2013) found the same pattern of cognitive impairments, although in that study the interplay between attention and perception was not taken into account. Moreover, we reported a significant correlation between NPI hallucination scores and performance on the copy of the Rey figure, and a trend towards poorer visuoconstructive abilities in patients with VH, although not significant (Experiment 1, section 4.1). The current study provides evidence of the presence of significantly more severe deficits in visuoconstruction in hallucinating DLB patients, which were independent of attention abilities. Similarly, other studies have shown more severe impairments in visual perception in hallucinating patients in LB dementia (Mori et al., 2000, Mosimann et al., 2004) and PD (Barnes et al., 2003, Ibarretxe-Bilbao et al., 2010, Koerts et al., 2010,

Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a). These findings highlight the contribution of visual perception deficits to VH. On the other hand, the present investigation revealed no differences in visual attention. Contrasting findings between our two experiments might be explained by the more severe global cognitive impairment, although not significant, shown by patients with VH in Experiment 1. In the present study, instead, the two subgroups of DLB patients were better matched for global cognitive decline, as shown by scores on the MMSE. In this context, the investigation of the specific cognitive deficits contributing to the development of hallucinatory phenomena may be complicated by the very close relationship between VH and the presence of dementia. Findings showing slightly more severe global cognitive impairment in hallucinating patients might be driven by their poorer attention abilities that, in turn, might be contributing to both the development of VH and worse global cognitive decline. In fact, as highlighted previously, DLB and PDD have been defined as attentional, executive and visuoperceptive dementias (Collerton et al., 2003, Goldmann Gross et al., 2008). Thus, hallucinating patients may represent more severe phenotypes reflecting a pattern of cognitive alterations typical of underlying LB pathology, of which VH are the strongest predictor (Onofrj et al., 2013). Within this process, deficits in visual perception may be necessary contributors to VH. The role of visual attention, instead, may be more subtle at earlier stages of dementia, and may manifest more clearly with the progression of dementia. In line with this view, both attention and perception deficits may contribute to hallucinatory phenomena, as proposed by Collerton et al. (2005). These deficits may be supported by structural and functional alterations within attention networks and visual pathways, as suggested by the findings outlined in Chapter 4.

An intriguing finding of the present study is the presence of more severe verbal memory impairment at baseline as the only significant predictor of VH at follow-up. Longitudinal investigations have previously shown that PD patients with VH presented faster verbal memory decline over time as opposed to those without (Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2007a). Other studies have explored this cognitive function in PD patients with hallucinations in comparison with those without and, overall, they have reported more severe deficits in hallucinating patients (Grossi et al., 2005, Hepp et al., 2013, Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a, Santangelo et al., 2007). All these findings suggest that verbal memory impairments are significantly related to VH, although the mechanisms underlying this association remain unknown. Moreover, this cognitive function in hallucinating DLB patients is largely understudied as opposed to PD. The present

investigation adds further insight to the current literature, by showing that patients with DLB are more likely to develop VH at follow-up if presenting more severe verbal memory impairment at baseline, thus presenting an AD-like profile of cognitive impairments.

The key role of the hippocampus and MTL regions in episodic memory is well-established (Gyorfi et al., 2018, Moscovitch et al., 2016). Impairment of these structures has been related to memory deficits not only in AD, but also in other neurodegenerative conditions, including PD (Gyorfi et al., 2018, Jahn, 2013). Evidence has shown a relationship between volumetric measures of MTL structures and VH severity in DLB and PD (Iizuka and Kameyama, 2016, Lenka et al., 2018). This may be linked to the high burden of LB pathology in temporal areas that has been found in hallucinating patients (Gallagher et al., 2011, Harding et al., 2002a, Harding et al., 2002b, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006). Notably, VH has also been associated with AD pathology in MTL structures in patients with PD. Specifically, a neuropathological study has shown a relationship between VH and plaques and neurofibrillary tangles density in frontal, parietal and hippocampal regions in PD, as well as high burden of LB pathology in temporal, parietal, and cingulate cortices (Jacobson et al., 2014). These findings suggest that both LB and AD pathology may somehow contribute in disrupting neural mechanisms subsequently resulting in VH. Similarly, the neuropathological substrates of dementia in LBD have been related to LB pathology alone or in combination with AD pathology (Jellinger, 2012, Jellinger, 2018). In fact, temporal LBs and neuritic plaques have both been associated with dementia severity and duration in LBD (Harding and Halliday, 2001). In this respect, LB pathology with or without additional AD-related pathology in medial temporal areas may be contributing to both VH and dementia in LBD, which may share some dysfunctional underlying mechanisms. Within this framework, a speculative interpretation may be formulated to explain the AD-like cognitive profile observed in pre-hallucinating DLB patients. Specifically, LB with or without concomitant AD pathology, especially in MTL areas, and subsequent disruption of neural circuits sustaining memory abilities, may eventually form the basis for hallucinatory phenomena, along with impaired visual perception and attention, typical of DLB symptomatology. Differences between groups in these latter deficits may arise only later, together with the actual manifestation of VH.

The role of memory impairment as underlying mechanisms for VH may be explained in the light of DMN-related dysfunctions, as proposed by Shine et al. (2011). The DMN is a resting-state network comprising the posterior cingulate cortex, precuneus,

inferior parietal lobule, dorsal and ventral medial prefrontal cortex, and MTL areas (Buckner et al., 2008, Greicius et al., 2003, Mevel et al., 2011, Raichle et al., 2001, Rosazza and Minati, 2011, Utevsky et al., 2014). The functions that have been attributed to this network include task-unrelated activities, recollection of autobiographical memories, mind wandering, and self-projection to future events, thus, all related to inner experiences (Mevel et al., 2011). Another hypothesis suggested that it allows the monitoring of the external world for unexpected events (Mevel et al., 2011). DMN dysfunctions have been repeatedly found in AD, especially between the posterior cingulate cortex and the hippocampus, probably due to early damage of the latter (Mevel et al., 2011). Less evidence is available for DLB, and a few published studies revealed relatively spared activity in this part of the network (Franciotti et al., 2013, Peraza et al., 2014). DMN alterations have been related to cognitive decline in PD (Wolters et al., 2018). Moreover, studies have found increased DMN co-activation in PD patients with VH in comparison with those without, while a pattern of decreased connectivity was identified in both subgroups when independently compared to controls (Franciotti et al., 2015, Yao et al., 2014). Moreover, in Experiment 2 (section 4.2) we demonstrated for the first time altered functional connectivity of the DMN in hallucinating DLB patients, suggesting a contribution of this network to the symptomatology. Dysfunctional DMN may result in the selection and emergence of inappropriate memories, and deficits in the recall of relevant information, thus forming the basis for the emergence of false images (Shine et al., 2011). We can speculate that the accumulation of LBs, and even AD-related pathology, in MTL areas of the DMN might disrupt the activity of this network that, along with visual pathways and attention networks impairments, might ultimately contribute to the genesis of VH.

Alternatively, the more severe memory deficits presented by DLB patients with VH at follow-up may originate from alterations in thalamic nuclei, especially anterior and mediodorsal nuclei, involved in memory processes, and their connections with the cortex (Carlesimo et al., 2015, Jankowski et al., 2013, Mitchell and Chakraborty, 2013). In Experiment 4.3, we explored this hypothesis *post hoc* in the sample of DLB patients included in Experiment 1 (section 4.1), by restricting VBM analyses to the thalamus bilaterally. Consistently with what expected, we found reduced GM volume in the left medial dorsal nucleus of the thalamus in patients with VH compared with those without. The mediodorsal thalamus is implicated in high cognitive processes, especially memory, learning and decision-making abilities (Mitchell, 2015, Mitchell and Chakraborty, 2013, Saalmann and Kastner, 2015). Lesions to this nucleus have been shown to produce memory deficits (Mitchell and Chakraborty, 2013, Saalmann

and Kastner, 2015). Along with other thalamic nuclei, such as the pulvinar, the mediodorsal thalamus has been defined as a high-order nucleus, interconnected with the cerebral cortex through cortico-thalamo-cortical connections, and forming pathways between cortical areas (Mitchell, 2015, Saalmann and Kastner, 2015). The mediodorsal thalamus is highly interconnected with the prefrontal cortex (Mitchell and Chakraborty, 2013, Mitchell, 2015). It has been proposed that the memory deficits related to damage to the mediodorsal thalamus might be secondary to executive dysfunctions, especially difficulties in retrieval selection strategies, but also in learning new information (Mitchell and Chakraborty, 2013, Mitchell, 2015). In this context, we speculate that GM loss in the mediodorsal nucleus might be a structural hallmark of disrupted circuits and connections between this nucleus and the prefrontal cortex, eventually manifesting in memory deficits, and predisposing patients to hallucinatory phenomena.

The main strength of the present study is the longitudinal investigation, the largest on VH in DLB, even though the sample size was still relatively small. Nevertheless, other longitudinal studies exploring the cognitive features predicting the development of VH in PD did not include larger samples (Muller et al., 2017, Santangelo et al., 2007). Moreover, DLB subgroups were well matched for demographic and other clinical features, including global cognitive impairment, which might have affected the results. Expert neurologists assessed the presence of VH clinically; however, no information was available about severity, frequency and other phenomenological features.

Chapter 6. Meta-analyses of grey matter volumes and neuropsychology of visual hallucinations in Parkinson's disease and dementia with Lewy bodies

A growing body of evidence suggests the presence of neurocognitive and brain abnormalities in patients with LBD and VH, as outlined in previous chapters. However, findings from both neuroimaging and neuropsychological studies are often contradictory and have not always been replicated (see Chapter 2 for a review). Such inconsistencies may be due to a combination of factors, including between-study heterogeneity related to differences in demographic and clinical features, diagnostic criteria, use of medications and methodologies used. Moreover, individual studies are often low-powered and include small sample sizes, increasing the likelihood of false negative results (Button et al., 2013, Muller et al., 2018). This is complicated further by the common use of inadequate analyses and thresholds leading to higher rates of false positive results, an issue that has been highlighted as particularly problematic in neuroimaging studies (Muller et al., 2018, Wager et al., 2009). Thus, reproducibility and consistency of findings represent a controversial issue of the current scientific research, highlighting the importance to detect those findings that have been replicated by different studies (Muller et al., 2018, Wager et al., 2009). Within this framework, meta-analyses are unique tools to summarise and integrate findings from individual studies in a quantitative way. They are also extremely useful to assess publication bias, between-study heterogeneity, and the influence of other variables through meta-regression analyses (Radua and Mataix-Cols, 2012).

Meta-analytic methods have been widely used to combine statistically results from studies exploring brain alterations in different disorders and using different neuroimaging techniques, such as VBM, but also neuropsychological data. For example, voxel-wise meta-analyses have been performed to investigate structural brain features in several neurological and psychiatric disorders, including PD (Pan et al., 2012, Yu et al., 2015), DLB (Zhong et al., 2014), PDD (Pan et al., 2013), AD (Wang et al., 2015), depression, bipolar disorder (Wise et al., 2017), and schizophrenia (Bora et al., 2011). Meta-analyses have also been used to combine findings from VBM studies on hallucinations in psychiatric and neurodegenerative disorders, although none was specific for VH in LBD (Modinos et al., 2013, Palaniyappan et al., 2012, Rollins et al., 2019).

The aim of the present chapter was to combine statistically findings from VBM and neuropsychological studies of VH in LBD. Specifically, we included studies focusing on the comparison between hallucinating and non-hallucinating patients with PD, PDD and DLB. VH are a common symptom in LBD, and tend to be more complex and severe in patients with cognitive impairment (McKeith et al., 2017, Onofrj et al., 2013). Other related minor hallucinatory phenomena, including false sensations of presence and sideway passages, are also frequently observed, especially in PD, and may be experienced in conjunction with more complex VH (Aarsland et al., 2009, McKeith et al., 2017, Onofrj et al., 2013). In the current meta-analyses, we included studies comprising LBD patients with complex and/or minor VH, compared with those without hallucinations.

6.1 Experiment 5: Voxel-based meta-analysis of regional grey matter volumes associated with visual hallucinations in Parkinson's disease and dementia with Lewy bodies

6.1.1 Introduction

Following our systematic literature review (section 2.4.1.1), we found 16 VBM studies on VH in LBD. Of these studies, 11 used a whole brain approach to investigate differences between patients with and without VH, of which only four reported results using correction for multiple comparisons (Bejr-Kasem et al., 2019, Meppelink et al., 2011, Ramirez-Ruiz et al., 2007b, Shin et al., 2012). As mentioned previously, this poses interpretative issues, since the use of more liberal thresholds (e.g. uncorrected p-values) may generate a higher number of false positives, a problem that has been linked to neuroimaging studies in general (Muller et al., 2018, Wager et al., 2009). For this reason, findings from studies using uncorrected thresholds should be interpreted more cautiously. In addition, apart from a few exceptions, sample sizes were relatively small. Thus, the need of combining findings using a meta-analytic approach, with higher statistical power than single studies taken individually, appears clearly from the current literature.

Voxel-based meta-analyses have been previously applied to the study of the structural brain correlates of auditory hallucinations in schizophrenia (Modinos et al., 2013, Palaniyappan et al., 2012). Furthermore, a whole brain VBM meta-analysis of hallucinations has been published recently, which included patients with psychiatric

and neurodegenerative disorders (Rollins et al., 2019). In particular, the authors performed two separate meta-analyses, comprising studies respectively on neurodegenerative and psychiatric conditions. Patients with PD have also been included in this study, along with patients with AD, schizophrenia, first episode psychosis, and participants at risk of psychosis (Rollins et al., 2019). In this meta-analysis, however, auditory hallucinations were also taken into account, for a total of only 8 studies on neurodegenerative disorders, and 8 on psychiatric conditions. VH in neurodegeneration have been associated with GM loss in occipital, temporal and parietal areas (Rollins et al., 2019). Nevertheless, since the aim was to investigate transdiagnostic structural brain correlates of hallucinations, this meta-analysis was not specific for VH in LBD (Rollins et al., 2019). Even though hallucinations in different sensory modalities often occur in conjunction, they may be the result of distinct pathophysiological mechanisms. Focusing on VH in LBD, instead, may add further insight on disease and symptom-specific neural alterations.

A voxel-based meta-analysis of neuroimaging studies may be performed in two main ways, namely image-based and coordinate-based meta-analyses (Muller et al., 2018, Radua and Mataix-Cols, 2012). The abovementioned meta-analyses on hallucinations in psychiatric and neurodegenerative disorders were all coordinate-based (Modinos et al., 2013, Palaniyappan et al., 2012, Rollins et al., 2019). This type of meta-analysis is performed using peak coordinate data available in published articles that represent summarised results reaching statistical significance at a specified threshold. Image-based meta-analyses, instead, include statistical maps (T-maps), unthresholded three-dimensional maps containing results of statistical comparisons for every single voxel in the brain. The use of T-maps allows the implementation of more accurate meta-analyses compared with those including peak coordinates only, as combining T-maps takes into account also subthreshold results. Nevertheless, coordinate-based meta-analyses are more common, mainly due to the limited availability of T-maps (Radua and Mataix-Cols, 2012). Indeed, t-maps may be obtained only if shared by authors of individual studies. Recently, web-based repositories for collecting and sharing brain statistical maps have been developed (Gorgolewski et al., 2015), although they are still rarely available. Thus, in most cases, carrying out a t-map meta-analysis requires authors of single studies to be contacted directly. A meta-analytic method recently developed by Radua et al. (2012), namely the Seed-based d Mapping (SDM) software, allows the combination of peak coordinates and t-maps in the same meta-analysis. This approach allows a comprehensive inclusion of studies, but also more accurate meta-analyses than those

comprising coordinate data only. In fact, it has been noted that including t-maps, even for just one sample, improves the meta-analysis considerably (Radua et al., 2012).

Aims and hypotheses

The aim of the present study was to use SDM to perform a meta-analysis of VBM studies on VH in LBD combining peak coordinate data and T-maps. To our knowledge, this is the first voxel-based meta-analysis investigating the structural brain differences between hallucinating and non-hallucinating patients with PD/DLB focusing on the visual modality. Based on current literature and our previous studies, we hypothesised an involvement of brain regions within large-scale attention networks (fronto-parietal and subcortical areas) and occipital/occipito-temporal regions (see Chapter 4 for further details).

6.1.2 Methods

6.1.2.1 Literature search and study selection

A systematic search, following the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009), was conducted up to April 2019 using the PubMed and Web of Science databases. The aim was to identify VBM studies focusing on VH in LBD using the following key words: "visual hallucinations", "visual hallucination", "Lewy body", "dementia with Lewy bodies", "Parkinson's disease", "magnetic resonance imaging", "MRI", "voxel-based morphometry", "VBM". The reference section of the identified studies were also screened to search for additional records. The following exclusion criteria were used to select relevant studies: (1) pathologies other than DLB, PD, or PDD; (2) neuroimaging techniques other than MRI whole brain VBM; (3) analysis of grey matter volume not comparing LBD patients with and without VH and/or minor VH; (4) peak coordinates were not reported or t-maps were not available (5) studies restricting the analysis to *a priori* small volume corrections; (6) patients with medication-induced VH; (5) case studies; (6) review and theoretical articles; (7) articles not in English; and (8) non-peer reviewed articles. Authors of the VBM studies identified were contacted by email asking for unpublished data, including the T-maps of the whole brain grey matter volume analysis for the comparison between hallucinating and non-hallucinating patients. Sharing T-maps does not raise any ethical or anonymity issue as they contain pooled group data and no identifiable individual information.

6.1.2.2 Seed-based d Mapping meta-analysis

Regional GM volumetric differences between hallucinating and non-hallucinating patients were assessed using the anisotropic version of the Effect-size SDM software (AES-SDM, v5.141), available online at https://www.sdmproject.com/ (Radua et al., 2012, Radua et al., 2014). This method allows the combination of peak coordinates and t-maps in the same meta-analysis (Radua et al., 2012).

Firstly, studies were included only when the statistical threshold applied within each study was the same throughout the brain. This approach aimed at avoiding biases related to the application of more liberal thresholds to particular brain regions, such as small volume corrections. Therefore, only whole brain analyses were considered for this meta-analysis. When t-maps were available, they were firstly converted to unbiased effect size and variance maps using SDM (Radua et al., 2012). For studies including peak coordinates, an effect-size signed map of GM differences was recreated by SDM for each study, with both positive and negative coordinates within the same map (Radua and Mataix-Cols, 2009). SDM calculated the effect sizes within the peaks and estimated them for the rest of the voxels by assigning larger effect sizes to surrounding voxels. An isotropic kernel of 20mm was used, as suggested by Radua et al. (2012). In addition, the anisotropic version of the software estimates larger effect-sizes to highly spatially correlated voxels, which are more likely to be part of the same brain region (Radua et al., 2014). Full anisotropy was performed as recommended for coordinate-based meta-analysis (Radua et al., 2014). In order to do this, a correlation template for grey matter was used (Radua et al., 2014).

Effect sizes from each study were then combined using meta-analytic random-effects models. Each study was weighted by the inverse of its variance, between-study heterogeneity, and sample size (Radua et al., 2012). Statistically significant clusters were determined with the Monte Carlo randomizations, specifically performing 100 permutations. A statistical threshold of p=0.005 uncorrected was used as optimal balance between sensitivity and specificity (Radua et al., 2012). An additional threshold of $z > 2$, to decrease the possibility of false positive, and an extent threshold of 10 voxels were also applied as recommended by Radua et al. (2012). Grey matter brain regions labels were obtained automatically by SDM using the Automated Anatomical Labeling (AAL) software (Tzourio-Mazoyer et al., 2002).

Heterogeneity was examined for each significant peak with the I^2 statistic, which corresponds to the percentage of between-study variability. Publication bias was examined by carrying out the Egger's test for each peak. Robustness and reproducibility of the results were assessed with jackknife sensitivity analyses, which

consist in repeating the meta-analysis by removing a study sample each time (Radua et al., 2012). Sub-group analyses were also performed including only studies on PD.

6.1.3 Results

6.1.3.1 Included studies and sample characteristics

The initial literature search produced 342 studies of which 150 were duplicate publications. Among the 192 records screened for eligibility, the authors of 16 studies were contacted asking for additional or unpublished data. Two studies performed voxel-based ROI analyses (Ibarretxe-Bilbao et al., 2008, Sanchez-Castaneda et al., 2010), two compared patients with VH and controls (Gama et al., 2014, Nishio et al., 2017), and one investigated progression of brain atrophy (Ibarretxe-Bilbao et al., 2010). Authors of these latter studies were contacted to ask for unpublished whole brain analyses comparing patients with and without VH. A flow chart summarizing the selection process is shown in Figure 6.1. Peak coordinates reported on the published papers were included for 6 studies, all on PD (Lee et al., 2017, Meppelink et al., 2011, Pagonabarraga et al., 2014, Ramirez-Ruiz et al., 2007b, Shin et al., 2012, Watanabe et al., 2013). The authors of four studies agreed to send the t-maps of their analyses for the comparison between hallucinating and non-hallucinating patients, three on PD (Bejr-Kasem et al., 2019, Firbank et al., 2018, Goldman et al., 2014) and one on DLB (Blanc et al., 2016). No sample overlap between studies was found.

The meta-analysis consisted of a total of 10 studies, including 190 LBD patients with VH and 227 without. The demographic, clinical and methodological characteristics available for each study are summarized in Table 6.1.

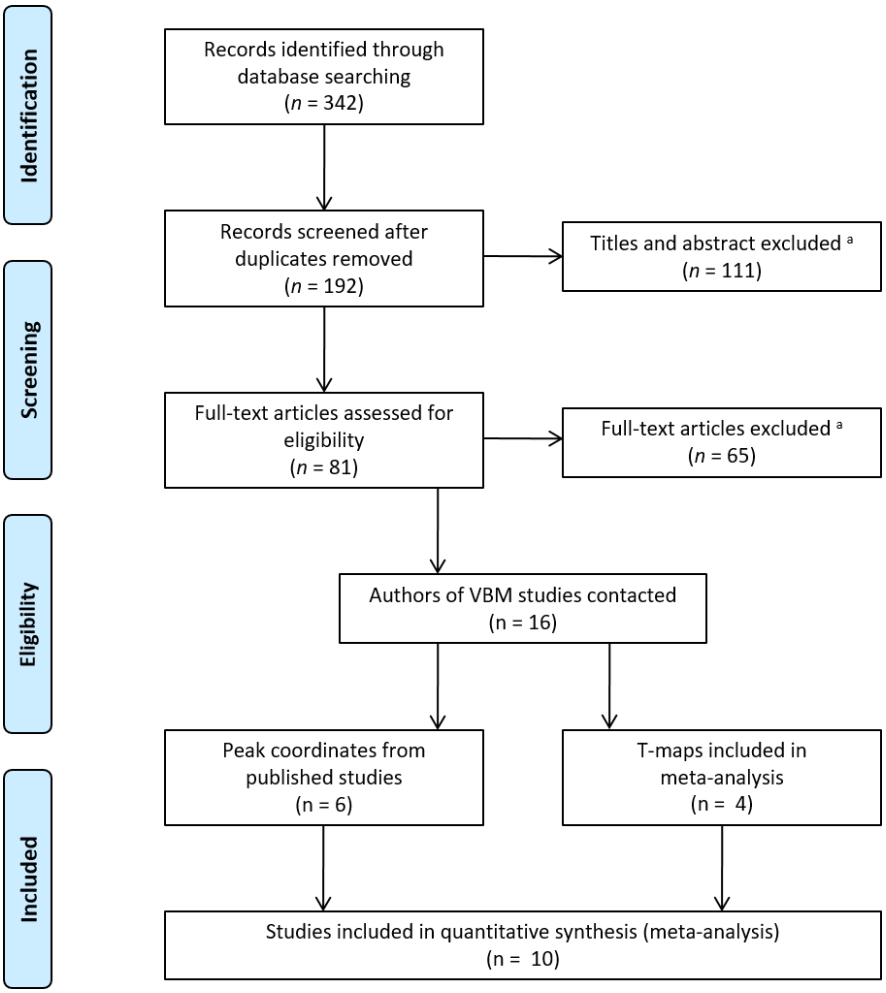

Figure 6.1 Flow chart describing the selection process of the studies included, adapted from Moher et al. (2009). [a] Exclusion criteria: (1) pathologies other than DLB, PD, or PDD; (2) neuroimaging techniques other than MRI whole brain VBM; (3) analysis of grey matter volume not comparing LBD patients with and without VH and/or minor VH; (4) peak coordinates were not reported or t-maps were not available (5) studies restricting the analysis to a priori small volume corrections; (6) patients with medication-induced VH; (5) case studies; (6) review and theoretical articles; (7) articles not in English; and (8) non-peer reviewed articles.

Table 6.1 Characteristics of the 10 studies included in the SDM meta-analysis. Mean and SD are reported for each variable.

Study	LBD patients	Age	MMSE	Covariates	Data
Bejr-Kasem et al. (2019)	18 PD mVH 14 PD NVH	70.4 (5.5) 65.8 (7.8)	NA	Age, sex, education, TIV	T-map
Blanc et al. (2016)	17 DLB VH 11 DLB NVH	68.5 (8.4) 66.0 (10.6)	27.5 (2.5) 27.8 (1.5)	TIV, age, sex	T-map
Firbank et al. (2018)	17 PD VH 19 PD NVH	75.5 (4.5) 72.3 (5.1)	23.1 (4.9) 25.6 (4.1)	Age, TIV, CAMCOG	T-map
Goldman et al. (2014)	25 PD VH 25 PD NVH	74.8 (6.0) 75.4 (6.1)	23.9 (5.4) 25.1 (4.4)	TIV	T-map
Lee et al. (2017)	10 PD VH 21 PD NVH	69.4 (5.3) 66.2 (6.8)	27.6 (1.8) 28.2 (1.4)	TIV, age, sex	Coordinates
Meppelink et al.(2011)	11 PD VH 13 PD NVH	NA	NA	Total GM volume	Coordinates
Pagonabarraga et al. (2014)	15 PD mVH 27 PD NVH	64.1 (9) 66.3 (8)	NA	Total GM volume, age, sex	Coordinates
Ramirez-Ruiz et al.(2007b)	18 PD VH 20 PD NVH	NA	27.0 (2.1) 29.1 (1.4)	TIV, MMSE, HDRS, H&Y	Coordinates
Shin et al. (2012)	46 PD VH 64 PD NVH	71.3 (5.9) 70.7 (5.7)	25.2 (3.0) 25.7 (2.9)	TIV, age, sex, MMSE, PD duration	Coordinates
Watanabe et al. (2013)	13 PD VH 13 PD NVH	66.6 (5.5) 63.6 (10.7)	27.9 (1.9) 29.0 (1.5)	TIV, age, sex	Coordinates

CAMCOG: Cambridge Cognition Examination; DLB: dementia with Lewy bodies; GM: grey matter; H&Y: Hoehn and Yahr; HDRS: Hamilton depression rating scale; LBD: Lewy body disease; MMSE: Mini-Mental State Examination; mVH: minor visual hallucinations; NA: not available; NPI: Neuropsychiatric Inventory; NVH: no VH; PD: Parkinson's disease; TIV: total intracranial volume; VH: visual hallucinations.

6.1.3.2 Seed-based d Mapping meta-analysis results

Grey matter volume differences between patients with and without hallucinations in LBD are shown in Table 6.2 and displayed in Figure 6.2. Regions of decreased grey matter volume in patients with VH were found mainly in the left hemisphere in the following regions: middle occipital, parahippocampal and inferior temporal gyri, calcarine fissure and surrounding cortex, and thalamus. Decreased GM volume was also detected in the right angular gyrus (BA 40) and inferior parietal lobule, and in the cerebellum.

Heterogeneity was low for all clusters ($I^2 < 25\%$) (Higgins et al., 2003), and it was equal to zero for 4 clusters (Figure 6.2). Significant publication bias was detected by means of the Egger test of funnel plot asymmetry in two clusters, namely those located in the left parahippocampal gyrus (p=0.02) and thalamus (p=0.002). No

significant publication bias was detected in any other cluster (all p values > 0.05). Sensitivity analyses revealed a cluster remaining significant in 10 out of 10 jacknife iterations, which was located in the left middle occipital gyrus (Table 6.2 and Figure 6.2). When the meta-analysis was performed on studies on PD only, four clusters were still significant, specifically located in the following regions: left middle occipital (BA 19) and parahippocampal gyri (BA 28), cerebellum, and right angular gyrus (BA 40).

Table 6.2 Regions of reduced GM volume in LBD patients with hallucinations compared to those without. JK shows the number of sensitivity analyses with the result remaining significant (out of 10).

Structure	Cluster size	MNI coordinates			SDM-Z	p value	I^2	Egger test (p)	JK
Left middle occipital gyrus (BA 19)	126	-46	-84	2	-2.43	0.00064	22%	0.21	10
Left parahippocampal gyrus (BA 28)	98	-18	0	-30	-2.56	0.00039	0%	0.02	9
Left calcarine fissure / surrounding cortex	314	-4	-84	10	-2.34	0.00094	2.5%	0.28	7
Cerebellum (vermic lobule IV / V)	91	2	-60	2	-2.22	0.0014	0%	0.48	7
Right angular gyrus (BA 40)	81	60	-52	30	-2.05	0.0027	9%	0.25	6
Right inferior parietal lobule (BA 40)	47	44	-56	42	-2.17	0.0017	15%	0.23	6
Left thalamus	12	-8	-4	12	-2.14	0.0019	0%	0.002	8
Left inferior temporal gyrus (BA 37)	10	-42	-38	-14	-2.09	0.0023	0%	0.67	5

BA: Brodmann area; GM: grey matter; JK: jackknife; LBD: Lewy body disease; NVH: no VH; VH: visual hallucinations.

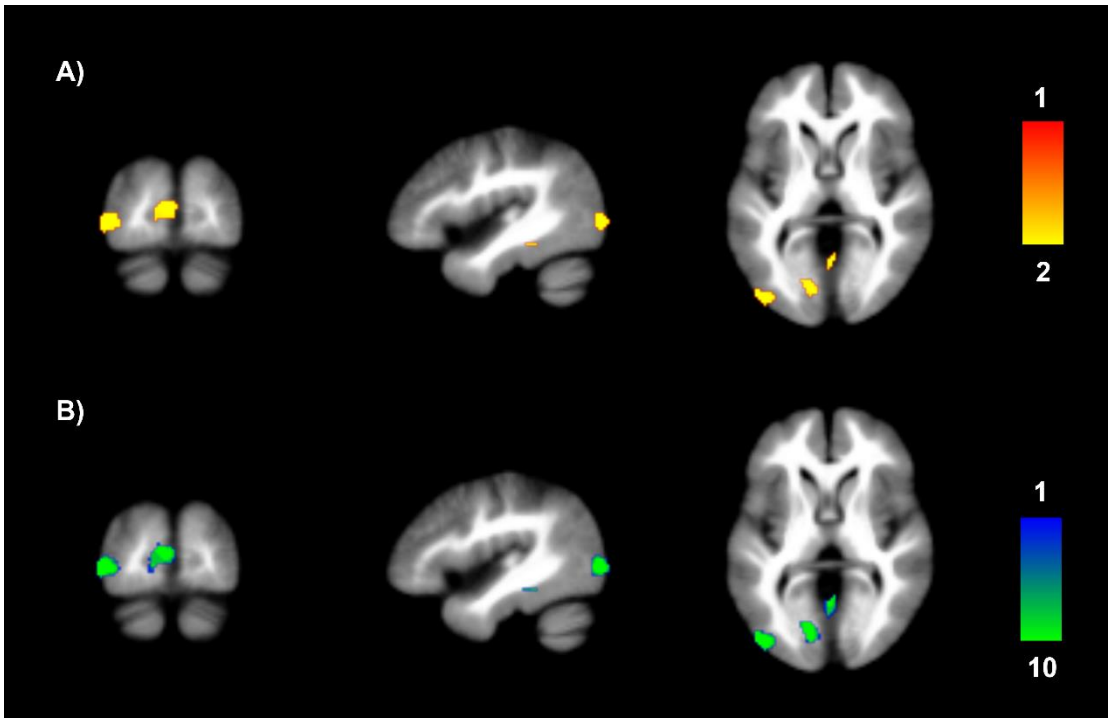

Figure 6.2 Meta-analysis results showing A) regions of reduced GM in LBD patients with VH compared to those without (the colour bar indicates the SDM-Z scores with a threshold of p<0.005 uncorrected, z>2, k> 10 voxels); B) binarised map of JK analyses representing regions of reduced GM in patients with VH (the colour map indicates the number of sensitivity analyses, out of 10, with the result remaining significant.

6.1.4 Discussion

The present meta-analysis provides evidence of structural brain differences between patients with and without VH in LBD. Specifically, we found regions of GM loss in hallucinating patients in occipital, temporal, parietal, cerebellar, and subcortical areas. However, sensitivity analyses showed that only one cluster, located in the left middle occipital gyrus was highly replicable, since it remained significant after repeating the meta-analysis 10 times removing one study each time. Heterogeneity was low for this cluster, and the Egger test of funnel plot asymmetry showed no evidence of publication bias. Importantly, when conducting the meta-analysis discarding the only study on DLB (Blanc et al., 2016), significant GM loss in the middle occipital gyrus, calcarine fissure and surrounding cortex remained significant. Given the very limited research that has been undertaken on the neuroanatomy of VH in DLB and PDD, it is difficult to infer disease-specific mechanisms across different diagnoses, especially concerning the presence of concomitant dementia. Other results from the present meta-analysis should be interpreted more cautiously, as they were not replicated by each sensitivity analysis, and significant publication bias was detected for two clusters

(left parahippocampal gyrus and thalamus), suggesting that some studies contributed more than others to such findings.

The present meta-analysis confirms our hypothesis of a contribution of occipital regions to VH in LBD, especially in PD. Occipital atrophy has been previously related to VH in different conditions, including LBD and AD (Carter and Ffytche, 2015). Other studies have reported an association between indices of VH and occipital metabolism in LBD, detected by means of FDG-PET (Firbank et al., 2016, Iaccarino et al., 2018, Kantarci et al., 2012). Accordingly, occipital and occipito-temporal hypometabolism or hypoperfusion have been found in hallucinating patients with PD (Gasca-Salas et al., 2016, Matsui et al., 2006), and DLB (Heitz et al., 2015, Pasquier et al., 2002, Perneczky et al., 2008). Functional MRI studies have also found altered activity in the occipital lobe. Specifically, decreased activity in occipital and temporal regions have been identified in response to visual stimuli in hallucinating patients with PD, compared with the non-hallucinating ones (Holroyd and Wooten, 2006, Lefebvre et al., 2016, Stebbins et al., 2004). In a resting-state fMRI study, Yao et al. (2016) found that patients with VH in PD had decreased functional connectivity between the hippocampus and occipito-temporal areas. Moreover, we previously found increased co-activation of visuoperceptive areas, namely the lateral geniculate body and the fusiform gyrus, in DLB patients with VH (Experiment 2, section 4.2), as well as alterations in WM integrity in bundles of fibres connecting occipital areas to temporal and frontal regions (Experiment 3, section 4.3). However, no occipital LB pathology has so far been associated with the presence of VH (Kalaitzakis et al., 2009), but significantly higher LB burden has been found mainly in temporal and frontal regions (Gallagher et al., 2011, Harding et al., 2002a, Harding et al., 2002b, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006). In this context, we speculate that occipital atrophy may represent a structural hallmark of disrupted functional and structural neural circuits contributing to VH in PD, especially involving visual areas, although not reflecting underlying neuropathological events directly.

The findings outlined above, together, suggest a contribution to VH of impaired ventral visual pathways, involved in the formation of object visual representations (Kravitz et al., 2013). This is in line with one of the leading models of VH, proposed by Collerton et al. (2005). Briefly, the authors proposed that recurrent, complex VH may generate from combined deficits in visual attention and object perception, the latter supported by impaired activity in the ventral visual stream (Collerton et al., 2005). However, the association between occipital atrophy and visual perception deficits could not be tested directly by the present study, due to the limited amount of data available, as

neuropsychological measures have been reported in only two studies (Goldman et al., 2014, Shin et al., 2012).

A number of limitations should be taken into account when interpreting the results of the present meta-analysis. Firstly, we were not able to retrieve t-maps for six studies and, therefore, subthreshold results were not included for these analyses. However, the limited availability of T-maps has generally led to the use of peak coordinates in most meta-analyses (Radua and Mataix-Cols, 2012). Moreover, the combination of both T-maps and coordinates in the same meta-analyses represents a well validated method, which has been shown to improve meta-analyses, even when T-maps are included for only one sample (Radua et al., 2012). Heterogeneity and publication bias were excluded for the main results. Nevertheless, between-study differences in demographics and other clinical features, and the implementation of different methodologies may have an impact on the results. Due to the low number of studies, meta-regression analyses exploring the association between regional GM loss and other sample characteristics were not performed. Thus, the influence of other clinical and demographic features cannot be completely ruled out. Moreover, the presence of potential differences across diagnostic populations (i.e. PD vs. DLB) could not be addressed, since patients with VH and concomitant dementia were highly underrepresented. Nevertheless, the main results remained significant even when only patients with PD were included, and sensitivity analyses suggest that they were highly replicable. Moreover, although publication bias cannot be completely ruled out, we also included studies not reporting significant differences in individual analyses (Meppelink et al., 2011), and subthreshold results through the use of T-maps (Bejr-Kasem et al., 2019, Blanc et al., 2016, Firbank et al., 2018, Goldman et al., 2014), ensuring that negative results were also well represented.

To our knowledge, this is the first meta-analysis investigating the structural brain features associated with VH in LBD, and represents an important addition to the current literature. The robustness of the meta-analytic method allowed a comprehensive summary of our current knowledge on the neural correlates of VH in LBD. This was improved further by the inclusion of whole brain T-maps, thus taking into account also brain regions not investigated by ROI studies, and results not reaching statistical significance in individual analyses.

With the present study, we demonstrated the presence of significant occipital GM loss in LBD patients with VH compared with those without, which may contribute to the genesis of this symptomatology, especially in patients with PD.

6.2 Experiment 6: Meta-analysis of neuropsychological studies of visual hallucinations in Parkinson's disease and dementia with Lewy bodies

6.2.1 Introduction

As reviewed in Chapter 2 (section 2.3), VH in LBD have been associated with specific cognitive deficits, including visual perception and visuoconstruction, attention, executive functioning, and long-term memory. Nevertheless, inconsistencies have also been reported, highlighting the need of a quantitative summary of studies exploring differences between LBD patients with and without VH in various cognitive domains. The importance of combining statistically results through meta-analyses has been highlighted in different areas of investigation in neuroscience, including neuropsychology (Demakis, 2006). Unlike qualitative literature reviews, meta-analyses allow the detection of precise measures of between-group differences, in which studies with larger sample sizes contribute more than smaller ones to the final effect size (Demakis, 2006).

Neuropsychological meta-analyses have been performed on different neurological and psychiatric conditions (Demakis, 2006), including PD (Henry and Crawford, 2004, Kudlicka et al., 2011, Ramanan and Kumar, 2013), DLB (Collerton et al., 2003), and AD (Weissberger et al., 2017). They have also been used to investigate the cognitive domains predicting the development of AD-type dementia in individuals with MCI (Belleville et al., 2017). Meta-analyses may also be used to explore differences in specific cognitive functions between subgroups of patients with and without a certain clinical symptom, but with the same diagnosis. For example, Pushpanathan et al. (2016) undertook a neuropsychological meta-analysis of studies exploring differences between PD patients with and without sleep problems, identifying significantly poorer performance in various cognitive domains in patients with sleep disorders. In this context, quantitatively summarising evidence on the specific cognitive deficits associated with VH in LBD would represent an important addition to our current knowledge on the neuropsychology of these symptoms.

Aims and hypotheses

The aim of the current meta-analysis was to combine findings from neuropsychological studies comparing patients with and without hallucinations in LBD, namely in PD, DLB and PDD, in a wide range of cognitive measures. In line with the

PAD model of VH (Collerton et al., 2005), we expected more severe impairments in hallucinating patients in visual perception and visual attention.

6.2.2 Methods

6.2.2.1 Literature search and study selection

The search strategy followed the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009). A systematic search was conducted up to April 2019 using the PubMed and Web of Science databases to identify neuropsychological studies of VH in LBD using the terms "visual hallucinations", "visual hallucination", "Lewy body", "dementia with Lewy bodies", "Parkinson's disease", "cognit*", "neuropsycholog*". The following exclusion criteria were applied: (1) pathologies other than DLB, PD, or PDD; (2) studies not using neuropsychological tests to investigate cognitive functioning; (3) statistical analysis not comparing LBD patients with and without VH and/or minor VH; (4) mean and standard deviation for the neuropsychological tests not available for each group of patients; (5) studies combining different neuropsychological tests into general cognitive domains (6) patients with medication-induced VH; (7) case studies; (8) review and theoretical articles; (9) articles not in English; and (10) non-peer reviewed articles.
Mean, standard deviation, t score and p-value were extracted for each test, when available. Moreover, we recorded the following data: age, gender, disease duration, education, MMSE and H&Y scores. Neuropsychological tests were considered for the meta-analysis only if investigated by three or more studies.

6.2.2.2 Statistical analysis

A separate random-effects meta-analysis was carried out for each neuropsychological test, each including at least three studies. In addition to the main results (effect size, confidence interval and p-value), the I^2 statistic was calculated, which describes the percentage of the variability between studies that might be due to between-study heterogeneity. Statistical tests for funnel plot asymmetry were also computed, which are useful to assess potential publication or reporting bias. Meta-regression analyses (by mean age, diagnosis, percentage of females, disease duration, education, MMSE and H&Y) were also carried out for those tests with statistically significant differences between patients with and without VH. All calculations were carried out with the “metansue” package for R (Radua et al., 2015).

Finally, the meta-analysis was repeated after discarding the three studies with LBD patients with dementia, namely PDD (Bronnick et al., 2011) and DLB (Cagnin et al., 2013, Heitz et al., 2015).

6.2.3 Results

6.2.3.1 Included studies and sample characteristics

The initial search yielded 1109 studies of which 371 were duplicate publications. In addition, four studies were identified by searching the reference lists of the articles obtained. Of the 738 records screened, 23 met inclusion criteria and were included in the meta-analysis (the selection process is described in Figure 6.3). Each test to be included in the meta-analysis had to have been investigated by three or more studies, for a total of 23 tests investigating different cognitive domains.

When overlapping samples of patients were detected, only the comparisons performed on the largest subgroups for each test were taken into account for the meta-analysis (Grossi et al., 2005, Santangelo et al., 2007). For longitudinal studies, only data collected at baseline were used (Santangelo et al., 2007). Wang et al. (2010) included three groups of patients with PD: 1) patients with VH and RBD, 2) patients with RBD but no VH, 3) patients without neither VH nor RBD. In the meta-analysis, we only included the first two groups, to take into account the presence of RBD as potential confounding factor. Llebaria et al. (2010) reported separate statistics for patients with minor VH, patients with major VH without insight, and patients with major VH with insight. The three samples were combined in a single global sample, calculating the global means and standard deviations of the three samples. Note that to calculate global standard deviations, both the standard deviations of the three samples, and the square differences between the means of the three samples and the global means were used. Clinical and demographic features for each study are summarized in

Table **6.3**. For the studies included in the meta-analysis, the weighted mean age was 69.32 for patients with VH and 67.12 for those without.

Neuropsychological tests included in the meta-analysis were as follows: TMT-A and B, RAVLT immediate and delayed recall, Rey figure copy and delayed recall, phonemic and semantic fluency, clock drawing test, digit span forward and backward, Boston naming test, Stroop test, FAB, Wisconsin card sorting test and the VOSP subtests (incomplete letters, silhouettes, object decision, progressive silhouettes, number location, position discrimination, dot counting and cube analysis).

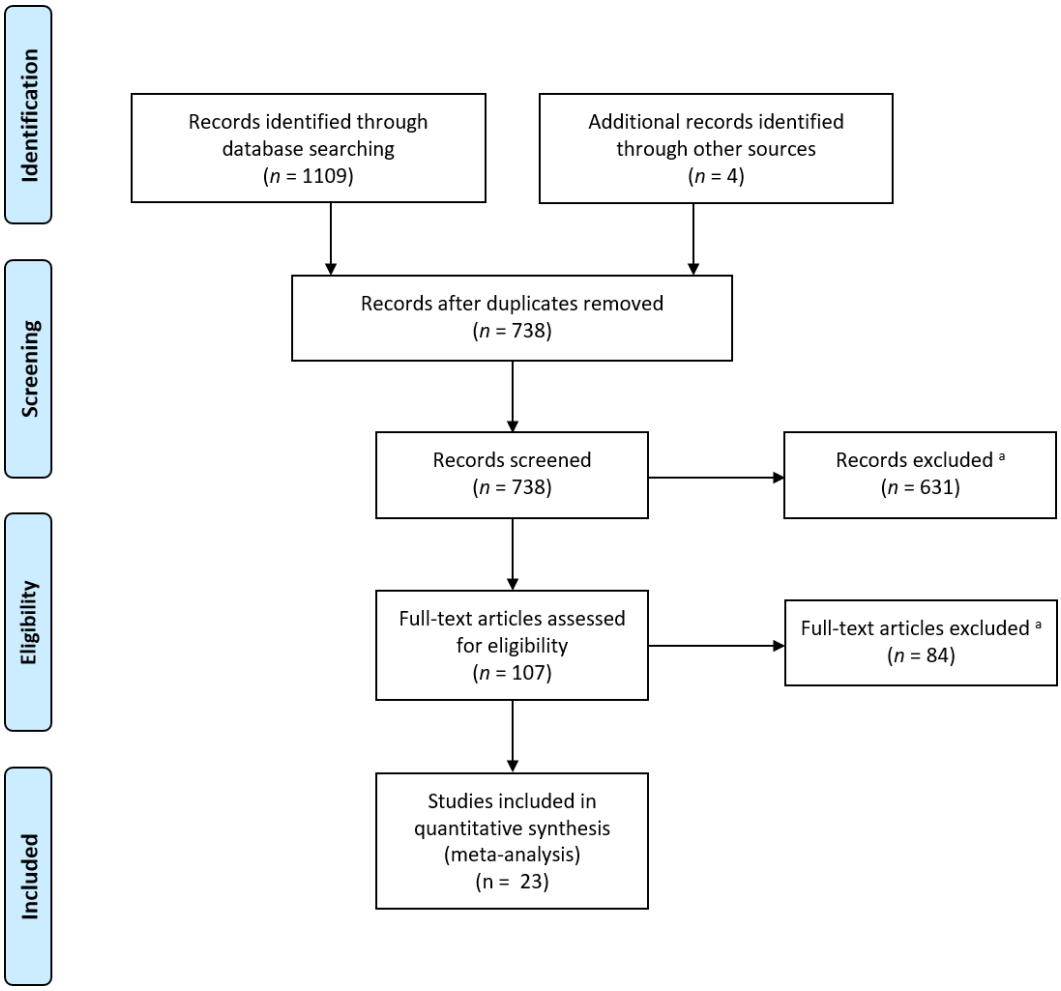

Figure 6.3 Flow chart describing the selection process of the studies included, adapted from Moher et al. (2009). [a] Exclusion criteria: (1) pathologies other than DLB, PD, or PDD; (2) studies not using neuropsychological tests to investigate cognitive functioning; (3) statistical analysis not comparing LBD patients with and without VH and/or minor VH; (4) mean and standard deviation for the neuropsychological tests not available for each group of patients; (5) studies combining different neuropsychological tests into general cognitive domains (6) patients with medication-induced VH; (7) case studies; (8) review and theoretical articles; (9) non-English articles; and (10) non-peer reviewed articles.

Table 6.3 Characteristics of the 23 studies included in the meta-analysis. Mean and SD are reported for each variable unless otherwise specified.

Study	Patients	Age	Ed. (y)	Disease duration (y)	MMSE	H&Y
Barnes et al. (2003)	17 PD VH 20 PD NVH	67.9 (5.9) 62.8 (10.9)	NA	11.9 (4.3) 8.8 (4.4)	26.7 (1.1) 27.5 (1.4)	3.4 (0.6) 2.9 (0.5)
Barnes and Boubert (2008)	19 PD VH 20 PD NVH	67.5 (4.7) 63.7 (9.5)	NA	11.9 (4.8) 9.7 (4.8)	26.4 (1.1) 27.2 (1.2)	3.8 (0.5) 2.9 (0.7)
Barnes and Boubert (2011)	36 PD VH 32 PD NVH	68.5 (4.3) 67.4 (6.5)	NA	10.0 (4.4) 9.5 (4.32)	27.3 (1.9) 27.6 (1.6)	3.8 (0.3) 2.5 (0.4)

Table 6.3 Continued.

Study	Patients	Age	Ed. (y)	Disease duration (y)	MMSE	H&Y
Bronnick et al. (2011)	86 PDD VH 86 PDD NVH	73.2 (5.9) 73.2 (6.1)	8.8 (3.9) 8.7 (3.8)	11.5 (6.4) 9.15 (5.1)	19.4 (3.8) 20.8 (3.0)	NA
Chang et al. (2016)	12 PD VH 23 PD NVH	67.8 (7.9) 66.4 (9.7)	9.3 (6.7) 10.9 (4.2)	11.7 (6.4) 6.2 (4.9)	27.7 (2.2) 27.6 (1.4)	2.7 (0.9) 1.5 (0.7)
Cagnin et al. (2013)	45 DLB VH 36 DLB NVH	76.6 (5.5) 72.4 (6.2)	6.8 (3.9) 8.5 (4.6)	2.3 (1.5) 2.1 (1.6)	21.7 (4.8) 23.9 (4.1)	NA
Creese et al. (2018)	24 PD VH 45 PD NVH	67.8 (7.8) 65.9 (8.5)	2 (2) [a] 2 (2) [a]	64.5 (99)[a,b] 41.4 (38)[a,b]	NA	NA
Gasca-Salas et al. (2016)	9 PD VH 12 PD NVH	70.7 (3.9) 70.8 (3.4)	12 (4) 9 (2.5)	14.7 (5.4) 14.3 (6.3)	27 (1.7) 25.9 (2.7)	NA
Grossi et al. (2005)	14 PD VH 34 PD NVH	67.4 (10.7) 66.9 (9.2)	12.7 (4.1) 8.5 (4.4)	10.4 (7.3) 6.3 (4.2)	26.6 (2.2) 27 (2.1)	2.8 (0.6) 2.5 (0.8)
Heitz et al. (2015)	36 DLB VH 30 DLB NVH	71.7 (10.2) 73.5 (6.9)	NA	NA	21.7 (5.6) 23.3 (4.3)	NA
Hepp et al. (2013)	31 PD VH 31 PD NVH	66 (11) 65 (11)	NA	7 (5) 8 (5)	27 (2) 28 (2)	2.5 (1-4) [c] 2.5 (1-4) [c]
Imamura et al. (2008)	11 PD VH 23 PD NVH	74.2 (10.4) 69.3 (6.9)	NA	9.5 (7.8) 5.7 (4.2)	26.5 (2.7) 28.1 (2.0)	NA
Koerts et al. (2010)	14 PD VH 14 PD NVH	69.0 (5.0) 67.1 (6.8)	4.4 (1.7) 4.2 (1.9)	10.7 (4.9) 6.0 (5.7)	26.2 (1.3) 26.4 (1.6)	NA
Lenka et al. (2018)	42 PD VH 51 PD NVH	58.7 (7.7) 57.8 (6.9)	NA	6.6 (3.2) 5.8 (2.4)	NA	2.4 (0.2) 2.3 (0.3)
Llebaria et al. (2010)	29 PD VH 28 PD NVH	74.96 (5.2) 72.7 (6)	8.5 (4.8) 8.4 (5)	8.6 (4.1) 7.9 (5)	NA	2.5 (0.7) 2 (0.5)
Manganelli et al. (2009)	10 PD VH 12 PD NVH	70.4 (5.3) 65.5 (10.1)	12 (6) 12 (5)	8.7 (6.3) 9 (5.5)	27.4 (1.6) 27.8 (1.9)	NA
Nishio et al. (2018)	19 PD VH 53 PD NVH	69.4 (6.3) 65.7 (6.4)	12.7 (1.9) 11.2 (2.1)	7.3 (4.5) 6.7 (4.2)	26.6 (2.9) 28.4 (1.7)	NA
Ozer et al. (2007)	33 PD VH 30 PD NVH	67.4 (8.3) 65.5 (9.4)	NA	6.7 (4.4) 5.9 (3.6)	NA	NA
Ramirez-Ruiz et al. (2006)	24 PD VH 21 PD NVH	74.7 (5.4) 73.3 (6.1)	7.3 (3.4) 7.7 (3.4)	NA	26.7 (2.1) 29.2 (1.4)	3.3 (1.1) 2.5 (0.7)
Santangelo et al.(2007)	9 PD VH 15 PD NVH	72.1 (9) 70.1 (8.6)	11.7 (4.7) 10.3 (4.3)	10.5 (5) 6.2 (2.9)	23.3 (6.2) 26.2 (2.7)	2.8 (0.9) 2 (0.5)

Table 6.3 Continued.

Study	Patients	Age	Ed. (y)	Disease duration (y)	MMSE	H&Y
Shin et al. (2012)	46 PD VH 64 PD NVH	71.3 (5.9) 70.7 (5.7)	8.3 (5.1) 8.4 (5.2)	3.3 (3.0) [b] 2.8 (3.0)	25.2 (3.0) 25.7 (2.9)	NA
Thota et al. (2017)	34 PD VH 35 PD NVH	58.7 (8.4) 55.7 (8.2)	NA	NA	28.2 (1.9) 28.7 (1.2)	2.3 (0.3) 2.2 (0.3)
Wang et al. (2010)	10 PD VH 10 PD NVH	68.4 (7.1) 67 (8.98)	NA	7.6 (4.3) 5.9 (2.2)	25.7 (1.57) 26.9 (1.1)	2.1 (0.6) 1.8 (0.6)

DLB: dementia with Lewy bodies; Ed.: education; H&Y: Hoehn and Yahr; IQR: interquartile range; MMSE: Mini-Mental State Examination; NA: not available; NVH: no VH; PD: Parkinson's disease; PDD: Parkinson's disease dementia; VH: visual hallucinations; y= years. [a] median (IQR); [b] months; [c] median (range).

6.2.3.2 Meta-analysis of neuropsychological tests results

Results from the comparison between hallucinating and non-hallucinating patients for each neuropsychological test are reported in Table 6.4. Forest plots for tests where statistically significant differences were found are shown in Figure 6.4, Figure 6.5, Figure 6.6 and Figure 6.7. Patients with VH had lower scores on the RAVLT immediate recall, assessing verbal long-term memory (k=5; *d*=-0.48, 95% CI=-0.73 to -0.24; *p*=0.0001), result that survived correction for multiple comparisons (p<0.002). Hallucinating patients also showed poorer performance in the RAVLT delayed recall (k=4; *d*=-0.40, 95% CI=-0.67 to -0.13; *p*=0.004), phonemic fluency (k=9; *d*=-0.22, 95% CI=-0.38 to -0.06; *p*=0.008), and TMT-A (k=5; *d*=0.33, 95% CI=0.07 to 0.59; *p*=0.01), although not surviving multiple comparison correction (p<0.002). No significant differences were found in the TMT-B, clock drawing, Rey figure copy and delayed recall, any VOSP subtest, digit span forward and backward, semantic fluency, Stroop colour-word, FAB, WCST, and Boston naming test. Heterogeneity across studies was examined with the I^2 statistic, which was 0% for all the neuropsychological tests except the FAB (I^2=20%), TMT-B (I^2=58%) and Rey figure delayed recall (I^2=58%). Heterogeneity was only marginally significant for the TMT-B and Rey figure delayed recall (p=0.05). No evidence of significant publication bias was found using the Egger's test (Table 6.4). Funnel plots for the RAVLT immediate and delayed recall, phonemic fluency, and TMT-A are displayed in Appendix 5.

Meta-regression analyses were also performed for the tests that resulted significantly different between groups from the meta-analysis (RAVLT immediate and delayed recall, phonemic fluency, and TMT-A). None of the variables investigated (age,

gender, disease duration, education, MMSE and H&Y scores) was predictive of the differences detected between groups.

Table 6.4 Meta-analysis of neuropsychological tests results.

Test	k	n		*d*	95% CI		p value	I^2	Q (p)	Egger test (p)
		VH	NVH		upper	lower				
TMT-A	5	114	123	0.33	0.07	0.59	**0.01**	0%	0.54	0.22
TMT-B	4	80	107	0.19	-0.30	0.68	0.50	58%	0.05	0.11
Clock drawing	4	117	106	-0.11	-0.37	0.16	0.43	0%	0.98	0.68
Rey figure:										
Copy	7	197	230	-0.05	-0.25	0.14	0.59	0%	0.91	0.79
Delayed recall	5	176	205	-0.27	-0.60	0.05	0.10	58%	0.05	0.28
VOSP:										
Incomplete letters	4	95	90	-0.23	-0.52	0.06	0.12	0%	0.98	0.90
Silhouettes	4	95	90	-0.04	-0.32	0.25	0.81	0%	0.98	0.70
Object decision	4	95	90	-0.21	-0.51	0.08	0.15	0%	0.61	0.26
Progressive silhouettes	4	95	90	0.14	-0.15	0.43	0.35	0%	0.76	0.88
Dot counting	4	95	90	-0.14	-0.43	0.15	0.35	0%	0.86	0.39
Position discrimination	4	95	90	-0.22	-0.51	0.07	0.14	0%	0.63	0.23
Number location	4	95	90	-0.05	-0.34	0.24	0.73	0%	0.84	0.53
Cube analysis	4	95	90	-0.08	-0.37	0.21	0.61	0%	0.99	0.80
RAVLT:										
Immediate recall	5	121	149	-0.48	-0.73	-0.24	**0.0001**[a]	0%	0.75	0.63
Delayed recall	4	97	128	-0.40	-0.67	-0.13	**0.004**	0%	0.76	0.29
Digit span:										
Forward	8	234	294	0.03	-0.14	0.21	0.71	0%	0.97	0.83
Backward	6	195	265	-0.08	-0.27	0.11	0.39	0%	0.65	0.30
Phonemic fluency	9	286	313	-0.22	-0.38	-0.06	**0.008**	0%	0.48	0.77
Semantic fluency	10	235	297	-0.17	-0.34	0.004	0.06	0%	0.31	0.95
Stroop colour-word	3	39	41	-0.18	-0.62	0.26	0.43	0%	0.82	0.66
FAB	5	116	130	-0.22	-0.51	0.08	0.15	20%	0.36	0.15
WCST	3	55	65	0.00	-0.36	0.36	1.00	0%	0.96	0.89
BNT	4	110	128	0.12	-0.14	0.38	0.36	0%	0.22	0.13

BNT: Boston naming test; CI: confidence interval; FAB: Frontal Assessment Battery; LBD: Lewy body disease; NVH: no visual hallucinations; RAVLT: Rey Auditory Verbal Learning Test; TMT: Trail Making Test; VH: visual hallucinations; VOSP: Visual and Object Space Perception battery; WCST: Wisconsin Card Sorting test. [a] significant after correction for multiple comparisons ($p<0.002$).

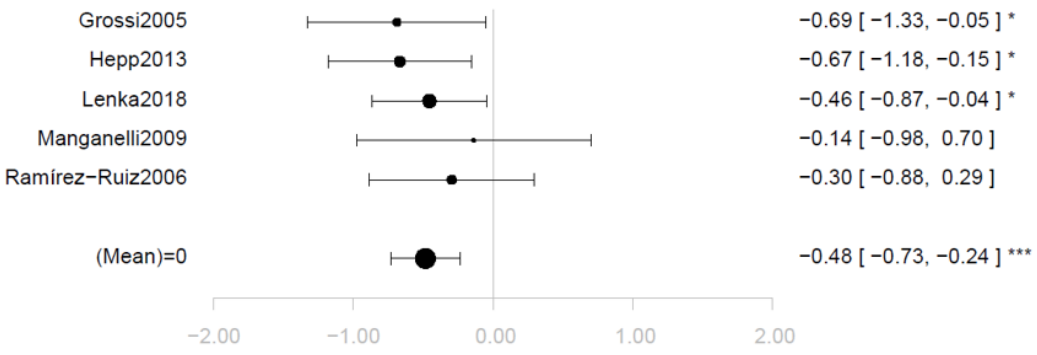

Figure 6.4 Forrest plot displaying mean effect sizes and 95% confidence intervals for the difference between patients with and without VH on the RAVLT immediate recall test. * p<0.05, *** p<0.001.

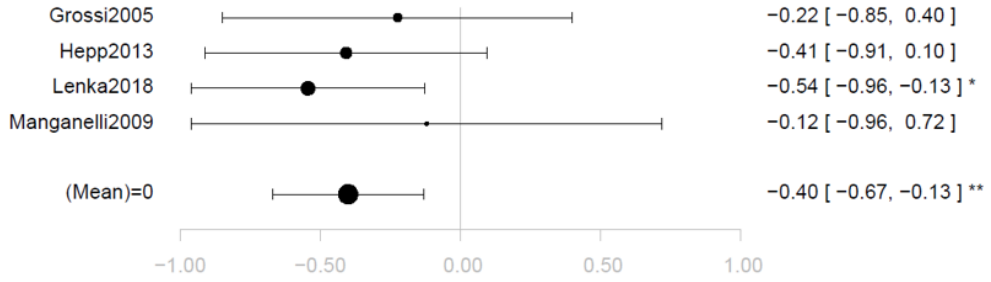

Figure 6.5 Forrest plot displaying mean effect sizes and 95% confidence intervals for the difference between patients with and without VH on the RAVLT delayed recall test. * p<0.05, ** p<0.01.

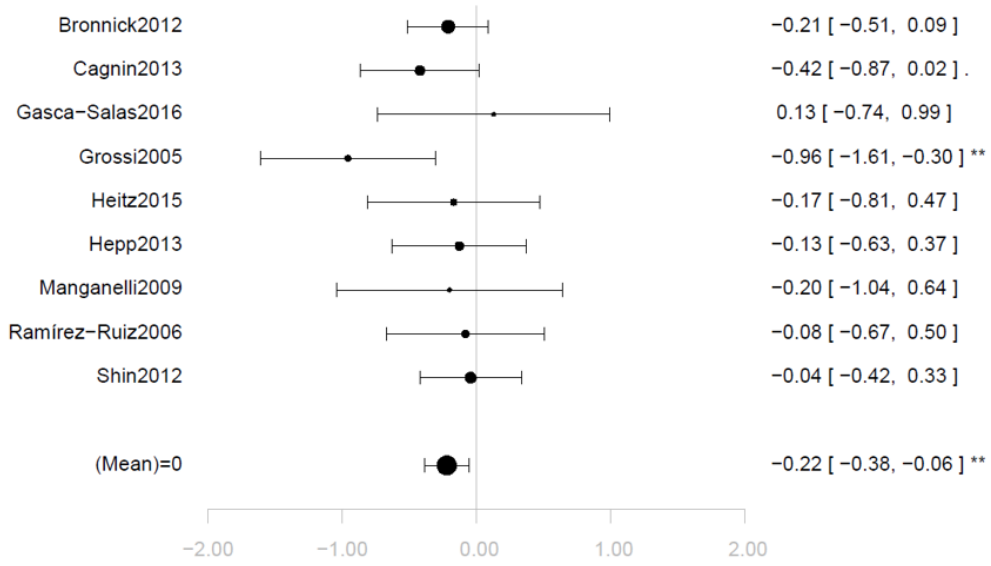

Figure 6.6 Forrest plot displaying mean effect sizes and 95% confidence intervals for the difference between patients with and without VH on the phonemic fluency test. ** p<0.01.

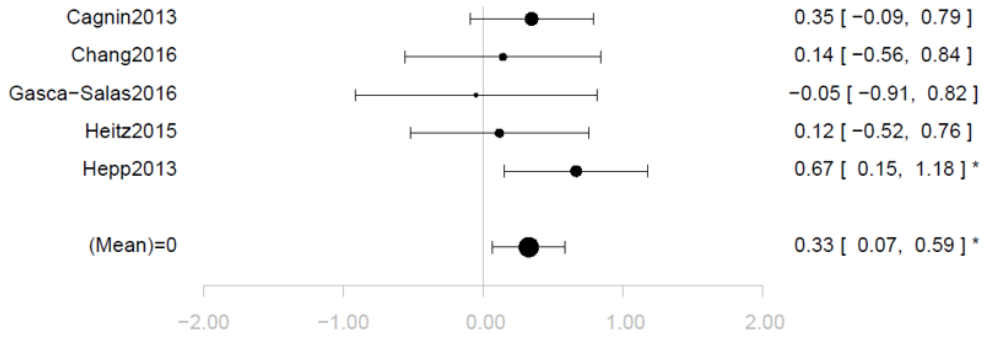

Figure 6.7 Forrest plot displaying mean effect sizes and 95% confidence intervals for the difference between patients with and without VH on the TMT-A test. * p<0.05.

The meta-analysis was also carried out excluding patients with a diagnosis of DLB (Cagnin et al., 2013, Heitz et al., 2015) and PDD (Bronnick et al., 2011). The RAVLT immediate recall was the only test presenting significant differences at a threshold corrected for multiple comparisons (k=5; *d*=-0.48, 95% CI=-0.73 to -0.24; p=0.0001). Although not surviving correction for multiple comparisons, differences between groups were also found in the RAVLT delayed recall (k=4; *d*=-0.40, 95% CI=-0.67 to -0.13; p=0.004) and in semantic fluency (k=9; *d*=-0.19, 95% CI=-0.37 to -0.01; p=0.04). Marginally significant findings were reported for the object decision subtest of the VOSP (k=3; *d*=-0.38, 95% CI=-0.77 to 0.01; *p*=0.05). No differences were detected in the TMT-A (k=3; *d*=0.35, 95% CI=-0.11 to 0.80; *p*=0.14) and in phonemic fluency (k=6; *d*=-0.19, 95% CI=-0.46 to 0.07; *p*=0.15). Meta-regression analyses revealed no significant effect of age, gender, disease duration, education, MMSE and H&Y scores on the differences in the RAVLT immediate and delayed recall, and semantic fluency. The I^2 statistic was 0% for these tests, and the Egger test showed no evidence of publication bias.

6.2.4 Discussion

The current meta-analysis provides evidence of the presence of verbal memory deficits in LBD patients with visual hallucinations compared with those without. In particular, hallucinating patients presented poorer performance on the RAVLT immediate recall, result that was significant after correction for multiple comparisons. More severe deficits were also found in executive functioning (phonemic fluency) and visual attention (TMT-A), although using an uncorrected threshold of significance. For these tests, no evidence of publication bias and heterogeneity was reported. Importantly, demographic and clinical variables showed no association with such

cognitive impairments, as highlighted by meta-regression analyses, suggesting that these deficits may characterise patients with VH regardless of other confounding factors. Similarly to the VBM meta-analysis described in section 6.1, LBD patients with dementia were highly underrepresented, therefore, subgroup analyses on this population could not be carried out. On the other hand, most studies were on PD. None of the studies included used the RAVLT immediate and delayed recall to explore differences in memory deficits between patients with and without VH in DLB/PDD. Thus, the interpretation of such findings cannot be extended to hallucinating patients with concomitant dementia.

Although less severe than those observed in AD, memory deficits have been shown in PDD, as well as PD with MCI (Emre et al., 2007, Fields, 2017, Goldman et al., 2018, Goldman and Litvan, 2011). At early stages, encoding and free recall impairments may be detected, while recognition memory is often spared, suggesting the presence of deficits in retrieval which might reflect executive dysfunctions (Aarsland, 2016, Fields, 2017). However, other studies have shown MTL-related deficits, namely storing and learning difficulties, which have been linked to a higher risk of developing of dementia, while frontal-related dysfunctions appeared more stable over the progression of the disease (Aarsland, 2016, Chiaravalloti et al., 2014). In a longitudinal study, Galtier et al. (2016) found that memory deficits, but not other cognitive dysfunctions, significantly predicted the subsequent development of dementia in patients with PD-MCI, probably due to MTL changes. Consistently, other studies reported memory impairments as significant predictors of the presence of dementia at follow-up in PD (Hobson and Meara, 2004, Levy et al., 2002, Pedersen et al., 2013). Evidence suggested a very close relationship between presence of VH and future development of cognitive impairment and dementia in PD (Onofrj et al., 2013). Indeed, longitudinal studies reported an increased risk of developing dementia at 4 to 8 years follow-up in patients with VH at baseline (Aarsland et al., 2003a, Anang et al., 2014). More severe progressive cognitive decline has also been shown in hallucinating PD patients compared with non-hallucinating ones, including deficits in verbal and visual memory, semantic fluency, language, and visuospatial abilities (Ibarretxe-Bilbao et al., 2010, Ramirez-Ruiz et al., 2007a). Notably, a recent neuropsychological meta-analysis of longitudinal studies found that verbal memory deficits in older adults with MCI predicted the subsequent development of AD-type dementia (Belleville et al., 2017). In this context, the presence of an AD-like cognitive profile in hallucinating PD patients may be driven by the presentation of early signs of dementia. Neuropathological studies reported a heterogeneous pattern of

pathological events underlying cognitive decline and dementia in PD, including limbic and cortical LB and AD pathology (Aarsland et al., 2017, Halliday et al., 2014). A high burden of LB pathology in frontal and temporal areas has also been found in patients with VH (Gallagher et al., 2011, Harding et al., 2002a, Kalaitzakis et al., 2009, Papapetropoulos et al., 2006). Interestingly, LB pathology in limbic areas has been related to both dementia and VH in PD (Kalaitzakis et al., 2009). In another study on PD, the presence of VH has been associated with both LB and AD pathology, and their comorbidity was significantly more common in hallucinating patients (Jacobson et al., 2014). These findings suggest that VH and dementia in PD may share some underlying pathological mechanisms, including the presence of LBs with or without concomitant AD-related pathology, which may foster the development of more severe memory deficits, as well as VH and dementia.

Alternatively to what is outlined above, the more severe memory deficits that we observed may be secondary to executive dysfunctions linked to more severely impaired fronto-striatal circuits. Such deficits may be more related to retrieval impairments, rather than difficulties in storing and learning due to MTL damage. Although some studies indicated more stable frontal-related dysfunctions in PD regardless of the presence of dementia, they have also been shown to worsen with disease progression (Aarsland et al., 2017, Dirnberger and Jahanshahi, 2013, Goldman et al., 2018). An association between executive deficits and development of cognitive decline has also been reported (Kehagia et al., 2010), suggesting the presence of differential patterns of cognitive deficits leading to dementia in PD, namely MTL and/or frontal-related dysfunctions. We found poorer executive performance in hallucinating patients, evaluated with the phonemic fluency test, result that disappeared when excluding from the meta-analysis patients with dementia. Moreover, tests assessing other aspects of executive functioning, such as the TMT-B, FAB and Wisconsin card sorting test, failed to show significant differences. It should be noted that the main finding of the present meta-analysis highlights the presence of more severe deficits in the RAVLT immediate recall, which might be influenced by working memory impairments. Selective attention and working memory are highly interrelated constructs sustained by common neural mechanisms, specifically related to the top-down modulation of prefrontal and parietal control regions (Gazzaley and Nobre, 2012). Working memory abilities also influence episodic memory performance by facilitating an efficient encoding of information (Wolk and Dickerson, 2011). In AD, early immediate recall of information, assessed with the initial encoding trials of the RAVLT, has been found to be associated with regions supporting working memory,

including frontal and parietal areas, while delayed memory performance has been found associated with MTL structures (Wolk and Dickerson, 2011). Executive dysfunction and working memory deficits have been related to impaired fronto-striatal dopaminergic circuits in PD (de la Fuente-Fernandez, 2012, Kehagia et al., 2010). Within this framework, impaired memory abilities in immediate recall might be explained by working memory difficulties due to fronto-striatal dopaminergic dysfunctions in LBD that, in turn, might constitute a susceptibility to VH. The nature of the memory deficits specifically characterizing LBD patients with VH needs to be explored more in depth, along with the specific executive domains that may affect this process.

In addition to the above, the role of memory deficits in the development of VH (discussed previously in section 5.1.4) might also be explained by dysfunctions of large-scale functional brain networks, especially in the DMN. In this context, as proposed by Shine et al. (2011), VH may be fostered by the emergence of inappropriate memories due to altered functional connectivity of the DMN. This, in conjunction with other disrupted neural circuits, most likely related to visual pathways, as shown by our VBM meta-analysis, may form the basis for the formation of false memories. However, no evidence of visual perception deficits was identified in the present neuropsychological meta-analysis. Individual studies reported worst performance in visual perception in hallucinating patients with PD (Barnes et al., 2003, Ibarretxe-Bilbao et al., 2010, Koerts et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a). Heterogeneity in the tests used by different studies might partially account for the negative result reported by our meta-analysis. None of the neuropsychological tests included was specific for the study of the cognitive correlates of VH in PD and therefore, may not be sensitive enough to detect deficits in specific visuoperceptive aspects linked to this symptomatology. Moreover, distinct cognitive mechanisms may underlie VH across different diagnoses. In support of this view, when including only patients with PD, differences in the VOSP subtest object decision were marginally significant. In addition, significant differences in visual attention in patients with VH disappeared when repeating the meta-analysis discarding studies on DLB. In this context, visual attention deficits might be driven by the inclusion of patients with dementia, while visual perception impairments may be more distinctive of hallucinating patients with PD without dementia. Nevertheless, this interpretation remains purely speculative and thus, future studies need to clarify the role of visual perception and visual attention in the development of VH across different LBD diagnoses.

The present meta-analysis is the first of its kind, and represents a valuable summary of our current knowledge on the cognitive mechanisms underlying VH in PD. However, we acknowledge the presence of some limitations. Firstly, the number of studies included for each neuropsychological test was relatively small. To decreased between-study heterogeneity in the tasks used, we only meta-analysed data if available for single neuropsychological tests, instead of combining multiple measures for similar cognitive constructs. This approach allows more precise analyses to be undertaken for each test, although it might have contributed in decreasing the number of studies included. Due to the limited amount of studies available, no subgroup analyses including only patients with concomitant dementia were performed. Therefore, differences between clinical diagnosis could not be tested. In spite of this, our results suggest that memory impairments may be distinctive of PD patients with VH regardless of other demographic and clinical features, as shown by meta-regression analyses. However, not all studies included such information and therefore, the influence of other variables cannot be completely ruled out.

6.3 General discussion

The meta-analyses described in this chapter provide evidence of the presence of structural GM alterations and neuropsychological deficits associated with the presence of VH in LBD, especially in PD. In particular, we found occipital GM atrophy and verbal memory deficits in hallucinating patients in comparison with non-hallucinating ones.

As outlined previously, the presence of occipital GM atrophy in patients with VH suggests an involvement of the ventral visual stream and related impairments in visual information processing, in line with multifactorial models of VH (Collerton et al., 2005). However, when meta-analysing neuropsychological data, no differences were detected in visual perception, but hallucinating patients were characterised by more severe memory deficits. We previously found that poorer performance on a verbal memory task at baseline significantly predicted the development of VH at follow-up in patients with DLB (Chapter 5), further highlighting the link between these clinical features. We suggested that LB and/or AD-related pathology in MTL areas might constitute a vulnerability to both VH and dementia in LBD, which may initially manifest as verbal memory impairments. These neuropathological processes may not necessarily lead to GM atrophy in MTL areas, but they may contribute in disrupting neural circuits involved in visual processing, ultimately resulting in occipital atrophy,

as suggested by our VBM meta-analysis. In this context, VH may be the result of a complex combination of dysfunctional brain mechanisms, involving memory-related circuits, and impaired activity of visuoperceptive regions, of which occipital atrophy may represent a structural marker.

To our knowledge, these are the first meta-analyses investigating structural brain abnormalities and neuropsychological features associated with VH in LBD. To note, only one study was included in both meta-analyses (Shin et al., 2012). Thus, interpretations inferring a direct correspondence between GM alterations and cognitive deficits should be formulated with caution, and remain purely speculative. Future studies including both structural MRI analysis and neuropsychological evaluation on the same sample of patients may aid our knowledge on the link between GM loss and cognitive deficits in relation to VH in LBD. Moreover, a substantial lack of studies comprising patients with dementia appeared clearly from the present meta-analyses, highlighting the need for future investigations systematically exploring potentially distinct patterns of alterations across different diagnoses.

Chapter 7. Visual hallucinations in Alzheimer's disease

7.1 Experiment 7. Cognitive, structural and functional brain correlates of visual hallucinations in Alzheimer's disease

7.1.1 Introduction

7.1.1.1 Alzheimer's disease

Alzheimer's disease is the most common cause of neurodegenerative dementia, accounting for around 50-70% of all dementia cases (Lane et al., 2018). Like DLB, sporadic AD is mainly a late-life condition. Along with having a family history of AD and carrying the APOE ε4 gene, older age is the main risk factor for AD (Alzheimer's Association, 2016, Lane et al., 2018). In fact, the likelihood of having the disease increases with age, especially after 65 years old (Alzheimer's Association, 2016, Lane et al., 2018). In addition, there are modifiable factors that increase/decrease the likelihood of developing AD. For example, variables associated with higher risk of developing cardiovascular disease, are also risk factors for AD, like diabetes, obesity, smoking and hypertension (Alzheimer's Association, 2016, Lane et al., 2018). Other lifestyle factors, instead, have been shown to protect against the disease, including education, physical exercise and diet (Alzheimer's Association, 2016, Lane et al., 2018, Mayeux and Stern, 2012). However, the causes of AD remains unknown, which is probably the result of the combination of genetic and environmental variables (Alzheimer's Association, 2016, Lane et al., 2018, Mayeux and Stern, 2012). No disease-modifying cure is currently available, but only symptom-related pharmacological and non-pharmacological therapies (Alzheimer's Association, 2016, Scheltens et al., 2016).

Neuropathological characteristics of AD include the accumulation of Aβ and tau proteins in amyloid plaques and neurofibrillary tangles, respectively, and consequent neurodegeneration (Lane et al., 2018, Scheltens et al., 2016). Both amyloid and tau pathology are required for a diagnosis of AD, however, the precise biological mechanisms involved still need to be elucidated (Lane et al., 2018). The neuropathological alterations precede the clinical symptoms of many years. As for

LBD, definite diagnosis of AD can be made only post-mortem with neuropathological confirmation of AD pathology. Biomarkers have been developed to support the diagnosis *in vivo*, which have been associated to specific disease-related pathophysiological mechanisms, and include CSF Aβ, total tau and phosphorylated tau (p-tau), PET amyloid imaging, temporo-parietal hypometabolism and MTL atrophy detected with FDG-PET and structural MRI, respectively (Dubois, 2018, Jack et al., 2013). In addition to amyloid plaques and neurofibrillary tangles, patients with AD pathology may also present accumulation of LBs. In fact, as outlined previously (see section 1.6), diagnosing DLB needs to take into account the AD-related pathological load, and the degree of AD and LB pathology reflecting the clinical syndrome (McKeith et al., 2017, McKeith et al., 2005). LB and AD pathology often coexist. Neuropathological findings have shown that roughly 50% of patients with LB pathology clinically resemble AD, and present high degree of AD pathology (Outeiro et al., 2019). However, robust evidence on epidemiological and clinical characteristics of such mixed AD/DLB cases is still lacking.

The main clinical feature of AD is cognitive decline, most commonly characterized by early episodic memory problems, considered a marker of typical AD and usually manifesting as amnestic MCI (Dubois, 2018, Lane et al., 2018). From a neuropsychological point of view, AD is characterized by more severe memory deficits, while DLB and PDD by more pronounced visual perception, attention and executive dysfunctions, especially at the early stages (Collerton et al., 2003, Goldmann Gross et al., 2008, McKeith et al., 2017). Moreover, faster decline in long-term memory was found in AD, and in executive functioning in DLB (Breitve et al., 2014). Nevertheless, AD and DLB are often misdiagnosed, mainly due to overlapping clinical, cognitive and neuropathological features (McKeith et al., 2017, Morra and Donovick, 2014). Neuropsychological assessment represents an essential tool for the differential diagnosis, especially in the early stages. Visuospatial/constructive impairment has been found to be particularly useful in differentiating between the two conditions, both at prodromal stages and as the disease progresses (Cagnin et al., 2015b, Mitolo et al., 2014, Tiraboschi et al., 2006). Moreover, it has been shown that the best model differentiating autopsy confirmed AD from DLB in the early stages included the presence of VH and lack of visuospatial impairment, being positive and negative predictors of LB pathology, respectively (Tiraboschi et al., 2006).

To complicate further the differential diagnosis problem there is the presence of cases with mixed AD/DLB pathology. As reported by a systematic review, studies have shown that patients with mixed AD/DLB had a faster global cognitive decline than

those with pure DLB or AD (Breitve et al., 2014). However, the sensitivity of clinical diagnosis for such mixed cases has been found to be very low, around 12% (Nelson et al., 2010). Importantly, VH have been identified not only as the most specific clinical symptom differentiating DLB from AD in the early stages, but also as the only feature suggesting the presence of LBs in mixed AD/LB pathology cases (Thomas et al., 2018, Tiraboschi et al., 2006, Toledo et al., 2013). In a neuropathological and multimodal biomarker study, Toledo et al. (2013) studied 22 autopsy-confirmed AD patients. They found that hallucinations predicted, with 100% specificity, the presence of concomitant LB pathology, as well as more severe executive dysfunction (80.0% sensitivity and 83.3% specificity), and occipital FDG-PET hypometabolism (80% sensitivity and 100% specificity) (Toledo et al., 2013).

Research on epidemiological and other clinical features, such as progression and prognosis, of mixed AD/DLB cases is still lacking and the sensitivity of the clinical diagnosis is very low (Lane et al., 2018, Nelson et al., 2010, Outeiro et al., 2019). Successfully diagnosing such mixed cases may improve clinical prognosis, and may allow the implementation of more effective treatments. This will have an even more significant impact when disease-modifying treatments will be available for specific neuropathological features (Thomas et al., 2018). Within this framework, the detection of VH may aid the identification of such mixed cases in patients with a clinical diagnosis of AD.

7.1.1.2 Hallucinations in Alzheimer's disease

Although cognitive impairment represents the core feature of AD, neuropsychiatric symptoms are also common, affect quality of life of both patients and caregivers negatively, and are associated with early institutionalisation (Lane et al., 2018, Zhao et al., 2016). These symptoms include depression, apathy, agitation and, usually in later stages, hallucinations, delusions and aggression (Lyketsos et al., 2011). Psychotic symptoms, including hallucinations and delusions, may be found in approximately 41% of patients with AD, with a 3-year cumulative incidence of around 50%, and have been found to be less common in early and prodromal AD (Murray et al., 2014). Hallucinations are relatively common, with a prevalence of 13% on average, although a wide range, from 7% to 35% has been shown between studies (Linszen et al., 2018). They have been found to be less common in the early stages, around 4% (Linszen et al., 2018). The wide prevalence range might be due to different disease stages between studies, being more common in later stages. VH appeare to be the

most common type of hallucinations, even though they can be found in any sensory modality, especially auditory hallucinations (Bassiony and Lyketsos, 2003, El Haj et al., 2017, Linszen et al., 2018).

Hallucinations have been linked to more severe cognitive and functional decline (Bassiony and Lyketsos, 2003, El Haj et al., 2017). Given the high comorbidity with delusions, these symptoms have often been investigated together in AD. Generally, psychotic symptoms in AD have been linked to executive dysfunction (Hopkins and Libon, 2005, Swanberg et al., 2004), more rapid cognitive decline, and frontal atrophy and hypometabolism (Murray et al., 2014). The presence of hallucinations and delusions has been related to a more severe phenotype of AD (Fuller et al., 2019, Sweet et al., 2003). However, whether AD with psychosis reflects a phenotype with distinct underlying neurobiological mechanisms is still unclear (Fuller et al., 2019, Sweet et al., 2003). Nevertheless, the study of psychosis in AD as a unitary phenomenon may introduce interpretative issues on symptom-specific neural and cognitive processes that may vary between different psychotic manifestations. This relates to the investigation of hallucinations and delusions separately, but also hallucinations in different sensory modalities.

VH in DLB tend to occur earlier in the disease progression, while patients with AD usually experience them later in the disease course (Chiu et al., 2017). VH in AD have been associated with older age, impaired visual acuity and more severe dementia (Chapman et al., 1999, Chiu et al., 2017, Holroyd and Sheldon-Keller, 1995). Chiu et al. (2017) examined the core features of DLB symptomatology in AD patients with VH. All patients fulfilled the criteria for AD, had the typical AD presentation, and patients with probable or possible DLB were excluded. After controlling for age, sex, and dementia severity, AD patients with VH (n=42) had higher rates of RBD, cognitive fluctuations, severe neuroleptic sensitivity, and other neuropsychiatric and psychotic symptoms compared to patients without VH (n=253). Although hallucinating patients had more severe global cognitive impairment, the use of screening tests only is not sensitive enough to investigate the role of specific cognitive features (Chiu et al., 2017). Studies delineating the cognitive profile of AD patients with VH are still lacking, as well as those investigating the neural processes involved.

7.1.1.2.1 Cognition and hallucinations in AD

Evidence reporting neuropsychological features associated with hallucinations in AD is very limited, and even less specifically focusing on VH. In fact, most studies did not

differentiate between sensory modalities, therefore providing only partial knowledge of hallucinatory phenomena in this disease.

Generally, hallucinations have been related to more severe and rapid cognitive impairment (El Haj et al., 2017, Wilson et al., 2000). For example, faster cognitive decline in AD patients with hallucinations compared to those without has been shown in a wide range of cognitive measures, including memory, visuoconstruction, repetition, and naming (Wilson et al., 2000). Overall, the annual rate of global cognitive decline in hallucinating patients was almost 50% more than that of non-hallucinating ones (Wilson et al., 2000). In terms of specific cognitive deficits associated with hallucinations, executive dysfunctions have been suggested to play a role, particularly as a result of dysfunctional inhibitory mechanisms of irrelevant memories (El Haj et al., 2017). El Haj et al. (2015) investigated the features associated with hallucinations in 31 patients with probable AD, specifically focusing on executive aspects, namely shifting, updating and inhibition. They found that response inhibition, evaluated with the Stroop task, was the only significant predictor of hallucinations in AD (El Haj et al., 2015). In another study aiming to test the ability to inhibit irrelevant memories, and how this function relates to hallucinations in AD, El Haj et al. (2018) used a directed forgetting task. Specifically, 26 AD patients and 30 control participants were instructed to memorise a list of words, and then half patients were asked to forget it, and half to remember it. Subsequently they were all asked to retain another list of words, and then to recall words from both lists, regardless of the remember/forget instruction. AD patients presented deficits in memory suppression, while controls presented better performance in the “remember” condition than in the “forget” one. Moreover, a significant association between the presence of hallucinations and memory performance was found in the AD group in both experimental conditions. The authors interpreted these findings as indicating a memory suppression deficit in AD fostering the development of hallucinations through the activation of irrelevant memories (El Haj et al., 2018). In the abovementioned studies, however, no distinction was made concerning the sensory modality, as patients with both visual and auditory hallucinations were included (El Haj et al., 2018, El Haj et al., 2015). Moreover, no other cognitive function was explored in relation to the presence of hallucinations (El Haj et al., 2018, El Haj et al., 2015).

With the aim to differentiate between different psychotic symptoms, Quaranta et al. (2015) divided AD patients into those experiencing VH, paranoid delusions and delusional misidentifications. They found that VH were associated with impairments in several cognitive domains, specifically verbal and visuospatial long-term memory,

executive functioning and semantic memory. Of these cognitive functions, only visual memory predicted the severity of VH, as shown by linear regression analysis. Age, education and MMSE scores were controlled for in the final regression model to take into account differences in age and global cognitive impairment, since hallucinating patients were significantly older and cognitively more impaired than non-hallucinating patients (Quaranta et al., 2015). On the other hand, patients with paranoid delusions performed similarly to non-delusional patients, while those experiencing misidentifications were significantly more cognitively impaired, and presented a cognitive profile more similar to patients with VH (Quaranta et al., 2015). These findings suggest the need to explore further the neurocognitive correlates of psychotic symptoms in AD differentiating between symptomatology subtypes, which may have different underlying mechanisms. Within this framework, very little evidence concerns the presence of VH that remains a poorly understood phenomenon in AD.

7.1.1.2.2 Structural and functional brain imaging of hallucinations in AD

Evidence on structural and functional brain features associated with VH in AD is still lacking (see Table 7.1 for a summary of the main findings). Only a few studies focused on the visual modality, and all had a small sample size, less than 10 AD patients with VH in each study (Holroyd et al., 2000, Lin et al., 2006, Lopez et al., 2001, Middelkoop et al., 2001).

Some studies reported evidence of brain alterations in the occipital lobe in patients with VH (Holroyd et al., 2000, Lin et al., 2006). Holroyd et al. (2000) found significantly smaller occipital/whole brain ratio in AD patients with VH (n=7) compared with those without (n=7). In this study, an ROI approach was used, limiting the analysis to the occipital lobe. Conversely, no differences in the occipital lobe volume was detected in another study that included, however, only three AD patients with VH (Middelkoop et al., 2001). In another study, Lin et al. (2006) used a semiquantitative scoring method for rating WM signal hyperintensities to assess differences in occipital WM lesions between AD patients with (n=5) and without VH (n=5). Patients with VH had higher occipital periventricular hyperintensities scores, while both groups had no occipital deep white matter hyperintensities (Lin et al., 2006). Evidence also showed reduced occipital WM volume in AD patients with hallucinations compared with those without (Blanc et al., 2014).

Another study focused on hallucinations in the visual modality, and used [^{15}O]-water PET to investigate relative regional cerebral blood flow (Lopez et al., 2001). Dorsolateral prefrontal and medial temporal involvement was observed in patients

with delusions. In addition to these regions, hallucinating patients also showed reduced relative cerebral blood flow in the right parietal cortex compared with patients with no psychotic symptoms (Lopez et al., 2001). Consistently, in a SPECT study, Kotrla et al. (1995) found parietal hypoperfusion in AD patients with hallucinations. In a longitudinal study, Donovan et al. (2014) investigated changes in cortical thickness over time in a cohort of 812 participants, including 188 with AD dementia). Hallucinations were rare in cognitively normal and MCI participants, and were present in 5% of patients with AD. The authors found that lower baseline supramarginal cortical thickness predicted the worsening of hallucinations over time, but not occipital, frontal and superior parietal cortices (Donovan et al., 2014).

In another recent study, Blanc et al. (2014) used VBM and FDG PET to investigate structural and functional brain features associated with hallucinations in AD. Patients with hallucinations (n=39) had reduced GM volume and hypometabolism in the right anterior part of the insula and frontal areas compared with those without hallucinations (n=39). Notably, anterior insula GM volume also correlated with hallucinations intensity. The authors suggested a role of the insula in the development of hallucinations in AD, especially due to its involvement in the regulation and integration of external and internal stimuli, therefore disrupting the ability to discriminate between internally generated and external information (Blanc et al., 2014). However, in this study, hallucination sensory modality was not specified, and whole brain results were not corrected for multiple comparisons, thus increasing the likelihood of type I error.

Different types of hallucinations might have distinct neural mechanisms due to the sensory modality involved. Currently, there is still insufficient evidence on the structural and functional brain features associated with visual hallucinations in AD, and the few studies available had very small sample sizes. Therefore, the abovementioned results need to be interpreted cautiously, and suggest the need of further research.

Table 7.1 Summary of structural and functional neuroimaging studies of hallucinating patients with AD. Only main results related to hallucinations are reported.

Study	Participants	Method	Main results: Neuroimaging and hallucinations
Blanc et al. (2014)	39 AD-H 39 AD-NH	MRI VBM FDG PET	AD-H < AD-NH Grey matter: right anterior insula and inferior frontal gyrus, left superior frontal gyrus White matter: right and left lingual gyrus, occipital lobe Glucose hypometabolism: right inferior, middle frontal gyri and insula Glucose hypermetabolism: left superior frontal gyrus, fusiform gyrus, postcentral gyrus, precuneus, supramarginal gyrus Voxel-wise correlational analyses with hallucination intensity: Grey matter: right precentral, superior temporal gyri, anterior insula White matter: left precuneus Glucose metabolism: left cingulate gyrus, right precentral gyrus
Donovan et al. (2014)	188 AD 395 MCI 229 HC	MRI ROI cortical thickness	Longitudinal analysis Lower baseline supramarginal cortical thickness predicted worsening hallucinations
Holroyd et al. (2000)	7 AD VH 7 AD NVH	MRI ROI	AD VH < AD NVH Occipital/whole brain volume ratio
Kotrla et al. (1995)	10 AD-H 16 AD-NH	SPECT	AD-H < AD-NH Hypoperfusion: parietal lobe
Lin et al. (2006)	5 AD VH 5 AD NVH	MRI WM hyperintensity	AD VH > AD NVH Occipital periventricular hyperintensities Absence of occipital deep white matter hyperintensities
Lopez et al. (2001)	2 AD VH 5 AD NVH	[^{15}O]-water PET	AD VH < AD NVH Relative regional cerebral blood flow: Right parietal, left medial temporal and left dorsolateral prefrontal cortices
Middelkoop et al. (2001)	3 AD VH 22 AD NVH	MRI ROI	No differences in occipital lobe volume

AD: Alzheimer's disease; H: hallucinations; HC: healthy controls; MCI: mild cognitive impairment; NH: no hallucinations; NVH: no VH; ROI: region of interest; VH: visual hallucinations; VBM: voxel-based morphometry; WM: white matter.

Aims and hypotheses

The present study focused specifically on visual hallucinations in AD. In Experiment 4 (section 5.1), we found an AD-like cognitive profile predicting the development of VH at follow-up in DLB patients with no hallucinations at baseline. Moreover, our meta-analysis (section 6.2) provides evidence of more severe verbal memory deficits in LBD patients with VH, especially PD, compared to those without. These findings

suggest a role of MTL structures and related cognitive processes, known to be affected in AD, in the development of VH in LBD. Moreover, as noted above, VH has been found to be a strong predictor of LB pathology not only in DLB, but also in AD (Thomas et al., 2018, Tiraboschi et al., 2006, Toledo et al., 2013), highlighting the importance of delineating the cognitive profile and the neural features characterising this symptom in AD, so far under investigated. Moreover, to our knowledge, no whole brain VBM on structural MRI data and PET analyses has been previously undertaken that focused specifically on VH.

In the light of the findings described above, the present study aimed at exploring the neurocognitive and brain features associated with VH in AD. We hypothesised that VH in AD might be associated with cognitive and neural mechanisms in line with the PAD model for VH (Collerton et al., 2005), and resembling a DLB-like pattern of alterations. We expected that more severe deficits in attention and visual perception/construction, and related brain structures, would reflect the presence of VH in AD, in a background of significant deficits in verbal long-term memory and MTL atrophy, typical of AD-type dementia. Within this framework, we suggest that verbal long-term memory, visual attention and visual perception deficits would all form the basis for the development of VH in AD.

Specifically, in the first experiment of the present chapter (Experiment 7.1) we tested whether there was an interplay between visual attention and visuoconstruction abilities associated with the expression of VH in a sample of participants with MCI and dementia due to AD. We expected deficits in AD patients with VH in visual attention and visuoconstruction after accounting for the parallel variable. Then, we performed whole brain VBM analysis to investigate volumetric brain alterations associated with VH. We expected occipital and occipito-temporal volumetric brain abnormalities in hallucinating patients, underlying visual perception impairments, and frontal/subcortical atrophy, sustaining attention deficits, as shown in our previous experiment on DLB with VH (Experiment 1). Finally, in Experiment 7.2, we used PET to explore brain glucose metabolism. We expected occipital hypometabolism, in line with the hypothesis suggesting a DLB-like profile in AD with VH. In fact, occipital hypometabolism and hypoperfusion is typical of DLB, and is included among its supportive biomarkers (McKeith et al., 2017).

7.1.2 Methods

7.1.2.1 The ADNI database

Data used for this study were obtained from the Alzheimer's disease Neuroimaging Initiative, which is a longitudinal multicentre initiative that started in 2003 as a $60 million, 5-year public-private partnership between the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations. The original ADNI project has been followed by ADNI-GO, ADNI-2 and ADNI-3 (the latter started in 2016). The cohort has currently reached over 1500 individuals (aiming to enrol an additional 370-1200 new participants with ADNI-3) including cognitively normal elderly participants, people with early or late MCI, and patients with early AD. The main aim of ADNI has been to investigate the progression of MCI and AD by means of the combination of longitudinal MRI, PET, and other biological markers, clinical and neuropsychological assessments. The development and use of optimised methods have the purpose of identifying specific biomarkers of AD progression to improve its diagnosis, and to aid the development of new treatments and the assessment of their efficacy (Mueller et al., 2005). Further details and up-to-date information are available at www.adni-info.org.

The principal investigator of the initiative is Michael W. Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI has been recruiting from over 50 sites within the US and Canada, being the result of the work of several co-investigators and institutions. ADNI investigators were involved in the design and implementation of the ADNI protocol but not in the conceptualisation, analysis or writing of the present study. Data collection and sharing for the present study was funded by ADNI (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). A full list of ADNI investigators and funding bodies can be found on the ADNI website http://adni.loni.usc.edu.

All MRI, PET, demographic, clinical and neuropsychological data were downloaded from the ADNI website in April 2018, following successful application and authorisation for data access.

7.1.2.2 Study participants

ADNI inclusion and exclusion criteria are stated in the procedures manuals and clinical protocols available at http://adni.loni.usc.edu/methods/documents. Briefly, criteria for cognitively normal (CN) controls included: a) no subjective memory complaint; b) normal memory functioning (assessed with the education-adjusted score on the Logical Memory II subscale from the Wechsler Memory Scale-Revised; c) MMSE between 24 and 30; d) Clinical Dementia Rating (CDR) equal to zero. AD criteria: a) complaints of memory loss expressed by the patient or an informant; b) memory function deficit (Logical Memory II subscale); c) MMSE between 20 and 26; d) CDR of 0.5 or 1.0; e) NINCDS/ADRDA criteria for probable AD. MCI criteria: a) subjective memory concern; b) memory function deficit; c) MMSE between 24 and 30; CDR of 0.5; d) no diagnosis of AD. Other exclusion criteria for all the above included the following: a) age not between 55-90; b) Geriatric Depression Scale score higher or equal to 6; c) Hachinski Ischemic Score higher than 4; d) presence of any other significant neurological or psychiatric condition (including bipolar disorder and major depression within the previous year, and a history of schizophrenia). A stable dose of antidepressant (with no significant side effects) was allowed if participants were not depressed at time of assessment or had a history of major depression within the previous year. Cholinesterase inhibitors and memantine were allowed in participants with MCI and AD if on stable dose for 12 weeks prior to the screening visit. A full lists of permitted and not permitted medications is available within the ADNI protocols at http://adni.loni.usc.edu/methods/documents.

Experiment 7.1. From the ADNI cohort, a systematic search of patients with VH was undertaken and participants for whom the following data were available were screened further: T1 MRI scan, NPI, MMSE and a comprehensive neuropsychological assessment. All data were collected within a 6-month period for each participant. In case of patients with data collected at two different points in time, the earlier visit was chosen. The presence of VH was assessed with the NPI subsection for visual hallucinations, namely by answering the question “Does [P] describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)?” with yes/no. Of the 26 selected patients with VH, 12 also presented hallucinations in other sensory modalities, namely auditory (n=9) and tactile (n=4) hallucinations. Six patients were also reported talking with people who were not present. Six participants had MCI due to suspected AD (including two that converted in dementia one year after the assessment selected for this study), and 20 patients

with a diagnosis of AD. Mean age for the VH group was 75.31 (SD=9.08), 11 males and 15 females, with mean years of education of 15.62 (SD=2.58). Mean MMSE was 22.54 (SD=3.98). Subsequently, a group of 26 AD patients with no hallucinations in any sensory modality was selected to match the VH group for age, gender, years of education, MMSE and NPI total score subtracting the NPI hallucinations subscore. Seven participants had MCI due to suspected AD (one of whom converted to dementia three years after the present assessment), and 19 with dementia due to AD. Mean age for this sample was 74.92 (SD=8.29), 11 males and 15 females, with mean years of education of 15.50 (SD=2.67). Mean MMSE was 22.96 (SD=2.47). A group of matched CN (n=26), with no neuropsychiatric symptoms (NPI equal to zero) was also identified (mean age=74.77, SD=7.81; 11 males and 15 females; mean years of education=16.15, SD=2.81; mean MMSE=29.15, SD=0.97). Data for all participants (n=78) were part of ADNI 2 (n=74) and ADNI 3 (n=4).

Experiment 7.2. This experiment included a subsample of patients with VH described above (Experiment 7.1), for which FDG-PET was available (n=12). Six out of 12 patients with VH also presented other types of hallucinations, specifically auditory (n=4), and tactile (n=2), and three patients were reported talking with people who were not present. Three patients had MCI due to suspected AD (of whom two converted to dementia within a 6 to 12-month period), and 9 were diagnosed with AD dementia. Mean age for the AD VH group was 73.75 (SD=8.57; 5 males and 7 females), mean years of education 16.50 (SD=2.88), mean MMSE 22.42 (SD=4.60). A group of 12 patients with MCI (n=2) and dementia (n=10) due to AD with no hallucinations (mean age=73.17, SD=7.60; 5 males and 7 females; mean years of education=15.58, SD=2.78; mean MMSE=22.83, SD=2.86) was then selected to match the VH one.

In order to explore differences between the whole AD group (mean age=73.46, SD=7.93; 10 males and 14 females; mean years of education=16.04, SD=2.81; mean MMSE=22.63, SD=3.79), a group of matched CN participants (mean age=73.29, SD=7.31; 10 males and 14 females; mean years of education=16.67, SD=3.00; mean MMSE=29.13, SD=0.99) was also identified.

For each participant described above, the following data were available: T1 MRI, FDG-PET, NPI, MMSE and a comprehensive neuropsychological assessment, all collected within a 6-month period. Data were part of ADNI 2 (n=46) and ADNI 3 (n=2).

7.1.2.3 Neuropsychiatric and neuropsychological assessment

A detailed description of the clinical protocol, neuropsychiatric and neuropsychological assessments is available at http://adni.loni.usc.edu/methods.
The presence of VH and other neuropsychiatric symptoms, including frequency and severity for each, was assessed with the NPI questionnaire (described in section 4.1.2.2).
The MMSE (described in section 4.1.2.3) was chosen for the present study as a measure of global cognitive functioning. Scores for the following neuropsychological tests were retrieved:

Trail Making Test (TMT). This test has been described previously in section 4.1.2.3. For the purpose of the present study, primary outcome measures consisted in the time needed to complete part A (up to 150 seconds), and B (up to 300 seconds). If the time limit was reached, testing would be stopped.

Logical memory test. Used to assess episodic memory through a prose memory test, ADNI uses a modified version from the Wechsler Memory Scale-Revised. The test consists in a free recall of a short story immediately after presentation (immediate recall) and after thirty minutes (delayed recall).

Rey Auditory Verbal Learning Test (RAVLT). See section 4.1.2.3 for a description of this test.

Category fluency test. This is a verbal fluency test widely used to assess semantic memory. Participants are asked to generate as many words as they can from a certain semantic category (e.g. animals) in one minute.

Clock drawing test. This test has been described in section 4.1.2.3. The administration procedure for ADNI consisted of two components. Firstly, a drawing condition in response to verbal instructions, consisting of drawing the clock, putting all the numbers and setting the hands at a certain time. This condition was followed by the copy component, where patients are asked to copy a clock drawing.

Boston naming test. This test assesses visual confrontation naming, and it is often used to assess language in AD (Mack et al., 1992). ADNI uses a short version of the full test, which requires participants to name 30 drawings of objects (of the 60 items of the full version), of increasing difficulty. In case of difficulties, a semantic cue may be given. Final scores include the number of items correctly named with and without cueing (maximum total score equal to 30).

7.1.2.4 Statistical analyses

Experiment 7.1. Differences in demographic, clinical and neuropsychological measures between patients with and without VH and CN participants were assessed using IBM SPSS Statistics 22. The following tests were used: one-way ANOVA and Independent-samples Kruskal-Wallis test for numerical normally and non-normally distributed variables, respectively. Post hoc Dunn's pairwise tests were conducted for *post-hoc* comparisons between groups. Differences between AD subgroups in NPI total scores were assessed with Mann-Whitney U test, while differences in the presence of neuropsychiatric symptoms were investigated with the Fisher's Exact Test.

Experiment 7.2. SPSS 22 was used to assess between-group differences in demographic, neuropsychiatric and cognitive measures. Specifically, independent sample t-test and Mann-Whitney U test were used for normally and non-normally distributed numerical variables respectively, and Fisher's Exact Test for categorical variables. Bonferroni correction for multiple comparisons was applied, by which statistical significance is reached with a p value < α/n, where α is equal to the p value for each comparison (p=0.05) and n the number of comparisons.

7.1.2.5 Structural MRI and PET analyses

7.1.2.5.1 MRI acquisition, VBM pre-processing and statistical analyses

One of the ADNI goals has been to improve the methods for clinical research in AD, and the ADNI-MRI core has worked to achieve the standardisation of imaging methods (Jack et al., 2015). Therefore, MRI protocols were developed to be compatible with different scanners and over time, evolving across the ADNI phases (Jack et al., 2015). All images were acquired using a 3T MRI scanner, and had a quality control assessment at the Mayo Clinic by trained analysts. MRI acquisition information and imaging protocols are available at http://adni.loni.usc.edu/methods. All scans were downloaded from the Image Data Archive (IDA) (https://ida.loni.usc.edu).

VBM pre-processing and statistical analyses were performed as described in section 4.1.2.5. The following contrasts were performed to explore between-group differences: VH vs NVH, VH vs CN, NVH vs CN. Correlational whole brain VBM analyses were carried out to investigate the association between regional GM volumes and

measures of visual attention (TMT-A), and visuoconstruction (clock copy) in the whole sample (n=78). TIV and age were added as covariates of no interest in all the models.

7.1.2.5.2 PET acquisition, pre-processing and statistical analyses

All FDG-PET images were checked for quality control by the ADNI PET core team, and pre-processed to allow a better comparison between images from different scanners (Jagust et al., 2015).

Details on PET acquisition and pre-processing steps performed by ADNI are described at http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis. ADNI PET scans are available in four sets of pre-processed images. Processed FDG-PET data were downloaded from IDA (https://ida.loni.usc.edu) in April 2018. Firstly, four five-minute frames were acquired 30 to 60 minutes post-injection, co-registered to the first one, and averaged into a single 30-minute PET image in native space. Then, images were reoriented to the anterior commissure-posterior commissure line, written into a standard grid (160x160x96 with 1.5 mm^3 voxels), and intensity normalised using a subject-specific mask so that the global mean within each masked image was equal to one (Jagust et al., 2015). Finally, in-plane and spatial smoothing kernels defined for each specific scanner model were applied to produce images with an isotropic resolution of 8mm FWHM (Jagust et al., 2015).

Following the pre-processing steps performed by the ADNI team as described above, all images were processed further using SPM12. Firstly, each image was co-registered to the corresponding structural MRI scan and resliced using a trilinear interpolation. The output images were inspected visually to check for the accuracy of this process. Co-registered images were then affine registered into the MNI space using the ICBM standard template available on SPM, with 16 nonlinear iterations and nonlinear regularisation set to 1. Images were resliced by means of a trilinear interpolation and no modulation was applied. Within this step, an FDG-PET template developed for patients with dementia was used, and is available for download as an extension of SPM at https://www.fil.ion.ucl.ac.uk/spm/ext (Della Rosa et al., 2014). Images were also intensity normalised to reduce the effect of interindividual differences in brain metabolism by using the cerebellum as reference region. In order to do so, a region in the superior cerebellum, including the vermis, identified for this purpose by Rasmussen et al. (2012) was used, namely the following AAL atlas regions: cerebellum III, IV, V, VI and the whole vermis. Firstly, a mask based on these regions was created with the WFU PickAtlas toolbox, and the signal was extracted for each subject using the MarsBar toolbox. Then, the entire FDG-PET image for each

subject was intensity normalised to the cerebellar ROI mean signal using the SPM12 ImCalc tool. Finally, the images were smoothed using a FWHM 8mm isotropic Gaussian kernel.

All pre-processed images were then used for between-group comparisons and correlational analyses. First, differences in regional glucose metabolism were explored between the whole AD sample and CN participants, and then between hallucinating and non-hallucinating patients. Whole brain correlational analyses were performed to investigate the association between glucose metabolism and scores on the following neuropsychological tests: clock copying and TMT-A. TIV and age were included in all models as covariates of no interest. Brain region labels were obtained as described previously (section 4.1.2.5.3).

The cingulate island sign (CIS) refers to the relative preservation of the metabolism of the posterior cingulate relative to the precuneus and cuneus on FDG-PET imaging in DLB. It has been included as a supportive biomarker of DLB, and it has been shown to differentiate DLB from AD (Graff-Radford et al., 2014, Iizuka and Kameyama, 2016, McKeith et al., 2017). On the other hand, AD is characterised by more prominent parietotemporal and posterior cingulate hypometabolism (Sinha et al., 2012). To determine glucose metabolism in the posterior cingulate and to calculate the CIS ratio, ROIs were placed in the posterior cingulate, and in the cuneus plus precuneus. ROIs were created with the WFU PickAtlas toolbox, and the signal was extracted for each subject using the MarsBar toolbox. We calculated the CIS ratio by dividing the mean value in the posterior cingulate ROI by the mean value in the precuneus plus cuneus ROI. SPSS 22 was used to assess between group differences in the CIS ratio and signal in the posterior cingulate using a one-way ANOVA.

7.1.2.6 CSF β-Amyloid (1-42)

Low levels of CSF β-Amyloid $_{(1-42)}$ have been associated with cerebral β-Amyloid deposition, and represent valid *in vivo* biomarker for AD (Dubois, 2018, Jack et al., 2018). Thus, we checked whether CSF β-Amyloid $_{(1-42)}$ was available for this cohort of AD patients. Methodology has been described in detail elsewhere (Toledo et al., 2013). CSF β-Amyloid $_{(1-42)}$ was considered abnormal at a cut-off of 1130 pg/mL or below (Andreasen et al., 1999).

7.1.2.7 Post-hoc neuropathological diagnosis checking

Since VH have been found to be a strong predictor of LB pathology at autopsy, we checked *post-hoc* the neuropathological status of AD patients included in the present cohort. Methodology has been described in detail elsewhere (Toledo et al., 2013).

7.1.3 Results

7.1.3.1 Experiment 7.1. Neuropsychological and VBM findings

7.1.3.1.1 Demographic, neuropsychiatric and neuropsychological findings

AD patients with and without VH, and CN did not significantly differ in age, gender and years of education (Table 7.2). *Post-hoc* analyses (Dunn's pairwise test) on the MMSE scores revealed differences between both AD subgroups and CN ($p<0.001$), but not between AD VH and NVH ($p=1.00$). No differences were detected between AD patients with and without VH in NPI total score, NPI total minus NPI hallucination score, and presence of other neuropsychiatric symptoms (Table 7.2 and Table 7.3). Patients with VH only had higher NPI subscores related to appetite and eating disorders ($p=0.03$), even though this difference did not survive Bonferroni correction for multiple comparisons ($p<0.004$).

Table 7.2 Demographic and clinical characteristics for AD patients with and without VH and CN. Mean and SD are reported for each variable unless otherwise specified.

Characteristic	AD VH (n=26)	AD NVH (n=26)	CN (n=26)	p value
Age	75.31 (9.08)	74.92 (8.29)	74.77 (7.81)	0.97 [a]
Gender M:F	11:15	11:15	11:15	-
Years of education	15.62 (2.58)	15.50 (2.67)	16.15 (2.81)	0.40 [b]
MMSE	22.54 (3.98)	22.96 (2.47)	29.15 (0.97)	<0.001 [b]
NPI total score	19.69 (16.11)	13.92 (13.18)	-	0.09 [c]
NPI tot - NPI hallucination	17.31 (15.66)	13.92 (13.18)	-	0.34 [c]

AD: Alzheimer's disease; CN: cognitively normal; NPI: neuropsychiatric inventory; NVH: no visual hallucinations; VH: visual hallucinations. [a] One-way ANOVA; [b] Independent-samples Kruskal-Wallis test; [c] Mann-Whitney U test.

Table 7.3 Number of patients presenting with each neuropsychiatric symptom detected with the NPI, differences between AD patients with and without VH (Fisher's Exact Test).

Characteristic, n (%)	AD VH (n=26)	AD NVH (n=26)	p value
Delusions	11 (42.31%)	5 (19.23%)	0.13
Hallucinations	26 (100.00%)	0 (0.00%)	**<0.001**
Agitation/aggression	10 (38.46%)	7 (26,92%)	0.56
Depression/dysphoria	14 (53.85%)	10 (38,46%)	0.40
Anxiety	16 (61,54%)	9 (34,62%)	0.10
Elation/euphoria	1 (3,85%)	2 (7,69%)	1.00
Apathy/indifference	12 (46,15%)	15 (57,69%)	0.58
Disinhibition	4 (15,38%)	7 (26,92%)	0.50
Irritability/lability	13 (50.00%)	6 (23,08%)	0.08
Aberrant motor behaviour	6 (23,08%)	8 (30,77%)	0.76
Sleep	11 (42,31%)	12 (46,15%)	1.00
Appetite and eating disorders	12 (46,15%)	4 (15,38%)	**0.03**

AD: Alzheimer's disease; NPI: neuropsychiatric inventory; NVH: no VH; VH: visual hallucinations.

Results from independent-samples Kruskal-Wallis tests, comparing AD VH, NVH and CN, yielded significant results in all neuropsychological measures ($p \leq 0.001$). *Post hoc* analyses (Dunn's pairwise tests) are reported in Table 7.4. When compared to CN, both AD subgroups significantly differed in most cognitive tests, namely TMT A and B, prose memory and RAVLT immediate and delayed recall, category fluency, and Boston naming test. On the other hand, AD NVH and CN presented comparable performance on the clock drawing and copying. In the direct comparison between AD VH and NVH, the only test that yielded significant differences was the clock copying, a measure of visuoconstructive abilities (Figure 7.1). Even though not significant, there was a trend difference in the TMT-A and B, with VH patients taking more time to complete the task, compared to both NVH and CN (Figure 7.2).

Table 7.4 Differences in neuropsychological tests between AD VH, NVH and CN.

Test	AD VH		AD NVH		CN		*Post hoc* comparisons (p)		
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	VH-NVH	VH-CN	NVH-CN
TMT-A (s)	24	85.4 (48.0)	26	56.2 (28.6)	26	33.4 (11)	0.10	**<0.001**	**0.01**
TMT-B (s)	21	252.5 (82)	26	189.7 (92.7)	26	83.6 (39.2)	0.18	**<0.001**	**<0.001**
Prose M:									
Immediate	25	5.6 (4.5)	25	5.7 (3.6)	26	15.9 (3.0)	1.00	**<0.001**	**<0.001**
Delayed	25	2.9 (4.6)	25	2.0 (2.3)	26	14.4 (3.5)	1.00	**<0.001**	**<0.001**
RAVLT:									
Immediate	25	23.8 (10.6)	26	23.9 (6.8)	26	47 (11.3)	1.00	**<0.001**	**<0.001**
Delayed	25	1.3 (3.3)	26	0.4 (1.0)	26	7.9 (4.5)	1.00	**<0.001**	**<0.001**
CT	25	11.7 (5.8)	26	12.0 (4.7)	26	23.0 (5.9)	1.00	**<0.001**	**<0.001**
Clock test:									
Drawing	25	2.8 (1.7)	26	3.8 (1.3)	26	4.6 (0.6)	0.10	**<0.001**	0.10
Copying	25	3.8 (1.5)	26	4.7 (0.8)	26	4.9 (0.3)	**0.002**	**<0.001**	1.00
BNT	21	22.9 (6.3)	26	24.5 (5.4)	25	28.4 (1.9)	0.10	**<0.001**	**0.01**

AD: Alzheimer's disease; BNT: Boston naming test; CN: cognitively normal; CT: category fluency; HC: healthy controls; M: memory; NVH: no VH; s: seconds; RAVLT: Rey Auditory Verbal Learning Test; SD: standard deviation; TMT: Trail Making Test; VH: visual hallucinations.

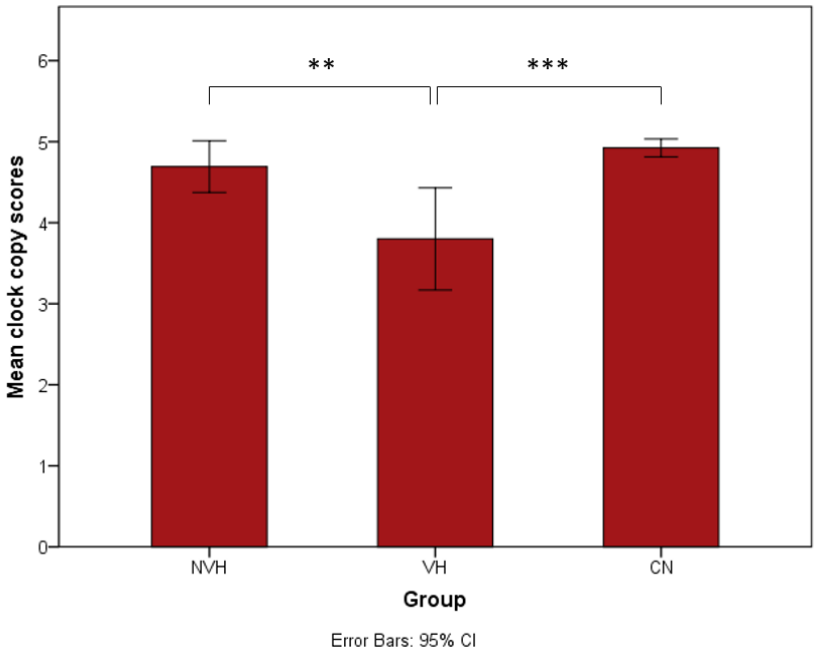

Figure 7.1 Differences between AD VH, NVH and CN on the clock copying test. ** p<0.01, *** p<0.001.

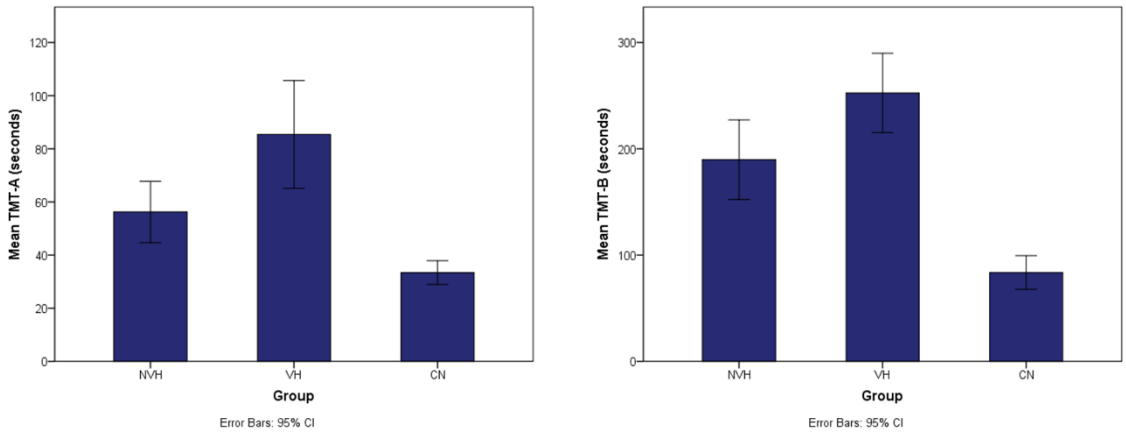

Figure 7.2 Differences between AD VH, NVH and CN on the TMT-A and B.

7.1.3.1.2 Whole brain VBM findings

One-way ANOVA analysis revealed significant differences between AD VH, NVH and CN in total CSF volume (p=0.001; Bonferroni *post hoc* comparisons: VH vs. NVH: p=1.00; VH vs. CN: p=0.002; NVH vs. HC: p=0.002), but not in total WM volume and TIV (Table 7.5). Marginally significant results were found for total GM volume (p=0.05).

Table 7.5 Total volumes in brain tissues in AD VH, NVH and CN (one-way ANOVA). Mean and standard deviation are reported for each variable.

Volume (ml)	AD VH (n=26)	AD NVH (n=26)	CN (n=26)	p value
Total GM volume	550.37 (70.47)	553.75 (91.56)	599.65 (73.69)	0.05
Total WM volume	401.63 (59.12)	398.34 (66.28)	396.19 (58.39)	0.95
Total CSF volume	527.60 (98.46)	526.33 (105.39)	430.15 (92.60)	**0.001**
Total intracranial volume	1479.60 (159.82)	1478.41 (146.40)	1425.98 (143.86)	0.35

AD: Alzheimer's disease; CN: cognitively normal; CSF: cerebrospinal fluid; GM: grey matter; NVH: no VH; VH: visual hallucinations; WM: white matter.

Whole brain VBM analysis of grey and white matter yielded no significant results between AD patients with and without VH using a FWE corrected threshold. When compared with CN, analysis of both patients with and without VH revealed regions of lower GM volume (Table 7.6, Table 7.7 and Figure 7.3). Overlapping regions of GM loss were located in medial and lateral temporal regions, namely the parahippocampal gyrus and middle temporal gyrus bilaterally, left inferior temporal gyrus, right superior temporal gyrus (Figure 7.4). Other common areas of reduced GM volume were the following: thalamus and insula bilaterally, and right caudate nucleus, inferior frontal and supramarginal gyri.

Table 7.6 Regions of lower grey and white matter volume in AD VH patients compared to CN (set-level threshold of p<0.05 with TIV and age as covariates of no interest, k>20).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Grey matter								
Parahippocampal gyrus	L	2780	-26	-10	-15	9.32	7.01	<0.001
Parahippocampal gyrus (BA 34)	L		-30	4	-22	8.72	6.72	
Parahippocampal gyrus	L		-32	-38	-6	7.48	6.06	
Parahippocampal gyrus	R	2645	26	-8	-15	8.75	6.73	<0.001
Inferior Frontal gyrus (BA 47)	R		34	9	-21	8.42	6.57	
Insula (BA 13)	R		44	10	-15	7.31	5.96	
Inferior Temporal gyrus (BA 20)	L	692	-60	-50	-12	8.03	6.36	<0.001
Middle Temporal gyrus (BA 21)	L		-64	-42	-8	7.11	5.85	
Inferior Temporal gyrus (BA 37)	L		-58	-57	-3	6.31	5.36	
Thalamus	L	576	-3	-2	3	7.91	6.30	<0.001
Caudate head	R		6	4	2	6.65	5.57	
Caudate body	R		9	9	8	5.76	4.99	
Insula (BA 13)	R	70	40	20	0	6.43	5.44	0.001
Anterior cingulate (BA 32)	R	70	3	44	16	6.32	5.37	0.001
Superior temporal gyrus (BA 21)	R	179	54	-26	-3	6.32	5.36	0.000
Middle temporal gyrus (BA 21)	R		62	-27	-6	5.64	4.92	
Supramarginal gyrus (BA 40)	R	97	58	-48	38	6.20	5.29	0.001
Insula (BA 13)	R	256	45	-4	-3	6.19	5.28	0.000
Claustrum	R		42	-6	6	6.03	5.17	
Middle occipital gyrus (BA 19)	L	239	-39	-86	16	6.07	5.20	0.000
Inferior occipital gyrus (BA 18)	L		-39	-90	-3	5.92	5.11	
Middle temporal gyrus (BA 21)	R	72	39	-4	-40	5.96	5.13	0.001
Inferior temporal gyrus	L	39	-51	-74	6	5.84	5.05	0.004
Insula (BA 13)	L	42	-39	14	0	5.83	5.04	0.004
Insula (BA 13)	L	41	-39	-15	9	5.82	5.04	0.004
Middle temporal gyrus (BA 21)	L	24	-64	-30	-18	5.81	5.03	0.009
Fusiform gyrus (BA 20)	R	36	57	-9	-33	5.72	4.97	0.005
Middle temporal gyrus (BA 21)	R	34	60	-18	-21	5.69	4.95	0.006
Precentral gyrus (BA 6)	R	14	58	-4	4	5.68	4.95	0.015
Posterior cingulate (BA 30)	R	13	8	-58	9	5.52	4.84	0.016
Thalamus	R	12	22	-32	-4	5.52	4.83	0.017
Middle temporal gyrus (BA 21)	R	20	48	3	-42	5.51	4.83	0.011
White matter								
Inferior fronto-occipital fasciculus	R	283	36	-33	-6	5.95	5.12	<0.001
Inferior longitudinal fasciculus	L	222	-38	-51	4	5.92	5.11	<0.001
Inferior longitudinal fasciculus	L		-34	-60	6	5.34	4.71	
Inferior fronto-occipital fasciculus	L	73	-33	-33	-6	5.81	5.03	0.002

AD: Alzheimer's disease; CN: cognitively normal; BA: Brodmann area; L: left; R: right; VH: visual hallucinations.

Additional regions of reduced GM were detected in VH patients in the left middle and inferior occipital gyri and in the right anterior cingulate. Decreased volume in temporal regions in patients with no VH extended to the left superior temporal gyrus and uncus. Moreover, they presented GM loss in left parietal regions. All results were significant at a cluster and peak-level threshold of p<0.05 FWE corrected for multiple comparisons.

Table 7.7 Regions of reduced grey and white matter volume in AD NVH patients compared to CN (set-level threshold of p<0.05 with TIV and age as covariates of no interest, k>20).

Structure		Cluster size	MNI coordinates			T score	Z score	p value [a]
Grey matter								
Parahippocampal gyrus	L	3802	-22	-9	-18	8.77	6.74	0.000
Superior temporal gyrus (BA 38)	L		-34	6	-22	7.50	6.07	
Parahippocampal gyrus	L		-32	-38	-8	7.15	5.87	
Parahippocampal gyrus	R	3185	22	-8	-16	8.62	6.67	0.000
Thalamus	R		24	-32	-4	6.95	5.75	
Uncus (BA 28)	R		26	-12	-36	6.45	5.45	
Caudate head	R	179	2	4	-3	6.60	5.54	0.000
Middle temporal gyrus (BA 37)	L	193	-56	-56	-8	6.42	5.43	0.000
Inferior temporal gyrus (BA 20)	L	70	-57	-38	-20	6.20	5.29	0.001
Insula (BA 13)	R	214	44	-4	-2	6.16	5.26	0.000
Middle temporal gyrus (BA 21)	R	105	57	-22	-22	6.09	5.21	0.000
Middle temporal gyrus (BA 21)	R		57	-16	-28	5.75	4.99	
Posterior cingulate (BA 31)	L	196	-8	-56	27	6.07	5.20	0.000
Precuneus (BA 31)	L		-9	-44	32	6.01	5.17	
Inferior frontal gyrus (BA 47)	R	30	32	18	-15	5.92	5.10	0.006
Insula (BA 13)	L	88	-44	-8	-6	5.83	5.05	0.001
Insula (BA 13)	L		-42	-2	-12	5.75	4.99	
Superior temporal gyrus (BA 39)	R	24	51	-51	24	5.70	4.96	0.009
Middle temporal gyrus (BA 21)	L	40	-62	-38	-3	5.69	4.95	0.004
Thalamus (ventral lateral nucleus)	L	16	-14	-14	16	5.68	4.95	0.013
Superior temporal gyrus (BA 21)	R	78	58	-24	-8	5.66	4.93	0.001
Parahippocampal gyrus (BA 35)	R	26	33	-27	-27	5.63	4.91	0.008
Supramarginal gyrus (BA 40)	R	16	58	-46	36	5.61	4.89	0.013
Cingulate gyrus (BA 31)	R	26	9	-42	36	5.59	4.88	0.008
Uncus (BA 38)	L	22	-27	3	-44	5.54	4.84	0.009
White matter								
Cingulum (hippocampus)	L	127	-18	-27	-20	6.02	5.17	<0.001
Cingulum (hippocampus)	L		-26	-21	-22	5.27	4.66	
Cingulum (hippocampus)	R	42	22	-28	-16	5.90	5.09	0.005
Cingulum (hippocampus)	R		26	-20	-21	5.18	4.60	

AD: Alzheimer's disease; CN: cognitively normal; BA: Brodmann area; L: left; R: right; NVH: no visual hallucinations. [a] cluster-level FWE corrected p value.

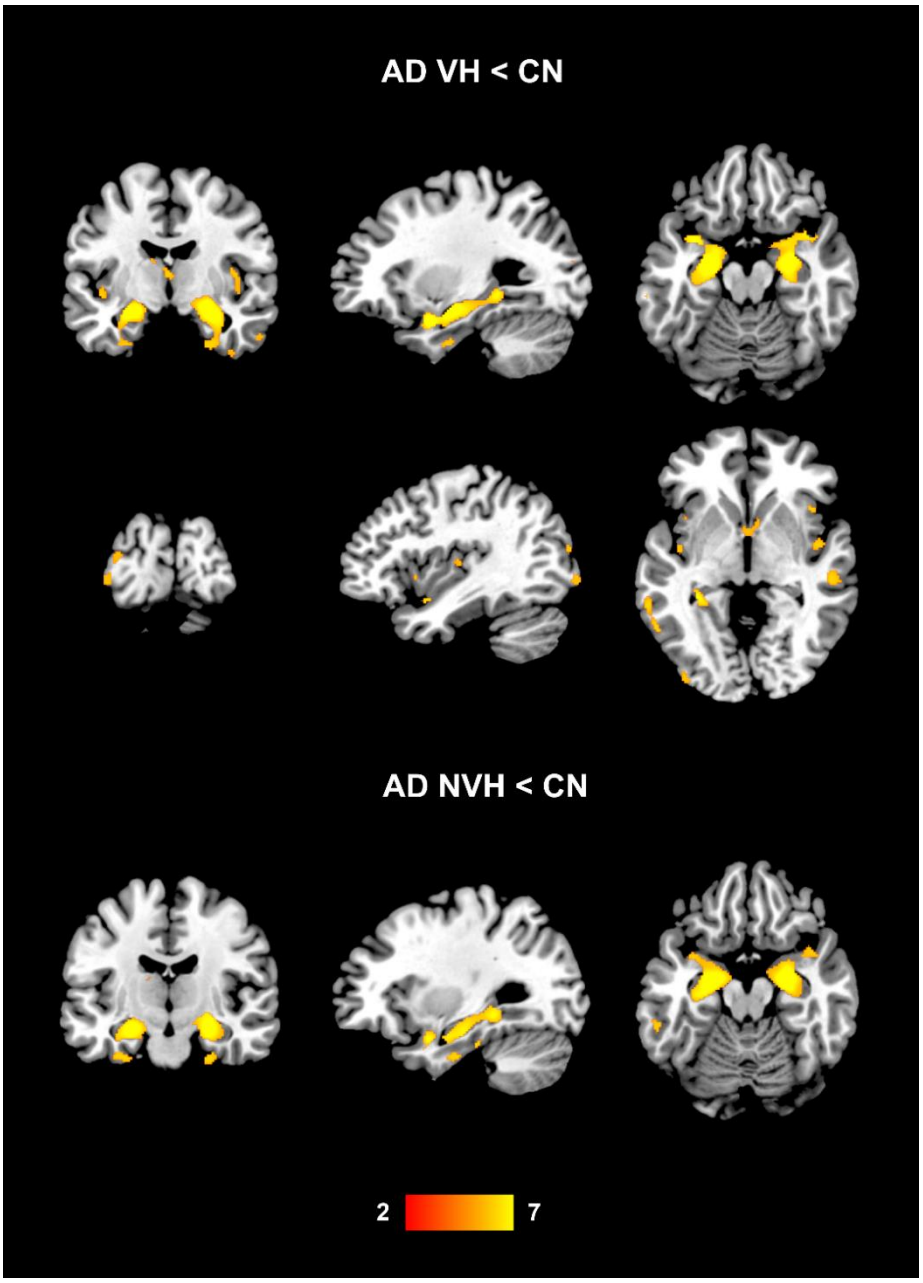

Figure 7.3 Regions of reduced GM volume in AD VH (at the top) and NVH (at the bottom) compared with CN. The colour bar indicates the z scores at a FWE corrected threshold with TIV and age as covariates of no interest.

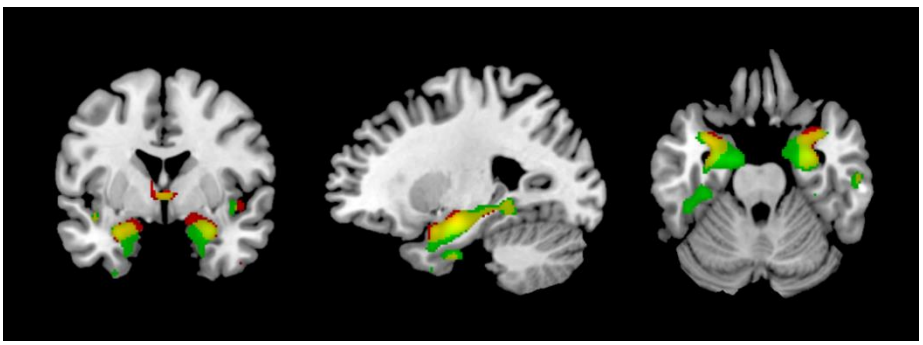

Figure 7.4 Regions of overlapping GM loss in VH and NVH patients (yellow), VH only (red) and NV (green).

As for regional WM differences, they were located in the inferior fronto-occipital fasciculus bilaterally and left inferior longitudinal fasciculus in patients with VH (Table 7.6), and in the cingulum bilaterally in patients without VH (Table 7.7). Results from group comparisons in WM volumes are displayed in Figure 7.5.

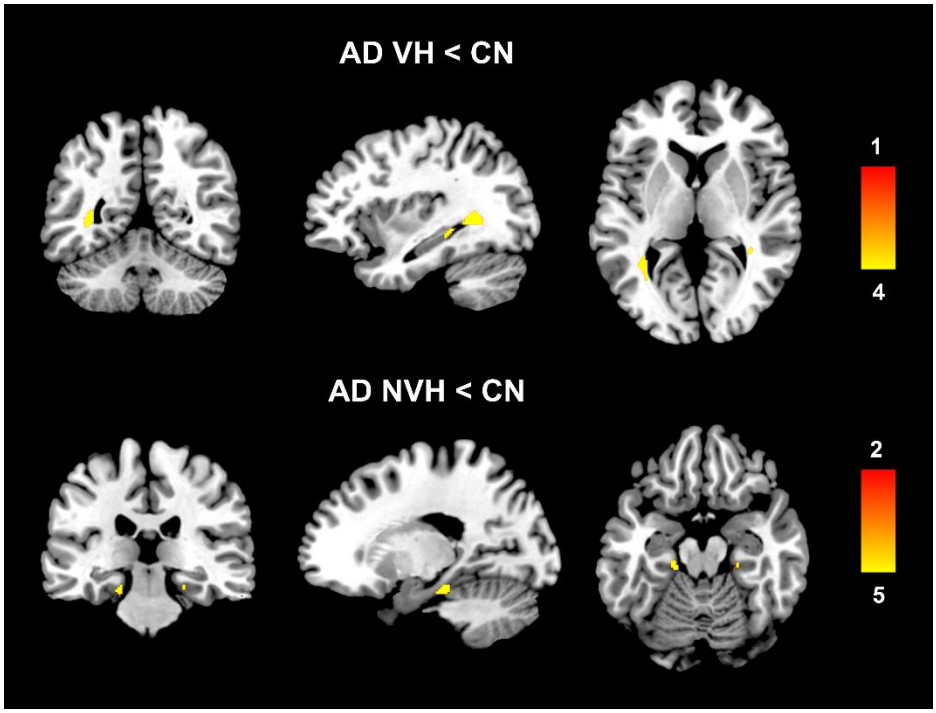

Figure 7.5 Regions of reduced WM volume in AD VH (at the top) and NVH (at the bottom) compared with CN. The colour bar indicates the z scores at a FWE corrected threshold with TIV and age as covariates of no interest.

Whole brain VBM correlation analysis carried out on the whole sample (n=78), revealed a positive association between clock copying and GM volume in the right fusiform and inferior temporal gyri. A negative association was found between TMT-A scores (seconds) and right cerebellar regions, left frontal and temporal areas, and the caudate nucleus bilaterally (Table 7.8 and Figure 7.6).

Table 7.8 Regions of significant correlations between clock copying and TMT-A, and GM volumes (cluster-level threshold of p<0.05 FWE corrected, with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Positive correlation – clock copying								
Fusiform gyrus (BA 19)	R	1261	48	-80	-12	4.34	4.08	0.003
Inferior temporal gyrus (20)	R		64	-38	-20	4.28	4.03	
Inferior temporal gyrus (37)	R		62	-51	-21	4.21	3.97	
Negative correlation – TMT-A (seconds)								
Cerebellar tonsil	R	1776	48	-60	-40	5.27	4.83	0.000
Culmen	R		39	-40	-28	3.71	3.53	
Fusiform gyrus (BA 20)	R		50	-33	-30	3.68	3.51	
Parahippocampal gyrus	L	1944	-33	-9	-30	5.06	4.66	0.000
Parahippocampal gyrus	L		-27	-9	-20	4.60	4.29	
Hippocampus	L		-30	-42	-3	4.13	3.90	
Caudate body	R	2089	8	9	2	4.79	4.45	0.000
Caudate body	L		-9	12	3	4.73	4.40	
Caudate body	R		10	10	9	4.59	4.29	
Inferior Frontal gyrus (BA 13)	L	876	-34	8	-21	4.76	4.42	0.015
Inferior Frontal gyrus (BA 47)	L		-22	16	-30	4.54	4.24	
Insula (BA 13)	L		-42	15	-8	3.65	3.48	
Middle temporal gyrus (BA 21)	L	1546	-60	-8	-16	4.76	4.42	0.001
Middle temporal gyrus (BA 21)	L		-62	-58	2	4.45	4.17	
Middle temporal gyrus (BA 21)	L		-58	-15	-12	4.07	3.85	

BA: Brodmann area; GM: grey matter; L: left; R: right; TIV: total intracranial volume; TMT: Trail Making Test.

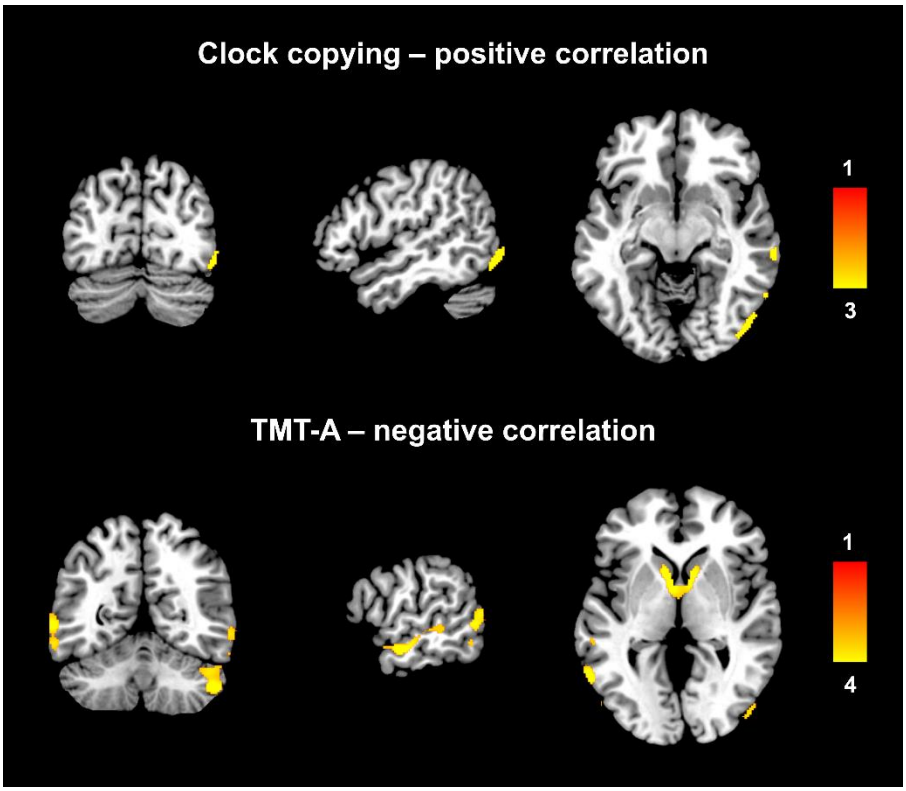

Figure 7.6 Regions of significant correlations between cognitive tests and GM volumes. The colour bar indicates the z scores at a FWE corrected threshold with TIV and age as covariates of no interest.

7.1.3.2 Experiment 7.2. Positron emission tomography findings

7.1.3.2.1 Demographic, neuropsychiatric and neuropsychological findings

Firstly, the whole AD sample was compared with CN matched participants (Table 7.9). No differences were detected in age, gender, years of education. AD patients presented poorer performance in all neuropsychological tests, and higher scores on the NPI.

Table 7.9 Demographic, clinical and neuropsychological characteristics for AD patients and cognitively normal controls.

Test	AD		CN		P value
	n	Mean (SD)	n	Mean (SD)	
Age	24	73.46 (7.93)	24	73.29 (7.31)	0.94 [a]
Gender M:F	24	10:14	24	10:14	-
Years of education	24	16.04 (2.81)	24	16.67 (3.00)	0.34 [c]
MMSE	24	22.63 (3.79)	24	29.13 (0.99)	<0.001 [c]
NPI total score	24	20.33 (20.86)	24	0.00	<0.001 [c]
TMT-A (s)	23	74.96 (42.93)	24	32.46 (10.10)	<0.001 [c]
TMT-B (s)	23	210.35 (105.22)	24	80.38 (39.15)	<0.001 [c]
Prose memory:					
Immediate recall	23	4.61 (3.56)	24	15.54 (2.99)	<0.001 [c]
Delayed recall	23	2.22 (3.22)	24	14.33 (3.54)	<0.001 [c]
RAVLT:					
Immediate recall	23	24.48 (7.75)	24	45.38 (9.55)	<0.001 [c]
Delayed recall	23	0.70 (1.85)	24	7.75 (3.96)	<0.001 [c]
Category fluency	23	12.35 (3.63)	24	24.29 (6.03)	<0.001 [a]
Clock drawing	23	3.04 (1.61)	24	4.67 (0.57)	<0.001 [c]
Clock copying	23	3.96 (1.15)	24	4.92 (0.28)	<0.001 [c]
Boston naming test	21	23.57 (5.43)	24	28.50 (1.72)	<0.001 [c]

AD: Alzheimer's disease; CN: cognitively normal; F: female; M: male; MMSE: Mini-Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; SD: standard deviation; TMT: Trail Making Test. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Mann-Whitney U test.

When AD with and without VH were compared, no between-group differences were observed in age, gender, years of education, MMSE, NPI scores, and presence of neuropsychiatric symptoms other than VH (Table 7.10 and Table 7.11). Although not surviving correction for multiple comparisons ($p<0.005$), the only neuropsychological test that reached statistical significance was the TMT-A (Table 7.12). When the clock copying test was added as covariate of no interest, this result remained significant, suggesting that the deficit observed in visual attention persisted even when accounting for more visuoperceptive impairments (ANCOVA analysis, $p=0.02$).

Table 7.10 Demographic and clinical characteristics for AD patients with and without VH. Mean and SD are reported for each variable unless otherwise specified.

Characteristic	AD VH (n=12)	AD NVH (n=12)	p value
Age	73.75 (8.57)	73.17 (7.60)	0.86 [a]
Gender M:F	5:7	5:7	1.00 [b]
Years of education	16.50 (2.88)	15.58 (2.78)	0.44 [c]
MMSE	22.42 (4.60)	22.83 (2.86)	0.79 [a]
NPI total score	21.83 (18.48)	18.83 (23.73)	0.29 [c]
NPI tot - NPI VH	18.58 (17.91)	18.83 (23.73)	0.67 [c]

AD: Alzheimer's disease; CN: cognitively normal; F: female; M: male; MMSE: Mini-Mental State Examination; NVH: no VH; VH: visual hallucinations. [a] Independent-sample t-test; [b] Fisher's Exact Test; [c] Mann-Whitney U test.

Table 7.11 Number of patients presenting with each neuropsychiatric symptom detected with the NPI, differences between AD patients with and without VH (Fisher's Exact Test).

Characteristic, n (%)	AD VH (n=12)	AD NVH (n=12)	p value
Delusions	6 (50.00%)	3 (25,00%)	0.40
Hallucinations	12 (100%)	0 (00.00%)	**<0.001**
Agitation/aggression	8 (66.67%)	6 (50.00%)	0.68
Depression/dysphoria	8 (66.67%)	5 (41,67%)	0.41
Anxiety	7 (58,33%)	5 (41,67%)	0.68
Elation/euphoria	1 (8,33%)	2 (16,67%)	1.00
Apathy/indifference	3 (25,00%)	8 (66,67%)	0.10
Disinhibition	2 (16,67%)	4 (33,33%)	0.64
Irritability/lability	5 (41,6%)	6 (50.00%)	1.00
Aberrant motor behaviour	2 (16,6%)	4 (33,33%)	0.64
Sleep	6 (50.00%)	5 (41,67%)	1.00
Appetite and eating disorders	5 (41,67%)	2 (16,67%)	0.37

AD: Alzheimer's disease; NPI: neuropsychiatric inventory; NVH: no VH; VH: visual hallucinations.

7.1.3.2.2 PET findings

In the comparison between AD and CN, FDG-PET analysis revealed a pattern of glucose metabolism consistent with the one usually observed in AD. Specifically, regions of hypometabolism were found in temporal and parietal regions, including the left posterior cingulate, consistent with a diagnosis of AD (Dubois, 2018). Details are shown in Table 7.13 and displayed in Figure 7.7. When comparing both AD subgroups (VH and NVH) separately with CN participants, regions of hypometabolism were found mainly in temporal, parietal and occipital areas in patients with VH, and temporal regions in patients without VH (Table 7.14). Results were reported if significant at a set-level threshold of $p<0.05$ FWE corrected for multiple comparisons.

These PET findings suggest a DLB-like profile of features in AD patients with VH, namely the presence of occipital hypometabolism.

One-way ANOVA analyses reported significant differences between groups in the posterior cingulate ROI ($p<0.001$). Bonferroni *post-hoc* comparisons revealed significant differences between cognitive normal participants and patients with VH ($p<0.001$) and without VH ($p=0.01$), but no differences between VH and NVH groups ($p=0.06$). No significant differences were found between groups in the CIS ratio (one-way ANOVA analysis, $p=0.17$).

Table 7.12 Differences in neuropsychological tests between AD VH and NVH.

Test	AD VH		AD NVH		p value
	n	Mean (SD)	n	Mean (SD)	
TMT-A (s)	11	98.45 (44.36)	12	53.42 (28.98)	**0.02** [a]
TMT-B (s)	11	233.91 (102.69)	12	188.75 (107.19)	0.41 [a]
Prose memory:					
Immediate recall	11	4.27 (3.85)	12	4.92 (3.42)	0.41 [a]
Delayed recall	11	2.18 (3.16)	12	2.25 (3.42)	0.79 [a]
RAVLT:					
Immediate recall	11	24.55 (9.26)	12	24.42 (6.50)	0.97 [b]
Delayed recall	11	1.09 (2.59)	12	0.33 (0.65)	0.93 [a]
Category fluency	11	11.55 (3.14)	12	13.08 (4.01)	0.32 [b]
Clock drawing	11	2.36 (1.57)	12	3.67 (1.44)	0.06 [a]
Clock copying	11	3.64 (1.21)	12	4.25 (1.06)	0.21 [a]
Boston naming test	9	22.78 (6.20)	12	24.17 (4.97)	0.60 [a]

AD: Alzheimer's disease; CN: cognitively normal; NVH: no VH; RAVLT: Rey Auditory Verbal Learning Test; SD: standard deviation; TMT: Trail Making Test; VH: visual hallucinations. [a] Mann-Whitney U test; [b] Independent-sample t-test.

Table 7.13 Regions of hypometabolism in AD patients compared with CN (set-level threshold of p<0.05 with TIV and age as covariates of no interest, k>20).

Structure	Side	Cluster size	MNI coordinates			T score	Z score	p value [a]
Uncus	L	1021	-26	-8	-38	7.41	5.94	<0.001
Parahippocampal gyrus	L		-18	-34	-10	6.11	5.17	
Parahippocampal gyrus	L		-28	-36	-14	6.05	5.13	
Posterior cingulate	L	1428	-2	-46	28	7.22	5.83	<0.001
Precuneus	L		-4	-68	30	6.44	5.37	
Inferior temporal gyrus	R	1219	62	-24	-24	7.18	5.81	<0.001
Middle temporal gyrus	R		62	-44	-8	6.14	5.19	
Inferior temporal gyrus	L	1037	-60	-26	-24	6.88	5.64	<0.001
Inferior temporal gyrus	L		-60	-36	-18	6.78	5.58	
Uncus	R	475	30	-12	-34	6.81	5.60	<0.001
Precuneus	R	343	44	-64	40	6.28	5.28	<0.001
Middle temporal gyrus	L	575	-40	-68	32	6.07	5.15	<0.001
Angular gyrus	L		-46	-66	40	6.06	5.14	
Precuneus	L		-32	-78	44	5.69	4.90	
Inferior semi-lunar lobule (cerebellum)	R	21	52	-70	-38	5.37	4.69	0.019

AD: Alzheimer's disease; BA: Brodmann area; CN: cognitively normal; L: left; R: right; TIV: total intracranial volume. [a] cluster-level FWE corrected p value.

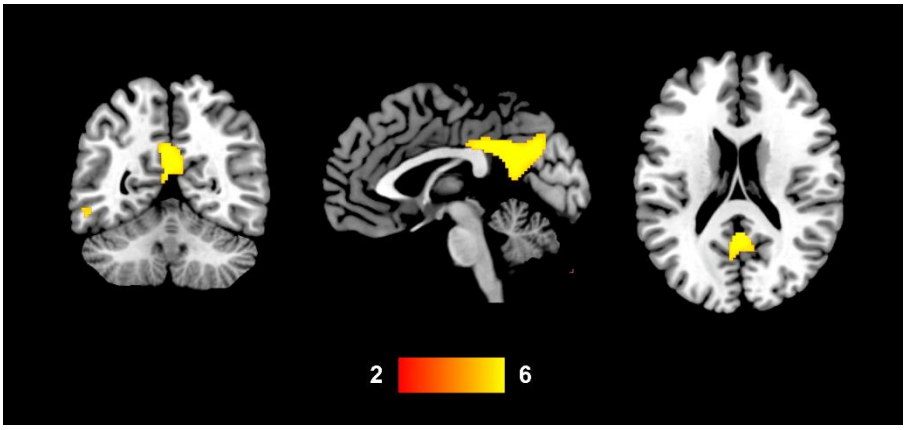

Figure 7.7 Regions of hypometabolism in AD patients compared to CN. The colour bar indicates the z scores with the set-level threshold of p<0.05 FWE corrected for multiple comparisons, with TIV and age as covariates of no interest.

Table 7.14 Regions of hypometabolism in AD patients with and without VH independently compared with CN (set-level threshold of p<0.05 with TIV and age as covariates of no interest, k>20).

Structure	Side	Cluster size	MNI coordinates			T score	Z score	p value [a]
AD VH < CN								
Middle temporal gyrus	R	2108	62	-24	-22	8.34	6.04	<0.001
Precuneus	R	2182	48	-64	42	8.20	5.97	<0.001
Middle temporal gyrus	L	2310	-42	-66	32	8.17	5.96	<0.001
Cingulate gyrus	L	2906	0	-48	30	7.63	5.72	<0.001
Inferior occipital gyrus	L	427	-36	-96	-4	7.56	5.69	<0.001
Inferior temporal gyrus	L	1085	-62	-38	-18	7.37	5.59	<0.001
Middle occipital gyrus	R	312	38	-94	6	6.39	5.09	<0.001
Inferior semi-lunar lobule (cerebellum)	R	59	14	-88	-42	6.25	5.01	0.005
Declive (cerebellum)	L	36	-24	-82	-14	5.99	4.87	0.009
Inferior semi-lunar lobule (cerebellum)	R	24	52	-72	-38	5.89	4.82	0.014
AD NVH < CN								
Uncus	R	480	22	-2	-30	7.58	5.69	<0.001
Uncus	L	185	-24	-6	-38	6.57	5.19	<0.001

AD: Alzheimer's disease; BA: Brodmann area; CN: cognitively normal; L: left; R: right; TIV: total intracranial volume; VH: visual hallucinations. [a] cluster-level FWE corrected p value.

Regional differences in metabolism between AD VH and AD NVH were found in occipital areas, specifically in the bilateral cuneus and the left lingual gyrus (Table 7.15 and Figure 7.8), with significant lower level of metabolism found in AD VH.

Correlational analyses with cognitive scores revealed a positive association between glucose metabolism in the right lingual gyrus and clock copying, while a negative correlation was observed between scores at the TMT-A and occipital regions bilaterally (inferior occipital gyrus and cuneus) in the whole AD group (Table 7.16 and Figure 7.9).

Table 7.15 Regions of hypometabolism in AD VH compared to AD NVH (cluster-level threshold of p<0.05 FWE corrected for multiple comparisons with TIV and age as covariates of no interest).

Structure	Side	Cluster size	MNI coordinates			T score	Z score	p value
Cuneus (BA 17)	R	1834	16	-86	12	5.03	4.00	0.002
Cuneus (BA 17)	L		-2	-88	12	4.73	3.83	
Lingual gyrus (BA 18)	L		-2	-90	0	4.53	3.71	

AD: Alzheimer's disease; BA: Brodmann area; L: left; NVH: no VH; R: right; TIV: total intracranial volume; VH: visual hallucinations.

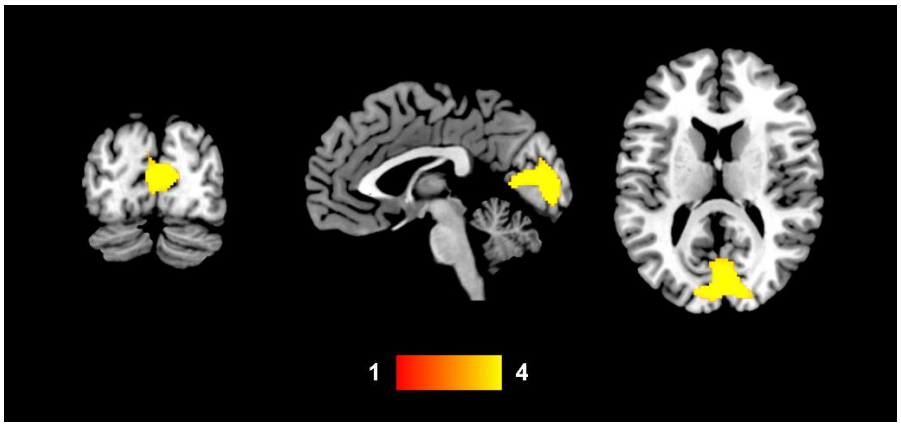

Figure 7.8 Regions of hypometabolism in AD VH patients compared to NVH. The colour bar indicates the z scores with the cluster-level threshold of p<0.05 FWE corrected for multiple comparisons, with TIV and age as covariates of no interest.

Table 7.16 Regions of significant correlations between clock copying and TMT-A, and regional glucose metabolism in the whole AD group (cluster-level threshold of p<0.05 FWE corrected, with TIV and age as covariates of no interest).

Structure		Cluster size	MNI coordinates			T score	Z score	p value
Positive correlation – clock copying								
Lingual gyrus (BA 19)	R	1583	18	-70	-4	5.01	3.95	0.002
Culmen	R		60	-44	-32	4.66	3.76	
Declive	R		48	-86	-18	4.63	3.74	
Negative correlation – TMT-A (seconds)								
Inferior occipital gyrus (BA 19)	R	7213	48	-72	-6	6.84	4.80	<0.001
Cuneus (BA 17)	R		16	-84	14	5.66	4.28	
Precuneus (BA 7)	R		22	-56	58	5.59	4.25	
Cuneus (BA 18)	L	4625	-16	-82	26	6.27	4.56	<0.001
Inferior occipital gyrus (BA 19)	L		-36	-82	6	5.47	4.19	
Fusiform gyrus (BA 18)	L		-28	-92	-12	5.06	3.98	

BA: Brodmann area; L: left; R: right; TIV: total intracranial volume; TMT: Trail Making Test.

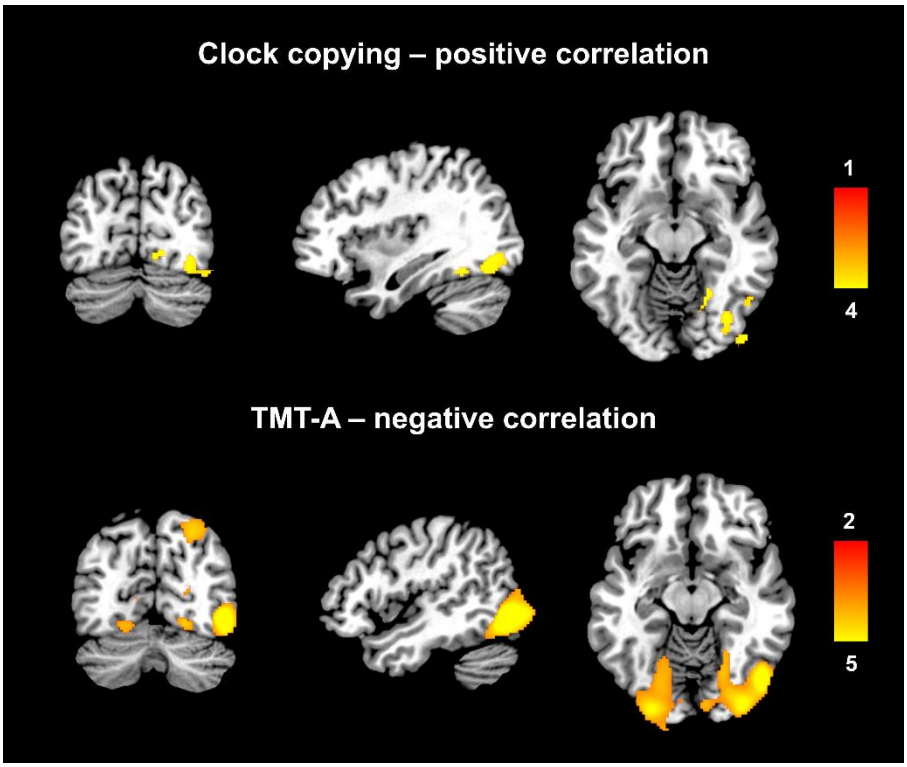

Figure 7.9 Regions of significant correlations between cognitive tests and regional glucose metabolism. The colour bar indicates the z scores at a FWE corrected threshold with TIV and age as covariates of no interest.

7.1.3.3 CSF β-Amyloid (1-42)

In Experiment 7.1, CSF β-Amyloid $_{(1-42)}$ levels were available for 6 patients with VH and 14 without VH. Only two patients, one with VH and one without, had Aβ $_{(1-42)}$ levels above the cut-off >1130 pg/mL. All the other patients were CSF Aβ $_{(1-42)}$ positive.
In Experiment 7.2, CSF Aβ $_{(1-42)}$ was available for 6 patients with VH and 9 without VH. All patients with VH and 7 without were positive, while two non-hallucinating patients were negative, with CSF Aβ $_{(1-42)}$ levels above the cut-off.

7.1.3.4 Neuropathological diagnosis

Autopsy was available for only four patients, two with VH and two without. The primary neuropathological diagnosis was AD for all cases. In addition, both patients with VH had concomitant TAR DNA binding protein 43 (TDP-43) proteinopathy circumscribed to the medial temporal lobe. One patient without VH had pure AD pathology, while the other had AD with amygdala LBs. The latter patients was only included in the VBM study (Experiment 7.1), but not in the PET analyses (Experiment 7.2).

7.1.4 Discussion

This study provides evidence of the presence of occipital atrophy, occipital hypometabolism, and visuoconstructive deficits associated with VH in AD. Table 7.17 summarised the main findings. To our knowledge, this is the first whole brain investigation of regional GM volumes and glucose metabolism focusing on the differences between patients with and without VH in AD, thus representing an important addition to the current literature.

Table 7.17 Summary of the main findings from Experiment 7.

Comparison	Cognitive deficits	Grey matter loss	Hypometabolism
AD VH < AD NVH	Visuoconstructive deficits (clock copying)	None	Cuneus bilaterally Left lingual gyrus
AD VH < CN	All neuropsychological measures	Left middle occipital gyrus Right anterior cingulate gyrus Medial and lateral temporal areas	Temporal, parietal and occipital areas
AD NVH < CN	All neuropsychological measures excluding clock drawing and copying	Medial and lateral temporal areas	Temporal areas

AD: Alzheimer's disease; CN: cognitively normal; NVH: no visual hallucinations; VH: visual hallucinations.

Our first aim was to explore the neuropsychology associated with VH in a sample of participants with MCI and dementia due to AD. Firstly, both subgroups of AD patients presented deficits in verbal long-term and semantic memory, visual attention, and executive functioning when compared with cognitively normal participants. On the other hand, performance on the clock drawing test, both copying and drawing, was significantly poorer only in hallucinating patients, while comparable performance with controls was detected for the non-hallucinating group. As for the direct comparison between patients with and without VH, the only test reaching statistical significance was the clock copying, assessing visuoconstructive abilities, which was significant even when controlling for visual attention deficits, evaluated with the TMT-A. Interestingly, non-hallucinating patients performed similarly to cognitively normal controls on this test, suggesting that visuoconstructive impairment may be a deficit specifically characterising patients with VH, confirming our *a priori* hypothesis. This

finding is in line with the PAD model, proposing that VH are the result of the combination of visual perception and attention impairments (Collerton et al., 2005). Lower scores on the Rey figure copy have been detected previously in hallucinating PD patients (Chang et al., 2016, Manganelli et al., 2009, Shin et al., 2012), finding that is also consistent with what we have previously shown in DLB with VH (Experiment 4.1). Several other studies identified visual perception impairments in patients with VH both in PD (Barnes et al., 2003, Ibarretxe-Bilbao et al., 2010, Koerts et al., 2010, Ramirez-Ruiz et al., 2006, Ramirez-Ruiz et al., 2007a), and LB dementia (Mori et al., 2000, Mosimann et al., 2004). Less evidence can be found for hallucinating AD patients, most likely due to the limited amount of studies available, which focused mainly on other cognitive domains, such as executive functioning (El Haj et al., 2018, El Haj et al., 2015). Most studies, however, did not differentiate between the sensory modality of the hallucinations, thus being less informative on the mechanisms underlying VH in particular. Quaranta et al. (2015) focused on VH in AD. They found that visual memory was the only cognitive function predicting the severity of VH. This finding was interpreted as reflective of visuoperceptive involvement in the manifestation of VH in this disease (Quaranta et al., 2015). Nevertheless, no differences between AD with and without VH were detected in the copy of the Rey figure, while worse performance in hallucinating patients was found in executive functioning, and verbal, visuospatial and semantic memory. These findings are in contrast with the abovementioned results, and this may be due to other demographic and clinical variables. In fact, in Quaranta et al.'s (2015) AD patients with VH were significantly older with more severe global cognitive impairment, compared to those without VH. Moreover, along with visual memory impairment, age predicted the severity of VH (Quaranta et al., 2015). Thus, these variables may partially explain the widespread cognitive deficits linked to VH found by Quaranta et al. (2015). Indeed, other studies have reported an association between VH, older age and more severe dementia in AD (Chiu et al., 2017, Holroyd and Sheldon-Keller, 1995). On the other hand, in our experiment, AD patients with and without VH were well matched for age, gender, years of education and other neuropsychiatric features. Additionally, our cohort included only mild to moderate cognitively impaired patients and thus, may be more informative than other studies in identifying specific cognitive domains associated with VH.

We previously observed more severe attention deficits in hallucinating DLB patients (Experiment 1), consistently with other previous studies on LBD (Cagnin et al., 2013, Hepp et al., 2013). In the present study (Experiment 7.1), no differences between AD

VH and NVH were found in visual attention, although a non-significant trend towards more severe deficits in hallucinating patients was observed. Moreover, when comparing neuropsychological performance in a subsample of patients (Experiment 7.2), those with VH presented more severe visual attention impairment, even though not surviving correction for multiple comparisons. These findings, together, suggest a contribution of visual attention difficulties in the development of VH also in AD, even though such deficits appear to be more subtle than visuoconstructive impairments.

As for structural brain alterations, we expected volumetric brain differences in occipital and occipito-temporal regions in AD with VH. No differences were identified in the direct comparison between hallucinating and non-hallucinating patients. Only another study used whole brain VBM in the investigation of hallucinations in AD, reporting insular and frontal GM loss (Blanc et al., 2014). The threshold used, however, was uncorrected for multiple comparisons, thus increasing the likelihood of false positives, and no differentiation was made concerning hallucinations sensory modality (Blanc et al., 2014). To our knowledge, this is the first whole brain investigation of volumetric alterations linked to VH in AD, since other studies focused on predefined ROIs, all with small sample sizes (Holroyd et al., 2000, Middelkoop et al., 2001). Although we detected no differences in the direct comparison between patients with and without VH, the results we obtained when independently comparing both AD subgroups with cognitively healthy controls confirmed our hypothesis. Firstly, overlapping regions of GM loss when compared with controls were located mainly in medial lateral temporal areas in both VH and NVH groups, in line with a diagnosis of AD (Dubois, 2018). Additional regions of reduced GM were detected in patients with VH in the left middle occipital and right anterior cingulate gyri. Consistently, our PET analysis revealed hypometabolism in the occipital lobe in AD patients with VH compared with those without, mainly in the cuneus bilaterally. No FDG-PET investigation has previously focused on VH in AD. Other PET and SPECT studies explored hallucinations in AD, and reported conflicting results, including frontal altered glucose metabolism and reduced parietal blood flow (Blanc et al., 2014, Kotrla et al., 1995, Lopez et al., 2001). Contrasting findings may be due to methodological and clinical differences between studies, including those not distinguishing between hallucinations in different sensory modalities (Blanc et al., 2014, Kotrla et al., 1995, Lopez et al., 2001).

Susceptibility to VH has been associated with grey matter atrophy in occipital and parietal regions in different neurological and psychiatric conditions, as suggested by a recent trans-diagnostic literature review (Carter and Ffytche, 2015). Occipital atrophy has been related to VH in other studies of patients with AD (Holroyd et al.,

2000, Lin et al., 2006) and PD (Bejr-Kasem et al., 2019, Goldman et al., 2014, Watanabe et al., 2013). Importantly, our meta-analysis on LBD (Experiment 6.1), including mainly PD patients, showed reduced GM volume in the left middle occipital gyrus, calcarine fissure and surrounding cortex, confirming these findings. The association between dysfunction in occipital regions and VH has also been reported by PET and SPECT studies. Occipital/occipito-temporal hypometabolism/perfusion was found in hallucinating patients with PD (Gasca-Salas et al., 2016, Matsui et al., 2006) and DLB (Heitz et al., 2015, Pasquier et al., 2002, Perneczky et al., 2008). In addition, occipital hypometabolism was found to correlate with severity/frequency of VH in patients with both PD and DLB (Firbank et al., 2016, Iaccarino et al., 2018, Kantarci et al., 2012). Occipital atrophy and hypometabolism may be related to dysfunctional visuoperceptive processes observed not only in hallucinating patients with LBD (see Chapter 2 for a review), but also in our sample of AD patients. Moreover, we found that deficits in visuoconstruction, evaluated with the clock copying test, positively correlated with both atrophy and hypometabolism in right occipito-temporal areas, further corroborating this hypothesis. Such brain alterations, therefore, may underlie dysfunctional visual information processing, of which occipital hypometabolism may be a functional hallmark. Occipital atrophy may be more subtle, although present, and this may explain the volumetric GM reduction detected only when comparing both AD subgroups independently with CN participants.

Despite the findings described above, no evidence of LB pathological burden has been previously reported in the occipital lobe in relation to VH (Kalaitzakis et al., 2009). Thus, findings from the present study may not inform on underlying occipital neuropathological features. Instead, they might reflect aberrant connections between brain regions within functional and structural networks sustaining cognitive functions that, if dysfunctional, contribute to the development of VH. In line with this view, our previous studies reported alterations in structural and functional connectivity of occipital areas in hallucinating DLB patients. Firstly, in Experiment 2 (section 4.2) we found disrupted functional connectivity of visual areas with the anterior cingulate and precuneus in addition to increased co-activation of visuoperceptive areas (lateral geniculate body and fusiform gyrus). Then, in Experiment 3 (section 4.3), we found damaged WM microstructure in hallucinating DLB patients in the ILF, connecting occipital and temporal areas, and in the IFOF, connecting occipital and frontal areas, both associated with visual processing (Catani and Thiebaut de Schotten, 2008, Wu et al., 2016). Alterations in WM integrity have also been detected by another study on VH in DLB (Kantarci et al., 2010). Consistent with these findings, the present study

also showed decreased WM volume in the IFOF in patients with AD and VH when compared with controls, but not in non-hallucinating patients, suggesting that alterations in this WM tract may contribute to VH also in AD.

We also found reduced GM volume in the right anterior cingulate in AD patients with VH, but not in those without, compared with controls. It has been proposed that hallucinations in AD may generate from dysfunctional inhibitory mechanisms of irrelevant memories (El Haj et al., 2017). The anterior cingulate might be implicated in this process, given its role in response inhibition (Gasquoine, 2013). In this study, however, no measure of inhibitory processes was available, thus suggesting the need of exploring further the role played by this region and response inhibition in relation to VH in AD. We previously proposed (section 4.2.4) that dysfunctional connectivity of the anterior cingulate may facilitate the development of VH in DLB, which might be modulated by cholinergic dysregulation (Diederich et al., 2005, Teaktong et al., 2005). In addition, along with the insula, the anterior cingulate is a core hub of the ventral attention network that has been proposed to facilitate the development of VH (Shine et al., 2011).

In addition to the pattern of abnormalities typical of AD, findings from the present study indicate the presence of brain and cognitive changes in patients with VH similar to those usually observed in DLB. In a previous study, Chiu et al. (2017) demonstrated the presence of DLB core features in AD patients with VH, namely higher rates of RBD, cognitive fluctuations and more severe neuroleptic sensitivity. However, they did not explore the role of specific cognitive impairments linked to this symptom. The present findings complement those reported by Chiu et al. (2017), by showing occipital hypometabolism and visuoconstructive deficits in hallucinating AD patients, features that are usually distinctive of DLB (McKeith et al., 2017). A previous study on the ADNI cohort reported concomitant LB pathology in 10 out of 22 cases with a clinical diagnosis of MCI or dementia due to AD (Toledo et al., 2013). Notably, patients with hallucinations (n=4) had mixed AD/LB pathology, although the sensory modality was not specified (Toledo et al., 2013). In the present study, however, neuropathological data were available only for two patients with VH. Contrary to our hypothesis, none of the hallucinating patients had concomitant LB pathology, but AD with TDP-43 proteinopathy in the medial temporal lobe. TDP-43 intracellular inclusions are a hallmark pathology of fronto-temporal lobar degeneration (FTLD) and motor neuron disease, but are also observed in DLB, and more commonly in AD (McAleese et al., 2017, Outeiro et al., 2019). Patients with concomitant TDP-43 pathology have been associated with more severe cognitive impairment, especially in

episodic and working memory, and language (McAleese et al., 2017, Outeiro et al., 2019). In both AD and DLB, TDP-43 has been mainly observed in MTL, especially in the amygdala, showing a different distribution than FTLD patients (McAleese et al., 2017).

Findings from the present study suggest that VH in AD may be linked to concomitant TDP pathology. However, autopsy was available for very few patients, making it difficult to draw any firm conclusions. We can only speculate, therefore, that MTL pathology may contribute to VH. We previously put forward a speculative interpretation suggesting that LB pathology in MTL areas, with or without AD pathology, may disrupt neural circuits eventually forming the basis for hallucinations in DLB (section 5.1.4). In this context, VH in AD may arise from disease-specific AD pathology, but also other pathological events affecting MTL areas. Specifically, they could reflect concomitant TDP pathology or even LB pathology, in line with the abovementioned studies on hallucinations in AD. In addition, LBs in DLB patients with VH have been found predominantly in MTL structures, especially in the amygdala (Harding et al., 2002a, Papapetropoulos et al., 2006). Therefore, the neuropathology underlying VH might differ between conditions, although still involving the MTL. This, along with more severe visual perception and attention impairments, and related dysfunctional brain networks, may eventually facilitate the genesis of hallucinatory phenomena. Thus, we speculate that MTL-related alterations might constitute necessary but not sufficient impairments leading to VH. In this context, AD patients, characterised by MTL pathology, may experience VH only in the presence of additional brain dysfunctions, especially related to the visual system (e.g. occipital hypometabolism). Within this framework, however, our finding of concomitant LB pathology in the amygdala in a patient without hallucinations remains unexplained. Due to the very limited neuropathological data for our sample, it is difficult to formulate interpretations, which remain purely speculative. Future neuropathological studies may explore further symptom-specific cognitive and neural mechanisms facilitating the genesis of VH in patients with underlying mixed pathological processes. Neuroimaging methods and neuropsychological assessment may be used to clarify *pre-mortem* features characterising autopsy confirmed cases. In this sense, the ADNI project, and multicentre studies in general, represent valuable resources in the study of such specific symptomatology.

We acknowledge the presence of some limitations. Firstly, pathological data were available only for four patients, thus being only partially informative of underlying neuropathological processes. Moreover, the neuropsychological assessment was

limited to tests available in the ADNI cohort. Thus, some cognitive processes previously associated with hallucinations in AD could not be tested, such as response inhibition. Moreover, since the NPI was used, no information on the phenomenology of VH was included, which may differ between conditions. VH have been shown also in pure AD cases. For example, Thomas et al. (2018) found that three out of 19 patients with autopsy confirmed pure AD had VH that were, however, less complex than those usually observed in DLB. This suggests that the phenomenological features of VH may be very informative in investigating their underlying cognitive and neural mechanisms that may differ in relation to complexity and severity of the symptoms. The present study focused specifically on VH, thus being a valuable addition to the current literature, whereas previous investigations did not specify the sensory modality. However, it should be noted that of the 26 patients with VH, 12 also presented hallucinations in other sensory modalities. The total NPI hallucination score is based on the severity and frequency of hallucinations in general, thus not distinguishing between sensory modality. The presence of VH, however, was assessed using the NPI subsection specific for visual hallucinations. Another limitation is that FDG-PET was available only for 12 out of 26 hallucinating AD patients. To our knowledge, this is the first whole brain VBM and FDG-PET study on VH in AD, a symptom that appears to be rather rare in AD, considering the limited number of patients experiencing this symptom in the entirety of the ADNI cohorts. In addition to a pattern of disease-specific abnormalities, we found occipital atrophy and hypometabolism, as well as visuoconstructive impairments in association with VH, a combination of impairments that may contribute to the genesis of these symptoms in AD. These alterations, along with underlying mixed pathological processes might result in disrupted neural circuits contributing to the development of this disabling symptomatology.

Chapter 8. General discussion

Visual hallucinations are involuntary visual perceptions, experienced during wakefulness as real percepts in the absence of external sensory inputs (Collerton et al., 2005, Waters et al., 2014). For the purpose of the present thesis, we referred to complex VH, experienced as repetitive and involuntary well-formed images, usually of people, animals and objects (Collerton et al., 2005). Patients with different conditions may experience this type of hallucinations, above all those with DLB and PD, but also patients with other types of dementia, including AD, and other psychiatric disorders (Collerton et al., 2005, Waters et al., 2014).

VH are severe and disabling symptoms, with a deleterious impact on the overall quality of life of patients and significantly higher caregiver distress (Onofrj et al., 2013, Swann and O'Brien, 2018). Their frequent comorbidity with other symptoms contributes significantly in worsening the clinical and prognostic profile of hallucinating patients (Aynsworth et al., 2017, Onofrj et al., 2013). VH have been associated with the occurrence of other neuropsychiatric symptoms, more severe and rapid cognitive decline, and earlier institutionalisation (Aarsland et al., 2000, Onofrj et al., 2013, Swann and O'Brien, 2018). Nevertheless, there is currently no effective targeted treatment, problem that is worsen further by the lack of evidence-based interventions (Swann and O'Brien, 2018, Wilson et al., 2016).

Although different models have been theorised to explain the neural processes underlying VH (Collerton et al., 2005, Diederich et al., 2005, Diederich et al., 2015, Shine et al., 2011), the exact mechanisms involved are not well established. Generally, different models have been proposed suggesting the contribution of top-down and bottom-up processes, thus, these symptoms would result from a complex interaction of different neural and cognitive mechanisms. For example, Collerton et al. (2005) proposed that combined deficits in visual attention and perception constitute a vulnerability to VH. Similarly, Shine et al. (2011) suggested a role of dysfunctional brain networks regulating bottom-up and top-down attention mechanisms. Nevertheless, relatively little evidence corroborating these models is available on PD, and even less concerning patients with dementia due to LBD and AD. Findings are often contradictory and inconsistent (reviewed in Chapter 2), suggesting the need of further research to widen our current knowledge on this disabling symptomatology, in terms of both symptom and disease-specific processes involved. Since patients with dementia are underrepresented within the current VH-related research, very little may

be inferred on potentially different mechanisms across conditions, and how they relate with the presence of different types of dementia. For these reasons, the overall aim of the present work was to explore the neurocognitive, structural and functional brain features associated with VH across different clinical diagnosis, specifically in PD, DLB and AD. In order to do so, we used a wide range of methodologies, including neuropsychological testing, structural and functional MRI, PET and meta-analytic approaches. In the following sections, findings reported within this thesis will be summarised in relations to different clinical diagnoses. Then, we propose possible common and distinct mechanisms underlying VH across conditions, followed by study limitations and future research directions.

8.1 Dementia with Lewy bodies

In Experiment 1, we tested whether there was an interplay between visual perception and attention deficits, and related brain features, contributing to VH in patients with DLB and PD, in line with multifactorial models. Our findings suggest a significant contribution of visual attention deficits, consistent with the pattern of brain atrophy indicating significant GM loss in frontal and striatal areas in hallucinating DLB patients compared with those without. Moreover, the finding that visual attention deficits persisted even when controlling for visual perception suggests that such attentional dysfunction may be independent of disrupted visuoperceptive abilities. Within this framework, top-down attention mechanisms appeared to play a predominant role in the development of VH in DLB. Indeed, the top-down control of spatial attention has been shown to rely on frontal and parietal brain regions, directly interconnected to each other, and indirectly through subcortical hubs, including the striatum (Gazzaley and Nobre, 2012, Nobre and Mesulam, 2014). Consistently, whole brain correlation analyses showed a significant association between visual attention deficits and GM volumes in the putamen and caudate, further highlighting the contribution of these structures.

In the attempt to replicate the abovementioned results, in Experiment 4.1 we investigated cognitive performance in a completely independent sample of DLB patients with and without VH, demonstrating the presence of more severe visuoconstructive impairments in those hallucinating, persisting even when controlling for visual attention. In addition, performance on the copy of the Rey figure was the only significant predictor of the presence of VH. On the other hand, no evidence of visual attention deficits was reported in this experiment, in contrast with what found in

Experiment 1. We explained these apparently contrasting findings in the light of the more severe global cognitive impairment, even though not significant, shown by patients with VH in Experiment 1, while the subgroups of patients included in Experiment 4.1 were better matched for global cognitive decline. Given the very close relationship between VH and dementia, these findings are not surprising. In this regard, we speculated that impairment in visual attention in hallucinating patients may drive the slightly more severe global cognitive impairment, and may foster both the development of VH and more severe dementia. This view is further corroborated by the fact that attention deficits, along with visual perception and executive impairment, represent distinctive features of DLB (Collerton et al., 2003) and thus, hallucinating patients might represent a more severe cognitive phenotype of dementia due to LB pathology. In this context, the poorer attention abilities shown by patients with VH might appear more clearly with the progression of dementia. Visuoperceptive deficits, instead, seem to become less distinctive with the worsening of cognitive decline, probably due to the substantial impairment of these abilities also in non-hallucinating patients. In this context, both visual perception and attention deficits would represent necessary contributors to VH. Consistent with this view, in Experiment 1, performance on both attention and visuoconstructive tasks significantly correlated with indices of VH, further suggesting an involvement of both cognitive domains.

In Experiments 2 and 3, we investigated functional and structural connectivity features related to VH in DLB providing additional evidence of underlying top-down and bottom-up brain processes. Specifically, DLB patients with VH presented microstructural damage in tracts connecting frontal areas with parietal (SLF, sustaining attention abilities), and occipital regions, passing through the temporal and parietal lobes (IFOF, associated with both attention and visuoperceptive mechanisms), but also connecting occipital and temporal areas (ILF, involved in visual processing). Interestingly, functional connectivity analyses led us to the speculative interpretation that a combined top-down attentional control dysfunction (anterior cingulate impaired connectivity), together with increased co-activation of visuoperceptive areas (geniculate nucleus and visual associative cortex), may foster the generation of false and internally generated visual images. This may be facilitated by increased DMN-related connectivity, associated with abnormal self-referential processes, which may form the basis for VH. In this context, dysfunctional DMN may contribute to the emergence of irrelevant memories, as well as deficits in the recall of appropriate information, in line with the interpretation proposed by Shine et al. (2011). Intriguingly, in the longitudinal investigation described in Experiment 4.2, we found that the only

significant cognitive predictor of the development of VH at follow-up was the presence of more severe verbal memory deficits at baseline, when none of the patients was hallucinating. In the light of these findings, we can speculate an involvement of MTL areas, possibly due to LB and/or AD pathology, which might also be responsible of the aforementioned DMN dysfunctions and, eventually, hallucinatory phenomena. Alternatively, the memory deficits observed in DLB patients with VH at follow-up may be secondary to thalamic damage. We tested this hypothesis *post hoc* in Experiment 4.3 that showed reduced GM volume in the mediodorsal thalamus in DLB patients with VH compared with those without. The mediodorsal thalamus is part of a fronto-thalamic circuit that has been proposed to contribute to memory processes, mediated by executive functioning. Thus, GM loss in this nucleus may represent a structural hallmark of disrupted neural circuits supporting memory, eventually predisposing DLB patients to hallucinate. Subsequently, concomitant deficits in visual perception and attention, and related dysfunctional neural circuits, may result in recurrent complex VH.

8.2 Parkinson's disease

In addition to the findings summarised in the previous section, Experiment 1 also provides evidence of the presence of cognitive and structural brain abnormalities in hallucinating PD patients without dementia. Even though whole brain VBM analyses did not yield significant results, when restricting the analyses to predefined ROIs, we identified striatal atrophy in PD patients with VH compared with those without, consistently with what found in DLB. Furthermore, performance on measures of both visual attention and executive functioning significantly correlated with GM volumes in the caudate nucleus, and worse executive dysfunction was detected in patients with hallucinations. Impaired fronto-striatal circuits, underlying executive dysfunctions in PD (Kehagia et al., 2010, Lewis et al., 2003) might explain or facilitate these symptoms. In this context, executive dysfunctions and attention deficits, of which striatal atrophy may represent a structural hallmark, might contribute to VH in patients with PD without dementia.

In order to reconcile findings available in the literature, in Experiments 5 and 6, we decided to meta-analyse results from VBM and neuropsychological studies on VH in PD, PDD and DLB. Since studies including patients with LB dementias were very limited, our interpretations mainly referred to PD. Most measures of executive functioning included in the neuropsychological meta-analysis showed no significant

differences between hallucinating and non-hallucinating patients, while poorer performance in patients with VH was detected only in the phonemic fluency test. This result, however, disappeared when excluding from the meta-analysis patients with LB dementias, suggesting that such executive impairments might be driven by the presence of progressive cognitive decline. In this context, the executive dysfunction observed in Experiment 1 may also be exacerbated by the presence of comorbid neuropsychiatric symptoms, which have been previously associated with executive impairment in PD (Alzahrani and Venneri, 2015). Thus, these deficits in PD with VH may reflect disorder-specific features, maybe reflecting a more severe phenotype of PD, possibly affected by greater global cognitive impairment and other neuropsychiatric symptoms.

In our neuropsychological meta-analysis, verbal memory performance was the only significant difference between PD patients with and without VH surviving correction for multiple comparisons, finding that was reported also in the individual sample of PD patients included in Experiment 1. These results are in line with our longitudinal study on DLB (Experiment 4.2), and provide strong evidence for the association between VH and verbal memory impairment. Given the close relationship between dementia, VH and memory deficits, the latter might reflect an increased risk of developing more severe progressive cognitive decline in hallucinating PD patients, and might be the result of common neuropathological features underlying these symptoms (i.e. LB burden with or without AD pathology). A speculative interpretation on the VH-related mechanisms within this process has been outlined in the previous section, and may be linked with the emergence of inappropriate memories and deficits in the recall of relevant information, forming the basis for the generation of false visual images. Alternatively, such memory deficits may be secondary to executive dysfunctions linked to more severely impaired fronto-striatal circuits, and might reflect difficulties in retrieval of information.

In terms of structural brain features, the VBM meta-analysis described in Experiment 5 demonstrated the presence of occipital GM loss in patients with LBD and, once again, most studies comprised PD patients without dementia. Occipital atrophy might be the result of impaired visuoperceptive mechanisms, ultimately manifesting as GM atrophy.

8.3 Alzheimer's disease

In the light of the AD-like cognitive profile described in patients with DLB and VH at follow-up (Experiment 4.2), and PD with VH (Experiments 1 and 6), namely verbal memory deficits, we decided to explore the neural and cognitive features associated with these symptoms in patients with MCI or dementia due to AD. In Experiment 7.1, we included AD patients with and without VH and cognitively normal controls. In comparison with controls, both subgroups of patients presented verbal memory deficits and MTL atrophy, typical of AD. In the direct comparison between patients with and without VH, we found more severe visuoconstructive deficits in those hallucinating, but no structural brain differences were detected. When both subgroups of patients were independently compared with controls, those hallucinating presented additional regions of GM loss located in the occipital lobe and anterior cingulate cortex. Consistent with this pattern of alterations, WM macrostructural alterations were found in patients with VH in the IFOF, tract that has been previously associated with both attention and visuoperceptive mechanisms (Catani and Thiebaut de Schotten, 2008, Wu et al., 2016). In addition to bottom-up perceptual processes, impaired top-down control mechanisms seem also to play a role, of which anterior cingulate atrophy may be a structural brain indicator.

In a subsample of AD patients, described in Experiment 7.2, we found occipital hypometabolism and more severe attention deficits in relation to VH. Within this picture, both visual perception and attention deficits would contribute to VH in AD, in line with multifactorial models (Collerton et al., 2005). Occipital alterations and visuoconstructive impairment, however, appeared to be predominantly involved, and might be a hallmark of disrupted visual processing circuits, which we propose to be a significant contributor to VH. We also found that deficits in visuoconstruction correlated with both atrophy and hypometabolism in right occipito-temporal areas, further corroborating this hypothesis.

Finally, we found that the only two hallucinating patients with autopsy available had concomitant TDP pathology circumscribed to the MTL, in addition to AD-related pathology, although the very small sample prevented any firm conclusion to be drawn on the type of pathology. We can speculate, however, that MTL pathology may constitute a vulnerability to VH, which might disrupt neural circuits eventually leading to the development of these symptoms. This process might initiate in the MTL, arising from disease-specific AD pathology and other comorbid pathological events. The fact

that VH in LBD has been associated with LB pathology in MTL areas (Harding et al., 2002a, Papapetropoulos et al., 2006) is in line with this view.

8.4 Common and distinct neurocognitive mechanisms across conditions

The findings described in this thesis suggest the presence of common neural mechanisms underlying VH in DLB, PD and AD, mediated by deficits in verbal memory, visual attention and visual perception, suggesting an involvement of both top-down and bottom-up processes. Figure 8.1 shows a summary diagram with the main findings and suggested brain mechanisms contributing to VH.

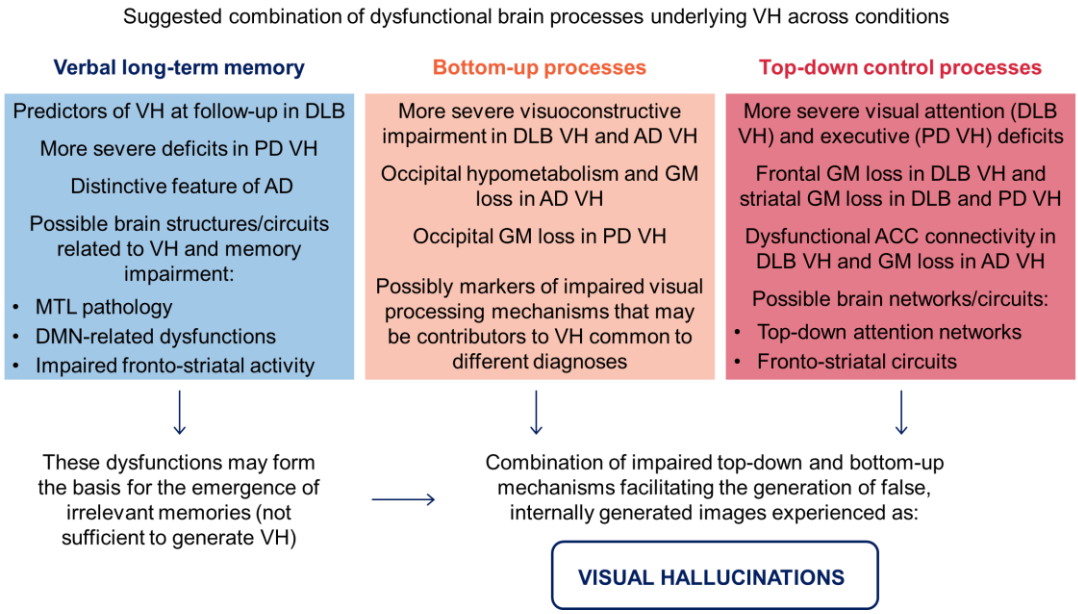

Figure 8.1 Summary diagram showing the main findings and suggested brain mechanisms contributing to VH across different conditions. ACC: anterior cingulate cortex; AD: Alzheimer's disease; DLB: dementia with Lewy bodies; DMN: default mode network; GM: grey matter; MTL: medial temporal lobe; PD: Parkinson's disease; VH: visual hallucinations.

Firstly, verbal memory deficits were found in DLB with VH at follow-up (Experiment 4.2), PD with VH (Experiments 1 and 6), and both subgroups of AD patients when compared with controls (Experiment 7), being a distinctive feature of AD-type dementia. We speculated an involvement of MTL pathology, including LB and/or AD pathology, which may be responsible for disrupting neural circuits eventually leading to VH. Within this process, DMN dysfunctions may play a significant role, and might form the basis for the emergence of irrelevant memories, aberrant recall of information,

and the intrusion of false visual images. We also found increased DMN functional connectivity in DLB patients with VH (Experiment 2), corroborating this hypothesis. Other studies have previously associated disrupted DMN with the presence of VH (Franciotti et al., 2015, Yao et al., 2014), and cognitive impairment (Wolters et al., 2018) in PD, as well as disease-related alterations in AD (Badhwar et al., 2017, Hafkemeijer et al., 2012).

A speculative interpretation for the aforementioned results, therefore, could be that MTL, DMN and verbal memory impairments might constitute necessary but not sufficient dysfunctions leading to the generation of false visual percepts. In fact, in order to be actually experienced, VH seem to require additional bottom-up and top-down impaired mechanisms. Deficient visuoperceptive abilities and underlying brain dysfunctions appeared to play a role in this process. Firstly, we found more severe visuoconstructive impairments in hallucinating patients with DLB (Experiment 4.1) and AD (Experiment 7.1). In addition, AD patients with VH were characterised by more prominent occipital atrophy and hypometabolism, which we found to correlate with visual construction performance (Experiments 7.1 and 7.2). Consistently, our VBM meta-analysis identified significantly greater GM loss in occipital areas in PD with VH compared with those without. In this context, visuoconstructive deficits, occipital atrophy and hypometabolism might represent markers of impaired visual processing mechanisms that we suggest to be necessary contributors to VH, common to different clinical diagnoses.

Within this framework, VH may also be conceptualised as mental images misinterpreted as real percepts due to disconnections of mental imagery circuits, involving different areas found to be impaired in patients with hallucinations. The generation of mental images would originate from the activation of visual representations from long-term memory, supported by MTL lobe structures, as well as occipital regions, sustaining visual processing, and ventral visual stream areas, involved in storage and retrieval of objects semantic memory (Gardini et al., 2009). Subsequently, the generation of specific images would rely on frontal and thalamic areas, especially the medial dorsal thalamus, guiding the retrieval of visual objects details (Gardini et al., 2009, Gardini et al., 2005). The inability to discriminate between mental images and visual perceptions based on real stimuli might form the basis for the generation of false visual images and, ultimately, VH.

Different signs of top-down control mechanisms have also been detected in all three conditions. Specifically, hallucinating patients with DLB (Experiment 1) and AD (Experiment 7.2) presented more severe attention deficits compared with those

without. Moreover, the pattern of volumetric, and structural and functional connectivity features in DLB with VH was consistent with an involvement of regions/tracts implicated in both perceptive and attention abilities (Experiments 1, 2, 3). We suggested that dysfunctional top-down control mechanisms of the anterior cingulate over visual processing pathways might contribute to the emergence of false images from the DMN (Experiment 2), but also the generation of visual mental images supported by MTL, occipital, and fronto-thalamic areas. Interestingly, VBM analyses on AD identified GM loss in the anterior cingulate cortex in patients with VH, but not in those without (Experiment 7.1), suggesting that top-down mechanisms might be similar across conditions. However, no fMRI and DTI were available for this cohort, and thus, this hypothesis needs further investigation.

Striatal atrophy was found in hallucinating patients with DLB and PD, which correlated with attention deficits in both conditions, and executive functioning in PD only (Experiment 1). These cognitive deficits, therefore, might be modulated by compromised striatal activity, possibly due to disrupted fronto-striatal circuits, known to be dysfunctional in LBD, especially in PD, and might contribute to the complex interaction of impairments leading to VH. Hallucinating PD patients also had significantly more severe executive dysfunction; on the other hand, attention deficits appeared to play a predominant role in DLB, and, to a lesser extent, in AD.

Frontal atrophy was observed only in DLB with VH and might represent a structural hallmark of impaired large-scale attention networks, and may emerge only with the progression of LB-type dementia and more severe attention deficits. These networks might be impaired by diffuse cortical deposition of LBs, possibly with concomitant AD-related pathology. On the other hand, occipital GM loss has been observed in PD and AD with VH, but not in DLB. However, cognitive, functional and structural connectivity analyses suggested the presence of altered top-down and bottom-up processes, including visual processing pathways impairment, which may be due to networks disconnections in DLB, not necessarily resulting in occipital GM loss. We identified, however, occipital GM loss in hallucinating AD patients only in comparison with controls, suggesting that it may be subtle and not easily detectable. On the other hand, occipital hypometabolism appeared to be more prominent and thus, functional alterations may be hallmarks that are more sensitive to the type of visual information processing impairment leading to VH. Interestingly, our VBM meta-analysis revealed occipital GM loss in the direct comparison between PD patients with and without VH. Therefore, it might be that more subtle alterations may reach significance only in bigger samples or when increasing statistical power through meta-analytic methods.

8.5 Limitations

Limitations for each study have already been outlined in the discussion session of each chapter. Overall, the main limitation is represented by small sample sizes. Even though up to 80% of patients with DLB present VH, dementia due to LB pathology only represents roughly 20% of all dementia cases, not being as common as other neurodegenerative conditions. The prevalence of VH in PD without dementia is even lower, with roughly 25-40% of patients experiencing this symptomatology. Approximately 13% of AD patients present hallucinations, VH being the most common type. Therefore, investigating the features related to VH using bigger sample sizes is problematic and not easily implementable. In fact, the presence of small sample sizes represents an issue that may be generalised to many studies in the current literature, as noticed following careful literature review. To overcome this issue, and increase statistical power, undertaking meta-analyses represents a very useful approach (Chapter 6), as well as using data from multicentre initiatives, such as ADNI (Chapter 7), to increase sample sizes.

Another main limitation is the use of the NPI to assess the presence, severity and frequency of VH. Although the NPI has been used by most studies in the literature, it is not sufficiently specific to capture the whole spectrum of phenomenology of VH. False sensation of presence and sideway passage, referred as minor hallucinations, are also frequent in LBD, especially in early PD, often together with more complex VH (Aarsland et al., 2009, McKeith et al., 2017, Onofrj et al., 2013). Patients with more severe cognitive decline usually develop more severe and complex VH that are more commonly experienced in LB dementias, as opposed to cognitively normal PD patients (Aarsland et al., 2001a, Emre et al., 2007, Onofrj et al., 2013, Williams and Lees, 2005). Moreover, complex VH usually occur early in the progression of DLB, while tend to be experienced at later disease stages in PD and AD (Chiu et al., 2017, Ffytche et al., 2017, McKeith et al., 2005). Although the phenomenology of complex VH has been found to be similar across conditions, and includes VH of people and animals, they tend to be multiple, persistent and more likely to speak in DLB (Ballard et al., 1997, Frei and Truong, 2017). The phenomenological content of hallucinations might be sustained by different neural and cognitive dysfunctional mechanisms. For example, Boubert and Barnes (2015) found that PD patients with externally driven VH had more severe inhibitory abilities than those with internally driven memory-based VH, highlighting the importance of differentiating types of hallucinatory phenomena.

Finally, none of the neuropsychological tests used were conceived to assess cognitive features specifically associated with VH. Thus, neuropsychological tests designed *ad hoc* might be more informative on the neurocognitive processes involved in the development of this symptomatology. Nevertheless, the tests used are widely applied to clinical settings, suggesting that, in the future, they may be more easily transferable to clinical practice in relation to VH. Other study-specific limitations and those concerning methodologies are described within each chapter.

8.6 Future research directions

Neuroimaging techniques represent very helpful tools for studying structural and functional brain features *in vivo*, how they differ between groups and correlate with clinical symptoms. Multimodal neuroimaging, in particular, allows the investigation of different brain features at the same time, including GM structural damage and glucose metabolism, but also the interconnections between brain regions, both structurally and functionally. In addition, the inclusion of comprehensive neuropsychological evaluations allows the investigation of the association between such brain measures and cognitive deficits. The main strength of the present work is the use of different imaging methods and neuropsychological measures to investigate VH in a variety of conditions experiencing this symptom, namely DLB, PD and AD. This allowed the formulation of interpretative hypotheses concerning symptom and disease-specific alterations linked to VH in neurodegeneration. To our knowledge, Experiment 1 was the first multimodal study exploring the differences between DLB patients with and without VH combining structural MRI, resting-state fMRI, DTI, as well as neuropsychological measures. Although we used a wide variety of techniques to investigate VH in DLB, PD and AD, not all methods were used for each study. For example, resting-state fMRI and DTI were not available for the PD and AD cohorts and thus, functional and structural connectivity could not be investigated in these conditions. However, we used other imaging techniques in addition to structural MRI, namely FDG-PET, and meta-analytic methods. The present thesis also included the largest longitudinal investigation of the cognitive predictors of VH in DLB. Future studies may combine longitudinal multimodal neuroimaging techniques and neuropsychological data to explore common and distinct patterns of neurocognitive alterations in different neurodegenerative conditions, as well as brain and cognitive features predicting the development of VH. This will allow a deeper understanding of

the symptomatology and its pathophysiology, which may aid the identification, in the future, of new, targeted treatments.

We acknowledge that, however, such complex investigations may be of difficult implementation in individual datasets, often characterised by small sample sizes. In this context, research may benefit by collaborations between different research centres combining longitudinal data from multicentre international cohorts, such as the European Consortium for DLB (Kramberger et al., 2017). An alternative is represented by multicentre data-sharing initiatives. For example, in Experiment 7, we used the ADNI database, a longitudinal, multicentre initiative comprising multimodal brain imaging data and other biological, clinical, neuropathological and neuropsychological markers in participants with mild cognitive impairment or dementia due to AD, and cognitively normal people. The ADNI data-sharing policy allows the accessibility of the data to qualified researchers around the world, and the investigations of symptoms-specific alterations otherwise difficult to capture through single studies. Other examples of multicentre data-sharing initiatives include the Dementia Platform UK (https://www.dementiasplatform.uk), and the UK Biobank (https://www.ukbiobank.ac.uk).

Another reflection worth mentioning relates to the phenomenology of VH. In fact, differential patterns of phenomenological features might reflect distinct underlying neurocognitive and biological processes. Thus, a more accurate evaluation of this symptom might be beneficial to investigate the neuropsychological and brain correlates of VH. For example, the North-East Visual Hallucinations Interview (NEVHI) is a semi-structured interview, which was designed specifically to assess VH in older people with cognitive impairment (Mosimann et al., 2008). It includes questions on phenomenology, temporal features, and emotions related to recurrent VH (Mosimann et al., 2008). This instrument might be a more suitable measure to evaluate different aspects of VH across LBD conditions, as well as in AD. Slightly different neural mechanisms might also be detected between patients with the same clinical diagnosis but distinct VH-related features. In this context, comparisons between patients with different characteristics might be beneficial to clarify the mechanisms underpinning the symptomatology and its variants.

8.7 Final conclusion

The present thesis provides evidence of the presence of cognitive, structural and functional brain alterations related to VH in different neurodegenerative conditions,

namely DLB, PD and AD, representing an important addition to the current literature. Overall, the findings suggest a complex combination of cognitive and neural dysfunctions related to VH. In particular, impairments in visual processing and visual attention appeared to play a significant role, underpinned by dysfunctional large-scale attention networks and deficient visual pathways. The role of specific top-down control functions might be slightly different across conditions, and seemed to involve a more severe executive dysfunction in PD. In addition, MTL and DMN-related impairments might form the basis for the selection of irrelevant information. Within this process, dysfunctional top-down control mechanisms over visual pathways, along with deficient visuoperceptive abilities, might foster the generation and emergence of false images in the absence of real stimuli, thus manifesting as visual hallucinations. Future research may explore further the specific cognitive functions involved in such top-down and bottom-up processes across neurodegenerative conditions. Within this framework, longitudinal multimodal neuroimaging studies, comprising detailed neuropsychological assessments, would elucidate further the pathophysiology of this disabling symptomatology, and the cognitive and brain characteristics predicting the development of VH.

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Appendices

Appendix 1

Originally published literature review included in Chapter 2, and supplementary materials.

brain sciences

MDPI

Review

Structural and Functional Neuroimaging of Visual Hallucinations in Lewy Body Disease: A Systematic Literature Review

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Abstract: Patients with Lewy body disease (LBD) frequently experience visual hallucinations (VH), well-formed images perceived without the presence of real stimuli. The structural and functional brain mechanisms underlying VH in LBD are still unclear. The present review summarises the current literature on the neural correlates of VH in LBD, namely Parkinson's disease (PD), and dementia with Lewy bodies (DLB). Following a systematic literature search, 56 neuroimaging studies of VH in PD and DLB were critically reviewed and evaluated for quality assessment. The main structural neuroimaging results on VH in LBD revealed grey matter loss in frontal areas in patients with dementia, and parietal and occipito-temporal regions in PD without dementia. Parietal and temporal hypometabolism was also reported in hallucinating PD patients. Disrupted functional connectivity was detected especially in the default mode network and fronto-parietal regions. However, evidence on structural and functional connectivity is still limited and requires further investigation. The current literature is in line with integrative models of VH suggesting a role of attention and perception deficits in the development of VH. However, despite the close relationship between VH and cognitive impairment, its associations with brain structure and function have been explored only by a limited number of studies.

Keywords: visual hallucinations; Lewy body; Parkinson's disease; Parkinson's disease dementia; dementia with Lewy bodies; MRI; fMRI; DTI; PET; SPECT

1. Introduction

The term Lewy body disease (LBD) refers to disorders characterised by the neural inclusion of pathologic α-synuclein aggregates called Lewy bodies [1,2]. Clinical manifestations of Lewy body pathology include dementia with Lewy bodies (DLB), Parkinson's disease (PD), and Parkinson's disease dementia (PDD). These diseases share some clinical characteristics, including motor symptoms, sleep disorders, cognitive impairment, and visual hallucinations (VH) [3]. VHs represent a common symptom experienced by patients with LBD, and they are among the core features of the DLB symptomatology [4]. Recurrent and complex VHs have been defined as repetitive and well-formed images, which are perceived without the presence of real stimuli [5]. The most commonly reported VHs consist of people, animals, and inanimate objects, which appear to have similar features between clinical conditions, especially DLB and PD with dementia [5–7]. Early false sensations of presence are also common, mainly in PD [7]. Patients with LBD may also experience illusions or misperceptions,

which are defined as incorrect perceptions of real stimuli [5,8]. VHs seem to be more severe and complex in LBD patients with cognitive impairment, which often present with lack of insight about the unreal nature of their experience [7].

The presence of VHs is a strong predictor of Lewy body pathology at autopsy [9,10]. Lewy body pathology associated with VHs was shown to affect temporal lobe areas predominantly, mainly the amygdala [11–13]. The structural and functional brain correlates underlying this symptomatology are, however, still not well understood. Moreover, it is not clear whether different diseases within the LBD spectrum share common neural mechanisms associated with VH, or whether they differ between conditions. Neuroimaging techniques represent valuable tools, which may help in detecting in vivo biomarkers that specifically characterise patients with VHs in PD and DLB. This may help the achievement of a more accurate understanding of the biological vulnerabilities leading to VHs, and may help future prediction of patients who are likely to develop these disabling symptoms, leading to the possible implementation of preventive treatments.

The aim of the present review was to summarise the current literature on structural and functional brain abnormalities associated with VHs in LBD, namely PD and DLB. Specifically, findings from structural magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional MRI (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) studies were critically reviewed.

2. Materials and Methods

Articles were identified through a systematic literature search, which was carried out in January 2017 by using the PubMed and Web of Science databases with no time limit. The following key words were used: “visual hallucinations”, “visual hallucination”, “Lewy body", "dementia with Lewy bodies”, “Parkinson’s disease”, “magnetic resonance imaging”, “MRI”, “voxel-based morphometry” (VBM) and “VBM”, “fMRI”, "resting-state", “diffusion tensor imaging”, “DTI”, “positron emission tomography” and “PET”, and “single photon emission computed tomography” and “SPECT”. An additional manual search of references was also undertaken. Studies were excluded according to the following exclusion criteria: (1) pathologies other than DLB, PD, or PDD; (2) neuroimaging analysis not related to VH; (3) patients with medication-induced VH; (4) studies not using MRI, fMRI, DTI, PET, SPECT; (5) PET and studies not investigating glucose metabolism and regional cerebral blood flow; (6) MRI studies using visual rating; (7) magnetic resonance spectroscopic imaging; (8) pharmacological studies; (9) case studies (except for fMRI during VH); (10) review and theoretical articles; (11) non-English articles; and (12) non-peer reviewed articles. The search strategy used followed the PRISMA guidelines [14]. The articles included were assessed for scientific suitability to the aim of the present review, by using a set of 14 criteria adapted from Welton et al. [15], (these criteria are listed in Supplementary Materials Table S1). Each article was rated from 0 to 14, assessing the scientific quality of its structural and functional neuroimaging analyses related to VH only.

3. Results

The initial search retrieved 646 titles, among which 387 were duplicate publications, which were excluded. Three studies were identified through manual search. A total number of 262 titles and abstracts were assessed, of which 88 full-text articles were retrieved and screened for eligibility. The final review included 56 studies investigating the structural and functional brain correlates of VH in LBD by using structural and functional MRI, DTI, PET, and SPECT. A flow chart describing the selection process of the studies included in the final review is shown in Figure 1 (adapted from Moher et al. [14]).

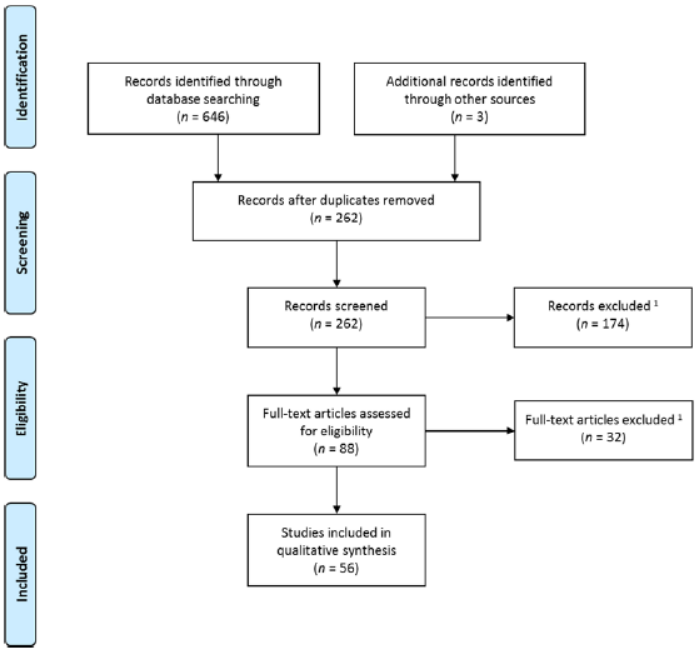

Figure 1. Flow chart describing the selection process of the studies included (adapted from Moher et al. [14]). [1] Exclusion criteria: (1) pathologies other than dementia with Lewy bodies (DLB), Parkinson's disease (PD), or Parkinson's disease dementia (PDD); (2) neuroimaging analysis not related to visual hallucinations (VH); (3) patients with medication-induced VH; (4) studies not using magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), positron emission tomography (PET), and single photon emission computed tomography (SPECT); (5) PET and SPECT studies not investigating glucose metabolism and regional cerebral blood flow; (6) MRI studies using visual rating; (7) magnetic resonance spectroscopic imaging; (8) pharmacological studies; (9) case studies (except for fMRI during VH); (10) review and theoretical articles; (11) non-English articles; and (12) non-peer reviewed articles.

Studies investigating VH in LBD using more than one approach or imaging technique were included in more than one section of the review and the findings for each technique reported separately in the relevant section. There were eight studies combining different techniques, specifically structural and functional MRI [16,17]; structural MRI and PET [18,19]; structural MRI and DTI [20,21]; structural MRI, DTI, and fMRI [22]; and fMRI and arterial spin labelling (ASL)-MRI [23]. Moreover, in two structural MRI studies, different methods were used to investigate regional brain volumes [24,25].

Suitability assessment of the articles reviewed revealed that structural (mean = 7.92), and functional (mean = 7.06) neuroimaging analyses related to VH were of comparable quality. Overall, among the main limitations of the studies, we found lack of a priori hypotheses on VH (n = 27 studies), sample sizes <15 participants per group (n = 39 studies), and absence of correlational analyses with VH indices (n = 35 studies) and cognitive measures (n = 49 studies). Quality assessment of each study can be found in supplementary Table S2.

3.1. Structural Brain Imaging

The brain structural changes associated with VH in LBD, detected with MRI, were investigated by 24 studies. The findings are summarised according to the analytic approach used, namely VBM, other methods to investigate brain morphology, namely regional volumes, shape, and cortical thickness; and DTI. For each study, detailed demographic, clinical, and methodological information—and imaging results related to VH—are reported in Appendix A (Table A1).

3.1.1. Voxel-Based Morphometry

A total of 12 VBM studies were identified. Ten studies focused on regional volumetric brain differences between LBD patients with and without VH, including nine studies which used whole brain analyses [21,24–31], and three voxel-based analyses restricted to predefined regions of interest (ROI) [28,32,33]. Four studies also included results on the association between grey matter loss and VH or other cognitive variables [27,32–34]. Moreover, one study included only the comparison between PD subgroups and controls [35], and another investigated progression of brain atrophy [34]. The VBM methodology implemented was largely consistent between studies. All used the Statistical Parametric Mapping (SPM) software for imaging analysis, and seven [21,25–28,31,35] used the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) algorithm to create a study-specific template. A threshold corrected for multiple comparisons was applied in four whole brain [24,25,30,34], and four ROI [28,32,33,35] studies. The results of those studies which used uncorrected thresholds [21,25–28,31] should be interpreted more cautiously, since analyses using an uncorrected threshold may generate a higher number of false positives. Clinical and demographic features, including severity of cognitive impairment, disease duration, age, and years of education varied between studies. Some of them reported no differences between patients with and without VH in global cognitive impairment [21,24,25,27,28,31,33], while others showed more severe cognitive decline in hallucinating patients [30,32,34,35]. Furthermore, some studies on PD reported more advanced disease stage (Hoehn and Yahr, H&Y, stage) in patients with VH than in those without [21,28,30,34].

Ibarretxe-Bilbao et al. investigated the progression of brain atrophy in PD patients with and without VH [34]. Hallucinating patients presented more extensive grey matter loss over time, accompanied by faster cognitive decline. Progressive grey matter reduction from baseline to follow-up extended to parietal, temporal, frontal, thalamic, and limbic areas in patients with VH, whereas only small clusters in frontal and cerebellar regions showed reductions in those without. Cognitive impairment and disease severity at baseline, however, were greater in patients with VH than in those without [34]. Additionally, significant associations between grey matter loss and cognitive functions were detected in patients with VH, specifically in measures of learning (left hippocampus, $r = 0.88$), delayed recall (left prefrontal cortex, $r = 0.95$), semantic fluency (left thalamus, $r = 0.95$), and language comprehension (left amygdala, $r = 0.89$).

In a whole brain VBM study, Ramirez-Ruiz et al. found grey matter volumetric reductions in the left lingual gyrus, and bilateral superior parietal lobe in PD patients with VH when compared with those without ($p < 0.05$ corrected at the cluster level) [30]. In this study, PD patients were matched with healthy controls. In this study, no information about the age of the included cohorts was given, and in the comparison between hallucinating and non-hallucinating patients the authors do not appear to have controlled for age in their analysis. Furthermore, patients with VH had more severe impairments in global cognitive status (as measured by the Mini-Mental State Examination, MMSE [36]), more advanced PD stage (rated with the Hoehn and Yahr scale [37]), and more severe depression (measured by the Hamilton depression rating scale [38]) [30]. These variables were included as covariates in the VBM statistical analyses [30]. Consistently with these findings, other studies reported decreased grey matter volume in PD patients with VH, compared with those without, in occipito-temporal regions, namely in the lingual and fusiform gyri, bilaterally [27,31]. Goldman et al. reported positive associations between VH severity, and grey matter volume of the left parietal lobule, and cuneus, and right lingual gyrus ($p < 0.01$ uncorrected) [27]. In addition to these findings, grey matter reductions

have been reported in widespread brain areas, which were mainly located in the inferior parietal lobes [21,27], cingulate cortex [27,31], frontal [25,31], temporal [25,31], and occipital [27,31] areas bilaterally, and in the right supramarginal gyrus [21,31]. Another whole brain VBM study reported differences between PD patients with and without mild VH (presence and passage hallucinations), both decreases, mainly in the right vermis and precuneus, and increases, mainly in the cerebellum and the left inferior frontal cortex were detected in patients with mild VH [29]. These VBM studies, however, used thresholds uncorrected for multiple comparisons [21,25,27,31]. Differently from the study above, Meppelink et al. did not detect a difference between non-demented PD patients with and without VH [24], which may have been due to the more conservative threshold of $p < 0.05$ cluster-level corrected for multiple comparisons being used in this study. These apparently contrasting findings could, therefore, be a simple reflection of the application of a less rigorous statistical thresholding approach by the studies reviewed above.

In addition to the whole brain studies described above, two VBM studies investigated volumetric brain differences between hallucinating and non-hallucinating PD patients by using an ROI approach [28,32]. Specifically, Janzen et al. investigated the grey matter volume of the pedunculopontine nucleus due to its cholinergic function, thought to be involved in the development of VH, and the thalamus as one of its projection areas [28]. The authors found reduced grey matter in the left and right pedunculopontine nucleus between non-demented PD patients with and without VH, but not in the thalamus by using a threshold corrected for multiple comparisons. Hallucinating patients had significantly longer disease duration (VH: 11.5 $\pm$ 5.2 years; no VH 3.1 $\pm$ 3.6 years), were at a more severe Hoehn and Yahr stage (VH: 2.5 $\pm$ 0.3; no VH: 2.1 $\pm$ 0.5) and were taking higher levodopa equivalent doses. Furthermore, when hallucinating PD patients with and without dementia were combined and compared with non-demented patients without VH, the reduction in volume extended to the thalamus bilaterally [28].

In another voxel-based ROI study, the analyses were restricted to the hippocampus, due to its link with dementia development [32]. This region was chosen since the presence of VH is thought to be a risk factor for dementia, and therefore VH patients might exhibit the same pattern of atrophy shown by patients with dementia. The authors reported no differences in the direct comparison of non-demented PD patients with and without VH. When the two PD groups were independently compared with healthy controls, only hallucinating patients showed reduced grey matter in the anterior hippocampus bilaterally ($p < 0.05$ corrected); hippocampal volume also correlated with the learning scores achieved on a verbal memory test [32]. Overall, however, the PD patients with VH had more severe cognitive impairment, as shown by their lower MMSE scores and poorer scores on a verbal memory test [32]. Negative findings were reported by another VBM study, which found no differences in the hippocampus in any PD group, when compared with controls [35]. These contrasting findings might be due to differences in clinical and demographic variables—such as cognitive performance, disease duration, and age—and methodological differences in the analyses (i.e., standard VBM vs. DARTEL). In the latter study, when PD patients with and without VH were compared separately with healthy controls, using an ROI approach with ROI in temporal and frontal areas, reduced grey matter was found in the left superior frontal gyrus in both PD groups, while reduction in grey matter in the left frontal operculum was detected only in hallucinating patients [35]. The two PD groups, however, differed from each other in some clinical variables—including global cognitive level (measured with the MMSE), motor symptoms (evaluated with the Unified Parkinson's Disease Rating Scale motor score subsection, UPDRS III [39]), and depression (assessed with the Beck Depression Inventory, BDI [40])—with the hallucinating group being more severe in all these measures [35].

Only two studies used VBM to investigate differences between hallucinating and non-hallucinating patients with DLB [26,33]. Despite the small sample size (six DLB with VH, six without VH), Sanchez-Castaneda et al. [33] found a reduction of grey matter volume in the right inferior frontal gyrus in hallucinating patients ($p < 0.05$ corrected) using a voxel-based ROI approach. In the same study, patients with PDD presented grey matter volumetric reductions in the left orbitofrontal

cortex, which was no longer significant when controlling for age [33]. In the hallucinating DLB subgroup, VH severity was strongly associated with reduction in the volume of the right inferior frontal gyrus ($r = 0.89$) and left precuneus ($r = 0.95$), while no significant correlations were found in the PDD subgroup. Another VBM study in DLB identified volumetric grey matter reductions posteriorly, in the left cuneus, by using a whole brain approach [26]. These findings, however, should be taken with caution as the threshold used in this study was not corrected for multiple comparisons. Moreover, demographic and clinical comparisons between patients with and without VH were not reported, probably due to the exploratory nature of the analysis of VH (the main aim of the study was to compare DLB with Alzheimer's disease, AD, patients and with controls) [26].

3.1.2. Other Structural MRI Studies

In addition to the VBM studies described above, other studies have investigated brain morphological features of predefined ROI, especially their overall volume [18–20,22,24,41,42], and shape [22] in LBD. Three studies examined group differences in cortical thickness using the Freesurfer software package (and adopting thresholds corrected for multiple comparisons) [16,17,43]. Seven studies investigated volumetric [20,22,24,25,42] or cortical thickness [16,17] differences between PD patients with and without VH. Only three studies focused on the comparison between DLB and AD patients, and reported an association with VH indices [18,19,41,43].

Medial temporal lobe (MTL) structures, especially the hippocampus, were investigated by five studies [18,19,22,41,42]. Two of them focused on PD, and argued for an involvement of the hippocampus in the formation of VH mainly based on its role in memory, and evidence suggesting the presence of a high burden of Lewy body pathology in this region [22,42]. Yao et al. [22] used a multimodal MRI approach to investigate hippocampal volume, shape, mean diffusivity (MD), and functional connectivity. The authors found no differences between groups (PD with and without VH, and controls) in hippocampal volume and shape (MD and functional connectivity results are described in subsequent sections). Another MRI study reported significant volumetric reduction in hippocampal substructures, namely CA2-3 and CA4-DG, in PD patients with VH compared with those without [42]. Differences in the hippocampus as a whole were reported, however, only when hallucinating patients were compared with healthy controls. The more severe cognitive impairment in patients with VH, however, might have affected the results [42]. The value of the findings of these studies is limited by the relatively small size of the samples included in both studies [22,42]. Three MRI studies investigated the association between VH indices in DLB and MTL [18], hippocampus [19], and hippocampal substructure volumes [41]. A negative correlation was reported between severity of VHs and volumetric measures in MTL (entorhinal cortex, hippocampus, and amygdala) [18]. However, these three studies failed to report a priori hypotheses based on the involvement of MTL regions in the development of VH, probably because VH were not the primary objective of investigation.

Lee et al. [20] selected five ROI within the visual pathway to investigate differences between hallucinating and non-hallucinating PD patients in the optic chiasm area, lateral geniculate nucleus, and V1 volumes and white matter microstructure features in the optic nerve and optic radiation (the latter are described in Section 3.1.3). These regions were selected to examine the neural bases of VH in relation to their role in processing visual information. Volumetric reductions in VH patients were reported only in the lateral geniculate nucleus [20]. In addition to the whole brain analysis described in the previous section, Meppelink et al. focused on an ROI in the left fusiform gyrus, detecting no differences between PD with and without VH [24]. Finally, another structural MRI study carried out an ROI analysis by delineating the left and right substantia innominata boundaries (in addition to the VBM analysis reported above) and identified a smaller volume of this structure in hallucinating PD patients (46 PD with VH, 64 PD without VHs) [25]. Furthermore, the volume of this region correlated with scores on verbal memory, semantic fluency, and go/no-go tests [25].

Studies investigating cortical thickness did not detect any differences between PD patients with and without VH [16,17]. However, when hallucinating PD patients were compared with

non-hallucinating patients at a less advanced disease stage (H&Y; PD with VH: 3.0 ± 0.5; no VH: 2.1 ± 0.4) and controls, reduced cortical thickness was reported in frontal and parietal regions [16]. In the latter study, the analysis was restricted to regions within the default mode network (DMN) [16]. On the other hand, Yao et al. [17] found no differences between PD subgroups and controls in the analysis of the whole cortical surface. Finally, Delli Pizzi et al. [43] found a significant association between the Neuropsychiatric Inventory (NPI) [44] hallucination score, and cortical thickness in right lateralised parietal regions, namely the precuneus, and superior parietal gyrus in DLB patients ($p < 0.05$ corrected).

3.1.3. Diffusion Tensor Imaging

Four DTI studies were found, two on PD [20,21], and two on DLB [45,46]. Three studies investigated predefined ROIs of grey or white matter [20,45,46], while only one used a whole brain approach, namely tract-based spatial statistics TBSS (using a threshold corrected for multiple comparisons) [21]. Most of the studies used the FMRIB software library (FLS) for DTI analysis [20,21,45]. One study did not include a sample of LBD patients without VHs, and hallucinating patients where compared to healthy controls and AD [45].

Lee et al. [20] reported disrupted white matter integrity in the right optic nerve, and in the left optic radiation by using an ROI approach. In another multimodal study (VBM analysis reviewed above), Lee et al. [21] performed voxelwise analysis of fractional anisotropy (FA) and MD by using TBSS. No differences were found between non-demented PD subgroups with and without VH, and a similar pattern of abnormalities was reported when independently compared with age-matched healthy subjects, specifically in fronto-temporo-parietal and brainstem regions [21]. In these two studies, PD with and without VH did not differ for age, disease duration, MMSE score, and motor symptoms [20,21], but in one of these studies hallucinating patients were at a more advanced disease stage than non-hallucinating patients [21]. From the articles, however, it could not be established whether some of the patients investigated in the latter two references were the same in both studies [20,21].

Although DTI is mainly used to investigate microstructural white matter abnormalities, two studies focused on grey matter [22,45]. Yao et al. [22] reported increased MD in the right hippocampus in hallucinating PD patients. Moreover, Delli Pizzi et al. [45] investigated grey matter MD differences between DLB patients with VH and healthy controls by using a tractography-based subdivision of the thalami. The authors found increased MD in thalamic sub-regions projecting to prefrontal, parieto-occipital cortex (bilaterally), amygdala (right lateralised), and motor cortex (left lateralised). Moreover, MD in the right thalamic sub-region projecting to parietal and occipital cortex was associated with severity of VHs [45]. Finally, among the studies that focused on DLB, Kantarci et al. [46] showed increased MD in the inferior longitudinal fasciculus in patients with VHs compared with those without. Demographic and clinical differences between these groups of patients were not reported, however, probably because the main purpose was to differentiate DLB and AD patients [46].

3.2. Functional Brain Imaging

A total of 37 studies undertook functional imaging focusing on VH in LBD, including studies using task-based and resting-state fMRI, PET, and SPECT.

Details regarding demographic, clinical, and methodological information, and imaging results related to VH are reported in Table A2 for each study.

3.2.1. Task-Based fMRI

Ten studies used fMRI to identify brain activation patterns in response to simple visual stimuli [23,47–50], perception recognition tasks [51–53], and two single cases during VH [54,55]. The majority of them were in PD [48–54], while only three included patients with DLB [23,47,55]. Two studies performed different analyses on the same sample of DLB patients who had performed a visual

task in the scanner [23,47]. Methodology and fMRI paradigm differed between studies, which may partly account for some inconsistencies in the findings. Other differences between studies include the threshold used to report the results, age, cognitive impairment, and duration of the disease. One study described in this section included PD patients experiencing minor VHs, including sensation of passage, presence, or misperceptions [49].

Five studies examined blood-oxygenation level-dependent (BOLD) signal in response to simple visual stimuli [23,47–50]. Specifically, they investigated the perception of moving stimuli [23,47,48], apparent motion [50], circular gratings [49], checkboards, objects [47], and stroboscopic stimulation [50]. Regions of both increased and decreased activation were found in hallucinating PD patients, compared with the non-hallucinating ones [48–50]. The most consistent finding was decreased activity in occipital and temporal regions [48–50], even though increases in occipital [49], and temporal [48] areas were also reported. One of these studies, however, had a very small sample size (three PD with VHs, three PD without VHs) [48]. In addition, reduced activity was found in the parietal and cingulate cortex [50]. On the other hand, increased activity was reported mainly in the frontal lobe [49,50]. Two studies focusing on DLB reported no correlation between BOLD signal and VH indices, but no comparison with patients without VHs was performed [23,47]. One of the latter studies reported a negative association between the NPI hallucination score and perfusion in V4, detected by using arterial spin labelling (ASL)-MRI [23].

Three studies on PD focused on perceptual recognition of complex visual stimuli [51–53]. In comparison with non-hallucinating patients, those with VH presented decreased activity in the right superior frontal gyrus ($p < 0.05$ cluster-level corrected) during perceptual recognition of faces [52], animals, and objects [51]. In addition to these regions, decreased activation was found in the right inferior frontal (face recognition) [52], left lingual, and bilateral fusiform gyri (animal/object recognition) [51]. In one of these studies [52], however, patients with VH had more severe cognitive impairment and behavioural performance (fMRI task) than those without, which might have partially affected the results. Shine et al. [53] identified dysfunctional connectivity in and between attention networks and the DMN during the bistable percept paradigm (BPP) in PD patients with VH [53]. During this task, patients were asked to discriminate between images containing only one perceptual interpretation (stable, e.g., a candlestick) and images containing more than one (bistable, e.g., two faces and a candlestick) [53]. In this study, PD patients were divided into two groups according to the percentage of misperceptions at the BPP. Patients performing above a previously established cut-off score [56] also presented clinically assessed VH, while those performing below did not [53].

Two fMRI studies recorded brain activity during the occurrence of visual hallucinations in single cases [54,55]. Both patients experienced complex VH, namely seeing animals [54,55] and people [54] in the MRI scanner. Howard et al. [55] scanned a DLB patient in the hallucination-free state (the patient was taking risperidone), and a second time whilst he was hallucinating (seven days after risperidone was stopped). They found decreased activation in V1 and V2 in response to photic stimulation while the patient was hallucinating compared with the hallucination-free scan [55]. On the other hand, Goetz et al. [54] performed an event-related design in order to compare hallucinating and non-hallucinating events in a patient with PD. While the patient was experiencing VH, decreased activity was reported mainly in occipito-temporal areas, but activity increased in the anterior and posterior cingulate cortex [54].

3.2.2. Resting-State fMRI

Seven studies [16,17,22,57–60] performed resting-state fMRI analysis, including five statistical comparisons between patients with and without VH in PD [16,17,22,59,60]. Only two studies included a sample of hallucinating DLB patients and adopted correlational analyses [57,58]. Heterogeneity in methodology was found between studies. Specifically, independent component analysis (ICA) [16,17], ROI, and seed-based analyses [16,22,60] of functional connectivity, amplitude of low-frequency fluctuation (ALFF) [16,60], and graph analysis [58] were used. Moreover, between-study differences

were detected for age, disease duration, motor symptoms, and global cognitive impairment, even though patients with and without VH were usually well matched within single studies. In addition, overall sample sizes were relatively small.

Two resting-state fMRI studies investigated differences between PD patients with and without VH in the functional connectivity of the DMN [16,17]. In both studies, the DMN was identified by performing ICA. The methodology implemented to investigate group differences in functional connectivity, however, was different. Specifically, in Franciotti et al. [16] pairwise ROI centred on the DMN were compared between groups. On the other hand, Yao et al. more broadly investigated the differences in the spatial map of the DMN [17]. Both studies reported increased functional connectivity in hallucinating patients in comparison with the non-hallucinating ones, mainly in fronto-parietal regions. Specifically, Franciotti et al. [16] detected increased connectivity between the superior frontal sulcus bilaterally with ipsilateral and contralateral parietal regions, and also between contralateral parietal regions. Yao et al. found increased activity in the right superior middle frontal lobe and bilateral precuneus and posterior cingulate gyrus within the DMN ($p < 0.05$ corrected) [17]. Both PD patients with and without VH presented a pattern of decreased functional connectivity when independently compared to healthy controls [16,17]. Furthermore, results from another resting-state fMRI study [59] were consistent with an association between VH and disrupted activity of the DMN, and other attention networks. The authors performed regression analyses to investigate the association between misperceptions at the BPP (the paradigm described above in Section 3.2.1) [56] and resting-state networks connectivity. All patients performing below a predefined BPP cut-off were also clinically classified as hallucinating. BPP error scores predicted connectivity between the ventral attention network (VAN) and the dorsal attention network (DAN), and increased connectivity within the DMN and the VAN [59].

In addition to the functional connectivity analyses reviewed above, Franciotti et al. [16] also investigated the fractional ALFF on the DMN centred ROI. Compared with non-hallucinating patients, PD with VH presented higher spectral power in fronto-parietal areas bilaterally [16]. Yao et al. [60] performed spectral analysis on the same sample in a previous study [17], reviewed above in Section 3.1.2. They found increased ALFF in VH patients in areas located in the cerebellum, temporal, and parietal lobes. Decreased ALFF was reported in occipital regions, namely the lingual gyrus, and cuneus bilaterally. These latter results were used to perform seed-based functional connectivity analysis. Compared with controls, both PD groups showed decreased functional connectivity, but in VH patients it was increased when compared with non-hallucinating patients [60]. In a multimodal MRI study, Yao et al. [22] reported both increased and decreased functional connectivity of the hippocampus in patients with VH compared with those without, using a seed-based approach. Specifically, increased connectivity was found with fronto-parietal regions, while it was decreased with occipito-temporal areas [22]. When compared to controls, however, both PD subgroups presented decreased connectivity of the hippocampus, bilaterally [22]. These latter studies performed different analyses on the same cohort of patients and this needs to be taken into account when interpreting the results [17,22,60].

Yao et al. [22] also performed correlational analyses between cognitive measures and the regions of differential connectivity between PD groups. Specifically, the functional connectivity of the right hippocampus with right occipital, and medial temporal areas was negatively associated with visuospatial memory performance, which was in turn associated with VH severity [22]. On the other hand, other studies found no association between measures of VH and functional connectivity within regions in the DMN in PD [17], and in the temporal network in DLB [57]. Peraza et al. [58] explored functional connectivity in DLB by using a graph theory approach. They found no significant correlation between the NPI hallucination score and integrated global network measures [58]. However, they found an association with local network measures of node degree (negative for the left postcentral gyrus and positive for the putamen), and nodal betweenness centrality (negative for the right intracalcarine cortex and positive for the fusiform cortex) [58]. In another study, Peraza et al. performed secondary analyses on VHs in DLB, which showed an association between the NPI hallucination score and the left

fronto-parietal, and sensory-motor networks [57]. It is not clear whether for two of the latter studies a subsample of the patients was from the same cohort of patients or not [57,58].

3.2.3. Positron Emission Tomography

We identified 11 studies investigating regional cerebral glucose metabolism using PET. Among them, six focused on the differences between patients with and without VH, four in PD [61–64], and two in DLB [65,66]. Other studies examined associations between glucose metabolism and VH indices, such as severity and frequency [18,19,64,67,68]. Among the voxel-wise whole brain analyses, three out of five studies compared subgroups of patients [61–63], and one out of three used a correlation approach [67] and used thresholds corrected for multiple comparisons. Overall, sample sizes were relatively small.

PD patients with VH presented hypometabolism mainly in posterior regions, especially in the parietal and temporal lobes [61,62,64]. The bilateral precuneus and lingual gyrus were particularly affected [61,62]. Gasca-Salas et al. [62] also reported two smaller clusters in the right occipital lobe, while Boecker et al. [61] reported frontal hypometabolism in VH patients. In contrast, Nagano-Saito et al. [63] found frontal hypermetabolism, specifically in the left superior frontal gyrus. Discrepancies might be partially explained by differences in demographic and clinical features between studies, including age, disease duration, and global cognitive impairment. Moreover, in Boecker et al. [61], hallucinating patients were at a more advanced disease stage, and had more severe motor symptoms than non-hallucinating patients. However, UPDRS III scores were included as covariate of no interest in the statistical analysis [61]. Only two studies compared DLB subgroups and reported contrasting findings. In a whole brain analysis, Perneczky et al. [66] showed hypometabolism in right lateralised temporo-occipital and frontal regions. Although results from the latter study were not corrected for multiple comparisons, differences were only expected in regions found to be hypometabolic when compared with controls (occipital, temporo-parietal, and frontal areas) [66]. In contrast, Imamura et al. [65] reported increased regional cerebral glucose metabolic rate in temporal and parietal regions. In the latter study, however, patient groups significantly differed in MMSE scores (DLB with VH: 19.5 $\pm$ 3.9; no VH: 15.0 $\pm$ 3.0; AD: 19.7 $\pm$ 3.5) [65]. Moreover, different methods were used, namely whole brain voxel-wise comparisons [66] and ROI analyses [65]. In addition to these findings, a PET study divided DLB patients into two subgroups, based on the hypermetabolism of peri-motor areas, cerebellum, and basal ganglia. The group with more regions of hypermetabolism was associated with more frequent VHs [69].

Studies investigating correlations between glucose metabolism and VH indices mainly reported negative associations with posterior regions [18,19,64,67,68]. Specifically, occipital hypometabolism has been related to severity [67] and frequency [19,67] of VH. A negative correlation with the NPI hallucination score has also been found in parietal [68] and temporal regions [64]. Finally, Iizuka and Kameyama [18] found a negative association with the standardized uptake value ratio in the precuneus/cuneus ($r = -0.62$, $p < 0.01$), and a positive association with the cingulate island sign ratio on [18F]-Fluorodeoxyglucose (FDG)-PET ($r = 0.44$, $p < 0.05$).

3.2.4. Single Photon Emission Computed Tomography

Regional cerebral blood flow in LBD patients with VHs has been investigated by nine SPECT studies, four on PD [70–72], five on DLB [73–76], one on PDD and DLB combined [77], and a single case on PDD [78]. Six studies examined the differences between hallucinating and non-hallucinating patients, three whole brain analyses [70,71,73] and three ROI analyses [72,74,76]. Different tracers were used to investigate cerebral blood flow using SPECT, including N-isopropyl-p-[^{123}I]iodoamphetamine, [^{99m}Tc]ethyl cysteinate dimer, and ^{99m}Tc-HMPAO. Three studies investigated areas of association between perfusion and VH indices [73,75,77] and one study performed a SPECT scan during VH [78]. Overall, hallucinating patients showed regions of reduced brain perfusion compared with non-hallucinating patients. Only two studies reported no differences between groups [72,74].

Occipital hypoperfusion has been reported in both hallucinating PD [70] and DLB [73,76] patients, even though these studies present some limitations. For example, one only reported demographic and clinical characteristics of DLB and AD, without differentiating between patients with ($n = 26$) and without ($n = 4$) VH [76]. Moreover, Heitz et al. performed whole brain analyses without correcting the results for multiple comparisons [73]. Other ROI SPECT studies found no differences in occipital perfusion [72,74]. In another whole brain SPECT study, Oishi et al. [71] compared PD patients with ($n = 24$) and without ($n = 41$) VH. The authors found reduced cerebral blood flow in the right fusiform gyrus, which remained significant when correcting for multiple comparisons. Other temporal and parietal regions were found to be different between groups by using an uncorrected threshold [71]. In another whole brain study, O'Brien et al. [77] investigated the relationship between changes in brain perfusion and hallucinations over one year in a combined group of patients with DLB and PDD. They found a negative association with left parietal regions, namely the posterior cingulate gyrus and the precuneus ($p < 0.05$ cluster-level corrected) [77]. Another SPECT study performed factor analysis in order to investigate associations between regional cerebral blood flow and psychotic symptoms in DLB [75]. The authors showed a relationship between parietal and occipital hypoperfusion, and the sense of presence and hallucinations of people, but not of animals, insects and objects [75]. Finally, Kataoka et al. [78] described a patient with PDD having VHs during a SPECT scan, showing increased regional cerebral blood flow in the temporal lobe bilaterally, and in the left inferior frontal gyrus.

4. Discussion

The aim of the present review was to provide an overview of the neuroimaging findings from studies, which have investigated the neural bases of VHs in LBD by critically reviewing the current literature in the field. What emerged is that LBD patients with VH are characterized by widespread structural and functional brain abnormalities in cortical, but also subcortical regions. Given the more limited evidence in DLB and PDD than PD without dementia, it is difficult to infer disease-specific mechanisms within the LBD spectrum. A summary of the most consistent neuroimaging findings associated with VHs in LBD patients is shown in Table 1.

Table 1. Summary of the most consistent findings associated with VHs in LBD.

Brain Regions	GM Volume	Functional Connectivity	Task-Related BOLD Activation	Glucose Metabolism	Brain Perfusion
Frontal	↓	↑	↑↓	↓↑	
Parietal	↓	↑		↓↑	
Temporal				↓↑	
Occipito- temporal	↓		↓↑	↓	
Occipital			↓↑		↓

BOLD: blood-oxygenation level-dependent; GM: grey matter; LBD: Lewy body disease; VH: visual hallucinations; ↓: decrease; ↑: increase.

Overall, the most consistent finding among structural MRI studies of VH in LBD is grey matter loss in frontal areas, mainly in patients with dementia [33], and parietal and occipito-temporal regions [30] in non-demented PD patients. The presence of frontal and parietal impairment is consistent with results reported by neuropsychological studies showing more severe deficits in executive functions and visual attention in hallucinating patients [79–82]. This is in line with multifactorial models of VHs, proposing a role of visual attention deficits and disrupted engagement of attention networks in the development of VHs [5,83].

Notably, cholinergic treatment has been shown to ameliorate VHs and cognitive functioning, especially attention [84], corroborating the hypothesis of an involvement of attention dysfunction in the development of VH. Collerton et al. [5] proposed the Perception and Attention Deficit model, and suggested that VH result from the combination of impaired top-down and bottom-up processes,

specifically coexisting deficits in attention and visual perception. These deficits would be supported by impaired activity in the lateral frontal cortex, and the ventral visual stream, respectively [5]. Surprisingly, given the established deficits in visual perception in LBD patients with VH [34,85–87], evidence of structural grey matter and brain metabolism differences in the occipital lobe is limited. Occipito-temporal and parietal grey matter loss, and reduction of cerebral blood flow were present mainly in PD [30,71]. Occipital hypoperfusion detected by SPECT has been reported [70,73,76], even though negative findings were also reported [72,74]. Discrepancies were reported in resting state FDG-PET studies. The most consistent finding is parietal and temporal glucose hypometabolism in PD with VH, even though inconsistencies were shown in frontal areas. The findings of these studies were both decreased and increased metabolism in the same regions in DLB, which might reflect demographic, clinical, and methodological differences between studies. In summary, resting state functional studies point towards hypometabolism/reduced blood flow in occipito-temporal and parietal regions in LBD patients with VH. This dysfunction in visual association regions might play a role in the genesis of VHs in LBD. This finding is further supported by the demonstration of disrupted white matter integrity in hallucinating DLB patients in the inferior longitudinal fasciculus [46], a bundle of associative fibres that connects the occipital and temporal lobes, which has been related to visual memory and perception [88].

To date, only a few studies have investigated how resting-state networks are disrupted in VH, and these studies have focused mainly on PD. Overall, increased functional connectivity in the DMN has been shown in hallucinating patients compared with those without hallucinations, while reduction in functional connectivity was a consistent finding in both PD subgroups when compared with healthy controls. Therefore, dysfunctional increased connectivity might play a significant role in the genesis of VH, especially within the DMN and fronto-parietal regions [16,17]. A speculative interpretation can be put forward, suggesting that a dysfunctional compensatory mechanism, resulting in increased functional connectivity in hallucinating patients, may foster the emergence of these symptoms. Functional abnormalities in frontal, temporo-occipital, and occipital areas have been reported by task-based fMRI studies. The direction of such alterations in the BOLD signal activity is still unclear, however, which might be due to differences in the behavioural tasks and in the stimuli used in the different studies.

Taken together, the results of imaging studies in LBD patients with VH are scarce for DLB but more frequent for PD. There is a mismatch between a more prominent involvement of primary and association visual regions in brain metabolism and blood flow studies and a more prominent involvement of more frontal regions when studying GM volume or cortical thickness. None of these findings appears to be associated with a different burden of neuropathological changes. In fact, despite the association between Lewy body pathology and VH in medial temporal lobe areas [11–13], substantial structural alterations in these regions have not emerged from this review. Neuropathological findings have shown a negative association between Lewy body pathology and regional brain atrophy, specifically in the frontal lobe, but conflicting evidence has been reported for the amygdala [89,90] and no associations have been found with occipital lobe dysfunction. Neither the macrostructural alterations observed with MRI nor the functional PET/SPECT findings, therefore, appear directly informative of the different underlying cellular events and neuropathology [91]. We can, therefore, speculate that VH in LBD emerge only in the presence of a double hit—i.e., concomitant alterations of large functional and structural attentional networks—of which frontal lobe atrophy may be a surrogate marker, and dysfunction of visual information processing, of which occipital-temporal and parietal hypometabolism is the functional hallmark. Large attentional networks may be impaired by diffuse cortical deposition of synuclein, and even amyloid. The cause of reduction in metabolism in posterior brain regions—i.e., which crucial cortical or subcortical projections are deafferenting the occipital cortex—remains still unexplained.

Visual hallucinations in LBD have been consistently associated with cognitive impairment. Firstly, their prevalence was found to be significantly higher in patients with dementia, and cognitive decline

has been shown to be a significant predictor of VH [92,93]. In addition, there is an increased risk of developing dementia in PD in patients with early hallucinations [94]. LBD patients with VH have more severe deficits in a number of cognitive domains, especially visual perception and visual attention in both DLB [79,86,87] and PD [34,81,95–97], executive functioning [80,82,98,99], and long-term memory [80–82] in PD. Therefore, an important future development of research in this field may be the study of the association between cognitive functions and brain regions and networks specifically altered in LBD patients with VHs.

A limitation of the current literature in the field is that there have been only a few studies investigating structural brain alterations related to VH in DLB. In particular, only two studies compared patients with and without VHs directly [33,46], and no whole brain VBM analysis to date focused on VH in DLB. The neuroanatomical correlates of this symptom were assessed more extensively in PD. Further research is, therefore, needed to clarify better how these structural changes are related to cognitive functioning and connectivity between brain regions. This may be achieved by integrating studies using different imaging techniques, specifically resting-state fMRI and DTI, for the simultaneous study of functional and structural connectivity respectively. Although some resting-state fMRI studies were conducted in PD, none is available in which DLB patients with and without VHs have been directly compared. Similarly, lack of DTI studies examining white matter integrity emerged from this literature review. Future studies may benefit from the investigation of functional and structural networks associated with those cognitive functions impaired in patients with VHs. To our knowledge, only a few studies have explored the relationship between cognitive functioning and brain abnormalities in hallucinating LBD patients [22,25,32,34]. Other studies performed correlational analysis using clinical variables, especially VH severity and frequency, which have been mainly associated with parietal regions by both structural [27,33,43] and functional studies [18,57,68,77], but other correlational analyses showed no relationship with any brain region [17,19,41,46,47,58]. Furthermore, most of the studies reviewed above used the NPI questionnaire, which is not specific to capture the whole spectrum of phenomenology of VHs in this disease. Therefore, a more accurate evaluation of this symptom might be beneficial in the investigation of the neural correlates of visual hallucination. For example, the North-East Visual Hallucinations Interview (NEVHI) is a semi-structured interview, which was designed specifically to assess VH in older people with cognitive impairment [100] and this instrument might be more accurate to fine grain VH in LBD.

Finally, the present review itself presents some limitations. Even though negative results were reported by some studies, publication bias cannot be completely ruled out. In addition, we tried to reduce selection bias by undertaking an extensive literature search in two different databases with no time limit. Despite this, the possibility of having missed suitable studies cannot be fully excluded. We reviewed neuroimaging studies which had analysed VH in LBD that met the inclusion criteria. However, not all the studies had VH as their primary focus of investigation (e.g., analysis on VH in studies assessing differences between different types of dementia), and several studies failed to report clearly stated a priori hypotheses on the mechanisms underlying VH. Moreover, studies performing whole brain analyses were included even when results were not corrected for multiple comparisons, which may increase the occurrence of false positives. These factors, together with the inclusion of small sample sizes and other methodological limitations (e.g., statistical analyses not including covariates of no interest) might contribute to lowering the overall quality of the records included.

5. Conclusions

VHs are severe and disabling symptoms frequently observed in patients with LBD. The present review provides an up to date summary of current knowledge about the neural bases of VH in LBD. Overall, the findings suggest the involvement of structural and functional alterations in several brain areas in frontal, parietal, and occipito-temporal cortex. The mechanisms underlying VH in LBD, especially in patients with dementia, and how these differ between conditions remain still unclear, however. Future research might benefit from a combined investigation of structural and

functional connectivity, as well as its association with neuropsychological measures. This might aid the understanding of the pathophysiology underlying VH in LBD and its relationship with cognitive decline. Neuroimaging techniques might help in the detection of symptom-specific biomarkers, which might be used to assess efficacy of treatments in the future, and as targets for new interventions.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3425/7/7/84/s1. Table S1: Suitability assessment criteria focusing on structural and functional imaging analyses related to VH only. Table S2: Suitability assessment of the neuroimaging studies included. The present suitability assessment focused on structural and functional imaging analyses related to VH only (excluding single cases).

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. Summary of structural neuroimaging studies of hallucinating patients with LBD. Only main results related to VH are reported.

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Blanc et al. (2016) [26]	28 pro-DLB 27 pro-AD 33 HC	67.5 (9.2) 69.3 (7.8) 72.4 (10.4)	NA	60.7% DLB patients	27.6 (2.1) 26.9 (1.9) 29.4 (0.9)	NA	Whole brain VBM Covariates: age, TIV, sex, group comparison	Grey matter volume $p < 0.005$ uncorrected VH < NVH: L cuneus
Delli Pizzi et al. (2016) [41]	19 DLB VH 15 AD 19 HC	76.37 (4.35) 76.47 (7.17) 76.21 (4.49)	2.95 (0.91) 3.00 (0.93) -	NPI	18.00 (4.83) 16.73 (6.31) 27.58 (0.69)	NA	ROI MRI ROIs: hippocampal substructures; covariates: age, ed., TIV; relationship with NPI^{hall}	Grey matter volume Correlation with NPI^{hall}: NS
Delli Pizzi et al. (2014) [43]	18 DLB VH 15 AD 14 HC	75.4 (4.0) [2] 75.6 (7.6) 75.5 (5.3)	2.9 (0.6) [2] 3.1 (0.6) -	NPI	19.1 (2.6) [3,4] 18.3 (4.1) 28.1 (1.6)	NA	Cortical thickness Covariates: MMSE, CAF, and UPDRS; correlation with NPI^{hall} (entire cortex and ROI where DLB ≠ AD)	Cortical thickness $p < 0.05$ corrected DLB VH < HC: bilat. pericalcarine, LG, cuneus, precuneus, SPG Correlation with NPI^{hall}: R precuneus and SPG
Delli Pizzi et al. (2014) [45]	15 DLB VH 15 AD 13 HC	76.3 (4.1) [2] 76.1 (4.9) 76.0 (4.2)	2.9 (7) [2] 3.1 (6) -	NPI	17.7 (5.2) [4,5] 16.7 (5.4) 28.3 (1.5)	NA	DTI ROI Tractography-based subdivision of the thalami; nuisance factors: MMSE, CAF, and UPDRS; correlation with NPI^{hall}	Grey matter MD DLB VH > HC: thalamic sub-regions project. to PFC and parieto-occipital cortex bilaterally; R thalamic region project. to amygdala; L thalamic region project. to motor cortex Positive association with NPI^{hall}: R thalamus to parietal (VH freq. and sev.) and occipital cortices (VH sev.)
Franciotti et al. (2015) [16]	15 sPD VH 15 sPD NVH 15 ePD NVH 15 MSA 15 HC	70 (6) [2] 68 (11) 66 (9) 67 (5) 69 (6)	11.3 (4.3) [6,7] 12.0 (4.5) [7] 3.3 (1.8) 3.9 (1.8) -	NPI and semi-structured interview	24.3 (2.2) [2] 24.7 (1.8) 26.2 (1.8) 25.2 (1.7) 28.7 (0.7)	3.0 (0.5) [7] 3.0 (0.6) [7] 2.1 (0.4) 3.2 (0.8) -	Cortical thickness Analysis within DMN cortical regions; nuisance factor: age; group comparison Resting-state fMRI [8]	Cortical thickness sPD VH vs. sPD NVH: NS sPD VH < ePD: L SFS and IPL, bilat. MFG, LPC sPD VH < HC: L SFS, bilat. MFG, LPC, IPL, PCC sPD NVH < HC: R LPC, bilat. IPL, PCC
Gama et al. (2014) [35]	11 PD VH 28 PD NVH 10 HC	70.6 (9.1) [2] 65.7 (7.8) 68.1 (7.0)	7.4 (6.1) [2] 6.5 (5.0) -	Based on definition of VH	19.3 (3.7) [9] 25.6 (4.3) 25.6 (4.3)	From stage I to stage IV	ROI VBM ROIs (SVC): temporal and frontal regions; group comparisons	Grey matter volume $p < 0.05$ corrected VH < HC: L opercula and SFG NVH < HC: L SFG
Goldman et al. (2014) [27]	25 PD VH 25 PD NVH	74.8 (6.0) [2] 75.4 (6.1)	13.1 (4.6) [2] 10.8 (4.4)	MDS-UPDRS	23.9 (5.4) [2] 25.1 (4.4)	3 (2-5) [2,10] 3 (2-5) [10]	Whole brain VBM Covariate: TIV; group comparison; association between regions where VH < NVH and VH sev.	Grey matter volume $p < 0.01$ uncorrected VH < NVH: bilat. occipital, occipito-temporal, and parietal regions Correlation with VH sev.: parietal, occipital, and occipito-temporal regions

Table A1. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Ibarretxe-Bilbao et al. (2010) [34]	12 PD VH	73.3 (5.9) [2]	12.1 (5.7) [2]	Structured interview; NPI	26.9 (1.9) [4,9,11]	3.1 (1.1) [9]	Whole brain VBM Covariate: MMSE; comparison between baseline and follow-up in each group; correlations between atrophy progression and cognitive decline in PD VH	Grey matter loss form baseline to follow-up $p < 0.05$ corrected VH: bilat. parietal cortex, insula, STG, ITG, SFG, IFG, thalamus and limbic areas, L dorsal PCC NVH: R frontal areas and cerebellum Correlations with grey matter loss in PD VH: learning with L hippocampus, delayed recall with L prefrontal cortex, semantic fluency with L thalamus, language comprehension with L amygdala
	14 PD VH	71.1 (5.7)	11.9 (4.3)		29.3 (1.6)	2.3 (0.5)		
	12 HC	70.7 (7.2)	-		29.5 (2.6)	-		
Ibarretxe-Bilbao et al. (2008) [32]	16 PD VH	73.5 (5.1) [2]	12.9 (5.9) [2]	Structured interview	26.0 (2.1) [4,9]	3.2 (1.1)	ROI VBM ROI: hippocampus; group comparison; correlation analysis with cognitive measures	Grey matter density $p < 0.05$ corrected VH vs. NVH and NVH vs. HC: NS VH < HC: bilat. anterior hippocampus Correlation with grey matter loss in anterior hippocampus bilaterally: learning scores in patients with PD VH, but not PD NVH and PDD
	19 PD NVH	72.5 (5.8)	10.9 (4.2)		28.2 (1.7)	2.5 (0.7)		
	9 PDD	69.8 (9.5)	13.1 (5.4)		15.7 (5.4)	3.8 (1.0) [12]		
	56 HC	73 (6.7)	-		28.7 (3.1)	-		
Iizuka and Kameyama (2016) [18]	24 DLB	73 (68, 79) [13]	2.8 (1.8, 3.2) [13]	NPI	23 (20.5, 24) [13]	NA	ROI MRI ROI: medial temporal lobe, correlation analysis PET [8]	Negative correlation with NPI^{hall} in DLB: MTL atrophy
	24 AD	74 (69, 81) [13]	2.3 (1.6, 2.6) [13]		23 (21, 24.5) [13]			
Janzen et al. (2012) [28]	13 PD VH	66.0 (6.9) [2]	11.5 (5.2)	SCOPA-PC	28.0 (1.7)	2.5 (0.3) [16]	ROI VBM ROI: thalamus and pedunculopontine nucleus; covariates: age, TIV; group comparisons Whole brain VBM Post-hoc analysis; group comparisons	Grey matter volume ROI VBM $p < 0.05$ corrected PD VH < PD NVH: bilat. PPN PD/PDD VH < PD NVH: bilat. PPN and thalamus Whole brain VBM $p < 0.001$ uncorrected PD/PDD VH < PD NVH: PPN and thalamus DLB/PDD VH < PD VH: R MFC
	13 PDD VH	67.7 (7.1)	10.9 (5.5)		21.2 (2.7) [12,14]	3.5 (1.0) [12,14]		
	16 PD NVH	64.3 (8.0)	3.1 (3.6)		28.9 (1.6) [15]	2.1 (0.5)		
	11 DLB	62.6 (6.5)	4.6 (4.5)		24.5 (1.4)	NA		
Kantarci et al. (2010) [46]	30 DLB	71 (55, 85) [10]	NA	VH definition; 64% of DLB	27 (14, 34) [10,17]	NA	DTI ROI ROI: cortical GM regions and white matter tracts; group comparisons	Mean diffusivity VH > NVH: ILF
	30 AD	74 (48, 89) [10]			24 (5, 33) [10,17]			
	60 HC	73 (54, 86) [10]			36 (28, 38) [10,17]			
Kantarci et al. (2012) [19]	21 DLB	73 (60, 87) [10]	NA	Freq. of VH: 4 point scale90% of DLB	22 (6, 29) [10]	NA	ROI MRI Association between freq. of VH and hippocampal volumes in DLB PET [8]	Hippocampal volume Association with VH freq.: NS
	21 AD	77 (58, 92) [10]			21 (6, 28) [10]			
	42 HC	74 (59, 87) [10]			29 (27, 30) [10]			
Lee et al. (2016) [20]	10 PD VH	69.2 (5.2) [2]	7.2 (3.7) [2]	Semi-structured interview	27.7 (1.6) [2]	2.2 (0.5) [2]	DTI ROI ROI: optic nerve, optic radiation bilaterally; group comparisons ROI MRI ROIs: optic chiasm area; LGN volume; V1 volume; each volume divided by TIV; group comparison	White matter integrity $p < 0.016$ corrected VH < HC: FA: L optic nerve FA NVH < HC: MD: bilat. optic nerve VH > NVH and HC: MD: L optic radiation VH > NVH: axial diffusivity: R optic nerve VH > HC: RD: L optic radiation Grey matter volume VH < NVH: volume: L LGN VH < HC: volume: bilat. LGN
	14 PD NVH	66.1 (6.1)	7.3 (3.7)		28.4 (1.4)	2.1 (0.5)		
	15 HC	68.5 (6.6)	-		NA	-		

Table A1. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Lee et al. (2017) [21]	10 PD VH	69.4 (5.3) [2]	7.2 (3.7) [2]	Based on consensus criteria during clinical follow-up	27.6 (1.8)	2.2 (0.3) [12,14,16]	Whole brain VBM Covariates: age, gender, TIV; group comparisons; TBSS DTI Group comparisons; covariates: age, gender	Grey matter volume $p < 0.001$ uncorrected PD VH < PD NVH: R IPL, and SG White matter $p < 0.05$ corrected PD VH vs. PD NVH: FA: NS PD VH < HC: FA: fronto-temporo-parietal and brainstem regions bilaterally PD NVH < HC: FA: fronto-temporal-parietal areas, midbrain and pons bilaterally PD VH > HC: MD: L temporo-parietal, and lateral geniculate areas
	21 PD NVH	66.2 (6.8)	7.0 (4.2)		28.2 (1.4)	1.8 (0.5)		
	17 PDD VH	71.1 (5.0)	6.2 (3.0)		20.4 (3.7) [12,14]	2.8 (0.8)		
	30 HC	68.6 (6.0)	-		NA	-		
Meppelink et al. (2011) [24]	11 PD VH	NA [2]	8.0 (4.7)	NPI	NA [2]	NA	Whole brain VBM Group comparisons; covariates: total grey matter ROI MRI ROI: L FG	Grey matter volume Whole brain VBM $p < 0.05$ cluster-level corrected VH vs. NVH: NS VH < HC: L temporal areas, parietal, occipital, frontal regions bilaterally NVH < HC: L occipital, temporal regions, frontal and parietal regions bilaterally ROI: FG: NS
	13 PD NVH	NA	7.9 (2.4)		NA			
	14 HC	NA	-		NA			
Pagonabarraga et al. (2014) [29]	17 PD mVH	64.1 (9) [2]	9.8 (7) [2]	MDS-UPDRS	87.2 (13) [2,18]	1.9 (0.3) [2]	Whole brain VBM Covariates: age, gender, global grey matter volume; group comparisons; cluster threshold of 207 voxels determined through 1000 Monte Carlo simulations	Grey matter volume $p < 0.001$ uncorrected mVH < NVH: R vermis, and precuneus mVH > NVH: cerebellum, L IFC
	29 PD NVH	66.3 (8)	7.3 (4)		90.3 (13)	1.9 (0.4)		
	16 HC	66.8 (8)	-		91.6 (11)	-		
Pereira et al. (2013) [42]	6 PD VH	73.7 (5.4) [2]	12.9 (5.7) [2]	NPI	26.1 (2) [4,9]	3.1 (1) [2]	ROI MRI ROI: hippocampal subfields; correlations with cognitive measures	Grey matter volume VH vs. NVH: NS VH and NVH < HC: CA2-3, CA4-DG VH < HC: subiculum, whole hippocampus
	6 PD NVH	73.8 (6.8)	12.8 (6.3)		27.9 (1.4)	2.9 (0.9)		
	6 HC	73.6 (6.7)	-		27.9 (2.1)	-		
Ramirez-Ruiz et al. (2007) [30]	18 PD VH	PD matched with HC	12.6 (5.6) [2]	NPI and structured questionnaire	27.0 (2.1) [4,9]	3.2 (1.0) [9]	Whole brain VBM Covariates: TIV, MMSE, Hamilton, and H&Y scores; group comparison	Grey matter volume $p < 0.05$ cluster-level corrected VH < NVH: L LG and bilat. SPL
	20 PD NVH		10.6 (4.3)		29.1 (1.4)	2.5 (0.7)		
	21 HC		-		29.4 (2.3)	-		
Sanchez-Castaneda et al. (2010) [33]	6 DLB VH	70.17 (12.4) [2]	32.8 (17.7) [19]	NPI and Burnes Questionnaire	17.5 (5) [2]	2.6 (0.5) [2]	ROI VBM ROI: frontal, occipital, parietal, and temporal areas; covariates: TIV, disease duration, duration of dementia; group comparison; correlation analysis	Grey matter volume $p < 0.05$ corrected DLB VH < DLB NVH: R IFG PDD VH < PDD NVH: L OFC Correlations with VH sev. $p < 0.05$ corrected DLB: R IFG ($r = 0.89$), L precuneus ($r = 0.95$) PDD: NS
	6 DLB NVH	70.6 (7.1)	30 (11.8) [19]		21.2 (8.1)	3 (0.7)		
	8 PDD VH	75.3 (4.9)	40.5 (16.8) [19, 20]		21.5 (3.5)	2.8 (0.6)		
	7 PDD NVH	70.6 (7.1)	66 (24.8) [19]		23.5 (4)	2.6 (1)		

Table A1. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Shin et al. (2012) [25]	46 PD VH	71.3 (5.9) [2]	3.3 (3.0) [2]	NPI	25.2 (3.0) [2]	NA	Whole brain VBM Group comparison; covariates: age, sex, PD duration, intracerebral volume, MMSE score ROI MRI Manually delineation of the ROI; group comparisons	Grey matter volume VBM VH < NVH $p < 0.001$ uncorrected R IFC, L temporal, and thalamic areas VH < HC $p < 0.05$ corrected Parahippocampal area, insular cortex ROI VH < NVH: SI volume Correlations with SI volume: verbal memory immediate, and delayed recall, semantic fluency, go/no-go tests
	64 PD NVH	70.7 (5.7)	2.8 (3.0)		25.7 (2.9)			
Watanabe et al. (2013) [31]	13 PD VH	66.6 (5.5) [2]	10.0 (5.2) [2]	UPDRS I	27.9 (1.9) [2]	2.9 (0.6) [2]	Whole brain VBM Covariates: TIV, age, sex; group comparison	Grey matter volume VH < NVH $p < 0.005$ uncorrected Bilat. PFC, PFC, L ventral cingulate cortex, primary visual cortex, PCC, occipito-temporal regions, R parietal, temporal, occipital regions
	13 PD NVH	63.6 (10.7)	10.0 (4.0)		29.0 (1.5)	2.4 (0.8)		
	22 HC	63.4 (6.1)	-		29.8 (0.4)	-		
Yao et al. (2016) [22]	12 PD VH	70 (64, 72.75) [2,13]	9.1 (3.5) [2]	PPRS	28.5 (24, 29.75) [2,13]	3.1 (0.7) [2]	ROI MRI Volume, and shape of the hippocampus; covariates: age, MMSE, intracranial volume; group comparison ROI DTI MD of the hippocampus; voxel-based MD of the hippocampus; covariates: age, MMSE; group comparison Resting-state fMRI [8]	Hippocampal volume and shape: NS VH > NVH and HC: MD: R hippocampus; voxel-based MD ($p < 0.05$ corrected): R posterior hippocampal regions
	15 PD NVH	66 (62, 72) [2]	7.1 (5.1)		29 (28, 30) [13]	2.9 (0.7)		
	14 HC	63 (62, 68.75) [2]	-		29 (28, 29.25) [13]	-		
Yao et al. (2014) [17]	12 PD VH	67.6 (7.4) [2]	10.0 (3.5) [2]	PPRS	27.6 (2.4) [2]	3.2 (0.7) [2]	Cortical thickness Covariates: age, MMSE score and levodopa-equivalent dosage; group comparison Resting-state fMRI [8]	Cortical thickness $p < 0.05$ cluster-level corrected No differences between groups
	12 PD NVH	63.4 (7.4)	8.4 (5.1)		28.5 (1.7)	2.8 (0.9)		
	14 HC	64.1 (4.0)	-		29.1 (0.7)	-		

[1] Mean (SD); [2] no significant differences between groups; [3] no significant differences with AD; [4] VH ≠ HC; [5] no differences between DLB and AD; [6] no differences between sPD VH and sPD NVH; [7] sPD VH and NVH ≠ ePD; [8] functional neuroimaging is reported in Table A2; [9] VH ≠ NVH; [10] median (range); [11] MMSE: VH 6.5 point decline after 2 years follow-up (higher percentage of loss compared to NVH); [12] PDD ≠ PD NVH; [13] median (interquartile range); [14] PDD ≠ PD VH; [15] PD NVH ≠ DLB; [16] PD VH ≠ PD NVH; [17] Short test of Mental Status; [18] Parkinson's disease-Cognitive Rating Scale; [19] months; [20] PDD VH ≠ DLB VH, DLB NVH, PDD VH. AD: Alzheimer's disease; bilat.: bilateral; CAF: Clinician Assessment of Fluctuations; DLB: dementia with Lewy bodies; ed.: education; ePD: early PD; FA: fractional anisotropy ; FAB: Frontal Assessment Battery; FG: fusiform gyrus; freq.: frequency; H&Y: Hoehn and Yahr stage; HC: healthy controls; IFC: inferior frontal cortex; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; LG: lingual gyrus; LGN: lateral geniculate nucleus; LPC: lateral parietal cortex; MD: mean diffusivity; MDS: Movement Disorders Society; MF: middle frontal gyrus; MFC: middle frontal cortex; MMSE: Mini-Mental State Examination; MRI: magnetic resonance imaging; MSA: multiple system atrophy; NA: not available; NPI: Neuropsychiatric Inventory; NPIhall: NPI hallucination score; NS: not significant; NVH: no VH; OFC: orbitofrontal cortex; PCC: posterior cingulate cortex; PD: Parkinson's disease; PDD: Parkinson's disease dementia; PFC: prefrontal cortex; PPN: pedunculopontine nucleus; PPRS: Parkinson psychosis rating scale; pro-AD: prodromal AD; pro-DLB: prodromal DLB; project.: projecting; RD: radial diffusivity; ROI: region of interest; SCOPA-PC: Scales for Outcome in Parkinson's disease Psychiatric Complications; sev.:severity; SFC: superior frontal gyrus; SFS: superior frontal sulcus; SG: supramarginal gyrus; SI: Substantia innominate; sPD: severe PD; SPG: superior parietal gyrus; SPL: superior parietal lobe; STG: superior temporal gyrus; UPDRS: Unified Parkinson's Disease Rating Scale; VBM: voxel-based morphometry; VH: visual hallucinations.

Table A2. Summary of functional neuroimaging studies of hallucinating patients with LBD. Only main results related to VH are reported.

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Boecker et al. (2007) [61]	8 PD VH 13 PD NVH	72.88 (6.60) [2] 70.56 (6.96)	11.00 (6.46) [2] 8.05 (5.85)	NPI	25.75 (1.67) [2] 26.82 (1.54)	3.31 (0.59) [3] 2.68 (1.54)	FDG-PET Whole brain; covariate: UPDRS III; group comparison	Cerebral glucose metabolism $p < 0.05$ corrected VH < NVH: bilat. IPL, precuneus, L SG, MFG, MTG, parahippocampal gyrus, LG, R cingulate gyrus
Erskine et al. (2015) [47]	17 DLB 15 AD 19 HC	81.5 (5.5) 82.5 (9.2) 77.6 (7.1)	NA	NPI	19.0 (5.1) 20.8 (4.4) 29.0 (1.2)	NA	Task-based fMRI fMRI protocol: see Taylor et al. (2012) [23]; ROI: LGN; correlation analysis with NPI^{hall}	fMRI activations Correlations between NPI^{hall} and BOLD activation in the LGN: NS
Firbank et al. (2016) [67]	30 DLB	76.4 (6.0)	39.3 (27.9) [7]	NPI	21.7 (4.2)	NA	FDG-PET Covariates: CAMCOG, UPDRS-III, disease duration; voxel-wise correlation with NPI^{hall}	Cerebral glucose metabolism $p < 0.05$ cluster-level corrected VH sev. and freq. associated with occipital hypometabolism
Franciotti et al. (2015) [16]	15 sPD VH 15 sPD NVH 15 ePD NVH 15 MSA 15 HC	70 (6) [2] 68 (11) 66 (9) 67 (5) 69 (6)	11.3 (4.3) [4,5] 12.0 (4.5) [5] 3.3 (1.8) 3.9 (1.8) -	NPI and semi-structured interview	24.3 (2.2) [2] 24.7 (1.8) 26.2 (1.8) 25.2 (1.7) 28.7 (0.7)	3.0 (0.5) [5] 3.0 (0.6) [5] 2.1 (0.4) 3.2 (0.8) -	Resting-state fMRI ICA (30 components), 9 ROIs centred on the DMN clusters; nuisance factor: age; fALFF of each ROI; group comparisons Cortical thickness [6]	Functional connectivity of ROIs centred on the DMN sPD VH > sPD NVH: L SFS – L IPL; LSFS – L IPL; LSFS – R IPL; L SFS – PCC; R SFS – L IPL; R SFS; R IPL; R SFS – PCC; L LPC – R LPC; L IPL – R IPL; L IPL – PCC; R IPL – PCC sPD VH > ePD NVH L SFS and L IPL fALFF sPD VH > sPD: R SFS, MFG, LPC, IPL; L MFG, IPL
Gasca-Salas et al. (2016) [62]	9 PD VH 12 PD NVH 19 HC	70.7 (3.9) [2] 70.8 (3.4) 70.1 (3.1)	14.7 (5.4) [2] 14.3 (6.3) -	UPDRS I	27 (1.7) [2] 25.9 (2.7) 29.1 (1.2)	NS differences	FDG-PET Whole brain; covariates: age, ed., group comparison	Cerebral glucose metabolism $p < 0.05$ corrected VH < NVH: R LG, ITG, precuneus, precentral gyrus, L postcentral gyrus, bilat. MOG
Goetz et al. (2014) [54]	1 PD VH	66	4	African tribesmen, chimpanzees, people in civil war uniform, catholic nuns	Intact cognitive function	NA	fMRI during VH VH during scan: African tribesmen and chimpanzees; event-related design; comparison between hallucination and non-hallucination	$p < 0.001$ uncorrected Increased activations during VH: bilat. ACC, PCC, insula, R medial frontal gyrus, postcentral gyrus, thalamus, brainstem Decreased activations during VH: R LG, FG, IOG, cingulate, L MFG, R STG
Heitz et al. (2015) [73]	36 DLB VH 30 DLB NVH	71.7 (10.2) [2] 73.5 (6.9)	NA	Assessed by expert neurologists	21.7 (5.6) [2] 23.3 (4.3)	NA	SPECT [99mTc]ECD; covariates: age, type of tracer; voxel-based comparison; association between cerebral perfusion and sev. of VH	Cerebral perfusion $p < 0.001$ uncorrected VH < NVH: L ACC, orbitofrontal cortex, cuneus Association with VH sev.: bilat. ACC, R parahippocampal gyrus, L orbitofrontal cortex, L cuneus
Holroyd and Wooten (2006) [48]	3 PD VH 3 PD NVH	69.7 (8.7) [2] 66.0 (2.7)	NA	Based on definition of VH	31.7 (2.1) [2,8] 34.3 (2.1) [8]	NA	Task-based fMRI Visual task: coloured geometric shapes moving in random directions; baseline: stationary crosshair; group comparison	fMRI activations VH > NVH: bilat. cuneus, LG, FG, and MTG VH < NVH: primary visual cortex
Howard et al. (1997) [55]	1 DLB VH	74	18 [7]	Markets, factories, busy roads, docks; no insight	16	NA	fMRI during VH VH during scan: pigeons, sparrows, pheasants; exposure to photic stimulation; comparison between hallucination, and hallucination-free state	Hallucination-free activations: V1 and V2 bilaterally Activations during VH: limited activation in V1 and V2

Table A2. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Iizuka and Kameyama (2016) [18]	24 DLB 24 AD	73 (68, 79) [11] 74 (69, 81) [11]	2.8 (1.8, 3.2) [11] 2.3 (1.6, 2.6) [11]	NPI	23 (20.5, 24) [11] 23 (21, 24.5) [11]	NA	FDG-PET Voxel-wise; ROI: CIS ratio; SUVR in PCC and precuneus + cuneus; correlations with NPI^{hall} Structural MRI [6]	Positive correlation with NPI^{hall} in DLB: CIS ratio Negative correlation with NPI^{hall} in DLB: SUVR in precuneus/cuneus
Imamura et al. (1999) [65]	16 DLB VH 6 DLB NVH 16 AD	72.5 (4.6) [2] 72.8 (5.3) 73.2 (4.6)	23.1 (13.0) [27] 28.0 (14.4) [7] 22.2 (13.8) [7]	NPI	19.5 (3.9) 15.0 (3.0) 19.7 (3.5)	NA	FDG-PET 66 ROIs; covariate: MMSE	Cerebral metabolic rate of glucose VH > NVH: R posterior temporal and parietal areas
Kantarci et al. (2012) [19]	21 DLB 21 AD 42 HC	73 (60, 87) [9] 77 (58, 92) [9] 74 (59, 87) [9]	NA	Freq. of VH: four-point scale 90% of DLB with VH	22 (6, 29) [9] 21 (6, 28) [9] 29 (27, 30) [9]	NA	FDG-PET Association between FDG uptake and freq. of VH Structural MRI [6]	Cerebral glucose metabolism Negative association with VH freq.: occipital FDG uptake
Kataoka et al. (2008) [78]	1 PDD VH	72	NA	Well-formed objects, humans, animals; VH developed four years after the onset of parkinsonians symptoms	27 [10]	NA	SPECT during VH [99mTc]ECD; VH during scan: spider without delusions	Increased regional cerebral blood flow: L STG, MTG, IFG, and apex of R temporal lobe
Lefebvre et al. (2016) [49]	18 PD VH 16 PD NVH 17 HC	63.50 (5.94) [2] 62.69 (4.09) 62.76 (4.19)	9.06 (4.11) [2] 8.00 (5.74) -	NPI Minor VH	28.00 (1.24) [2] 28.88 (1.20) 28.47 (1.70)	2 (2, 2) [2,11] 2 (2, 2) [2,11] -	Task-based fMRI Visual detection task (threshold evaluation): circular gratings; whole brain analysis; covariates: HDRS, TMT-B/TMT-A, Stroop error score	Behavioural results Visual detection threshold: NS fMRI activations at visual threshold $p < 0.01$ cluster-level corrected VH > NVH: R cerebellum, occipital cortex, PFC VH < NVH: L cingulate, temporal, occipital cortices, caudate nucleus
Lobotesis et al. (2001) [74]	23 DLB 50 AD 20 HC	79.4 (9) 81.6 (7) 78.1 (5)	60.7 (32) [7] 83.1 (34) -	Detailed psychiatric history 18 DLB VH	16.0 (6.1) 17.3 (5.5) 28.4 (1.5)	NA	SPECT 99mTc-HMPAO; ROI: occipital hypoperfusion; group comparison	Regional cerebral blood flow VH vs. NVH: NS
Matsui et al. (2006) [70]	31 PD VH 39 PD NVH	71.1 (8.0) [2] 69.0 (7.7)	10.9 (5.1) [3] 6.7 (5.7)	Clinical evaluation and information from patients and caregivers	25.7 (3.2) [2] 26.4 (2.8)	3.2 (0.4) [2] 3.0 (0.6)	SPECT [123I]IMP; group comparison; multivariate logistic regression analysis with disease duration and levodopa equivalent dose as explanatory variables	Brain perfusion VH < NVH: bilat. IPL, ITG, precuneus gyrus, occipital cortex Significant after correcting for disease duration and levodopa equivalent dose: bilat. precuneus, L IPL, R occipital cortex
Meppelink et al. (2009) [51]	9 PD VH 14 PD NVH 13 HC	61.2 (8.2) [2] 64.6 (7.8) 58.5 (7.5)	8.1 (5.0) [2] 8.7 (4.7) -	NPI and questionnaire based on VH characteristics in PD	26.8 (1) [2] 27.4 (1.3) 27.9 (0.9)	NA	Task-based fMRI Perceptual recognition task: animals, well-known objects, and meaningless objects gradually popping out; covariates: movement parameters	Behavioural results VH vs. NVH (both PD groups were slower than HC): NS; images recognised: VH 76%; NVH 86% fMRI activations During pop-out: NS between groups $p < 0.001$ cluster-level corrected Before pop-out: VH < NVH: R SFG, L LG, bilat. FG

Table A2. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Miyazawa et al. (2010) [69]	22 DLB Group A Group B	74.5 (6.9) 74.8 (6.44) [2] 76.6 (6.29)	NA	Reported by patients and relatives 10/ in group A, and 4/ in group B	16.2 (6.95) [2] 21.0 (5.67)	NA	FDG-PET Two groups: (A) hypermetab. in peri-motor areas, cerebellum, and basal ganglia; (B) hypermetab. in none, one, or two regions; group comparison in VH freq.	Visual hallucinations more frequent in group A
Nagahama et al. (2010) [75]	100 DLB 21 HC	76.7 (6.7) 77.2 (4.8)	NA	Semi-structured interview Factor 3: hallucination of person and feeling of presence Factor 4: hallucination of animals, insects and objects	21.0 (3.9) -	NA	DLB patients: Factor analysis, four factors of psychotic symptoms identified SPECT ROIs DLB ≠ HC; relationship between psychotic symptoms factors and regional cerebral blood flow; covariates: age, sex, MMSE, UPDRS-III, dysphoria	Regional cerebral blood flow Areas of hypoperfusion associated to factor 3 compared to the others: bilat. angular gyrus, R SG, L ventral occipital gyrus No areas of hypoperfusion associated to factor 4
Nagano-Saito et al. (2004) [63]	8 PD VH 11 PD NVH 13 HC	67.6 (6.2) [2] 66.0 (7.5) 66.2 (4.9)	8.6 (5.0) [2] 5.1 (3.8) -	NA	28.3 (1.8) [2] 28.5 (1.7) 29.1 (1.0)	3.6 (0.9) [2] 3.2 (0.5) -	FDG-PET Whole brain; ROI: dorsolateral PFC, primary visual cortex, occipital association cortex, primary motor cortex; group comparison	Relative regional cerebral metabolic rate for glucose $p < 0.05$ cluster-level corrected VH > NVH: L SFG ROI: dorsal PFC
O'Brien et al. (2005) [77]	15 DLB 14 PDD	73.8 (7) 71.9 (6)	2.8 (2.1) 2.9 (2.8)	NPI^{hall} decreased over one year	16.5 (4) 20.9 (4)	NA	SPECT 99mTc-HMPAO; changes after one year; multiple regression between change in perfusion and change in NPI^{hall}	Change in perfusion $p < 0.05$ cluster-level corrected DLB/PDD: negative association between hallucination score and perfusion in L PCC and precuneus
Oishi et al. (2005) [71]	24 PD VH 41 PD NVH	69.5 (7.2) [2] 68.6 (7.3)	11.1 (5.0) [2] 9.1 (5.0)	Clinical evaluation and information from patients and caregivers	25.1 (3.7) [2] 26.5 (3.1)	3.3 (0.5) [2] 3.0 (0.5)	SPECT [123I]IMP; voxel-by-voxel comparison; covariates: MMSE, duration of disease	Regional cerebral blood flow $p < 0.05$ corrected VH < NVH: R FG
Osaki et al. (2005) [72]	20 PD 10 PDD	60.0 (11.3) 61.0 (8.5)	8.4 (4.2) 11.6 (4.1)	Structured clinical assessment 9 PD with VH, 10 PDD with VH	26.4 (4.1) 17.4 (6.3)	NA	SPECT [123I]IMP; 23 ROIs: frontal, temporal, parietal, occipital areas, pons; group comparison	Regional cerebral blood flow VH vs. NVH: NS
Park et al. (2013) [64]	7 PD VH 8 PD CI VH 13 NVH	71.0 (4.7) [2] 67.8 (6.8) 66.3 (5.0)	5.4 (3.5) [2] 6.8 (3.1) 5.1 (3.1)	NPI	26.1 (1.7) [12] 21.6 (5.1) 26.9 (1.4)	2..0 (0.0) [2] 2.2 (0.7) 1.5 (0.8)	FDG-PET Whole brain; group comparison; whole brain correlation with NPI^{hall}	Cerebral glucose metabolism $p < 0.001$ uncorrected VH < NVH: bilat. middle and inferior temporal cortex, L LG, and L angular gyrus CI VH < NVH: temporo-parieto-occipital cortices Negative correlation with NPI hallucinations score: glucose metabolism in bilat. STG, L FG, L Heschl's gyrus
Pasquier et al. (2002) [76]	34 DLB 28 AD	73.8 (8) 76.3 (7.3)	3.3 (2.5) 3.4 (2.7)	NPI 26 DLB VH	17.1 (6.7) 15.8 (6.5)	NA	SPECT [99mTc]ECD; ROI: R and L occipital region; group comparison	Cerebral perfusion VH < NVH: R occipital region

Table A2. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Peraza et al. (2014) [57]	16 DLB	76.2 (5.7)	NA	NPI	24.2 (3.75)	NA	Resting-state fMRI Covariates: age, sex, grey matter; regression of sev. and freq. of VH with seeded significant cluster from dual regression DLB < HC	Association with NPI^{hall}: L fronto-parietal, and sensory-motor networks (uncorrected) No association with temporal resting-state network
	17 HC	77.3 (4.7)			29.1 (0.83)			
Peraza et al. (2015) [58]	18 DLB	77.2 (6.18)	NA	NPI	23.6 (3.9)	NA	Resting-state fMRI Graph analysis; correlation between NPI^{hall} and integrated networks measures	No association between integrated network measures and NPI^{hall} Correlation with NPI^{hall}: node degree (L postcentral gyrus, putamen), nodal betweenness centrality (R intracalcarine cortex and FG)
	19 AD	74.7 (8.5)			22.58 (2.9)			
	17 HC	76.8 (5.7)			29.1 (0.85)			
Perneczky et al. (2008) [66]	14 DLB VH	69.86 (6.76) [2]	5.85 (4.88) [2]	NPI	19.57 (5.27) [2]	NA	FDG-PET Whole brain; covariate: MMSE, UPDRS III, group comparison	Relative cerebral metabolic rate of glucose $p < 0.001$ uncorrected VH < NVH: R temporo-occipital conjunction, and MFG
	7 DLB NVH	68.86 (3.02)	5.71 (2.67)		23.14 (2.55)			
	16 HC	65 (8)	-		30 (0)			
Ramirez-Ruiz et al. (2008) [52]	10 PD VH	73 (1.9) [2]	11.1 (1.7) [2]	Presence of VHs at least seven times per week, NPI	25.8 (0.6) [3,13]	3.1 (0.4) [2]	Task-based fMRI One back repetition detection task (face recognition); group comparison	Behavioural results VH < NVH: number of correct responses VH > NVH: false-positive recognition fMRI activations $p < 0.05$ cluster-level corrected VH < NVH: R IFG (controlling for antipsychotic intake) and SFG VH > NVH: R IFG
	10 PD NVH	72.5 (1.9)	11 (1.5)		29.4 (0.4)	2.5 (0.2)		
	10 HC	71.6 (1.6)	-		29.9 (0.5)	-		
Shine et al. (2015) [59]	10 PD pBPP	69.5 (8) [2]	6.9 (4) [2]	MDS criteria for VH Patients with high % of misperceptions on the BPP (PD pBPP, based on a cut score) also presented VH	26.0 (3) [2,14]	NA	Resting-state fMRI ROI: DAN, DMN, VAN, visual network; multiple regression analysis between BPP error scale, strength of mental imagery, and strength of connectivity within and between each network	BPP error score and strength of mental imagery predicted increased connectivity within the VAN and DMN, and decreased connectivity between the DAN and VAN, and the VAN and visual network, and DAN and visual network. BPP error score predicted increased connectivity within VAN and DMN, and impaired connectivity between the VAN and DAN. Strength of mental imagery was related to degree of impaired connectivity between the VAN and visual network
	9 PD nBPP	67.1 (7)	4.4 (3)		27.6 (2) [14]			
	10 HC	63.5 (8)	-		28.5 (1) [14]			
Shine et al. (2015) [53]	21 PD pBPP	69.3 (6) [2]	6.0 (3) [2]	UPDRS-II, SCOPA-PC Patients with high % of misperceptions on the BPP (PD pBPP, based on a cut score) also presented VH	27.2 (2) [2,14]	2.2 (1) [2]	Task-based fMRI BPP paradigm during fMRI; ICA, networks of interest: DMN, DAN, VAN, VIS; activity during correct stable items; comparison in BOLD signal between misperceptions and correct stable images; functional coupling between networks; group comparisons	Activity during correctly identified stable items: Increased activity in the VIS, VH vs. NVH: VIS, DMN, VAN: NS; decreased activity in DAN Activity during misperceptions: decreased activity in the DAN Misperceptions vs. correct stable images in VH: visual misperception increased activity in VAN, DMN Functional coupling between networks during misperceptions in VH: increase in functional coupling between DMN and VIS; decreased in functional coupling between DAN and DMN, and VAN
	14 PD nBPP	66.3 (5)	4.7 (4)		28.6 (2) [14]	2.1 (1)		

Table A2. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Stebbins et al. (2004) [50]	12 PD VH 12 PD NVH	71.08 (6.39) [2] 73.25 (7.58)	13.92 (4.89) [2] 11.17 (3.90)	Self-report, NPI, SAPS	26.17 (2.25) [2] 27.96 (2.09)	3 (2–4) [2,9] 3 (2–4)	Task-based fMRI Stroboscopic task; kinematic task (apparent motion); whole brain and SVC; covariate: MMSE; group comparisons	fMRI activations Whole brain, $p < 0.001$ uncorrected Stroboscopic stimulation: NVH > VH: L IPL, R cingulate gyrus VH > NVH: R IFG, R caudate nucleus Kinematic stimulation: NVH > VH: R middle temporal/ occipital lobe, R cingulate gyrus, bilat. SG, L IPL VH > NVH: L SFG SMV during apparent kinematic stimulation, $p < 0.05$ corrected VH < NVH: area V5/MT
Taylor et al. (2012) [23]	17 DLB 19 HC	81.2 (5.6) 77.6 (7.1)	45.4 (32.2) [7,15] -	NPI	18.8 (5.1) 29.0 (1.2)	NA	Task-based fMRI Passively view of simple visual stimuli (checkboards, pictures of objects, moving dot fields); block design; whole brain analysis; ROIs: V5/MT, V1, V2, and V3 combined, ROI in the lateral occipital cortex; correlation between fMRI beta values in the ROIs and NPI^{hall} ASL-MRI Perfusion; voxel-based analysis; ROI: same as fMRI analysis, precuneus and superior lateral occipital region; correlation between ASL perfusion and NPI^{hall}	fMRI activations No correlation with NPI^{hall} Perfusion Negative association with NPI^{hall}: V4 perfusion
Uchiyama et al. (2015) [68]	11 PD VH 42 PD NVH 24 HC	68.3 (1.6) [2] 65.5 (1.0) 68.0 (1.0)	6.2 (1.1) [2] 6.3 (0.6) -	NPI	27.6 (0.6) [2] 28.2 (0.3) 28.6 (0.3)	3.0 (2, 4) [3] 2.5 (1, 4) -	FDG-PET Covariates: age and sex; whole brain correlation analysis with NPI^{hall}	Glucose cerebral metabolic rate $p < 0.001$ uncorrected Negative correlation with NPI^{hall}: metabolism in the L IPL
Yao et al. (2016) [22]	12 PD VH 15 PD NVH 14 HC	70 (64, 72.75) [2,11] 66 (62, 72) [11] 63 (62, 68.75) [11]	9.1 (3.5) [2] 7.1 (5.1) -	PPRS VH duration: 2.4 (1.1) years	28.5 (24, 29.75) [2,11] 29 (28, 30) [11] 29 (28, 29.25) [11]	3.1 (0.7) [2] 2.9 (0.7) -	Resting-state fMRI Seed-based approach: hippocampus FC; covariates: age, MMSE; correlation between cognitive tests and mean FC scores in clusters where FC was different between VH and NVH (controlling for age and visual accuracy scores) Structural MRI and DTI (ROI) [6]	Functional connectivity of the hippocampus $p < 0.05$ corrected VH < NVH: R hippocampus: occipital, temporal regions; L hippocampus: temporal, occipital regions, and cerebellum VH > NVH: R hippocampus: frontal and temporal regions; L hippocampus: frontal and parietal regions Negative correlation between R hippocampal FC with R occipital gyrus, and medial temporal lobe and visuospatial memory performance

Table A2. *Cont.*

Study	Sample	Age [1]	Disease Duration (years) [1]	VH	MMSE [1]	H&Y	Neuroimaging Methods—VH	Main Results: Neuroimaging and VH
Yao et al. (2015) [60]	12 PD VH	67.6 (7.4) [2]	10.0 (3.5) [2]	PPRS VH duration: 22.6 (17.3) months	27.6 (2.4) [2]	3.2 (0.7) [2]	Resting-state fMRI ALFF; FC seed-region based on ALFF analysis (occipital lobe)	ALFF $p < 0.05$ corrected VH < NVH: occipital lobe: LG, cuneus bilaterally VH > NVH: R cerebellum posterior lobe, MTL, IPL/STL Functional connectivity of occipital seed-region VH > NVH: bilat. IFG, SFG, MFG, medial frontal gyrus and STL; R STG, caudate/thalamus, dorsal anterior cingulate cortex/ventral medial PFC
	12 PD NVH	63.4 (7.4)	8.4 (5.1)		28.5 (1.7)	2.8 (0.9)		
	14 HC	64.1 (4.0)	-		29.1 (0.7)	-		
Yao et al. (2014) [17]	12 PD VH	67.6 (7.4) [2]	10.0 (3.5) [2]	PPRS VH duration: 22.6 (17.3) months	27.6 (2.4) [2]	3.2 (0.7) [2]	Resting-state fMRI Covariates: age, MMSE score, and levodopa-equivalent dosage; ICA (40 components) FC in the DMN; group comparison; correlation between VH sev. and FC in the clusters that differed between PD groups Cortical thickness [6]	Functional connectivity in the DMN $p < 0.05$ corrected VH > NVH: L and R precuneus/ PCC, R superior middle frontal lobe No correlation with VH
	12 PD NVH	63.4 (7.4)	8.4 (5.1)		28.5 (1.7)	2.8 (0.9)		
	14 HC	64.1 (4.0)	-		29.1 (0.7)	-		

[1] Mean (SD); [2] no significant differences between groups; [3] VH ≠ NVH; [4] no differences between sPD VH and sPD NVH; [5] sPD VH and NVH ≠ ePD; [6] structural neuroimaging is reported in Table A1; [7] months; [8] Telephone Interview for Cognitive Status; [9] median (range); [10] one year before the development of VH, while three years after was 23; [11] median (interquartile range); [12] differences between groups; [13] VH ≠ HC; [14] MoCA; [15] duration of dementia. ACC: anterior cingulate cortex; AD: Alzheimer's disease; ALFF: amplitude of low-frequency fluctuation; ASL: arterial spin labelling; BOLD: blood-oxygenation level-dependent; BPP: bistable percept paradigm; CAMCOG: Cambridge cognitive examination; ChEI: cholinesterase inhibitor; CI: cognitive impairment; CIS: cingulate island sign; DAN: dorsal attention network; DLB: dementia with Lewy bodies; DMN: default mode network; DTI: diffusion tensor imaging; ed.: education; ePD: early PD; fALFF: fractional amplitude of low-frequency fluctuation; FC: functional connectivity; FDG: [18F]-Fluorodeoxyglucose; freq.: frequency; FG: fusiform gyrus; fMRI: functional MRI; H&Y: Hoehn and Yahr stage; HDRS: Hamilton depression rating scale; hypermetab.: hypermetabolism; ICA: independent component analysis; IFG: inferior frontal gyrus; IOG: inferior occipital gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; L: left; LG: lingual gyrus; LGN: lateral geniculate nucleus; LPC: lateral parietal cortex sPD; MFG: middle frontal gyrus; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MOG: middle occipital gyrus; MRI: magnetic resonance imaging; MSA: multiple system atrophy; MTG: middle temporal gyrus; MTL: medial temporal lobe; NA: not available; nBPP; NPI: Neuropsychiatric Inventory; NPI^{hall}: NPI hallucination score; NS: not significant; NVH: no VH; pBPP: positive bistable percept paradigm; PCC: posterior cingulate cortex; PD: Parkinson's disease; PDD: Parkinson's disease dementia; PET: positron emission tomography; PFC: prefrontal cortex; R: right; ROI: region of interest; sev.: severity; SFS: superior frontal sulcus; SG: supramarginal gyrus; STG: superior temporal gyrus; STL: superior temporal lobe; SUVR: standardized uptake value ratio; SVC: small volume correction; TMT: trial making test; UPDRS: Unified Parkinson's Disease Rating Scale; VAN: ventral attention network; VH: visual hallucinations; VIS: visual network.

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Supplementary materials of the published article included in Chapter 2.

Supplementary tables

Table S1. Suitability assessment criteria used to assess structural and functional imaging studies focusing on VH.

	Questions	Values
1.	Were aims related to VH clearly stated?	no = 0; yes = 1
2.	Were a priori hypotheses on VH clearly stated?	no = 0; yes = 1
3.	How large was the sample size for each group? [1]	< 15 = 0; ≥ 15 = 1
4.	Were demographic and clinical features clearly stated for LBD patients?	no = 0; yes = 1
5.	Was a group comparison between LBD patients with and without VH performed?	no = 0; yes = 1
6.	Were LBD patients with and without VH matched for age, global cognitive performance, and disease duration and/or severity?	no = 0; yes = 1
7.	Was information on pharmacological treatments reported?	no = 0; yes = 1
8.	Was a multimodal imaging approach used?	no = 0; yes = 1
9.	Was a whole brain approach used (as opposed to a ROI approach)?	no = 0; yes = 1
10.	Was correction for multiple comparisons used for voxel-based analyses?	no = 0; yes = 1
11.	Were covariates of no interest included in the analysis?	no = 0; yes = 1
12.	Were correlation analyses with VH indices included?	no = 0; yes = 1
13.	Were correlation analyses with cognitive measures included?	no = 0; yes = 1
14.	Were limitations of the studies clearly stated?	no = 0; yes = 1

[1] For studies performing only correlation analyses, a value of 0 was assigned if the number of patients with VH was not clearly reported.

Table S2. Suitability assessment of the neuroimaging studies included. The quality assessment focused on structural and functional neuroimaging imaging analyses related to VH only (excluding single cases).

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Blanc et al. (2016) [1]	0	0	0	1	1	0	1	0	1	0	1	0	0	1	6
Boecker et al. (2007) [2]	1	0	0	1	1	0	1	0	1	1	1	0	0	0	7
Delli Pizzi et al. (2016) [3]	0	0	1	1	0	0	1	0	0	0	1	1	1	1	7
Delli Pizzi et al. (2014) [4]	1	0	0	1	0	0	0	0	1	1	1	1	0	0	6
Delli Pizzi et al. (2014) [5]	1	1	0	1	0	0	1	0	0	0	1	1	0	1	7
Erskine et al. (2015) [6]	1	1	0	1	0	0	1	0	0	0	0	0	0	0	4
Firbank et al. (2016) [7]	1	1	1	1	0	0	1	0	1	1	1	1	0	1	10
Franciotti et al. (2015) [8]	1	1	1	1	1	1	1	1	0	0	1	0	0	1	10
Gama et al. (2014) [9]	1	1	0	1	0	0	1	0	0	1	0	0	0	1	6
Gasca-Salas et al. (2016) [10]	1	0	0	1	1	1	1	0	1	1	1	0	0	1	9
Goldman et al. (2014) [11]	1	0	1	1	1	1	1	0	1	0	1	1	0	1	10
Heitz et al. (2015) [12]	1	1	1	1	1	0	1	0	1	0	1	1	0	1	10
Holroyd and Wooten (2006) [13]	1	0	0	1	1	0	0	0	1	0	0	0	0	1	5
Ibarretxe-Bilbao et al. (2010) [14]	1	1	0	1	0	0	1	0	1	1	1	0	1	1	9
Ibarretxe-Bilbao et al. (2008) [15]	1	1	1	1	1	1	0	0	0	1	0	0	1	1	9
Iizuka and Kameyama (2016) [16]	0	0	0	1	0	0	0	1	0	0	0	1	0	1	4
Imamura et al. (1999) [17]	1	0	0	1	1	0	0	0	0	0	1	0	0	0	4
Janzen et al. (2012) [18]	1	1	0	1	1	0	1	0	1	1	1	0	0	1	9
Kantarci et al. (2010) [19]	0	0	0	1	1	0	0	1	0	0	0	0	0	1	4
Kantarci et al. (2012) [20]	0	0	1	1	0	0	0	1	0	0	0	1	0	0	4
Lee et al. (2016) [21]	1	1	0	1	1	1	1	1	0	1	0	0	0	1	9
Lee et al. (2017) [22]	1	0	0	1	1	0	1	1	1	1	1	0	0	1	9
Lefebvre et al. (2016) [23]	1	1	1	1	1	1	1	0	1	1	1	0	0	1	11
Lobotesis et al. (2001) [24]	0	0	0	1	1	0	0	0	0	0	0	0	0	1	3
Matsui et al. (2006) [25]	1	1	1	1	1	0	1	0	1	0	1	0	0	1	9
Meppelink et al. (2009) [26]	1	1	0	1	1	0	1	0	1	1	1	0	0	0	8
Meppelink et al. (2011) [27]	1	0	0	0	1	0	0	1	1	1	1	0	0	0	6
Miyazawa et al. (2010) [28]	0	0	0	0	0	0	1	0	0	0	0	1	0	1	3
Nagahama et al. (2010) [29]	1	0	1	1	0	0	1	0	0	0	1	1	0	1	7

Table S2 (continued). Suitability assessment of the neuroimaging studies included. Quality assessment focused on structural and functional neuroimaging imaging analyses related to VH only (excluding single cases).

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Nagano-Saito et al. (2004) [30]	1	0	0	1	1	1	1	0	0	1	0	0	0	0	**6**
O'Brien et al. (2005) [31]	1	1	0	1	0	0	1	0	1	1	0	1	0	1	**8**
Oishi et al. (2005) [32]	1	0	1	1	1	1	1	0	1	1	1	0	0	0	**9**
Osaki et al. (2005) [33]	1	0	0	1	1	0	1	0	0	0	0	0	0	1	**5**
Pagonabarraga et al. (2014) [34]	1	0	1	1	1	1	1	0	1	0	1	0	0	1	**9**
Park et al. (2013) [35]	1	1	0	1	1	1	1	0	1	0	0	1	0	1	**9**
Pasquier et al. (2002) [36]	0	0	0	1	1	0	0	0	0	0	0	0	0	1	**3**
Peraza et al. (2014) [37]	0	0	0	1	0	0	1	0	1	0	1	1	0	1	**6**
Peraza et al. (2015) [38]	1	0	0	1	0	0	1	0	1	0	0	1	0	0	**5**
Pereira et al. (2013) [39]	1	1	0	1	1	0	1	0	0	0	0	0	1	1	**7**
Pemeczky et al. (2008) [40]	1	1	0	1	1	1	1	0	1	0	1	0	0	1	**9**
Ramirez-Ruiz et al. (2008) [41]	1	0	0	1	1	0	1	0	1	1	1	0	0	1	**8**
Ramirez-Ruiz et al. (2007) [42]	1	1	1	0	1	0	1	0	1	1	1	0	0	0	**8**
Sanchez-Castaneda et al. (2010) [43]	1	1	0	1	1	1	1	0	0	1	1	1	0	1	**10**
Shin et al. (2012) [44]	1	1	1	1	1	1	1	1	1	0	1	0	0	1	**11**
Shine et al. (2015) [45]	1	1	0	1	1	1	1	0	0	0	0	0	0	0	**6**
Shine et al. (2015) [46]	1	1	0	1	0	1	1	0	0	0	0	0	0	0	**5**
Stebbins et al. (2004) [47]	1	0	0	1	1	1	1	0	1	0	1	0	0	1	**8**
Taylor et al. (2012) [48]	0	0	0	1	0	0	1	1	0	0	0	1	0	0	**4**
Uchiyama et al. (2015) [49]	1	1	0	1	0	0	1	0	1	0	1	1	0	1	**8**
Watanabe et al. (2013) [50]	1	0	0	1	1	1	1	0	1	0	1	0	0	1	**8**
Yao et al. (2016) [51]	1	1	0	1	1	1	1	1	0	1	1	0	0	1	**10**
Yao et al. (2015) [52]	1	1	0	1	1	1	1	0	1	1	0	0	0	1	**9**
Yao et al. (2014) [53]	1	1	0	1	1	1	1	1	1	1	1	1	0	1	**12**

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Appendix 2

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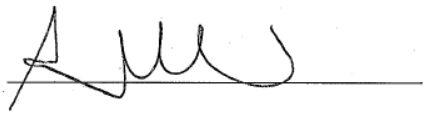
Annalena Venneri 

Appendix 3

Ethical approval, Chapter 4.

FONDAZIONE OSPEDALE SAN CAMILLO
OSPEDALE NEURORIABILITATIVO | ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
SEDE LEGALE: 30126 | VENEZIA-LIDO | VIA ALBERONI 70 | TEL. 041 22 07 111 | FAX 041 73 13 30
C.F. 94071440278 | P.I. 03953700279 | ISCRITTA PREFETTURA DI VENEZIA: REG. P.G. N. 409
IRCCS

Lido di Venezia, 21 dicembre 2011
Rif. CE: Protocollo 11.09

Preg.mo Signore
Prof. Leontino BATTISTIN
IRCCS S. Camillo

Oggetto: Protocollo 11/09 – vers. 2: Studio dei pattern dell'attività cerebrale di default nelle patologie neurodegenerative. Parere del Comitato etico.

Preg.mo Prof. Battistin,

il Comitato Etico per la Sperimentazione dell'IRCCS S. Camillo, nella seduta del 15 dicembre u.s., ha esaminato la versione 2 del protocollo da Lei presentato, di cui in oggetto, e ha espresso PARERE FAVOREVOLE alla sua effettuazione. Si allega alla presente estratto del Verbale della seduta.

Colgo l'occasione per salutarLa cordialmente.

Il Presidente
Don Corrado Cannizzaro

FONDAZIONE PROVINCIA LOMBARDO - VENETA DELL'ORDINE RELIGIOSO DEI CHIERICI REGOLARI MINISTRI DEGLI INFERMI (CAMILLIANI)
ENTE ECCL. CIVILM. RICON. - R.D. N° 682 DEL 22/05/33 | ISCRIZ. PREFETTURA DI MILANO - REG. P.G. N° 514 VOL. III PAG. 893

IRCSS Ospedale San Camillo
Comitato Etico per la Sperimentazione

Verbale della riunione del 15 dicembre 2011

---------- estratto ----------

[omissis]

Il giorno 15 dicembre 2011 alle ore 11.30, presso la sede dell'IRCCS San Camillo si riunisce il Comitato Etico per la Sperimentazione (CESC), così composto:

Don Corrado **Cannizzaro**, *Presidente*	*Esperto di bioetica*	PRESENTE
Prof. Francesco **Grigoletto**, *Vice presidente*	*Biostatistico*	PRESENTE
Prof. Leontino **Battistin**	*Direttore scientifico dell'IRCCS*	ASS. GIUST.
Prof.ssa Gabriella **Cargnelli**	*Farmacologa*	ASS. GIUST.
Dott. Mauro **Cenedese**	*Clinico*	PRESENTE
Sig.ra Antonella **Chinellato**	*Rappresentante del settore infermieristico*	PRESENTE
Dott. Tiziano **Lazzari**	*Medico di Medicina Generale*	PRESENTE
---	*Direttore sanitario dell'IRCCS*	---
Dott. Francesco **Palladin**	*Clinico*	ASS. GIUST.
Dott. Pietro Emilio **Pisani**	*Esperto in materia giuridica*	PRESENTE
Dott.ssa Olivia **Rabbaglietti**	*Rappresentante del volontariato*	PRESENTE
Dott.ssa Susanna **Zardo**	*Farmacista*	ASS. GIUST.

[omissis]

4. Esame del protocollo 11/09 – vers. 2. Studio dei pattern dell'attività cerebrale di default nelle patologie neurodegenerative

A – DATI GENERALI DEL PROTOCOLLO DI STUDIO 11/09

A.1 – Identificazione del protocollo	
Titolo	Studio dei pattern dell'attività cerebrale di default nelle patologie neurodegenerative
Versione:	2.0
Data:	07/12/2011
Codice/nome	-
Codice EudraCT	---
Tipologia:	studio sperimentale
Fase clinica:	---
A. 2 – Caratteristiche del protocollo	
Pazienti coinvolti	400
Pazienti presso IRCCS	400
Tipologia di pazienti	Pazienti affetti da patologie neurodegenerative
Copertura economica	Approvata dal Dott. Stigliano (vedi allegato)
Copertura assicurativa	Polizza n. 270269323 Assicurazioni Generali emessa in data 08/09/2011
A.2 – Sponsor e promotore	
Sponsor	---
CRO	---
A.3 – Centro coordinatore	

Centro Coordinatore	IRCCS- Fondazione ospedale San Camillo
Sperimentatore principale	*Prof. Leontino Battistin*
Parere Unico Favorevole	---
Emesso il	---
A.4 – IRCCS San Camillo – Lido di Venezia	
Responsabile IRCCS	*Prof. Leontino Battistin*
Num. Protocollo IRCCS	11.09

B – DOCUMENTAZIONE ESIBITA

Lettera di intenti e di richiesta di emissione parere al Comitato etico datata 13 giugno 2011, a cui è allegato il fascicolo del progetto contenente i seguenti documenti:

1. progetto 11/08 versione 1.0;
2. elenco dei centri coinvolti
3. test e scale di valutazione;
4. scheda di raccolta dati;
5. foglio informativo per il paziente;
6. dichiarazione di consenso del paziente;
7. modulo informativo per il medico di famiglia;
8. quantificazione delle risorse e dei costi impiegati nel progetto;
9. delibera regionale approvazione finanziamento.

C – PARERE

Il Comitato Etico dell'IRCCS San Camillo esprime PARERE FAVOREVOLE purché venga osservato quanto previsto dalla normativa vigente e regionale nonché dai regolamenti aziendali.

Contestualmente il Comitato etico ricorda che:

- la sperimentazione clinica nell'uomo deve essere seguita secondo i principi etici fissati nella dichiarazione di Helsinki e successivi emendamenti e che tutte le fasi degli studi clinici devono essere predisposte, attuate e descritte secondo i principi della buona pratica clinica;
- sussiste l'obbligo di non avviare deviazioni dal protocollo, né modifiche allo stesso, senza che il Comitato etico abbia espresso per iscritto approvazione o parere favorevole ad ogni singolo e specifico emendamento;
- deve essere garantito il diritto alla diffusione e/o pubblicazione dei risultati favorevoli o non favorevoli da parte degli sperimentatori che hanno condotto lo studio, nel rispetto delle disposizioni vigenti in tema di riservatezza dei dati sensibili e di tutela brevettuale e che non devono sussistere vincoli di diffusione e pubblicazione dei risultati da parte del Promotore;
- il Responsabile della sperimentazione è tenuto a dare comunicazione al Comitato etico dell'effettivo inizio della sperimentazione, in occasione dell'arruolamento del primo paziente;
- il Responsabile della sperimentazione è infine tenuto a far pervenire una relazione finale sull'esito della sperimentazione.

In difetto delle suddette indicazioni, l'efficacia dell'approvazione del protocollo deve intendersi sospesa a tutti gli effetti.

[omissis]

Il Segretario Verbalizzatore
Dott. Nicolò Anesa

il Presidente
Don Corrado Cannizzaro

Venezia, 15 dicembre 2011

Appendix 4

Ethical approval, Chapter 5.

REGIONE DEL VENETO-AZIENDA OSPEDALIERA DI PADOVA
COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DELLA PROVINCIA DI PADOVA

Azienda Ospedaliera - Padova
AMM.: azos AOO: aoo0 REG.: 1
Tit. II Cl. 10 Fasc. Anno:
N. 0056791 12/10/2016
UOR C.C. RPA
clneu prc

A chi di competenza

Oggetto: trasmissione parere espresso dal Comitato Etico per la Sperimentazione Clinica nella seduta del **22 Settembre 2016.**

Si trasmette in allegato estratto conforme all'originale.

Distinti saluti.

La Segreteria Scientifica del Comitato
Etico per la Sperimentazione Clinica

REGIONE DEL VENETO
AZIENDA OSPEDALIERA DI PADOVA
SEGRETERIA
Comitato Etico della Provincia di Padova

Via Giustiniani, 1 – 35128 Padova Tel. 0498212341-42 fax 0498212827
e-mail: ce.sperimentazione@sanita.padova.it

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REGIONE DEL VENETO-AZIENDA OSPEDALIERA DI PADOVA
COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DELLA PROVINCIA DI PADOVA

VERBALE

della riunione del Comitato Etico per la Sperimentazione Clinica della Provincia di Padova, nominato con deliberazione n. 1033 del 03 Ottobre 2013 e con Decreto di Convalida della Regione del Veneto n.148 del 24 ottobre 2013, e successiva Deliberazione n.1329 del 13 Novembre 2014, esecutivi ai sensi di legge, tenutasi presso la Sala Riunioni della Direzione Generale il **22 Settembre 2016**, ore 14,30.

COMPONENTE	QUALIFICA		
Dr. Matteo Atzori	Clinico ULSS 16 (I)		Assente
Don Corrado Cannizzaro	Esperto di Bioetica (E)	Presente	
Dr. Carlo Castoro	Esperto in Metodologia Clinica (E)		Assente
Dr. Massimo Castoro	Esperto in Dispositivi Medici AOP (I)	Presente	
Dr.ssa Raffaella Colombatti	Pediatra AOP (I)	Presente	
Avv.to Benedetto Cortese	Esperto in materia giuridica e assicurativa (E)		Assente
Dr.ssa Franca De Lazzari	Clinico ULSS 16 (I)	Presente	
Prof.ssa Anna Chiara Frigo	Biostatistica (E)	Presente	
Dr.ssa Anna Maria Grion	Farmacista ULSS 16 (I)		Assente
Dr.ssa Girolama Iadicicco	Farmacista AOP (I)		Assente
Dr. Andrea Merlo	Infermiere designato IPASVI (E)		Assente
Dr.ssa Nadia Minicuci	Biostatistica (E)	Presente	
Prof.ssa Daria Minucci	Rappresentante del volontariato per l'assistenza o associazionismo di tutela dei pazienti (E)	Presente	
Dr. Francesco Morbiato	Medico di Medicina Generale (E)		Assente
Prof. Carlo Ori	Clinico AOP (I)		Assente
Prof. Roberto Padrini	Farmacologo Clinico AOP (I)	Presente	
Dr. Giampaolo Pasquetto	Clinico ULSS 17 (I)		Assente
Dr. Teodoro Sava	Clinico ULSS 15 (I)	Presente	
Dr. Claudio Terranova	Medico Legale AOP (I)	Presente	
Dr.ssa Silvia Tusino	Figura di Bioetico ritenuta essenziale per la complessità e numerosità dei casi trattati (E)	Presente	
Dr. Renato Zambello	Clinico AOP (I)	Presente	

COMPONENTI convocati in rapporto alla sede di svolgimento degli studi			
Dr. Antonio Amato	Delegato del Direttore Sanitario ULSS 17 (I)		Assente
Dr.ssa Michela Galdarossa	Delegato del Direttore Sanitario ULSS 16 (I)	Presente	
Dr.ssa Elena Narne	Delegato del Direttore Sanitario Azienda Ospedaliera di Padova (I)	Presente	
Dr.ssa Roberta Rampazzo	Delegato del Direttore Sanitario ULSS 15 (I)		Assente
ESPERTI convocati su indicazione del Presidente			
Prof. Paolo Stritoni	Esperto clinico in relazione allo studio di nuove procedure tecniche, diagnostiche e terapeutiche, invasive e semi invasive (E)	Presente	

Legenda
(I): Componente Interno
(E): Componente Esterno

La Prof.ssa Anna Chiara Frigo presiede la seduta mentre la Dott.ssa Donatella Piovan, coadiuvata dalla Dott.ssa Lodovica Gambato e dalla Dott.ssa Maria Furfaro, della Segreteria Scientifica del Comitato Etico, svolge la funzione di verbalizzante.

REGIONE DEL VENETO-AZIENDA OSPEDALIERA DI PADOVA
COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DELLA PROVINCIA DI PADOVA

Viene messa a disposizione del Comitato la seguente documentazione:

-omissis-

15) Lettera, datata 25.08.2016, pervenuta il 31.08.2016, da parte della Prof.ssa Annachiara Cagnin (U.O.C. Clinica Neurologica), di risposta alle richieste espresse dal Comitato nella seduta del 14 Luglio 2016 per l'approvazione definitiva dello studio RP-2014-00000400 dal titolo: "*Sperimentazione di una rete clinica per la diagnosi delle demenze a rapida progressione*" (3872/AO/16). In allegato alla lettera vengono inviati i seguenti documenti: Protocollo integrale di studio, versione 2 del 18.08.2016; Sinossi del protocollo, versione 2 del 18.08.2016; Scheda Raccolta Dati, versione 2 del 18.08.2016; Foglio informativo e Modulo per l'espressione del consenso informato, versione 1 del 01.04.2016 aggiornata.
Il Comitato esprime **parere favorevole definitivo** sullo studio clinico presentato.

-omissis-

La Responsabile della Segreteria Scientifica del Comitato Etico per la Sperimentazione Clinica (Dr.ssa Donatella Piovan)

Il Presidente del Comitato Etico per la Sperimentazione Clinica (Prof.ssa Anna Chiara Frigo)

Estratto conforme all'originale.

REGIONE DEL VENETO
AZIENDA OSPEDALIERA DI PADOVA
SEGRETERIA
Tecnico Scientifico per la Sperimentazione Clinica
Comitato Etico della Provincia di Padova

Verbale del 22 Settembre 2016

Appendix 5

Funnel plots for the tests that emerged as significant from the meta-analysis of neuropsychological tests (Chapter 6, section 6.2), namely the RAVLT immediate and delayed recall, phonemic fluency, and TMT-A. No significant publication bias was detected by means of the Egger test of funnel plot asymmetry.

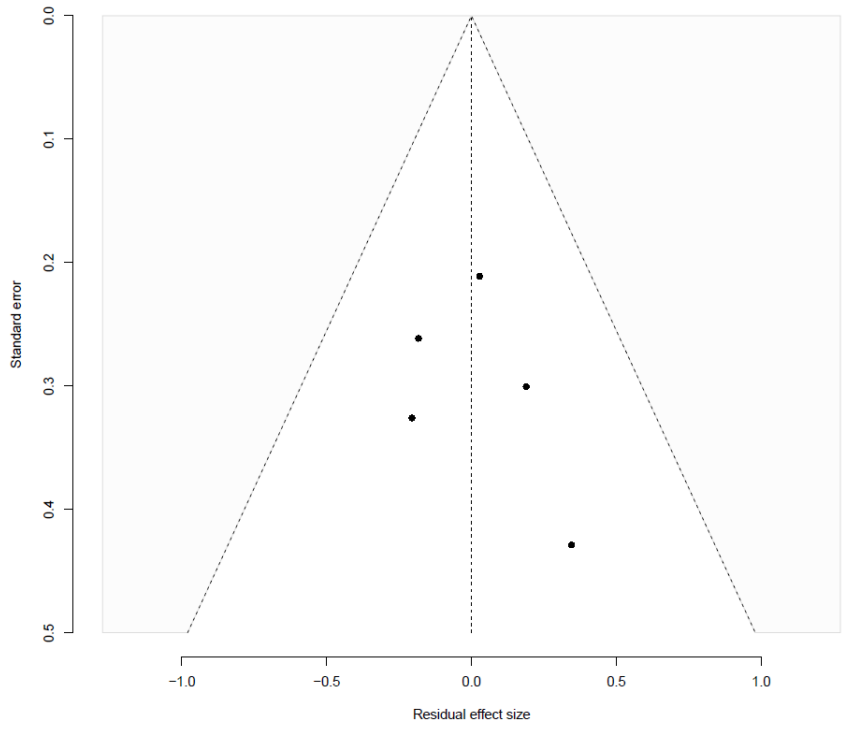

Figure A1 Funnel plot for the RAVLT immediate recall.

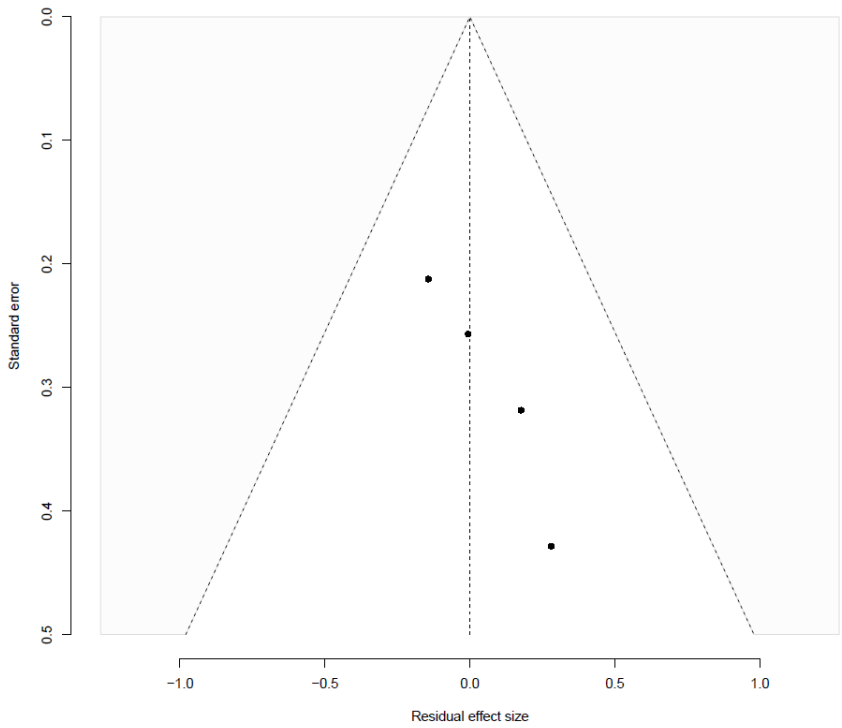

Figure A2 Funnel plot for the RAVLT delayed recall.

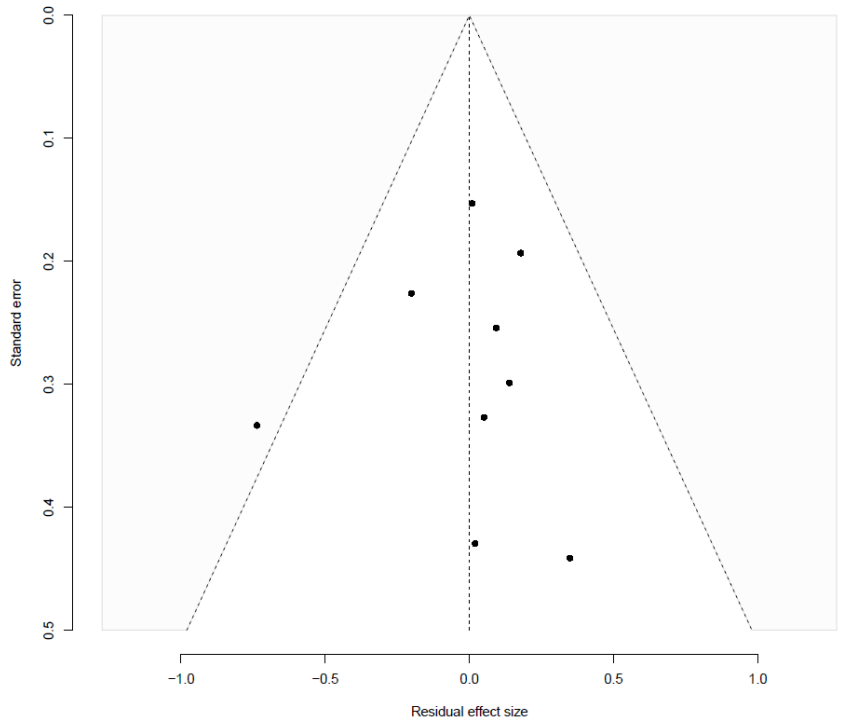

Figure A3 Funnel plot for the phonemic fluency test.

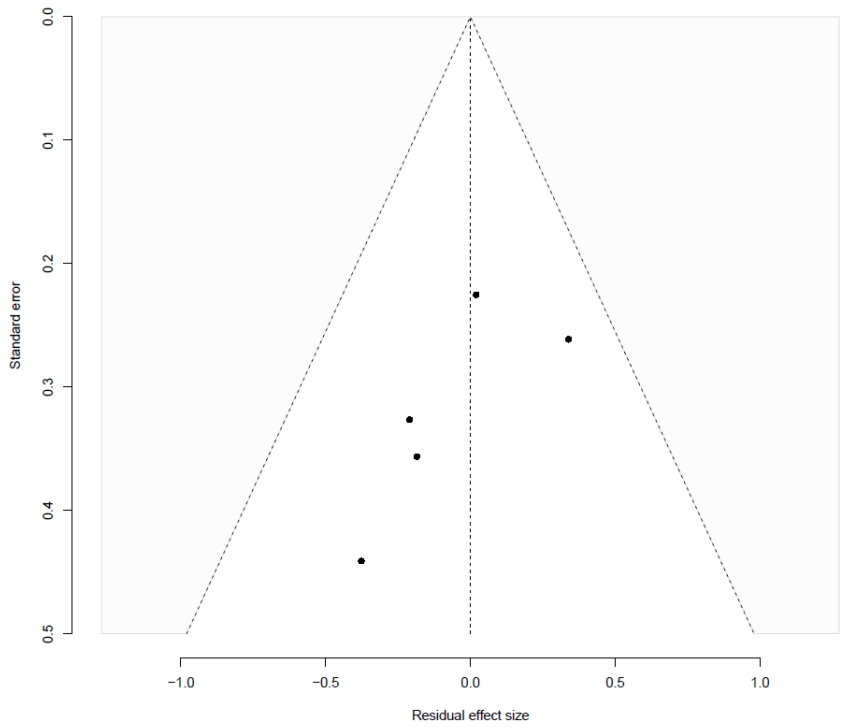

Figure A4 Funnel plot for the TMT-A.