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THESIS TITLE: Cognitive biomarkers in late-onset psychiatric disorders at high risk for dementia

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Abstract

Background: Psychiatric disturbances of neurodegenerative diseases were the main topic of this project. Two perspectives were considered: (1) the psychiatric onset of undiagnosed neurodegenerative diseases. (2) the neuroanatomical basis of psychosis.

Aim: (1) to study a cohort of patients with late-onset psychiatric symptoms, assessing baseline clinical characteristics, cognitive profiles and longitudinal follow-up to determine the frequency of a diagnosis of neurodegenerative diseases according to standardized criteria. (2) to investigate structural, functional and metabolic changes in DLB patients with and without visual hallucinations (VH).

Methods: (1) 78 subjects with late-onset psychiatric disorders were prospectively enrolled at Neurology Clinic of Padova Hospital and Casa di Cura-Parco dei Tigli. An epidemiological analysis was performed evaluating the prevalence of neurological diseases versus primary psychiatric disorders at admission and after clinical evaluations and follow-up. A principal component analysis (PCA) was conducted in the whole group using the minimum complete cognitive dataset. We compared neuropsychological tests' results between the group of patients with neurological diseases and with PPD. We further investigated differences between types of neurodegenerative diseases i.e. DLB, bvFTD, AD and PPD. We validated the results of the analysis on a subsample of patients that received a biological diagnosis of neurodegenerative biomarkers (n=32). (2) DLB patients were enrolled and divided into VH and non-VH. They underwent T1w-MRI to measure CT, whole-brain DTI, single tract microstructural properties and rs-fMRI of the default mode, dorsal and ventral attention, and visual networks. We acquired FDG-PET data to investigate brain metabolic connectivity applying the graph theory and cerebellar activity.

Results: (1) Almost 50% (n=42) of the full cohort of patients received a diagnosis of neurological disorders (mainly neurodegenerative diseases). Considering the psychiatric phenotypes at presentation, 50% of patients with major depression would have been classified with a neurological disorder after baseline assessment and follow-up, 33% of BD, almost 100% of psychosis and 66% of OCD (CHI2 = 7.5, $p<0.01$). The multivariate analysis showed worse cognitive performances in psychotic patients compared to

patients with affective disorders. There were different cognitive profiles between AD and DLB groups versus FTD-PPD. TMT-A test and prose memory-delayed test scores were significantly worse in dementia group compared to PPD ($p<0.01$). (2) We found lower FA in the right inferior and superior (ventral part) longitudinal fasciculi (ILF and SLF) ($p<0.05$, corrected), and greater MD ($p <0.05$), that correlated with the severity of VH ($r =0.55$, $p<0.01$; $r =0.42$, $p<0.05$, respectively). CT in the projection areas of the right SLF was significantly reduced ($p<0.05$). Patients with VH also showed an altered functional connectivity in the ventral attention network ($p<0.05$). The mean 18F-FDG-PET SUVr values of parcels belonging to the visual and dorsal attention networks were significantly lower in the VH group ($p=0.01$). Metabolism in the right temporoparietal cortex correlated with VH severity ($R=-0.58$; $p<0.01$). VH patients showed weaker metabolic connectivity in the parietal, temporal, and occipital cortex of the default, dorsal attention, and visual networks, but more robust connectivity in the right insula and orbitofrontal cortex. A lower global efficiency characterized the VH group, except for ventral attention and limbic networks.

Conclusion: (1) Late-onset psychiatric symptoms mask a diagnosis of neurodegenerative disease in about 50% of cases. We encourage multidisciplinary evaluation in the assessment of late-onset psychiatric manifestations and suggest some clinical and cognitive red flags to help with differential diagnosis. (2) combination of microstructural, functional and metabolic alterations involving the attention networks in the right hemisphere may be important in the genesis of VH.

Introduction

Mood disorders and dementia

The growing of the mean population age and the percentage of elderly around the world rises the prevalence of dementia disorders and cognitive impairment, that are age-related conditions. Mood disorders and dementia are two of the most common neurological conditions in the elderlies.

Looking at the most frequent neurodegenerative diseases manifesting with dementia, e.g. Alzheimer disease (AD), dementia with Lewy Bodies (DLB) and frontotemporal dementia (FTD), it is well known that mood disorders may often occur during the course of the disease. More than 80% of patients with dementia present at least one neuropsychiatric symptom the beginning of cognitive impairment through disease course (Lyketsos CG et al. 2002).

These neurodegenerative diseases are characterized by brain changes of frontotemporal cortex, important in the control of emotions, and of limbic structures, such as the amygdala, anterior insula, and anterior cingulate cortex that are crucial in the production of emotions. These disorders are also associated with alterations in the neurotransmitter systems that regulate the computational properties of the cortico-limbic networks that are engaged in emotional processing. The resulting alterations in emotion and mood can include depression, anxiety, hypo-emotionality, loss of empathy, and a number of less frequent emotional disturbances.

Depression and anxiety are the most common psychiatric symptoms associated with neurodegenerative disease, particularly in AD (Woolley JD et al. 2011). Up to 75% of patients with AD experience depression or anxiety as part of their neurodegenerative disorder (Sturm VE et al. 2013). Bipolar disorder (BD) with manic, hypomanic, or manic-like behaviour appears primarily in association with FTD. In addition, patients with FTD may have severe loss of emotion and empathy, a core criterion for the diagnosis of behavioural variant FTD (bvFTD). AD and FTD may be associated with several other disorders of emotion. Episodic emotional behaviours, such as emotional dysregulation with agitation or aggressive outbursts, are common in moderate-to-severely advanced dementia. These outbursts reflect decreased impulse control and often occur in the

presence of precipitating factors such as pain or discomfort, metabolic disturbances, adverse pharmacological effects, or frustration with impairments.

In DLB patients mood disorders are very common, even in the prodromal stage of the disease, along with delusions and disperceptions e.g. visual hallucinations (VH). Recurrent complex VH are a core feature pointing to the diagnosis of DLB (McKeith IG et al. 2017). They occur in about 60% of suspected cases of DLB (Aarsland D et al. 2001), and are considered a strong predictor of this condition (Tiraboschi P et al. 2006).

Therefore, late-onset psychiatric disorders are key symptoms of dementias and their correct interpretation in a more complex neurodegenerative disease is important because of they could lead to early institutionalization, hospitalization and interfere with treatment effect and prognosis (Lyketsos CG *et al.* 2002).

Depression, Anxiety, Apathy, and dementia

Alzheimer Disease

Depression is the most common neuropsychiatric symptom among patients with AD (Woolley JD *et al.* 2011; Galts CPC et al. 2019).

The prevalence of depression was reported in a wide range in literature because of the different diagnostic criteria used (Chi S et al. 2014), but recently an extensive metanalysis shows a prevalence of about 30%–40%, and depression is most evident within 3 years from the onset of cognitive impairment (Zhao QF et al. 2016). Depression in AD can range from major depressive disorder to milder dysthymic states (Galts CPC *et al.* 2019). Most studies agree that the most common symptom of depression in AD are dysphoria and loss of interest (Olin JT et al. 2003). Major depression in the setting of AD is associated with increased hospitalizations and a higher mortality rate (Lara E et al. 2016). On autopsy, patients with AD and depression, appear to have more severe neuropathology and greater amyloid deposition and ischemic vascular burden compared to those without depression. There is also a greater loss of serotonin receptors and reduction in serotonin transporters binding. The presence of depression is a risk factor for the development of AD (Burke AD et al. 2019). Patients with atypical

forms of AD, such as posterior cortical atrophy, in which there is relatively preserved insight, may be especially susceptible to depression.

Depression is often associated with apathy and the loss of interest or motivation. These symptoms increase their frequency through the progression of disease, from 42% in early stages to 90% in severe AD (Mega MS et al. 1996).

On the other hand, anxiety is also a common problem in patients with AD. The prevalence of anxiety disorders is 5%–21%, and anxiety symptoms are observed in 8%–81% of patients (Lyketsos CG et al. 2001; Kaiser NC et al. 2014). A meta-analysis of 48 studies using the Neuropsychiatric Inventory (NPI) questionnaire reported a pooled prevalence estimate of anxiety in AD of 39% (95% CI 32%–46%) (Zhao QF *et al.* 2016). Initial or prodromal anxiety is more prevalent among patients with young-onset AD than among those with late-onset (Porter VR et al. 2003; Kaiser NC *et al.* 2014). As dementia progresses, however, symptoms of anxiety can increase among those with typical late-onset AD, usually in association with comorbid psychiatric and behavioral symptoms such as psychosis and agitation (Hynninen et al., 2012; van Vliet et al., 2012; Tanaka et al., 2015). Anxiety in the middle or late stages of AD may manifest as agitation and signs of emotional distress, such as inappropriate or excessive vocal or motor activity.

Dementia with Lewy Bodies

Despite depression is not one of the core features for the diagnosis of DLB and patients experienced mainly symptoms of the psychosis spectrum, previous studies show that depression is common in DLB. A cluster of symptoms of depression, anxiety and apathy is included among the clinical suggestive features of DLB or MCI- Lewy bodies. It has been descried a higher prevalence of depression in DLB than in AD (Ballard CG et al. 2001; Ballard CG et al. 2004). The features of depression, anhedonia, sleep disruption, and worthlessness are similar in DLB and AD but they are more severe in DLB (Chiu PY et al. 2017). The neural substrates underlying depression in DLB and AD may be different. The major neurochemical difference between AD and DLB is in the dopaminergic neurotransmission. A postmortem study of brains from patients with Parkinson disease (PD), DLB, or AD, and elderly controls showed reduction of dopamine concentration in the putamen of DLB and PD patients, while there was no change in AD

patients (Piggott MA et al. 1999). Besides a dopaminergic metabolism, the serotonergic system also differs between DLB and AD. These studies revealed that marked reduction of serotonin levels have been reported in the striatum, neocortex and frontal cortex; however, DLB patients with major depression had relatively preserved 5HT transporter re-uptake sites, compared to those without (Ballard C et al. 2002; Sharp SI et al. 2008).
Anxiety is often associated with depression in DLB and it is present in more than half patients with DLB, the second symptom following psychosis (Borroni B et al. 2008) and there is evidence that it could be a risk factor for developing DLB (Boot BP et al. 2013)

Behavioural variant of fronto-temopral dementia

Patients with bv-FTD feel mainly hypoemotionality or emotional blunting such as apathy, abulia, and loss of empathy and sympathy, as well as a decline in executive and other cognitive abilities (Lanata SC and BL Miller 2016). Diagnostic criteria for bvFTD include many behaviors suggesting hypoemotionality, including decreased engagement in previously rewarding activities, inability to initiate or sustain conversations, diminished responses to other people's needs and feelings, and absence of personal warmth (Rascovsky K et al. 2011). Hypoemotionality also affects their lack of disease insight. This condition has a significant impact on caregivers, who report adverse effects on their own health (Brown CL et al. 2020).
A recent systematic review shows that apathy is the most frequent symptom in FTD (ranging 50-100%), mostly in the bv-FTD (range 73-100%), followed by depression (range 22-52%) and anxiety (range 10-53%). (Collins JD et al. 2020).
Mood disorders may be due to deficits of general emotional processing related to atrophy or hypoactivity of core structures affected by bvFTD-related neuropathology, such as the anterior insula and the pregenual and middle regions of the cingulate cortex, particularly on the right (Caminiti SP et al. 2015). All of these structures are components of the Salience Network. Previous studies showed the crucial role of the limbic circuit that includes the orbitofrontal cortex, uncinate fasciculus, anterior temporal lobe, the amygdala, and connected regions of the thalamus for mediating emotions (Sturm VE et al. 2018).

Psychosis and dementia

Alzheimer Disease

In AD psychotic symptoms are common and they are estimated to occur in approximately one third to one-half of patients with a point prevalence of approximately 10% per year (Fischer CE and RA Sweet 2016). Moreover, recent research suggests that their presence may be associated with dramatically worse outcomes compared to patients without psychosis, in terms of rates of conversion from MACI to dementia, mortality, caregiver burden, and accelerated cognitive decline (Ballard C et al. 2020). Psychosis usually includes delusions (frequently persecutory) and hallucinations (mostly visual), and they usually overlapped with mood disorders such as apathy and or other negative symptoms (Assal F and JL Cummings 2002). Zhao and colleagues in a systematic review showed in 10.526 persons a prevalence of delusions ranging from 9% to 59%. The overall pooled prevalence of delusion was 31%. Hallucinations were reported with a prevalence in a range from 16% (Zhao QF *et al.* 2016) and 23% (Ballard C *et al.* 2020).
As regard delusions we can identify two main categories: persecutory (such as the delusion of theft) or misidentification (such as a persistent belief that someone well known to the patient is someone else) (Rubin EH et al. 1988; Ropacki SA and DV Jeste 2005). Delusions may introduce as phantom boarders (the belief that the house is occupied by strangers), mirror delusion (belief that someone in the mirror is a different person), and Capgras syndrome (the belief that a person is not who they appear to be but rather an imitation). In some case patients may exhibit delusions of abandonment and infidelity may also be observed. Delusions in AD are less likely to be bizarre in quality compared to some primary psychiatric disorders like schizophrenia (Jeste DV et al. 2005).
Hallucinations, mainly visual, are the other symptom leading to psychosis in AD. Previous works shows an onset in advanced stage of the disease, suggesting that delusions and hallucinations are the same symptom but expressed differently depending on the severity of disease. Patients with more advanced cognitive decline may be more likely to be diagnosed with hallucinations as they may no longer have the cognitive ability to express delusions (Fischer CE and RA Sweet 2016).

Psychotic symptoms are frequently distressing for the individual and their caregivers and are associated with poorer disease outcomes. Psychosis is also associated with more rapid progression of functional impairment, hospital admissions, earlier admission to institutional care and increased mortality. It has also been reported that psychosis at disease onset is associated with increased dependency, independently of cognitive decline. In addition, psychotic symptoms are often antecedent to or comorbid with other neuropsychiatric symptoms like agitation, aggression and depression, further adding to the impact on the individual and others (Lyketsos CG *et al.* 2001).

Fisher and colleagues recently overviewed the neurobiological basis of psychotic symptoms in AD, that nowadays remains largely unclear. In fact, in this review emerged that there is a gray matter loss in frontal areas, cingulate gyrus and precuneus in patients with dementia and psychotic symptoms; many studies demonstrated hypoperfusion to the frontal cortices and prefrontal regions; it was highlighted that psychosis in AD may be heritable. There are also numerous studies that have examined the role of chemical neurotransmitters in various brain regions and how they correlate with the presence of psychotic symptoms in AD, but mechanism remain largely unclear (Fischer CE and RA Sweet 2016).

Dementia with Lewy bodies

Psychosis in the spectrum of a-synuclein pathologies is a very common symptom. In particular VH are one of the core criteria for the diagnosis of DLB (McKeith IG *et al.* 2017), and often VH are the presenting symptom highly suggestive symptom of a-synucleinopathy (Tiraboschi P *et al.* 2006). Up to 80% of DLB patients suffer from complex VH (McKeith IG *et al.* 2017). In DLB psychotic symptoms lead to higher risk of hospitalization and death (Capouch SD et al. 2018) and caregiver burden than in AD patients, e.g. increased incidence of stress and depression in caregivers (Schrag A et al. 2006).

VH are often described as people, children, or animals. Other visual perceptive symptoms such as flashing lights, visual patterns, and shadows have been reported. Patients may respond to these hallucinations with varying degrees of insight and

emotional reaction. These complex neuropsychiatric symptoms, including also delusions, and diurnal rhythm disturbances, are exacerbated by anticholinergic activity as these disorders worsen (Hori et al., 2016). In fact, cholinergic changes appear to be the most pronounced in the occipital region, which may contribute to the VHs that are commonly described in DLB (O'Brien JT et al. 2008). The vividness of these VHs in patients with DLB and PDD are suspected to be a result of the significant Lewy body pathologic burden within the inferior temporal cortex, parahippocampal cortex, and amygdala (Cagnin A et al. 2013). (For detailed revision of VHs mechanisms in DLB see further "Neuroanatomical basis of Psycosis – model VH in DLB").

Delusions, false beliefs that run contrary to the evidence, are less frequent in patients with DLB compared to VHs, some work estimate up to 40% of patients (Borroni B *et al.* 2008). They range from misidentification to paranoia, infidelity, and abandonment. Capgras syndrome, which is the belief that a familiar person (spouse or children) has been replaced by an imposter, is common in patients with DLB. Patients with Capgras delusions reported more anxiety and had worse behavioral ratings (Tousi B 2017).

Behavioural frontotemporal dementia

Although the most frequent variant of FTD, bvFTD, is characterized by behavioral symptoms such as mood changes, depression, and psychotic symptoms, it is relevant that these symptoms are not part of any established clinical FTD criteria (Rascovsky K *et al.* 2011).

In literature previous studies showed a low prevalence of psychotic symptoms in FTD compared to other dementia (Shinagawa S et al. 2014) , but other studies have found a higher proportion of patients with psychotic features as part of FTD symptomatology (Mendez MF et al. 2013). In the last years some authors estimated the prevalence of psychotic symptom in FTD in about 10% and highlighted that this prevalence was higher in some specific molecular and genetic subgroups of FTD (Shinagawa S *et al.* 2014). A recent study investigates psychosis in the amyotrophic lateral sclerosis (ALS) -FTD spectrum disorders and highlights that half of the patients with C9ORF72 mutations have psychosis. Psychosis in these patients were correlated with atrophy of prefrontal

cortex, bilateral superior temporal gyrus and inferior frontal, anterior thalamus gyrus. Authors speculate that the involvement of somatosensory body schema processing and an alteration in thalamo-cortico-cerebellar network may be involved in the development of psychosis (Devenney EM et al. 2021) underling also a possible contribution of the cerebellum in internal monitoring. These hypotheses are supported by previous work that studied carriers of FTD-related mutations which have impaired somatosensory body scheme processing (Fusar-Poli P et al. 2012).

As regard the type of psychotic symptom, a study in neuropathologically verified FTD population showed that the prevalence of hallucinations and delusions were similar, about 17%; paranoid ideas were seen in 20% (Landqvist Waldo M et al. 2015).

Delusion in bvFTD may assume specific feature that differ from other dementia; i.e. delusions of grandiosity is associated with the C9orf72 (Shinagawa S et al. 2015). In contrast, delusions associated with AD are often of a paranoid nature, such as delusions of theft or persecution, and may be associated with volume loss in the right hippocampus (Geroldi C et al. 2000).

A recent study suggests that specific content of hallucinations and delusions may be associated with a specific dementia and can help clinicians to predict specific type of dementia. Patients with DLB and AD were more likely to have visual misperceptions, and hallucinations that are shapeless, peripheral and with images that moved, in addition to well-formed hallucinations, and were more likely to experience the feeling of presence. Delusions of misidentification occurred more frequently in patients with DLB/AD and patients with FTD-TDP. Furthermore, patients with FTLD-TDP were more likely than those with any other pathology to report paranoid delusions, as well as delusions that were self-elevating, including grandiosity and erotomania (Naasan G et al. 2021).

Bipolar disorder and dementia

Considering bipolar disorder (BD), we need to focus the attention into the so-called late onset BD (onset age >50y). In literature is well described there is a complex link between BD and bvFTD (Papazacharias A et al. 2017), both clinically and neuroanatomically.

Some patients with bvFTD can look like patients with BD, manifesting manic-like behaviour, such as euphoria or emotional outbursts, excessive or pressured speech, racing thoughts, compulsive task-oriented behaviour, increased energy and psychomotor activity, as well as irritability, distractibility, and disinhibition (Galimberti D et al. 2015). BD was the second most common psychiatric diagnosis and usually occurred in bvFTD, in fact some epidemiologic studies suggest that over 8% of new BD cases occur in geriatric patients (Woolley JD *et al.* 2011). Symptoms of bvFTD such as euphoria, disinhibition, impulsivity, poor decision-making, and compulsive behaviors (Weder ND et al. 2007) are similar to those seen in primary mania, which may lead to diagnostic confusion. In literature are described bvFTD patients with a look similar to bipolar disorder on initial presentation (Ibanez N 2012). This overlap in symptoms of BD and bvFTD suggests possible shared origins and mechanisms between these two disorders and raises the question of whether BD precedes or leads to bvFTD (Nascimento C et al. 2019)

Late onset OCD and dementia

Obsessive-compulsive disorder (OCD) is defined as recurrent and persistent thoughts and behaviors, urges or impulses, experienced as intrusive and unwanted. Repetitive or mental acts that the individual feels driven to perform in response to an obsessive thought. These disturbs are time-consuming, cause distress and impair social life (Luigjes J et al. 2019). OCD usually has a young or adult-onset, so a late-onset of OCD in the elderly might represent a very challenging diagnostic and therapeutic issue for clinicians regarding the differential diagnosis between primary psychiatric disorder and initial neurodegenerative disease (Ducharme S et al. 2020).

Repetitive or obsessive-compulsive behaviour are relatively common in patients with FTD. Since 1994 Ames and colleagues highlight in a series of 46 pathologically proven FTD patients that 78% displayed repetitive behaviours, ranging from simple motor stereotypies to complex obsessions and compulsions. Moreover, the repetitive behaviours begin early in the course and obsession and compulsion are sometimes the presenting manifestation (Ames D et al. 1994). Stereotypic and ritualistic behaviors are

more common in the frontal and semantic variants of FTD compared with Alzheimer's disease. Behavioral disorders are frequent during the disease. Obsessive and compulsive (OC) symptoms are present in 30% of patients during the clinical course of semantic dementia, however, are rarely the symptoms of onset without accompanying cognitive deficits (Hodges JR and K Patterson 2007).

As regard OCD in typical AD and behavioral variant of AD, in literature we can find only few cases of patients with OCD symptoms. A case report was recently published by Ruggeri et al. of a women suffering of late-onset OCD with contamination obsessions and washing compulsions as isolating symptomatology of behavioral variant AD (Ruggeri M et al. 2022).

The challenge of disentangling neurological and psychiatric diagnosis

In the last decades there are growing evidence in clinical practice that mood disorders may be the symptoms of onset in neurodegenerative diseases. Progressive cognitive impairment and functional decline have been established as typical clinical hallmarks of dementia in neurodegenerative diseases; neuropsychiatric symptoms are also considered an intrinsic condition associated with neurodegenerative processes (McKhann GM et al. 2011). However, these latter symptoms have been less emphasized in the prodromal stages of dementia. Recognition of psychiatric disorders can facilitate the recognition of dementia cases, their prompt diagnosis, and, in turn, tailored clinical care (Onyike CU 2016).

Considering one of the most representative dementia with mood disorders at onset, behavioural variant of fronto-temporal dementia, since the mid-2000s some studies identified a subgroup of patients with the clinical characteristic of bvFTD but without the expected dementia progression in the follow-up (Davies RR et al. 2006; Kipps CM et al. 2008). The interest in this subgroup of patients grew during the following years looking at neuropsychiatric disorders as onset of a possible dementia and not only as manifestation along the disease course. In 2007 Hallam and colleagues identify three frameworks for the clinical identification of prodromal FTD: (1) cognitive profiling, (2) the presence of behavioral/psychiatric symptoms in the absence of memory complaints,

and (3) a combined approach of cognitive, behavioral, and neuroimaging features (Hallam BJ et al. 2007). In 2015 in a study on psychotic symptoms in a large FTD cohort Waldo and colleagues showed that only 14.4% of the patients were initially diagnosed as FTD, but subsequently 78% received a diagnosis of FTD and the median time from symptom debut to FTD diagnosis was four years. Moreover, they found that about 40% of patients with a final diagnosis of FTD received a first diagnosis of psychiatric disorder, with dramatic consequences on a medical and social manner. The study highlights the importance of educational interventions for general psychiatrists and other doctors in order to recognize these patients (Landqvist Waldo M *et al.* 2015).

There is evidence in literature of symptoms overlap between FTD and psychiatric disorders such as major depressive disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, autism spectrum disorders and even personality disorders (Ducharme S et al. 2015). “Late-onset” variants occurring between 40 and 50 years of age, which represents the peak age of onset for FTD, that can make difficult the differential diagnosis and ultimately modify the prognosis of the disorders, mainly secondary to delayed and incorrect diagnosis and lack of treatment effect. Development of symptoms in the third decade of life or a family history of a highly penetrate illness should raise concern for an underlying ND (Woolley JD *et al.* 2011).

Nevertheless, an early diagnosis of FTD in patients with or without pre-existing psychiatric disorders is the main and most important objective of clinicians to help families to implement more specific caregiving strategies and provide more informed and overall better management to their patients (Galimberti D *et al.* 2015).

The interest into behavioral onset of dementias rises up progressively and the concept of mild behavioral impairment (MBI) has been described to enhance awareness concerning NPS as an early manifestation of AD and other types of dementia (Ismail Z et al. 2016).

Recently as regards the differential diagnosis of FTD from primary psychiatric disorder Ducharme and colleagues proposed a diagnostic flow to improve the diagnostic process. They emphasized the importance of high-resolution 3D-T1 brain MRI with a standardized review protocol with validated visual atrophy rating scales, and to consider volumetric analyses if available in one hand, and social cognition test on the other.

Despite the application of optimal clinical investigations, some patients remain with ambiguous diagnoses. In those cases, longitudinal follow-up often becomes the diagnostic arbiter until pathology is available (Ducharme S *et al.* 2020).

In AD although memory loss is usually the primary presenting complaint, in some cases other forms of cognitive impairment can be a significant concern early in the disease. These may involve speech problems such as difficulties with finding words (anomic aphasia), decreased planning ability, or psychiatric and behavioural changes such as agitation and delusions (Burns A and S Iliffe 2009). In 2010 Davier et al. suggested that depression is the presenting symptom in a proportion of patients with AD and mild cognitive impairment (MCI) (Devier DJ et al. 2010).

To improve the recognition of neuro-psychiatric symptoms in AD, consensus criteria have been developed for apathy (Robert PH et al. 2010), psychosis (Fischer CE et al. 2020), and depression (Olin JT *et al.* 2003). Despite the growing knowledge on the prevalence and diagnosis of neuro-psychiatric symptoms, AD is still primarily considered a cognitive disorder in clinical practice and therefore AD is often not considered in cases in which psychiatric symptoms emerge in late adulthood, resulting in misclassification of AD as psychiatric conditions. A large cohort study of 252 patients with various form of neurodegenerative disease shows early dementia symptoms may mimic psychiatric symptoms, leading to psychiatric misdiagnosis. an average 28% received a diagnosis of psychiatric disorder prior to neurodegenerative disease. Furthermore, the authors highlight the misdiagnosis vary depending on the disease, from a range > 12% in neurodegenerative disease such as cortico-basal syndrome to 23% in AD and 50% in bvFTD (Woolley JD *et al.* 2011).

Evidence in literature remarks the challenging of diagnosis in late onset neuropsychiatric symptoms because of the potential overlap with the neurodegenerative conditions and due to a lack of accurate biomarkers.

Although the underlying neuropathological hallmarks are the same, there is some evidence that there are differences in aspects of the disease between early-onset AD (EOAD) and late-onset AD (LOAD). Neuropsychiatric symptoms are higher in EOAD mainly anxiety and depression (Baillon S et al. 2019).

Neuroanatomical basis of Psycosis – the model of VHs in DLB

Visual hallucinations (VH) are visual experiences not elicited by external stimuli. They are common in numerous pathological conditions, including: ocular diseases (ffytche DH and RJ Howard 1999; ffytche DH 2009; Schadlu AP et al. 2009); epilepsy (Panayiotopoulos CP 1999; Saha R et al. 2016; Duarte Mangas M et al. 2017); primary psychiatric disorders with psychosis (Goodwin DW et al. 1971; Bracha HS et al. 1989; Baethge C et al. 2005); and neurodegenerative diseases (Fenelon G et al. 2000; Williams DR et al. 2008; Diederich NJ et al. 2009; Cagnin A *et al.* 2013; Urwyler P et al. 2016).

As reviewed by ffytche (ffytche DH 2008), the literature on VH originally focused on the abnormal functioning of specific brain regions, such as the occipital lobe, and the role of topological hyperfunction (Panayiotopoulos CP 1999; Holroyd S et al. 2000). There is plenty of evidence of VH being associated with transient increases in activity in localized cortical regions, and the specialization of the regions affected decides the content of the VH. Indirect evidence comes from patients experiencing types of VH that relate to their abilities that are still intact, not to those they have lost (ffytche DH et al. 2004; Hubl D et al. 2007). In many brain diseases, VH are characterized mainly by recurrent complex visions (seeing objects, animals and human beings, for instance), rather than simple VH such as seeing dots, lines, flashes, and amorphous shapes (Collerton D et al. 2005). A topology-based approach seems unable to explain the complexity of the symptoms adequately, so a functional model has been proposed that emphasizes the altered integration and segregation of information, and the neural activity involved in promoting efficient information processing (Park HJ and K Friston 2013). This "hodological" view has been applied to neuropsychological theories of VH, according to which they would result from: an abnormal processing of visual information combined with an impaired top-down monitoring of visual attention (Collerton D *et al.* 2005); or from an imbalance between the dorsal and ventral attention networks (Shine JM et al. 2011; O'Brien J et al. 2020). In the last two decades, attention and visual perception networks have been elucidated both anatomically and functionally, and the activity and interaction between networks have been investigated (Corbetta M and GL Shulman 2011; Thiebaut de Schotten M, F Dell'Acqua, et al. 2011; Bartolomeo P et al. 2012). It

has emerged that dorsal and ventral attention networks have different functions, and functional localizations. The dorsal attention network has a bilateral organization, and is involved in representing contralateral spatial information, and in shifting attention and eye movements. The ventral attention network has a right-hemisphere dominance and is involved in vigilance, in re-orienting attention to sensory-driven or behaviorally-relevant stimuli, and in task resetting (Corbetta M and GL Shulman 2002; He BJ, AZ Snyder, et al. 2007).

As concerns structural connectivity, the inferior longitudinal fasciculus (ILF) bi-directionally connects the occipital regions to the medial and lateral anterior temporal lobes. It is involved in processing visual emotion and visual memory information (Latini F et al. 2017). The inferior fronto-occipital fasciculus (IFOF) connects regions of the occipital and ventral frontal lobes. Connections between the visual part of the parietal lobe and the frontal cortex are via the superior longitudinal fasciculus (SLF), while those between the occipital and limbic cortex are via the cingulum and the ILF. The SLF and IFOF contain projections of neuronal networks involved in processing visual attention, visual working memory, visual praxis, visuo-vestibular function, and eye movement control (ffytche DH et al. 2010).

These methods are only indirectly related to neuronal activity and energy consumption, which are affected by neurodegeneration. The 18F-Fluorodeoxyglucose PET method measures glucose metabolism directly related to the level of neuronal activity.

Cellular metabolism is depressed in the parieto-occipital cortex of DLB patients (Nobili F et al. 2018). However, the correlation with VH is more controversial, with some studies reporting decrements in the right occipito-temporal and frontal cortex (Perneczky R et al. 2008) or bilaterally in the frontal cortex (Morbelli S et al. 2019), while others have reported increased metabolism in the temporal and parietal regions (Imamura T et al. 1999).

A relative novel measure of functional interaction closer to cellular activity is the co-variation of glucose metabolism across brain regions, i.e., metabolic connectivity. Two regions showing correlated glucose metabolism levels across subjects can be assumed to interact functionally (Passow S et al. 2015). There have been only a handful of studies that used connectivity models of 18F-FDG PET data in DLB. These studies have reported

altered metabolic connectivity in DLB patients with VH within the visual (Iaccarino L et al. 2018), dorsal attention and salience networks (Iaccarino L *et al.* 2018; Sala A et al. 2019). Graph theory allows us to study complex networks' features in data obtained with EEG and fMRI (Bullmore E and O Sporns 2009). In the case of metabolic connectivity, graph methods exploit the covariance matrix of the mean uptake value from a region of interest to all other regions across a sample of subjects (Horowitz MJ 1964). The application of covariance statistics and network-based methods has good reproducibility and applicability when applied to PET data to characterize pathological conditions (Veronese M et al. 2019).

Aims of PhD project

The main topic of this project are psychiatric disturbances in neurodegenerative dementia. Two perspectives were considered: on one side the psychiatric onset of undiagnosed neurodegenerative disease an on the other the neuroanatomical basis of psychosis. For the latter subject the paradigm of visual hallucinations in dementia of Lewy bodies was chosen and prototypical and based on theoretical frameworks.

The aims of this project could be therefore summarized as following:

1. To investigate epidemiology, clinical and cognitive traits of psychiatric onset of neurodegenerative dementia, specifically:
    a. to explore the frequency distribution of psychiatric onset of three different types of neurodegenerative diseases (Alzheimer disease, dementia with Lewy bodies and behavioural frontotemporal dementia) in a cohort of patients with late atypical first-time psychiatric symptoms admitted to a psychiatric inpatients/outpatients clinic.
    b. to explore the cognitive profile of these patients respect to those with primary psychiatric disorders.
2. To investigate the neuroanatomical and functional basis of visual hallucinations in dementia with Lew bodies.

Experiments

Study 1: psychiatric onset of dementia

Part 1: observational longitudinal study on a cohort of patients with late atypical first-time psychiatric symptoms admitted to psychiatric inpatients/outpatients clinic

Neurodegenerative diseases leading to dementia may present with behavioral changes typical of primary psychiatric disorders (PDD) such as major depression and bipolar disorders. The diagnosis of neurodegenerative diseases with psychiatric-onset remains a challenge. A proportion of patients with neurodegenerative dementia (DLB, FTD or AD) present with treatment-resistant affective disorder or psychosis (Devier DJ *et al.* 2010; Ismail Z *et al.* 2016; Baillon S *et al.* 2019; Ducharme S *et al.* 2020).

Objective: We therefore aim studying a cohort of patients presenting at outpatients/inpatients clinic with late-onset atypical psychiatric symptoms, assessing clinical characteristics, cognitive profiles and longitudinal follow-up to determine the proportion of such patients with a diagnosis of neurodegenerative diseases according to standardized criteria.

Methods: This is an observational longitudinal study recruiting 93 patients with late-onset psychiatric symptoms admitted to the inpatients clinic “Casa di cura Parco dei Tigli” and outpatients clinic of neuropsychiatric disorders of “Azienda Ospedale Università di Padova“ between April 2019 and January 2021. Sixteen patients were excluded due to poor compliance of diagnostic work-up and follow-up visits. Seventy-eight patients were completed the study. Inclusion criteria were one of the following psychiatric diagnosis: late onset bipolar disorder over 50 years old (Sajatovic M et al. 2015) or

- late onset depression over 50 years old, including patients with a single past depression episode (20yr before) or
- a late onset psychosis over 60 years old or
- late onset OCD over 50 years old.

Exclusion criteria were past medical history of drug or alcohol abuse (ongoing or past), head trauma, other severe neurological diseases, severe white matter vascular disease (evaluate using imaging applying the Fazekas scale) and absence of available past medical history.

At baseline all patients underwent evaluation by an expert evaluation in order to define the diagnosis according to the DSM-5. The scales used to achieve diagnosis were SCID5 interview, Hamilton depression scale (Hamilton M 1967) and Clinical Global Impression scale (CGI) (Busner J and SD Targum 2007). Subsequently each subject underwent a neurological assessment collecting family history for neurological and psychiatric diseases, medications history, standard neurological examination, including the motor UPDRS scale, assessment of RBD with the RBD single question screening questionnaire (RBDsq), and fluctuations with the Clinician Assessment of Fluctuation (CAF). All patients underwent to an extensive neuropsychological assessment including: a global cognitive screening with Mini Mental State Examination test (MMSE); assessment of attention and working memory through the digit span forward and backward and the Trial Making A for the evaluation of working memory, phonemic and semantic fluency test for language, prose recall immediate and delayed for memory assessment, Rey-Osterrieth Complex Figure for visual-constructional abilities and visual memory, Stroop test (Cagnin A *et al.* 2013). The functionality of daily living were investigated using specifically theKats index of independence in activity of daily living (ADL) (Shelkey M and M Wallace 1999) and instrumental activity of daily living with Lawton instrument activity in daily living (IADL) (Graf C 2008). In the second level we collected prose memory.

All patients performed MRI scan to exclude other causes of psychiatric symptoms (stroke, tumor, CNS vasculitis, etc). A group of patients were studied with second level diagnostic investigations, i.e. CSF examination and/or PET-FDG scan. In CSF total tau protein, phosphotau181 and Aβ1-42 were measured using enzyme immunoassays. Each patient underwent at least one follow-up visit (due to multiple covid break-out patients were followed up telephonically) after 12 months from baseline assessment to detect progression or remission of symptoms, the modification of daily living functionalities.

The study was approved by the local ethical committee at Padova Hospital (n. 0038879).

After the clinical follow-up, considering the progression or remission of neurological and psychiatric symptoms and the day-life functions, and the diagnostic work up at baseline, we categorized patients into two main groups: neurological disorder or primary psychiatric disorder (PPD). Diagnosis of neurodegenerative disease were further specified in Alzheimer disease, dementia with Lewy bodies and frontotemporal dementia according to standardized criteria of each disease (Rascovsky K *et al.* 2011; Dubois B et al. 2014; McKeith IG *et al.* 2017).

Statistical analysis was performed using R v3.6.1 (R Core Team, 2019). Continuous variables were tested for normality of distribution and visual inspection of variable histograms and qqplots were performed. Demographic, clinical and neuropsychological features were assessed using analysis of variance, Kruskal-Wallis and Mann-Whitney U test as appropriate. Fisher's Exact test was performed for categorical variables. The significative level was set at $p<0.05$. The exploration analysis was performed using principal component analysis. In this study we consider the first two component that explain about the 70% of the variance of the sample

Multiple independent T-test corrected for Bonferroni was performed to evaluate differences between the two groups.

Results

Seventy-eight patients (48 female and 30 male, mean age of 68.1 ± 9.78 years) were enrolled. The mean age of symptoms onset was 65.2 ± 10.7 years and mean disease duration 2.92 ± 3.8 years.

At baseline the type of psychiatric diagnosis was distributed as follows:

- 49 patients (62.8%; female 71,4%) with a diagnosis of depression,
- 13 patients (16.7%; male 61.5%) with a diagnosis of bipolar disorder,
- 10 patients (12.8%; female 60%) with a diagnosis of psychosis,
- 6 patients (7.8%; male 66.7%) with a diagnosis of obsessive-compulsive disorder.

There was no difference in age, onset, disease duration between the groups. Overall we did find no difference in gender distribution, except from the depression group where there was prevalence of female. See table 1.1 and figure 1.1.

	BD		DEPRESSION		DOC		PSYCHOSIS			
	mean	sd	mean	sd	mean	sd	mean	sd	stat	p
AGE (Y)	63,85	8,83	69,12	10,39	67,67	5,79	69,10	9,40	1,04	0,38
ONSET AGE (Y)	58,85	11,83	66,33	10,76	65,83	5,12	67,60	9,50	0,13	0,12
DISEASE DURATION (Y)	5,17	6,94	2,81	3,19	1,83	1,17	1,50	1,72	2,04	0,11
SEX (F/M)	5/8		35/14		2/4		6/4		6,98	0,07

Table 1.1 Distribution of late-onset psychiatric phenotypes and demographic characteristics

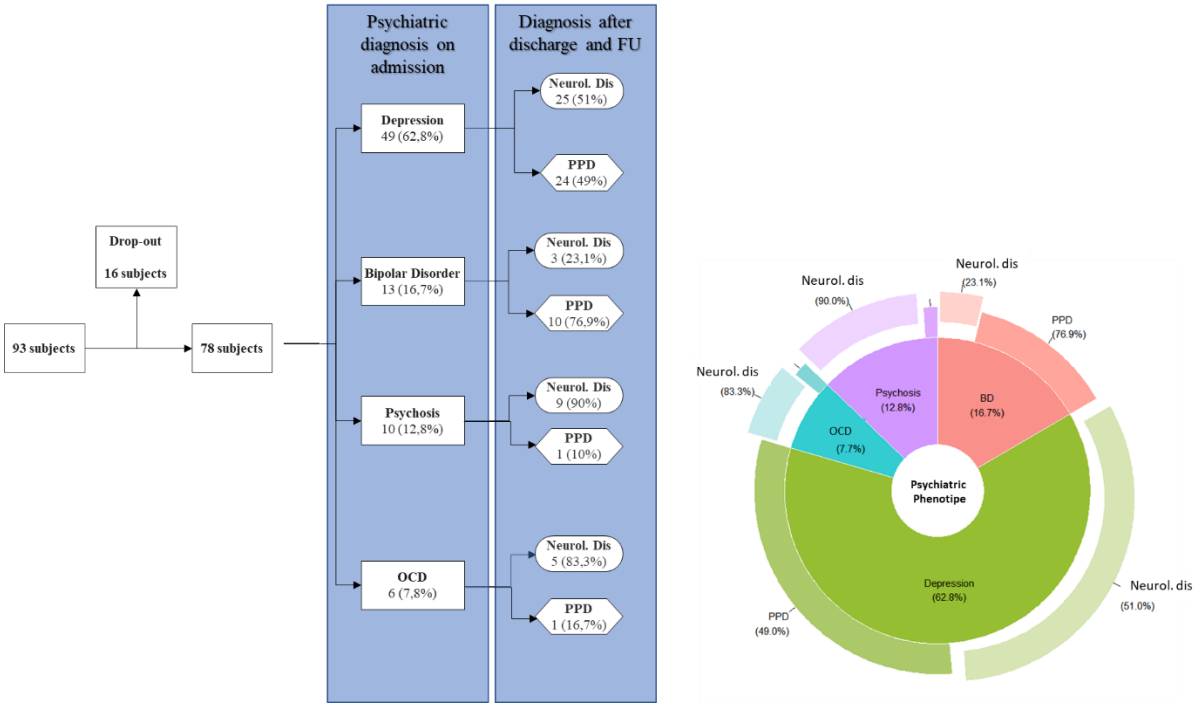


Figure 1.1 Tree plot and donut plot representing patients' diagnosis at admission and at discharge.

42 of 78 of patients with late-onset psychiatric disorders received a clinical diagnosis of neurological disorder, specifically 39 of 78 (50%) with a dementia diagnosis (see Figure 1.2). There was a significant different distribution of psychiatric phenotypes between the group with a diagnosis of neurodegenerative diseases and the group without (primary psychiatric diseases) (Chi2 12.4, p = 0.005). A diagnosis of neurological disorder

was most frequent among patients with psychotic symptoms (90%), and OCD (83.3%) while a diagnosis of PPD was most frequent among patients with a clinical phenotype of bipolar disorder. Patients with depression received a diagnosis of neurological disorder diseases in half the cases.

	Neurological disorder		PPD			
	mean	sd	mean	sd	statistic	p
Age	68,167	10,597	68,083	8,904	0,001	0,97
Age at onset	65,762	10,638	64,556	10,898	0,224	0,623
Duration	2,4	3,365	3,528	4,359	1,612	0,2
Gender (F/M)	25/17		23/13		0,872	1

Table 1.2 Demographic features of neurological disorder and PPD group

Diagnosis of neurological disorder was further specified see figure 1.2. In the entire group of neurodegenerative diseases, the most frequent specific diagnosis was bvFTD (45.2%), followed by DLB (26.2%) and AD (21.4%). Three patients were diagnosed during the follow-up with other form of a possible neurological disorder (e.g. vascular cognitive decline, neoplastic related). bvFTD was the most represented in every group, except from the psychotic one in which DLB was the most represented disease.

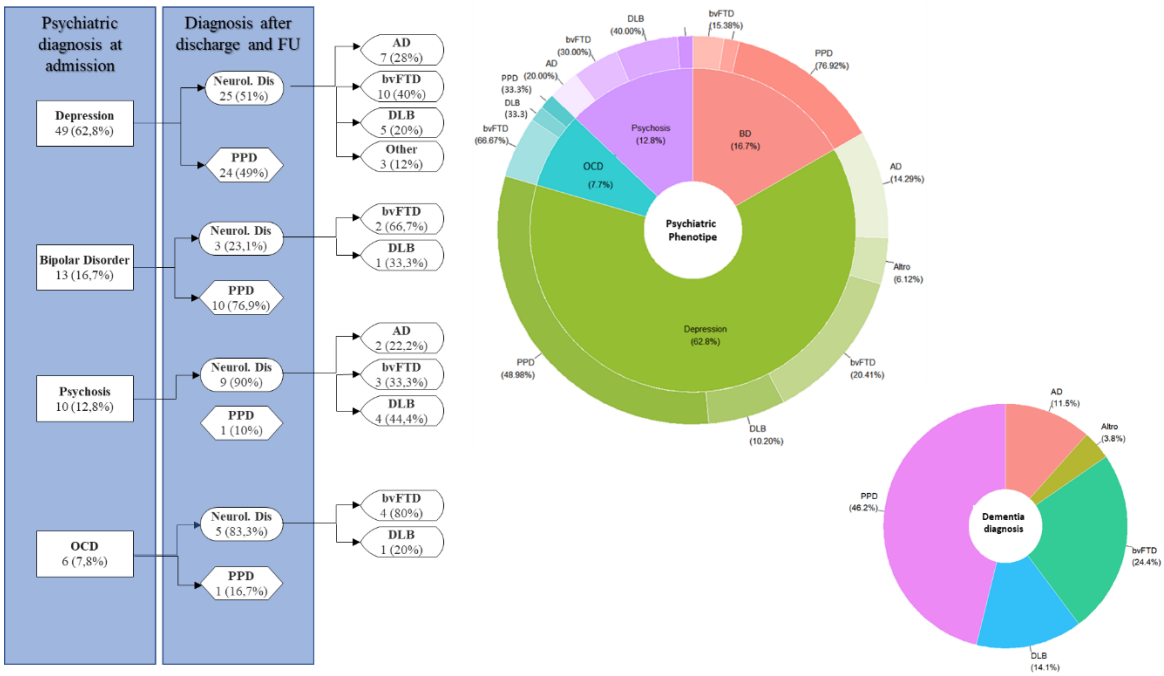


Figure 1.2: tree plot and donut plot of neurological diagnosis classification

A subgroup of 32 subjects (about 41%) of the cohort was studied at baseline with second level diagnostic investigations (i.e. 19 patients PET/FDG, 3 patients CSF study and 10 patients both ones). The distribution of psychiatric phenotypes in this sub-sample is comparable with that in the whole population. Depression was the most frequent psychiatric diagnosis at baseline (43%), followed by BD (28.1%), psychosis (18.8%) and OCD (9.4%). We identify about 70% of patients with depression with a possible neurodegenerative disease. Bipolar disorder was mainly categorized to PPD; on the contrary patients with psychotic onset were all categorized to dementia. The same for OCD group. Overall, in our cohort, we identified 21/32 patients, about 50%, with a clinical profile of a possible neurodegenerative disease, with no significative difference distribution between the groups (Chi2 7.51, p = 0.05). Figure1.3 and table 1.3

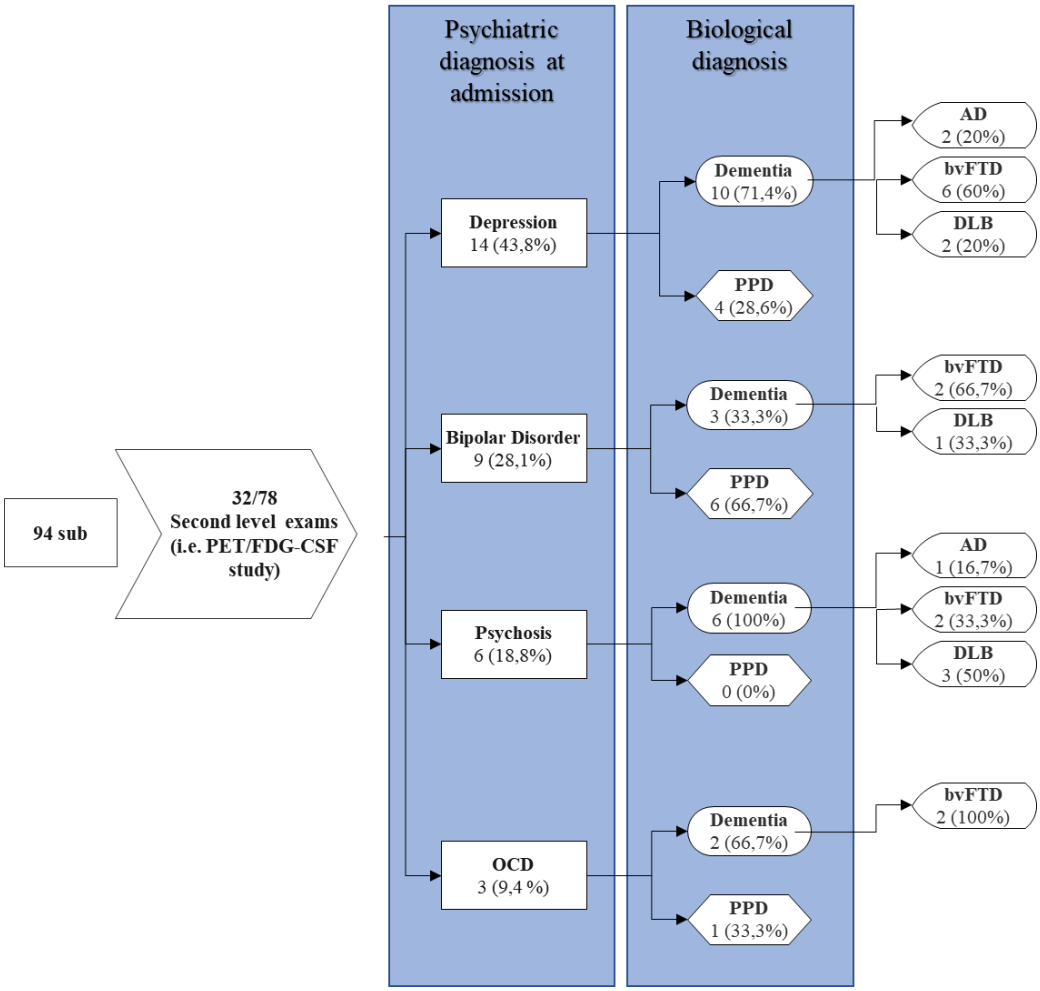


Figure 1.3 Tree plot and donut plot representing patients' diagnosis, who underwent to second level exams, at admission and at discharge

The most represented neurodegenerative disease was bvFTD (57.1%), followed by DLB (28.57%) and AD (14.28%). The two groups have comparable demographic features.

	BD		*Depression*		**OCD**		*Psychosis*			
	mean	sd	mean	sd	mean	sd	mean	sd	stat	p
Age (y)	61,67	8,24	64,14	11,95	69,33	3,51	67,33	11,25	0,6	0,6
Onset Age (y)	58,66	1,85	61,85	11,51	67	2	66,67	11,5	0,84	0,48
Disease duration (y)	3	4,30	2,28	2,43	1,83	2,33	1,52	0,80	0,49	0,62
Sex (F/M)	3/6		8/6		0/3		4/2		0,23	0,62

Table 1.3 Demographic features of neurological disorder and PPD group

Part 2: cognitive profile of patients with psychiatric onset of a possible dementia

Objective: to explore the cognitive profile of patients with a psychiatric onset of a possible dementia, and to find neuropsychological markers helping identifying patients with a possible neurodegenerative dementia versus patient with a primary psychiatric disorder.

Methods: we performed a two-step analysis. The first was an explorative analysis using principal component analysis to evaluate if there were differences in cognitive performances according to the psychiatric phenotypes. We considered the minimum informative cognitive dataset administered to all patients: digit span forward and backward, the Trial Making A, prose memory, phonemic fluency test, Rey-Osterrieth Complex Figure. The second step consisted of evaluating differences in cognitive tests' performances between neurodegenerative and PDD groups. Finally, we investigated differences between different dementia group and PPD.

Results: the results of the explorative analysis is showed in the figure 3.

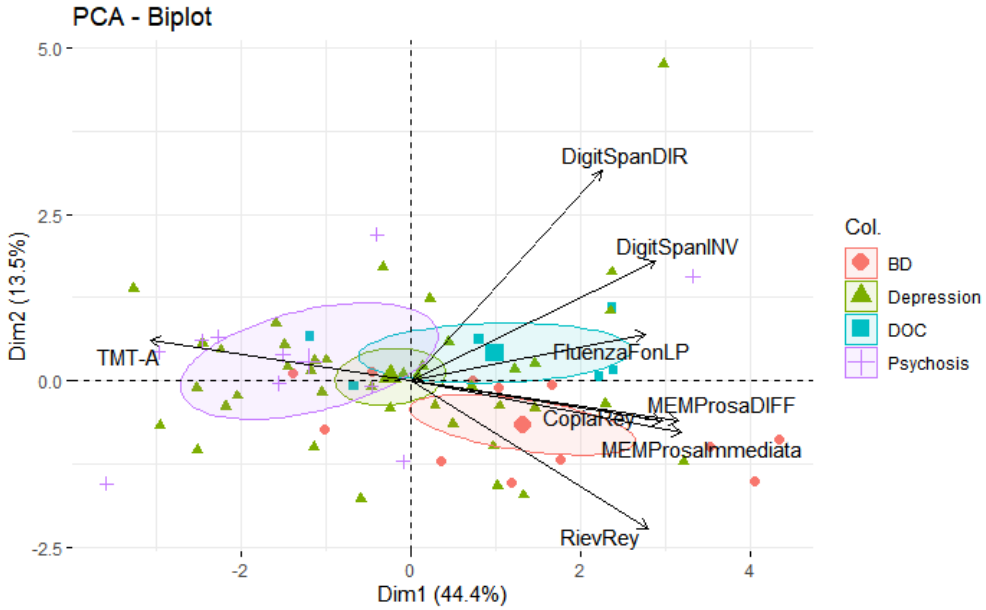


Figure 1.4 Principal component analysis biplot of individual and explanatory variables. Colored concentration ellipses (size determined by 0.95-probability level) show the observations grouped by mark class (i.e. psychiatric diagnosis).

The figure 1.4 shows the distribution of cognitive tests' performances according to the psychiatric diagnosis. Psychotic patients are clustered in the left side of the plot and they are the group that performed worse in the overall cognitive battery. Patients with depression are shown in the middle of the plot. Mean cognitive scores had a high variability within this group. Patients with BD and OCD are represented on the right side of the plot, and they had the best performances.

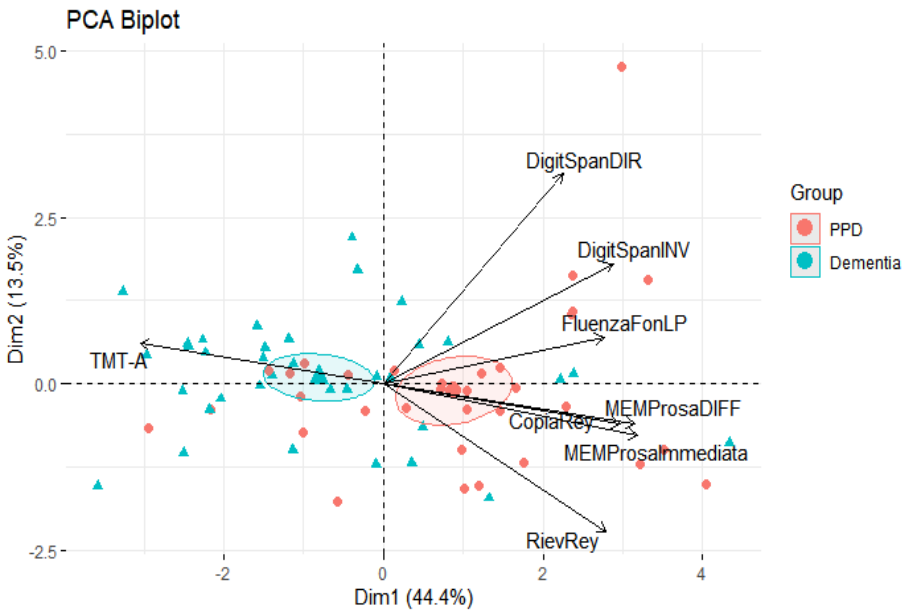


Figure 1.5 Principal component analysis biplot of individual and explanatory variables. Colored concentration ellipses (size determined by 0.95-probability level) show the observations grouped by mark class (i.e. dementia vs PPD).

The figure 1.5 shows the mean cognitive test's scores in the two groups of possible dementia and PPD. The two groups are represented in two clusters on the horizontal plane: the dementia group is mainly in the left side of the plot and performed globally worse, on the opposite the PPD group clusters in the right side, performing globally better.

The comparison of neuropsychological assessment between dementia and PPD groups is summarized in the table 1.4 and figure 1.6.

	Dementia				PPD						
variable	**mean**	**sd**	**median**	**iqr**	**mean**	**sd**	**median**	**iqr**	**Statistic**	**p**	**p corr**
MMSE	23	3,044	22	5	24,44	3,14	25,50	5,25	3,65	0,056	0,7
ADL	5,29	1,49	6,00	1,00	5,39	1,20	6,00	1,00	0,20	0,8	1,00
IADL	5,75	2,97	6,00	5,00	5,96	2,50	7,00	4,00	0,35	0,55	0,7
TMT-A	132,95	80,88	101,50	95,00	75,60	49,16	65,00	31,50	15,55	<0,01	**<0,01**
Fluency Phonemic	20,06	8,83	21,00	13,03	26,53	10,18	24,50	13,50	6,39	0,01	0,21
Fluency Semantic	23,03	9,34	20,00	10,00	29,03	9,80	29,00	12,00	7,24	<0,01	0,13
StroopTEST_Int_E	8,93	6,78	9,50	9,88	5,54	7,66	2,00	7,00	5,05	0,02	0,44
StroopTEST_Int_T	52,67	31,88	45,50	38,55	36,34	28,02	33,00	23,25	2,56	0,10	1,00
DigitSpan-forward	5,48	1,52	5,00	2,00	5,92	2,02	6,00	1,00	0,73	0,39	1,00
DigitSpan-backward	2,72	1,30	3,00	1,00	3,34	1,63	4,00	1,50	4,30	0,04	0,68
Rey Figure-recall	6,40	7,39	4,00	9,50	11,04	8,92	8,50	11,25	5,91	0,37	0,27
Prose memory-delay	6,82	5,20	6,50	6,50	11,92	6,83	11,50	9,00	11,33	0,02	0,01
Prose memory-immediate	6,55	3,96	6,00	5,25	8,83	3,98	9,00	5,25	5,58	0,02	0,33

Rey Figure-Copy	19,30	11,80	23,00	18,50	25,64	8,98	28,00	14,00	5,40	0,02	0,36

Table 4: Neuropsychological assessment of dementia group and PPD one

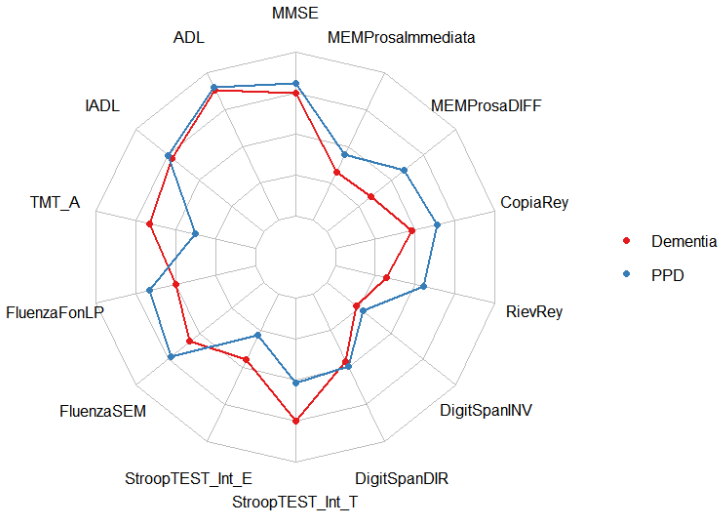


Figure 1.6 Radar plot showing the mean score of neuropsychological assessment comparing dementia group and PPD.

The two groups did not differ for global cognition measured with the MMSE screening test. Patients with possible neurodegenerative disease have worse performance at the TMT-A test (pcorr<0.01) and delayed memory prose (pcorr = 0.01). No other differences survived after multiple comparison correction. We found no difference in daily life functions.

We therefore performed a logistic regression to investigate the single contribution in identifying a patient as belonging to the neurodegenerative or PDD group. In the first model we add as predictors age, gender, digit span forward and backward, the Trial Making A, prose memory, phonemic fluency test, Rey-Osterrieth Complex. The results shows that age, TMT-A and delay-prose memory are significative predictor for the group. Younger age and lower score in memory prose-delay test increase the probability having a possible dementia (about 25% for unit). See figure 1.7and table 1.5.

Variable		**Units**	**OddsRatio CI,95**	**p-value**
`TMT-A`		1,01	[1,00;1,02]	0,038
Prose memory- delay		0,81	[0,67;0,99]	0,014
Age		0,94	[0,87;1,00]	0,041
Sex	F		Ref	
	M	0,75	[0,20;2,77]	0,66
DigitSpan-forward		1,25	[0,81;1,92]	0,31

DigitSpan-backward	0,93	[0,55;1,55]	0,77
Prose memory-immediate	1,12	[0,86;1,46]	0,39
Rey Figure-Copy	0,97	[0,90;1,05]	0,45
Rey Figure-recall	1,03	[0,93;1,14]	0,57
Fluency Phonemic	0,95	[0,88;1,03]	0,19

Table 1.5: Result of logistic regression.

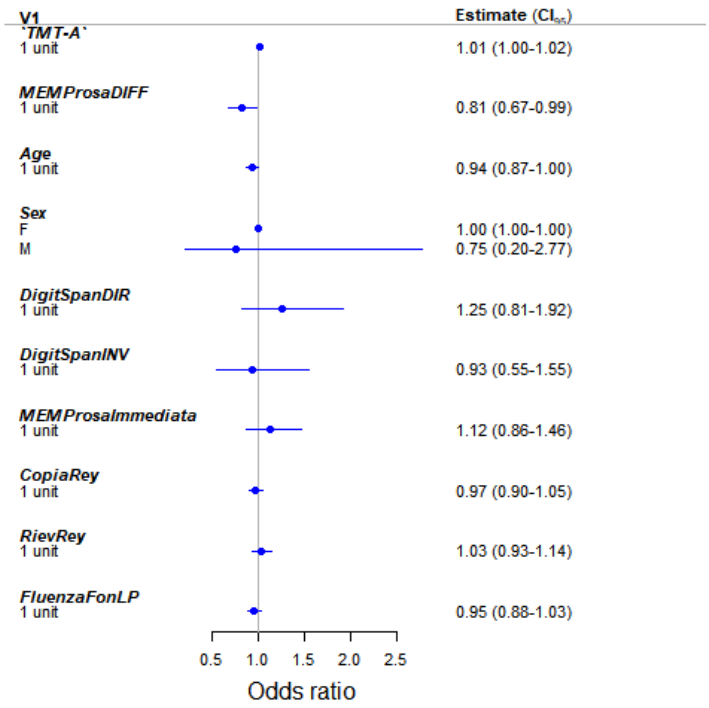


Figure 1.7

Furthermore, we investigate the differences of neuropsychological profile between specific dementia and PPD. Results are summarized in table 1.6 and figures 1.8.

	AD				bvFTD				DLB				PPD					
variable	**mean**	**sd**	**median**	**iqr**	**mean**	**sd**	**median**	**iqr**	**mean**	**sd**	**median**	**iqr**	**mean**	**median**	**iqr**	**Statistic**	**p**	**p corr**
MMSE	20,56	2,83	20,00	2,00	23,47	3,45	24,00	5,50	21,91	3,59	21,00	6,00	24,44	25,50	5,25	10,65	0,01	0,06
ADL	5,80	0,45	6,00	0,00	4,92	1,89	6,00	1,00	5,67	0,82	6,00	0,00	5,39	6,00	1,00	1,41	0,70	1,00
IADL	5,00	2,65	6,00	2,00	6,54	3,18	7,00	2,00	4,67	2,66	3,50	4,00	5,96	7,00	4,00	1,80	0,62	1,00
TMT-A	172,56	93,33	180,00	140,00	88,49	44,50	92,00	41,50	181,80	82,42	167,00	99,50	75,60	65,00	31,50	23,14	<0,001	**<0,01**
Fluency Phonemic	19,03	8,17	22,00	13,00	19,95	9,65	20,00	12,00	21,20	8,52	20,00	8,25	26,53	24,50	13,50	6,53	0,09	1,00
Fluency Semantic	17,50	4,18	17,00	3,75	23,58	9,41	20,00	9,00	25,30	10,77	21,50	10,50	29,03	29,00	12,00	10,16	0,02	0,28
StroopTEST_Int_E	9,50	0,71	9,50	0,50	7,50	6,48	6,00	10,75	13,00	8,09	10,50	7,00	5,54	2,00	7,00	6,88	0,08	1,00
StroopTEST_Int_T	73,75	47,73	73,75	33,75	42,61	24,30	44,00	25,13	74,44	38,81	62,18	27,00	36,34	33,00	23,25	6,12	0,11	1,00
DigitSpan-forward	5,00	1,41	5,00	1,00	6,04	1,51	5,68	2,00	4,91	1,38	4,00	1,00	5,92	6,00	1,00	6,02	0,11	1,00
DigitSpan-backward	2,38	1,06	3,00	1,00	2,93	1,42	3,00	0,79	2,60	1,27	2,50	1,75	3,34	4,00	1,50	5,48	0,14	1,00
Rey Figure-recall	3,81	3,82	3,75	5,75	9,34	8,65	9,00	13,00	2,90	4,47	1,75	2,63	11,04	8,50	11,25	11,48	0,01	0,15
Prose memory- delay	3,22	3,11	3,00	6,00	8,72	5,25	8,00	5,75	6,64	5,24	6,00	3,00	11,92	11,50	9,00	17,42	0,00	**0,01**
Prose memory-immediate	4,00	2,24	5,00	4,00	8,28	4,50	6,50	6,50	5,82	2,79	5,00	2,50	8,83	9,00	5,25	12,70	0,01	0,09
Rey Figure-Copy	15,63	11,00	15,25	14,25	23,00	11,08	26,00	16,25	15,20	12,56	10,25	19,13	25,64	28,00	14,00	9,45	0,02	0,38
Age	76,11	5,56	77,00	4,00	60,74	9,82	58,00	16,00	71,82	6,81	72,00	7,00	68,08	70,50	12,50	17,63	0,01	0,01

Table 1.6: mean scores of neuropsychological assessment comparing the four neurological dementia groups.

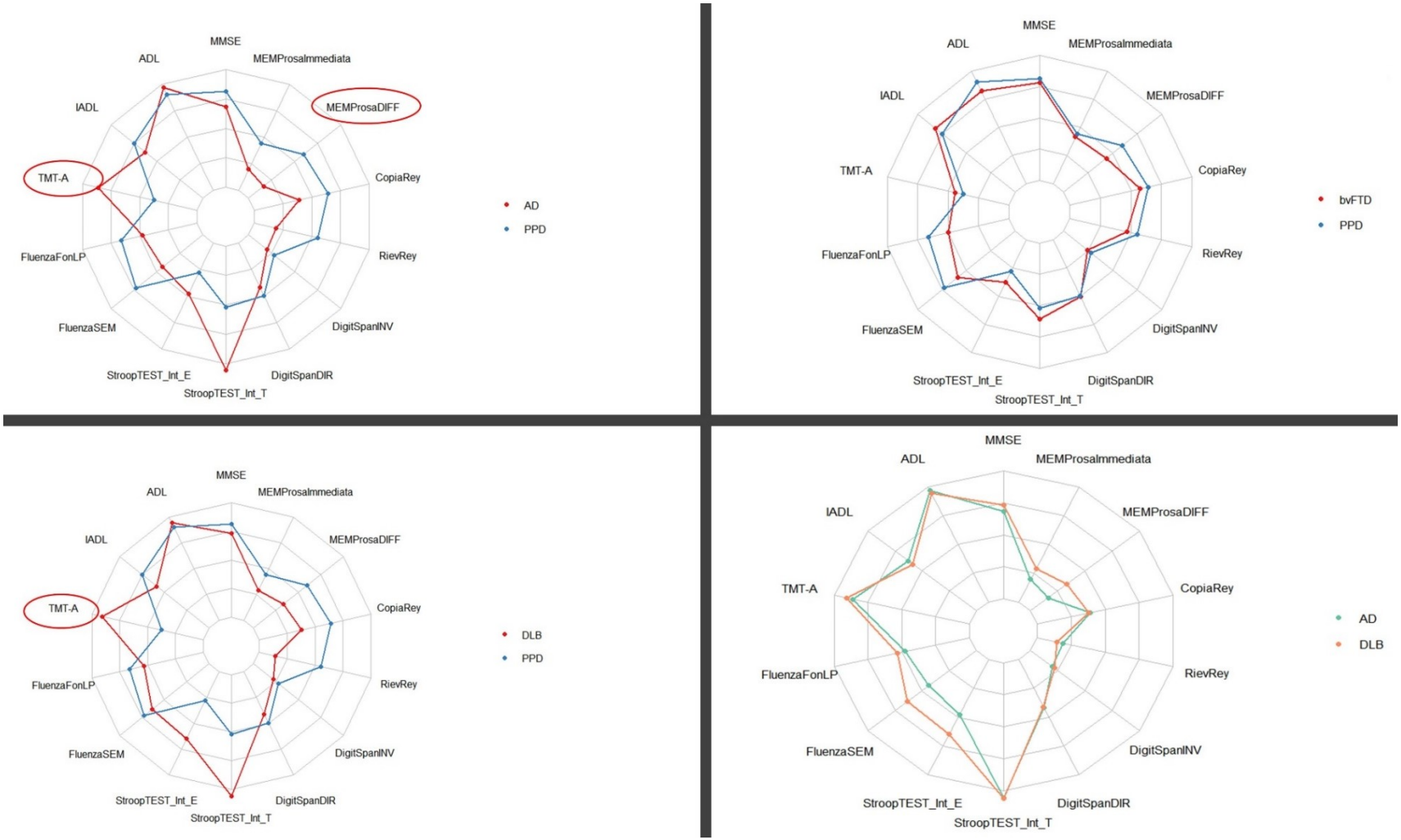


Figure 1.8: radar plot comparing neuropsychological assessment between each dementia group and PPD. From the top left in clockwise order: AD and PPD, bvFTD and PPD, DLB and PPD, AD vs DLB. Red circle represents the tests differ significantly. bvFTD vs PPD and AD vs DLB have comparable neuropsychological pattern.

Age differ significatively between groups (H= 17.63, p = 0,01), and post-hoc analysis showed differences between all groups except between DLB and AD. As for neuropsychological profile memory prose delay and TMT-A differ significatively (H = 17.42 p=0.01 and H 23.14 p<0.01 respectively). The post hoc analysis showed significative worse performance in TMTA and memory prose-delay in AD group compared to PPD, and only of TMTA of DLB group compared to PPD. Figure 8 shows an overlap between NPS pattern of AD and DLB group on one side and between bvFTD and DLB one on the other.

To validate the findings above, we managed the same analysis in the subgroup the sample of our cohort with biological diagnosis of neurodegenerative disease. The results are comparable.

Study 2: neuroanatomical correlates of VHs in psychosis of DLB

Objective: functional alterations of the visual attention networks in a setting of impaired visual information processing have a role in the genesis of visual hallucinations (VH) in dementia with Lewy bodies (DLB). Here, we use diffusion tensor imaging tractography to examine the involvement of white matter tracts connecting the visual cortex to regions of the attention networks in patients with DLB with and without VH. We also explore: whether changes in the white matter bundles of subjects who experience VH lead to a reduction in cortical thickness; and whether functional changes in the attention and visual networks are detectable on resting-state functional MRI images (rs-fMRI).

Methods: 23 DLB patients (10 with and 13 without VH) and 13 healthy controls were studied. They underwent MRI with T1-w sequences to measure cortical thickness, DTI for whole-brain and single tract microstructural properties and rs-fMRI of the default mode, dorsal and ventral attention, and visual networks. **(For extensive methodology description see below "Methods experiment 3")**

Results

Demographic and clinical features

The sample's demographic and clinical data are summarized in Table 2.1. The groups of patients with DLB and controls matched for age and education level. The VH subgroup had symptoms of RBD more frequently than the no-VH subgroup. No significant differences emerged for duration of the disease, cognitive fluctuations, severity of parkinsonism, degree of cognitive impairment or burden of behavioral disturbances (excluding the scores obtained from the NPI sub-item of VH burden). Patients in the no-VH group did not report appearance of VH in the 12-month follow-up period after the MRI scans and no VH were reported by the VH group during resting state fMRI.

Table 2.2 shows the sample's neuropsychological data. As regards cognitive impairment, only the Digit Cancellation test scores were worse in the VH subgroup.

Table 2.1*: Demographic and clinical features in DLB patients according to presence or absence of VH and healthy controls*

DLB VH	DLB NVH	Controls		
N=10	N=13	N=13		

	Mean	Std. Dev	Mean	Std. Dev	Mean	Std. Dev	Test	p value
Age (years)	76.63	7.35	74.44	5.18	70.84	10.85	F=0.13	0.13a
Education (years)	6.63	5.84	8.11	3.66	6.84	3.05	χ2=1.52	0.42a
SEX (M:F)	4:6		7:6		6:7		χ2=0.4	0.80c
MMSE score	23.50	3.20	26.33	3.51	29.2	2.1	U=38	0.06b
Disease duration (years)	2.70	1.25	1.92	1.11	N/A		U=41	0.12b
NPI total score	14.30	8.51	4.92	3.22	N/A		U=18	**0.001b**
NPI VH-subitem score	4.2	2.62	0	0				
NPI total without VH score	10.1	8.02	4.92	3.22	N/A		U=21	0.06
UPDRS score	6.60	9.90	3.53	5.73	N/A		U=51.5	0.39b
Fluctuations (YES:NO)	8:2		11:2		N/A		χ2=0.08	0.77c
RBD (YES:NO)	10:0		5:8		N/A		χ2=8.7	**0.003c**
ChE-Inhibitors (YES:NO)	7:3		6:7				χ2=1.30	0.40
Antipsychotics (YES:NO)	3:7		0:13				χ2=4.48	0.06
L-Dopa (YES:NO)	2:8		2:11				χ2=0.08	1

Legend: DLB: dementia with Lewy bodies; VH: visual hallucinations; NVH: no-visual hallucinations; MMSE: Mini-Mental State Examination, NPI: neuropsychiatric inventory, UPDRS: Unified Parkinson Disease Rating Scale, RBD: REM behavioural disorders.
a: ANOVA or Kruskal-Wallis test between groups. b: Mann-Whitney between DLB groups (VH and NVH); c: χ^2 between DLB groups (VH and NVH), N/A: not applicable

***Table 2.2**: Neuropsychological features in DLB patients according to presence or absence of VH*

	DLB VH		DLB NVH			
	N=10		N=13		Kruskal-Wallis	
	Mean	Std. Dev	Mean	Std. Dev	χ2	p value
Visuo-spatial Function						
VOSP						
Screening	19.75	0.50	19.67	0.46	0.006	0.94
Incomplete Letters	12.25	6.11	15.56	5.39	1.124	0.29
Silhouettes	11.25	4.55	12.78	5.23	0.133	0.71
Object Decision	10.75	3.07	11.22	2.71	0.991	0.32
Progressive Silhouettes	12.38	2.86	11.22	3.66	0.364	0.55
Dot Counting	8.88	0.33	9.89	2.03	1.338	0.25
Position Discrimination	18.13	2.65	18.44	2.64	0.341	0.56
Number Location	5.50	2.24	6.56	4.14	0.047	0.83
Cube Analysis	4.88	3.02	7.11	3.27	1.431	0.23
Digit cancellation	26.25	8.12	38.89	7.85	5.472	**0.02**
Rey-Osterrieth copy	13.06	8.83	25.84	15.37	0.222	0.15
Rey-Osterrieth recall	4.06	5.13	10.83	4.36	2.309	0.08
Executive Functions						
Digit span forward	3.63	1.17	4.89	1.69	2.309	0.13

Digit span backword	2.13	1.05	3.11	0.99	2.867	0.09
Clock test	4.25	3.05	6.11	3.33	0.222	0.64
Phonemic fluency	14.13	12.33	16.78	12.28	0.637	0.4
Memory Functions						
Immediate prose recall	8.00	4.50	8.44	5.68	0.143	0.71
Delayed prose recall	9.25	5.85	9.67	4.46	0.048	0.83

Legend: VOSP: Visual Object and Space Perception Battery

MRI-DTI findings and cortical thickness in projection areas

Whole-brain TBSS analysis revealed widespread impairment of white matter tracts in patients with DLB, with significant differences compared to controls (p_{FWE} <0.01). Post-hoc analysis comparing the VH and no-VH subgroups of patients with DLB showed a lower FA in the right tempo-parietal ILF, frontal IFOF, and UNC (p_{FWE} <0.05), and a diffuse increase in MD in the above-mentioned tracts and right SLF3 in the VH subgroup (p_{FWE} <0.05) (Figure 2.1, Supplemental Table 2.1).

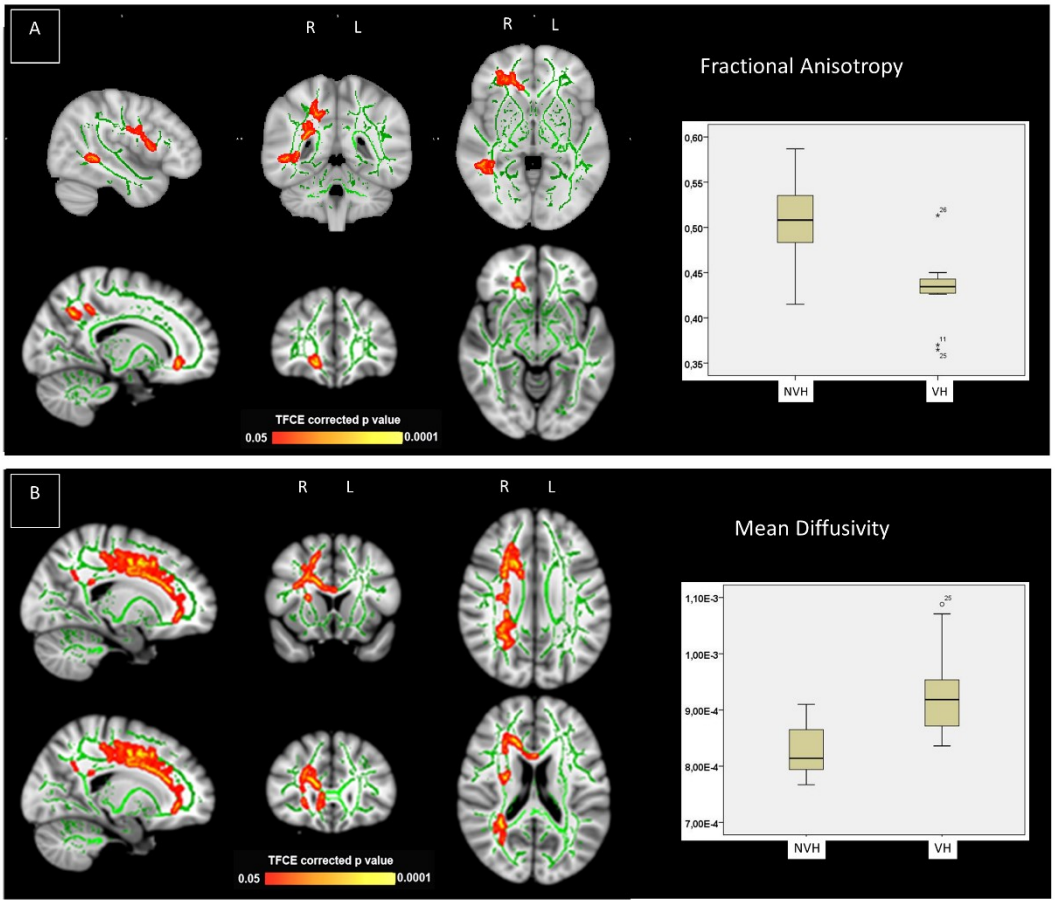


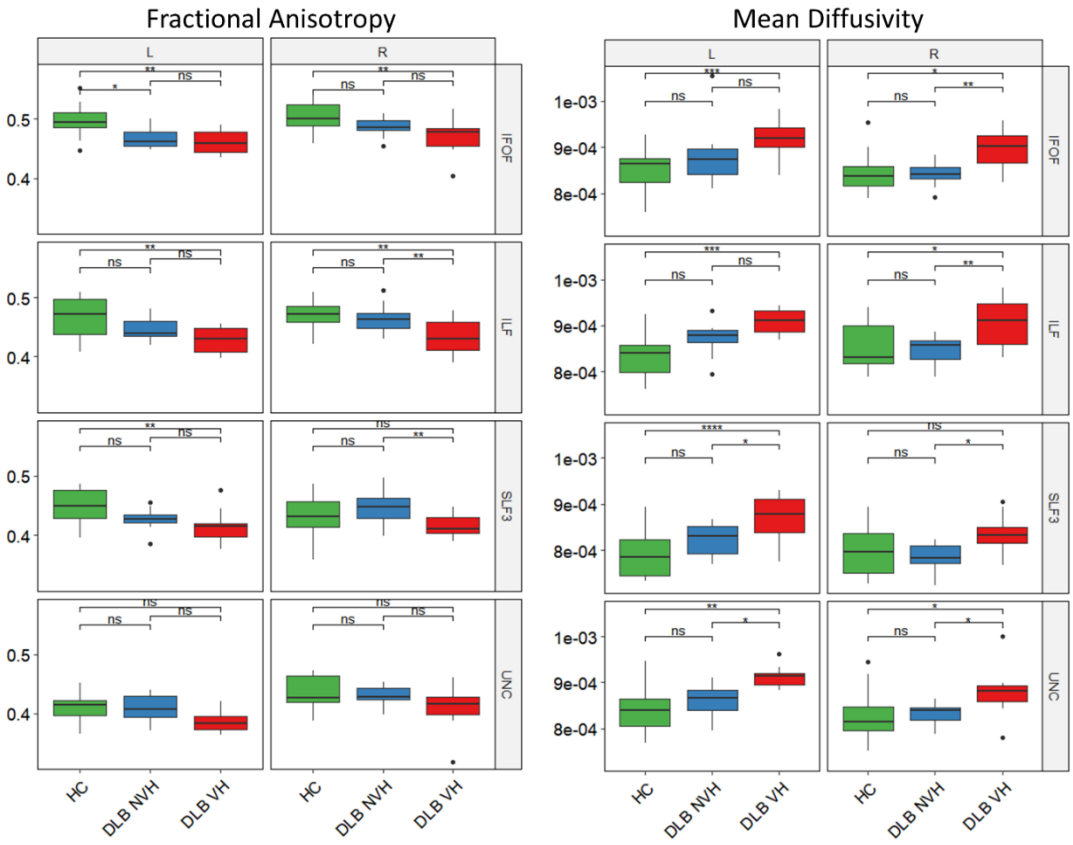
Figure 2.1 TBSS parametric maps of the subgroups of patients with DLB (VH vs. no-VH). (A) Regions highlighted in red showed tracts with a reduced FA. They localized in right ILF, IFOF and UNC in patients with VH (pFWE <0.05). (B) Regions highlighted in red showed greater MD in patients with VH, which was widespread along several white matter tracts (IFOF, ILF, SLF) in the right hemisphere.

FA $p_{FWE} \leq 0,05$						**Atlas**
Cluster Index	Voxels	Z-MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	
4	323	0.959	16	-58	37	ILF R
3	308	0.958	30	-49	17	ILF R
2	160	0.957	16	35	-8	IFOF R
1	96	0.952	17	-46	42	

MD $p_{FWE} \leq 0,05$						**Atlas**
Cluster Index	Voxels	Z-MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	
5	2634	0.974	19	16	29	CC
4	815	0.959	28	-51	30	SLF R
3	260	0.952	13	31	-3	

Supplemental Table 2.1 TBSS results. FA and MD significative cluster coordinates

Multivariate analysis of the variance in the DTI data obtained from tract dissection showed a significant effect of group for FA ($F = 2.98$, $p < 0.001$) and MD ($F = 2.28$, $p = 0.013$). The data are available in the Supplemental materials (Supplemental Figure 2.2). Post-hoc univariate analysis with Bonferroni's correction comparing the VH and no-VH subgroups with DLB showed a significantly lower FA in the right ILF and SLF3 ($p <0.05$) and greater MD in the right IFOF, ILF and SLF3 ($p <0.01$), and left UNC ($p = 0.01$) in the former subgroup (Supplemental Table 2.2).



Supplemental Figure 2.1 Boxplot of mean diffusivity and fractional anisotropy of with matter tracts. Comparison between groups of anisotropy indices considering each white matter tract.

Univariate analysis VH groups (DLB VH, DLB NVH, HC)			p_{FWE} post-hoc DLB VH vs DLB NVH
Dependent Variable	F	Sig.	Sig.
FA IFOF L	8.628	<0.01	1
FA IFOF R	5.641	<0.01	0.479
FA_ILFL	5.761	<0.01	0.320
FA_ILFR	6.753	<0.01	**0.016**
FA_SLF3L	5.839	<0.01	0.767
FA_SLF3R	3.797	<0.01	**0.031**
FA_UNCL	4.019	<0.01	0.074
FA_UNCR	2.413	0.105	---------
MD_IFOFL	5,518	<0.01	0,264
MD_IFOFR	6,933	<0.01	**0,006**
MD_ILFL	8,901	<0.01	0,072
MD_ILFR	5,975	<0.01	**0,008**
MD_SLF3L	8,631	<0.01	0,066
MD_SLF3R	3,706	<0.01	**0,038**
MD_UNCL	7,823	<0.01	**0,014**
MD_UNCR	3,699	0.03	0,084

Supplemental Table 2.2 ANOVA between groups for each tract dissected

The severity of VH, measured with the VH sub-item of the NPI, correlated negatively with the FA values in the right SLF3 ($r = -0.57$, $p = 0.004$), and positively with MD values in the right SLF3 ($r = 0.55$, $p < 0.01$), ILF ($r = 0.42$, $p = 0.048$), IFOF ($r = 0.47$, $p < 0.05$), and left UNC ($r = 0.68$, $p < 0.001$) (Figure 2.2A). Performance in the Digit Cancellation task (the only test in which the VH subgroup scored significantly worse than the no-VH subgroup) also correlated with MD in the right SLF 3 ($r = -0.56$, $p = 0.006$), and ILF ($r = -0.61$, $p = 0.003$), a worse performance correlating with greater MD values (Figure 2.2B). No significant correlations were found with FA values.

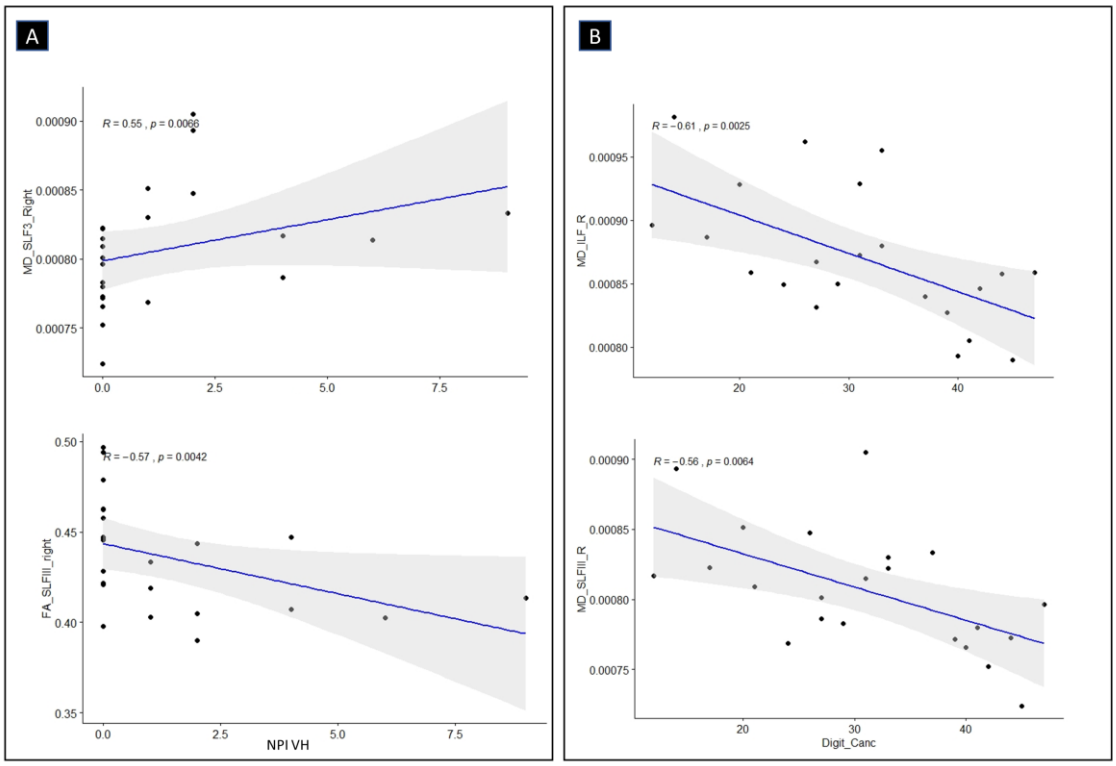


Figure 2.2 Correlation between anisotropy measures and neurophysiological tests. A) Correlation between anisotropy measures and NPI subitem scores for VH. B) Correlation between anisotropy measures and Digit Cancellation task scores.

Cortical thickness was reduced in the projection areas of SLF3 in the VH subgroup (mean CTh: VH= 1.09±0.11 mm, no-VH= 1.27±0.13 mm; F=12.79, p <0.01), but not in the projection areas of ILF (mean CTh: VH= 1.49±0.26 mm, no-VH= 1.59±0.17 mm; F=1.31, p = 0.26). (Figure 2.3)

Results of Bayesian linear regressions indicate a small influence of the projections of the right SLF3 cortical thickness on the FA of the right SLF3 (BF10 = 1.604) and no evidence for the influence of right SLF3's FA on its projections cortical thickness (BF10 = 1). All other models demonstrated substantial evidence for the absence of influence between the cortical thickness and the FA (all BF10 < 0.33). Hence the results indicate that tract changes were influenced by cortical atrophy.

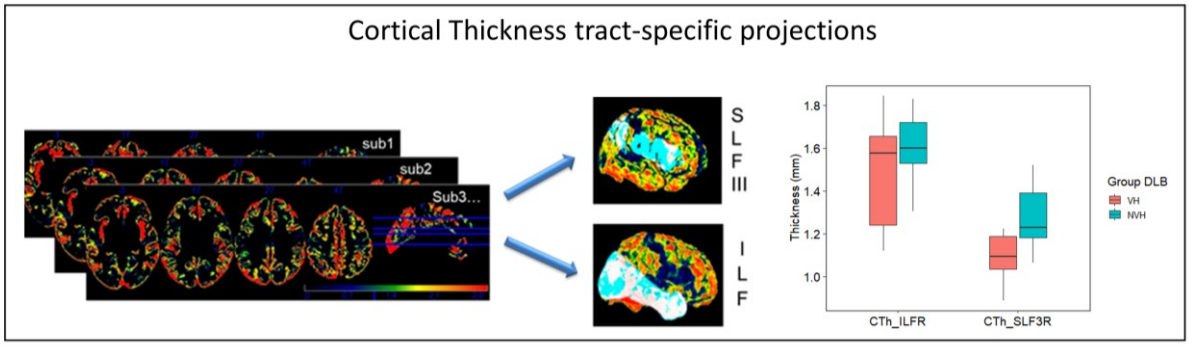


Figure 2.3 Cortical thickness tract-specific projections. Cortical thickness extraction method (left): first the individual cortical thickness map normalized in the MNI152 space were calculated and reconstructed in 3D for each subject; next the masks of ILF and SLF3 cortical projection areas (shown in blue) are overlapped to each subject thickness map. Lastly the mean cortical thickness of each subject projection was extracted. The graph on the right shows the differences in mean cortical thickness in the same projection areas between the DLB subgroups.

Resting-state fMRI findings

For the four networks (DAN, VAN, DMN and VN) of the right hemisphere, the correlation matrices showed a lower DAN and DMN connectivity, and higher VAN connectivity in the VH subgroup than in the no-VH subgroup of patients with DLB. VN connectivity was similar in the two subgroups. Figure 2.4A shows the 66-ROI correlation matrices for the two subgroups, and the corresponding matrix with the p-value uncorrected ($p < 0.05$) (bottom left).

Mean intra-network connectivity of each network did not differ significantly between the VH and no-VH subgroups. However, a moderate effect size was found for DMN ($r = 0.37$), DAN ($r = 0.30$) and VAN connectivity ($r = 0.30$), with the VH group showing a higher mean value for VAN (VH= 0.52 ± 0.04, no-VH= 0.41 ± 0.08), and a lower mean value for DMN (VH= 0.34 ± 0.03, no-VH= 0.44 ± 0.05) and DAN (VH= 0.34 ± 0.05, no-VH= 0.44 ± 0.07) (Figure 2.4B).

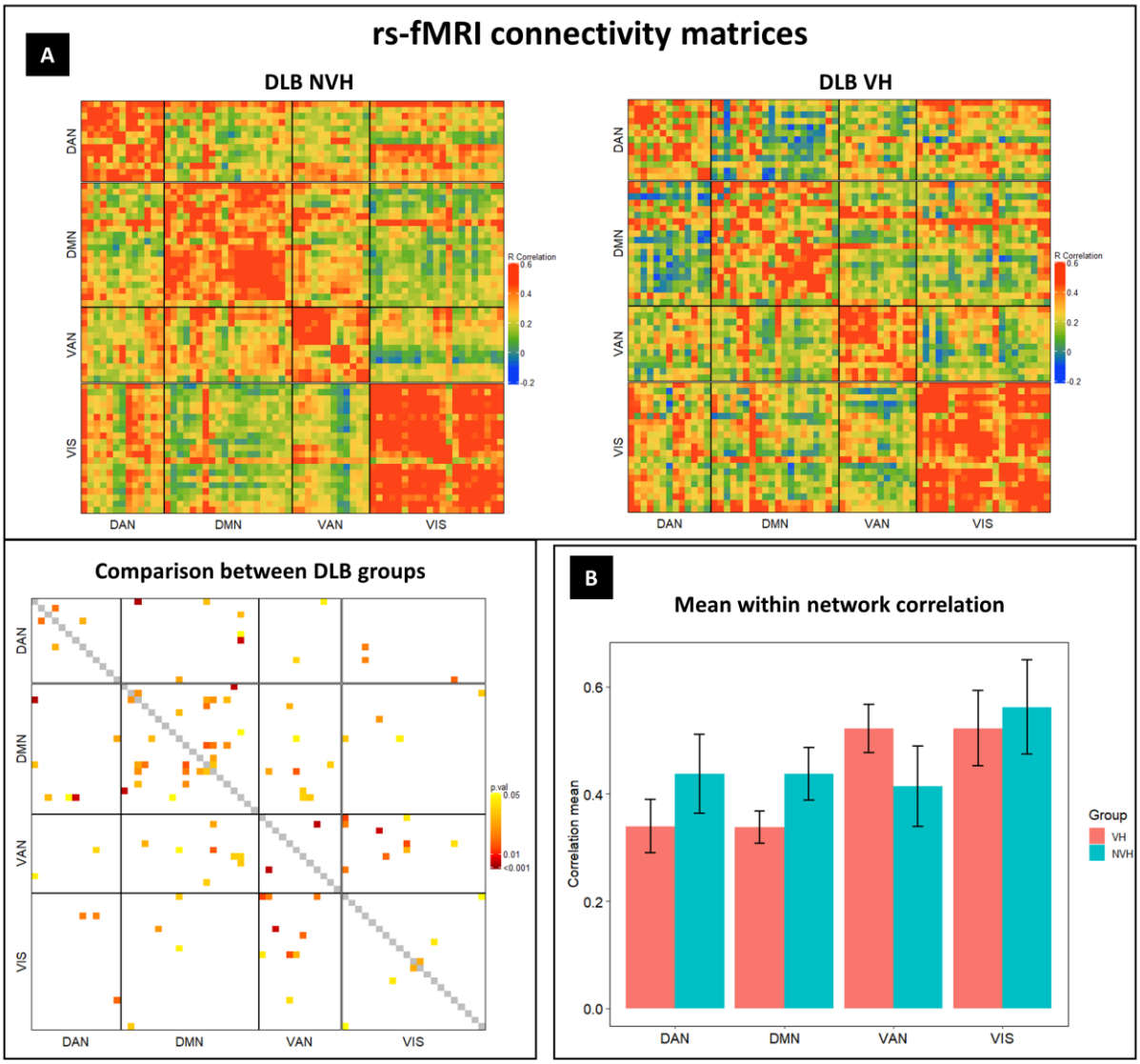
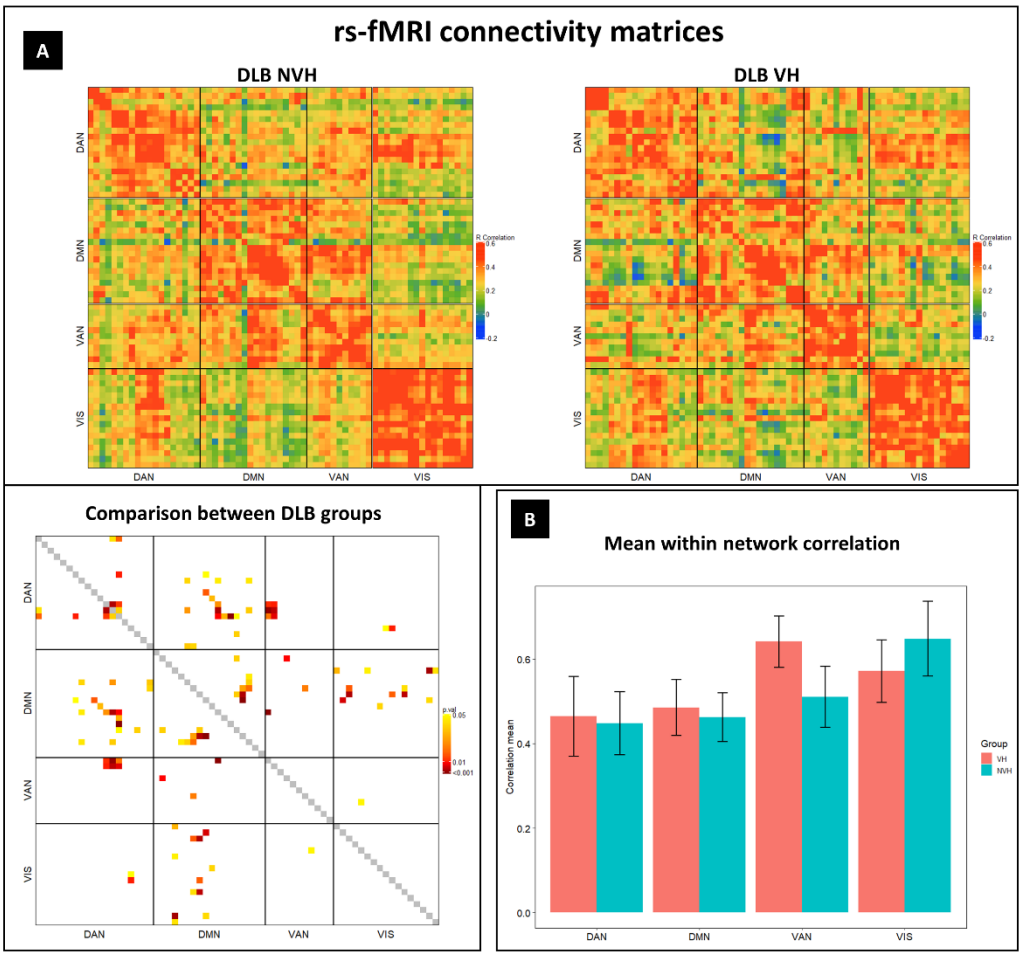


Figure 2.4 fMRI analysis (right hemisphere). A) The first row shows the group-level 66x66 ROI correlation matrices for the no-VH and VH subgroups. The ROIs are grouped by resting-state network (DAN, DMN, VAN, VIS). Intra-network correlations appear on diagonal blocks; inter-network correlations appear in off diagonal blocks. The rainbow scale shows the ROI-ROI correlations strength and direction, where positive correlations are more red, negative correlations more blue. The second row shows the p-values comparing separate individuals' matrices between the two groups. B) Mean intra-network correlations for the networks studied.

Correlation matrices for the left hemisphere in the two subgroups are shown in the Supplemental material (Supplemental Figure *2.3*). The results were much the same as for the right hemisphere.



Supplemental Figure 2.2 *. fMRI connectivity analysis – left hemisphere. A) The first row shows 66x66 ROI correlation matrices for the no-VH and VH subgroups. A square shape identifies ROI belonging to the DMN, DAN, VAN and visual network. The rainbow scale shows the ROI-ROI correlations, where positive correlations are more red, negative correlations more blue. The second row shows the p-values comparing separate individuals' matrices between the two groups. B) Mean intra-network correlations for the networks studied.*

Study 3: functional and structural correlates of VHs in psychosis of dementias

Objective: Recurrent complex visual hallucinations (VH) are common in dementia with Lewy bodies (DLB). Previous investigations suggest that VH are associated with connectivity changes within and between large scale networks involved in visual processing and attention. Here we combine metabolic connectivity with 18F-FDG PET data in DLB patients and graph theory to study the functional brain architecture's alterations related to VH. We characterize graphs of metabolic connectivity embedded in the Shaefer-Yeo 100 region functional atlas (Schaefer A et al. 2018) to measure differences in the functional architecture of DLB patients, with or without VH. Alterations of the functional architecture predispose to VH and are potential targets for neuromodulation.

Methods: Twenty-six patients with probable DLB (13VH and 13 no-VH; mean age: 72.9±6.87 years versus 70.2±7.96 years) were enrolled. T1-weighted 3T-MRI images and FDG-PET data were co-acquired using an integrated PET/MR scanner. MRI images defined cortical parcels of the Shaefer-Yeo atlas for multiple functional networks. We computed in each parcel the regional standardized-uptake-values (SUVr) corrected for partial volume and normalized to the cerebellar cortex. We then computed using graph analysis strength degree, clustering coefficient, characteristic path length, and hubs.

Results

Patients characteristics

Demographic and clinical features of the sample are summarized in Table 3.1. Patient groups were comparable for demographic variables, degree of cognitive impairment and parkinsonism. Burden of behavioural disorders was similar except for the NPI-subitem for VH. As for cognitive evaluation, the mean score at the Rey-Osterrieth copy test was worst in the VH group (F=24.5, p=0.02). The two groups performed similarly in the remaining cognitive tests.

Demographic and clinical data					
	NVH (n=13)		**VH (n=13)**		
	mean	sd	mean	sd	p
Age (years)	70.31	7.92	72.31	6.09	0.54
Sex F/M	4/9		7/6		0.4
Disease duration (years)	2.04	1.29	3.04	1.76	0.84
NPI total score	19.25	21.59	23.46	11.67	0.54
NPI-VH subitem	0.00	0.00	5.85	4.08	**<0.001**
NPI Psychosis-subitem	0.67	2.31	1.85	2.67	0.07
Fluctuations (Y/N)	8/4		11/2		0.38
Probable RBD (Y/N)	7/6		7/6		1
UPDRS-III score	4.25	4.83	6.92	3.88	0.09
ChE-Inhibitors (Y/N)	4/9		4/9		1
Antipsychotics (Y/N)	0/13		2/11		0.14
L-Dopa (Y/N)	1/12		1/12		1
Neuropsychological Evaluation					
MMSE score	24.38	4.81	21.77	4.11	0.23
VOSP Screening	19.00	1.94	18.90	0.74	0.80
VOSP 1	14.22	6.10	12.56	6.69	0.65
VOSP 2	14.50	4.20	11.50	5.89	0.36
VOSP 3	12.50	4.12	12.00	3.46	0.87
VOSP 5	9.56	1.01	8.60	1.90	0.13
VOSP 6	16.89	2.62	16.50	3.47	0.98
VOSP 7	5.89	3.06	6.44	2.65	0.39
VOSP 8	6.44	2.51	5.70	2.50	0.87
Clock test	5.22	3.73	4.80	3.43	0.48
Rey-Osterrieth copy	25.04	9.70	14.65	9.80	**0.04**
Digit cancellation	39.15	14.37	30.00	12.18	0.15
TMT-A (sec)	113.40	85.19	130.22	61.62	0.84
Phonemic fluency	20.45	12.04	18.70	7.15	0.82
Semantic fluency	27.10	12.30	20.90	6.10	0.38
Digit span forward	4.64	1.12	4.91	1.30	0.21
Digit span backword	2.91	1.14	3.27	1.10	0.33
Immediate prose recall	6.70	4.92	7.80	3.08	0.78
Delayed prose recall	8.00	5.31	9.00	5.21	0.77
Immediate RAVLT	36.17	10.57	24.50	0.71	0.19
Delayed RAVLT	5.17	2.23	5.00	1.41	0.93
Rey-Osterrieth recall	10.70	5.47	6.56	3.68	0.14

Table 3.1: Demographic, clinical and neuropsychological data

Legend: NVH: DLB without visual hallucination. VH: DLB with visual hallucinations. NPI: Neuropsychiatric inventory. RBD: REM-Sleep behaviour disorders. UDRPS: Unified Parkinson's Disease Rating Scale. MMSE: Mini-mental status examination scale. VOSP: Visual Object and Space Perception Battery. TMT-A: Trial making A. RAVLT: Rey Auditory Verbal Learning Test.

Network-based ^{18}F-FDG PET uptake

Mean ^{18}F-FDG PET SUVr (PVE corrected) values for each network comparing DLB VH with no-VH groups are shown in *Figure 3.2*. In the VH group, mean FDG SUVr values were lower in the DAN (left: F=8.03, p=0.01 and right: F=12.86, p=0.01) and in the visual network (left: F=6.88, p=0.01 and right: F=9.38, p=0.006) bilaterally. Mean SUVr data are available in Supplementary material table 3.1.

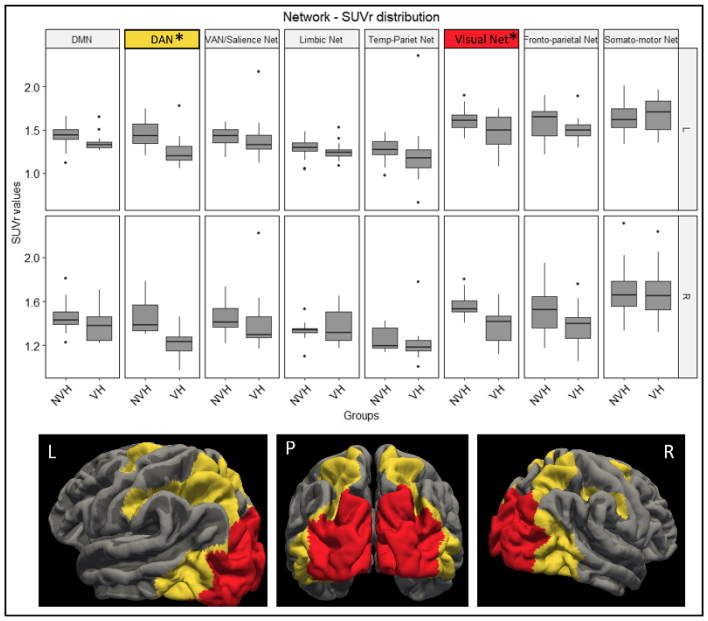


Figure 3.2: Boxplot graph represents the FDG-PET SUVr variance distribution of different networks in DLB patients with VH (VH) and without VH (NVH). Mean SUVr values in the DAN and visual networks are lower in VH than in NVH group. Images in the lower part of the box illustrate the topographical localization of regions belonging to the DAN (yellow) and visual network (red). Legend: DMN: Default Mode Network. DAN: Dorsal Attentive Network. VAN: Ventral Attentive Network. Marked network $p < 0.05$.

Graph analysis

Differences of within and between networks connectivity in the DLB VH and no-VH groups are shown in Figure 3.3 and in Supplementary table 3.2. The VH group had lower connectivity within DAN, DMN and somato-motor networks, and higher connectivity within VAN and visual networks. As for the differences in between-networks connectivity, we found both higher and lower values in VH in comparison to no-VH

group. In details, the DLB VH group manifested lower connectivity between the visual network and all other networks, except the limbic network, and between DAN, fronto-parietal, and DMN; higher connectivity was found between both VAN and somato-motor networks with all the other networks; the limbic network had higher connectivity with VAN and somato-motor network (see results in Supplementary material Table 3.2).

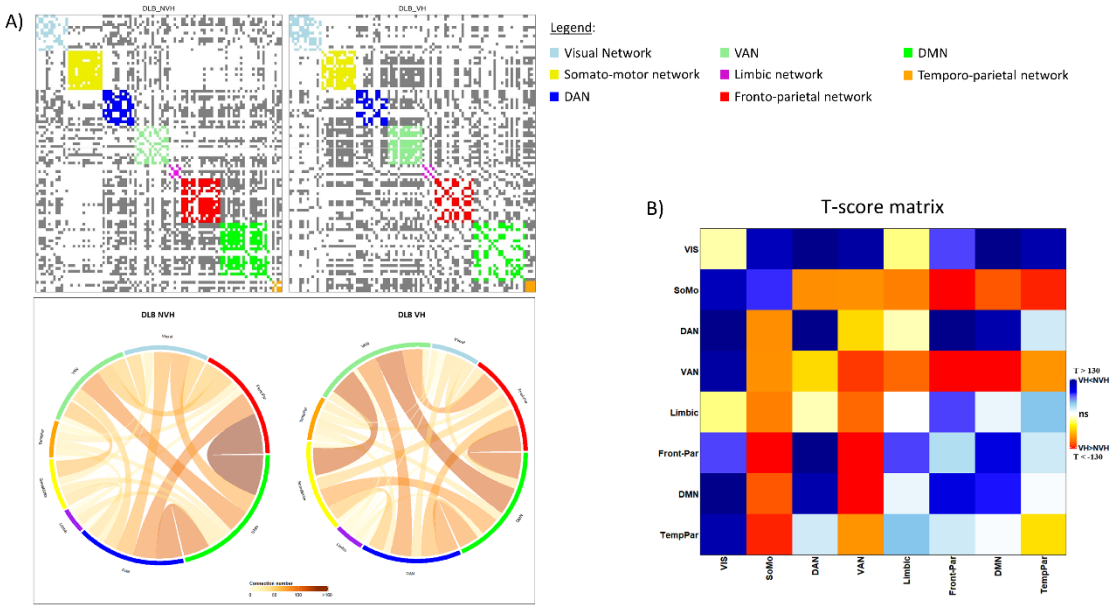


Figure 3.3: A) The image on the top represents the differences of intra-network number of connections compared between the two groups. The image on bottom shows the connectograms of the two DLB groups which represent the number of between-networks connections at fixed sparsity of 29%., the darker the connection, the higher the connection number. B) The T-score matrix represents statistical differences in the number of connections within (on diagonal squares) and between (off diagonal squares) each functional network in VH versus NVH. More bluish represents less connections in VH group, on the opposite more reddish represent more connections

We also ran an analysis at the single parcel level to identify the cortical nodes whose metabolic connectivity was more altered in VH (Figure 3.4). In patients with visual hallucinations, the strength of metabolic connectivity was lower in the superior lateral and medial parietal (DAN, DMN and fronto-parietal networks) and in occipital cortex (visual network) ($p < 0.05$). In contrast, it was stronger in the right frontal (VAN/Salience network) and orbito-frontal cortex (limbic), and in regions of the somato-motor network bilaterally ($p < 0.05$). Detailed values are available in Supplementary table 3.3.

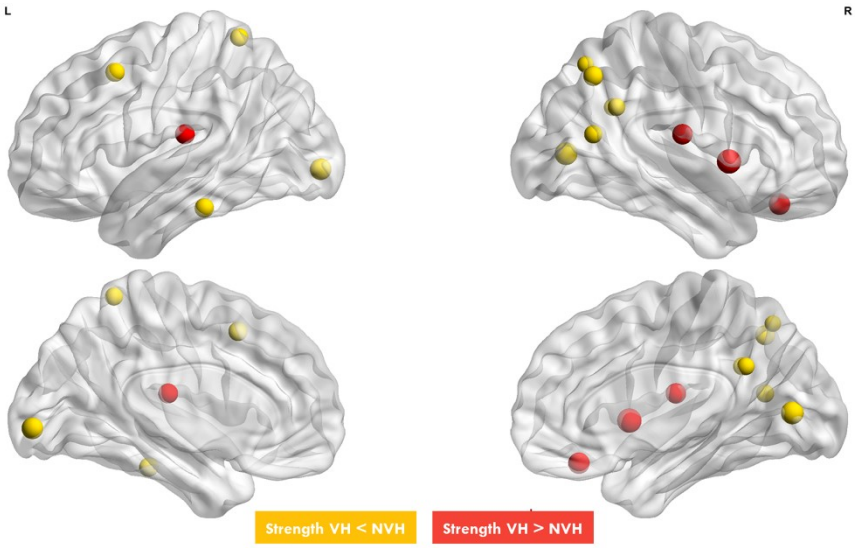


Figure 3.4: The figure shows nodes differ in nodal strength between DLB NVH and DLB VH. Yellow node belonging to DMN, DAN and visual network have a lower nodal strength in DLV VH compared to DLB NVH. Red node mainly belonging to limbic network and VAN have a higher nodal strength in DLV VH compared to DLB NVH.

Next, we examined whether regional metabolism was related to the level of VH experienced (NPI-VH scores) (*Figure 3.5*). Low metabolism in two regions of the occipito-parietal cortex, part of the DAN, showed correlation with the severity of hallucinations (DorsAttnA_ParOcc_1: R= -0.42; p= 0.03; DorsAttnA_TempOcc_1: R = -0.58; p < 0.01). Interestingly, a trend of positive correlation was found between the metabolism of a right orbitofrontal region belonging to the limbic network and severity of hallucinations (R = 0.37, p = 0.065).

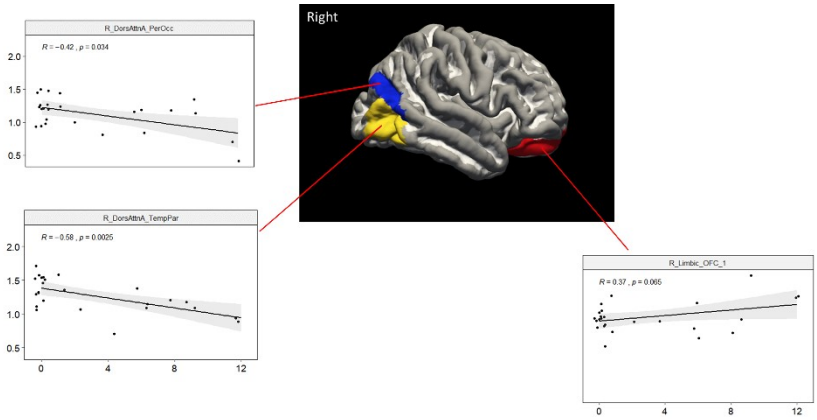


Figure 3.5: Plots describe the significant correlations between VH severity (NPI VH) and SUVr in three regions of the right hemisphere outlined in the image (see coordinate information at: https://github.com/ThomasYeoLab/CBIG/blob/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal/Parcellations/MNI/Centroid_coordinates/Schaefer2018_100Parcels_17Networks_order_FSLMNI152_1mm.Centroid_RAS.csv)

The whole brain analysis of graph metrics is shown in Supplementary materials (Supplementary material figure 3.1 and table 3.4). The DLB VH group showed a higher Lp.wt and trend of higher clustering coefficient, while nodal strength was similar.

A global modification of hubs distribution was found in VH compared to no-VH group, with a gain of hubs mainly in the anterior regions of the limbic network, VAN/Salience network and temporoparietal networks, and a loss of in the DAN and DMN networks. (see Supplementary figure 3.2 and table 3.5).

Supplemental material table 3.1: Network SUVr values by side and group

SUVr						
	Left Hemisphere			Right Hemisphere		
	DLB NVH	DLB VH	p	DLB NVH	DLB VH	p
	mean ± sd	mean ± sd		mean ± sd	mean ± sd	
DMN	1.43±0.15	1.36±0.11	0.12	1.46±0.15	1.38±0.15	0.25
VAN/salience	1.42±0.12	1.40±0.26	0.44	1.44±0.14	1.40±0.28	0.38

DAN	1.44±0.15	1.26±0.19	**0.01**	1.45±0.15	1.24±0.14	**0.01**
Visual Network	1.62±0.15	1.50±0.20	**0.01**	1.56±0.12	1.38±0.17	**<0.01**
Fronto-Parietal Network	1.60±0.21	1.50±0.16	0.11	1.53±0.22	1.40±0.18	0.11
Limbic Network	1.28±0.13	1.26±0.11	0.99	1.33±0.09	1.37±0.16	0.52
Temporo-Parietal Network	1.27±0.15	1.22±0.39	0.27	1.26±0.11	1.22±0.18	0.47
Somato-motor network	1.65±0.19	1.65±0.20	0.64	1.71±0.25	1.69±0.29	0.48

DMN: default mode network, VAN: ventral attentive network, DAN: dorsal attentive network

Supplemental material table 3.2: Comparison of between and within number of connections in VH vs NVH

Difference in conncections between NVH and VH			
From	To	T-score	P*
Control	Control	26,62	<0.0001
Default	Control	89,52	<0.0001
Default	Default	77,43	<0.0001
DorsalAttn	Control	133,70	<0.0001
DorsalAttn	Default	116,89	<0.0001
DorsalAttn	DorsalAttn	157,90	<0.0001
Limbic	Control	68,60	<0.0001
Limbic	Default	9,31	<0.0001
Limbic	DorsalAttn	-18,03	<0.0001
Limbic	Limbic	-0,67	1
SomaMotor	Control	-223,31	<0.0001
SomaMotor	Default	-109,93	<0.0001
SomaMotor	DorsalAttn	-88,56	<0.0001
SomaMotor	Limbic	-98,79	<0.0001
SomaMotor	SomaMotor	75,95	<0.0001
TempPar	Control	19,39	<0.0001
TempPar	Default	6,25	0,01
TempPar	DorsalAttn	19,94	<0.0001
TempPar	Limbic	41,16	<0.0001
TempPar	SomaMotor	-124,99	<0.0001
TempPar	TempPar	-52,96	<0.0001
VentralAttn	Control	-134,42	<0.0001
VentralAttn	Default	-161,96	<0.0001
VentralAttn	DorsalAttn	-55,73	<0.0001
VentralAttn	Limbic	-109,76	<0.0001
VentralAttn	SomaMotor	-89,23	<0.0001
VentralAttn	TempPar	-86,41	<0.0001

VentralAttn	VentralAttn	-120,51	<0.0001
Visual	Control	70,88	<0.0001
Visual	Default	136,60	<0.0001
Visual	DorsalAttn	153,56	<0.0001
Visual	Limbic	-27,16	<0.0001
Visual	SomaMotor	107,44	<0.0001
Visual	TempPar	115,27	<0.0001
Visual	VentralAttn	119,27	<0.0001
Visual	Visual	-21,53	<0.0001

*Statistics are corrected with Bonferroni.

Supplemental material table 3.3: **Nodal strength node differences between the two groups.**

region	x.mni	y.mni	z.mni	strength.DLB_NVH	strength.DLB_VH	p_{FDR}
L_DefaultB_PFCl_1	-40	14	48	27.44	0.70	0.01
L_DorsAttnB_PostC_3	-22	-50	66	43.25	18.45	0.01
L_Limbic_TempPole_2	-58	-32	-22	27.79	0.60	<0.01
L_SomMotB_Aud_1	-54	-22	8	12.92	40.68	0.03
L_VisCent_Striate_1	-18	-60	-6	34.59	4.00	0.01
R_ContB_IPL_1	46	-62	46	30.70	3.03	0.01
R_DefaultA_IPL_1	54	-50	30	27.59	3.05	0.01
R_DefaultA_pCunPCC_1	6	-28	34	32.43	8.05	0.03
R_DorsAttnA_ParOcc_1	26	-66	52	25.81	0.79	0.03
R_DorsAttnA_SPL_1	50	-60	-10	27.13	5.02	0.05
R_Limbic_OFC_1	12	34	-20	10.51	41.28	0.01
R_SalVentAttnA_Ins_1	40	8	2	9.33	45.51	0.04
R_SomMotB_S2_1	52	-16	6	14.97	43.95	0.03
R_VisPeri_StriCal_1	28	-66	-12	36.71	4.13	0.03

Supplemental material table 3.4: Global metrics comparisons

Density	Lp.Wt.DLB_NVH	Lp.Wt.DLB_VH	p_{FDR}
0.16	2.97	4.52	0.02
0.17	2.91	4.56	0.02
0.18	2.85	4.47	0.03
0.19	2.78	4.44	0.04
0.20	2.74	4.64	0.02
0.21	2.70	4.57	0.02
0.22	2.67	4.62	0.01
0.23	2.64	4.62	0.01
0.24	2.61	4.30	0.03
0.25	2.60	4.17	0.03

0.28	2.61	3.82	0.04
0.29	2.59	3.90	0.01
0.37	2.45	3.20	0.03
0.38	2.44	3.18	0.03
0.39	2.43	3.13	0.03
0.40	2.41	3.12	0.04
Density	Cp.DLB_NVH	Cp.DLB_VH	p_{FDR}
0.13	0.59	0.72	0.048
0.16	0.60	0.73	0.029
0.17	0.61	0.73	0.049

Legend: Global metrics, i.e. clustering coefficient (Cp) and Lp.wt, differences between the two groups by density. Global nodal strength does not differ between the two groups.

Supplemental material table 3.5: HUBs list and region coordinates.

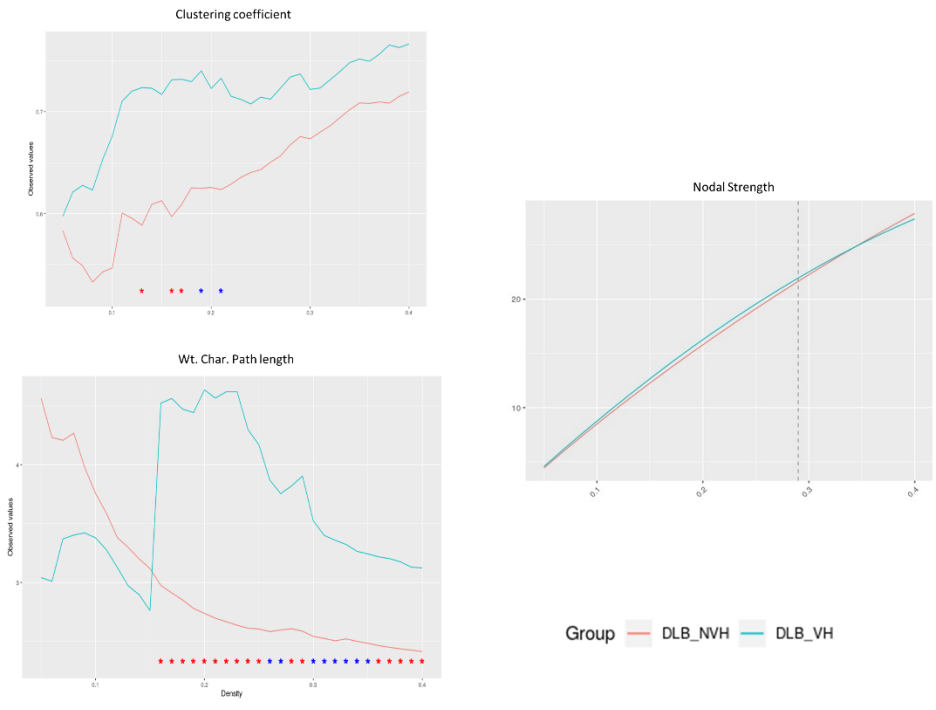
HUBs DLB VH				
Region	**x.mni**	**y.mni**	**z.mni**	**Network**
L_ContA_PFCl_1	-44	32	20	Fronto-parietal network
L_ContA_PFCl_2	-48	6	28	Fronto-parietal network
L_DefaultA_PCC_1	-6	-52	34	DMN
L_DefaultA_PFCm_1	-6	46	0	DMN
L_DorsAttnB_PostC_2	-42	-34	48	DAN
L_SalVentAttnA_Ins_2	-38	12	6	VAN
L_SalVentAttnA_ParMed_1	-12	-34	46	VAN
L_SalVentAttnA_ParOper_1 *	-58	-38	30	VAN
L_SalVentAttnB_PFCl_1	-30	44	30	VAN
L_SalVentAttnB_PFCmp_1	-6	20	34	VAN
L_SomMotB_Aud_2	-36	-22	16	Somato-Motor
L_SomMotB_Aud_3	-54	-12	14	Somato-Motor
L_TempPar_1	-58	-50	12	TempPar
R_ContA_PFCl_1	46	38	16	Fronto-parietal network
R_DefaultA_PFCm_1	6	48	0	DMN
R_Limbic_OFC_1	12	34	-20	Limbic
R_SalVentAttnA_FrMed_1	12	-32	46	VAN
R_SalVentAttnA_Ins_1	40	8	2	VAN
R_SalVentAttnA_ParOper_1 *	60	-26	28	VAN
R_SalVentAttnB_PFCmp_1 *	6	28	30	VAN
R_SomMotA_1	46	-12	48	Somato-Motor
R_SomMotB_S2_1	52	-16	6	Somato-Motor
R_SomMotB_S2_2	40	-16	16	Somato-Motor
R_SomMotB_S2_3	56	-4	12	Somato-Motor
R_TempPar_2	58	-26	-2	TempPar

HUBs DLB NVH				
Region	**x.mni**	**y.mni**	**z.mni**	**Network**

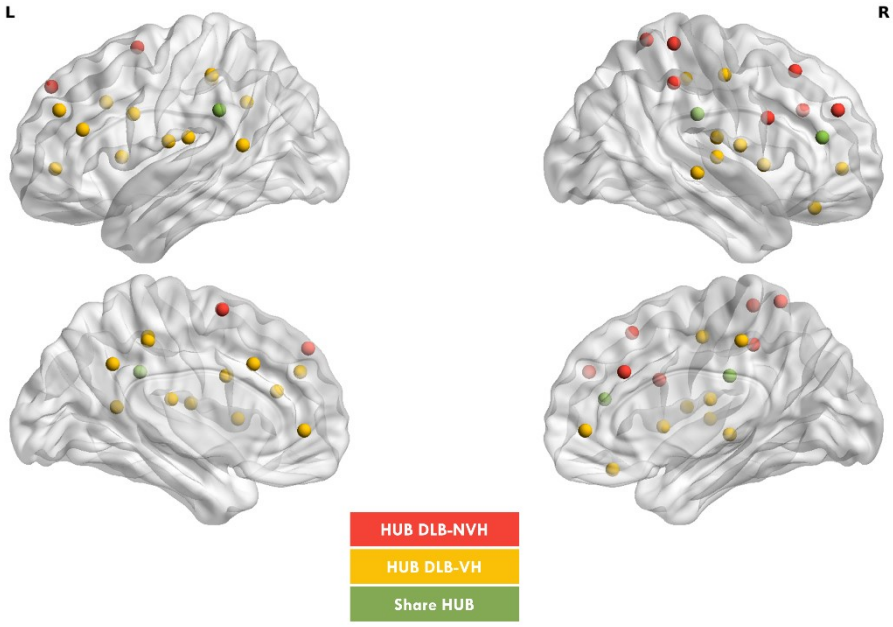
L_DefaultB_PFCd_1	-8	48	42	DMN
L_DorsAttnB_PostC_3	-22	-50	66	DAN
L_SalVentAttnA_FrMed_1	-6	4	62	VAN
L_SalVentAttnA_ParOper_1 *	-58	-38	30	VAN
R_ContA_PFCl_1	46	38	16	Fronto-parietal network
R_ContA_PFCl_2	48	10	26	Fronto-parietal network
R_DefaultA_PFCd_1	26	24	50	DMN
R_DorsAttnA_SPL_1	50	-60	-10	DAN
R_DorsAttnB_PostC_2	14	-52	66	DAN
R_SalVentAttnA_ParOper_1 *	60	-26	28	VAN
R_SalVentAttnB_IPL_1	58	-38	44	VAN
R_SalVentAttnB_PFCl_1	32	46	30	VAN
R_SalVentAttnB_PFCmp_1 *	6	28	30	VAN
R_SomMotA_3	30	-38	64	Somato-Motor

Legend: DMN: default mode network, VAN: ventral attentive network, DAN: dorsal attentive network. Stars (*) are for shared hubs.

Figures



Supplementary material figure 3.1: the figure shows the results of graph metrics whole brain analysis. The red star indicates $p<0.05$. The blue star indicates a tendency of significativity.



Supplementary material figure 3.2: the figure shows the distribution of HUBs. The red dots are HUBs belonging to non-hallucinated patients, the yellow hubs are those belonging to hallucinated patients. Green dots indicate shared HUBs.

Study 4: role of cerebellum in VHs of DLB

The non-motor contribution of cerebellum in cognition and behavioral processes raised up in the last decade and the role of the cerebellum in behavioral symptoms of dementia is still largely unknown.

We read with particular interest the recent research by Lawn and ffytche published in Cortex 2020 (Lawn T and D Ffytche 2021), who studied neuro-anatomical correlates of visual hallucinations (VH) comparing white and gray cerebellum volumes in Parkinson disease and in subjects with eye-diseases compared to healthy subjects. The authors found in hallucinators lower gray matter volumes bilaterally within the cerebellar lobule VIII extending to IX/VII and Crus 1. A correlation was observed between white matter volume in the brainstem and gray matter volume of the lobule VIIIb suggesting a functional association.

Previous task-based MRI and resting-state fMRI studies demonstrated that lobule VII, VIII and IX of the cerebellum are subcortical components of well known cortical attentive functional networks (Buckner RL et al. 2011; Bernard JA et al. 2012; Ramanoel S et al. 2018). Since some theoretical models for the genesis of VH in Parkinson disease and dementia with Lewy bodies (DLB) include an aberrant activation of visual attention networks., the authors suggest that cerebellum could have a key role in VH.

Here we would like to integrate the results by Lawn and ffytche with our preliminary findings in patients with probable DLB, a disease in which VH are core feature, assessing of the glucose metabolism of the cerebellum In DLB with and without VH.

Thirty-five subjects with a diagnosis of probable DLB (21 without VH and 14 with VH) (McKeith IG *et al.* 2017) matched for age and sex (69.4 ± 6.93 years and 72.8 ± 6.18 years respectively) were studied with PET-MR integrated scan, collecting ^{18}F-FDG PET and 3T RM data. We used SUIT algorithm for cerebellum segmentation and anatomical parcellation to extract cerebellar volumes. Partial volume correction was performed with an inhouse algorithm using the Symmetric Geometric Transfer Matrix (SGTM) of PET data. We used the brainstem as reference region in order to obtain regional cerebellar standard uptake values ratio (SUVr). We conduct an analysis of variance controlled for estimated total intracranial volume to evaluate differences for each

anatomical volumes of the cerebellum between the two groups, following by an analysis of ^{18}F-FDG PET SUVr. Age and sex were added as covariate.

Hallucinators showed lower FDG-uptake in the right and left, lobule VI and IX and Crus I, in the left lobule VIIb and VIIIa (p corr < 0.05). We found a negative correlation between the severity of VH evaluated with the hallucination subitem of Neuropsychiatric Inventory and the values of metabolism in the left and right lobule IX (rho = -0.52 and rho = -0.54 respectively, p corr = 0.005). As for the analysis of atrophy we found a volume reduction in hallucinators of right Crus I, lobule IX and X (p uncorr <0.05) but the results did not survive after correction for multiple comparisons. Fig 4.1.

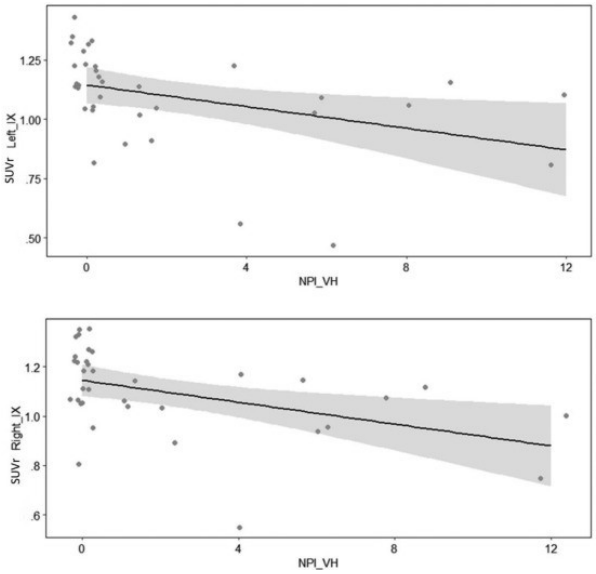


Fig. 4.1. The images show the correlation between individual scores for VH-subitem of the NPI questionnaire and the patient's mean FDG standard uptake values of the left lobule IX (rho = −.52, p corr = .005) and right lobule IX (rho = −.54, p corr = .005).

Discussion

Psychiatric onset of dementia

In the first part of study 1 we conducted an epidemiological study on a population longitudinally recruited among patients referring for the first time to a psychiatric clinic due to late onset psychiatric symptoms. After a multidisciplinary psychiatric and neurological evaluation, the neuropsychological assessment and the clinical follow up for at least one about 50% of these patients could be classified as having a possible neurological disorder, mainly neurodegenerative diseases. The same proportion was found in the sample that underwent second level investigations. Most of the patients with a final diagnosis of neurological disorder fell into the bvFTD group, followed by AD and DLB. As phenotype of psychiatric presentation, the majority of patients with a baseline diagnosis of BD-like symptoms was finally classified as PPD, on the contrary late-onset psychosis and late-onset OCD were more frequent presentation of dementia neurodegenerative disease.

Affective disorders are well known symptoms associated with dementia. However, during the last decades emerged the knowledge that some patients with dementia may have late-onset psychiatric symptoms as clinical presentation of the neurodegenerative disease. Wolley and colleagues showed that a total of 28.2% of patients with a neurodegenerative disease received a prior psychiatric diagnosis, delaying the right diagnosis, increasing the distress of family and caregivers, and receiving incorrect treatment and prognosis (Woolley JD *et al.* 2011).

Traditionally bvFTD was the most studied neurodegenerative disease with psychiatric symptoms at onset. In the first years of 2000's some studies highlighted the importance of psychiatric symptoms at disease onset, introducing the concept of "Mild Behavioural Impairment (MBI)" (Hallam BJ *et al.* 2007; Taragano FE et al. 2009). Moreover, these studies showed evidence that the right identification of patients with a changed behavioural profile was also relevant to identify other neurodegenerative diseases: 36% patients had FTD, 28% had AD, 18% had vascular dementia (VaD), and 18% had other types of dementia suggesting that any type of dementia syndromes can first present only with behavioural symptoms (Taragano F and R Allegri 2003). In literature is well known that neuropsychiatric symptoms are common in MCI cohorts, with estimation of

increasing the risk of dementia of 25% (Rosenberg PB et al. 2013); therefore neuropsychiatric symptoms were recognized progressively as core to the dementia process (McKhann GM *et al.* 2011). The scientific community remarked the importance of a correct investigation of behavioural and psychiatric symptoms especially in patients with atypical presentation of dementia (Rossor MN et al. 2010).

In 2016 the Neuropsychiatric Syndromes Professional Interest Area (PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART) defined MBI as an umbrella concept describing a syndrome in which late-life onset of psychiatric symptoms could be early manifestations of a neurodegenerative disease, not only bvFTD (Ismail Z *et al.* 2016). In 2020 Ducharme and colleagues published a paper aimed at providing the best clinical recommendation to specifically distinguishing bvFTD versus PPD (Ducharme S *et al.* 2020). Despite that, nowadays disentangling a primary psychiatric disorder from a psychiatric onset of a neurodegenerative disease is still a clinical challenge.

Many studies in literature, either in psychiatric and neurological field, underlie the higher risk to develop dementia in patients with mood disorders or shows that those symptoms could be indicate a prodromal phase of dementia with high risk to conversion (Porter VR *et al.* 2003; Kaiser NC *et al.* 2014; Zhao QF *et al.* 2016).

Despite that, to our knowledge there is only one recent study that explore the diagnostic challenge of a possible neurodegenerative disease in psychiatric settings. In a recent study, authors found that 41.73% of psychiatric inpatients with late-onset psychiatric symptoms have a final diagnose of a dementia (Shao Y et al. 2021). In our study we confirm these recently published data, with 50% of late onset psychiatric patients having a final diagnosis of dementia.

The psychiatric phenotypes in our cohort is representative of those described in literature. In 2011 a review on psychiatric disorders in elderly showed that depression was the most frequent psychiatric diagnosis. On the contrary, OCD was less common among the elderly than among younger people. Population studies reported the prevalence of psychotic symptoms in elderly population being from 2% to 4.2% (Henderson AS et al. 1998; Lyketsos CG et al. 2000), but it raised up to 10% in other

studies (Ostling S and I Skoog 2002). The authors suggested that late-onset psychosis may be underreported since elderlies were reluctant to report these types of symptoms. Moreover, considering gender distribution in our whole cohort, the results are consistent with literature findings, showing a higher prevalence of women. We find also an higher prevalence of women in the groups with depression and late onset-psychosys, although evidences for this second group were heterogeneous (Skoog I 2011). As regard as OCD, considering the smallest numerosity of the samples compared to the others, we find a higher prevalence of men, consistently with previous studies (Grenier S et al. 2009).

In our cohort of patients with late-onset psychiatric disorders the most frequent type of dementia was bvFTD (45.2%), confirming that this is the most relevant differential diagnosis with a primary psychiatric disorder (Lanata SC and BL Miller 2016), followed by AD (21.4%) and DLB (26.2%). This frequency distribution is different from what is known from the epidemiological studies on dementia, where AD is the most common, covering about 60% of dementias, followed by vascular disease 20% (Cao Q et al. 2020). We can explain this difference with two observations. First, looking at the inclusion criteria of our study we excluded patients with a high level of vascular impairment at neuroimaging or patients with previous stroke. This choice was done because we wanted to exclude secondary causes of dementia. Second, from the literature, it is well known that in early phases of the disease there is a higher prevalence of psychiatric disorders in bvFTD when compared to AD.

Depression is the major mood disorder in the elderly, and some studies report that the incidence increases after 80 years old (Skoog I 2011).

In our population, we show that 50% of patients with a diagnosis of depression have diagnosis of a dementia. This result highlights the extreme variability of the underlying brain disease in this group. Moreover, patients presenting with depression as onset of a neurodegenerative disease were diagnosed similarly with AD, bvFTD and DLB. A possible explanation of the result is the extreme transversality of this symptom across all dementias (Ballard C et al. 2013; Galts CPC *et al.* 2019; Collins JD *et al.* 2020).

BD is the second most frequent group in our cohort. Prevalence of BD is relatively high, up to 6%, in previous epidemiological studies and in subjects older than 65 years from 0.1 to 0.5% (Maia da Silva MN et al. 2021). A review of 2012 showed that in older adults bipolar depression may account for 8–10% of psychiatric admissions, and it is likely that persons aged 60 years and older constitute about 25% of the population with bipolar disorder (Azorin JM et al. 2012). We found that most patients with a BD diagnosis had a final PPD diagnosis.

Interestingly about 90% of patients with late onset psychosis in our study after clinical monitoring and follow up have a final diagnosis of a dementia. The result is consistent with a previous study conducted on a Swedish population-based cohort where authors demonstrate that the late onset psychosis in the first year after the beginning of symptoms is related to higher diagnosis of dementia, highlighting the importance of ongoing symptom monitoring in this group of patients (Stafford J et al. 2021). On the other side, psychotic symptoms are core features of some neurodegenerative disease, like DLB, and are considered a strong predictor of this condition (Tiraboschi P *et al.* 2006), therefore it is likely that the majority of patients have an underling dementia.

The last group to consider is the less represented in our cohort: the OCD group. About 80% of patients with late onset OCD, like late onset psychotic patients, were classified to the dementia. In literature the OCD onset of a dementia is rarely described when compared to the other psychiatric disorders at onset, instead it is well known the dementia strongest association with bvFTD (Meyer S et al. 2019; Mitchell E et al. 2019). On the contrary, the rarest dementia associated with late-onset OCD is AD, with only one case-report described in literature (Ruggeri M *et al.* 2022). Our results are consistent with literature, in fact 80% of this group had a final diagnosis of bvFTD and no one had a diagnosis of AD.

In the second part of this study, we investigated the cognitive profile of patients with late-onset psychiatric disorders. The first finding was that each psychiatric group had a characteristic cognitive profile and that psychotic patients had the poorer performance at cognitive tests. Our results overlapped the ones of an extensive review investigated the cognitive dysfunction in psychiatric disorders. Patients with schizophrenic-psychotic

symptoms had a severe impairment in all cognitive domines: working memory, attention, executive function, semantic memory, visual memory, social cognition and language. The cognitive impairments were higher than in other psychiatric disorders (Millan MJ et al. 2012).

Patients with depression had a broad range of performances and this finding could be explained with the high heterogeneity of the underlying brain disorders. Finally, patients with late onset OCD and BD had a better performance when compared with other groups, consistently with a previous study in which these psychiatric conditions had a lower and non-specific cognitive impairment (Millan MJ *et al.* 2012).

When we took a step forward in the diagnostic process by comparing cognitive profiles between the PPD group versus the one with dementia, we did not see any differences in the MMSE mean scores and in functions of daily living. Our result is not in line with a recent work in which the authors found a significant lower MMSE score in patient with PPD (Shao Y *et al.* 2021) respect to patients with a final diagnosis of dementia. This difference can be explained with the inclusion criteria of our study, in particular only patients with their first episode of psychiatric disorder and a late onset of symptoms were enrolled. Therefore, our patients had a very short disease duration, about 3 years, with no difference between the two groups.

When we investigate the differences in individual cognitive tests between patients with dementia and PPD, only TMT-A and delayed prose-recall were significantly different. Our results highlight an overall severe impairment of visual attention and memory in the group with dementia, and in particular the likelihood of a diagnosis of dementia increased the risk to have lower cognitive test scores. Previous studies investigated the performance at the trail making test in patients with organic depression and primary depression. The authors showed that this cognitive test could be a marker of an organic disorder because, in their sample, patients with organic depression had lower TMT-A scores when compared with either the psychiatric depression group, that were in the middle, and healthy controls, who were the best performers (Talarowska M et al. 2012).

We then analysed the cognitive profile for each specific dementia groups compared to PPD. AD was characterized by a worse performance in the TMT-A and delayed memory

recall than PPD, while in DLB there was a worse performance only in the TMT-A test. bvFTD and PPD did not differ significantly on any cognitive test.

From the literature, the lower scores of memory delayed recall in AD patients compared to bvFTD is well known (Perri R et al. 2013); on the other hand, it is difficult to distinguish AD and DLB due to an overlapping neuropathology that complicate the differential diagnosis mainly in the early stages of the disease (Jellinger KA and J Attems 2008; Coughlin D et al. 2019). Reus and colleagues found no difference between bvFTD and primary psychiatric patients in social cognitive functioning (Reus LM et al. 2018). Difficulties in characterizing the pathology-specific cognitive profile of the subgroup at an early stage of the disease also make it difficult to distinguish PPD from a specific type of dementia. For AD and DLB we have some more sensitive tests that might help think about the presence of a possible neurodegenerative disease, instead for bvFTD the is no turning point.

As seen in our results, the diagnosis of dementia can be masked by late onset psychiatric disorders in half of the patients accessing to a psychiatric unit. It is important that both neurologist and psychiatrist are aware of those evidences in order to reduce the delay of the correct diagnosis as well as to reduce patients and caregiver distress and in hospital length of stay. The results showed that among the late onset psychiatric disorders patents, the groups that could be a red flag for a possible diagnosis of dementia are late onset psychosis and late onset OCD. The cognitive profiling of those patients can be useful to identify a possible dementia, especially AD or DLB, unfortunately NPT are not specific enough to distinguish PPD and bvFTD. Thus, the follow up on a clinical and cognitive level is highly recommended.

VH circuit in DLB: anatomical point of view

In study 2 we examined structural and functional connectivity abnormalities in patients with DLB and visual hallucinations (VH). Four findings are worth noting. First, whole-brain tractography analysis showed damage to white matter tracts in patients with VH, especially in the right hemisphere: FA was decreased in the right ILF and SLF3, and MD was increased in the right ILF, SLF3, IFOF, and left UNC. Second, cortical thickness in regions connected through the right SLF3 was reduced in patients with VH. Third, changes in anisotropic variables in the right SLF3 and ILF correlated significantly with severity of VH and visual attention impairment. Finally, resting-state fMRI showed a reduced within-network signal synchronization in regions of the DMN, and (to a lesser extent) of the DAN, and an increased synchronization in regions of the VAN in patients with VH. Overall, these findings strongly support the importance of right-hemisphere attention networks in the generation of VH in patients with DLB.

White matter bundle alterations in visual hallucinations

Previous structural connectivity studies in DLB found changes in the long associative white matter bundles in patients with VH. Kantarci and collaborators found increased MD in the right ILF of patients with VH (Kantarci K et al. 2010). Delli Pizzi et al. found a reduced FA in the right ILF of patients with DLB who experienced VH, and an increased MD in the thalamic regions projecting towards the bilateral prefrontal and parieto-occipital cortex, right amygdala, and left motor cortex. MD in the right thalamic sub-region projecting towards the parieto-occipital cortex also correlated with the severity of VH (Delli Pizzi S, R Franciotti, JP Taylor, R Esposito, et al. 2015; Delli Pizzi S, R Franciotti, JP Taylor, A Thomas, et al. 2015).

Our study supports previous findings that right ILF is a target of microstructural changes in patients with DLB and VH.

The ILF connects the occipital cortex to the inferior-temporal cortex. It is part of the ventral visual stream essential for object recognition (Ungerleider LG and JV Haxby 1994; Milner AD GM 1995), face recognition (Grossi D et al. 2014), and related emotional processes (Marstaller L et al. 2016; Unger A et al. 2016; Jiang W et al. 2017). Microstructural changes in associative white matter tracts may impair bottom-up visual processing, and comparison with top-down information stored in the inferotemporal

cortex. This effect may contribute to the generation of VH, in which case the experience of VH by patients with DLB would reflect a mismatch between incoming visual information and top-down priors. Loss of top-down feedback may cause hypo-activation of the occipital visual regions, which are hypometabolic in DLB, although this occipital hypometabolism per se does not seem to explain the occurrence of VH (Pezzoli S et al. 2017).

The ILF's anatomy might be the cause of the absence of relation between the ILF projection cortical thickness and FA. The ILF is composed of direct and indirect u-shaped fibres (Catani et al. 2003). The ILF measures reported in the manuscript include solely direct connections between the occipital and the anterior temporal lobes, which, putatively, may have maintained their functioning via the indirect u-shaped route. This rerouting of information via the u-shaped fibres may also cause VH as visual areas skipped initially by the direct route became a relay for the visual information. In summary, cortico-cortical disconnection of the occipital cortex from regions of the temporal lobe though ILF, may play a role in the genesis of the VH and contribute to the deficit of visual attention. However, occipital cortical disconnection from subcortical regions of the midbrain should also be considered for the genesis of VH. In fact, In fact, presence of RBD has been found associated with a greater frequency of VH in PD (Gallagher DA et al. 2011) and DLB (Cagnin A *et al.* 2013) as it was found in the present study.

Our study shows another neural correlate of VH in DLB, namely damage to the right SLF3, associated with microstructural alterations (FA, MD), and abnormal correlation with functional connectivity on fMRI. The SLF is a white fiber bundle connecting the frontal and parietal lobes (Thiebaut de Schotten M, DH Ffytche, et al. 2011). It has three main tracts - the dorsal (SLF1), middle (SLF2) and ventral (SLF3) components - respectively connecting the DAN cortical areas, the VAN to the DAN networks, and the VAN cortical areas (Thiebaut de Schotten M, F Dell'Acqua*, et al.* 2011). SLF1 connects parietal (IPS) to prefrontal (FEF) regions of the dorsal attention network (DAN) (Corbetta M and GL Shulman 2002; He BJ, AZ Snyder*, et al.* 2007). SLF2 connects the temporo-parietal junction (TPJ) to the FEF regions. SLF3 connects the TPJ to the anterior insula and inferior frontal cortex, the primary nodes of the VAN (Parlatini V et al. 2017). There

are SLF1 and SLF2 pathways in both hemispheres, and their hemispheric lateralization correlates with visuospatial processing biases ordinarily present in healthy individuals, whereas the main volume of SLF3 is in the right hemisphere (Thiebaut de Schotten M, F Dell'Acqua*, et al.* 2011). Functionally, the DAN controls eye movements and spatial attention, while the VAN is activated during vigilance and sustained attention tasks. Target detection and reorienting of attention to behaviorally relevant stimuli also recruit the VAN, mainly in the right hemisphere (He BJ, AZ Snyder*, et al.* 2007).

Recently Zarkali et al highlighted the importance of loss of fronto-occipital connectivity in the development of hallucinations in a group of PD hallucinators, specifically those connecting frontal and occipital lobes (Zarkali A et al. 2020).

Our findings indicate that VH in patients with DLB are associated with an abnormal functioning of the VAN in the right hemisphere. The detection of microstructural white matter abnormalities in SLF3, the correlation of SLF3 anisotropic variables with severity of VH and visual attention impairment, the reduced cortical thickness of the SLF3 projecting regions, and the abnormal synchronization within VAN may reflect two primary information processing deficits:

1. Patients with DLB suffer from fluctuations in attention and vigilance due to noradrenergic input from the locus coeruleus to the right inferior parietal (TPJ) cortex, the posterior core region of the VAN (Aston-Jones G and JD Cohen 2005; He BJ, GL Shulman, et al. 2007; Shulman GL et al. 2007). A low state of alertness associated with a weaker firing of the locus coeruleus and lower TPJ activity may reduce the cortical signal-to-noise ratio, leading to abnormal perception, misperceptions, and hallucinations. This hypothesis can be tested by measuring autonomic activity and pupillary responses during visual tasks.

2. Damage to the right SLF3/VAN impairs our ability to shift attention and focus of processing between objects in our visual field. Remaining focused on a particular location can engender hallucinations – in fact, VH can be induced in healthy individuals if they fixate on flickering stimuli (Pearson J et al. 2016). This second hypothesis can also be tested by demonstrating that DLB patients with and without hallucinations differ in their ability to use eye movements to explore visual scenes.

The lateralization on the right hemisphere of microstructural white matter changes and cortical thickness could therefore better explained by a de-arrangement of functional circuits (VAN) and neurochemical pathways (i.e. locus coeruleus) with a main right lateralization than by asymmetric DLB-related neuropathological changes affecting the right side.

Derangement of functional attentional networks

We found a high correlation of fMRI connectivity in the right VAN of VH patients, notwithstanding a decrease of microstructure and volume of the right SLF3.

The healthy brain shows a positive correlation between the strengths of its structural and functional connectivity (Straathof M et al. 2019), although this correlation at the individual level is weak (Misic B et al. 2015). Acute damage (e.g. stroke) alters functional and structural connectivity, and the positive correlation between them (Griffis JC et al. 2019, 2020). Intriguingly, functional connections become weaker in the event of anatomical damage, but synaptic re-weighting (especially of indirectly-connected regions) may lead to abnormally high correlations (Siegel JS et al. 2016; Griffis JC *et al.* 2019). This is also seen in experimental models of traumatic brain injury (Harris NG et al. 2016), and in early stages of multiple sclerosis (Hawellek DJ et al. 2011; Filippi M and MA Rocca 2013). In the case of DLB, in which alpha-synuclein slowly accumulates in cortical circuitries and spreads via trans-synaptic routes, a similar mechanism may be involved when early microstructural changes in the right SLF3 is associated with increases in connectivity in the right VAN on fMRI.

We found alterations across multiple networks (DAN, DMN, VAN), as seen in previous studies (Kenny ER et al. 2012; Kobeleva X et al. 2017; Onofrj M et al. 2019). Changes found in the functional correlations between the networks mainly concerned the visual network. These results suggest that individuals with VH have an impairment of the main network involved in processing visual environmental information and are consistent with the results of previous studies of fMRI data in which patient with DLB pathology have an alteration on coupling between the DAN and the VAN, with a consequently “disconnection” between the two networks during the presentation of external stimuli.

A few theoretical models have been proposed to explain the cognitive derangement responsible for the genesis of recurrent complex VH typical of DLB and Parkinson’s

disease. One is the perceptive and attention deficit model proposed by Collerton et al. (Collerton D *et al.* 2005), in which a combination of visual perception impairment and attention deficit, possibly caused by network misalignment in the frontal and parieto-occipital areas, is needed to promote VH. Visual attention deficits can be caused by an altered top-down control (from the frontal cortex to the visual association cortex), while impaired visual perception and spatial functions may be due to difficulties with elaborating visual stimuli in the associative visual regions (bottom-up control) (Cagnin A *et al.* 2013).

Another theoretical model of VH (Shine JM *et al.* 2011) emphasizes the importance of an imbalance between DAN and VAN. The former includes cortical regions in the intraparietal sulcus and the frontal eye fields of each hemisphere, while the latter contains the TPJ, the ventral frontal cortex and the anterior insula (Corbetta M et al. 2008). DAN is mainly activated by cue-target stimuli, and it is important in the voluntary orienting of attention (top-down control). VAN is activated by invalid stimuli and is involved in detecting unexpected but behaviorally relevant events (bottom-up control). In the light of our findings, it could be that patients with complex VH have an impaired involuntary environment-monitoring attention system. This would entail the loss of a regulatory process that, associated with a less efficient visuo-perceptive network for information processing, would lead to misperceptions, and generate VH. Further studies are needed to clarify the specific contributions of neurotransmitter alterations to synaptic dysfunction and resting-state network alterations, and ultimately to the promotion of VH.

This study has some limitations that we need to acknowledge. The deterministic approach to reconstruct DTI tracts and the manual ROI drawing for fiber bundles dissection have some known limitation described previously in literature (Chung HW et al. 2011; Ressel V et al. 2018): operator-dependency, difficulties resolving curving, crossing or kissing tracts. Lacking rs-fMRI data for a healthy control group restricts our interpretation of network impairment. We established a probable diagnosis of DLB in our sample based on clinical criteria alone; no autoptic confirmation was available (this diagnosis was obtained at specialized centers, however, and confirmed at follow-up). The size of our sample of patients with DLB is also relatively small. Finally, the NPI (item

2) used to assess the presence and severity of VH cannot further characterize these phenomena. More complex VH assessments will be needed in future work.

Our multimodal neuroimaging study nonetheless revealed altered neuro-anatomical and functional connections in patients with DLB who experienced VH. A disrupted interplay between attentional networks and DMN, sustained by white matter long tracts - mainly in the right hemisphere, such as SLF3 - has a crucial role in the genesis of VH.

VH circuits in DLB: functional and metabolic point of view

In study 4 we show that DLB patients with VH, compared to similar patients without VH, have lower glucose metabolism in the occipital and parietal cortex correlated with the severity of visual misperception in the right occipitotemporal cortex. The visual network was also relatively disconnected from other cognitive control networks (DAN, DMN, FPN), which were also affected. In contrast, regions of the ventral attention and limbic networks were relatively hyper-connected, with a positive correlation with visual hallucinations in the right orbitofrontal cortex metabolism.

The reduction of glucose metabolism in posterior cortical regions is characteristic of DLB (Firbank MJ et al. 2016) and DLB patients with VH show an association with both right hemisphere occipitotemporal, and prefrontal-parietal hypometabolism (Perneczky R *et al.* 2008). The Morbelli et al. study is notable for the large sample size (n=171) and correlation with multiple symptoms of DLB, including parkinsonism, VH, and rapid eye movement disorders. They found VH to covary with hypometabolism of bilateral dorsolateral-frontal cortex, posterior cingulate, and parietal cortex (Morbelli S *et al.* 2019). The metabolic changes are consistent with anatomical and structural changes in the same regions, e.g., in microstructural diffusion (Kantarci K *et al.* 2010; Delli Pizzi S, R Franciotti, JP Taylor, R Esposito*, et al.* 2015), or cortical thickness (Delli Pizzi S et al. 2014).

Our study is the first to perform a metabolic connectivity analysis using a functional cortical parcellation atlas to define specific networks and their interaction. This approach led to several novel insights.

First, while our regional metabolic analysis is consistent with previous work showing an association of occipitoparietal hypometabolism, especially in the right hemisphere, and visual hallucinations, here we also show a novel dramatic disconnection of visual occipital regions with control networks of frontal and parietal cortex (DAN, DMN, FPN). This disconnection parallels a relative hyperconnectivity between somatosensory, ventral attention, and limbic networks in the right hemisphere with other networks.

Second, these metabolic connectivity patterns resemble patterns of fMRI connectivity in the healthy brain. The visual network strongly correlates with other sensory and motor networks and the dorsal attention network (so-called, task-positive or external

networks). In turn, these networks show a negative correlation with the default and frontoparietal networks that are positively correlated (task-negative or internal networks) (Yeo BT et al. 2011; Hacker CD et al. 2013). Finally, the ventral attention is the most independent network with weak or no correlation with internal or external networks.

Metabolic connectivity in the DLB patients without VH resembles this healthy pattern (Fig.3A) with a relatively segregated ventral attention network and connectivity between visual, somatomotor, and dorsal attention on one hand and frontoparietal and DMN on the other. Interestingly, the negative fMRI correlation between DAN and DMN (Fox MD et al. 2005) appears as positive metabolic connectivity.

In DLB patients with VH, the ventral attention network becomes excessively connected vis-a-vis a disconnection with other control networks, which lose internal connectivity (e.g., FPN and DMN).

From a cognitive neuroscience standpoint, the loss of interaction between DAN and visual networks may reflect the loss of top-down control necessary for normal perception (Corbetta M and GL Shulman 2002). Top-down signals inhibit irrelevant information in the visual field and provide priors for perception. In the absence of top-down signals, visual information stored in the association cortex may be perceived (Collerton D et al. 2003; Shine JM et al. 2014). This is also the case in Anton Syndrome.

The hyperconnectivity in the right ventral attention and limbic regions positively associated with the frequency of hallucinations may reflect a loss of signals to disengage attention (Corbetta M and GL Shulman 2002) from limbic signals in the insula and orbitofrontal cortex. The insula responds to salient stimuli (Menon V and LQ Uddin 2010) and integrates internal and external states (Onofrj M *et al.* 2019). Orbitofrontal cortical regions may mediate visual hallucinations (Hall JM et al. 2019; Walpola IC et al. 2020) as the possible source of top-down predictions for object recognition (Chaumon M et al. 2014).

We indeed identify in study 4 in hallucinators a hypometabolism in crus I, lobule VIIb, VIIIa and IX, regions that are nodes within the DAN and DMN network (Buckner RL *et al.* 2011; Brissenden JA et al. 2016; Brissenden JA et al. 2018; Ramanoel S *et al.* 2018). The results support the theoretical framework of VH for which impaired functional

connectivity has been found in DAN and DMN, with an over-reliance on the activity of VAN (Collerton D *et al.* 2003; Shine JM *et al.* 2011; Onofrj M *et al.* 2019). DAN is mainly involved in the selection of valid sensory visual stimuli and goal-directed attention (Shulman GL et al. 1999; Corbetta M and GL Shulman 2002; Corbetta M *et al.* 2008). In the condition of hypoactivity of DAN, interpretation of ambiguous visual stimuli overly to the information elaborated by DMN, processing autobiography memory, and by VAN/salience networks, involved in internally driven attention. Functional alterations of the interplay between these three networks (DAN, VAN and DMN) may result in the emergence of proto-object (Collerton D *et al.* 2003) stored in the visual memory cortex, driven by internally oriented attention more than externally oriented attention (Onofrj M et al. 2013; Shine JM *et al.* 2014). The correlation between hypometabolism of lobule IX and the severity of VH in DLB may reflects the key role of cerebellum in VHs, as that region is linked with either DAN and DMN (Ramanoel S *et al.* 2018). We did not find differences in regional volumes of the cerebellum between DLB with and without VH, in contrast with findings by Lawn and ffytche in Parkinson disease. One explanation is the different image analysis for detection of atrophy and small sample size. Secondly, DLB patients have a relatively shorter disease duration (no-VH: 2.04±0.29 years and VH: 3.04±1.76 years) compared with the groups considered by Lawn and ffytche (CBS: 11.5±5.43, AMD: 8±4.87, PDHAL: 8.71±4.43 and PD: 5.8±2.39).

This reply to Lawn and ffytche would highlight another way to evaluate the contribution of cerebellum in VHs, focusing not only on structural changes but also on metabolic alterations. We confirm a possible contribution of cerebellar region belonging to DAN and DMN in VHs and we show how metabolic changes may pre-empt a structural change.

Appendix: methods

Methods: study 2

Patients

Thirty patients with a diagnosis of probable DLB according to McKeith criteria (McKeith IG *et al.* 2017) and 13 age-matched healthy controls were enrolled in the study at the Memory Clinic of the Department of Neurosciences at Padua University (Italy). Among the patients with DLB, 7/30 were not considered in subsequent imaging analyses due to movement artifacts. The final sample thus consisted of: 23 patients with DLB, 10 of whom experienced VH (the VH subgroup), and 13 who never experienced VH (the no-VH subgroup); and 13 age-matched healthy controls.

Exclusion criteria were: brain MRI evidence of severe cerebrovascular disease; a history of primary psychiatric disorders; and severe ocular diseases with impaired visual acuity. Patients treated with cholinesterase inhibitors or levodopa were only eligible for the study if they had been on stable doses for at least three months.

Clinical assessments included visual acuity, to exclude ocular diseases; severity of extrapyramidal signs using the motor part of the Unified Parkinson Disease Rating Scale (UPDRS), (Goetz CG et al. 2008); fluctuations of cognition and alertness, using the Clinician Assessment of Fluctuations scale (Ferman TJ et al. 2004); symptoms suggestive of REM sleep behaviour disorder (RBD) using the single-question RBD screening tool (Boeve BF et al. 2011); burden of behavioral disturbances, measured with the Neuropsychiatric Inventory (NPI) questionnaire (Cummings JL et al. 1994).

Participants' cognitive profile was examined with the following neuropsychological tests: the MMSE for global cognition (Folstein MF et al. 1975); the Visual Object and Space Perception Battery (VOSP) to assess visuo-perceptual and visuo-spatial impairments (Warrington EK et al. 1991); the Trial Making A, Trial Making B (Mondini S MD, Vestri A, et al. 2003) and Digit Cancellation tests to assess visual attention (Spinnler H and G Tognoni 1987); the clock drawing test to examine visuo-constructional abilities and executive functions; digit spans (forward and backward) (Orsini A et al. 1987) and prose recall to assess short- and long-term verbal memory (Mondini S MD, Vestri A, et al. 2003); the letter fluency test for language (Mondini S MD, Vestri A, et al. 2003); and the Rey-Osterrieth Complex Figures to test visuo-constructional abilities and visual memory (Caffarra P et al. 2002). Legal copyright restrictions prevent public archiving of

the various clinical assessments and tests used in this study, which can be obtained from the copyright holders in the cited references. The study was approved by the local ethical committee at Padova Hospital (n. 0038879) and all participants signed an informed consent.

MRI acquisition and analysis

Acquisition

Brain MRIs were acquired at 1.5 T (Achieva, Philips Medical Systems, Best, Netherlands) with a standard quadrature head coil. For all participants, the MRI study protocol included: (a) 3D T1-weighted imaging (repetition/echo times: 20/3.8 msec; flip angle: 20°; voxel size: 1x1x1 mm; field of view: 210 mm; acquisition time: 7.02 minutes); (b) diffusion tensor images (DTI) acquired with a single-shot echo-planar diffusion-weighted imaging method (TR/TE: 11,114/80 ms; acquisition matrix: 112x110, echo train length: 59; reconstructed matrix: 128x128; reconstructed voxel: 1.75x1.75x2 mm, SENSE p-reduction: 2; number of excitations: 2; acquisition time: 12.24 minutes). The axial sections covered the whole brain. Diffusion sensitizing gradients were applied along 32 non-collinear gradient-encoding directions with a maximum b = 800 s/mm^2; an additional image without any diffusion gradients (b = 0 s/mm^2) was acquired as well. A T2-weighted spin echo (to investigate other causes of focal or diffuse brain damage) was also obtained.

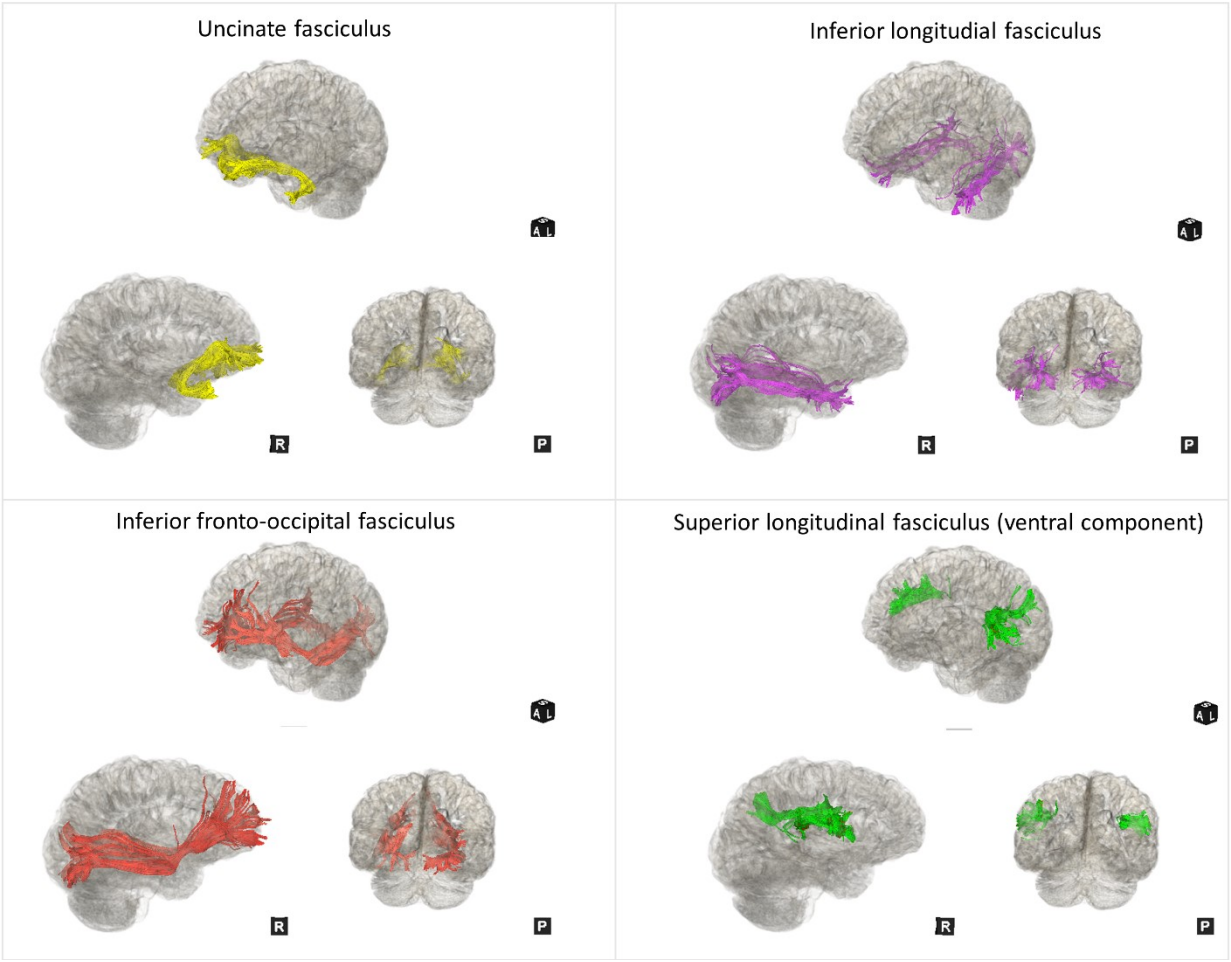
rs-fMRI echo-planar images were only acquired for patients with DLB (TR/TE= 2,035/50 ms, flip angle= 90°, 21 axial slices, matrix 128x128, voxel 1.8x1.8x6 mm, acquisition time ≈ 8', FOV 23 cm, brain volume n= 250).

Diffusion tensor imaging analyses

Subsequently to eddy current and movement distortion correction, a whole-brain Tract-Based Spatial Statistics (TBSS) of the DTI data was carried out with FSL 5.0 (FMRIB), - as previously described by Smith et al. (Smith SM et al. 2006; Smith SM et al. 2007) - generating fractional anisotropy (FA) and mean diffusivity (MD) maps.

In parallel, a single-tract dissection analysis was undertaken. A deterministic tractography algorithm based on Euler integration (Jones et al., 2002) (step length 1 mm; FA threshold of 0.15, angle threshold of 45) was used to calculate streamlines for the whole brain in ExploreDTI (Leemans A JB, Sijbers J, Jones DK 2009). Dissections of the uncinate fasciculus (UNC), the ILF, the IFOF, and the frontoparietal SLF (the so-called

branch III) were obtained for each hemisphere using TrackVis (www.trackvis.org) (Wang R et al. 2007; Wedeen VJ et al. 2008) (see also Supplemental Figure 1). Multiple ROIs were defined manually on axial, coronal, and sagittal FA images for each subject, and were used as target regions for tracking purposes (Rojkova K et al. 2016).



Supplemental Figure 3 3D reconstruction of white matter tracts. The image shows a 3D reconstruction of the tracts in one subject.

Cortical thickness in the regions of the projecting bundles

Cortical thickness was derived from individual T1-MRI using the BCB toolkit (Foulon C et al. 2018). This toolkit adopts a method called diffeomorphic registration based cortical thickness (DiReCT) to estimate cortical thickness (Das SR et al. 2009) from T1-weighted imaging datasets. Then a subject's T1 image was registered to the MNI152 template and the same deformation was applied to individual cortical thickness maps using 'normalize' in the BCB toolkit (Foulon C *et al.* 2018). The 'normalize' function uses affine and diffeomorphic deformations (Klein A et al. 2009; Avants BB et al. 2011) to register

T1 images. Target ROIs were chosen among those representing the cortical projections of white matter tracks found different in the comparison between VH and no-VH patients with DLB. The target ROI were selected by masking subjects' cortical thickness template obtained in the previous step with a specific tract template from the tracts atlas in the BCB toolkit (Rojkova K *et al.* 2016). Then the mean cortical thickness of a target ROIs was extracted.

Resting-state functional analysis

Correction, registration and seed-based connectivity analyses were done with the BCB toolkit (Foulon C *et al.* 2018) in the following steps. The fMRI images were corrected for motion using MCFLIRT (Jenkinson M et al. 2002), then corrected for slice timing, smoothed with a full half width maximum 1.5 times the largest voxel size, and filtered for low temporal frequencies using a Gaussian-weighted local fit to a straight line. All these steps are also available in Feat as part of the FSL package (Woolrich MW et al. 2009). The fMRI images were linearly registered to the T1 images, and then to the MNI152 template (2mm) using affine transformation. Confounding signals were discarded from the fMRI images by regressing out a confounding matrix from the functional data. The confounding matrix included the estimated motion parameters obtained from the previously-performed motion correction, the first eigenvariate of the white matter and cerebrospinal fluid, and their first derivative. Eigenvariates can be extracted using 'fslmeants' combined with the '-eig' option. White matter and cerebrospinal fluid eigenvariates were extracted using masks based on the T1-derived three-class segmentation thresholded to a probability of 0.9, registered to the rs-fMRI images, and binarized. The first derivative of the motion parameters, white matter and cerebrospinal fluid signal was then calculated by linear convolution between their time course and a [-1 0 1]. The time courses were extracted from a previously-obtained set of 66 ROI defining the default mode network (DMN), ventral attention network (VAN), dorsal attention network (DAN), and visual network (VIS) (Gordon EM et al. 2016).

Statistical analysis

Clinical, demographic and cognitive data were analyzed with SPSS 21.0. The Shapiro-Wilk test was used to check for a normal distribution of our data. Demographic and

clinical characteristics were analyzed with ANOVA, Student's t, the Kruskal-Wallis, and the Mann-Whitney tests, as appropriate, and using the χ^2 test for categorical variables. The alpha level was set at 0.05.

The DTI-TBSS voxelwise analyses were conducted using the 'randomize' FSL tool for non-parametric statistics. Statistical tests were run with a mean FA skeleton threshold of 5000 permutations, and a significance level at p-value corrected for a multiple-comparison family-wise error ≤0.05. DTI data were corrected for age, years of education, and MMSE score.

The DTI descriptors of the dissected tracts were analyzed using multivariate analysis of variance (MANOVA), followed by a post-hoc t-test with Bonferroni's correction, performed between groups with significant differences ($p < 0.05$). Cortical atrophy was tested with a t-test comparing the groups with DLB ($p < 0.05$).

To test the relationship between DTI changes and cortical thickness, 2 successive Bayesian linear regressions were used to test the prediction of each measure. For instance, we tested whether the cortical thickness of the projection of the right SLF3 (i.e. the dependent variable) could be predicted using FA values in the left and right SLF3 and ILF (i.e. the independent variable). Reversely we tested whether the FA values of the right SLF3 could be predicted using the cortical thickness of the projections of the left and right SLF3 and ILF. Analyses were performed using JASP (https://jasp-stats.org).

As in the rs-fMRI data analysis, a correlation matrix was built, calculating the correlation of the time course of each ROI with that of every other ROI, which gave rise to a 66x66 correlation matrix for each subject. A separate ANOVA was run to compare the DLB groups, and statistical significance was set at $p < 0.05$.

Methods: study 3

Patients

Twenty-six patients with a diagnosis of probable DLB according to current criteria (McKeith IG *et al.* 2017) were recruited at the Neurological Memory Clinic at the University of Padova and divided in two age-matched subgroups according to presence of recurrent complex VH: 13 with VH (mean age 72.3 ± 6.09, sex F/M: 7/6) and 13 without VH (no-VH) (70.3 ± 7.92 years, sex F/M: 4/9). Diagnosis of DLB was made by mean of clinical criteria in most of the patients. Patients without VH never experienced

spontaneous complex VH before recruitment. Exclusion criteria were brain MRI evidence of severe cerebrovascular disease, diagnosis of concomitant diseases contributing to cognitive decline and presence of eye diseases causing significant loss of visual acuity. Each subject underwent a clinical assessments evaluating: 1) visual acuity; 2) severity of extrapyramidal signs using the motor part of the Unified Parkinson Disease Rating Scale (UPDRS) 3) presence of fluctuations of cognition and alertness using the Clinician Assessment of Fluctuations (CAF) scale; 4) presence of symptoms suggestive of REM sleep behavior disorder (RBD) using the single-question RBD screening tool; and, 5) the burden of behavioral disturbances with the Neuropsychiatric Inventory (NPI) questionnaire. DaT scan was done in almost half patients (5/13 patients in the VH group and 6/13 patients in the no-VH group) demonstrating striato-nigral degeneration). Brain FDG-PET images were qualitatively evaluated in each subject by an experienced nuclear medicine physician to define presence of cingulate island sign (CIS) (present in 13/13 of VH-DLB and in 12/13 no-VH-DLB). The only one patient with absent CIS had abnormal DaT-scan findings. Profile of cognitive impairment was investigated with the following neuropsychological tests: MMSE for global cognition; Visual Object and Space Perception Battery (VOSP) to assess visual-perceptual and visual-spatial impairments; Digit Cancellation test to evaluate visual attention ; clock drawing test for visuo-constructional abilities and executive functions; digit span forward and backward and prose memory for the evaluation of short and long term verbal memory ; letter fluency test for language , and Rey-Osterrieth Complex Figure for visual-constructional abilities and visual memory (Cagnin A *et al.* 2013). The study was approved by the local ethical committee at Padova Hospital (n. 0038879) and all participants signed an informed consent.

Image analyses

Acquisition and processing of 18F-FDG PET/MRI

Following the European Association of Nuclear Medicine (EANM) guidelines for neurodegenerative diseases (Varrone A et al. 2009), after fasting for about 8 hours, subjects received an intravenous injection of 3 MBq/kg of ^{18}F-FDG (using a Medrad Intego PET infusion system) in a quiet, dimly lit room after been instructed to keep eyes closed and not to speak or be otherwise active for 25 minutes. No significant

hyperglycemia was detected (<150 mg/dl) before injection. One hour after injection, all subjects underwent a whole brain ^{18}F-FDG PET/MRI study on a 3T clinical PET/MR scanner (Biograph mMR, Siemens Healthcare, Erlangen, Germany) with scan lasting 25 minutes. A radial VIBE (UTE) sequence (1.6x1.6x1.6) was used to generate attenuation coefficient maps. PET was reconstructed into a 344x344 matrix using a single frame. Standard corrections for decay, scatter and dead time were performed.

T1-MPRAGE images cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite (v 6.01) , which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Technical details of these procedures are described in previous publications.

^{18}F-FDG PET images were processed using PetSurfer, a built-in package of Freesurfer. The package allows to correct for partial volume through a wide range of models, but for our purpose we used the Symmetric Geometric Transfer Matrix (SGTM). We used the standard pipeline to process the images as described in https://surfer.nmr.mgh.harvard.edu/fswiki/PetSurfer, using for the cortical parcellation the Shaefer-Yeo 100 ROIs functional atlas https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal (Schaefer A *et al.* 2018); a resolution of 5mm (FWHW) was used. We used the cerebellum cortex as reference region in order to obtain standard uptake value (SUV) ratios (SUVr). At the final step of analysis, FDG SUVr values, corrected for partial volume effect, were obtained for each region of the Shaefer-Yeo Atlas from every subject.

Graph analysis

The graph reconstruction and analysis were performed in R v3.6.1 (R Core Team, 2019), using igraph and brainGraph packages (https://cran.r-project.org/web/packages/brainGraph) (Kolaczyk & Csárdi, 2014). First, a general linear model was specified for each brain region, with SUVr values as the outcome variable and age, sex, and MMSE values as covariates. Second, Pearson correlation coefficients between the model residuals for all pairs of regions were calculated, and an adjacency matrix of size 100 × 100 was created for each group of patients (VH and no-VH). The

adjacency matrix of each group was binarized by thresholding and removing any correlations lower than the threshold level. Negative correlations were not considered. To ensure equal network sizes for both groups, the threshold level was chosen to result in a specific density (i.e., a ratio of the number of edges present in the network to total possible number of edges); a range of densities from 0.05 to 0.40 (step size: 0.01) was investigated. A fixed density at 29%, the minimum in which all nodes have at least one connection with another node (connected network) in all groups, has been chosen for single network and nodal level analysis. The networks created were un-directed, weighted, and simples (i.e. without loops). Figure 1 summarize all processing steps of PET/MRI data.

As previously described in literature, the static nature of PET measures would limit the interpretation of many graph theory parameters (Veronese M *et al.* 2019), therefore we focused on a limited number of network parameters: degree strength, cluster coefficient, and weighted characteristic path length. Degree strength describes the mean strength of all connections of one selected node to neighborhood nodes: the strength of the connection is weighted by the strength of correlation between two nodes. Cluster coefficient is calculated as the average fraction in which pairs of neighboring nodes are also neighbors of each other, and represents a measure of the degree to which nodes in the graph tend to be clustered together (Latora V and M Marchiori 2001). The average of the shortest path length between all pairs of nodes considering the edge weighted is called the weighted characteristic path length (Lp.wt) of the network and it describes the efficiency of the information flow between all pairs of nodes (Watts DJ and SH Strogatz 1998). In topology, the shortest path length was defined as the shortest path distance from node “i" to node “j”. In practice, it represents the minimum number of points connecting node “i" with node “j”.

Moreover, distribution of hubs has also been investigated for each group. Hub is defined as a special node with a significative relevance in the network due to its centrality in flowing information (van den Heuvel MP and HE Hulshoff Pol 2010). Despite the simplicity of this definition, there are no standardized ways to calculate network’s hubs and several measures have been proposed (Sporns O et al. 2007). For the purpose of this study, a node with a nodal strength higher than the mean strength of the network,

calculated for each density value and in at least 50% of the density, was considered a hub. BrainNet Viewer and built-in braingraph functions were used for visualization of network descriptors (Xia M et al. 2013).

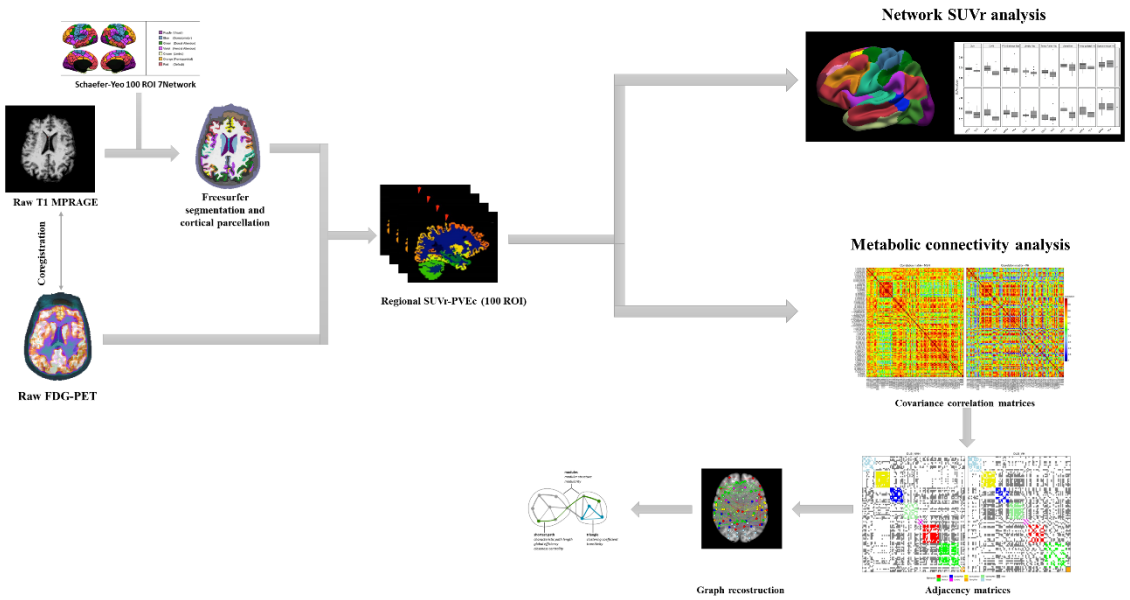


Figure 1: Schematic representation of MRI-PET images data processing

Statistical analysis

Statistical analysis was performed using R v3.6.1 (R Core Team, 2019). Continuous variables were tested for normality of distribution and visual inspection of variable histograms and qqplots were performed. Demographic, clinical and neuropsychological features were assessed using analysis of variance, Kruskal-Wallis and Mann-Whitney U test as appropriate. Fisher's Exact test was performed for categorical variables. The significative level was set at $p<0.05$. PET data were analyzed with analysis of variance with significance level set at $p<0.05$. The statistical analyses were done using age, sex and MMSE score as nuisance covariates.

Differences between DLB groups in the number of connections within and between networks were studied using a resample with replacement method namely bootstrap. For each connectivity matrix we built 5000 samples with replacement of 13 subjects for each group. A threshold to each of the 5000 bootstrapped samples at 29% of sparsity was applied and number of connections within and between network calculated. Multiple independent T-test corrected for Bonferroni was performed to evaluate differences between the two DLB groups.

Differences of strength at global and nodal levels, clustering coefficient and characteristic path length parameters were evaluated using permutation-based analysis (5000 permutations) with $p<0.05$ and controlling with False Discovery Rate.

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