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Neural correlates of altered insight in frontotemporal dementia

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Abstract

Neural correlates of altered insight in frontotemporal dementia

Background and main objective: Impaired insight is highly frequent in frontotemporal dementia (FTD) and especially prominent in its behavioural variant (bvFTD). The intrinsic complexity of this symptom seems to have hampered the accurate study of its underlying neuroanatomical substrates. The overarching goal of the present investigation was to explore the neural correlates of altered insight in FTD in order to determine whether broad and more specific objects of insight are underpinned by different or the same brain areas in this disease.
Methods: A systematic review on the matter was conducted to set the theoretical background of this thesis. A sample made up of 15 FTD patients (11 bvFTD and 4 language variant FTD -lvFTD-), 12 Alzheimer's disease patients (AD), 6 motor neuron disease (MND)/amyotrophic lateral sclerosis patients (ALS) and 34 cognitively healthy controls (HC) was evaluated with an extensive battery of insight assessment methods, neuropsychological tests, and self-administered and informant-based neuropsychiatric/behavioural scales. Several analyses were conducted in this research project, including an examination of the psychometric properties of different insight assessment approaches, a characterization of the cohort in terms of levels of insight, neuropsychological performances, neuropsychiatric symptoms and functionality in activities of daily living (ADL), an effort to identify neuropsychological/behavioural predictors of insight and an evaluation of the caregiver burden associated with all those variables. 3 Tesla high resolution Magnetic Resonance Imaging (MRI) brain anatomical scans were acquired from a part of the sample. A voxel-based morphometry (VBM) analysis was carried out to find correlations between altered insight into broad and specific objects and gray matter densities.
Results: Literature suggests that different modalities of insight are mediated by distinct brain areas in FTD. Participant-informant level of agreement and clinical judgement are valid and reliable insight assessment methods to be used in dementia. The same applies to self-appraisal accuracy, although this approach appears to be a measure of metacognition instead. Levels of insight into health condition (broad object) and insight into memory, social cognition and functionality in ADL (specific objects) in bvFTD were significantly worse than those observed in the other neurodegenerative diseases under analysis and HC. Also, compared to HC, FTD and AD patients exhibited significantly worse scores in several insight, neuropsychological and neuropsychiatric measures. It was not possible to identify neuropsychological or behavioural predictors in the cohort with the analysis conducted. Caregiver burden for FTD and AD patients did not differ significantly. The VBM analysis did not show statistically significant correlations between different forms of insight and distinctive gray matter volumes in FTD using a conservative statistical approach.
Discussion and conclusions: Although insight seems to be conceptually and neuroanatomically differentiated into broad and specific objects of insight according to the literature, the present investigation found inconclusive results to support that different modalities of insight are underpinned by distinct brain areas in FTD. Further research is needed to elucidate the neuroanatomical substrates of this highly elusive concept in FTD and other types of dementia such as AD focusing on how insight can be broken down into broad and specific objects.

COVID-19 Statement

The present investigation was partially affected by COVID-19 due to the restrictions implemented in the UK from March 2020 to date. A full lockdown imposed across the UK, which officially began on 23rd of March 2020 and was slightly eased on 10th of May 2020, forced the author of this thesis to work from home and stop the recruitment of the present investigation. Social distancing and other disruptions implemented to mitigate the spread of coronavirus in the UK impeded continuing with the enrolment of more participants in this research project. Likewise, the sample size included here could have been larger if recruitment would have been normally continued. All the same, all the data collected for this research project were cautiously analysed and interpreted. Consequently, the findings reported in this thesis are considered equally highly valuable.

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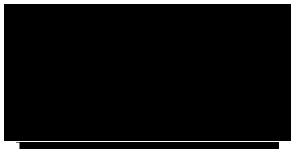
Finally, I would like to pay homage to my grandfather dedicating this doctoral thesis to him. Sadly, coronavirus took his life in June 2020 and now he is certainly resting in peace. He is one of the most hard-working men I have ever met in my life, and without a doubt, he has always inspired me to keep moving forward in hard times.



Carlos E[redacted]

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Bristol, UK

Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:  Carlos Eduardo Muñoz Neira. DATE: 31/12/2020

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Chapter 1: INTRODUCTION

1.1 OVERVIEW

The present study builds on the definition and classification of altered insight along with the appropriate identification of its neural substrates in frontotemporal dementia (FTD). The term 'altered insight' is clinically understood here to refer to those difficulties exhibited by certain patients to recognize their own pathological condition/symptoms. More precisely, this study investigates the neural correlates of broad and specific objects of altered insight in FTD in order to determine whether they are underpinned by different or the same brain areas in this disease. The relevance of studying this lies in several clinical and theoretical aspects. From a clinical perspective, such a search can lead to the identification of neuroimaging markers for a sign that is prominent in FTD and critical for its diagnosis. Delays in the presentation to clinical services and timely diagnosis are frequent in this form of dementia. Additionally, patients with FTD can exhibit risky behaviours when performing daily life tasks such as cooking, shopping and driving independently due to their potential difficulties to recognize their own symptoms, either neuropsychological, behavioural or physical/motor. A greater understanding of the neural correlates of insight in FTD may contribute to disease prognosis and suggest alternative indicators for its progression. Theoretically, the further study of self-referential processes might nourish the field of human neuroscience with interesting findings. Whilst there seems to be an inconsistency in the conceptualization of the term insight within clinical settings, the methods used to assess it and explore its neuroanatomical foundations have considerably varied across different brain disorders and forms of dementia. Likewise, the complexity of this scientific problem justifies its further investigation. An additional understanding into the neural correlates of altered insight in FTD by fractionating this clinical phenomenon into broad and specific objects is offered in this study. Little analytical attention has appeared to be paid to the proper conceptualization of altered insight in dementia and whether the different methods used to assess it, both in terms of neuropsychological and neuroimaging techniques, result in different or similar neural outcomes. This issue is addressed in this investigation by making use of different neuropsychological insight assessment methods and structural brain imaging analyses. Prior to further problematising the scientific need to look more closely into the conceptualization of insight and its potential neuroanatomical underpinnings in FTD, general aspects of dementia and FTD, impaired insight in dementia and FTD, and insight assessment methods are revised in this chapter. Lastly, a broad description of the content of every chapter of the present thesis are also included here.

1.2 DEMENTIA: GENERAL ASPECTS

1.2.1 Dementia: prevalence, costs and consequences

Dementia represents a major worry for public health on a global scale in the 21st century due to several reasons. Current data indicates that the presence of dementia worldwide will almost double every 20 years (Prince et al., 2015), which can even suggest an exponential growth for the disease. It is expected that roughly 74.7 and 131.5 million people in global population aged 60 and above will live with dementia by 2030 and 2050 respectively (Prince et al., 2015). Such figures might represent 0.847% in 2030 and 1.351% of the estimated population of the world in 2050 (United Nations, 2019). Additionally, from those cases, 63% by 2030 and 68% by 2050 will probably occur in low-income and middle-income countries (Prince et al., 2015). In terms of economic aspects, it has been calculated that the total costs of dementia range from 0.24% to 1.24% of the gross domestic product in low-income and high-income countries respectively (World Health Organization & Alzheimer's Disease International, 2012). Furthermore, a worldwide estimated expenditure of approximately US $2 trillion in dementia is expected for 2030 (Prince et al., 2015). In addition, dementia carers' burden has been labelled as severe in 63% of the cases, whereas 47% of them have presented a consequential psychiatric comorbidity (Slachevsky et al., 2013). Thus, such a scenario sets a rather worrisome prognostic for dementia, where efforts need to be maximized to avoid a potential catastrophic situation in the foreseeable future.

1.2.2 Dementia: definition

Dementia is an acquired neurodegenerative/vascular brain disorder characterised by a progressive cognitive decline which is strongly associated with a loss of functionality when performing activities of daily living (ADL). It also presents with a neuropsychiatric symptomatology and differs exclusively from delirium (American Psychiatric Association, 2000; World Health Organization, 1993). The cognitive impairment characteristic of dementia must involve one or more neuropsychological domains such as attention, episodic memory, language, visuospatial abilities or executive function (American Psychiatric Association, 2000; World Health Organization, 1993), whereas its related neuropsychiatric symptoms can include apathy, depression, emotional lability and impulsivity, among others (Munoz-Neira, Slachevsky, & Lopez, 2016).

Certain clarifications must be made around this definition. It should be noticed that dementia is an umbrella term for several neurodegenerative/vascular disorders that vary according to its corresponding aetiology, AD being the most frequent cause, followed by VD, FTD, dementia with Lewy bodies (DLB) and others (Rossor, Fox, Mummery, Schott, & Warren,

2010). Also, a prodromal stage of dementia called mild cognitive impairment (MCI) has now been precisely described and broadly accepted (Petersen, 2004, 2016; Petersen et al., 2014). Moreover, mild behavioural impairment (BCI), which may correspond to a condition preceding MCI, has been recently proposed as the earliest manifestation of dementia (Ismail et al., 2016), although more research is required to assess the validity of this theory.

The current definition for dementia comes from the traditional approach adopted by the widely known diagnostic manuals DSM-IV, DSM-IV-TR, ICD-10 and ICD-11 (American Psychiatric Association, 1994, 2000; World Health Organization, 1993, 2018), among which the concept 'dementia' itself is used. Lastly, attention has also be drawn to the term 'major neurocognitive disorder' coined as a new conceptualization for dementia by the recent diagnostic manual DSM-5 (American Psychiatric Association, 2013). Apart from this, the term 'mild neurocognitive disorder' was also proposed by DSM-5 to describe a syndrome that resembles what is currently understood as MCI (American Psychiatric Association, 2013).

1.2.3 Young-onset and late-onset dementias: definitions, incidence, prevalence and frequencies of the commonest presentations

In addition to identifying the emergence of MCI as a preceding stage of dementia (Petersen, 2016), distinguishing between young-onset dementia (YOD) and late-onset dementia (LOD) is critical for a an early and prompt diagnosis (Rossor et al., 2010). YOD has been defined as a dementia syndrome that has its onset point before the age of 65, which is an arbitrary cut-off agreed due to sociological/employment reasons and retirement age and has little biological relevance (Rossor et al., 2010). In contrast, LOD presents with a clinical manifestation of the dementia syndrome in people aged 65 or older (Kandiah et al., 2016).

Figures indicate that both incidence and prevalence of LOD greatly exceeds its YOD counterpart. In terms of incidence per age groups, dementia doubles every 6.3 years, ranging from 3.9 cases per 1,000 in people aged 60-64 to 104.8 cases per 1,000 in people aged 90 or older (Prince et al., 2015). Other figures suggest roughly 7.5 cases per 1,000 annually for people aged 60 and older (Ferri et al., 2005). Comparatively, concerning prevalence per age group, roughly 54 and 98.1 cases per 100,000 have been respectively estimated for group ages of 30-64 and 45-64 years (Harvey, Skelton-Robinson, & Rossor, 2003). In contrast, 3.9 cases per 100 have been reported for those aged 60 and older (Ferri et al., 2005).

When breaking down dementia according to its causes, patterns of frequency observed in YOD resemble those seen in LOD. Figures suggest that AD is the commonest form of dementia in both groups, reaching approximately a 17% of cases in YOD and a 52% in LOD (McMurtray, Clark, Christine, & Mendez, 2006). All the same, it is worth noting that AD seems to be particularly uncommon in cohorts of people younger than 45 hovering only around 2%

of all dementia cases (Kelley, Boeve, & Josephs, 2008). AD frequency is followed by VD and FTD frequencies respectively. VD cases represent a 29% of all dementia cases in YOD and 27% in LOD (McMurtray, Clark, et al., 2006), whereas FTD cases are expected to be nearly 12-14% of all dementia cases in YOD (Barker et al., 2002; Harvey et al., 2003), even in those younger than 45 (Kelley et al., 2008), and around 6-4% in LOD (Barker et al., 2002; McMurtray, Clark, et al., 2006).

1.3 FRONTOTEMPORAL DEMENTIA: GENERAL ASPECTS

1.3.1 Frontotemporal dementia: prevalence

FTD considered as a YOD appears to be the third most common type of dementia behind AD and VD in the UK (Harvey et al., 2003; Ratnavalli, Brayne, Dawson, & Hodges, 2002). Figures obtained in this geographic zone suggest that the prevalence of FTD ranges from 15.1 to 15.4 cases per 100,000, with a proportion that fluctuates between 12% and 17.1% of all dementia cases in the age group of 45-64 years (Harvey et al., 2003; Ratnavalli et al., 2002). These numbers decrease to 7.1 cases per 100,000 maintaining a 12% of all dementia cases in the age group of 30-64 years (Harvey et al., 2003). Similar numbers have been encountered in Australia, with a prevalence of 11.6 cases per 100,000 for the 45-64 age group and 5.4 cases per 100,000 for the 30-64 age group over a 11.3% of all dementia cases (Withall, Draper, Seeher, & Brodaty, 2014).

In contrast to both British and Australian data, studies from Netherlands and Japan report smaller rates of prevalence. Dutch figures indicate a potential prevalence of FTD of 4 and 9.4 cases per 100,000 in people aged 45-64 and 60-69 years respectively (Rosso et al., 2003). Japanese numbers are even lower, revealing a prevalence of FTD of 1, 2 and 4.4 cases per 100,000 in the age groups of 20-64, 45-64 and 60-64 years correspondingly, with an overall figure of 2.6% of all dementia cases (Ikejima et al., 2009).

A systematic review aimed at merging data collected from different countries, including Brazil, the UK, Finland, Italy, Turkey, and Japan (Hogan et al., 2016), estimated the overall prevalence of FTD to range from 0.01 to 4.6 cases per 1,000, representing an estimated 10.2% of all dementia cases within the YOD group and 2.7% of all dementia cases in the LOD group, where males were more likely to be diagnosed with this disease than females (52.5% versus 47.5%) (Hogan et al., 2016).

1.3.2 Frontotemporal dementia: challenges and issues related to its diagnosis

Although FTD cases are frequent and seem to represent the third cause of dementia in both YOD and LOD, the prevalence of FTD may be underestimated due to inaccurate diagnoses induced by its highly complex clinical pictures/presentations (Finger, 2016). This scenario entails an additional burden for carers as well as health care professionals and probably hinders the proper identification of FTD. Accordingly, the appropriate diagnosis of FTD poses several challenges. The approximate overall time from symptoms onset to diagnosis of FTD is 6.1 years, which exceeds roughly twice that of AD (3.6 years) and VD (3.1 years) (van Vliet et al., 2013). This pattern seems to resemble the additional overall time required to diagnose YOD (4.4 years) in comparison with that needed in LOD (2.8 years) (van Vliet et al., 2013). In the same vein, figures suggest that, unlike the case of dementia detection in elderly patients, diagnosing dementia phenotype in young adults appears to be more challenging. Diagnostic certainty for younger patients can be achieved roughly in only 60% of the possible cases of dementia (Salem et al., 2012), whereas this percentage increases to approximately 90% in the older adults (Phung et al., 2007).

Concerning the specific situation of FTD, the numerous medical efforts involved in its appropriate identification and their respective results attest its diagnostic complexity. For instance, a wide array of clinical procedures including neurological examination, brain imaging, neuropsychological assessment and laboratory tests, among others, are required for the diagnosis (Munoz-Neira et al., 2016). In addition, an accurate diagnosis of FTD in a traditional memory clinic can take approximately up to 5 visits to the specialist over nearly 2.5 years (Brzezicki, Kobetic, Neumann, & Pennington, 2019). Furthermore, distinguishing FTD from other types of dementia is particularly challenging. Patients whose final diagnosis is FTD can face changes in their diagnoses several times throughout their follow-ups, averaging from 6 to 8 modifications of their diagnoses (Brzezicki et al., 2019).

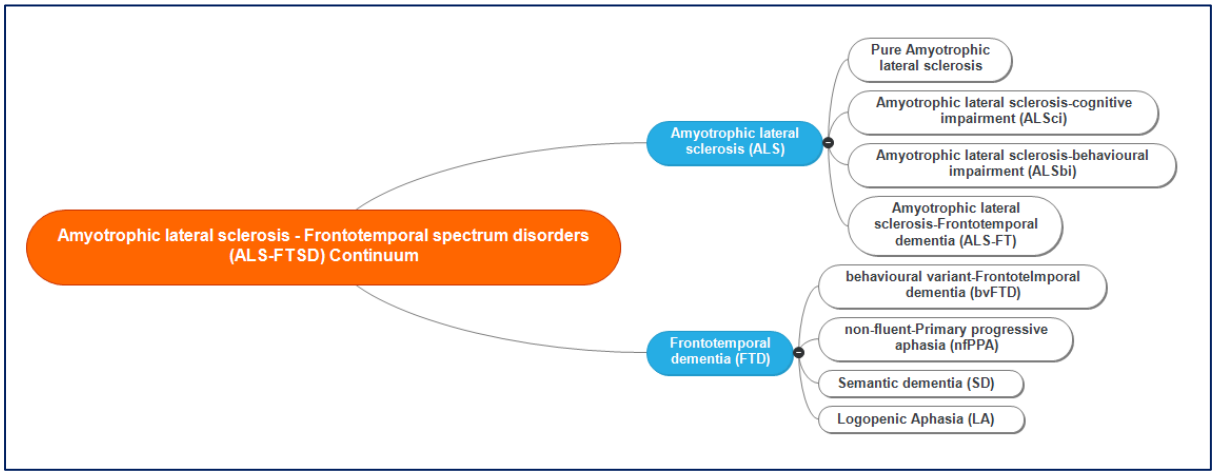
Differential diagnosis of FTD entails an additional difficulty probably due to its similarity to other brain disorders. Concerning dementia, a substantial symptomatic and neuroanatomical overlap between ‘frontal’ AD and FTD has been reported (Johnson, Head, Kim, Starr, & Cotman, 1999; Padovani et al., 2013). FTD and amyotrophic lateral sclerosis (ALS) have compatible neuropathological and clinical characteristics (Strong et al., 2017), in which the first one may present with the latter’s characteristic symptoms, and vice versa (Lillo, Savage, Mioshi, Kiernan, & Hodges, 2012). Moreover, high rates of misdiagnosis for FTD in healthcare settings have been encountered (Brzezicki et al., 2019). Several symptoms associated to other dementias such as the traditional forms of AD, DLB, VD have been mistaken for different

clinical manifestations of FTD (Brzezicki et al., 2019) or ALS (Strong et al., 2017). Also, even psychiatric signs from conditions like SCZ and bipolar disorder (BD) can resemble FTD's clinical picture (Galimberti, Dell'Osso, Altamura, & Scarpini, 2015).

1.3.3 Frontotemporal dementia: clinical pictures

FTD encompasses an array of dementia syndromes characterised by a profound behavioural disorder (bvFTD) (Hodges, 2013; Piguet, Hornberger, Mioshi, & Hodges, 2011) and/or notorious language problems (semantic dementia, SD; non-fluent primary progressive aphasia, nfPPA; or logopenic aphasia, LA) (Gorno-Tempini et al., 2011; Hodges, 2013). In addition, FTD has lately been shown to be closely associated with motor neuron disease (MND) and ALS (Strong et al., 2009). Likewise, it is now recognized that FTD and ALS configure a body of syndromes currently coined as ALS - frontotemporal spectrum disorder (ALS-FTSD) continuum (Strong et al., 2017), which was previously known as ALS-FTD continuum or spectrum (Strong et al., 2009) (see Figure 1.1).

Figure 1.1 Amyotrophic lateral sclerosis - Frontotemporal spectrum disorders (ALS-FTSD) continuum



Both FTD and ALS symptoms can be disruptive and overwhelming for the patient-carer dyad (Lillo, Mioshi, & Hodges, 2012; Uflacker, Edmondson, Onyike, & Appleby, 2016). Neuropsychiatric symptoms can predict and account for caregiver burden in FTD (Uflacker et al., 2016). Furthermore, FTD patients' carers can be even more affected by the load of stress associated to care activities than AD, Creutzfeldt-Jakob disease (CJD) (Uflacker et al., 2016), SD and ALS patients' caregivers (Hsieh et al., 2016). Apart from this, neuropsychiatric symptoms can be a greater trigger for carer stress in ALS than physical symptoms (Lillo, Mioshi, & Hodges, 2012). Also, the addition of behavioural problems to an individual with physical difficulties due to ALS may further impair quality of life and increase carer stress.

1.3.3.1 Frontotemporal dementia: behavioural variant

Both impaired insight into diagnosis/symptoms and a marked breakdown in social cognition are the most prominent symptoms of the behavioural variant of FTD (bvFTD) (Hodges, 2013; Neary et al., 1998; Seeley, 2019). In terms of cognition, bvFTD patients often have a multi-domain neuropsychological impairment which includes memory problems (Hornberger, Piguet, Graham, Nestor, & Hodges, 2010), although their neuropsychological profile is predominately marked by a dysexecutive syndrome (Lillo, Savage, et al., 2012).

Concerning neuropsychiatric symptoms, personality changes, apathy, disinhibition, increased eating and stereotypic behaviours, loss of self-care and hoarding, among other behavioural disorders, can be observed in bvFTD (Bozeat, Gregory, Ralph, & Hodges, 2000; Rascovsky et al., 2011). This symptomatology is considered to emerge from remarkable atrophies of frontal and temporal lobes, where the orbitofrontal, ventromedial and dorsolateral prefrontal cortices play a critical role (Rascovsky et al., 2011; Seeley, 2019).

Patients with bvFTD exhibit also a significantly decreased ability to properly perform basic and instrumental ADL in comparison with patients with SD, nfPPA and AD (Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2007).

1.3.3.2 Frontotemporal dementia: language variants

Patients with SD, nfPPA and LA are mainly characterised by the noticeable speech problems that they show as a consequence of an important degeneration of the neuroanatomical bases that mediate language (Finger, 2016; Hodges, 2013).

SD and nfPPA have been distinguished by anterolateral temporal and hippocampal atrophies or perisylvian involvement respectively (Hodges & Patterson, 2007; Nestor et al., 2003). Whilst SD is identifiable by its important lack of content words within the context of a well-articulated speech (Hodges & Patterson, 2007), nfPPA has been primarily associated with an impairment of the motor components of speech that can lead to grammatical, syntactic and phonemic errors, although with rather well preserved comprehension (Nestor et al., 2003).

LA patients tend to exhibit important problems in word retrieval and repetition of sentences, which can cause a slower speech and frequent pauses, although without agrammatism. These deficits are assumed to be secondary to perisylvian and/or parietal atrophies/dysfunctions (Gorno-Tempini et al., 2011). It should be noticed that LA has been lately closely related to AD due to the post-mortem detection of a high load of AD pathology in more than half of patients who had been diagnosed with LA considering their distinguishing symptoms (Giannini et al., 2017).

In terms of behavioural disorders, language variants of FTD can exhibit mood changes, depression and mental rigidity, as well as other neuropsychiatric symptoms during the course of the disease (Bozeat et al., 2000). Concerning functionality in ADL, these patients seem to be more independent than patients with bvFTD, although their language difficulties can have a negative effect on those everyday tasks that require communication skills (Wicklund et al., 2007).

1.3.3.3 Frontotemporal dementia and amyotrophic lateral sclerosis

ALS is a neurodegenerative disease that involves the progressive loss of upper and lower motor neurons. These types of neurons are in charge of controlling voluntary muscles movements such as eating, speaking and walking. ALS is at the same time a form of MND (Brooks, Miller, Swash, Munsat, & Gr, 2000; Strong et al., 2017) and as FTD, it is also a devastating neurological condition due to the severe impairment in the ability to perform ADL which they can cause (Cedarbaum & Stambler, 1997; Wicklund et al., 2007).

The main reason why ALS and FTD have been placed across the ALS-FTSD continuum is the strong connection observed between both diseases. This close relationship is reflected in their compatible genetic and pathological features, the similar patterns of brain atrophy (Lillo, Mioshi, Burrell, et al., 2012), and also the congruent neurological signs, neuropsychological profiles and neuropsychiatric symptoms that they both can present (Burrell, Kiernan, Vucic, & Hodges, 2011; Lillo, Mioshi, Zoing, Kiernan, & Hodges, 2011; Lillo, Savage, et al., 2012).

Across this continuum, some individuals will develop both ALS and FTD, while others may fulfil diagnostic criteria for FTD and show limited features of ALS, or vice versa. Also, on the one hand FTD can present as bvFTD, SD, nfPPA or LA (Hodges, 2013). On the other, ALS can be differentiated into ALS-behavioural impairment (ALSbi), ALS-cognitive impairment (ALSci) and ALS-FTD, among others, depending on its presentation (Strong et al., 2017) (see Figure 1.1).

Cognitive problems are often under-recognized in ALS or may be misattributed to the psychological impact of the ALS diagnosis, or its effects on communication. Although patients with pure ALS can exhibit a preserved global cognition at early stages of the disease, a slightly affected cognitive functioning (Lillo, Savage, et al., 2012) and executive disfunctions has also been reported in them (Lomen-Hoerth et al., 2003). In coherence with the neuropsychological profile of FTD, ALS-FTD also may show a multi-domain cognitive impairment predominately dysexecutive (Lillo, Savage, et al., 2012).

As with FTD, behavioural disorders characterized by apathy, disinhibition and stereotypical behaviours are commonly observed in patients ALS (Lillo et al., 2014; Lillo, Savage, et al., 2012). Also, patients labelled with syndromes belonging to the spectrum ALS-FTSD show an

important impairment in their performances on ADL (Cedarbaum et al., 1999; Strong et al., 2017), even greater than that observed in AD (Wicklund et al., 2007). In the case of pure ALS, the functional impairment appears to be mainly associated to a physical handicap secondary to the motor problems of this disease (Cedarbaum & Stambler, 1997).

1.3.4 Frontotemporal dementia: genetic origins

Diverse gene mutations have been associated to FTD and ALS, including anomalies in the microtubule-associated protein tau (MAPT), progranulin (GRN), chromosome 9 open reading frame 72 (C9orf72) (Greaves & Rohrer, 2019; Takada et al., 2016), and CYLD lysine 63 deubiquitinase (CYLD) (Dobson-Stone et al., 2020), among others. Approximately 40% of people with FTD cases have an affected close relative (Dobson-Stone et al., 2020). Several studies have identified anomalies in certain genes called MAPT and GRN, which can explain between 10% and 40% of familial cases of FTD (Dobson-Stone et al., 2020). Also, another gene called C9ORF72 seems to be the commonest pathologic gene found in 12% of cases of familial FTD and 24% of cases of familial ALS (Dobson-Stone et al., 2020). Other gene mutations have been reported as rarer causes of FTD and ALS, including VCP, OPTN, SQSTM1, TBK1, CCNF and TIA1 (Dobson-Stone et al., 2020). Recently, robust evidence has indicated that mutations of a gene called CYLD can be causative of FTD-ALS (Dobson-Stone et al., 2020).

1.3.5 Frontotemporal dementia: pathophysiology

FTD-like syndromes were originally called Pick's disease due to the presence of pathologic neuronal inclusions across both frontal and temporal lobes observed in patients who shown the characteristic clinical picture (The Lund and Manchester Groups, 1994). Post-mortem histological analyses carried out in those brain tissues presented pathologic structures named Pick bodies, hence the Pick's disease (PiD) (The Lund and Manchester Groups, 1994).

Current evidence has suggested that FTD and associated syndromes can be explained by certain molecular pathologic anomalies grouped into a wider label named frontotemporal lobar degeneration (FTLD) (Mackenzie et al., 2010). FTLD can be split into four molecular types according to the proteins that configure the inclusions placed over the neuronal and glial tissue. Those groups correspond to tauopathies, transactive response DNA binding protein of 43 kDA (TDP-43), fused in sarcoma (FUS) protein and FTLD no inclusion specified (FTLD-ni) (Kovacs, 2016). Although there seems to be heterogeneity in the links established between the particular brain pathology involved and its respective clinical phenotype, some classifications can still be proposed.

Post-mortem analyses have indicated that bvFTD can be primarily accounted for by the presence of TDP43, FTLD-tau (PiD subtype) and FUS proteinopathies. Remarkable right temporal atrophies in bvFTD have been related to higher loads of FTLD-tau pathology. Also, when FTLD-FUS pathology exists, bvFTD can present with or without MND signs (Pan & Chen, 2013).

Regarding the language variants of FTD, nfPPA seems to have a combined pathology including FTLD-tau and TDP43, with a more predominant FTLD-tau proteinopathy according to histopathological reports. It should be noted that apraxia of speech and orofacial apraxia have been mainly linked with tau pathology (Pan & Chen, 2013). SD is mostly associated with TDP-43-immunoreactive pathology; however, it can also present with tau pathology. Whilst FTLD-TDP-43 pathology has been correlated with right temporal atrophies in SD, acalculia in this disease has been related to FTLD-tau pathology (Pan & Chen, 2013). LA can have underlying FTD and AD pathologies at the same time (Giannini et al., 2017). All the same, AD pathology has been regularly found in LA through tau-beta amyloid ratio and PiB PET brain imaging (Pan & Chen, 2013). These techniques can aid the differential diagnosis of FTD language variants as recent findings suggest that 93% of LA patients tested positive in PiB imaging, whereas only 13% and 9% respectively did in nfPPA and SD (Pan & Chen, 2013).

In terms of the ALS-FTSD continuum, both TDP-43 and FUS pathologies have been observed in MND with or without FTLD. Extrapyramidal symptoms and apraxia, which can be suggestive of corticobasal syndrome (CBS), point towards the existence of tau pathology, whereas dementia FTLD-MND syndromes appears to be more related to TDP-43 pathology (Pan & Chen, 2013).

Lastly, tau pathology has been also found in FTLD with parkinsonism, progressive supranuclear palsy (PSP), CBS, argyrophilic grain disease (AGD) and PiD (Pan & Chen, 2013).

1.4 ALTERED INSIGHT: GENERAL ASPECTS

1.4.1 Altered insight in dementia: historical aspects

A foundational historical fact to consider for the understanding of altered insight is the origin of the term anosognosia. The formulation of this concept was proposed by the neurologist Dr Joseph Babinski close to the end of the 19th century (McGlynn & Schacter, 1989). Babinski coined the term anosognosia to illustrate the particular unawareness of left hemiplegia observed in patients who had suffered a right hemisphere stroke (Gainotti, 2018b; McGlynn & Schacter, 1989).

The finding of altered insight as a characteristic symptom of dementia can be probably traced back to the publication of the first case of dementia reported by the psychiatrist Dr Alois Alzheimer himself in the early years of the 20th century. The syndrome exhibited by Auguste D, who was Dr Alzheimer's widely known patient, suggested a clear loss of insight according to the clinical picture described in his medical notes (Maurer, Volk, & Gerbaldo, 1997). In fact, such an interpretation can be drawn from Auguste D's own words when she literally and repeatedly declared "*I have lost myself*" (Maurer et al., 1997, p. 1538).

Focusing on FTD, there is another historical effort that acquires relevance for the further study of altered insight. Much later, roughly by the mid-1990, the brain disorders associated to the so-called Pick's disease until then were labelled as FTD by a committee of experts from Sweden and the UK (The Lund and Manchester Groups, 1994). Consequently, behavioural, language and motor variants of FTD were defined with specific clinical and pathological features (The Lund and Manchester Groups, 1994). In addition to the speech disorder and the motor symptoms (early primitive reflexes, incontinence, akinesia, rigidity and tremor) characteristic of the language and motor variants of FTD respectively (The Lund and Manchester Groups, 1994; Neary et al., 1998), lack of social tact and altered insight were put forward as hallmarks of the emergent neurological condition now called bvFTD (The Lund and Manchester Groups, 1994; Neary et al., 1998). Likewise, the analysis of altered insight in FTD has attracted both clinical and research interest after the proper definition of such clinical categories associated with FTD (Evers, Kilander, & Lindau, 2007).

Complementary, several approaches have emerged from different moments of the history of the fields of neurology, psychiatry and neuroscience to delineate patients' incapability to describe and report their own diagnoses or specific symptoms (Gilleen, Greenwood, & David, 2010). Among them it is possible to highlight concepts such as anosognosia, denial, impaired metacognition, unawareness and altered insight (Gilleen et al., 2010; Markova & Berrios, 2011).

Anosognosia, which was a concept raised firstly from the field of neurology, has been commonly associated with a global lack of disease awareness (Evers et al., 2007; Mullen, Howard, David, & Levy, 1996) or an unawareness of a specific neurological/neuropsychological deficit (Mullen et al., 1996). Although anosognosia literally means 'lack of knowledge of disease' in ancient Greek and was purposed to reflect a specific problem in its initial definition (unawareness of hemiplegia) (Evers et al., 2007), the term has become more flexible, encompassing currently a general lack of awareness of either disease or symptoms (Mendez & Shapira, 2005) or an altered subjective experience for a broad array of neurological and neuropsychological disturbances (Prigatano, 2009). Nevertheless, it should be noticed that anosognosia entails the presence of an objective (that is to say,

something tangible) deficit in relation to what corresponds with a normal neurological/neuropsychological function (Markova & Berrios, 2011).

Other alternative theoretical points of view have focused on psychodynamic or motivational aspects of altered awareness of disease or symptoms in dementia. For instance, denial, which is a term taken from psychoanalysis, occurs when patients unconsciously or consciously reject to be ill or present symptoms (Ecklund-Johnson & Torres, 2005; Gilleen et al., 2010). In dementia and other neuropsychiatric disorders, such a behaviour would be conceptualized as a coping technique shown by patients to protect their self-esteem from the catastrophic reaction provoked by acknowledging the onset of a particular disease or deficit (Ecklund-Johnson & Torres, 2005). In a slightly different avenue, within the neurological field, lack of insight in FTD has been linked with an apathetic attitude towards symptoms named 'frontal anosodiaphoria' and characterized by a generalised lack of concern for presenting an illness or specific symptoms (Mendez & Shapira, 2011).

Lately, an interesting concept coined as metacognition has been developed in the field of cognitive neuroscience. Its main contribution is linked with the formulation of the elements that configure insight (David, Bedford, Wiffen, & Gilleen, 2012; Gilleen et al., 2010). Metacognition refers to cognition about cognitions (Krueger et al., 2011) and entails a reflection on one's cognition, emotions and behaviours (Frith & Frith, 2012). A metacognitive disorder appears to be in accordance with the implications of the types of altered insight observed in different brain disorders (David et al., 2012). As it seems to be the case of insight (Markova & Berrios, 2001), metacognition can be also parcelled into different modalities (David et al., 2012). Thus, it is possible to address metacognition towards distinct domains such as memory (metamemory), social cognition, behavioural disorders or even performance of ADL (David et al., 2012).

The use of this varied terminology leads to questions about whether the respective authors are referring to the same clinical phenomenon or are actually studying different problems (Markova & Berrios, 2000; Markova, Clare, Wang, Romero, & Kenny, 2005).

Insight, in contrast to other concepts, is a term that emanated from the field of psychiatry by the middle of the 19th century. Awareness or insight intended to account for the specific situation in which patients with severe psychiatric disorders experience a relative level of awareness of disease, that is to say, being conscious of having a mental disorder (Markova et al., 2005). In general terms, insight is currently defined as a concept that consists of at least three elements: the awareness of being ill, an understanding of the origin of the disease or the symptoms in reference, and the need of treatment acceptance (Landi, Marazziti, Rutigliano, & Dell'Osso, 2016). A more precise clinical conception defines insight as a relational concept based on a multidimensional structure of self-knowledge of the diagnosis, presence of an

illness or presence of a specific impairment along with the potential consequences for everyday functioning (Markova & Berrios, 2001). Thus, insight can be distributed across different objects, either a diagnosis, a global health condition or a particular symptom (Markova & Berrios, 2000, 2001, 2011) (see Figure 1.2). Complementary, insight has also been linked with the ability to accurately judge a range of personal and physical characteristics, including cognitive, emotional, behavioural and social skills (Evers et al., 2007). In contrast, altered insight within a clinical context is understood to mean an inability to identify, acknowledge, evaluate or report one's own symptoms or diagnosis when suffering from an actual disease (Zamboni & Wilcock, 2011; Zanetti et al., 1999). Lack of insight has been interchangeably used with unawareness of deficits in the clinical literature (McGlynn & Schacter, 1989). As a consequence, from a more specific approach, altered insight can be defined as an absent or impaired self-knowledge of disturbances and its implications, wherein such altered insight is channelled into different objects (Markova & Berrios, 2001; McGlynn & Schacter, 1989; Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019; Zanetti et al., 1999). These objects of insight can be either broad (diagnosis/global health condition) or specific (neuropsychological domains such as memory problems or executive dysfunction, neuropsychiatric symptoms, etc.) (Munoz-Neira et al., 2019) (see Figure 1.2). Furthermore, such modalities can be objectively ascertainable (neurological/neuropsychological diseases/deficits) or rather subjective inner experiences (mental symptoms/disorders) (Markova & Berrios, 2011). It is exactly this last definition of altered insight the conceptualization that will be used throughout this thesis.

Figure 1.2 Altered insight into broad and specific objects

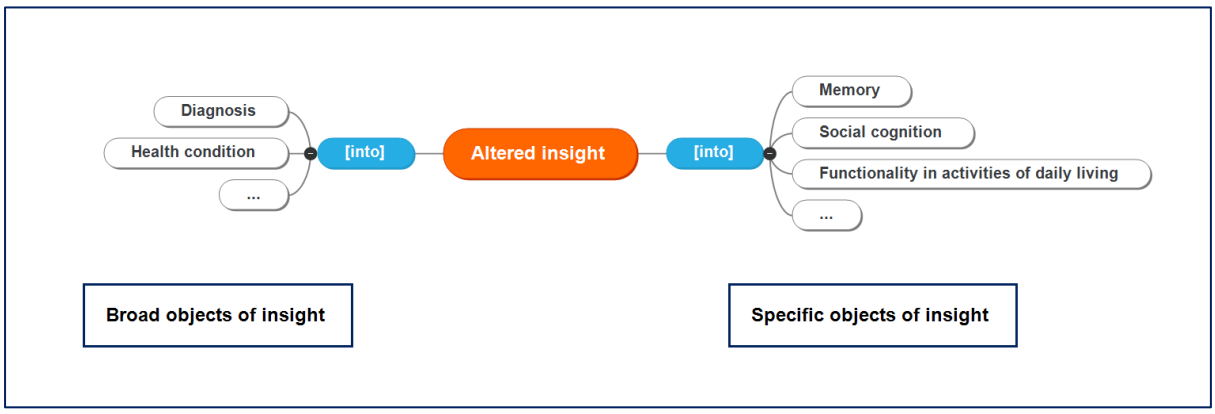


Diagram based on David et al. (2012) and Munoz-Neira et al. (2019).

1.4.2 Neural substrates of self-referential processes relevant for clinical insight

When considering that clinical insight comprises a certain extent of self-appraisal, it is reasonable to state that its neuroanatomical underpinnings are compatible with those brain areas that mediate self-referential processing, especially the ones involved in judging one's own multiple conditions or characteristics. Regarding this matter, sufficient scientific evidence has been lately encountered to confirm that the neural underpinnings of self-referential processes are mostly situated across cortical midline structures (Northoff et al., 2006), namely the medial prefrontal, orbital prefrontal and medial parietal cortices, the anterior and posterior cingulate and the retrosplenial cortex (Tagini & Raffone, 2010). For example, non-clinical children and young adults (aged approximately 10 and 26 correspondingly) have exhibited more pronounced activations in the medial prefrontal cortex when thinking of themselves in comparison with a worldwide well known fictional character such as Harry Potter (Pfeifer, Lieberman, & Dapretto, 2007). Similar findings have been found in healthy young adults (close to their thirties) when deciding whether they identified themselves according to positive or negative personality traits (Ochsner et al., 2005).

In addition to cortical midline brain regions, other neural substrates have also been linked with self-referential tasks, including the ventrolateral and dorsolateral prefrontal cortices, lateral parietal cortices, temporal poles, the insula and subcortical structures (Tagini & Raffone, 2010). For instance, self-knowledge of life events has been mainly associated with memory-related areas (hippocampi), and the medial prefrontal, superior posteromedial and anterior insular cortices in young subjects who were approximately in their twenties (Araujo, Kaplan, Damasio, & Damasio, 2015). In contrast, self-referential processing of interoceptive and exteroceptive changes has been mostly linked with body related areas like the somatosensory cortices, the posteromedial cortex and the posterior insula in the same cohort (Araujo et al., 2015).

It should be noticed that certain studies seem to suggest that the neural correlates of self-appraisal may vary with age. An illustration of this point can be seen when activity shown by children in the medial prefrontal cortex, anterior cingulate and posterior precuneus has shown to be significantly greater than that displayed by adults in those areas when judging some of their own general preferences and personality traits (Pfeifer et al., 2007). Differently, young adults activated lateral temporal cortices significantly more than children performing the same task (Pfeifer et al., 2007). Another example concerns older adults aged 60 to 85 years who have interestingly presented significant correlations between self-reports of memory functioning in everyday life and the cortical thickness of the left medial temporal lobe (Bjornebekk, Westlye, Walhovd, & Fjell, 2010)

1.4.3 Insight in ageing and clinical insight in dementia

Evidence suggests that there may be a clear effect of ageing on certain self-referential process. A clear example of this may be interoception, which refers to a self-perception of the internal physical condition/changes of one's own body. A study undertaken with young, middle-aged and older adults (with ages ranging from 20 to 65 years approximately) corroborated that the younger your age, the more accurate your ability to detect your own ongoing body changes (tracing heartbeats) and vice versa (Khalsa, Rudrauf, & Tranel, 2009). Along the same lines, another investigation which included participants in their young to very late adulthood (aged 20 to 90 years) indicated that body awareness (interoception related to digestion, breathing, sweating and heartbeats, among others) weakens with age (Murphy, Geary, Millgate, Catmur, & Bird, 2018). Moreover, age may shape brain changes and performances a metacognitive self-appraisal task in subjects at risk of developing AD. Reductions in medial prefrontal activity with an increased activity in temporal areas, orbital regions and the striatum when performing such a task appeared to be explained by age and by the AD risk factors of the cohort under analysis (Trivedi et al., 2008). Further complementary relevant studies which confirm the effect of age on other domains of insight were not found and seem to be needed to address deeper conclusions.

Contrary to the previously mentioned decline of self-knowledge of ongoing body's changes or metacognitive self-appraisal with age, other studies have reported a rather appropriate self-knowledge of health conditions in middle-aged and older adults. A large population-based study including 18,000 middle-aged subjects (aged approximately 43 years) managed to prove the existence of an important consistency between self-assessments and objective measures of health status in this cohort (Wu et al., 2013). The objectivity of these assessments included medical records on the presence of diseases, laboratory parameters, and health-related factors such as weight, body mass index, smoking, physical and social activities, work strain, and life stress, among other factors) (Wu et al., 2013). This situation also occurs in old age, where participants' self-ratings of health and objective measures of health status such as physicians' judgements or medical records have also correlated significantly in cross-sectionals investigations carried out with older adults aged between 65 and 74 years or 75 years and older (Ferraro, 1980; LaRue, Bank, Jarvik, & Hetland, 1979). A longitudinal study confirmed these findings in a follow-up that implied 6 observations over 15 years in subjects of 60 years of age or older (Maddox & Douglass, 1973).

Concerning dementia, insight into diagnosis/symptoms decreases progressively throughout the course of the disease. This is evident when observing that impaired insight worsens as the disease evolves from MCI into mild, moderate and severe dementia (Sunderaraman &

Cosentino, 2017). At the same time, once dementia has been diagnosed, the lack of clinical insight increases with time as the disease advances. This pattern can be reflected by one-year (Turro-Garriga et al., 2016) or three-year (Vogel, Waldorff, & Waldemar, 2015) follow-ups where dementia severity is the principal determinant to account for impaired insight into AD as time progresses or the consideration that disease unawareness tends to be milder in YOD than in LOD (Baptista et al., 2019).

1.4.4 Frontotemporal dementia and altered insight

Although altered insight is common in a wide array of brain disorders including addictions, TBI, SCZ and BD (David, Bedford, Wiffen, & Gilleen, 2014; Gilleen et al., 2010), among others, this symptom is more remarkable in different forms of dementias such as AD and FTD (David et al., 2014; Wilson, Sytsma, Barnes, & Boyle, 2016). Lack of awareness of diagnosis or symptoms in dementia has been associated with dysthymia, apathy, psychosis, loss of capacity to perform ADL and caregiver stress (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005; Aalten et al., 2006).

Insight is not an 'all-or-nothing clinical phenomenon' (Hughes, 2019). Different patterns of impaired insight can be observed in different brain disorders (Gilleen et al., 2010). For example, it seems plausible to differentiate insight into behavioural disorders according to its levels of impairment in AD, TBI and SCZ. The degree of altered insight can be sorted in descending order, where AD exhibit a greater unawareness compared with TBI and then with SCZ. At the same time, the level of insight seen in patients with TBI is smaller than the one showed by patients with AD, but worse than that presented by SCZ. For its part, SCZ appears to have a milder insight loss in comparison with both TBI and AD (Gilleen et al., 2010).

When comparing different forms of dementia, failures of overall insight and impaired insight into social interactions, emotion processing and motivation are more severe in FTD than in AD, especially in bvFTD (Hornberger et al., 2014). Also, FTD patients are significantly more impaired than patients with CBS and PSP in different domains of awareness that involve anticipatory and monitoring tasks (O'Keeffe et al., 2007).

Severe insight and awareness loss have been reported in approximately 75% of cases with FTD (Wedderburn et al., 2008). For its part, altered insight remains underexplored in patients with ALS and associated syndromes. Regarding the variations of insight across the different types of FTD, broadly speaking, altered insight is more pronounced in bvFTD than in SD, nfPPA and LA) (Hornberger et al., 2014).

In relation to broad objects, bvFTD has exhibited a remarkable impaired insight into diagnosis and health condition (Mendez & Shapira, 2005), an overall estimate of insight made up of components like diagnosis and treatment, motivation and social cognition (Hornberger et al.,

2014), and an averaged multi-domain cognitive performance calculated from scores on language and memory tasks (Massimo et al., 2013). Comparatively, language variants of FTD appear to have a relatively preserved disease awareness and other broad objects of insight (Savage, Piguet, & Hodges, 2015). For instance, both nfPPA and SD seem to exhibit a more spared insight into their own condition when compared to more social-dysexecutive forms of FTD according to measures that considered an average of multiple behaviours such as disruptive behaviours, memory, motivation, planning and flexibility, among others (Eslinger et al., 2005). ALS patients have also shown a global altered insight, especially in those patients who live with a comorbid dementia (Ichikawa et al., 2013).

Concerning specific objects, altered insight into memory problems (Banks & Weintraub, 2008), social cognition (Sollberger et al., 2014), behavioural disorders (Banks & Weintraub, 2009) and performances in ADL (Amanzio et al., 2016) have been reported in bvFTD. In parallel, nfPPA patients have also shown altered insight into behavioural disorders, but a rather preserved awareness of language problems (Banks & Weintraub, 2008). Such a spared insight into language difficulties has been also observed in SD (Savage et al., 2015) and bvFTD patients (Banks & Weintraub, 2009). On the other hand, SD patients have exhibited altered insight into social cognition (Sollberger et al., 2014).

1.4.5 Insight assessment methods

Altered insight into broad and specific objects in dementia has been assessed making use of different approaches. Among the most frequently used insight assessment methods, it is possible to mention the estimation of a participant-informant discrepancy score, a self-rated-standardised neuropsychological performances discrepancy score and the clinical judgment (Clare, Markova, Verhey, & Kenny, 2005; Zamboni & Wilcock, 2011). Such approaches have been combined with both structural and functional brain imaging techniques to propose neural correlates of altered insight in dementia (Munoz-Neira et al., 2019; Zamboni & Wilcock, 2011). Other insight assessment methods include subjective experiences or the combination of the just mentioned approaches, along with contrasting participants' views about themselves with informants' opinions about the participants in reference (Clare et al., 2005).

Both participant-informant level of agreement and self-rated versus standardised neuropsychological performances discrepancy scores are based on a comparison between what is observed in the subject under study and the evidence provided by a collateral source (Clare et al., 2005). A participant-informant discrepancy score can be estimated by comparing the level of coherence observed between outcomes obtained from self-administered and informant-based paired questionnaires/scales of cognitive status, behavioural changes, neuropsychiatric symptoms or ADL. This procedure is conducted by simply subtracting reliable

informants' scores from the respective individuals' results or vice versa (Clare et al., 2005; Hornberger et al., 2014). The self-rated versus standardised neuropsychological performances discrepancy score is calculated by measuring the degree of difference between a self-appraisal judgment and a gold standard outcome (Rosen et al., 2010). Actual standardised scores on cognitive tasks (i.e. episodic memory or executive functions neuropsychological tools, among others) are subtracted from either pre or post-test judgments provided by the subjects on their own performances in the respective tasks in this approach (Clare et al., 2005). In contrast, the clinical judgment method implies the assessment of an examiner or clinician expert and the consequent evaluation of the extent of the potential altered insight of the patient in reference. This procedure can be conducted by filling in a rating scale or a predefined protocol after clinically interviewing the patient and their reliable informant (Clare et al., 2005; Mendez & Shapira, 2005).

Although the estimation of a discrepancy score between the outcomes of cognitive/behavioural questionnaires/scales filled in by patients and their reliable respective informants have been highlighted as one of the easiest and most pragmatic methods to assess insight (Clare et al., 2005), its validity has been questioned because this approach depend on informants' 'subjective' opinions, which may be biased due to depression or carer burden triggered by the dementia case they are taking care of (Clare et al., 2005). All the same, certain evidence suggest that overwhelming situations in dementia do not interfere or provoke a negative effect in informants' observations (Gilleen et al., 2010). Comparing self-rated with actual standardised performances on neuropsychological tests has been described as a more 'objective' technique to assess insight in dementia; however, the lack of ecological validity of this method has attracted criticism and hindered its widespread used (Clare et al., 2005). Concerning clinical judgment to characterise insight in dementia patients, this approach has the advantage of being quick in clinical settings, although some studies have considered it as limited due to its poor inter-rater reliability (Clare et al., 2005). Additionally, it should be noticed that this method requires high levels of precision from the clinician and a thorough knowledge of the patient in reference, which is often gained by interviewing their carer, spouse or close relative. Thus, inaccurate views provided by overwhelmed carers/proxies could influence clinicians' judgements when an special attention to biases is not considered.

1.5 RATIONALE AND RESEARCH QUESTION

This thesis sets out to investigate the neural correlates of altered insight in FTD aiming to determine whether broad and specific objects of insight are mediated by different or similar brain areas. The search for the neural foundations of altered insight across cohorts with different forms of dementia (Wilson et al., 2016), and especially in FTD (Hornberger et al.,

2014), has posed several challenges. The conceptualization of the insight (Gilleen et al., 2010; Markova et al., 2005), its assessment methods (Clare et al., 2005) and the techniques used to study its relationship with brain function (Wilson et al., 2016) have varied widely. Consequently, this situation has led to a rethink of the study of altered insight in dementia (Markova & Berrios, 2000, 2011).

Casual and clinical definitions of insight differ importantly. Whilst a colloquial meaning of the term appears to be rather bounded, the clinical definition of insight has several different aspects. Colloquially, insight encompasses the act of having an accurate vision or understanding something clearly (Oxford English Dictionary, 2017). The original notion was taken from Northern European languages such as English, Dutch or Scandinavian (Markova & Berrios, 2011) implying the presence of an 'internal sight' obtained through the eyes or understanding either an inner state or an external situation (Oxford English Dictionary, 2017). In contrast, insight from a clinical point of view is generally understood to mean having the capability to identify appropriately a pathological condition affecting one's self along with its consequences (Zanetti et al., 1999). Although this definition directly refers to altered insight as a broad difficulty in recognizing the presence of a disease or symptoms of a medical condition (McGlynn & Schacter, 1989), a close look into how this term has been handled in the literature motivates its revision.

The conceptualization of altered insight as a clinical phenomenon has exhibited a considerable complexity (Markova & Berrios, 2001). Nevertheless, there seems to be a consensus in terms of its the understanding in different brain disorders (McGlynn & Schacter, 1989). References made to the potentially distorted attitude adopted by patients towards their own ongoing health issues have varied and moved throughout conceptions related to a refusal of disease, global reduced disease awareness or failures at reporting specific symptoms (Gainotti, 2018a, 2018b). Likewise, within the context of dementia research, diverse concepts have been used for such purposes, including denial, anosognosia, lack of insight or awareness, unawareness and impaired metacognition, among others (Markova & Berrios, 2011, 2014).

In parallel, the search for neural correlates of altered insight in different forms of dementia has employed a wide array of insight assessment methods and brain imaging techniques both in several types of dementia in general (Clare et al., 2005; Wilson et al., 2016), and in FTD in particular (Munoz-Neira et al., 2019). Approaches aimed at assessing insight changes seen in dementia have included the degree of agreement between individuals' self-perception and reliable informants' evaluations, the contrast between self-rated and standardised neuropsychological performances and judgements provided by clinicians, among others (Clare et al., 2005). The combination of these insight assessment methods and both structural and functional brain imaging have yielded interesting findings on how insight may be

widespread across diverse brain areas in dementia (Wilson et al., 2016; Zamboni & Wilcock, 2011).

Neural foundations of altered insight in dementia seem to differ according to its targeted domains. Global altered disease awareness has been associated with decreased function of frontal lobes in Alzheimer's disease (AD) (Harwood et al., 2005) and FTD (Mendez & Shapira, 2005). In accordance with this, right frontal lobe appears to be particularly critical for global clinical insight in FTD (McMurtray, Chen, et al., 2006; Mendez & Shapira, 2005). Similar results have been obtained in patients with other brain disorders such as vascular dementia (VD) (Tezuka et al., 2013), CBS (Graff-Radford et al., 2013), traumatic brain injury (TBI) (Schmitz, Rowley, Kawahara, & Johnson, 2006) and schizophrenia (SCZ) (Shad & Keshavan, 2015). On the other hand, reduced insight into specific cognitive domains has correlated with other cortical and subcortical brain areas in dementia. For example, impaired insight into social cognition is probably linked with the amygdala, other limbic zones, the cingulate, and parietal and frontal areas in AD and FTD (Sollberger et al., 2014). Additionally, inaccurate perceptions into memory problems seem to be mostly underpinned by medial temporal and prefrontal areas in early AD (Mimura & Yano, 2006). Although these results suggest that altered insight can be neuroanatomically differentiated under its modality, it should be also noticed that there is a considerable variability in the insight assessment methods and brain imaging techniques used in these studies.

The inconsistency observed in the definition of altered insight has hampered the accurate search for the neural bases of altered insight in dementia (Markova & Berrios, 2011). Similarly, the diversity of the methodological designs in terms of the measurement of insight and types of neuroimaging used has limited the extent of conclusive neural outcomes, especially in FTD (Munoz-Neira et al., 2019). Thus, one may question whether different authors have been studying the same clinical phenomenon or rather distinct concepts and whether the neural correlates of altered insight reported so far have been preconditioned by the conceptualization of the phenomenon itself. At the same time, such a scenario invites us to analyse how neural findings could be influenced by the different neuropsychological and brain imaging methodologies used to explore the neural correlates of altered insight in FTD.

A potential solution to tackle the aforementioned problematization emerges from the conceptualization of insight as a relational concept (Markova & Berrios, 2001, 2011; Markova et al., 2005). From this approach, insight is directly targeted at a particular object, either the precise acknowledgement of a diagnosis/disease/global health condition or the identification of a specific symptom taken from a particular neuropsychological, behavioural or neuropsychiatric domain (Markova & Berrios, 2001) (see Figure 1.2). Consequently, deficits can be broken down into different modalities, that is to say, altered insight can be focused on

a broad object of insight, namely patient's diagnosis, health status or global clinical picture, or a specific object instead, such as a particular neuropsychological domain, like memory, or a specific behavioural or neuropsychiatric aspect. Pursuing this line of reasoning, there is evidence to confirm that altered insight into memory problems and behavioural disorders unawareness are dissociated in AD (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996). In the same vein, patients with FTD may exhibit reduced insight into their overall neurological condition (Mendez & Shapira, 2011) or into altered social cognition (Sollberger et al., 2014), or both (Hornberger et al., 2014).

A useful operational definition for altered insight then entails an inaccurate self-knowledge or unawareness into a particular object (Markova & Berrios, 2011), either broad or specific objects of insight, i.e. a diagnosis/global health condition or a particular cognitive/behavioural/neuropsychiatric symptoms respectively (see Figure 1.2). It is predicted that fractionating altered insight across different objects can set a semiotic distinction able to enhance an appropriate handling of the concept and also, through different insight assessment methods and brain imaging techniques, facilitate and properly address the exploration of its neural correlates in FTD.

This thesis intends to provide answers to the scientific question of what the neural correlates of altered insight are in FTD. More precisely, it explores whether altered insight into broad and specific objects are underpinned by different or the same neural substrates in FTD. The relevance of studying is this based on several clinical and theoretical arguments. From a clinical point of view, examining the neuroanatomical foundations of altered insight can contribute to the finding of brain imaging markers for a symptom that is critical in the diagnosis of FTD (Munoz-Neira et al., 2019). Impaired insight in dementia can be highly challenging for patients, their relatives and health care professionals. Also, insight loss can be associated with low mood, impaired functionality in ADL, poor quality of life and high levels of caregiver burden (Aalten et al., 2005). Moreover, FTD patients can display risky behaviours, for example, performing daily life tasks such as cooking, shopping and driving autonomously when they are no longer capable of doing so. These unsafe behaviours are likely to be explained by the emergence of an altered insight, which can be the result of a impaired self-perception of neuropsychological, behavioural or motor symptoms (Munoz-Neira et al., 2019). In addition, impaired insight into health problems can entail delayed diagnoses in dementia (van Vliet et al., 2013), refusal of clinical examinations, lack of adherence to treatment, untimely follow-ups and late presentations to clinical services. A deeper understanding of the neural substrates of insight may aid disease prognosis and provide surrogate markers of disease progression (Munoz-Neira et al., 2019). Finally, from a theoretical point of view, exploring the neural correlates of altered insight in FTD benefits the further study of self-referential processes in

humans, which can turn into a valuable input to cognitive neuroscience (Zamboni & Wilcock, 2011).

1.6 OBJECTIVES

1.6.1 Overarching objective

In the light of the above, the overarching objective of the present doctoral thesis is:

- ✓ Explore the neural correlates of altered insight in FTD in order to determine whether broad and specific objects of insight are underpinned by different or the same brain areas.

1.6.2 Specific objectives

Such an overarching objective leads to also focusing on other relevant issues related to impaired insight in FTD. Thus, the specific objectives of this doctoral thesis are as follows:

1. Analyse the state-of-the-art literature on neural correlates of altered insight in FTD through the conduction of a systematic review.
2. Estimate the validity and reliability of different insight assessment methods including self-administered and informant-based questionnaires discrepancy scores, self-rated versus standardised neuropsychological performances on neuropsychological tests discrepancy scores and clinical judgment.
3. Characterize a cohort of patients with FTD and HC in terms of their levels of insight into broad and specific objects assessed through different insight assessment methods.
4. Characterize a cohort of patients with FTD and healthy controls (HC) according to an extensive battery of neuropsychological tests, self-report scales and informant-based questionnaires.
5. Identify correlations between altered insight, performances on neuropsychological tests and results from the behavioural questionnaires used in this study to observe potential associations between altered insight, different neuropsychological domains (memory, social cognition, executive functions) and behavioural symptoms (functionality in everyday life tasks and neuropsychiatric symptoms).
6. Identify correlations between the outcomes obtained from different insight assessment methods and specific regional grey matter densities in order to determine whether altered insight into broad and specific objects of insight are underpinned by different or the same neural correlates in FTD.

1.7 HYPOTHESES

The revised literature suggests that different forms of insight seem to be mediated by distinct brain areas in dementia. At the same time, despite the diversity observed in the

conceptualization and methodologies employed to study the elusive nature of the term insight in several brain disorders, authors appear to be examining a clinical phenomenon compatible with an impaired self-knowledge of a diagnosis or its symptoms, which corresponds to the conceptualization of insight used here. Likewise, the following hypotheses can be drawn:

1. Altered insight into broad objects (diagnosis/health status/global clinical picture) and altered insight into specific objects (neuropsychological, behavioural or neuropsychiatric domains) will be underpinned by different brain areas widespread across subcortical and frontotemporal areas in FTD. (H_1).
2. Different insight assessment methods (participant-informant and self-rated-standardised neuropsychological outcomes discrepancy scores; clinical judgment) will be valid and reliable measures to be used in FTD (H_2).
3. Altered insight will be linearly distributed from inta ct insight (healthy controls) to more pronounced altered insight (bvFTD) across different variants of FTD (H_3).
4. Different insight assessment methods will show similar structural neural correlates in FTD (H_4).

1.8 THESIS CHAPTERS

‘Chapter 1: Introduction’ defines the scope of the present thesis, including a rationale amid the reasons that support the exploration of the neural correlates of altered insight of dementia. It also narrows down its respective research question, objectives and hypotheses. General information on dementia and FTD is also provided in this chapter, covering aspects such as definitions, prevalence, pathophysiology and clinical picture of FTD and its associated syndromes, as well as a brief historical reference on the study of insight in dementia.

‘Chapter 2: General Methods’ describes the procedures used to reach the objectives proposed for this thesis, including the definition of the variable studied, criteria for selection of participants, insight assessment methods, neuropsychological assessments and brain imaging techniques included in the research project implemented by the author of this thesis during his doctoral studies.

‘Chapter 3: Neural correlates of altered insight in frontotemporal dementia, a systematic review’ provides details on the theoretical framework upon which this thesis relies. It should be noticed that this chapter corresponds to a paper entitled with the same name published recently in the scientific journal ‘NeuroImage: Clinical’ (Munoz-Neira et al., 2019).

‘Chapter 4: Psychometric properties of different insight assessment methods in frontotemporal dementia and associated disorders’ focuses on the estimation of the validity and reliability of the insight assessment approaches used in this study.

‘Chapter 5: Insight, neuropsychological and behavioural characteristics of frontotemporal dementia’ describes the demographic, insight, neuropsychological and neuropsychiatric profiles of the cohort included in this project according to the extensive battery of insight assessments, neuropsychological tests and self-administered and informant-based questionnaires employed in this study. Furthermore, it assesses the configuration of insight examining whether this clinical phenomenon corresponds to a fractionated or unified term. In addition, neuropsychological domains (episodic memory, social cognition, executive functions, etc.) and different behavioural/neuropsychiatric symptoms (apathy, depression, abnormal behaviours, etc.) are analysed as predictors of level of insight. Lastly, this chapter explores what the best predictors of caregiver burden are in the cohort under study among levels of insight, cognitive domains and/or neuropsychiatric/behavioural symptoms.

‘Chapter 6: Structural neural correlates of broad and specific objects of insight in frontotemporal dementia’ presents the outcomes of the structural brain imaging analysis conducted with the magnetic resonance imaging (MRI) brain scans taken in this study. A voxel-based morphometry (VBM) analysis is used to report correlations between grey matter densities and altered insight into health condition (broad object of insight), memory, social cognition and performances in ADL (specific objects of insight) measured through different approaches in the cohort of the present study.

‘Chapter 7: General Discussion’ summarizes and integrates the findings of the present study through a thorough and critical analysis of the work carried out in this research project, along with commenting on its main limitations, and suggesting implications and future research directions.

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Chapter 2: GENERAL METHODS

2.1 OVERVIEW

Relevant literature reveals that multiple procedures have been used to study the conceptualization of impaired insight and its respective neuroanatomical foundations in dementia. The present chapter provides a general picture of the particular methods employed in this PhD research project to address the objectives proposed in 'Chapter 1: Introduction'. In addition to conducting a systematic review on the potential the neural underpinnings of broad and specific objects of insight in frontotemporal dementia (FTD), the psychometric properties of different insight assessment methods, as well as their associations with other neuropsychological/behavioural variables, were examined analysing data collected from a cohort of patients with FTD, Alzheimer's disease (AD), motor neuron disease (MND)/amyotrophic lateral sclerosis (ALS), cognitively healthy older adults (HC) and their respective reliable informants. Complementary, Magnetic Resonance Imaging (MRI) brain scans were obtained from a part of the cohort to identify potential correlations between measures of insight and brain areas of interest, especially in the group of patients with FTD.

2.2 FORMULATION OF THE PRESENT PHD RESEARCH PROJECT

The formulation of this PhD research project was created after discussions carried out between the author of this thesis PhD student Carlos Muñoz Neira (Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences, University of Bristol) and his PhD Supervisors Dr Catherine Pennington (Centre for Dementia Prevention, University of Edinburgh), Dr Jade Thai (Bristol Clinical Research Imaging Centre -CRICBristol-, Translational Health Sciences, Bristol Medical School, Faculty of Sciences, University of Bristol) and Associate Professor Dr Elizabeth Coulthard (Research into Memory, Brain sciences and dementia Group -ReMemBr Group-, Translational Health Sciences, Bristol Medical School, Faculty of Sciences, University of Bristol). Professor Dr Michael Hornberger (Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia), who acted as a collaborator of this investigation, also participated in some of these discussions.

Dr Pennington firstly suggested the scientific problem to be addressed in this PhD research project and proposed a pertinent experimental design. Whilst Professor Coulthard helped to shape the problematization of this project, Dr Thai suggested a relevant MRI protocol to be applied and suggested amendments in the methodological aspects of this study. Additionally,

Professor Hornberger suggested gold standard measures for insight assessment and suggested relevant types of brain imaging analysis.

PhD student Carlos Muñoz Neira worked on every single stage of the present investigation and was responsible for its complete implementation. These tasks included the delimitation of the experimental design and research question, definition of objectives and formulation of hypotheses, adjustment of methodological aspects, recruitment of participants, conduction of insight and neuropsychological/behavioural assessments, brain imaging acquisition, analysis of neuropsychological/behavioural and brain imaging data, and presentation of results. Likewise, PhD student Carlos Muñoz Neira wrote all the chapters of this PhD thesis himself. A broad presentation of the main phases entailed in this PhD research project together with an estimation of the time taken by them can be seen in Figure 2.1.

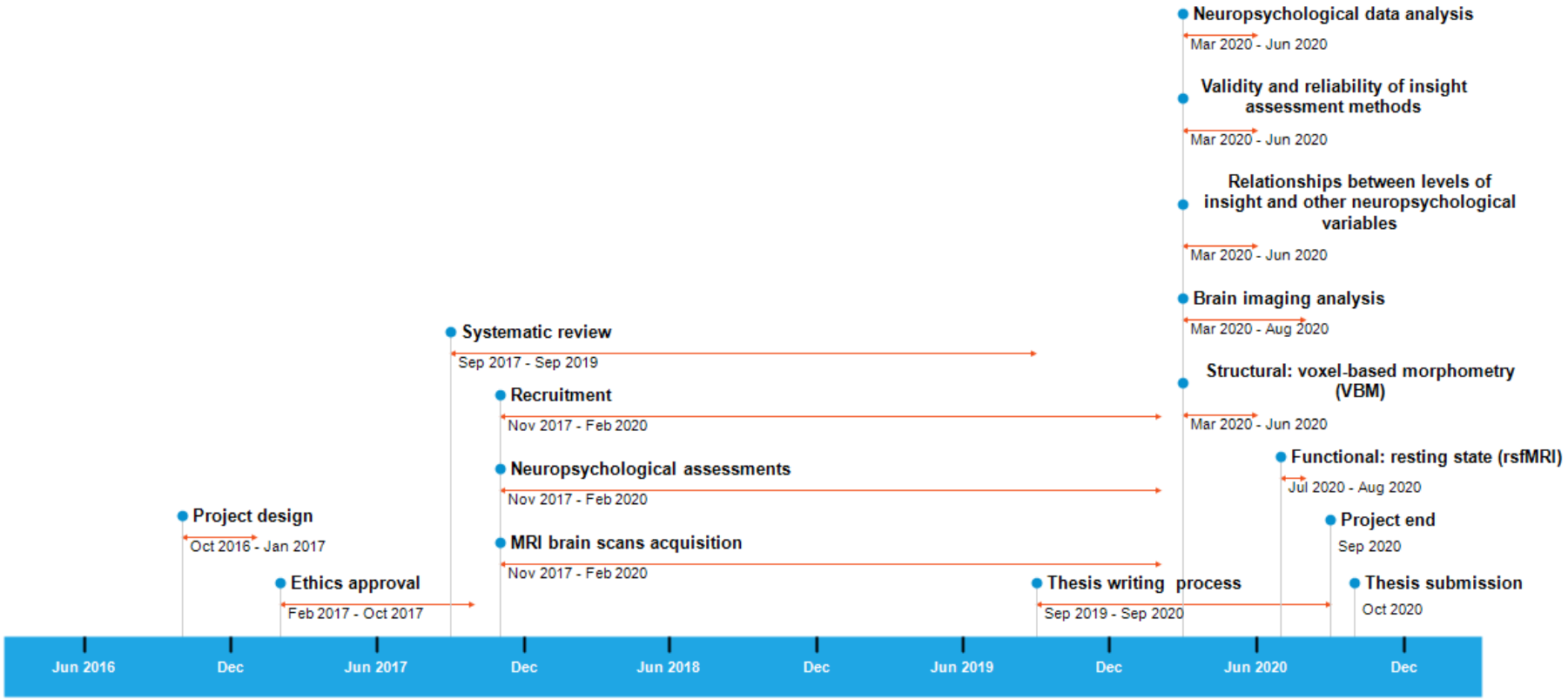
2.3 EXPERIMENTAL DESIGN AND PROCEDURES

The present investigation was conducted using cross-sectional and quantitative approaches. All the procedures required to reach its objectives can be split into 3 parts (see Figure 2.1):

5. the conduction of a systematic review to gain state-of-the-art knowledge on neural correlates of impaired insight in frontotemporal dementia (FTD),
6. the data analyses of neuropsychological/behavioural variables aimed at estimating the psychometric properties (validity and reliability) of different insight assessment methods along with exploring the potential relationships between insight and other neuropsychological/behavioural variables over a cohort of patients with diagnoses resulting from frontotemporal involvement, cognitively healthy controls, and their reliable informants, and
7. the structural brain imaging analysis for the examination of the neuroanatomical bases of broad and specific objects of altered insight in FTD.

General pictures on how such efforts were carried out are described below and their corresponding further elaborations are specified throughout the following chapters. A brief theoretical background on the methods employed for data collection of in this doctoral thesis can be found in ‘Chapter 8: Appendix’ (Supplementary Material 1).

Figure 2.1 Stages and timeline for the study entitled 'Neural correlates of altered insight in frontotemporal dementia'



2.3.1 Systematic review

A systematic review on neural correlates of altered insight in FTD was conducted to rely on a theoretical framework that could guide this investigation. Its main aim was to observe whether broad and specific objects of insight are underpinned by different or similar brain areas in this disease. 6 databases, namely Medline, Embase, PsycInfo, Web of Science, Biosis and ProQuest Dissertations and Theses Global, were thoroughly inspected for this purpose, and the main findings encountered were reported and published in the scientific journal 'NeuroImage: Clinical' (Chapter 3, 'Neural correlates of altered insight in dementia: a systematic review') (Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019).

2.3.2 Neuropsychological/behavioural data analyses

Patients who fulfilled diagnostic criteria for FTD were evaluated with a large number of insight assessments, neuropsychological tests and behavioural questionnaires. The same evaluation was performed on other patients with diagnoses resulting from frontotemporal involvement such as Alzheimer's disease (AD) and motor neuron disease (MND)/amyotrophic lateral sclerosis (ALS). Cognitively healthy older adults (HC) were also correspondingly evaluated. It should be noticed that part of these assessments included self-administered questionnaires completed by all the participants and informant-based questionnaires filled in by their respective informants.

The informant required by each participant was either a reliable informant or proxy. For those participants with neurological conditions, a reliable informant was someone who is familiar with the participant's day-to-day behaviour, i.e. someone who had known the participant for 10 years at least (generally a carer, the spouse or a close relative) and was able to provide relevant clinical information about them. In case of HC, a reliable informant/proxy was someone who had known the subject in reference very well, having at least weekly contact with them (generally the spouse, a relative or a close friend).

Concerning the insight assessment methods employed to evaluate altered insight, 3 different structured approaches were considered including i) self-administered and informant-based questionnaires/scales discrepancy scores (participant-informant level of agreement), ii) self-appraised and standardised performances on neuropsychological tests discrepancy scores (self-appraisal accuracy) and iii) clinician-based assessments (clinical judgement).

In terms of neuropsychological assessments, all participants underwent a battery of tests which incorporated tools for the evaluation of global cognitive function, attention, memory, language, visuospatial abilities, executive functions and social cognition. They also completed self-administered scales for the assessment of behavioural changes.

Reliable informants filled in informant-based questionnaires aimed at assessing participants' levels of insight, functional capacity in activities of daily living (ADL), behavioural changes and presence of neuropsychiatric symptoms, as well as scales used to assess caregiver burden and carers' symptoms of depression, anxiety and stress.

Participants completed insight, neuropsychological and behavioural assessments over 1 or 2 testing sessions in conformity with their preference, which took in total up to 2.5 hours. These assessments were conducted either at Southmead Hospital (North Bristol Trust facilities), CRICBristol or participants' homes. Self-administered questionnaires answered by participants and informant-based scales filled in by reliable informants took up to 20 minutes to be fully completed and were mostly finished off at participants' homes.

Once data collection was completed, neuropsychological data analyses were organised and separated into 2 main studies.

2.3.2.1 Validity and reliability of insight assessment methods

Psychometric properties (validity and reliability) of the insight assessment methods used in this research project were estimated before continuing with further analyses. Concerning validity, content-, construct- and criterion-related evidence was examined. It should be noticed that participant-informant level of agreement measured through discrepancy scores obtained between participant and informant versions of the Cambridge Behavioural Inventory - Revised (CBI-R) (Wear et al., 2008) was considered as the gold standard assessment of altered insight for both broad and specific objects. This decision was made reproducing the methodological approach used by the study that inspired the present research project (Hornberger et al., 2014). Outcomes obtained through this procedure were statistically contrasted with the results yielded by the other insight assessment approaches used to calculate their different types of validity. Regarding reliability, indices of internal and external consistency were calculated to estimate the respective reliability of the insight assessment methods employed in this investigation. Further details on the methodology used for such purposes are described in the respective chapter of this thesis ('Chapter 4: Psychometric properties of different insight assessment methods in frontotemporal dementia and associated disorders').

2.3.2.2 Relationships between levels of insight and other neuropsychological variables

Levels of altered insight into broad and specific objects were examined to determine whether certain modalities of insight were particularly impaired or preserved across the cohort. Additionally, analyses to explore whether the structure of insight is unitary or fractionated were performed. Also, outcomes taken from different neuropsychological and

neuropsychiatric/behavioural variables were covaried with scores of altered insight in multiple linear regressions to observe whether specific cognitive domains could account for/predict levels of insight. Moreover, altered insight and other neuropsychological and behavioural variables were compared in terms of the potential effect they can have on caregiver burden. Further details on the methodology used for these purposes are described in the respective chapter of this thesis ('Chapter 5: Insight, neuropsychological and behavioural characteristics of frontotemporal dementia').

2.3.3 Brain imaging data analysis

Neural correlates of altered insight into broad and specific objects in FTD were explored through structural brain imaging analysis.

2.3.3.1 Structural brain imaging

Several voxel-based morphometry (VBM) analyses were conducted in patients with FTD and associated syndromes, HC, and a combination of both types of subjects to identify statistically significant correlations between grey matter density and scores obtained from the insight assessment methods employed in this study. Further details on the methods used for these purposes are described in the respective chapter of this thesis ('Chapter 6: Structural neural correlates of altered insight into broad and specific objects in frontotemporal dementia').

2.3.3.2 Functional brain imaging

Resting state functional MRI (rsfMRI) sequences were also taken in this investigation even though the analyses carried out with these data are not reported in this thesis.

2.4 PARTICIPANTS

A convenience sample of volunteers were recruited from the North Bristol Trust Memory Clinic run by the Research into Memory, Brain sciences and dementia Group (ReMemBr Group, Translational Health Sciences, Bristol Medical School, Faculty of Sciences, University of Bristol), North Bristol Trust Motor Neuron Disease Clinic and the online source Join Dementia Research.

Inclusion criteria considered subjects:

- ✓ who were English speakers aged 50 or older,
- ✓ who presented an appropriate capacity for consent for research,
- ✓ were able to be assessed and
- ✓ were either drug free or on stable treatment.

Exclusion criteria considered:

- ✓ incapability to give informed consent,
- ✓ inability to read or illiteracy,
- ✓ incapability to complete neuropsychological tests due to lack of fluency in English, physical limitations (severe sensory deficits like blindness and/or deafness) or psychological issues (excessive anxiety) that could impede the administration of neuropsychological tests,
- ✓ significant psychological limitations or psychiatric illnesses (including past or current substance abuse) and/or
- ✓ use of medication likely to interfere significantly with cognitive function (except for cholinesterase inhibitors and memantine used routinely in dementia).

The sample of this research project included both patients and healthy controls (HC) as well as their respective reliable informants:

- ✓ Patients: subjects diagnosed with frontotemporal dementia (FTD) and other neurodegenerative conditions resulting from frontotemporal involvement including amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD). Patients with FTD comprised both the behavioural variant of FTD (bvFTD) and language variants of FTD (semantic dementia, SD; non-fluent primary progressive aphasia, nfPPA; or logopenic aphasia, LA). Diagnoses were made by a team of experts (neurologists complemented by neuropsychologists, psychiatrists or other specialists where necessary) following well established standard procedures necessary for individuals with cognitive decline or suspected dementia. Thus, based on widely known and used published criteria, clinical examinations, laboratory tests, neuropsychological assessments, brain imaging (MRI or CT where MRI was not possible) and follow-ups were involved in the diagnostic process (Bhogal et al., 2013; Borson, 2010). The core features of bvFTD patients encompassed a change of personality characterised by impaired insight, lack of empathy and social tact, hoarding, sweet tooth, hyperorality, hypersexuality, disinhibition and irritability, among other frontal behaviours (Piguet, Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011). The main symptoms of language variants of FTD were impaired verbal communication and speech problems, difficulties at naming items or recalling the desired word, articulatory deficits and/or failures of semantic knowledge depending on its particular type (SD, nfPPA or LA) (Gorno-Tempini et al., 2011). AD was understood as a typical dementia syndrome characterized by a memory disorder, frontal behaviours and impaired dysexecutive functions (Lam, Masellis, Freedman, Stuss, & Black, 2013). Lastly, MND/ALS patients were identified as such due to their neurological signs, namely muscle atrophy in superior and inferior limbs, spasticity, presence of clonus, hyporeflexia or hyperreflexia, and other symptoms secondary to their distinctive progressive loss of upper and lower motor neurons (Brooks, Miller, Swash, Munsat, & Gr, 2000; Strong et al., 2017).

- ✓ HC: cognitively healthy individuals with no significant medical history, that is to say, normal health with no neurological or psychiatric antecedents that could have caused neuropsychological or neuropsychiatric symptoms.
- ✓ Reliable informants: each participant required a reliable informant or proxy. For patients, this person is someone who is familiar with the participant's day-to-day behaviour (a person who has known the patient in deep for at least 10 years) and is capable of providing accurate and trustworthy information about the subject's current levels of insight, cognitive status, behavioural disorders/neuropsychiatric disorders and functionality in ADL (generally the patient's spouse, a close relative or their carer). In case of HC, this person is someone who knows the individual very well (a person has known the subject for no less than 10 years) and who report to have at least weekly contact with the subject (generally the subject's spouse, a close a relative or a close friend).
- ✓ Details on how every diagnostic group was conformed in these investigations are provided in the Methods sections of the following chapters of this thesis.

2.5 BATTERY OF NEUROPSYCHOLOGICAL TESTS, INSIGHT ASSESSMENTS AND NEUROPSYCHIATRIC/BEHAVIOURAL SCALES

The extensive battery of neuropsychological tools administered to the entire cohort of this investigation included neuropsychological tests and self-administered scales for the participants, and informant-based questionnaires for their respective reliable informants. The primary focus of the neuropsychological evaluation was placed on the assessment of a broad and several specific objects of insight. More precisely, altered insight into health status (broad object), memory, social cognition and performance in ADL (specific objects) were measured through participant-informant level of agreement, self-appraisal accuracy and clinical judgement. Both self-administered and informant-based questionnaires were contrasted to estimate participant-informant level of agreement over those objects of insight. Cognitive tests employed were aimed at assessing global cognitive functioning, episodic memory, social cognition, executive functions and language. An insight tool intended to measure self-appraisal accuracy was administered after every neuropsychological test used. Self-informant scales and informant-based questionnaires were aimed at assessing behavioural disorders, neuropsychiatric symptoms, performance in ADL and also the level of caregiver burden. Lastly, altered insight into the aforementioned objects of insight was assessed with a clinical judgment protocol.

Details on the conceptual and the operational definitions of the variables under study in this investigation can be found in 'Chapter 8: Appendix' (Supplementary Material 1). Additionally,

an outline of the tools included in the battery of neuropsychological tests (including insight assessments and neuropsychiatric/behavioural scales) can be found below.

✓ Tests for participants:

- Global cognitive functioning: Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams & Bak, 2013; Abrahams, Newton, Niven, Foley, & Bak, 2014).

The MoCA is a brief cognitive screening useful to rapidly evaluate attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation and orientation. It was originally created to detect cognitive impairment in MCI; however, its use has been extended to different conditions including AD, FTD, VD and many others. The MoCA has a maximum score of 30 and is a rather straightforward tool to administer, where its administration take should take no longer than 10 minutes (Nasreddine et al., 2005).

The ECAS is neuropsychological screening tool that includes several brief cognitive tests for the assessment of 5 domains: language, verbal fluency, executive skills, memory, and visuospatial skills. Unlike the traditional test Addenbrooke's Cognitive Examination - Revised (ACE-R), the ECAS incorporate tasks such as spelling, generation of words made up of only four letters and beginning with T, alternation between numbers and letters, a Hayling task (unconnected sentence completion), a short social cognition (judgment of preference), recall of a story, cube counting, and number location. Additionally, it can be applied to patients who have lost their motor ability to speak or use their hands, and includes an informant-based evaluation to examine the behavioural changes or the potential presence of psychosis. The ECAS has been designed to be sensitive to capture cognitive impairment not only ALS, but also in depression, AD and FTD, among others. Depending on the examinee, its administration time should be approximately 15 minutes in average. Lastly, its total score is 136 points, which can split into 28 points for language, 24 points for verbal fluency, 48 points for executive skills, 24 points for memory, and 12 points for visuospatial skills (Abrahams et al., 2014).

- Attention (and/or executive functions): Trail Making Test (TMT) (Reitan, 1958; Tombaugh, 2004).

The TMT is a traditional neuropsychological tool that has been considered as a measure of either attentional capacity or executive functions. It offers information on visual and scanning capabilities, speed of processing, and flexibility/shifting. The TMT has two parts. The Part A requires the examinee to draw a continuous line, without lifting the pen, so they can connect 25 numbered circles spread over a sheet of paper. The Part B requires the individual to alternate between circles with letters and circles with numbers also distributed on a sheet of

paper. The subject is told to perform the tasks as quick as possible in ascending order (1, 2, 3, etc. for TMT-A, and 1-A, 2-B, 3-C for TMB-T). Time of performance and errors are recorded. Also, whenever the examinee makes a mistake, its trajectory tends to be rectified where applicable. Scores in both parts of the TMT are represented by the time taken by the individual to complete the task. The TMT is a widely known neuropsychological test that has been utilized in both clinical and research settings to assess patients with a wide array of brain disorders (Reitan, 1958; Tombaugh, 2004).

- Episodic memory: California Verbal Learning Test - Second Edition (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000).

The CVLT-II is a widely known test used to assess episodic memory in clinical and research settings. Its administration requires several trials in which the examinee must attempt to memorize a list of words read aloud by the examiner. Short-delay free recall, long-delay free recall and cued recall, and long-delay yes/no recognition are evaluated in this test. Also, repetitions and intrusions are recorded. The time of administration of this tool depends on the condition of the examinee (patients with brain disorders take longer than healthy subjects) and the time employed to test the delayed recall, which is 10 minutes for the short form and 20 minutes for the standard form. Consequently, the total time to perform this test can fluctuate between 20 minutes to one hour (Delis et al., 2000).

- Social cognition: The mini-Social cognition and Emotion Assessment (Mini-SEA) (Bertoux et al., 2012).

The mini-SEA is a neuropsychological tool designed to assess social cognition. This test is made up of 2 parts. The first one aims to evaluate theory of mid (the capability to infer others' intentions or thoughts) and requires the examinee to detect a 'faux-pas' (interpersonal inappropriate/awkward interactions) errors throughout 10 social situations, which are presented as brief stories supported by pictorial aids. The second one examines emotion processing through the presentation of 35 faces expressing a particular emotion (happiness, surprise, neutral, sadness, fear, disgust, anger or neutral/no emotion). After rating conversions, each part has a maximum score of 15 points, being 30 points the maximum total score of the tool then. Its complete administration time of the Mini-SEA should range between 20 and 30 minutes. The Mini-SEA has shown to be helpful to assess social cognition in bvFTD, AD, depression and other brain disorders.

- Executive function: Frontier Executive Screen (FES) (Leslie et al., 2016)

The FES includes three quick tasks commonly utilized for the assessment of frontal functions: verbal fluency, inhibitory control and working memory. Every task has a can be rated with

scores ranging from 0 to 5, combined can generate a maximum of 15 points (greater scores suggest better executive functioning) (Leslie et al., 2016).

- Language: Sydney Language Battery (SydBat) (Savage et al., 2013).

The SydBat intends to evaluate language abilities including 4 subtests: naming, repetition, comprehension and semantic knowledge. 30 stimuli are presented with different pictures in each task of this battery, which should take no longer than 20 minutes in total to be administered (Savage et al., 2013).

- Insight Task:

In this task, which intends to measure of self-appraisal accuracy, participants are asked to rate their own performances according to where they think their scores could be placed across a normal curve. This task is performed after every neuropsychological test of this battery is administered. Equivalent actual standardised scores obtained on those tools are later subtracted from the respective resulting values of this task (Rosen et al., 2010; Williamson et al., 2010). Averaged scores calculated among self-appraisal accuracy on episodic memory, social cognition and executive function represented a measure of insight into health condition. Particular scores estimated from self-appraisal accuracy for episodic memory, social cognition and executive functions corresponded respectively to measures of altered insight into memory, social cognition and executive functions.

✓ Self-administered scales for participants:

- Self-administered version of the Cambridge Behavioural Inventory - Revised (CBI-R) (Wear et al., 2008).
- Insight Questionnaire - Participant Version (Hornberger et al., 2014).

✓ Informant-based questionnaires for reliable informants:

- Informant version of the CBI-R (Wear et al., 2008).

The CBI-R is an informant-based questionnaire employed to assess the presence of diverse behavioural changes/neuropsychiatric symptoms in patients with brain disorders. The CBI-R was designed as a shorter version of the original CBI (Wedderburn et al., 2008). It should be noticed that while the original CBI has 81 items, the CBI-R has only 45. The CBI-R has 9 sub-scales including assessments for abnormal behaviour, mood, beliefs, eating, sleep, stereotypic behaviours, motivation, self-care and everyday skills. These sub-scales can be rated with scores ranging from 0 to 4 depending on the frequency of the symptom (0 = no impairment, 1 = occasional occurrence -a few times per month-, 2 = repeated occurrence -a few times per week, 3 = daily occurrence, and 4 = constant occurrence, representing the latter two scores a severe behavioural deficit) (Wear et al., 2008; Wedderburn et al., 2008)..

- Insight Questionnaire - Informant Version (Hornberger et al., 2014).

The Insight Questionnaire is a tool used in dementia to evaluate different modalities of insight. It has both a self-administered and an informant-based version useful to estimate discrepancy scores between them as an index of insight. The Insight Questionnaire has 28 items which are distributed into 5 sub-scales: social interaction, emotion, diagnosis/treatment, language and motivation/organization. Every item of the scale must be answered with a yes (agreement) or a no (disagreement) to a specified statement such as 'I believe I have a brain condition' and others (Hornberger et al., 2014).

Scores obtained through informant-based questionnaires (CBI-R and Insight Questionnaire) filled in by reliable informants for every object considered relevant to the ends of this study were subtracted from the outcomes yielded by their respective paired self-administered questionnaires completed by the subjects enrolled in this research project to calculate participant-informant level of agreement.

- Edinburgh ECAS - Informant Section (Abrahams & Bak, 2013).

Previously described above, this part of the ECAS contains 18 items.

- Disability Assessment for Dementia (DAD) (Gelinas, Gauthier, McIntyre, & Gauthier, 1999).

The DAD is a questionnaire filled in by a reliable informant with the purpose of assessing functionality in ADL in patients with dementia. The DAD considers basic (hygiene, dressing, continence and eating) and instrumental (meal preparation, telephoning, going on an outing, finances and correspondence, medications, housework and leisure) ADL including 40 items which must be answered with a yes or a no.

- Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991).

Based informant questionnaire made up of 18 items and aimed at assessing the presence of apathy in neuropsychiatric patients (lack of motivation) (Marin et al., 1991).

- The Depression Anxiety Stress Scale 21 (DASS21) (Lovibond & Lovibond, 1995).
- Tool used to measure levels of psychological distress, in particular depression, anxiety and stress made up of 21 items (Lovibond & Lovibond, 1995).
- The Zarit Burden Interview (Whitlatch, Zarit, & von Eye, 1991).

Tool with 22 items which used in research and clinical settings as a self-report scale to evaluate caregiver burden (Whitlatch et al., 1991).

✓ Clinical judgement

- Clinical Insight Rating Scale (CIRS) (Lichtenberg, 2010; Ott & Fogel, 1992).

The CIRS is as a measure of clinical judgement useful to assess insight. This tool yields an overall insight score along with scores for specific domains such as awareness on the reason for assessment, memory, performances on ADL and progression of the disease. The overall score of the scale corresponds to the sum of its specific domains, wherein each of them can be labelled with either good insight (0 points, no changes of awareness of health condition), relatively impaired insight (1 point) or severe altered insight (2 points). Higher scores in this scale represent greater impaired insight and vice versa (possible scores range from 0 to 8) (Lichtenberg, 2010; Ott & Fogel, 1992).

2.6 BRAIN IMAGING ACQUISITION

Part of the cohort of this investigation underwent MRI brain scans at CRICBristol acquired using a 3 T scanner (Siemens Magnetom Skyra MRI scanner) with a parallel transmit body coil and a 32-channel head receiver array coil. MRI brain scans were taken according to a predesigned MRI protocol, which included T1-weighted (~6 minutes), MPRAGE, TSE, DTI (~5-7 minutes), T2-weighted for hippocampal subfield demarcation (~3 minutes; TSE), T2 mapping (~5 minutes) and resting state (~12 minutes) images. MRI brain scans took 30 minutes approximately in total and participants were monitored for signs for distress or claustrophobia during scanning to cancel them whenever necessary.

Participants recruited from North Bristol Trust Memory Clinic could opt out of the MRI brain scan if they had already undergone one within the last 6 months of the date neuropsychological data were collected.

2.7 SAMPLE SIZE

Group sizes in this investigation were estimated on the basis of expert judgment and previous neuropsychological and brain imaging studies using similar methods of analysis. The conditions under investigation are relatively uncommon, and often have a late diagnosis, which makes recruitment particularly challenging. In addition, patients who have severe frontotemporal atrophies due to their neurological conditions can be frequently agitated and therefore not tolerate the procedures involved MRI brain scans acquisition. All the same, an effort to recruit between 10 and 20 FTD, AD and MND/ALS patients and 30 HC was made.

2.8 STATISTICAL ANALYSES

Variables under study (demographics, levels of insight and different neuropsychological and behavioural domains) were compared across the diagnostic groups with Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests, or Chi-square

tests or one-way ANOVA tests with Tukey's or Games-Howell's tests in terms of post hoc analyses where applicable.

Validity for the insight assessment methods used in this investigation were calculated with either Pearson's or Spearman's correlation indices where required. Correspondingly, reliability for the measures of altered insight employed was calculated with Cronbach's alpha coefficients considered as indices of internal consistency.

Levels of insight into health condition, memory, social cognition and performance on ADL were compared across the diagnostic groups made up in this research project to observe statistically significant differences and determine which of those insight modalities were relevant to significantly distinguish between groups. Complementarily, mean differences and effect sizes were estimated with the purpose of assessing which of the mentioned broad and specific objects of insight better discriminated across the diagnostic groups and measuring the effect of diagnosis on those forms of insight. Stepwise linear regressions were run to observe what particular cognitive domains could account for altered insight into broad and specific objects. This procedure was also carried out to contrast the impact of altered insight, neuropsychological variables and neuropsychiatric symptoms on caregiver burden.

Structural brain imaging analysis carried out with VBM looked into how failures of insight into broad and specific objects correlated/covaried with specific atrophies throughout the brain. A priori, structural differences across the brains of the diagnostic groups were compared also with VBM. Neural correlates of altered insight into broad and specific objects were estimated only in those insight modalities which presented relevant significant differences across the diagnostic groups.

2.9 DATA ANALYSIS, QUALITY CONTROL AND QUALITY ASSURANCE

Data were analysed under the supervision of Dr Pennington, Dr Thai and Dr Coulthard on secure University of Bristol or North Bristol Trust servers. Dr Hornberger suggested procedures to affine those results of interest.

Dr Pennington, Dr Thai and Dr Coulthard reviewed results from preliminary neuropsychological data and brain imaging analyses. Thereafter, regular data quality control was ensured by research team meetings.

2.10 DATA HANDLING

Data were collected in paper and electronic form (for the MRI brain scans). Signed consent forms were the only non-anonymous data collected and were kept safe in the site file stored in the ReMemBr Group secure storage room at Brain Centre in Southmead Hospital, Bristol,

UK. Data filled out on paper forms were also kept there. Paper data are expected to be converted to electronic format, and along with the other electronic data, these will be stored on secure University of Bristol and North Bristol Trust servers. These data will be kept for a minimum of 10 years.

All study participants were assigned a unique, pseudononymised study number. Their paper tests were labelled with this number. No other personal identifying information were written on the paper tests. The results were transcribed by Carlos Muñoz Neira who obtained a NHS research passport (and is therefore bounded by NHS confidentiality rules) and received training on data protection and good clinical practice. The paper tests used in this investigation are stored in hard copy in a locked office at the Bristol Brain Centre in Southmead Hospital, Bristol, uK. The same codes were used to identify patients' imaging data which were also pseudoanonymised after collection.

Anonymous data may be published in data repositories (such as the University of Bristol's data repository service, or other online data repositories), or as required by scientific journals to accompany article publication. These data may contain raw data, or summary data (e.g. means and standard deviations) from any measures collected. No identifiable information (e.g. names, date of birth, etc.) will be published. The anonymous data will be made available to any researchers from bona fide research organisations (e.g. Universities or Hospitals) through a reputable data repository. Anonymous data may be used for future research purposes by the research team, or other researchers, provided the research has ethical approval in place.

Participants were asked to initial a box on the consent form to give permission for their anonymous data to be published. Participants will be able to withdraw their data, without giving a reason, until the point at which their data is published in an anonymised form.

2.11 ETHICAL APPROVALS AND CONSENT

The present investigation obtained the pertinent ethics approvals required by the National Health System (NHS) in England, United Kingdom. Its study title is 'Insight and social cognition across the spectrum of frontotemporal dementia and amyotrophic lateral sclerosis', REC reference: 17/LO/0966; Protocol number: 2792; IRAS project ID: 224529.

Ethics approval by London - Surrey Research Ethics Committee (REC) and NHS Health Research Authority (HRA) was provided respectively on 17th of July 2017 and 9th of August 2017. Confirmation of capacity and capability at North Bristol Trust and CRICBristol study sites was given respectively on 26th of September 2017 and 4th of October 2017. Final approval for sponsorship by the University of Bristol was confirmed on 5th of October 2017.

This study was carried out according to good clinical and research practices instructed in the Declaration of Helsinki. Informed consent was obtained from all participants and their informants after discussing with them all the relevant information of the study and their doubts were allayed.

2.12 CONFIDENTIALITY

Anonymisation of all data obtained will ensure confidentiality. All data will be stored in compliance with the Data Protection Act 2000 and Bristol University Data Protection Policy.

2.13 RISKS AND BURDENS

There were no serious risks involved in taking part in this investigation. Cognitive testing took 2.5 hours approximately with plenty of breaks whenever required. Similar cognitive testing has been undertaken regularly in North Bristol Trust Memory Clinic and almost all patients tolerate it and many enjoy it. Occasionally patients felt bored or frustrated by testing and, in that case, breaks were offered to continue later. Participants were free to withdraw from this investigation at any time for any reason.

2.14 BENEFITS TO PARTICIPANTS

There were no direct benefits to patients and HC taking part in this investigation other than the knowledge they are contributing to research which may help others in the future.

2.15 FUNDING

This investigation corresponds to the PhD project of Carlos Munoz Neira. All the costs involved in its implementation were financially sponsored by 'Becas Chile', CONICYT - National Commission for Scientific and Technological Research [CONICYT - Comisión Nacional de Investigación Científica y Tecnológica], Government of Chile through University of Bristol Grant Code G100030-150. Carlos Munoz Neira was awarded with a full scholarship provided by the Government of Chile to cover his tuition fees, bench fees and living expenses for the length of his PhD programme in Translational Health Sciences. He joined this programme at Translational Health Sciences, Bristol Medical School, Faculty of Health Sciences, University of Bristol in September 2016 and his doctoral studies were intended to last up to 4 years.

2.16 CONFLICT OF INTEREST

The present investigation was conducted by Carlos Muñoz Neira, author of this thesis, under the supervision of Dr Catherine Pennington, Dr Jade Thai and Associate Professor Dr Elizabeth Coulthard. Professor Dr Michael Hornberger participated as an external collaborator

of this research project. There was no potential for conflict of interest from any of the researchers involved in this investigation.

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Chapter 3: NEURAL CORRELATES OF ALTERED INSIGHT IN FRONTOTEMPORAL DEMENTIA, A SYSTEMATIC REVIEW

3.1 CONTRIBUTION STATEMENT

The present chapter corresponds to the following publication:

Muñoz-Neira, C., Tedde, A., Coulthard, E., Thai, N. J., & Pennington, C. (2019). Neural correlates of altered insight in frontotemporal dementia: a systematic review. *Neuroimage-Clinical, 24*. doi:ARTN 102066

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This article has open access and can be found in the following link:

https://www.sciencedirect.com/science/article/pii/S2213158219304139

Minor amendments to its original publication have been made to improve the clarity of this chapter. In brief, this systematic review was entirely materialized by the author of the present thesis under the supervision of Dr Pennington, Dr Thai and Dr Coulthard. Details of the contributions made by each author are as follow:

- ✓ **Munoz-Neira, C.**, first author: delimitation of the scientific problem proposed by the Senior author of the article (Dr Pennington); implementation of the entire study; design of the search strategy; organisation of the literature found; screening, review and analysis of relevant papers; selection of the final papers included in the systematic review; preparation and writing up of the entire manuscript; creation of tables and figures, inclusion of the feedback provided by the all the Senior authors of the article (Dr Coulthard, Dr Thai and Dr Pennington); submission of the article to the journal 'NeuroImage: Clinical'; addressing rectifications, amendments and improvements of the manuscript after the first peer-reviewed process was completed, and re-submission of the manuscript before its final approval.
- ✓ Tedde, A., co-author: screening of papers and participation on the final selection of relevant articles (independent reviewer).
- ✓ Coulthard, E., co-author: guidance on the writing up of the article and suggestion of amendments to improve its quality.
- ✓ Thai, N. J., co-author: methodological advice; guidance on the writing up of the article and selection of the pertinent scientific journal to present the article.
- ✓ Pennington, C., Senior author: intellectual author of the scientific problem addressed by the systematic review; advice on the delimitation of the main objective of the article; suggestion of relevant methodological procedures to achieve its purpose; guidance on the writing up

of the article; critical revision of its sections, and suggestion of amendments to improve its quality.

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3.4 ABSTRACT

Altered insight into disease or specific symptoms is a prominent clinical feature of frontotemporal dementia (FTD). Understanding the neural bases of insight is crucial to help improve FTD diagnosis, classification and management. A systematic review to explore the neural correlates of altered insight in FTD and associated syndromes was conducted. Insight was fractionated to examine whether altered insight into different neuropsychological/behavioural objects is underpinned by different or compatible neural correlates. Six databases (Medline, Embase, PsycInfo, Web of Science, Biosis and Proquest Dissertation and Theses global) were interrogated between 1980 and August 2019. 15

relevant papers were found out of 660 titles screened. The studies included suggest that different objects of altered insight are associated with distinctive brain areas in FTD. For example, disease unawareness appears to predominantly correlate with right frontal involvement. In contrast, altered insight into social cognition potentially involves, in addition to frontal areas, the temporal gyrus, insula, parahippocampus and amygdala. Impaired insight into memory problems appears to be related to the frontal lobes, postcentral gyrus, parietal cortex and posterior cingulate. These results reflect to a certain extent those observed in other neurodegenerative conditions like Alzheimer's disease (AD) and also other brain disorders. Nevertheless, they should be cautiously interpreted due to variability in the methodological aspects used to reach those conclusions. Future work should triangulate different insight assessment approaches and brain imaging techniques to increase the understanding of this highly relevant clinical phenomenon in dementia.

Key words: insight, neural correlates, frontotemporal dementia

3.5 LIST OF ABBREVIATIONS

ACC = Anterior Cingulate Cortex	FP = Frontopolar	MND = Motor Neuron Disease
AD = Patients with Alzheimer's disease	FrSBe = Frontal System Behaviour Scale	MPFC = Medial Prefrontal Cortex
ALS = Amyotrophic Lateral Sclerosis	FSL = FMRIB's Software Library,Oxford University's Centre for Functional Magnetic Resonance Imaging of the Brain	MRI = Magnetic Resonance Imaging
AMG = Amygdala	FTD = Patients with Frontotemporal Dementia	MRS = Magnetic Resonance Spectroscopy
AQ-D_iADL = Awareness of Deficit - Dementia scale, instrumental activities of daily living domain	FTLD = Frontotemporal Lobar Degeneration	MTG = Middle Temporal Gyrus
BA = Brodmann Area	FWE =Family Wise Error	nfPAA/PNFA/PPA = Progressive non-fluent Primary Aphasia patients
bvFTD = Patients with frontotemporal dementia behavioural variant	GM = Grey Matter	OFC = Orbitofrontal Cortex
CT = computed tomography	HBD = Heart Beat Detection	PCC = Posterior Cingulate Cortex
CBD = Corticobasal Degeneration	HC = Cognitively healthy controls	PET = Positron Emission Tomography
CBD = Corticobasal Syndrome	HEP = Heart Evoked Potentials	PHP = Parahippocampus
CERAD = Consortium to establish a registry in Alzheimer's disease	HP = Hippocampus	PiD = Pick's Disease

DLPFC = Dorsolateral Prefrontal Cortex	iADL = Instrumental Activities of Daily Living	PSP = progressive supranuclear palsy.
DS = Discrepancy Score	ICC = Inferior Cingulate Cortex	R^2 = R-squared
DTI = diffusion tensor imaging	IFG = Inferior Frontal Gyrus	RFT = Random Field Theory
EEG = Electroencephalography	ITG = Inferior Temporal Gyrus	RS = Resting State
ERP = Evoked Related Potentials	Ke = Cluster extent	SD = Semantic Dementia patients
FC = Frontal Cortex	LA = Logopenic Aphasia patients	SFG = Superior Frontal Gyrus
FDG-PET/PET = Fluorodeoxyglucose (18F) positron emission tomography	mm2 = square milimetre	SPECT = Single-Photon Emission Computed Tomography
FDR = False Discovery Rate	MC = multiple comparisons	SPM = Statistical Parametric Mapping, University College London's Wellcome Trust Centre for Neuroimaging ("The FIL")
FIS = Fronto-insular Stroke patients	MARS = Memory Awareness Rating Scale	STG = Superior Temporal Gyrus
FIS = Patients with fronto-insular strokes	MCC = Mid Cingulate Cortex	TFCE = Threshold-free Cluster Enhancement
fMRI = Functional Magnetic Resonance	MEG = Magnetoencephalography	VBM = Voxel-based Morphometry
FOK = Feeling of knowing	MFG = Middle Frontal Gyrus	X^2 = Chi squared

3.6 INTRODUCTION

Colloquially, insight is understood as the capacity to have a deep understanding of a specific situation, or, as the word itself may suggest, an ‘internal sight’ (""insight, n.1".", 2017). In a clinical context, ‘insight’ refers to a conscious knowledge of health conditions and the capability to identify or judge the presence or severity of disease or symptoms (Zanetti et al., 1999) . Likewise, the term ‘altered insight’ embraces an inaccurate self-perception of a particular health status and/or its associated symptoms and potential consequences (Markova, Clare, Wang, Romero, & Kenny, 2005; McGlynn & Schacter, 1989; Mullen, Howard, David, & Levy, 1996).

Altered insight cuts across different brain disorders including multiple forms of dementia (Wilson, Sytsma, Barnes, & Boyle, 2016), traumatic brain injury (TBI) and schizophrenia (SCZ) (David, Bedford, Wiffen, & Gilleen, 2012), among others. Reduced insight is commonly observed in Alzheimer’s disease (AD) and is especially prominent in frontotemporal dementia (FTD) (Wilson et al., 2016). Severely impaired insight has been reported in 75% of cases with FTD (Wedderburn et al., 2008), and is one of the main clinical features of behavioural variant

FTD (bvFTD) (Neary et al., 1998; Rascovsky et al., 2011; Wedderburn et al., 2008). Although altered insight is a critical symptom in FTD, its neural foundations have not yet been fully explored.

Exploring the neural correlates of altered insight in FTD and associated syndromes has significant clinical relevance for several reasons. Diagnosing FTD is frequently clinically challenging and often delayed (van Vliet et al., 2013). Identifying potential neuroimaging biomarkers specific to the patterns of reduced insight, a highly frequent symptom observed in FTD variants (Neary et al., 1998; Rascovsky et al., 2011; Wedderburn et al., 2008; Wilson et al., 2016), is of great clinical interest. The timely detection of cognitive decline and dementia may be interfered by altered insight (Iliffe et al., 2005; Koch, Iliffe, & project, 2010) probably due to its role in the recognition and reporting of neuropsychological and behavioural symptoms (Markova et al., 2005; McGlynn & Schacter, 1989; Mullen et al., 1996). Greater understanding of the neural underpinnings of insight will aid disease prognostication, and may provide surrogate markers of disease progression for use in clinical trials.

Altered insight in dementia is associated with difficulties in performing activities of daily living (ADL), impaired decision making, dysthymia, apathy, psychosis, reduced adherence to treatment, increase in risky behaviours and caregiver burden (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005; Aalten et al., 2006; Zamboni & Wilcock, 2011). As a consequence, altered insight can impair quality of life and limit independence. Affected individuals may continue to perform everyday tasks such as cooking or driving when they are unsafe to do so, due to their reduced insight into cognitive or motor symptoms. Moreover, altered insight can lead to delayed presentation to clinical services, refusal of appropriate clinical investigations, and delayed diagnosis.

There is a theoretical importance to the study of the brain areas implicated in altered insight in dementia. The notion of ‘self’ encompasses a system of personal representations (or mental constructs), traits and attitudes that shape behaviour and social interactions (Orfei, Robinson, Bria, Caltagirone, & Spalletta, 2008) and provide a sense of personal identity (Mograbi, Brown, & Morris, 2009). These will clearly be influenced by the degree of insight one has into personal

abilities and disabilities. Congruently, exploring insight can offer a window onto neural mechanisms underlying the self itself (Mograbi et al., 2009) and other self-referential processes such as self-evaluation, self-awareness and consciousness, and can therefore potentially make a significant contribution to our understanding of human cognitive neuroscience (Zamboni & Wilcock, 2011).

Research into the neural correlates of insight has been hampered by the high complexity of the term and a certain lack of consistency in its definition (Markova & Berrios, 2011). Patients' reduced conscious knowledge of their own disease status or specific symptoms has been differently conceptualized as anosognosia, unawareness, lack of insight, denial, or impaired metacognition, among other terms (David et al., 2012; Gilleen, Greenwood, & David, 2010; Markova & Berrios, 2011). Anosognosia is often used to refer to reduced insight into specific symptoms such as amnesia (Shibata, Narumoto, Kitabayashi, Ushijima, & Fukui, 2008; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005) or a broader disease unawareness in dementia (Prigatano, 2009). This scenario differs from its original connotation referring to the clinical consequences of stroke (McGlynn & Schacter, 1989). The concepts of unawareness and lack of insight have had similar definitions in the literature (McGlynn & Schacter, 1989; Mullen et al., 1996). The term metacognition has been recently used in dementia when investigating self-perception and self-monitoring (DeLozier & Davalos, 2016; Eslinger et al., 2005).

A potential resolution to the problem of conceptualizing insight is to define it at the object level (Markova et al., 2005). Insight only emerges when it is related to something (an object) either pathological or non-pathological, and it cannot be expressed without having something to have insight into (Markova & Berrios, 2001, 2011; Markova et al., 2005). From this approach, object is understood as a "particular mental or physical state (e.g., mental illness, neuropsychological deficit) in relation to which insight is being assessed" (Markova & Berrios, 2001 p.245). Thus, the relational nature of the term is highlighted, and insight can be fractionated into different clinical phenomena that are targeted at their respective objects (Markova & Berrios, 2011). For instance, insight into having a specific disease (e.g. dementia) would differ from insight

into a specific function such as memory, language or walking ability (Gilleen et al., 2010; Markova & Berrios, 2011). This approach may facilitate the search for the neural correlates of altered insight in dementia (Gilleen et al., 2010; Markova & Berrios, 2011).

Altered insight is not an 'all-or-nothing' phenomenon (Aalten et al., 2005). One may over or underestimate one's abilities, to a greater or lesser degree. Previous work in neuropsychiatric disorders has shown insight to be more severely reduced in patients with AD compared to people with TBI and SCZ (Gilleen et al., 2010). In dementia, individuals with FTD tends to show less insight into their symptoms than people with AD (Salmon et al., 2008). Insight is also more severely affected in bvFTD than in the language variants of FTD (Banks & Weintraub, 2009). Additionally, some patients may exhibit impaired insight into some objects but not others. For example, impaired insight into cognitive functions or into behavioural disorders can be presented independently in patients with AD (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996).

Emerging evidence supports the hypothesis that insight is object specific. Research suggests that several types of self-referential mechanisms can be differentiated across particular brain areas (Mograbi et al., 2009). For instance, a global conception of the self has been correlated with midline cortical anterior and posterior structures including the prefrontal, parietal, cingulate and retrosplenial cortices (Mograbi et al., 2009). On the other hand, encoding of self-relatedness for external and internal inputs may be mostly situated at ventral midline cortical areas, whereas revaluation of self-related stimuli seems to principally face dorsal midline cortical networks. For its part, temporal functions might be sustained by interactions between posterior midline cortical areas and the hippocampal complex (Mograbi et al., 2009).

Alternatively, disorders presenting with variable types of altered insight can illustrate the potential neuroanatomical specialization of this symptom. The right hemisphere is particularly implicated in the altered insight seen post stroke (Bisiach, Vallar, Perani, Papagno, & Berti, 1986), whereas in Anton's syndrome, where an individual loses vision but continues to believe they can see, a bilateral deterioration of the visual cortex in the occipital lobes occurs (Prigatano, 2009). On the other hand, the striking neurological sign known as 'alien limb',

which consists of sense of estrangement towards a limb that moves involuntarily, has been associated to callosal, parietal and frontal brain anomalies not only mainly in corticobasal syndrome (CBS), but also in Creutzfeldt-Jakob disease (CJD) (Graff-Radford et al., 2013).

The Dissociable Interactions and Conscious Experience (DICE) model was initially developed to account for the differentiation between explicit and implicit memory processes (Schacter, 1989). Later, this approach was used to describe the neural processes underpinning altered insight (McGlynn & Schacter, 1989). It is theorized that the brain networks supporting altered insight into specific objects differ from those that configure broader overarching awareness of health status (McGlynn & Schacter, 1989). The model includes an operational centre in charge of mediating insight named the Conscious Awareness System (CAS). The CAS is strategically set up throughout posterior callosal, cingulate and parietal brain areas, and receives inputs from objects such as perception, memory, and language (Agnew & Morris, 1998; McGlynn & Schacter, 1989). Thus, damage to partial areas of the CAS or one of its connections may result in the expression of isolated altered insight into a specific object (Agnew & Morris, 1998; McGlynn & Schacter, 1989). Frontal lobes and executive functioning are also postulated to play a crucial role in this model. In DICE, disruptions involving the entire CAS or executive functions can create overarching altered insight into health status (Agnew & Morris, 1998; McGlynn & Schacter, 1989).

Studies conducted in AD patients suggest that distinctive neural substrates underlie insight into different objects. For instance, overarching insight into having dementia has been linked with AD pathology in the right prosubiculum of the hippocampus on histopathological analysis (Marshall et al., 2004), whereas insight into broad cognitive and functional impairment correlated with low metabolic rate in right lateral and dorsolateral frontal cortex (Harwood et al., 2005). Altered insight into memory impairment in AD appears to be linked to reduced blood flow in the left orbitofrontal cortex (Shibata et al., 2008) or hypometabolism in medial and lateral frontal lobes, left inferior parietal areas and the cingulate on functional brain imaging studies (Hanyu et al., 2008), whereas this symptom appears to be related to dysfunctions in inferior frontal areas in both MCI and AD (Vogel et al., 2005).

Variable associations between different types of insight and brain involvement have been also reported in patients with stroke, vascular dementia (VD) and TBI. Correlations between impaired insight into hemiplegia and damage to frontal, parietal, insula and basal ganglia areas have been found in many studies conducted with patients with strokes (Pia, Neppi-Modona, Ricci, & Berti, 2004). Disease unawareness in patients with VD has been associated with frontal lobes and basal ganglia dysfunction (Starkstein, Sabe, Vazquez, et al., 1996), while impaired insight into ADL ability was linked to damage to the insula and both right- and left-sided stroke disease (Tezuka et al., 2013). TBI studies highlight prefrontal and anterior temporal lobe areas as being crucial for insight into disease (Prigatano, 2005). In contrast, failure at judging personal traits and skills have been associated with decreased mid-line blood flow in the prefrontal and retrosplenial cortices in TBI (Schmitz, Rowley, Kawahara, & Johnson, 2006).

The overarching aim of this systematic review is to examine the neural bases of altered insight in FTD and its associated syndromes. We explore what the neural correlates of altered insight are in FTD and whether they differ across different objects of altered insight, either broad objects (i.e. altered insight into presence of disease/diagnosis or health condition) or more specific objects (i.e. altered insight into particular neuropsychological, neuropsychiatric or behavioural objects). Consequently, evidence for and against the concept of altered insight into different objects being subserved by different or compatible brain regions is reviewed. We hypothesized that altered insight into different objects is underpinned by distinctive brain areas. We predict that by utilising a more precise definition of subtypes of insight it will be possible to better understand neural correlates of altered insight. Detailed dissection of the neural correlates of different types of insight used in different studies may yield important information as to whether altered insight in FTD occurs at a broad or more specific object level. Exploring the neuroanatomical foundations of altered insight can contribute to the understanding of a clinical phenomenon critical for the early diagnosis and effective management of FTD and other forms of dementia.

3.7 METHODS

3.7.1 Procedure and definitions

The present systematic review was carried out in accordance with the procedures proposed by the Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) protocol guidelines (www.prisma-statement.org) (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & Group, 2009) and was correspondingly registered on the PROSPERO database (CRD42019078504) (Booth et al., 2012; Booth et al., 2011). The focus of this work was formulated considering the PICOS/PECOS approach (Liberati et al., 2009; Moher et al., 2009). This led to the design of a search strategy intended to be as inclusive as possible to properly address the main purpose of this systematic review.

Altered insight was defined as a relational clinical phenomenon characterised by reduced self-knowledge or awareness of an object, either broad objects (i.e. disease diagnosis or health condition) or more specific objects (i.e particular cognitive, behavioural, functional or neuropsychiatric symptoms) (Markova & Berrios, 2000, 2011; Markova et al., 2005). Concerning broad objects of insight, it should be noted that two connotations were considered in this systematic review: altered insight into the presence of a disease and diagnosis, or overall insight into health condition (either referring to self-perception of being in good or poor health and ability, or where authors combined insight scores into multiple objects, either cognitive or behavioural). FTD was defined as a neurodegenerative disease with diverse presentations, including behavioural (bvFTD), language (progressive non-fluent aphasia -PNFA-, semantic dementia -SD-, logopenic aphasia -LA-) and associated motor variants (motor neuron disease -MND-/amyotrophic lateral sclerosis -ALS-/FTD) (Cairns et al., 2007; Gorno-Tempini et al., 2011; Kovacs, 2016; Mackenzie et al., 2009, 2010; Piguet, Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011; Strong et al., 2017; Strong et al., 2009). Although LA can be explained by AD pathology in roughly 56% of the cases (Giannini et al., 2017) and therefore classified as such (Rohrer, Rossor, & Warren, 2012), it has been stated that frontotemporal lobar degeneration can account for 38% of the cases of LA (Giannini et

al., 2017), which the authors considered as sufficient justification to include it in the current review.

Diverse approaches were considered for the assessment of altered insight. In terms of the brain imaging methods used to explore the neural correlates of impaired insight in FTD, both structural and functional techniques were considered, including magnetic resonance imaging (MRI), functional MRI, positron emission tomography (PET), single-photon emission computed tomography (SPECT) and other methods used in cognitive neuroscience including EEG (electroencephalography) (Table 3.1).

Table 3.1 Generic model of the systematic review search strategy

Key words*	**Inputs****
FTD, bvFTD, PNFA, SD, LA, MND, ALS, FTLD PiD, CBD, PSP.	Frontotemporal dementia and its associated syndromes
insight, lack of insight, awareness, unawareness, self-appraisal, anosognosia, metacognition.	Lack of insight
neural correlates, anatomical or neuroanatomical bases, histopathological techniques, MRI, CAT, DTI, fMRI, PET, SPECT, MRS, EEG, MEG, RS.	Neural correlates and brain imaging methods

Search strategy performed onto five online databases including Medline, EMBASE, PsycInfo, Web of Science and BIOSIS and ProQuest Dissertations and Theses Global.

*****After every key word the command 'OR' was added
******Inputs were overlaid using the command 'AND'

3.7.2 Data sources and search strategy

A thorough search was performed across 6 online databases including Medline, EMBASE, PsycInfo, Web of Science, BIOSIS and ProQuest Dissertations & Theses Global in August 2019. References cited by the group of selected papers and pertinent reviews were manually examined to seek additional relevant papers. A generic model of the search strategy and key words used in this systematic review can be seen in Table 3.1. This generic search strategy

was modified to fit with the specific headings and/or sub-headings proposed by each of the databases. Examples of the particular search strategies run onto each database can be found in the supplementary section of this article ('Chapter 8: Appendix', Supplementary Material 2). Papers found across the databases included in this systematic review were merged into unified files that were then imported into EndNote X9 (Thomson_Reuters, 2018), where the final number of publications was deduplicated.

3.7.3 Study selection

Two independent reviewers (CMN and AT) screened titles and abstracts and where necessary full-texts. Agreement for relevant papers in the final selection was reached through the aid of the online tool Covidence (www.covidence.org) (Mavergames, 2013). Any disagreement was solved by discussion until consensus was obtained.

Inclusion criteria:

i. Studies of human beings published in English language between 1980 and August 2019.
ii. Studies seeking to correlate insight into any object (broad objects defined as insight into presence of disease/diagnosis status or health condition, or specific objects such neuropsychological, functional, behavioural or neuropsychiatric domains) with the outcomes of either structural or functional brain imaging.
iii. Studies with samples of patients with any form of FTD and/or associated syndromes.

Exclusion criteria:

i. Investigations conducted on animals.
ii. Articles published in languages different from English.
iii. Studies which did not include brain imaging.
iv. Investigations conducted solely with cognitively healthy normal controls.

3.7.4 Data extraction and analysis

Making use of a pre-defined structured data extraction form, two independent reviewers (CMN and AT) extracted the following details from each paper included in the final selection:

participant groups (including diagnoses), insight assessment methodology, object of insight measured, brain imaging modality and analysis methods, and study findings. A quality assessment based on a modified version of the Newcastle-Ottawa Scale (Sharmin et al., 2017; Wells et al., 2014) for cross-sectional studies ('Chapter 8: Appendix', Supplementary Material 3) was performed by two independent reviewers (CMN and AT) over the final selection of articles. Complementary, an examination utilising Crombie's items along with a global qualitative critical appraisal was conducted across those papers (Zeng et al., 2015). The results from the final selection of papers were organised according to broad or specific objects of insight and their respective neural correlates.

3.8 RESULTS

3.8.1 Study selection

A total of 660 records were identified and screened across the databases explored. 623 results were excluded following title or abstract screening where applied, which corresponded to postgraduate dissertation projects and theses (32), conference abstracts (126), other reviews (127), clinical cases (29), book sections (9) and other publications exploring FTD on issues not pertinent for this review, neuropsychiatric conditions other than FTD, diverse behavioural studies in dementia with no neuroimaging method utilised or general irrelevant topics (300) (Figure 3.1). Among the 37 papers shortlisted for full reading, 22 were considered not pertinent since they did not make use of neuroimaging or focused on neurogenerative diseases other than FTD. 15 studies met the selection criteria of this systematic review (Amanzio et al., 2016; Bastin et al., 2012; Garcia-Cordero et al., 2016; Hornberger et al., 2014; Ichikawa et al., 2013; Levy, Gansler, Huey, Wassermann, & Grafman, 2018; Massimo et al., 2013; McMurtray et al., 2006; Mendez & Shapira, 2005; Miller et al., 1997; Rosen et al., 2010; Ruby et al., 2007; Shany-Ur et al., 2014; Sollberger et al., 2014; Zamboni, Grafman, Krueger, Knutson, & Huey, 2010) (Tables 3.2 and 3.3).

Figure 3.1 PRISMA Flow Diagram

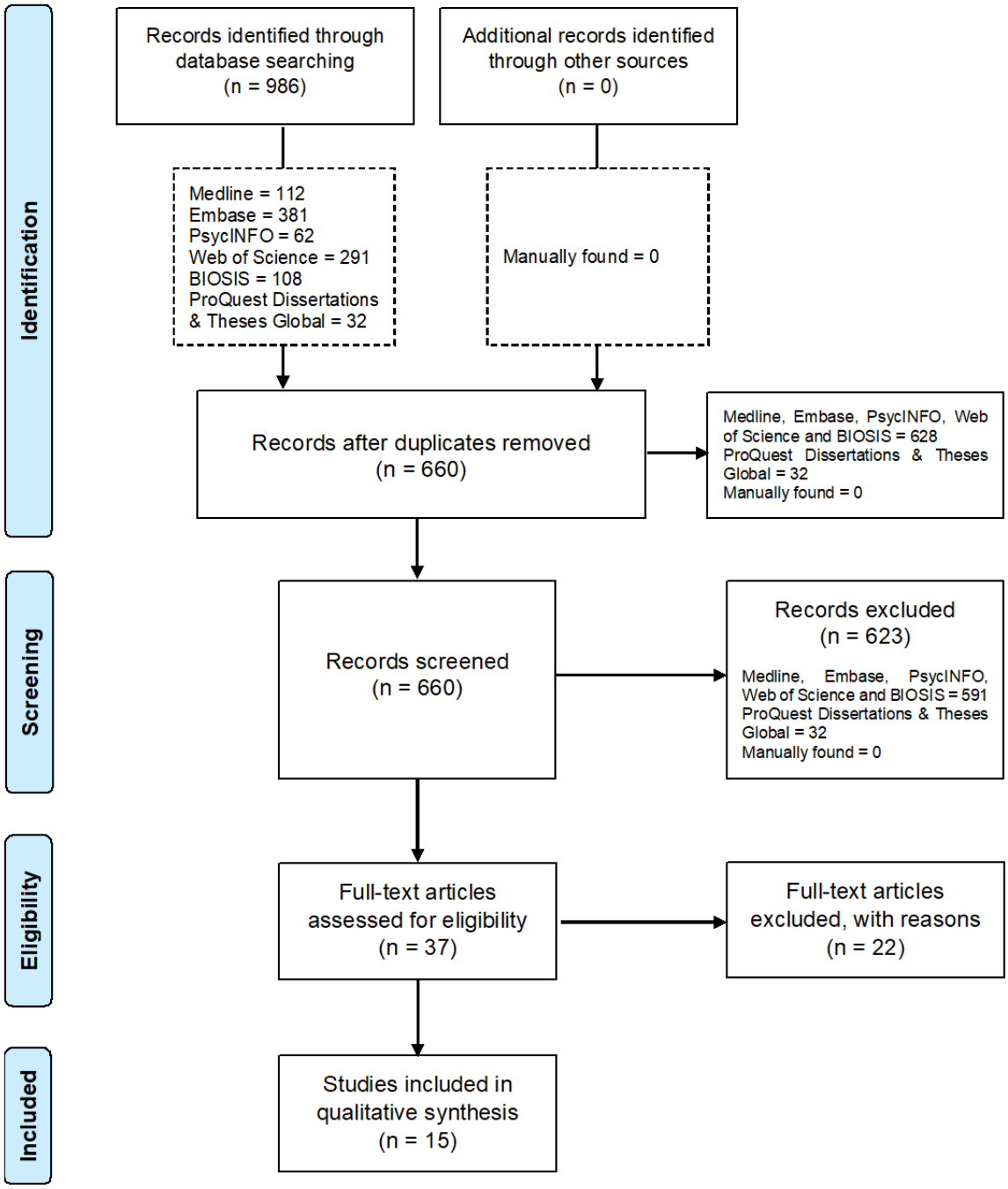


Table 3.2 Final selection of relevant papers: participants, insight assessment method, insight object targeted, brain imaging, and study quality

Paper	Participants	Insight assessment methodology	Insight object(s) assessed	Brain imaging methodology	Study Quality *
Mendez & Shapira (2005)	29 FTD	Insight question from CERAD plus 3 extra insight questions 4-point Likert scale ranging from total unawareness (0) to normal awareness (3)	Presence of disease Behavioural change	Visual rating of PET and SPECT images	Fair
Miller et al. (1997)	30 FTD 30 AD	Clinical judgment Presence or absence of patients' insight into illness	Presence of disease	Visual inspection of SPECT images	Fair
McMurtray et al. (2006)	74 bvFTD	Clinical judgment using Frontotemporal Dementia Inventory (degree of characterization of the object in reference ranging from 1 -not characteristic at all- to 5 -extremely characteristic-)	Behavioural change	Visual rating of SPECT images	Good
Levy et al. (2018)	26 bvFTD 29 CBS 12 PPA	Clinical judgment on the NRS item 'Inaccurate insight and self-appraisal' ranging from 1 (not present) to 7 (extremely severe) Participant - informant DS on the FrSBe.	Presence of disease & health status Executive dysfunction	MRI with automated parcellation of cerebral cortex into 68 regions of interest using FreeSurfer	Good
Ichikawa et al. (2013)	8 ALS 8 FTLD 11 HC	Combination of DS between patients' & clinicians' judgement on an Anosognosia scale (scores ranging from 0 to 32). Clinical judgement.	Overall motor, cognitive and emotional functioning.	Longitudinal changes of areas of bilateral anterior and inferior horns on CT images using Synapse	Good
Hornberger et al. (2014)	24 bvFTD 18 SD 13 PNFA 15 AD 11 LA	Patient - informant DS on the Insight Questionnaire	Specific scores on: Diagnosis and treatment Social behaviour Emotion Language Motivation/ organization Plus analysis of an overall, insight score across all objects	VBM analysis of MRI using FSL	Good
Massimo et al. (2013)	49 bvFTD 73 AD	DS between retrospective self-appraisal and standardized scores on language & episodic memory tasks	Multi-domain self appraisal (average performance on language and episodic memory tasks)	VBM analysis of MRI using SPM5	Good

Rosen et al. (2010)	2 ALS 2 MCI 9 AD 10 FTD 5 SD 5 PPA 4 CBD 2 HC	DS between retrospective self-rating of performance and standardize scores on attention, episodic memory, language & executive function tasks	Overall cognitive performance (average performance on working memory, attention, episodic memory and executive function tasks)	VMB analysis of MRI using SPM5	Fair
Shany-Ur et al. (2014)	35 AD 21 bvFTD 7 right-temporal variant FTD 8 svPPA 7 nfPPA 46 HC	Participant-informant DS using the Patient Competency Rating Scale (PCRS)	ADL competency Cognitive ability Interpersonal ability Emotional ability Composite score of all the above objects	VMB analysis of MRI using SPM5	Good
Sollberger at al. (2014)	28 bvFTD 16 svPPA 4 nfPPA 23 AD 12 CBS 19 HC	Participant-informant DS using the Interpersonal Reactivity Index (IRI)	Empathy	VMB analysis of MRI using SPM5	Good
Ruby et al. (2007)	16 bvFTD 16 HC	Participant-informant DS using questionnaires on behaviour prediction and personality assessment	Behavioural and personality changes	VBM analysis of PET images using SPM2	Good
Bastin et al. (2012)	8 bvFTD 26 HC	Participant - informant DS on the MARS Participants' performance prediction on a FOK task	Memory (autonoetic consciousness)	FDG-PET analysis using SPM8	Good
Zamboni et al. (2010)	27 bvFTD 12 aphasic variants of FTD 31 CBS 14 HC	Participant-informant DS on the FrSBe; clinical judgement	Executive function	VMB analysis of MRI using SPM5	Good
Amanzio et al. (2016)	23 bvFTD 30 HC	Participant - informant DS on the AQ-D_iADL	iADL	VBM analysis of MRI using SPM8	Good
García-Cordero et al. (2016)	18 bvFTD 21 AD 18 FIS 42 HC	Participants' ratings on their confidence to count their own heart beats (HBD) over accuracy, learning and feedback stages	Interoceptive awareness	VBM and lesion mapping analyses of MRI using SPM12, MRI resting state analysis using	*Good*

				SPM8 and HEP/ERP analysis of EEG.	

*Judgements made according to the quality assessment conducted with an adapted version of the Newcastle-Ottawa Scale (see Table 3.7).

Table 3.3 Final selection of relevant papers: strength of correlation between altered insight assessment and neuroimaging metrics, and main findings

Paper	**Strength of correlation between altered insight assessment and neuroimaging metrics**				**Study findings**
	Statistical analyses; Coefficient used	**Threshold**	**Threshold cluster extent where applicable**	**P value used for interpretation**	
Mendez & Shapira (2005)	Factorial analysis of variance (ANOVA), F-test	Not specified	N/A (visual inspection)	p<0.001 for main effect; p<0.01 for right-left hemispheres and frontal-temporal lobes effects; not significant interaction (however, right frontal predominance)	Loss of insight in FTD was associated with hypoperfusion/hypometabolism in the right hemisphere, especially in the frontal lobes.
Miller et al. (1997)	X^2	Not specified	N/A (visual inspection)	p=0.04	Patients with FTD showed an early loss of personal awareness related to uneven frontotemporal dysfunctions, either bilateral or unilateral
McMurtray et al. (2006)	Ordinal regression; F and Bonferroni tests	p < 0.005	N/A (visual inspection)	p<0.001	Loss of insight into behavioural change was associated with right frontal hypoperfusion
Levy et al. (2018)	Regression; R^2	Not specified	Not specified	R^2=0.45 for self-regulation mask	- Outcomes from measures of clinical judgement were more robust than patient-informant DS when correlating with brain structures. - Altered global insight correlated with left OFC and right rostral ACC in the whole cohort of patients (bvFTD, CBS and PPA). - Episodic memory functioning did not predict altered insight.
Ichikawa et al. (2013)	Two-tailed Fisher correlation	p < 0.05	N/A (areas of horns measured in mm2)	p = 0.0016 for anterior horn; p < 0.0001 for inferior horn	- Significant positive correlations between anosognosia scores and increase of anterior and inferior horns sizes (indexes of frontotemporal atrophy) in ALS, but especially ALS with FTLD. - Longitudinal increases of horn sizes were significantly more rapid in non-demented ALS patients compared with controls. - The anosognosia score was predominantly correlated with longitudinal enlargement of the inferior horn size (index of medial temporal lobes atrophy) in non-demented ALS patients.

Hornberger et al. (2014)	Voxel-wise general linear model; Covariate only model ; T-contrast	Significant clusters formed by TCE method (5,000 permutations); p < 0.001, FDR corrected for each voxel	20 voxels	p < 0.001	- Scores on insight into Diagnosis and treatment and Language domains did not differ among groups and were not covaried with GM volumes. -Whole group (bvFTD, SD, PNFA, AD and LA) significant correlations were found between GM volumes and insight into social interactions, emotion processing, and motivation/organization, but not on dementia subgroup analysis. -Social interactions insight correlated with left OFC, left PHPC, right MTG, bilateral insula, and right AMG atrophy. - Emotion processing insight correlated with bilateral FP cortices, right DLPC, supplementary motor area, bilateral ACC, and left AMG atrophy. - Motivation insight covaried with bilateral OFC, left ACC, right FP cortical atrophy. - Overall insight covaried with bilateral OFC and right FP cortical atrophy.
Massimo et al. (2013)	Regression	p < 0.05 FDR corrected for both voxel and cluster level analyses	15 voxels	p < 0.05	Impaired capacity to self-appraise cognitive performances correlated with GM density across ventral and rostral medial prefrontal regions in AD and bvFTD and especially with the subgenual cingulate (BA 25) in bvFTD.
Rosen et al. (2010)	Covariates only model	p<0.05 corrected for MC using FWE correction	25 voxels	p<0.05	Altered self-appraisal correlated with tissue content mainly in the right ventromedial prefrontal cortex in the whole cohort (behavioural and language variants of FTD, CBD, ALS, MCI, AD and HC).
Shany-Ur et al. (2014)	General linear models; T-test	p<0.05 FWE corrected	Study specific T-threshold at p<0.05 after 1000 permutations	p<0.05	- Whole group analysis (behavioural and language variants of FTD, AD and HC). Participants were split into under- and over-estimators. - Overestimating ADL competency correlated with atrophy of widespread right frontal regions, anterior insula, putamen, thalamus, medial & lateral temporal lobes & pons. - Overestimating cognitive functioning was associated with atrophy of right middle frontal & middle temporal gyri. - Overestimating emotional control correlated with atrophy in bilateral OFC, insula and right SFG. - Overestimating interpersonal abilities was linked with atrophy of putamen and fusiform gyrus.

					- Overestimating overall functioning was associated with atrophy of right orbital inferior frontal gyrus, middle frontal gyrus, caudate head, and putamen, left superior frontal gyrus, and the pons.
Sollberger at al. (2014)	Multiple regression design (covariates only); T-test	p < 0.001 voxel-wise	p<0.001 corrected for MC at p<0.05 based on cluster extent and a custom-fit error distribution determined by 1000 permutations	p<0.001 uncorrected	- Overestimation of empathic concern correlated with GM volumes in right-hemispheric anterior inferolateral temporal regions in the whole cohort of participants behavioural and language variants of FTD, AD, AD, CBS y HC). - bvFTD and nfPPA mostly overestimated their empathic concern compared to HC.
Ruby et al. (2007)	Behavioural-metabolic correlation analyses; Z-scores	p<0.05 corrected at cluster level	315 voxels	p<0.05	- Decreased metabolic activity in the left temporal pole correlated with reduced insight into behavioural change in bvFTD group - Reduced insight into personality changes did not exhibit significant neural correlates
Bastin et al. (2012)	Factorial analysis	p<0.05 FWE corrected for MC at the voxel level	20 voxels	p<0.05	bvFTD patients with reduced autonoetic consciousness exhibited hypometabolism across the anterior medial prefrontal cortex, the left dorsolateral prefrontal cortex (near the superior frontal sulcus), parietal regions, and the posterior cingulate cortex.
Zamboni et al. (2010)	Full factorial model; One tailed T-test	p<0.001 uncorrected	1,568 voxels	p<0.001 uncorrected; p<0.05 FWE corrected and FDR	- Combined cohort (behavioural and language variants of FTD, CBS and HC) showed correlations between reduced insight into behavioural change and GM loss in a region extending from the right superior temporal sulcus to the right ITG (posterior region of the right superior temporal sulcus, adjacent to the temporoparietal junction). - bvFTD patients underestimated their current behavioural disturbances and overestimated their premorbid ones.
Amanzio et al. (2016)	Explorative univariate linear regression	p<0.005 corrected for MC; statistical inferences made according to RFT	150 voxels; small clusters filtered with a p FWE corrected>0.05 (Ke> FWE corrected)	p < 0.001	bvFTD patients exhibited significant correlations between decreased awareness of performance on iADL and regional GM volume changes in the MPFC (predominantly MCC, dorsal anterior insula and cuneous) and areas of the anterior and posterior cerebellum.
García-Cordero et al. (2016)	Multiple regressions; T-tests and Spearman correlations	Structural and functional analysis: p > 0.001 uncorrected;	50 voxels in structural analysis and 10 voxels in	p < 0.05 or p < 0.001	*Correlations between interoceptive awareness & structural MRI:* - Combined bvFTD, AD & HC groups: IFG, STG, temporal pole, ACC, AMG, HPC and PHPC. - bvFTD group alone: temporal and parietal cortices plus the MCC, PHPC and AMG.

		lesion analysis: $p < 0.05$	functional analysis		*Correlations between interoceptive awareness & resting state MRI:* - Combined bvFTD, AD & HC group: IFG, HPC and PHPC. - bvFTD group alone: inferior, middle and superior frontal gyri including the prefrontal cortex.

3.8.2 Characteristics of the selected studies

Most of the studies (13 papers) focused on exploring the neural substrates of altered insight into presence of disease/diagnosis (2 papers) or health condition status (7 papers) or reduced of insight into social cognition (4 papers). Other publications examined the neural bases of impaired insight into other specific objects such as memory, executive functions, motivation, ADL or interoception (Table 3.4).

Table 3.4 Number of papers published (and its respective percentage) according to the objects of altered insight explored in frontotemporal dementia and associated syndromes*

Objects of insight	Number of papers	Percentage
Disease/diagnosis	2	13.33%
Health condition	7	46.67%
Social cognition	4	26.67%
Memory	1	6.67%
Motivation/Apathy	1	6.67%
Activities of daily living	2	13.33%
Executive functions	1	6.67%
Interoception	1	6.67%

*The total number of papers finally selected was 15. Certain studies explored more than one insight object (see Tables 2 and 3).

The commonest method used to assess insight was participant-informant discrepancy score (7 studies), followed by retrospective self-assessment versus actual performance discrepancy score and clinical judgement (4 papers respectively) (Table 3.5).

Table 3.5 Methodology used for insight assessment and brain imaging

Brain imaging technique	Method of insight assessment			Total
	Participant-informant discrepancy score	Self-ratings versus performances	Clinical judgment	
Structural*	6	2	1	9
Functional**	1	1	3	5

Combined***	0	1	0	1
Total	7	4	4	15

*8 studies (88.89%) used MRI [Amanzio et al. (2016), Hornberger et al. (2014), Levy et al. (2018), Massimo et al. (2012), Rosen et al. (2010), Shany-Ur et al. (2014), Sollberger et al. (2014) and Zamboni et al. (2010)] and 1 (11.11%) used CT [Ichikawa et al. (2013)).

**All studies used either PET or SPECT [Bastin et al. (2012), McMurtray et al. (2006), Mendez & Shapira (2005), Miller et al. (1997) and Ruby et al. (2007)].

***1 study used structural MRI, EEG and resting state functional MRI [Garcia-Cordero et al. (2016)]

No study used DTI, MEG, MRS or histological observations to explore any modality of lack of insight in FTD

The predominant brain imaging method used was structural brain imaging (9 studies, 8 with MRI and 1 with CT). In contrast, less preferred techniques were functional neuroimaging (5 studies with PET or SPECT) and combined brain imaging methods (1 study with MRI, EEG and resting state). No studies using DTI, MEG, MRS or histological observations were identified (Table 3.5).

In terms of the cohorts studied, most of the works included bvFTD patients (14 papers), language variants of FTD (13 papers; 6 PNFA, 5 SD and 2 LA) and healthy controls (9 papers). Less frequent diagnostic samples included across the publications were patients with ALS, CBS and AD (Table 3.6).

Table 3.6 Frontotemporal dementia-related diagnostic cohorts included across the studies reporting neural correlates of altered insight into diverse objects

Diagnoses	Numbers of studies including the diagnosis in reference	Percentage
bvFTD	14	93.33%
nfPPA	6	40.00%
SD	5	33.33%
LA	2	13.33%
ALS	2	13.33%
CBS	4	26.67%
AD	5	33.33%
Others*	2	13.33%
Controls	9	60.00%

*Others included patients with MCI and frontal strokes

3.8.3 Quality assessment of the papers selected for the present systematic review

The adapted version of the Newcastle-Ottawa Scale for cross-sectional studies utilized here ('Chapter 8: Appendix', Supplementary Material 3) evaluated the accuracy of participant selection, variables used to classify comparability of groups, potentially confounding variables accounted for, and the validity of outcomes measures. Using this scale, the quality of the articles finally selected for this systematic were rated as fair (4 to 6 stars) or good (7 to 9 stars) (Table 3.7). According to Crombie's items (Zeng et al., 2015), they included study designs coherent with their objectives, along with valid measures for the variables under study and appropriate statistical analyses ('Chapter 8: Appendix', Supplementary Material 4, Table 8). In addition, a qualitative examination suggested that they all included clear aims, collected data from reliable sources and used appropriate diagnostic inclusion and exclusion criteria to select participants ('Chapter 8: Appendix', Supplementary Material 4, Table 9). Only a minority of studies reported dropouts during the data collection process ('Chapter 8: Appendix', Supplementary Material 4, Table 9).

Table 3.7 Quality assessment for the papers included in the present systematic review according to an adapted version of the Newcastle-Ottawa Scale for cross-sectional studies

Paper	Selection (out of 4 stars)	Comparability (out of 2 stars)	Outcome (out of 3 stars)	Total (out of 9 stars)
Amanzio et al. (2016)	★★★	★★	★★	★★★★★★★ (7)
Bastin et al. (2012)	★★	★★	★★	★★★★★★ (6)
García-Cordero et al. (2016)	★★	★★	★★	★★★★★★ (6)
Hornberger et al. (2014)	★★★	★	★★	★★★★★★(6)
Ichikawa et al. (2013)	★★★★	★★	★★	★★★★★★★★ (8)
Levy el al. (2018)	★★★	★	★★	★★★★★★ (6)
Massimo et al. (2012)	★★★	★	★★	★★★★★★ (6)
McMurtray et al. (2006)	★★★	★	★	★★★★★ (5)
Mendez & Shapira (2005)	★★★		★	★★★★ (4)
Miller et al. (1997)	★★★	★	★	★★★★★ (5)
Rosen et al. (2010)	★★★		★★	★★★★★ (5)

Ruby et al. (2007)	★★★★	★★	★★	★★★★★★★★ (8)
Shany-Ur et al. (2014)	★★★★	★★	★★	★★★★★★★★ (8)
Sollberger at al. (2014)	★★★★	★★	★★	★★★★★★★★ (8)
Zamboni et al. (2010)	★★★	★	★★	★★★★★★ (6)

Thresholds for converting the Newcastle-Ottawa scales to Agency for Healthcare Research and Quality (AHRQ) standards (good, fair, and poor) as applied elsewhere*:

- 3 or 4 stars in selection domain plus 1 or 2 stars in comparability domain plus 2 or 3 stars in outcome/exposure domain = good quality
- 2 stars in selection domain plus 1 or 2 stars in comparability domain plus 2 or 3 stars in outcome/exposure domain = fair quality
- 0 or 1 star in selection domain plus 0 stars in comparability domain plus 0 or 1 stars in outcome/exposure domain = poor quality

*Sharmin S, Kypri K, Khanam M, Wadolowski M, Bruno R, Mattick RP. Parental Supply of Alcohol in Childhood and Risky Drinking in Adolescence: Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2017;14(3).

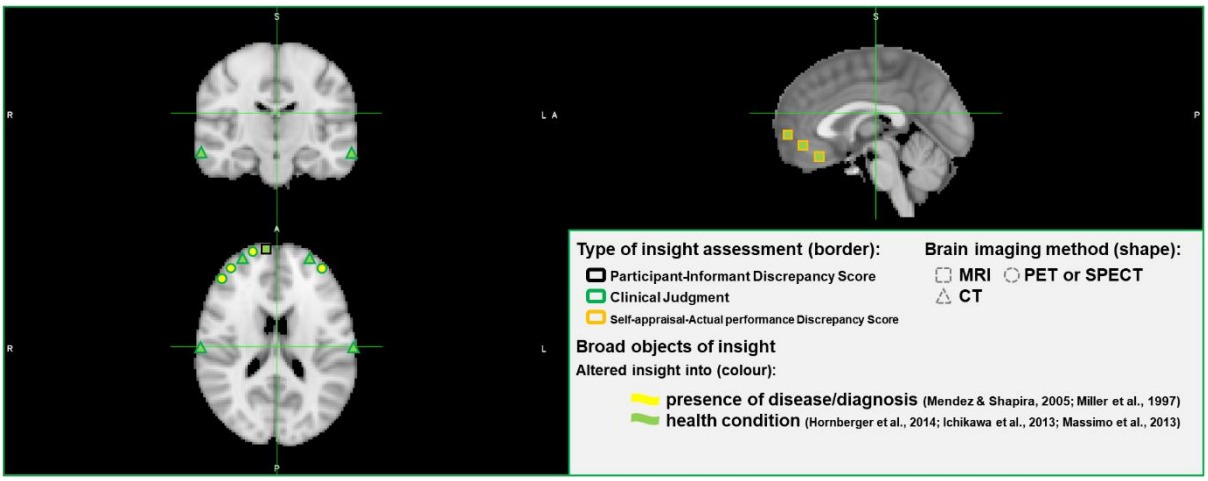
3.8.4 Broad objects of altered insight

3.8.4.1 Altered insight into presence of disease/diagnosis

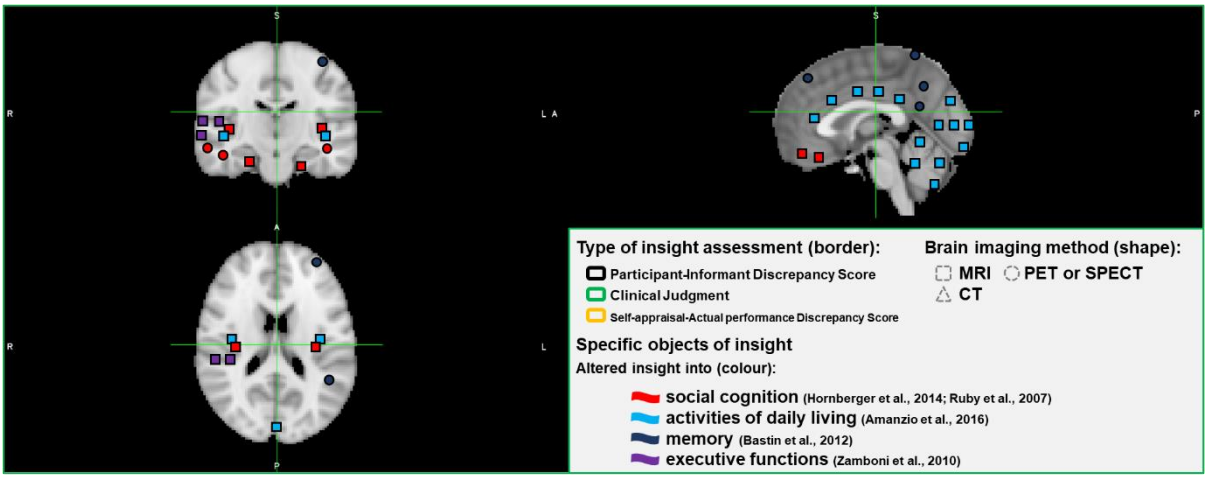
Utilizing clinical judgment, Mendez & Shapira (Mendez & Shapira, 2005) reported predominant right frontal dysfunctions (hypometabolism or hypoperfusion) in FTD patients showing impaired insight into disease status using either PET or SPECT, whereas Miller et al. (Miller et al., 1997) observed links between this object and variable bilateral, left- or right-sided frontotemporal dysfunction in FTD (Tables 3.2 and 3.3 and Figure 3.2a).

Figure 3.2 Brain areas involved in altered insight into different objects in patients with frontotemporal dementia and associated syndromes

a) Broad objects of insight



b) Specific objects of insight



MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography; CT = computed axial tomography

This figure was created with the Montreal Neurological Institute (MNI) template. The coloured figures represent spatial approximations only (see Tables 2 and 3 for more accurate details).

Garcia-Cordero et al. (2016), Levy et al., (2018), McMurtray et al. (2006), Rosen et al. (2010), Shany-Ur et al. (2014) and Sollberger et al. (2014) were not illustrated in this figure.

3.8.4.2 Altered insight into health condition

Using clinical judgement and SPECT and in accordance with Mendez & Shapira's results (Mendez & Shapira, 2005), McMurtray et al. (McMurtray et al., 2006) encountered associations between altered insight into health condition and right frontal hypoperfusion. In contrast, Levy et al.'s study (Levy et al., 2018) used clinical judgement and structural MRI brain scans, identifying correlations between this object and shrinkage of grey matter over the left orbitofrontal cortex and right regions of the anterior cingulate in FTD, CBS and PPA. After conducting a longitudinal study with CT brain scans, Ichikawa et al. (Ichikawa et al., 2013) found altered insight into health condition, measured through discrepancy scores between patients' and clinical judgements, to correlate with sizes of the anterior and inferior horns (indexes of frontotemporal atrophy), in ALS and especially in the ALS-FTD patients.

In a slightly different vein, Hornberger et al.'s study (Hornberger et al., 2014) reported neural correlates for overall insight, which represented an average of components such as diagnosis/treatment, social cognition, language and motivation/organization. Using patient-

informant discrepancy scores and structural brain imaging, correlations between altered overall insight and reduction of grey matter across bilateral ventromedial/orbitofrontal and left frontopolar areas were found in a mixed sample of behavioural and language variants of FTD and AD. Significant correlations did not emerge when each patient group was analysed separately (Hornberger et al., 2014) (Table 3.2 and Figure 3.2a).

Massimo et al. (Massimo et al., 2013) and Rosen et al. (Rosen et al., 2010) examined the discrepancy between subjective ratings of task performance and objective standardised performance scores, and explored correlations with structural MRI findings. Poor self-appraisal accuracy into multi-domain cognitive decline (average performance on grammatical, comprehension and visual episodic memory tasks) correlated with the grey matter density in ventral and rostral medial prefrontal cortex areas in AD and bvFTD, whilst exclusively with the subgenual cingulate (BA 25) in bvFTD (Massimo et al., 2013). Additionally, altered self-appraisal into multi-domain cognitive impairment (average performance on working memory/attention, episodic memory and executive functions tasks) was correlated with grey matter content in the right ventromedial prefrontal cortex in patients with a wide range of diagnoses including FTD, AD, ALS, MCI and controls (Rosen et al., 2010). On the other hand, through a patient-informant discrepancy score-based assessment, Shany-Ur's MRI study (Shany-Ur et al., 2014) found that overestimation of overall cognitive functioning corresponded with atrophy of bilateral superior and middle frontal gyri, right inferior frontal and cingulate gyri, middle temporal gyrus, insula and caudate in FTD, AD and controls (Tables 3.2 and 3.3, Figure 3.2a).

3.8.5 Specific objects of altered insight

3.8.5.1 Altered insight into social cognition

Findings on altered insight into social cognition can be divided into two aspects, those related to mentalizing and others linked with emotion processing. Mentalizing, also referred to as theory of mind, can be defined as inferring cognitive or emotional states in others (Amodio & Frith, 2006; Frith & Frith, 2012). Hornberger's study (Hornberger et al., 2014) found

correlations between impaired insight into social interactions (which may be compatible with reduced awareness into mentalizing) and atrophies across the insula bilaterally, the left orbitofrontal cortex, left parahippocampal zones, the right middle temporal gyrus and the right amygdala in a mixed group of FTD and AD patients. Using methods compatible with this work, Shany-Ur's study (Shany-Ur et al., 2014) and Sollberger et al. (Sollberger et al., 2014) found similar results. Shany-Ur's study (Shany-Ur et al., 2014) reported correlations between overestimation of interpersonal abilities and atrophy of the right orbitofrontal cortex, fusiform gyrus, anterior insula and putamen in a mixed group of AD, FTD and controls. Sollberger's study (Sollberger et al., 2014) found significant correlations between insight into mentalizing and grey matter density in right-hemispheric anterior inferolateral temporal regions in a combined cohort of people with behavioural and language variant of FTD, CBS and AD and controls. In contrast, Ruby et al. (Ruby et al., 2007) observed relations between bvFTD patients' insight into the capacity to interpret social situations and reduced metabolic activity in the left temporal pole using participant-informant discrepancy scores and PET (Table 3.2 and Figure 3.2b).

Emotion processing can also be defined as the ability to recognise emotions expressed by others (Amodio & Frith, 2006; Frith & Frith, 2012). Hornberger's study (Hornberger et al., 2014) reported significant associations between altered insight into emotion processing ability and atrophy of bilateral frontopolar regions, right dorsolateral prefrontal cortex, the supplementary motor area, the anterior cingulate bilaterally, and the left amygdala in AD and FTD. On the other hand, Shany-Ur's study (Shany-Ur et al., 2014) found that overestimation of competency in social interactions was associated with atrophy of bilateral orbitofrontal and anterior insular areas, right superior frontal gyrus, anterior cingulate cortex and the caudate across a mixed sample of patients with FTD, AD and controls.

3.8.5.2 Altered insight into memory problems

Only one study reported neural correlates of metamemory, that is, self-awareness and self-monitoring of memory, in patients with FTD. Bastin et al. (Bastin et al., 2012) conducted a study aimed at measuring autonoetic consciousness with a feeling-of-knowing task and PET

scans. Autonoetic consciousness, defined as the feeling of being able to recall the encoding context during memory retrieval, was markedly impaired in bvFTD patients. Those patients with reduced autonoetic consciousness showed reduced metabolism in the left anterior medial frontal cortex, the left middle frontal cortex near the superior frontal sulcus, the right postcentral gyrus, the left inferior parietal cortex, and the posterior cingulate cortex (Tables 3.2 and 3.3 and Figure 3.2b). No structural studies exploring altered insight into memory problems in FTD and its associated syndromes were found.

3.8.5.3 Altered insight into dysexecutive behaviours and executive function problems

When exploring altered insight into dysexecutive disorders and decline in executive function with the use of MRI scans and patient-informant discrepancy scores, Zamboni et al. (Zamboni et al., 2010) showed that grey matter loss in a region extending from the right superior temporal sulcus to the right inferior temporal gyrus (posterior region of the right superior temporal sulcus, adjacent to the temporoparietal junction) correlated with worsening of insight into behavioural disturbances in a cohort made up of patients with behavioural and language variants of FTD along with patients with CBS, where bvFTD patients tended to underestimate their present behavioural disturbances and overestimate their premorbid behavioural disturbances (Tables 3.2 and 3.3 and Figure 3.2b).

3.8.5.4 Impaired insight into performances on activities of daily living

After conducting a structural study with patients with bvFTD and controls, utilising patient versus informant discrepancy scores and MRI, Amanzio et al. (Amanzio et al., 2016) suggested that decreased density of grey matter in the cuneus, anterior and middle cingulate cortices and posterior cerebellum correlated with reduced insight into instrumental ADL. Complementary, Shany-Ur et al. (Shany-Ur et al., 2014) found, with a similar methodological design, that overestimation of performance on instrumental ADL corresponded with atrophy in widespread right frontal regions (orbital inferior and superior frontal gyri, medial orbitofrontal cortex, dorsal middle and superior frontal gyri), medial and lateral temporal lobe regions,

anterior insula, putamen, thalamus and the pons in FTD, AD and controls (Tables 3.2 and 3.3 and Figure 3.2b).

3.8.5.5 Altered insight into motivation

Hornberger et al.'s MRI study suggested that insight into motivation assessed by patient versus informant discrepancy score was associated to bilateral orbitofrontal, left anterior cingulate, and right frontopolar shrinkage in a mixed group of AD and FTD patients (Hornberger et al., 2014).

3.8.5.6 Altered insight into interoception

Garcia-Cordero et al. (Garcia-Cordero et al., 2016) explored the neural correlates of interoceptive awareness within a cohort of patients with bvFTD, AD, frontal strokes and controls using EEG, structural MRI and resting state sequences. First, interoceptive accuracy was assessed by asking participants to tap a keyboard in time with their own heartbeat over 3 phases: no feedback, learning (with a stethoscope as means of feedback) and no feedback again. Then, interoceptive awareness was measured by asking participants to estimate how confident they thought they were at performing the task. Compared to controls, patients with AD and FTD showed significant deficits in their confidence in reporting biological changes. Interoceptive awareness was related to atrophy/vascular impairment/dysfunction across a broad frontotemporal, parietal and limbic-insular network.

3.9 DISCUSSION

The present systematic review sheds certain lights on how different types of altered insight are mapped across the brain in FTD and associated symptoms; however, it also sparks several issues that require discussion.

3.9.1 Neural correlates of altered insight appear to vary according to the object of insight in reference in FTD and associated syndromes

The main goal of this systematic review was to investigate whether different objects of altered insight are linked to different or compatible brain areas in FTD. As hypothesized, overarching

altered insight and altered insight into specific neuropsychological/behavioural domains seem to be underpinned by different brain areas in FTD and associated syndromes. This hypothesis is supported by the findings of this review.

Overarching altered insight (into the presence of disease/diagnosis or health condition) in FTD is predominately associated with right frontal hypometabolism/hypoperfusion (McMurtray et al., 2006; Mendez & Shapira, 2005) or shrinkages of frontal regions that contain left orbitofrontal cortex and right anterior cingulate (Levy et al., 2018) when this insight modality is assessed by clinical judgement. In contrast, different modalities of insight into specific neuropsychological/behavioural domains are apparently mediated by specific brain regions. For example, altered insight into social cognition correlates with grey matter density in right inferotemporal regions in FTD, AD, CBS and controls (Sollberger et al., 2014) or the orbitofrontal cortex and limbic subcortical regions when combining FTD and AD patients (Hornberger et al., 2014) according to participant-informant levels of agreement. Additionally, inaccuracy in estimating memory performances in bvFTD can be accounted for by dysfunctions of the frontal, parietal and limbic lobes (Bastin et al., 2012), whereas poor insight into performances in ADL in bvFTD and controls seems to be supported by frontal medial regions, the insula and also posterior areas of the cerebellum (Amanzio et al., 2016) employing the same insight assessment approach.

3.9.2 Comparisons with neural foundations of altered insight in other brain disorders

The findings of the studies reviewed here on overarching altered insight resemble partly those seen in other neurodegenerative diseases. As noted in FTD (McMurtray et al., 2006; Mendez & Shapira, 2005), impaired disease/symptoms insight correlates with reduced blood flow in right frontal inferior and superior regions in AD (Starkstein et al., 1995). However, hypometabolism and atrophy in the left dorsal anterior cingulate has also been associated with reduced insight in AD (Guerrier et al., 2018). Conversely in other analyses, altered insight has not been shown to correlate with cortical thickness in a mixed group of MCI and AD (Senturk et al., 2017).

This scenario appears to be in accordance with observations made in other brain disorders. For instance, disease awareness appears to be associated to frontal lobes and basal ganglia in VD (Starkstein, Sabe, Vazquez, et al., 1996). In patients with TBI, overall insight into one's own personality traits has been paired with higher activity in the right anterior dorsal prefrontal cortex (Schmitz et al., 2006). Furthermore, patients with SCZ exhibit associations between disease unawareness and reductions of grey matter density in the right anterior cingulate, left posterior cingulate and bilateral temporal inferior regions (Ha et al., 2004), the prefrontal cortex (Shad, Muddasani, & Keshavan, 2006) and total cranial volume (Flashman, McAllister, Andreasen, & Saykin, 2000), together with hypoactivations of frontal, parietal, basal ganglia and limbic areas (Shad & Keshavan, 2015). However, results obtained from larger cohorts of SCZ patients have not found significant correlations between illness awareness and cortical thickness or subcortical involvement (Beland et al., 2019).

In healthy controls, activation in the right ventrolateral prefrontal cortex and the midbrain were respectively found when the assessment of insight was split into self-reflectiveness and self-certainty within an external memory paradigm (Buchy et al., 2014). Additionally, a cohort of healthy individuals and patients with subjective cognitive decline exhibited a significant correlation between altered insight into cognitive changes and grey matter volumes of the left posterior hippocampus and cerebellar areas (Sanchez-Benavides et al., 2018).

As observed in FTD, the brain areas of a particular insight object seem to be compatible with those that may be responsible for that object in control subjects and patients with different brain disorders. For example, social interoceptive accuracy in healthy controls has been accounted for by higher activations mainly in right frontal, cingulate and parahippocampal regions, whereas in SCZ patients this has been correlated with frontotemporal and occipital areas (Pinkham, Klein, Hardaway, Kemp, & Harvey, 2018). While metamemory in healthy controls appears to be primarily underpinned by a wide network of medial temporal, frontotemporal and parietal areas (Chua, Schacter, & Sperling, 2009), altered metamemory has been associated with reduced cortical thickness in right frontal and cingulate areas in a combined sample of controls and AD patients (Bertrand et al., 2018). In relation to AD patients

only, insight into memory performance is linked with grey matter volumes in the left superior frontal gyrus (Fujimoto et al., 2017), while in amnestic MCI patients both the posterior cingulate cortex and the hippocampi are compromised (Vannini et al., 2017).

3.9.3 Study methodologies may shape their respective outcomes

The evidence analysed in this systematic review suggests that distinct insight objects are subserved by different neural correlates in FTD. However, this affirmation should be interpreted with caution due to the diversity of methodological approaches that led to such results. Considerable variability was seen in the conceptualization of insight, insight assessment methods, and brain imaging techniques used.

3.9.3.1 Conceptualization of insight

The articles selected for this systematic review used various labels to denote impaired self-knowledge of disease/symptoms. Whilst anosognosia (McMurtray et al., 2006; Mendez & Shapira, 2005) and reduced self-awareness mostly addressed disease unawareness, reduced insight itself, autonoetic consciousness or awareness embraced respectively the insight objects of social cognition (Hornberger et al., 2014), episodic memory (Bastin et al., 2012) and ADL (Amanzio et al., 2016). Other publications specified with insufficient precision the insight object under study. Anosognosia appeared to be occasionally extrapolated to a global condition when seeking the neural bases of altered insight into the presence of frontal behaviours (Zamboni et al., 2010). Congruently, unsuccessful post-test judgements on particular attentional, language and memory performances, once averaged, tended to be overgeneralized to mean lack of overall insight (Rosen et al., 2010) or impaired multi-domain self-appraisal (Massimo et al., 2013). Such a remarkable variety in the terms used to characterize altered insight in neuropsychiatric disorders has been also highlighted previously elsewhere (Gilleen et al., 2010; Markova & Berrios, 2000; Zamboni & Wilcock, 2011).

The wide array of terms used to label insight raises doubts as to whether researchers were investigating the same phenomena. This inconsistency can be attributed to the intrinsic complexity of the conceptualization of insight (Markova & Berrios, 2011; Markova et al., 2005;

Markova et al., 2014). We propose that relating insight to a specified object will aid the search for its neural correlates in different neurodegenerative and neuropsychiatric conditions.

3.9.3.2 Insight assessment

A wide range of different insight assessment approaches have been reported, which coincides with the variability in the conceptualization of the term and may introduce further heterogeneity to the literature. This situation questions whether the resulting neural correlates of altered insight may be shaped by their definitions and insight assessment methods. Comparing the neural outcomes obtained from different types of insight evaluation procedures focused on a particular object over the same cohort may provide an answer (Table 3.2 and Figure 3.2).

Levy et al. (2018) partially addressed such a problem contrasting results from participant-informant discrepancy scores and clinical judgment assessment methods in FTD and CBS. In comparison with participant-informant discrepancy scores, clinical judgement accounted for more variance of altered insight in orbitofrontal and anterior cingulate grey matter. However, these findings are debatable as the insight objects respectively contrasted differed, corresponding to altered insight into dysexecutive behaviours when participant-informant discrepancy score was used and disease unawareness when clinical judgement was used (Levy et al., 2018).

A recent study investigated whether different insight assessment methods were linked with compatible neuroanatomical correlates in MCI and AD (Tondelli et al., 2018). Insight into disease status was measured by clinical judgement and patient-informant discrepancy scores, with compatible temporomedial neural correlates emerging from each measure. Moreover, discrepancy scores between self-appraisal and standardised scores on cognitive tasks yielded the same results (Tondelli et al., 2018). There is a need for comparison of different insight assessment methodologies in FTD cohorts, to establish whether experimental results will be influenced by the choice of assessment method.

3.9.3.3 Brain imaging

The influence of different brain imaging techniques on study results was not thoroughly investigated among the studies reviewed here. Only one study examined this issue to certain extent. Garcia-Cordero et al. (2016) used structural and functional MRI to investigate the neural substrates of interoceptive awareness and both imaging techniques suggested similar findings (Garcia-Cordero et al., 2016).

3.9.4 Considerations relating to the critical appraisal of the papers included in the present systematic review

Although the studies reviewed in this manuscript presented well-defined methods and were of satisfactory quality, methodological issues remain. No study explicitly declared whether the researchers who conducted the evaluation of insight were blind to the diagnoses of the participants or imaging findings. Additionally, certain studies did not include cognitively healthy controls (Hornberger et al., 2014; Levy et al., 2018; McMurtray et al., 2006; Mendez & Shapira, 2005; Miller et al., 1997). Other studies excluded covariables like age, years of education, disease severity or total intracranial volume from the regression models used to link altered insight and brain involvement (Ichikawa et al., 2013; Levy et al., 2018; Massimo et al., 2013; Ruby et al., 2007), which could have influenced the reported results. In the same line, certain investigations applied considerably less robust procedures (including visual inspection of PET images) and weak statistical techniques to suggest neural substrates for altered insight in FTD (McMurtray et al., 2006; Mendez & Shapira, 2005; Miller et al., 1997). Other confounders are small groups sizes, and the use of mixed cohorts including participants with different cognitive diagnoses. For example, several studies included small FTD subgroups of roughly 10 participants (Bastin et al., 2012; Ichikawa et al., 2013; Rosen et al., 2010). Moreover, others combined FTD with AD (Massimo et al., 2013), FTD, AD and patients with strokes (Garcia-Cordero et al., 2016) or FTD, MCI, AD, ALS and CBS (Rosen et al., 2010). Aside from this, the heterogeneity of the pathology that causes FTD (Cairns et al., 2007; Kovacs, 2016; Mackenzie et al., 2009, 2010) can result in syndromes characterised by different symptoms, either predominantly behavioural, language associated or motor (Gorno-Tempini et al., 2011;

Piguet et al., 2011; Rascovsky et al., 2011; Strong et al., 2017; Strong et al., 2009), which at the same time can hinder the search of the neural bases of altered insight in FTD.

To the best of the authors' knowledge this is the first systematic review on neural correlates of altered insight in FTD and associated syndromes conducted according to predefined structured procedures such as those propose by the PRISMA statement (Liberati et al., 2009; Moher et al., 2009). Other reviews on the matter using alternative methodologies have already reported assessment methods for insight in dementia (Clare, Markova, Verhey, & Kenny, 2005), neural bases of insight in AD and other dementias (Ecklund-Johnson & Torres, 2005); neuropsychological patterns of altered insight/unawareness (DeLozier & Davalos, 2016) and neuroanatomical correlates for lack of awareness (Zamboni & Wilcock, 2011) in AD and FTD.

3.9.5 Altered insight and models of awareness

The DICE model recognizes insight's neurocognitive multidimensionality; however it seems to oversimplify a highly complex phenomenon and explain insufficiently memory's crucial role in its formation (Agnew & Morris, 1998). The Cognitive Awareness Model (CAM) model vindicates memory as a critical centre for a 'personal knowledge base' (PKB). In CAM, a faulty functioning of a 'memory comparator' (MC) can trigger different forms of altered insight. Thus, inaccurate updates of the PKB generated by a MC can make a subject with altered insight assume their abilities are unchanged from their premorbid state (Agnew & Morris, 1998).

CAM was reformulated (CAM-R) to include other components that potentially support insight (Morris & Hannesdottir, 2004). A 'personal data base' (PDB), equivalent to the PKB, interacts with an 'Autobiographical Conceptual Memory System' (ACMS), 'comparator mechanisms' (CMs) and a 'Metacognitive Awareness System' (MAS) (Morris & Hannesdottir, 2004; Morris & Mograbi, 2013). In CAM-R, diverse types of impaired insight are a consequence of disruptions in CMs, which wrongly update the PDB. Complementary, the conscious recognition of both abilities and deficits is controlled by the MAS, which finally embodies insight mechanisms (Morris & Hannesdottir, 2004; Morris & Mograbi, 2013).

Other models like the Self-Memory System (SMS) (Conway, 2005) have also stressed the central role played by memory processes in the construction of self-images. In a similar line, it has been postulated that disruptions in the interplay between anterograde and retrograde memory may result in an incomplete upgrade of personal information (Mograbi et al., 2009). This reduced consolidation of self-knowledge (non-updated PDB) may generate then a "petrified self" made up of distorted previous representations (Mograbi et al., 2009).

Unlike DICE, the aforementioned models seem to fail at proposing specific neural correlates for different forms of altered insight. Recently, Berlingeri et al. (Berlingeri et al., 2015) experimentally tested the CAM-R with cognitive tasks and functional brain imaging in patients with dementia. Altered processing of new personal information (inability to update the PDB) and faulty consolidation (disintegrated PDB) correlated with dysfunctions in lateral temporal and insular cortices along with the hippocampal complex. Moreover, it was suggested that altered insight into memory was associated with the disrupted connectivity in the default mode network (DMN) (Berlingeri et al., 2015).

More research is needed to experimentally test models of insight in FTD and associated syndromes. Although the brain areas implicated in altered insight proposed by the cited models of awareness may be relatively equivalent with the findings summarized in this systematic review, the number of articles revised is insufficient to draw firmer conclusions on the neural circuits that underpin different types of insight. Further generalizations are subject to limitations and go beyond of the scope of this review.

3.9.6 Altered insight and neural networks

Several neural networks with structural and functional differentiations have attracted the attention of dementia researchers. Among them, the salience network (SN) processes external and internal significant socio-emotional information and includes the frontoinsula and the pregenual anterior cingulate (Ranasinghe et al., 2016). The semantic appraisal network (SAN), which is juxtaposed with the SN, is responsible for self-evaluation functions influenced by semantic frameworks and involves the temporal pole, ventral striatum, subgenual cingulate

and amygdala (Ranasinghe et al., 2016). The DMN, distributed across temporoparietal, cingulate and hippocampal areas, corresponds to circuits that deactivates when performing certain cognitive functions, but activates in memory retrieval, mental state attribution and visual imagery (Zhou & Seeley, 2014).

Both SN and SAN are predominantly affected in FTD (Ranasinghe et al., 2016), which contrasts with the characteristic vulnerability of the DMN in AD (Zhou & Seeley, 2014). Aside from this, FTD appears to exhibit reductions of activity in frontotemporal areas of the DMN and enhanced posterior DMN connectivity, whereas AD tend to have enhanced SN connectivity (Zhou & Seeley, 2014). It has been proposed that the patterns of deterioration described across those neural networks can account for the alterations of self-projection (Irish, Piguet, & Hodges, 2012), insight and other metacognitive phenomena (Zhou & Seeley, 2014) observed in FTD. Although it is possible to acknowledge certain overlap between the structures and functions of the mentioned networks and the findings analysed in this systematic review, more research is needed to clarify how insight can be shaped by those circuits.

3.9.7 Future directions

Larger group sizes with cognitively healthy control groups and triangulation of different neuropsychological methods for insight assessment and neuroimaging modalities are needed. Examining the findings obtained through different brain imaging techniques over the same insight object and cohort of participants may provide neuroanatomical validity to insight measures. Ideally, patients with clinical FTD should be subgrouped according to their exact clinical syndrome and likely underlying neuropathology, although this is challenging in a relatively rare disease. Counterintuitively, healthy controls from several studies reviewed here were inaccurate when judging their own abilities, although altered insight was significantly more severe in patients with bvFTD. It would be of great interest to elucidate whether different brain imaging techniques, for instance, voxel-based morphometry, cortical thickness, diffusion tensor imaging or resting state, yield compatible results in the examination of one particular

object of insight measured through a unique or several different approaches over the same cohort. Longitudinal studies with repeated measures of insight and brain imaging over a number of time points will also help enhance our understanding of how different brain regions contribute to the deterioration in insight seen over the disease course in FTD.

3.10 HIGHLIGHTS

- ✓ Fractionating insight into objects aids its neuroanatomical exploration in dementia.
- ✓ Distinctive neural correlates seem to underpin different insight objects in FTD.
- ✓ Altered insight into disease/health condition mostly involves right frontal areas.
- ✓ Altered insight into social cognition implicates frontal, temporal and limbic areas.
- ✓ Frontal, medial temporal and parietal areas underpin insight into memory problems.

3.11 CONFLICTS OF INTEREST

The authors of this paper declare no conflicts of interest.

3.12 FUNDING

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Chapter 4: PSYCHOMETRIC PROPERTIES OF INSIGHT ASSESSMENT METHODS IN FRONTOTEMPORAL DEMENTIA AND ASSOCIATED DISORDERS

4.1 ABSTRACT

Psychometric properties of insight assessment methods have been underexplored in neuropsychiatric disorders. The main objective of this chapter is to partially tackle this issue by exploring and estimating the validity and reliability of different approaches for the evaluation of insight in dementia. Participant-informant level of agreement, self-appraisal accuracy and clinical judgement were considered as insight assessment methods and measured with different tools across a cohort of patients with frontotemporal dementia (FTD) (15), Alzheimer's disease (AD) (12), motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) (6), cognitively healthy controls (HC) (34) and their corresponding reliable informants. Patients and HC underwent an extensive battery of neuropsychological tests and filled in self-administered scales focused on insight and behavioural changes assessment, whereas their respective proxies completed informant-based questionnaires with the same purposes. Validity and reliability were estimated for the insight assessment approaches under analysis. Participant-informant level of agreement and clinical judgement seem to have a better content-related validity for the assessment of clinical insight in dementia according to the conceptualization of insight employed in this thesis compared to self-appraisal accuracy, which probably measures metacognition instead. Likewise, although all the tools used through the 3 insight assessment methods studied exhibited acceptable construct- and criterion-related validity, both participant-informant level of agreement and clinical judgement appeared to be more adequate than self-appraisal accuracy for the evaluation of insight in dementia conceptualized here. Complementary, satisfactory levels of reliability (internal and external consistency) were found across all the assessment methods under analysis. Whilst the insight assessment methods included in this study show good psychometric properties, their use in dementia practice and research should be carried out cautiously considering the conceptual definitions entailed by these approaches.

4.2 INTRODUCTION

As discussed earlier in this thesis, the study of failures of insight seen in different brain disorders has attracted a wide interest in research (David, Bedford, Wiffen, & Gilleen, 2012; Gilleen, Greenwood, & David, 2010; Landi, Marazziti, Rutigliano, & Dell'Osso, 2016; Wilson, Sytsma, Barnes, & Boyle, 2016). Such a special attention has led to the design and use of

diverse approaches to assess this symptom in dementia clinical practice and dementia research (Clare, Markova, Verhey, & Kenny, 2005). Furthermore, it is highly likely that the complexity and elusive nature of term have probably triggered the development of the methodological variability observed in the literature in assessment of this clinical phenomenon (Markova & Berrios, 2000).

Insight assessment methods in dementia have ranged from reports on self-perceptions of health status and/or symptoms to comparisons between patients' and reliable informants' reports on the health issues that patients are experiencing (Clare et al., 2005). Other approaches have contrasted between pre- or post-self-judgements and standardised scores on computerised or traditional neuropsychological assessments (Fleming & Lau, 2014). Additionally, health care professionals' views on patients' disease awareness or their capacity to identify symptoms have been notably used throughout several studies on the matter (Harwood et al., 2005; McMurtray et al., 2006; Mendez & Shapira, 2005). Aside from these methods, certain approaches have included the combination of a priori or a posteriori self-ratings on diverse tasks with observational opinions from collateral sources or also semi-structured interviews conducted with the targeted subject and their reliable informant. Moreover, other efforts have even considered phenomenological theories focused on exploring the self to measure insight or the potential influence of denying the presence of health problems on illness awareness (Clare et al., 2005).

At first glance, the important attention paid to insight impairment across different neuropsychiatric disorders during the last decades (Landi et al., 2016) can support the assumption that solid assessment approaches have already been built for a deep exploration of the symptom over this period. Furthermore, the implementation of multiple insight assessment methodologies in dementia (Clare et al., 2005) may also suggest a natural development of robust and exhaustive assessment approaches in the clinical study of the concept. Nevertheless, such a diversity should also make researchers reflect on how compatible those insight assessments approaches have been across studies and whether authors have been exploring the same or a different clinical manifestation (or whether they have been addressing the same or different scientific problems) (Pennington, 2017). Whilst this scenario has already been identified and examined in cohorts of patients with frontotemporal dementia (FTD) (Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019), it can certainly be extrapolated to other forms of dementia and brain disorders. In addition, such a research gap poses questions concerning the authenticity and coherence associated to insight measurements in dementia (Bunnage & Hughes, 2017) and directly moves the focus of the discussion to the critical need to explore the validity and reliability of insight assessment methods.

Validity and reliability are critical concepts for scientific rigour and trustworthiness of findings in assessment methods (Roberts & Priest, 2006). These key terms are addressed in psychological sciences by the field of psychometrics, which deals with the quantitative aspects of psychology such as methods and models used to summarize, organise and describe empirical data, along with inferring conclusions from them (Jones & Thissen, 2006). Psychometrics, also called psychometric theory, sets quality criteria for psychological measurements and the development of standardised tests based on two main categories, namely the classical theory test and the item response theory (Turner, 2013). It is then within this context that validity and reliability can offer answers to tackle the aforementioned problematization. The psychometric properties of a particular assessment refer primarily to its associated validity and reliability (Ginty, 2013). Whilst validity focuses on the degree to which an assessment approach measures what is actually intended to be measured (Roach, 2006), reliability is understood to mean how consistent such an assessment is (Cook & Beckman, 2006), or in other words, whether it will yield similar results in different circumstances, when nothing else has changed (Roberts & Priest, 2006).

Taking into consideration such definitions of validity and reliability, it becomes sensible to understand why these notions are crucial for sciences (Roberts & Priest, 2006) in general, and for psychology (Jones & Thissen, 2006) and neuropsychology (Sherman, Brooks, Iverson, Slick, & Strauss, 2011) in particular. Measuring in science means assigning numbers or values to constructs in accordance with a predefined structure and order (Roach, 2006). With the purpose of making sure that the measurements that one handles are robust enough, it is of first priority then to know what one is certainly measuring and the respective extent of accuracy that one is using. Both validity and reliability are therefore crucial to cope with these problems (Cook & Beckman, 2006) providing information on the quality of the measures employed (Roach, 2006), which is an issue particularly important when choosing the appropriate tool over many others in neuropsychological assessments (Sherman et al., 2011).

Reports on the estimated validity and reliability of different insight assessment methods in dementia are scarce in the literature (Clare et al., 2005). For instance, several evaluation procedures based on discrepancy scores have failed at reporting transparently their psychometric properties. These includes comparisons made between self-administered and informant-based questionnaires for measures of insight into memory (Feher, Mahurin, Inbody, Crook, & et al., 1991; Mangone et al., 1991) and functional capacity (Mangone et al., 1991) in Alzheimer's disease (AD) patients. The same situation has been seen in comparisons between either pre- or post-test self-appraisal and standardised scores obtained in neuropsychological tests in AD and FTD (Williamson et al., 2010), as well as in contrasts carried out between clinical judgement and actual performances on cognitive tools in AD

(Wagner, Spangenberg, Bachman, & O'Connell, 1997). Other insight assessment approaches for global insight depending only on clinical judgment measures have exhibited, although not explicitly, acceptable content validity along with high coefficients of internal consistency and inter-rater coherence as indicators of reliability in AD (Ott & Fogel, 1992). On the contrary, studies on insight into diagnosis or health status according to clinical judgement in FTD have not clearly informed the respective indexes of validity and reliability of the tools used to measure insight (McMurtray et al., 2006; Mendez & Shapira, 2005).

The purpose of this chapter is to fill the research gap left by the lack of an exhaustive analysis of the psychometric properties of several assessment approaches of insight in frontotemporal dementia. More precisely, validity and reliability for 3 different insight assessment methods, including participant-informant level of agreement, self-appraisal accuracy and clinical judgment, were estimated in a cohort of patients with FTD, motor neuron disease/amyotrophic lateral sclerosis (MND/ALS), AD, cognitively healthy controls (HC) and their respective reliable informants. Validity across insight assessment methods was analysed according to the tripartite model, which encompasses content- (how well does the tool in reference measure the construct?), construct- (does the tool in reference correlate with tests that are believed to measure similar and/or dissimilar constructs?) and criterion-related (is the tool in reference sensitive to differences in the sample?) evidence. In addition, reliability for the approaches under study was mainly estimated by calculating their indicators of internal reliability (internal consistency), although indexes of external reliability were estimated for participant-informant level of agreement and self-appraisal accuracy.

4.3 METHODS

4.3.1 Participants

A convenience sample of patients with neurodegenerative disorders resulting from frontotemporal involvement, HC and their respective reliable informants was recruited according to the detailed criteria provided in 'Chapter 2: General Methods'. A total of 15 FTD patients (11 patients with the behavioural variant of FTD -bvFTD- and 4 patients with language variants of FTD -lvFTD-), 12 AD patients, 6 MND/ALS patients, 34 HC, and their respective reliable informants made up the cohort of this study.

4.3.2 Assessments and materials

With the purpose of reaching the goals pointed out in this study, demographics, insight, neuropsychological, neuropsychiatric and functional assessments were conducted.

4.3.2.1 Demographic data

Age, years of education and sex of the subjects of the sample were registered to provide a demographic description of the cohort.

4.3.2.2 Insight assessment

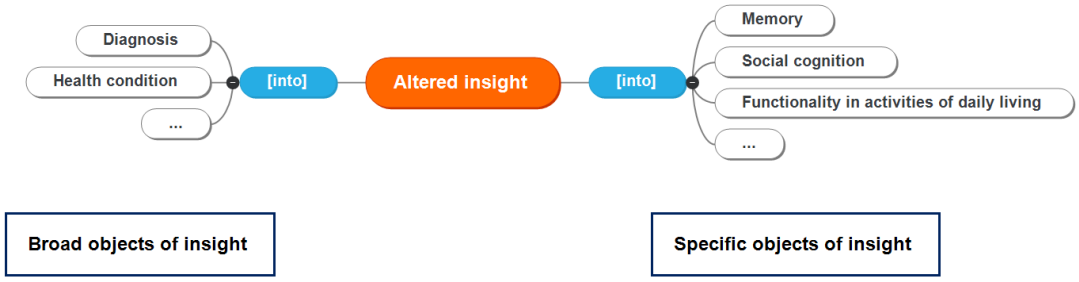
Insight was understood as self-knowledge of health issues or symptoms configured by a relational structure, which implies that insight can be targeted at either broad (health condition or diagnosis) or specific objects (neuropsychological or behavioural symptoms) (David et al., 2012; Markova & Berrios, 2001; Munoz-Neira et al., 2019) (Figure 4.1). A further discussion on such a conceptualization of insight can be found elsewhere (Munoz-Neira et al., 2019) and goes beyond the scope of the present chapter. 4 relevant modalities of insight were explored utilizing the 3 insight assessment methods. Participant-informant level of agreement and clinical judgement examined insight into health condition (broad object), memory, social cognition and performances on ADL (specific objects). In contrast, self-appraisal accuracy included an overall index and self-appraisal accuracy for memory, social cognition and executive functions. More details on the implementation of the 3 insight assessment methods taken into consideration for the analyses of their respective validity and reliability are as follows:

8. Participant-informant level of agreement (participant-informant discrepancy scores): this approach refers to the extent to which the participant's view of their own health status is in accordance with that of their respective reliable informant. Both the informant-based and self-administered versions of the CBI-R (Wear et al., 2008) as well as the Insight Questionnaire (Hornberger et al., 2014) were employed to assess insight into health condition, memory, social cognition and performances on ADL using the scores of the entire scales or their sub-scales where necessary. It should be noticed that the respective self-administered version of the CBI-R was properly modified from its original informant-based version (Wear et al., 2008) as suggested elsewhere (Hornberger et al., 2014). The contrast entailed here by the participant-informant discrepancy scores is pragmatically calculated by subtracting the outcomes of informant-based questionnaires about participants' deficits (filled in by reliable informants) from the scores of self-administered scales about participants' own perceptions of deficits (completed by participants). Thus, results can be grouped into 3 categories in accordance with the subtraction of participants' own scores minus informants' scores: negative discrepancy scores represent an underestimation of abilities, discrepancy scores surrounding 0 mean appropriate/neutral insight -agreement between the subject under study and their reliable informant- and positive discrepancy scores indicate overestimations (Hornberger et al., 2014).

9. Self-appraisal accuracy (participants' self-ratings versus standardised outcomes discrepancy scores): this method provides a measure of participants' precision to appropriately evaluating their own performances on different neuropsychological tests. This estimation is made as specified by the Insight Task (Rosen et al., 2010; Williamson et al., 2010), in which discrepancy scores are literally calculated by subtracting the final standardised scores obtained by the participants on specific neuropsychological tests from the results corresponding to their own post-test ratings or self-perceptions on their possible scores reached in the task performed. In order to obtain self-rating scores, participants are asked to point where they would place their own scores across a normal curve just after each cognitive tool was administered. Every participant is briefed highlighting that if a cohort with similar characteristics to them had performed the same task, most of the subjects' scores would have been allocated in the middle of the curve representing then average scores, whereas better or worse performances than the average would have been placed towards the right or the left of the average score respectively throughout the curve. Overall self-appraisal accuracy, which might be considered as insight into health condition, was estimated through the average of self-appraisal accuracy extracted from measures of global cognitive function (Montreal Cognitive Assessment [MoCA]), memory (California Verbal Learning Test - Second Version Short Form [CVLT-II SF]), executive functions (Frontier Executive Screening [FES]) and social cognition (Mini - Social and Emotional Assessment [Mini-SEA]). On the other hand, insight into memory and social cognition were represented by self-appraisal accuracy on the CVLT-II SF and the Mini-SEA respectively. Since it is not possible to evaluate insight into performances on ADL with this approach, self-appraisal accuracy into executive functions estimated with the FES was also included to complete the measurement of a fourth insight modality. Further details on what specific procedures are entailed by the Insight Task are appropriately explained elsewhere (Rosen et al., 2010; Williamson et al., 2010). Lastly, the discrepancy scores resulting from the subtraction of participants' self-ratings minus standardised outcomes were either negative (underestimation) close to 0 (appropriate/neutral -agreement between the subject under-study and their reliable informant-) or positive (overestimation).
10. Clinical judgement: this approach entails clinicians' or health care professionals' opinions on the degree of clinical insight observed in the subject in reference. Hence, these examiners are considered as experts capable of providing an actual representation of the level of insight exhibited by the subject under observation. The insight modalities considered here were examined through the Clinical Insight Rating Scale (CIRS) (Ott & Fogel, 1992), which was completed by the author of this thesis after interviews with participants' informants. This tool provides an overall insight score together with scores for specific domains such as awareness on the reason for assessment, memory,

performances on ADL and progression of the disease. The overall score of the scale corresponds to the sum of its specific domains, wherein each of them can be labelled with either good insight (no changes of awareness of health condition), relatively impaired insight or severe altered insight. Higher scores in this scale represent greater impaired insight and vice versa (Ott & Fogel, 1992). Although it should be noticed that the design of the CIRS yields indicators of insight into health condition, memory and performances on ADL, it does not include an index of insight into social cognition. A domain for the evaluation of this insight modality was adapted and introduced by the author of this thesis with the purpose of resolving this issue following the scoring procedure proposed by the original publication of this tool (Ott & Fogel, 1992).

Figure 4.1 Conceptualization of insight into broad and specific objects



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4.3.3 Neuropsychological assessment

Neuropsychological domains were evaluated to display a clinical characterization of the cohort. Participants underwent several neuropsychological tests for the evaluation of cognitive status. Global cognitive function was measured through the MoCA (Nasreddine et al., 2005). On the other hand, episodic memory was assessed with the CVLT-II SF (Delis, Kramer, Kaplan, & Ober, 2000), whereas the FES was used to measure executive function (Leslie et al., 2016) and the Mini-SEA (Bertoux et al., 2012) was employed to evaluate social cognition.

4.3.4 Neuropsychiatric and functional assessment

Reliable informants, who were considered as such in line with the description provided in 'Chapter 2: General Methods', were asked to complete a set of informant-based questionnaires for the assessment of participants' changes in behaviour and the course of their diseases. Whilst the Cambridge Behavioural Inventory - Revised (CBI-R) (Wear et al., 2008) was used to record multiple neuropsychiatric symptoms and also to provide a main reference for insight assessment (Hornberger et al., 2014) as described earlier, its Mood Sub-scale was utilized to evaluate the possible presence of depression in the sample. Moreover,

apathy was examined with the Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991). Lastly, functional impairment in ADL was assessed through the Disability Assessment for Dementia (DAD) (Gelinas, Gauthier, McIntyre, & Gauthier, 1999).

4.3.5 Procedures

Insight and neuropsychological and assessments were undertaken with the participants over 1 or 2 testing sessions, which took in total up to 2.5 hours. Participants and their reliable informants took up to 20 minutes to complete their self-administered and informant-based questionnaires respectively, which were mostly filled in at home. It must be emphasized that they were instructed to fill in their respective scales independently. Once data collection was finalised, statistical data analyses were consequently conducted.

4.3.6 Ethics approval

The present study was sponsored by University of Bristol and approved to be conducted in North Bristol Trust facilities by the London - Surrey Research Ethics Committee (REC) and NHS Health Research Authority (HRA). All subjects and their reliable informants were provided with approved participant information sheets to explain the objectives of the present investigation. They were also given the opportunity to ask any type of questions related to this study. Once their concerns were properly dispelled, written informed consent was acquired correspondingly from all the subjects and informants who took part in this research project. In parallel, good clinical and research practices instructed by the Declaration of Helsinki were closely followed in the implementation of this investigation.

4.3.7 Statistical Analysis

4.3.7.1 Analysis of demographic, insight, neuropsychological and behavioural data

All statistical analyses were carried out at a level of significance (p value) lower than 0.05 ($p<0.05$; two-tailed) using the IBM Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., 2016) or the RStudio Integrated Development Environment for R (RStudio Team, 2016) where applicable. The only exception for this was the manual estimation of the effect sizes of group categorization (Alhenshiri, 2020) on levels of insight. Additionally, plots that complemented such analyses were generated with the latter software (RStudio Team, 2016). Demographic data concerning age and years of education were compared across the groups with a one-way ANOVA test. Post-hoc analyses considered Tukey's tests if equal variances were assumed or Games-Howell's tests if equality of variances was not assumed. In contrast, comparisons related to sex across groups were conducted through Chi-square tests. The potential influence of these variables on levels of insight was estimated through a

multiple regression analysis (Enter Method) wherein age, years of education and sex were taken as predictors and the different insight assessment methods studied here were treated as outcomes. Prior to exploring correlations and comparisons among the main variables under study, results obtained from insight assessment methods, neuropsychological domains, neuropsychiatric symptoms and functional ability in ADL) were tested for normality through Kolmogorov-Smirnov tests. Variables which exhibited normal distributions were compared where required with one-way ANOVAs and post-hoc analyses as just described, while those with non-normal distributions were processed with Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests. In the same line, Person's or Spearman's correlation coefficients were used to examine associations between variables depending on whether their scores were normally distributed or not respectively. Correlational analyses involved in the analyses of validity and reliability of the insight approaches under study here were conducted on the patients and the entire sample (patients and HC combined) separately to increase the heterogeneity of the groups and obtain then more robust results.

4.3.7.2 Analysis of validity for the insight assessment methods under study

Evidence of validity for participant-informant level of agreement, self-appraisal accuracy and clinical judgement was estimated through different procedures. Content-related evidence was assessed by a committee of experts, who commented on the possible proximity existing between the definition of insight proposed here and its assessment methods under analysis. They also provided their professional opinions on how pertinent, clear and sufficient these approaches are to measure different insight modalities (insight into health condition, memory, social cognition and performances on ADL). Construct-related evidence was examined by correlating the same objects' insight scores measured through the different assessment approaches included in this study. To begin with, it should be noticed that participant-informant level of agreement was considered as the gold standard approach to assess insight into broad and specific objects. Likewise, both the original informant-based version of the CBI-R (Wear et al., 2008) along with an adapted self-administered version of this tool were employed to calculate a participant-informant discrepancy scores. Such a procedure was also conducted elsewhere to validate an alternative tool devoted to assessing changes of insight in dementia patients (Hornberger et al., 2014). Convergent validity for the insight assessment methods under analysis across broad (health condition) and specific objects (memory, social cognition and performance in ADL) was examined therefore beginning from the CBI-R discrepancy scores. These indicators of participant-informant level of agreement were then correspondingly correlated with their respective self-appraisal and clinical judgment paired measures. Divergent validity was explored correlating insight outcomes with evaluations different from those provided by insight assessment methods such as global cognitive

function, memory, executive functions, neuropsychiatric symptoms, depression, apathy and performances on ADL measures. Criterion-related evidence was estimated comparing levels of insight into broad and specific objects assessed by the insight assessment methods under study across the diagnostic groups of this study. Significant differences were calculated with one-way ANOVA or Kruskal-Wallis tests followed by their associated post-hoc analyses as specified above. Complementary, mean differences and effect sizes (Cohen's d statistic) were employed to calculate the effect of the group categorization across the different insight assessment approaches used in this study. Effect sizes can be labelled as small (0.2 to 0.49), medium (0.5 to 0.79), or large (0.8 or greater) (Cohen, 1988).

4.3.7.3 Analysis of reliability for the insight assessment methods under study

Reliability for the insight assessment methods utilized in this study was calculated with Cronbach's alpha coefficients considered as indexes of internal consistency. Alternatively, external reliability was estimated for participant-informant level of agreement by correlating participants' and informants' current observations of levels of insight with those perceptions of how their levels of insight were 10 years ago. This procedure was conducted by asking the participant-informant dyad to complete a modified version of the Insight Questionnaire devoted to trace back changes that could have taken place 10 years ago. Also, test-retest reliability for self-appraisal accuracy was estimated using intraclass correlation coefficients (average measures) between outcomes of the Insight Task obtained from compatible neuropsychological tools performed in 2 separate visits.

Results of validity and reliability per method are reported in the following section separated per type of insight assessment approach.

4.4 RESULTS

4.4.1 Demographic and clinical characterization of the sample

The total sample was made up of 67 participants (37 men, 30 women). Table 4.1 and Figure 4.1 display an overview of how they were grouped and presents their respective demographic and clinical characteristics. Groups were matched by age ($F_{(4, 66)} = 1.56$, $p = 0.204$), years of education ($F_{(4, 66)} = 0.876$, $p = 0.490$) and sex (Chi-square = 6.673, df = 4, $p = 0.154$). Insight, neuropsychological and behavioural variables exhibited non-normal distributions according to Kolmogorov-Smirnov tests ($p>0.05$), except for FES scores ($p<0.05$).

In terms of neuropsychological domains, as expected, scores of FTD, AD, MND/ALS and HC groups differed significantly on measures of global cognitive function (MoCA: Kruskall-Wallis $Test_{(4, 66)} = 32.646$; $p<0 .001$) (Figure 4.2), memory (CVLT-II SF: Kruskall-Wallis $Test_{(4, 66)} = 44.193$; $p<0.001$), executive function (FES: $F_{(4, 66)} = 8.177$, $p<0.001$) and social cognition (Mini-

SEA: Kruskall-Wallis Test$_{(4,\ 66)}$ = 32.993; p<0.001). Post-hoc analyses suggested that performances on global cognition, memory, executive functions and social cognition measures were significantly lower (p<0.05) in patients with bvFTD, lvFTD and AD compared to HC. No other significant differences were found across groups (Table 4.1). Concerning neuropsychiatric symptoms, significant differences were also observed across groups (CBI-R: Kruskall-Wallis Test$_{(4,\ 66)}$ = 31.514; p<0 .001). Both bvFTD and AD showed a significantly greater number of neuropsychiatric symptoms (p<0.05) compared to HC and the other groups. Moreover, significant differences regarding depressive and apathetic symptoms (CBI-R Mood: Kruskall-Wallis Test$_{(4,\ 66)}$ = 31.514; p<0.001 and AES: Kruskall-Wallis Test$_{(4,\ 66)}$ = 31.514; p <0.001) were found over groups, where AD patients presented significantly higher (p<0.05) levels of depression and apathy than HC and the other patients groups. Statistically significant differences were also found across groups in functional capacity in ADL (DAD: Kruskall-Wallis Test$_{(4,\ 66)}$ = 34.267; p <0.001), which was significantly impaired in patients with bvFTD, lvFTD and AD in comparison with MND/ALS and HC.

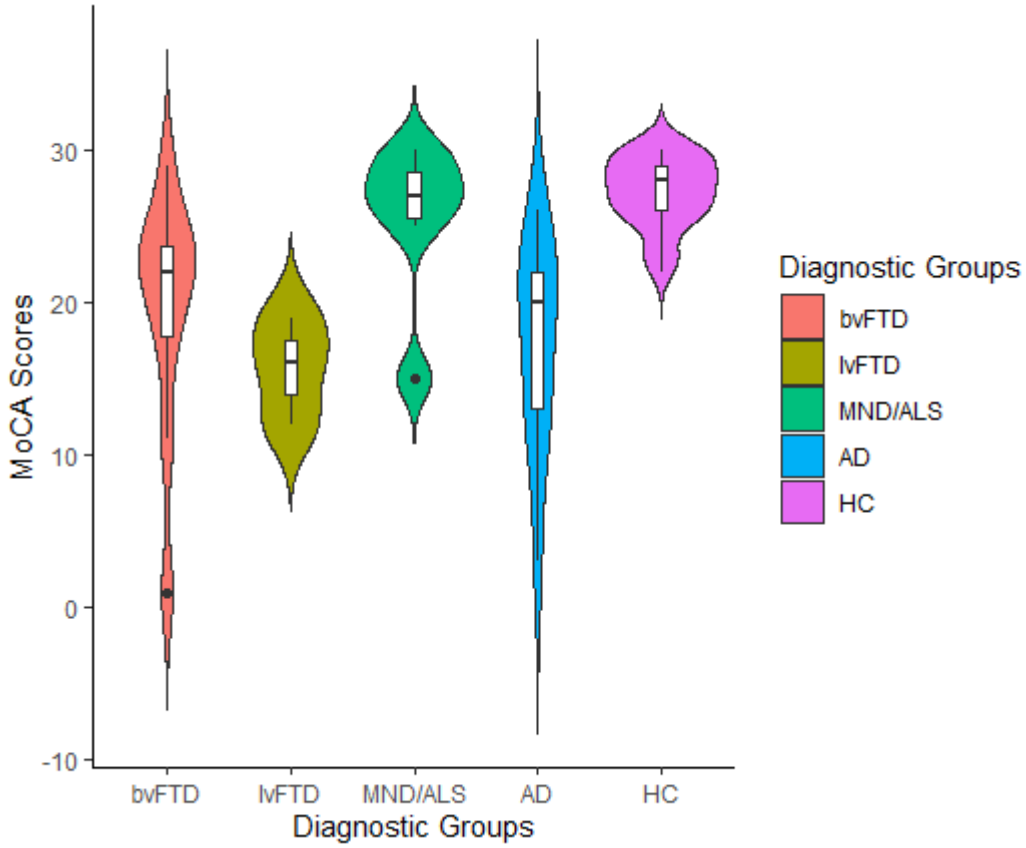
Table 4.1 Demographic and clinical characteristics of the sample

Parameter	Descriptive statistics per group					Comparisons
	bvFTD (*n* = 11)	**lvFTD (*n* = 4)**	**MND/ALS (*n* = 6)**	**AD (*n* = 12)**	**HC (*n* = 34)**	
Age‡	64.27 ± 11.11	70.25 ± 9.91	72.17 ± 11.29	74.30 ± 10.31	72.93 ± 9.43	*ns*
Years of Education‡	13.13 ± 2.64	11.00 ± 0	14.40 ± 2.88	13.00 ± 3.56	14.88 ± 3.18	*ns*
Sex‡						
%Women(*n*)	72.73%(3)	50%(2)	16.67% (1)	33.33% (4)	58.82%(20)	*ns*
%Men(*n*)	27.27%(8)	50% (2)	83.33 % (5)	67.67% (8)	41.18%(14)	
MoCA	19.40 ± 8.09	15.67 ± 3.51	25.50 ± 5.43	17.18 ± 6.90	27.24 ± 2.31	*bvFTD<HC* lvFTD<HC* AD<HC**
CVLT-II SF	3.63 ± 2.80	2.00 ± 1.41	5.67 ± 1.51	1.75 ± 2.56	7.91 ± 1.22	*bvFTD<HC* lvFTD<HC* AD<HC**
FES	5.40 ± 3.24	3.33 ± 2.08	8.17 ± 3.43	6.09 ± 2.98	9.85 ± 2.83	*bvFTD<HC** lvFTD<HC** AD<HC***
Mini-SEA	16.60 ± 7.32	12.75 ± 6.72	22.44 ± 2.93	17.75 ± 5.83	24.35 ± 2.03	*bvFTD<HC* lvFTD<HC* AD<HC**
CBI-R Total	37.40 ± 31.16	67.25 ± 39.08	32.50 ± 27.96	48.56 ± 33.29	9.73 ± 7.90	*HC < bvFTD * HC<AD **
CBI-R Mood	4.1 ± 3.98	1.50 ± 1.29	3.50 ± 2.65	4.30 ± 3.50	0.83 ± 1.26	*HC<AD **
AES	50.43 ± 12.82	45.33 ± 12.42	45.50 ± 9.15	43.67 ± 8.15	60.60 ± 5.18	*AD<HC**

DAD	33.50 ± 9.10	30.50 ± 6.95	36.33 ± 4.50	33.44 ± 9.55	40.00 ± 00	*bvFTD<HC* lvFTD<HC* AD<HC**

Results are expressed as Mean ± Standard Deviation. bvFTD = behavioural variant frontotemporal dementia; lvFTD = language variant frontotemporal dementia; MND/ALS = motor neuron disease/amyotrophic lateral sclerosis; AD = Alzheimer's disease; HC = cognitively healthy controls; MoCA = Montreal Cognitive Assessment; CVLT-II SF = California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall); FES = Frontier Executive Screen; Mini-SEA = Mini-Social Cognition and Emotion Assessment; CBI-R = Cambridge Behavioural Inventory - Revised; CBI-R Mood = Cambridge Behavioural Inventory - Revised Mood Sub-scale; AES = Apathy Evaluation Scale; DAD = Disability Assessment for Dementia.
ǂComparisons were made with one-way ANOVA tests (age and years of education) or Chi-square tests (sex).
ns = Non-significant differences (p>0.05).
*Significant differences (p<0.05) according to Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests.
**Significant differences (p<0.05) according to a one-way ANOVA test and Tukey's tests for post-hoc analysis.

Figure 4.2 Global cognitive profiles of the sample across diagnostic groups: violin plot



11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC, lvFTD<HC and AD<HC (p<0.05)

4.4.2 Administration of insight assessment methods

All the insight assessment methods under analysis were easily administered. At the same time, nearly all the participants of this study underwent such evaluations together with the other neuropsychological testing and questionnaires with no problems. Informants did not

refer complications whatsoever to complete their respective questionnaires. Scales employed for the participant-informant level of agreement approach were filled in by patients, HC and reliable informants in approximately 20-30, 10-20 and 15-20 minutes respectively. Self-estimation of cognitive performances used to calculate self-appraisal accuracy across different domains was quickly assessed in approximately 5 minutes after every neuropsychological test in reference was applied. Lastly, the health care professional in charge of providing the indexes of clinical judgment (the author of this thesis) took also roughly 5 minutes to complete the clinical insight tool used in this study.

4.4.3 Influence of demographic variables on insight assessment methods

Linear regression analysis models excluded age, years of education and sex as relevant predictors to account for the distinct insight modalities (insight into health condition, memory, social cognition and performances on ADL) measured through the different insight assessment methods (participant-informant level of agreement, self-appraisal accuracy and clinical judgement) employed in this study (Enter Methods, $p>0.05$). The only exception for this statement was self-appraisal accuracy into executive function, in which years of education had a significant positive effect explaining roughly 13% (Enter Method: R Square = 0.132, $F = 3.21$, $df = 3$, $p = 0.03$; $\beta = -5.28$, $p = 0.006$) of its variance.

4.4.4 Committee of experts

The committee of experts on dementia clinical practice which scrutinized the conceptualization of insight proposed here, including its relational nature distributed along broad and specific objects, and its proximity with the insight assessment methods employed in this study was made up by 11 members including 2 neurologists, 1 psychiatrist, 2 general practitioners, 5 neuropsychologists and 1 occupational therapist. Only one of the experts included in the panel (a neurologist) was in complete understanding of the design of this investigation, therefore this committee of experts was judged as impartial.

4.4.5 Conceptualization of insight

Insight understood from a clinical perspective as self-knowledge of health issues configured by a relational structure targeted at a diagnosis/global health condition (broad object) or different particular neuropsychological or behavioural symptoms (specific objects) (David et al., 2012; Markova & Berrios, 2001; Munoz-Neira et al., 2019) (Figure 4.1) was considered highly appropriate by the committee of experts consulted in this study. Considering a scale ranging from 0 (poor) to 10 (excellent), roughly 65-70% and 15% of the members of this committee rated correspondingly with 8-10 and 6-7 points this definition of insight in terms of its clarity, pertinence and sufficiency/adequacy.

4.4.6 Validity and reliability of insight assessment methods

4.4.6.1 Participant-Informant level of agreement

4.4.6.1.1 Content-related evidence of validity

The entire committee of experts either strongly agreed, agreed or slightly agreed that the participant-informant level of agreement is an appropriate method to assess insight fractionated into broad or specific objects. Thus, 100% of them claimed that this assessment approach suits the clinical definition employed in this study. Complementary, also 100% of the members of this committee of experts considered that this assessment approach is understandable/clear and pertinent/adequate, while 89% of them thought it was sufficient.

4.4.6.1.2 Construct-related evidence of validity

Concerning convergent validity, participant-informant level of agreement showed significant positive correlations (Spearman's coefficient correlation; $p<0.05$) between levels of insight into health condition assessed by CBIR- and the Insight Questionnaire (participant-informant discrepancy scores of CBI-R Total and Insight Questionnaire Diagnosis and Treatment Sub-scale) in the total of patients only and also in the whole sample. Both measures exhibited significant negative correlations (Spearman's coefficient correlation; $p<0.05$) with global impaired insight evaluated through clinical judgement (CIRS Total) (Figure 4.3). Similarly, insight into memory, social cognition and performances on ADL (CBI-R Memory, Abnormal Behaviour and Everyday Skills Sub-scales respectively) assessed by this approach presented significant negative correlations (Spearman's coefficient correlation; $p<0.05$) with impaired insight across those objects measured correspondingly by clinical judgment (CIRS Total, CIRS Memory sub-domain, CIRS Social Cognition sub-domain and CIRS ADL sub-domain) (Figure 4.3). No significant correlations (Spearman's coefficient correlation; $p>0.05$) were observed between outcomes resulting from this insight assessment method and different types of insight measured through self-appraisal accuracy (Figure 4.3).

In relation to divergent validity, participant-informant level of agreement across health condition, memory, social cognition and performances on ADL measured through the CBI-R showed significant correlations (Spearman's coefficient correlation; $p<0.05$) with tools used to assess variables different from insight in both patients and the entire cohort. These include global cognitive function (MoCA) (the total of patients and the entire sample), memory (CVLT-II SF) (the entire sample), executive function (FES) and social cognition (Mini-SEA) (also the whole cohort), neuropsychiatric symptoms (CBI-R) (patients and sample), depression (CBI-R Mood Sub-Scale) (patients and sample), apathy (AES) (only the cohort) and functional capacity in ADL (DAD) (only the cohort) (Figure 4.4a). In contrast, Insight Questionnaire Total,

Insight Questionnaire Social Interaction and Emotion Sub-Scales scores did not correlate significantly (Spearman's coefficient correlation; $p>0.05$) with cognitive function (MoCA), memory (CVLT-II SF), executive function (FES), social cognition (Mini-SEA), neuropsychiatric symptoms (CBI-R), apathy (AES) and functional capacity in ADL (DAD) in the total of patients and the entire sample (Figure 4.4a).

4.4.6.1.3 Criterion-related evidence of validity

Insight into global health condition, memory and social cognition represented by participant-informant level of agreement through CBI-R Total, CBI-R Memory Sub-scale and CBI-R Abnormal Behaviours scores managed to significantly differentiate between HC and different types of dementia ($p<0.05$, medium effect sizes) (Table 4.2 and Figure 4.5a). No significant differences across groups ($p>0.05$) were observed in terms of insight into performances on ADL (CBI-R Everyday Skills Sub-scale) measured by this method (Table 4.2 and Figure 4.5a).

4.4.6.1.4 Reliability

The measures of participant-informant level of agreement used in this study showed high coefficients of internal consistency. Whilst the 47 items of the CBI-R altogether presented a Cronbach's alpha of 0.97 for patients and of 0.95 for the entire sample, the 28 items that makes up the Insight Questionnaire showed Cronbach's alphas of 0.813 and 0.82 for both groups respectively. Looking into further details over both tools, CBI-R Memory, Everyday Skills, Self-care, Abnormal Behaviours, Motivation and Insight Sub-scales exhibited Cronbach's alpha coefficients that reached between 0.84 and 0.93 in all the patients and the cohort, whereas these coefficients ranged between 0.53 and 0.78 in CBI-R Mood, Beliefs, Eating Behaviours, Sleep and Stereotypic Behaviours Sub-scales in them. On the other hand, Cronbach's alphas for Insight Questionnaire Diagnosis and Treatment, Language and Motivation Sub-scales were between 0.74 and 0.85, while these coefficients were 0.51 and 0.10 for Social Cognition and Emotion Sub-Scales respectively. Lastly, results of self-administered and informant-based versions of the Insight Questionnaire which asked for current changes, on the one hand, and outcomes from paired versions aimed at examining how insight levels were supposed to be 10 years ago, on the other, correlated significantly ($p<0.01$) and positively according to Spearman's correlation coefficients, which may suggest consistency over time. These significant correlations were observed in patients (0.78) and the whole cohort (0.74) rating themselves ($p<0.01$). In contrast, outcomes from key informants rating patients according to that comparison over time did not correlate significantly ($p>0.01$) with Spearman's correlation coefficients.

Table 4.2 Criterion-evidence related validity corresponding to participant-informant level of agreement, self-appraisal accuracy and clinical judgment

	Parameters Descriptive statistics per group						Comparisons	Effect Sizes
		bvFTD (*n* = 11)	lvFTD (*n* = 4)	MND/ALS (*n* = 6)	AD (*n* = 12)	HC (*n* = 34)	p values' significance at 0.05	Cohen's d(r)ǂ
Participant-Informant level of agreement	**CBI-R Total**	-35.80 ± 41.89	24.00 ± 18.24	-16.75 ± 21.31	-22.30 ± 36.45	0.57 ± 9.11	*bvFTD<HC** *bvFTD<lvFTD** *lvFTD<AD**	*-1.67(-0.64)* *-1.70(-0.63)* *1.48(0.57)*
	Insight Questionnaire Total	-0.27 ± 6.47	0.50 ± 1.91	2.17 ± 6.05	-1.83 ± 5.56	0.79 ± 4.13	*ns*	*ne*
	CBI-R Memory	-8.10 ± 11.86	9.25 ± 9.95	-2.00 ± 2.45	-7.00 ± 9.31	0.27 ± 3.08	*bvFTD<HC** *lvFTD<AD**	*-1.62(-0.62)* *1.84(0.66)*
	CBI-R Abnormal Behaviour	-7.18 ± 8.00	3.50 ± 4.73	0.00 ± 2.76	-1.50 ± 6.53	0.47 ± 1.71	*bvFTD<HC** *bvFTD<lvFTD**	*-1.89(-0.68)* *-1.56(-0.59)*
	Insight Questionnaire Social Interaction	0.27 ± 1.90	0.75 ± 0.96	0.50 ± 0.84	-0.67 ± 1.23	0.12 ± 0.84	*ns*	*ne*
	CBI-R Everyday Skills	-4.18 ± 5.84	-4.00 ± 7.62	-2.00 ± 5.14	-2.83 ± 5.72	0.09 ± 0.29	*ns*	*ne*
Self-appraisal accuracy	**Overall**	35.41 ± 27.26	40.85 ± 27.12	28.09 ± 12.68	34.80 ± 20.07	5.83 ± 21.12	*bvFTD<HC** *AD<HC**	*-1.67(-0.64)* *1.48(0.57)*
	Memory (CVLT-II SF)	30.54 ± 26.43	23.00 ± 22.06	49.55 ± 14.73	35.81 ± 24.45	11.89 ± 28.39	*MND/ALS<HC*	*1.43(0.57)*
	Social Cognition (Mini-SEA)	59.32 ± 18.08	52.01 ± 27.47	37.14 ± 18.05	48.77 ± 22.81	5.23 ± 37.35	*bvFTD<HC** *AD<HC**	*1.63(0.63)* *1.30(0.54)*
	Executive function (FES)	27.00 ± 48.85	63.88 ± 32.71	11.21 ± 22.61	26.47 ± 27.36	-4.31 ± 26.22	*lvFTD<HC*	*2.61(0.79)*
Clinical judgement	**CIRS Total**	3.73 ± 2.53	1.25 ± 1.89	1.17 ± 1.47	2.25 ± 2.38	0.09 ± 0.29	*bvFTD>HC** *AD>HC**	*2.99(0.83)* *1.82(0.66)*
	CIRS Memory	1.36 ± 0.81	0.25 ± 0.50	0.33 ± 0.52	0.75 ± 0.75	0.09 ± 0.29	*bvFTD>HC** *AD>HC**	*2.79(0.81)* *1.50(0.59)*
	CIRS Social Cognition	1.36 ± 0.81	1.00 ± 0.82	0.17 ± 0.41	0.58 ± 0.90	0.00 ± 0.00	*bvFTD>HC** *bvFTD>MND/ALS* *AD>HC**	*3.56(0.87)* *1.80(0.65)* *1.32(0.54)*
	CIRS ADL	0.82 ± 0.87	0.25 ± 0.50	0.17 ± 0.41	0.50 ± 0.67	0.00 ± 0.00	*bvFTD>HC** *AD>HC*	*2.00(0.70)* *1.53(0.60)*

Results are expressed as Mean ± Standard Deviation. bvFTD = behavioural variant frontotemporal dementia; lvFTD = language variant frontotemporal dementia; MND/ALS = motor neuron disease/amyotrophic lateral sclerosis; AD = Alzheimer's disease; HC = cognitively healthy controls; CBI-R = Cambridge Behavioural Inventory - Revised; Overall = average self-appraisal accuracy calculated among global cognitive function (MoCA), memory (CVLT-II SF), executive function (FES) and social cognition (Mini-SEA) measures; MoCA = Montreal Cognitive Assessment; CVLT-II SF = California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall); FES = Frontier Executive Screen; Mini-SEA = Mini-Social Cognition and Emotion Assessment; CIRS = Clinical Insight Rating Scale; ADL = Activities of daily living.

ǂ Cohen's d(r) = Cohen's d refers to standardised mean differences. r corresponds to Pearson correlation considered as effect size. Effect sizes can be labelled as small (0.2-0.49), medium (0.5-0.79), or large (≥0.8).

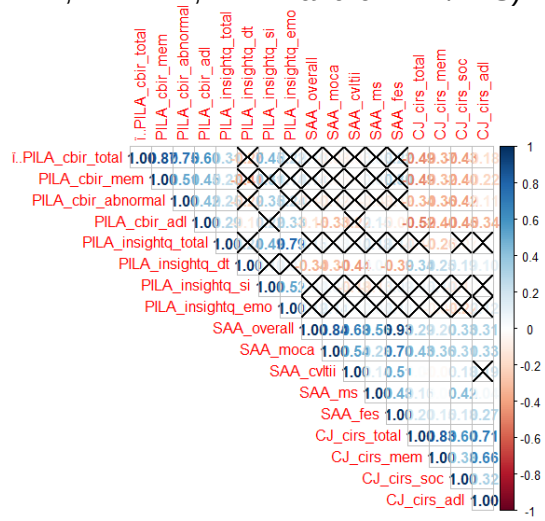
ns = Non-significant differences (p>0.05).

ne = Not estimated.

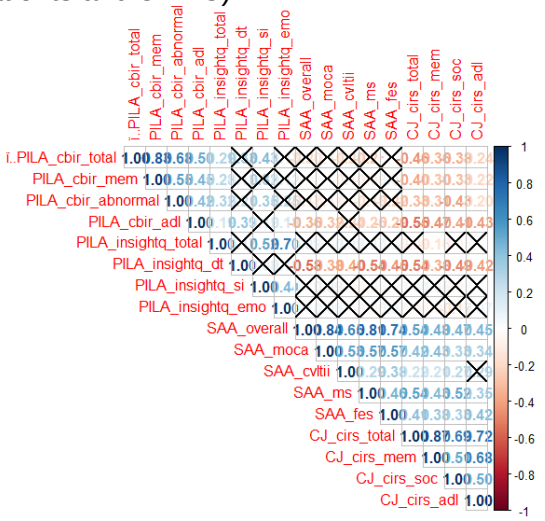
*Significant differences (p<0.05) according to Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests.

Figure 4.3 Spearman's coefficient correlations matrix corresponding to construct-related evidence of validity (convergent validity) for participant-informant level of agreement, self-appraisal accuracy and clinical judgement in patients and healthy controls

Spearman's coefficient correlations in patients (33 participants in total; 15 FTD -11 bvFTD, 4 lvFTD-, 12 AD and 6 MND/ALS)



Spearman's coefficient correlations in the entire sample (67 participants in total; 33 patients and 34 HC)



All values express statistically significant correlations (Spearman's coefficients correlations; p<0.05) except for the crossed boxes, which represent non-significant correlations (Spearman's coefficients correlations (p>0.05).

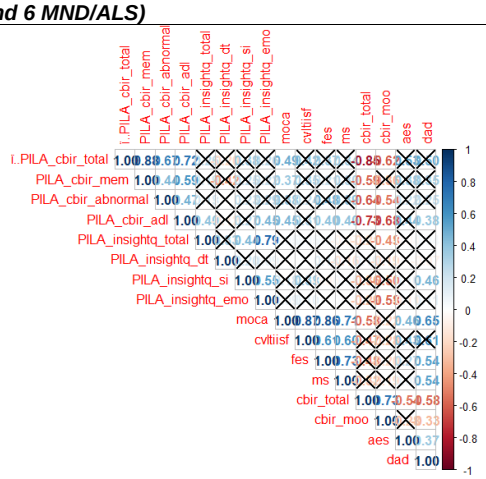
Name of the variable entered in R	**Insight assessment method**	**Modality of insight under assessment**	**Tool used to assess the respective variable**
PILA_cbir_total =	Participant-informant level of agreement	Insight into health condition	Cambridge Behavioural Inventory - Revised Total
PILA_cbir_mem =	Participant-informant level of agreement	Insight into memory	Cambridge Behavioural Inventory - Revised Memory Sub-scale
PILA_cbir_abnormal =	Participant-informant level of agreement	Insight into social cognition	Cambridge Behavioural Inventory - Revised Abnormal Behaviour (Social Cognition) Sub-scale
PILA_cbir_adl =	Participant-informant level of agreement	Insight into functionality in activities of daily living	Cambridge Behavioural Inventory - Revised Everyday Skills (Activities of Daily Living) Sub-scale
PILA_insightq_total =	Participant-informant level of agreement	Insight into health condition	Insight Questionnaire Total
PILA_insightq_dt =	Participant-informant level of agreement	Insight into health condition	Insight Questionnaire Diagnosis and Treatment Sub-scale
PILA_insightq_si =	Participant-informant level of agreement	Insight into social cognition	Insight Questionnaire Social Interaction Sub-scale
PILA_insightq_emo =	Participant-informant level of agreement	Insight into social cognition	Insight Questionnaire Emotion Sub-scale
SAA_overall =	Self-appraisal accuracy	Global insight (multi-domain)	Insight Task Overall (global cognitive function, memory, executive function and social cognition)
SAA_moca =	Self-appraisal accuracy	Insight into cognitive function	Insight Task - Montreal Cognitive Assessment
SAA_cvltii =	Self-appraisal accuracy	Insight into memory	Insight Task - California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall)
SAA_ms =	Self-appraisal accuracy	Insight into executive functions	Insight Task - Frontier Executive Screen
SAA_fes =	Self-appraisal accuracy	Insight into social cognition	Insight Task - Mini-Social Cognition and Emotion Assessment
CJ_cirs_total =	Clinical judgment	Insight into health condition	Clinical Insight Rating Scale Total

CJ_cirs_mem =	Clinical judgment	Insight into memory	Clinical Insight Rating Scale Memory Sub-scale
CJ_cirs_soc =	Clinical judgment	Insight into social cognition	Clinical Insight Rating Scale Social Cognition Sub-scale
CJ_cirs_adl =	Clinical judgment	Insight into functionality in activities of daily living	Clinical Insight Rating Scale Activities of Daily Living Sub-scale

Figure 4.4 Spearman's coefficient correlations matrices corresponding to construct-related evidence of validity (divergent validity) for participant-informant level of agreement, self-appraisal accuracy and clinical judgement in patients and healthy controls

Figure 4.4a. Participant-informant level of agreement

Spearman's coefficient correlations in patients (33 participants in total; 15 FTD -11 bvFTD, 4 lvFTD-, 12 AD and 6 MND/ALS)



Spearman's coefficient correlations in the entire sample (67 participants in total; 33 patients and 34 HC)

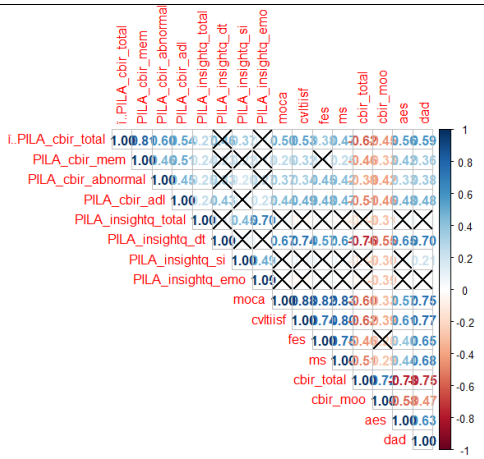
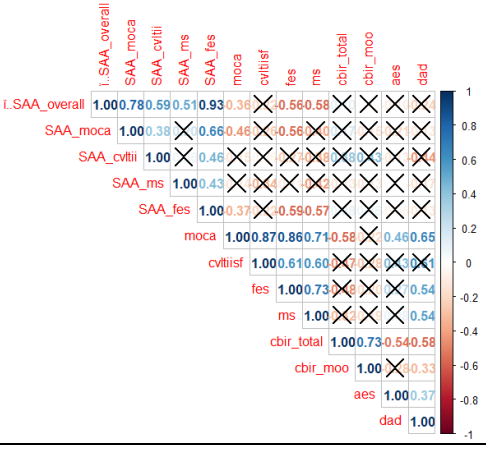


Figure 4.4b. Self-appraisal accuracy

Spearman's coefficient correlations in patients (33 participants in total; 15 FTD -11 bvFTD, 4 lvFTD-, 12 AD and 6 MND/ALS)



Spearman's coefficient correlations in the entire sample (67 participants in total; 33 patients and 34 HC)

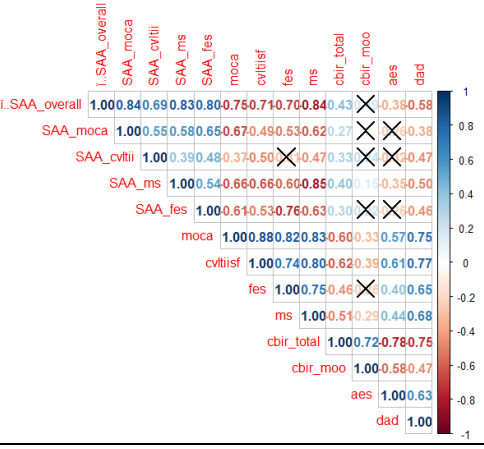
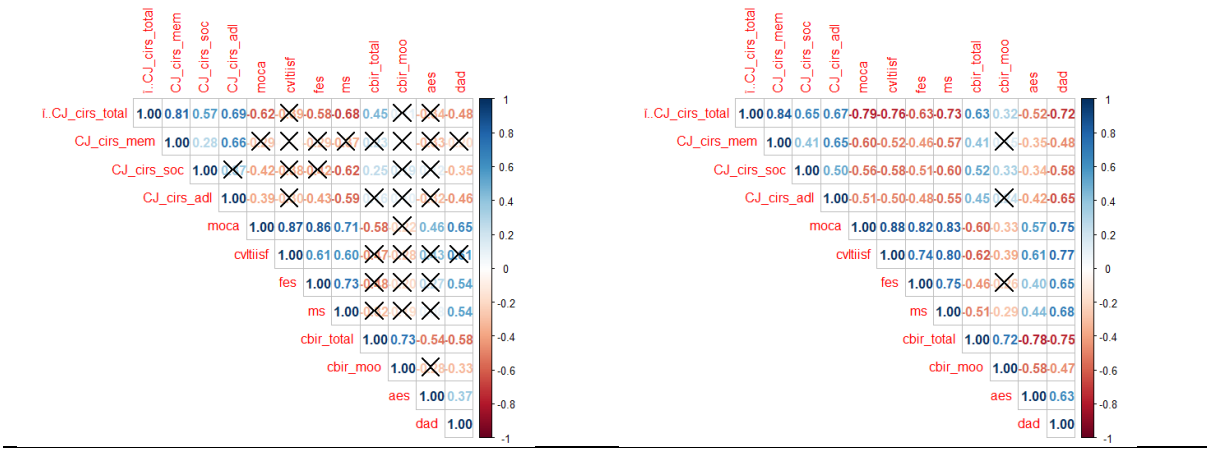


Figure 4.4c. Clinical judgement

Spearman's coefficient correlations in patients (33 participants in total; 15 FTD -11 bvFTD, 4 lvFTD-, 12 AD and 6 MND/ALS)

Spearman's coefficient correlations in the entire sample (67 participants in total; 33 patients and 34 HC)



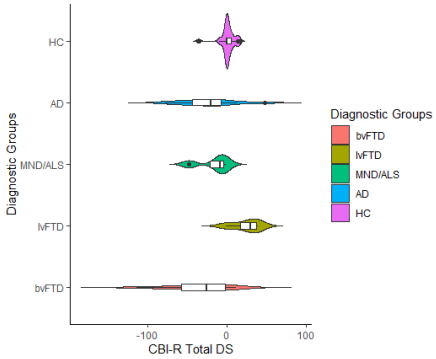
All values express statistically significant correlations (Spearman's coefficients correlations; p<0.05) except for the crossed boxes, which represent non-significant correlations (Spearman's coefficients correlations (p>0.05).

Name of the variable entered in R	**Insight assessment method**	**Modality of insight under assessment**	**Tool used to assess the respective variable**
PILA_cbir_total =	Participant-informant level of agreement	Insight into health condition	Cambridge Behavioural Inventory - Revised Total
PILA_cbir_mem =	Participant-informant level of agreement	Insight into memory	Cambridge Behavioural Inventory - Revised Memory Sub-scale
PILA_cbir_abnormal =	Participant-informant level of agreement	Insight into social cognition	Cambridge Behavioural Inventory - Revised Abnormal Behaviour (Social Cognition) Sub-scale
PILA_cbir_adl =	Participant-informant level of agreement	Insight into functionality in activities of daily living	Cambridge Behavioural Inventory - Revised Everyday Skills (Activities of Daily Living) Sub-scale
PILA_insightq_total =	Participant-informant level of agreement	Insight into health condition	Insight Questionnaire Total
PILA_insightq_dt =	Participant-informant level of agreement	Insight into health condition	Insight Questionnaire Diagnosis and Treatment Sub-scale
PILA_insightq_si =	Participant-informant level of agreement	Insight into social cognition	Insight Questionnaire Social Interaction Sub-scale
PILA_insightq_emo =	Participant-informant level of agreement	Insight into social cognition	Insight Questionnaire Emotion Sub-scale
SAA_overall =	Self-appraisal accuracy	Global insight (multi-domain)	Insight Task Overall (global cognitive function, memory, executive function and social cognition)
SAA_moca =	Self-appraisal accuracy	Insight into cognitive function	Insight Task - Montreal Cognitive Assessment
SAA_cvltii =	Self-appraisal accuracy	Insight into memory	Insight Task - California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall)
SAA_ms =	Self-appraisal accuracy	Insight into executive functions	Insight Task - Frontier Executive Screen
SAA_fes =	Self-appraisal accuracy	Insight into social cognition	Insight Task - Mini-Social Cognition and Emotion Assessment
CJ_cirs_total =	Clinical judgment	Insight into health condition	Clinical Insight Rating Scale Total
CJ_cirs_mem =	Clinical judgment	Insight into memory	Clinical Insight Rating Scale Memory Sub-scale
CJ_cirs_soc =	Clinical judgment	Insight into social cognition	Clinical Insight Rating Scale Social Cognition Sub-scale
CJ_cirs_adl =	Clinical judgment	Insight into functionality in activities of daily living	Clinical Insight Rating Scale Activities of Daily Living Sub-scale
Name of the variable entered in R	**-**	**-**	**Tool used to assess the respective variable**
moca =	-	-	Montreal Cognitive Assessment
cvltiisf =	-	-	California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall)
fes =	-	-	Frontier Executive Screen
ms =	-	-	Mini-Social Cognition and Emotion Assessment

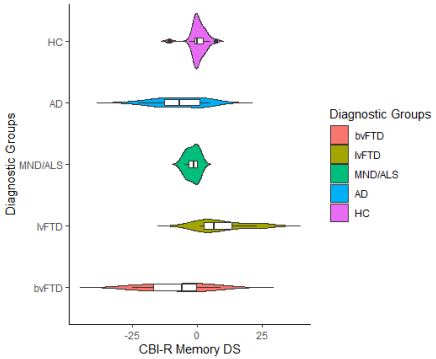
cbir_total =	-	-	Cambridge Behavioural Inventory - Revised Total
cbir_moo	-	-	Cambridge Behavioural Inventory - Revised Mood (Depression) Sub-scale
aes =	-	-	Apathy Evaluation Scale
dad =	-	-	Disability Assessment for Dementia

Figure 4.5 Insight profiles according to different assessment methods per diagnostic group

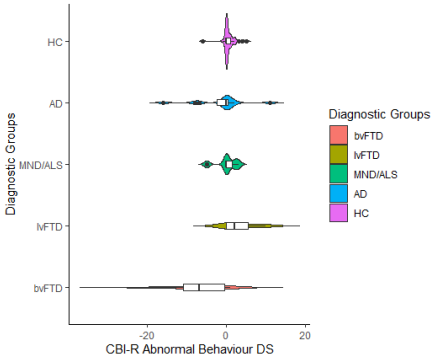
Figure 5a. Participant-informant level of agreement



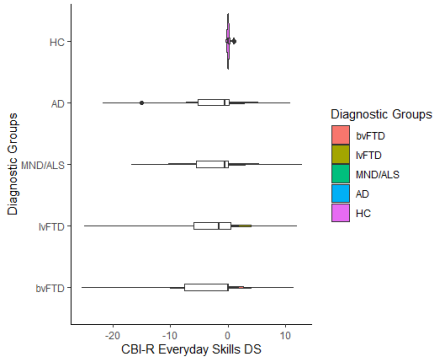
11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC, bvFTD<lvFTD and lvFTD<AD (p<0.05)



11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and lvFTD<AD (p<0.05)

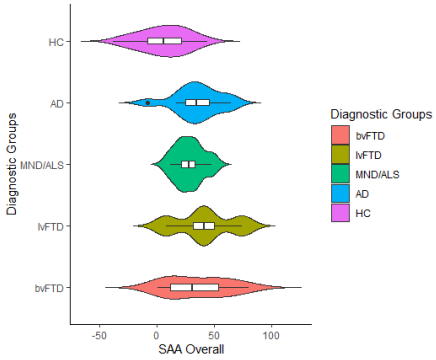


11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and bvFTD<lvFTD (p<0.05)

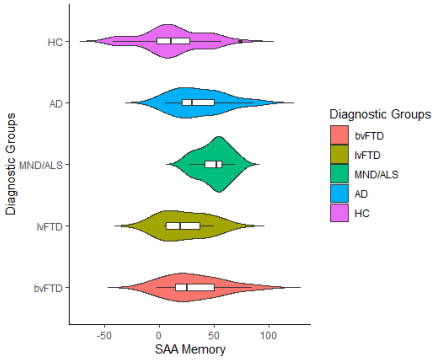


11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
None statistically significant differences (p>0.05)

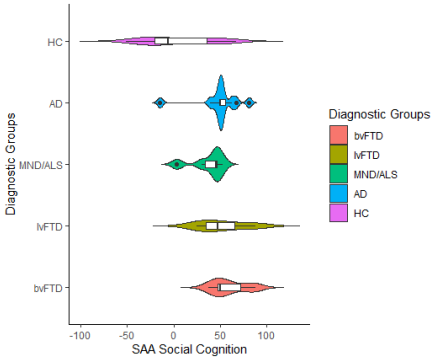
Figure 5b. Self-appraisal accuracy



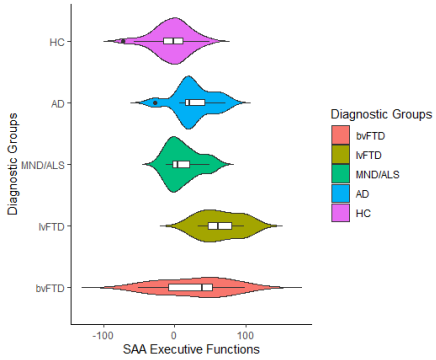
11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and AD<HC (p<0.05)



11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
MND/ALS<HC (p<0.05)

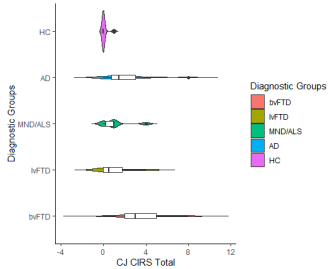


11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and AD<HC (p<0.05)

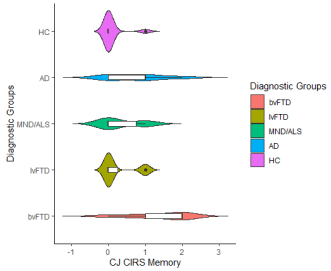


11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
lvFTD<HC (p<0.05)

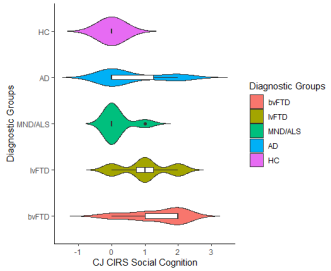
Figure 5c. Clinical judgment



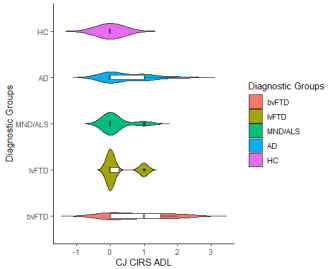
11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and AD<HC (p<0.05)



11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and AD<HC (p<0.05)



11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC, bvFTD>MND/ALS and AD<HC (p<0.05)



11 bvFTD, 4 lvFTD, 6 MND/ALS, 12 AD and 34 HC
bvFTD<HC and AD<HC (p<0.05)

4.4.6.2 Self-appraisal accuracy

4.4.6.2.1 Content-related evidence of validity

63% of the members of the committee of experts agreed that self-appraisal accuracy spread across broad and specific objects matches the clinical definition of insight proposed here. In the same line, 63% of them stated this assessment approach is clear/understandable and pertinent. Differently, only 38% of the committee of experts agreed that self-appraisal accuracy is a sufficient method to quantify insight from a clinical perspective.

4.4.6.2.2 Construct-related evidence of validity

In terms of convergent validity, almost no relevant significant correlation (Spearman's correlation coefficient; $p>0.05$) were observed between self-appraisal accuracy into the different modalities of insight under analysis measured through the Insight Task and the measures of participant-informant level of agreement in the total of patients only and also in the entire sample. On the other hand, self-appraisal accuracy into the objects of insight under study here presented significant positive correlations (Spearman's correlation coefficient; $p<0.05$) with their respective modalities of impaired insight measured through clinical judgment in patients and the entire cohort (Figure 4.3).

Regarding divergent validity, correlations estimated for patients and the total sample differed. In relation to patients, although the outcomes were mixed, different forms of self-appraisal accuracy tended to correlate significantly with cognition (MoCA, FES and Mini-SEA) (Spearman's correlation coefficient; $p<0.05$) but not with neuropsychiatric or behavioural symptoms (CBI-R Total, CBI-R Mood, AES and DAD) (Spearman's correlation coefficient; $p>0.05$) (Figure 4.4b). Concerning the entire cohort, overall self-appraisal accuracy and self-appraisal accuracy into health condition, memory and executive function did not show significant correlations (Spearman's correlation coefficient; $p>0.05$) with measures of depression (CBI-R Mood Sub-Scale). Similarly, no significant correlations (Spearman's correlation coefficient; $p>0.05$) were found between self-appraisal accuracy into memory or executive functions and indexes of apathy (AES) (Figure 4.4b). In contrast, overall self-appraisal accuracy and self-appraisal accuracy into social cognition did correlate significantly ($p>0.05$) with apathy (AES). Moreover, inaccurate self-appraisal across these 4 insight modalities assessed exhibited significant negative correlations (Spearman's correlation coefficient; $p<0.05$) with measures of neuropsychological domains including global cognitive function (MoCA), memory (CVLT-II SF), executive function (FES) and social cognition (Mini-SEA), as well as significant positive correlations (Spearman's correlation coefficient; $p<0.05$) with the presence of neuropsychiatric symptoms (CBI-R) (Figure 4.4b).

4.4.6.2.3 Criterion-related evidence of validity

Overall self-appraisal accuracy and self-appraisal accuracy into memory, social cognition and executive function significantly differentiated between HC and different types of dementia ($p<0.05$, medium effect sizes) (Table 4.2 and Figure 4.5b).

4.4.6.2.4 Reliability

Compatible measures of self-appraisal accuracy were performed on a small sub-sample (17 patients and 10 HC) in 2 different visits separated for no longer than 2 weeks with the purpose of estimating test-retest reliability. Significant positive intraclass correlation coefficients (average measures) were obtained with the Insight Task for the patients only and the patients and HC combined reaching respectively values of 0.92 and 0.97 in self-appraisal accuracy into global cognition, 0.72 and 0.63 in self-appraisal into memory and 0.82 and 0.80 in self-appraisal into executive function ($p<0.001$).

4.4.6.3 Clinical judgement

4.4.6.3.1 Content-related evidence of validity

81% of the members of the committee of experts agreed that insight into broad and specific objects assessed by clinical judgment suits the conceptualization of insight utilized in this study. Complementary, while 81% of this committee claimed this assessment approach was pertinent, 89% of them described it as clear/understandable and 69% of them considered it sufficient/adequate.

4.4.6.3.2 Construct-related evidence of validity

In respect of convergent validity, impaired insight into health condition, memory, social cognition and performances on ADL according to clinical judgement (CIRS Total, CIRS Memory, CIRS Social Cognition and CIRS ADL respectively) exhibited negative and positive significant correlations with levels of insight across their corresponding paired objects measured through participant-informant level of agreement and self-appraisal accuracy respectively (Spearman's correlation coefficient; $p<0.05$). This pattern of correlations was observed in both patients and the entire cohort (Figure 4.3).

In terms of divergent validity, correlations estimated for patients and the total sample varied. Regarding patients, clinical judgement for insight into different objects correlated significantly either with global cognition (MoCA), memory (CVLT-II), executive functions (FES) or social cognition (Mini-SEA) (Spearman's correlation coefficient; $p<0.05$). Differently, clinical judgment did not correlate significantly with neuropsychiatric or behavioural symptoms (CBI-R Total, CBI-R Mood, AES and DAD) (Spearman's correlation coefficient; $p>0.05$) (Figure

4.4c). Concerning the entire sample, impaired insight into memory (CIRS Memory) and performances on ADL (CIRS ADL) assessed by this approach did not exhibit significant correlations (Spearman's correlation coefficient; $p>0.05$) with indexes of depression (CBI-R Mood Sub-Scale). In contrast, depression correlated significantly and negatively ($p<0.05$) with insight into health condition (CIRS Total) and memory (CIRS Memory) through this assessment method (Figure 4.4c). Comparatively, impaired insight into global health condition, memory, social cognition and performances on ADL according to clinical judgement (CIRS Total, CIRS Memory, CIRS Social Cognition and CIRS ADL correspondingly) presented significant negative correlations (Spearman's correlation coefficient; $p>0.05$) global cognitive function (MoCA), memory (CVLT-II SF), executive function (FES), social cognition (Mini-SEA), neuropsychiatric symptoms (CBI-R) and apathy (Figure 4.4c).

4.4.6.3.3 Criterion-related evidence of validity

Impaired insight into global health condition, memory, social cognition and performances on ADL according to clinical judgement (CIRS Total, CIRS Memory, CIRS Social Cognition and CIRS ADL respectively) significantly differentiated between HC and different types of dementia ($p<0.05$, medium or large effect sizes) (Table 4.2 and Figure 4.5c).

4.4.6.3.4 Reliability

Impaired insight assessed by clinical judgement showed a high level of internal consistency through the CIRS with Cronbach's alphas of 0.85 for the total of patients and 0.86 for the entire sample.

4.5 DISCUSSION

The present chapter explored the psychometric properties of 3 different insight assessment methods tested over 4 modalities of insight across a cohort of patients with FTD, associated neurodegenerative disorders (AD and MND/ALS) and HC. Both validity and reliability were estimated for participant-informant level of agreement, self-appraisal accuracy and clinical judgement considered as measures of insight into health condition, memory, social cognition and performances on ADL. Results suggest that the tools used by these approaches to assess insight in dementia have adequate psychometric properties with appropriate indicators of validity and excellent indexes of reliability. Nevertheless, a closer look into the procedures conducted here provides certain distinctions which should be discussed.

The definition of clinical insight employed in this study (a relational concept which entails self-knowledge of a diagnosis or its symptoms -broad or specific objects-) (Figure 4.1) was judged as highly appropriate (concerning its clarity, pertinence and sufficiency/adequacy) by an

absolutely impartial committee of experts who mostly rated it with 8-10 (65-70% of the panel) or 6-7 (15% of the panel) points according to a scale ranging from 0 (poor) to 10 (excellent).

Participant-informant level of agreement proved to be a highly suitable paradigm to evaluate insight in dementia from a clinical perspective according to a committee of experts in the field, which was acknowledged by the entire panel of specialists included in this investigation. This assessment approach matches the definition of insight proposed in this study, which focuses on self-knowledge of health changes in dementia, either related to a global health condition or specific neuropsychological or behavioural symptoms (David et al., 2012; Markova & Berrios, 2001; Munoz-Neira et al., 2019) (Figure 4.1). Discrepancy scores estimated by comparing subjects' own views with reliable informants' paired opinions on participants' actual health condition, memory, social cognition and functional capacity in ADL were considered as apt (clear, adequate and sufficient) then to measure a multifaceted clinical manifestation like altered insight. Likewise, self-administered and informant-based versions of the CBI-R and the Insight Questionnaire employed through this assessment method are judged as tools with a proper content-related validity.

In terms of validity, participant-informant level of agreement evaluated with the CBI-R and the Insight Questionnaire presented good construct-related validity, especially in relation to convergent validity. For example, total participant-informant discrepancy scores obtained from the CBI-R and the Insight Questionnaire exhibited a significant positive correlation (Spearman's correlation coefficient of ~0.3, $p<0.05$) in patients and the entire cohort considered separately (Figure 4.3). Also, levels of insight into health condition, memory, social cognition and performances on ADL assessed by participant-informant discrepancy scores estimated with the CBI-R were found to be significantly and negatively associated with their corresponding modalities of impaired insight measured by clinical judgement (Spearman's correlation coefficients ranging between -0.3 and -0.46, $p<0.05$) also in patients the total sample (Figure 4.3). It should be noticed that the CBI-R utilized as an insight measure managed to differentiate among distinct types of dementia, i.e. FTD and AD, from HC, which turns it into a tool with a good criterion-related validity. Significant differences ($p<0.05$) in average levels of insight into health condition, memory and functionality in ADL were observed across diagnostic groups utilizing this assessment approach (Table 4.2). These significant differences coincided with the acceptable effects that the group categorization had on these measures of insight (r coefficients surrounding 0.6) (Table 4.2).

Concerning reliability, participant-informant level of agreement showed excellent values of Cronbach's alpha coefficients for both CBI-R and Insight Questionnaire (0.95 and 0.82 correspondingly) in patients as well as in the entire cohort. It should be noticed that the statistically significant associations found between self-administered and informant-based

versions of the Insight Questionnaire arranged for the assessment of current status and changes which could have approximately occurred 10 years ago is of particular interest. These results may suggest a considerable consistency throughout the time in participants' own self-perceptions/self-images and the respective façade they may project to their peers. Also, outcomes taken from the Insight Questionnaire in both instances (current and past) did not correlate significantly in patients according to their informants' opinions, which confirmed patients' changes in insight over time. A consistency in self-perceptions has also been reported in subjects' self-perceptions about their own personality traits, which tend to remain unchanged over a period of at least 10 years (Ruby et al., 2007).

Taking everything into consideration, these findings evidence the appropriate psychometric properties of the self-administered and informant-based versions of the CBI-R as an insight assessment and put participant-informant level of agreement forward as a valid and reliable method for the evaluation of insight in dementia. The usage of self-administered and informant-based versions of the CBI-R as an instrument for the evaluation of insight in dementia differs from its original aim and focus, which was the assessment of the presence of neuropsychiatric symptoms in cohorts of dementia patients according to reliable informants (Nagahama, Okina, Suzuki, & Matsuda, 2006; Wear et al., 2008; Wedderburn et al., 2008). All the same, this scale has also been successfully adapted elsewhere to be used as a gold standard insight measure (Hornberger et al., 2014) as carried out here. Contrary to expectations, the Insight Questionnaire (Hornberger et al., 2014) presented a smaller capacity to discriminate among groups compared to the CBI-R employed as an insight index. A potential explanation for this could be the inclusion of HC in the cohort analysed in this study, which were not included in its original publication (Hornberger et al., 2014). Anyway, the Insight Questionnaire has already proven to be an excellent scale for the evaluation of insight in dementia. The primary study of the Insight Questionnaire calculated its validity and reliability through sophisticated and traditional methods. Rash analysis and the estimation of concurrent validity with an amended patient-informant version of the CBI-R confirmed Insight Questionnaire's high-quality psychometric properties (Hornberger et al., 2014).

Self-appraisal accuracy and the Insight Task as insight assessment methods partially suited the proposed definition of insight. Thus, the content-related validity of this approach was considered less solid. This judgement was suggested by the ~40% of the experts who questioned the probity of self-appraisal accuracy to assess clinical insight in dementia. The entire procedure entailed by this method appears to be more applicable to the definition of metacognition, which is currently meant to refer to those thoughts that a person can have on their own cognitive status/activity (David et al., 2012). Additionally, although most of the participants of the present investigation seemed to have properly understood the Insight Task,

this procedure requires that subjects rate their own performances on cognitive tools looking at a normal curve, which may be highly challenging irrespective of the explanation provided to them to clarify where lower than average, average, and greater than average scores should be placed across this curve. Consequently, it should be also questioned whether failures at performing this self-appraisal task can be attributed to a genuine problem of metacognition or to the intrinsic high difficulty implied by this procedure.

In terms of construct-related validity, self-appraisal accuracy into health condition, memory, social cognition and functionality in ADL did not correlate significantly ($p>0.05$) with their paired participant-informant level of agreements (Figure 4.3) in the patients as well as in the entire cohort under study. This situation partially challenges the degrees of convergent validity associated with this assessment approach. In contrast, the different modalities of insight assessed with the Insight Task did correlate significantly ($p<0.05$) with their paired objects measured through clinical judgement, which controversially contributes to its convergent validity at the same time (Figure 4.3). It should be noticed that such reports of convergent validity with clinical judgement have not been reported so far for the Insight Task. Moreover, a good criterion-related validity was seen in its discriminatory capacity to significantly differentiate ($p<0.05$) across different diagnostic groups with medium effect sizes (~0.6) exerted by group categorization on levels of insight (Table 4.2).

In addition, acceptable external reliability for self-accuracy into global cognitive function, memory and executive function was found according to test-retest reliability (intraclass correlation coefficients ranging between ~0.3 and 0.97) in patients and the whole sample separately. To the best of the author of this chapter's knowledge, indicators of test-retest reliability for the Insight Task has not been reported either in the literature of disease/symptoms awareness in dementia.

Clinical judgment and the CIRS fit the conceptualization of insight used in this investigation. Approximately 80% of the committee of experts in dementia care who took part in this study agreed on the pertinence of this insight assessment method, providing it with a good content-related validity then. Nevertheless, it should be noticed that the inclusion of this insight assessment approach was not implemented in ideal conditions given that the author of this PhD thesis was not blind to the diagnoses of the patients in the cohort under study when completing the CIRS to rate different levels of insight. An effort to tackle this potential bias was made by adopting an objective attitude towards all the assessments employed in the data collection.

Clinical judgement evaluated through the CIRS exhibited acceptable indexes of construct validity, particularly regarding convergent validity, as shown by high significant negative

correlations (Spearman's correlation coefficients; $p<0.05$) found in patients and the entire sample between impaired insight into health cognition, memory, social cognition and performances on ADL assessed by this scale and its corresponding participant-informant level of agreement measures (Spearman's correlation coefficients of roughly -0.45 in almost all modalities of insight) (Figure 4.3). Similarly, CIRS also exhibited significant correlations (Spearman's correlation coefficients; $p<0.05$) in patients and the entire sample with different modalities of self-appraisal accuracy (Figure 4.3). Criterion-related validity of CIRS was also good as suggested by its capacity to significantly distinguish among different group categorizations ($p<0.05$), whose effect sizes on levels of impaired insight were medium or large (r coefficients of 0.6 or greater) (Table 4.2). Just as importantly, CIRS presented a high internal consistency with global Cronbach's alphas of 0.85 and 0.86 for patients and the whole cohort respectively. Altogether, these results indicate that the CIRS has very good psychometric properties and is a highly valid and reliable instrument for the assessment of insight in dementia.

Special attention should be drawn to the poor indexes of divergent validity encountered across the insight assessment methods analysed here (Figure 4.4). All of them distributed across insight into health status, memory, social cognition and functionality in ADL exhibited significant associations (Spearman's correlation coefficients $p<0.05$) with measures for the evaluation of other cognitive functions such as the MoCA (Figure 4.4) in the entire sample but not for the patients. These findings suggest that insight in dementia is a clinical manifestation with an extremely high load of cognitive functions. Similarly, the results obtained here indicate that distinct modalities of insight according to different assessment approaches are importantly shaped by depression and apathy (Figure 4.4). Such relationships between disease awareness in dementia and mood have been already reported in the literature (Conde-Sala et al., 2014; Ott & Fogel, 1992). At the same time, the associations seen between insight and depression and apathy may be in accordance with the idea of 'frontal anosodiaphoria' described for FTD patients, which addresses the possible decreased emotional interest in being aware of having the characteristic clinical picture of dementia (Mendez & Shapira, 2011). These issues, along with others related to possible relations between insight in dementia and cognitive and behavioural variables, will be further explored in 'Chapter 5: Insight, neuropsychological and behavioural characteristics of frontotemporal dementia'.

Interestingly, a practically absent effect of age and years of education (Enter Models, $p>0.05$) was found on distinctive types of levels of insight evaluated with different assessment approaches. These results may be counterintuitive to a certain extent provided the widely well know influence of demographic variables on neuropsychological variables (Lezak, Howieson, Bigler, & Tranel, 2012).

Surprisingly, HC enrolled in this investigation did show mild failures of insight assessed by different approaches across the objects under analysis, namely global health condition, memory, social cognition and functionality in ADL. These outcomes are also counterintuitive, as it appears to be that there is an assumption spread over the literature on the matter, which claims that levels of clinical insight observed in HC are unaffected. This assumption can be illustrated with the minor (Rosen et al., 2010; Williamson et al., 2010) or absolutely absent (Conde-Sala et al., 2014; Hornberger et al., 2014; Massimo et al., 2013; Mendez & Shapira, 2005, 2011; Ott & Fogel, 1992) incorporation of HC in diverse key publications on insight loss in dementia. Likewise, the results presented here clearly question the presumption of integrity of insight in HC. In relation to this point, although some studies have indicated that insight into global health condition may be accurate in healthy middle-aged individuals (aged roughly 43 years) (Wu et al., 2013) and older adults (aged between 65 and 74 years or 75 years and older) (Ferraro, 1980; LaRue, Bank, Jarvik, & Hetland, 1979), other studies undertaken in non-clinical subjects (with ages ranging from 20 to 65 or 20 to 90 years approximately) do suggest that certain self-referential processes (like the self-perception of the internal physical condition/changes of one's own body) decline with age (Khalsa, Rudrauf, & Tranel, 2009; Murphy, Geary, Millgate, Catmur, & Bird, 2018). Moreover, subjects at risk of developing AD have exhibited changes in brain function influenced by age in accordance with their performances in metacognitive self-appraisal task, which were not accounted for by the AD risk factors (Trivedi et al., 2008).

Finally, a considerable limitation of the present study is the size of the cohort analysed (a total 67 subjects, with groups of patients made up of approximately 6%, 9% or 18% of the total sample and a group of HC configured by roughly 51% of the total sample) which conditioned all the statistical analyses employed in this investigation to be conducted at nonparametric levels. In fact, the shapes of the variables analysed here mirrored the distributions observed in the violin plot presented to characterize the cohort's global cognitive profiles (Figure 4.2). This situation is like the two sides of the same coin. On the one hand, it leads to a cautious interpretation of the results, and on the other, it impedes a broad generalization of them. Future investigations may attempt to replicate these results with larger samples and parametric statistical analyses. In addition, including a measure of dementia severity such as the Clinical Dementia Rating (CDR) (Morris, 1997) or the Frontotemporal Dementia Rating Scale (FRS) (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) would have improved this investigation. Another drawback of this investigation may be the use of a convenience sample, which sets an ideal scenario that may be distant from the day-to-day actual circumstances seen in cognitive complaints and dementia clinical practice. Thus, much more robust findings could

be encountered conducting a similar study with a consecutive sample (Hancock & Larner, 2011) attending, for instance, to any traditional memory clinic.

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Chapter 5: INSIGHT, NEUROPSYCHOLOGICAL AND BEHAVIOURAL CHARACTERISTICS OF FRONTOTEMPORAL DEMENTIA

5.1 ABSTRACT

Studies which investigate impaired insight in dementia suggest that this clinical phenomenon has a highly complex structure. In the same vein, different elements related to its multifaceted nature have attracted attention and interest of researchers. The present chapter explores some of those aspects analysing both insight's structure and its clinical relevance concerning caregiver burden across a cohort made up of patients with frontotemporal dementia (FTD) (15), patients Alzheimer's disease (AD) (12) and cognitively healthy controls (HC) (34). Concerning insight's structure, its potential unitary or parcelled configuration in addition to its neuropsychological and neuropsychiatric/behavioural predictors were investigated. Regarding the clinical impact of insight on carers' burden, this examined in the FTD and AD groups, testing whether these variables are better predictors of burden than neuropsychological performances and/or neuropsychiatric/behavioural symptoms. Statistical evidence suggested that insight is fractionated into multiple domains, that is to say, insight is differently distributed into health condition, memory, social cognition and/or functionality in activities of daily living (ADL). No statistically relevant neuropsychological or neuropsychiatric/behavioural predictors for insight were found through the analyses undertaken here in the patients groups or the entire sample. No statistically significant differences in terms of caregiver burden were found between patients with FTD and AD. Also, no statistical evidence was found to suggest insight, neuropsychological, neuropsychiatric/behavioural predictors of caregiver burden in the patients groups.

5.2 INTRODUCTION

Impaired insight is a multifaceted symptom according to studies conducted with cohorts of diverse brain disorders, such as bipolar disorder, schizophrenia (SCZ), traumatic brain injury (TBI) and dementia, among others (David, Bedford, Wiffen, & Gilleen, 2012; Gilleen, Greenwood, & David, 2010; Wilson, Sytsma, Barnes, & Boyle, 2016). Evidence from dementia research suggests that there is a lack of clarity in terms of whether insight constitutes a unitary or domain specific phenomena (Clare, Markova, Verhey, & Kenny, 2005). In addition, altered insight in different forms of dementia seems to be associated to multiple clinical factors, such as cognitive and neuropsychiatric symptoms (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005; Aalten et al., 2006). Aside from this, the presence of low levels of insight coupled with

neuropsychological and behavioural symptoms can affect patients' quality of life (Trigg, Watts, Jones, & Tod, 2011) and increase carers' burden (Rocca et al., 2010).

Clinical insight in dementia appears to be configured by different modalities, whereby awareness/self-knowledge of health issues is distributed across broad (e.g. diagnosis or health status) or specific objects (e.g. specific neuropsychological or behavioural domains) (David et al., 2012; Markova & Berrios, 2011; Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019). Yet, impaired insight handled as global or parcelled notions has resulted in ambiguous conclusions. For instance, lack of insight into memory problems in AD (Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005) and an overall unawareness of disease in behavioural and language variants of frontotemporal dementia (FTD) (Kertesz, 2010) have been clinically addressed in a unitary manner and classified simply as anosognosia. On the contrary, other studies have indicated that insight is clearly spread out across modules pointing out the differentiation between altered insight into cognitive problems and behavioural disorders observed in AD (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996). Such a situation justifies a further examination of insight's modular structure split into broad and specific objects, for example, in FTD and associated syndromes.

Evidence on the neuropsychological components of insight in dementia has been mixed. Complex attentional/executive processes (sustained and selective attention along with shifting abilities) and episodic visual memory have accounted for disease unawareness in AD (Mangone et al., 1991). Impaired global cognitive function has also been associated with global insight loss into memory in AD (Vogel et al., 2005). In line with this, a close link between adequate metamemory abilities, self-monitoring skills and frontal functions have been described in AD patients who may tend to overestimate their episodic memory performances in cognitive tests and everyday life (Duke, Seltzer, Seltzer, & Vasterling, 2002). Differently, emotion recognition has been associated with both a broad conception of insight (metacognitive knowledge) and the ability to predict cognitive performances in FTD and associated syndromes (O'Keeffe et al., 2007). In the face of this inconclusive characterization of the cognitive predictors of insight in ND, greater understanding of the neuropsychological components of this clinical phenomenon is needed.

A clearer picture can be drawn around the associations observed between neuropsychiatric symptoms and lack of insight in prodromal stages of dementia, dementia itself and other ND. Depression and anxiety underpin impaired insight into cognitive and behavioural disorders in MCI secondary to Parkinson disease (PD), PD and PD dementia (PDD) (Orfei et al., 2018). Similarly, global insight into health condition has been shown to be importantly influenced by depression in AD (Conde-Sala et al., 2014; Ott & Fogel, 1992). Comparatively, while frontal behaviours have been correlated with insight into memory in MCI and AD (Vogel et al., 2005),

frontal behaviours and abilities to perform everyday actions seem to predict broad metacognitive abilities and anticipatory judgements of cognitive performance in FTD and associated syndromes (O'Keeffe et al., 2007). All the same, predictors of levels of insight based on the expression of other neuropsychiatric symptoms appeared to be underexplored in dementia.

On a slightly different note, the clinical importance of impaired insight, cognitive performances and behavioural symptoms concerning how they influence carers' burden also requires more research. On the one hand, neuropsychiatric symptoms have been shown to predict AD and FTD patients' caregiver burden (Liu et al., 2017; Uflacker, Edmondson, Onyike, & Appleby, 2016). On the other, FTD patients' caregivers tend to exhibit lower indexes of general and mental health together with higher burden than AD patients' carers (Riedijk et al., 2006). Complementary, abnormal behaviours have been reported to be highly overwhelming for carers of patients belonging to the FTD-amyotrophic lateral sclerosis (ALS) continuum (Hsieh et al., 2016), where neuropsychiatric symptoms have unfortunately been found to cause even more stress overload than physical symptoms in ALS (Burke, Elamin, Galvin, Hardiman, & Pender, 2015; Lillo, Mioshi, & Hodges, 2012). A proper distinction on whether altered insight or other neuropsychological or neuropsychiatric symptoms better predict caregiver burden remain to be elucidated.

In view of the above, this chapter intends to analyse both insight structure's and its clinical impact in patients' carers across a sample of patients with FTD, patients with AD and HC. Such purposes were explored by observing and comparing levels of insight into health condition, memory, social cognition and performances on activities of daily living (ADL) assessed with participant-informant level of agreement over the same cohort. Firstly, the conceptualization of insight as a unitary or fractionated issue was statistically tested. Complementary, both neuropsychological and neuropsychiatric/behavioural predictors of insight for the patients, HC and the entire sample of this study were examined. Secondly, the influence of impaired insight on caregiver burden, as well as the best possible predictors of carers' burden among impaired insight, cognitive decline and other neuropsychiatric/behavioural symptoms were analysed here.

5.3 METHODS

5.3.1 Participants

Part of the cohort considered in 'Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia' the cohort, which was a convenience sample, was used to carry out the procedures described in this section, although they were grouped differently.

Patients with motor neuron disease (MND)/amyotrophic lateral sclerosis (ALS) were excluded from the analyses carried out in this chapter. The sample under study here was split into 3 groups then: a FTD group of 15 patients with FTD (11 patients with the behavioural variant of FTD -bvFTD- and 4 patients with language variants of FTD -lvFTD-); an AD group of 12 patients with ADand a HC group of 34 HC. Details on the criteria employed to classify these subjects are specified in 'Chapter 2: General Methods'.

5.3.2 Assessments and materials

A thorough set of insight, neuropsychological, behavioural and complementary assessments were conducted in order to provide clinical profiles for each group across the cohort under analysis. Multiple cognitive domains, neuropsychiatric symptoms and functional capacity in activities of daily living (ADL) and caregiver burden evaluations were incorporated for this purpose prior to conducting the pertinent statistical analyses included in this study.

5.3.2.1 Demographic data

A demographic characterization of the sample split by diagnostic groups was conducted through the collection of subjects' ages, years of education and sexes.

5.3.2.2 Insight assessments

4 distinguishable modalities of insight including insight into health condition (broad object) as well as insight into memory, social cognition and performances on ADL (specific objects) were assessed using participant-informant level of agreement. Degrees of insight according to this insight assessment approach were evaluated with discrepancy scores (DS) obtained from the Cambridge Behavioural Inventory - Revised (CBI-R) (Hornberger et al., 2014; Wear et al., 2008) and its respective sub-scales depending on the object of insight under evaluation (CBI-R Total DS for insight into health condition, CBI-R Memory DS for insight into memory, CBI-R Abnormal Behaviour DS for insight into social cognition and CBI-R Everyday Skills DS for insight into performances in ADL). Participant-informant DS were estimated by subtracting reliable informants' outcomes yielded by the informant-based version of the CBI-R from the subjects' scores provided by the respective paired self-administered version of the CBI-R. The reason why this insight assessment procedure was chosen over others is supported by its appropriate psychometric properties, which appeared to be better compared to those shown by self-appraisal accuracy and clinical judgement according as analysed in 'Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia and associated disorders'. Further details on how participant-informant level of agreement was implemented can be found in 'Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia'.

5.3.2.3 Neuropsychological assessment

Patients with FTD and AD as well as HC underwent a thorough neuropsychological assessment. Global cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams, Newton, Niven, Foley, & Bak, 2014). Additionally, attention was measured with the Trail Making Test - A (TMT-A) (Reitan, 1958; Tombaugh, 2004). While memory was evaluated with the California Verbal Learning Test - Second Version Short Form (CVLT-II SF) (Delis, Kramer, Kaplan, & Ober, 2000), language was assessed with the Sydney Language Battery (SYDBAT) (Savage et al., 2013). Visuospatial abilities were measured with the Visuospatial Sub-Scale of the ECAS (Abrahams et al., 2014) and executive functions were evaluated with the Frontier Executive Screening (FES) (Leslie et al., 2016) and Trail Making Test - B (Reitan, 1958; Tombaugh, 2004). Lastly, social cognition was assessed with the Mini - Social and Emotional Assessment (Mini-SEA) (Leslie et al., 2016).

5.3.2.4 Behavioural assessment

Reliable informants, who were defined as such in 'Chapter 2: General Methods', filled in informant-based questionnaires for the assessment of subjects' behavioural changes. Neuropsychiatric/behavioural symptoms were assessed with the CBI-R (Wear et al., 2008) and functional capacity in ADL through the Disability Assessment for Dementia (DAD) (Gelinas, Gauthier, McIntyre, & Gauthier, 1999). Depression and apathy were respectively explored with the CBI-R Mood Sub-scale (Wear et al., 2008) and the Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991).

5.3.2.5 Complementary assessment

Caregiver burden and caregivers' symptoms of depression, anxiety and stress were assessed by the Zarit Burden Interview (ZBI) (J. M. Zarit & Zarit, 1982; S. H. Zarit, Anthony, & Boutselis, 1987) and the Depression, Anxiety and Stress Scale (DASS21) (Lovibond & Lovibond, 1995) correspondingly.

5.3.3 Procedures

Insight, neuropsychological, behavioural and complementary assessments undertaken with patients, HC and their reliable informants took roughly 2.5 hours spread over 1 or 2 sessions. Small breaks of no longer than 5 minutes were given to patients or HC in case they declared that they needed to pause, which occurred rarely. Self-administered and informant-based scales filled in by participants and their informants correspondingly were completed mostly at home in no more than 20 minutes.

5.3.4 Ethics approval

University of Bristol's sponsorship, London - Surrey Research Ethics Committee (REC) and NHS Health Research Authority (HRA) approval permitted to carry out this study in North Bristol Trust facilities (Southmead Hospital). Once any participant or informant questions related to the data collection or the entire research project were resolved, informed consent was acquired from all participants and their informants. Good clinical and research practices instructed by the Declaration of Helsinki were closely followed throughout the implementation of this investigation.

5.3.5 Statistical Analysis

5.3.5.1 Demographic, insight, neuropsychological and behavioural data

All the statistical analyses employed in this investigation were performed with parametric tests as if the variables under study were normally distributed. This theoretical assumption was made despite the fact that the shapes of their distributions differed significantly from Gaussian curves according to Kolmogorov-Smirnov tests as discussed in 'Chapter 4: Validity and reliability of insight assessment methods in frontotemporal dementia'. All the same, it should be noticed that all the nonparametric tests conducted in the previous chapter resulted in the same statistically significant outcomes as those yielded later by parametric tests, which were not reported. Such a situation supports to a certain extent the use of parametric statistic here and can increase the statistical power of the procedures described below. Both the IBM Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., 2016) or RStudio Integrated Development Environment for R (RStudio Team, 2016) were employed to carry out all the statistical analyses at a level of significance (p value) lower than 0.05 ($p<0.05$; two-tailed). Plots were created with the latter software where applicable.

Variables taken from insight, neuropsychological, behavioural and complementary assessments were compared across groups through one-way ANOVA tests to display a clinical characterization of the sample. Tukey's or Games-Howell's tests for post-hoc analyses were used depending on whether equality of variances was respectively assumed or not assumed. The exception for this analysis approach was the variable sex, which was contrasted with Chi-square tests according to group categorizations.

5.3.6 Insight's structure

Ratings corresponding to distinct forms of insight according to participant level of agreement were compared within the FTD group, AD group, HC group and the entire cohort separately to examine whether insight's configuration corresponds to a unified term or rather a modular concept fractionated into different modalities. Histograms of levels of insight into health

condition, memory, social cognition and performances on ADL assessed by CBI-R DS were overlaid onto the same charts to observe potential differences between each variable in reference through visual inspection. CBI-R DS were homogenized into percentile ranks prior to plotting their histograms and comparing distinct insight modalities due to the differences existing across the ratings entailed by them (i.e. CBI-R Total raw DS differ from their Memory, Social Cognition or ADL sub-scales raw scores with no conversion due to the number of items required to calculate them correspondingly). Paired-samples T-tests were conducted then between each pair of form of insight until the possibilities were exhausted (insight into global cognition versus insight into memory; insight into health condition versus insight into social cognition and so forth) in the patients groups (FTD and AD), the HC group and the entire cohort to seek for statistically significant differences between modalities of insight.

The main neuropsychological domains that could account for levels of insight were examined by running multiple linear regressions entering the first as predictors and the latter as outcomes. Multiple regressions were run considering patients groups (FTD and AD), the HC group and the entire cohort separately. Given the considerable influence exerted by cognitive functions, depression and apathy on insight/metacognitive capacities discussed in 'Chapter 4: Validity and reliability of insight assessment methods in frontotemporal dementia', multiple linear regressions were controlled by these variables. More precisely, 2 stages hierarchical multiple linear regressions were carried out to estimate neuropsychological predictors of insight. Stage 1 was framed into the Enter Method and set entering global cognitive function, depression and apathy (assessed respectively by the MoCA, the CBI-R Mood Sub-scale and the AES) as independent variables/predictors. Stage 2 was based on the Stepwise Method and structured entering attention, memory, language, visuospatial abilities, executive functions and social cognition (measured correspondingly by the TMT-A, SYDBAT Nomination, Repetition, Comprehension and Semantic Knowledge Sub-scales, the ECAS Visuospatial Sub-scale, the FES and the Mini-SEA) as independent variables/predictors. Scores of insight into health cognition, memory, social cognition and functionality in ADL (assessed by CBI-R DS) were incorporated as dependent variables/outcomes in stages 1 and 2 of the regression models. It should be noticed that while the Enter Method keeps fixed the variables entered in the multiple linear regression, the Stepwise Method rules out irrelevant predictors fitting models made up by variables that best predict the outcome in reference (Field, 2013). Likewise, stages 1 of hierarchical multiple linear regressions were utilized to control for global cognitive function, depression and apathy as confounding variables. Consequently, stages 2 of hierarchical multiple linear regressions were used to find models of neuropsychological predictors of the insight modalities in question.

Neuropsychiatric predictors of insight were estimated pursuing similar procedures. Thus, 2 stages hierarchical multiple linear regressions were conducted for patients groups (FTD and AD), the HC group and the whole cohort separately. The stages 1 of the hierarchical multiple linear regressions run were based on the Enter Method and entered only global cognitive function (measured by the MoCA) as independent variable to be considered as confounding factor. Stages 2 were set through the Stepwise Method incorporating different neuropsychiatric/behavioural symptoms as independent variables/predictors, including social interactions, mood, delusions, eating, sleep and stereotypic behaviours, motivation, self-care habits, everyday skills and apathy (evaluated by Abnormal Behaviour, Mood, Beliefs, Eating, Sleep, Stereotypic Behaviours, Motivation, Self-care and Everyday Skills CBI-R Sub-scales and the AES respectively).

In order to select statistically robust models which could represent the best predictors of the variables under study, assumptions for linear regressions were checked observing several criteria. Standardized residuals were estimated to confirm that extreme outliers did not affect the results (values within a range between -3.29 and 3.29 were considered as adequate). Normality of standardized residuals was tested revising probability-probability plots (P-P plots) (values must be aligned as close as possible with the 45° diagonal line or reference) to ensure proper regressions were found. The necessity of homoscedasticity in the data was revised looking into scatterplots of standardized predictors against standardized residuals (estimated scatterplots should tend to have elliptical shapes instead of conical or others). Also, independence of observations was assessed with the Durbin-Watson statistic (values close to 2 and not less than one or greater than 3 were taken as acceptable), whereas absence of multicollinearity was evaluated through balanced indices of tolerance and variance inflation factor (VIF) (tolerance being greater than 0.1 and VIF less than 10) (Field, 2013; Todd, 2021a, 2021b).

5.3.7 Clinical impact of insight on patients caregiver burden

Comparisons between levels of caregiver burden (evaluated by the ZBI) (J. M. Zarit & Zarit, 1982; S. H. Zarit et al., 1987) in patients with FTD and AD were carried out considering the HC group as a point of reference. Such contrasts were also conducted with indicators of depression, anxiety and stress reported by carers through the Depression, Anxiety and Stress Scale (DASS21) (Lovibond & Lovibond, 1995).

Variables that may affect caregivers' burden assessed by the ZBI (J. M. Zarit & Zarit, 1982; S. H. Zarit et al., 1987) were examined running additional multiple linear regressions through the Stepwise Method only, which were conducted considering both FTD and AD groups separately. Best predictors of caregiver burden (evaluated by the ZBI) among the different

forms of insight studied here (also assessed through participant-informant level of agreement with the CBI-R DS) were estimated by entering them separately into multiple linear regressions as independent variables/predictors and caregiver burden as dependent variable/outcome. Later, employing other multiple linear regressions based on the Stepwise Method, insight, neuropsychological and neuropsychiatric/behavioural variables (measured correspondingly with the aforementioned tools) were entered altogether as independent variables/predictors and caregiver burden (assessed by the ZBI) as dependent variable to encounter, among all the symptomatology, the best factors that could account for caregiver burden. The selection of appropriate models to these effects was based on the aforementioned assumptions for multiple linear regressions (absence of outliers, presence of normality of standardized residuals and homoscedasticity, etc.).

5.4 RESULTS

5.4.1 Demographic and clinical characterization of the cohort

The total sample was made up of 61 participants (32 men, 29 women). 3 diagnostic groups were conformed as planned: an FTD group, consisting of 15 patients with FTD (11 bvFTD and 4 lvFTD), an AD group made up of 12 patients with AD, and a HC group consisting of 34 subjects. Whilst Table 5.1 presents an overview of their demographic, neuropsychological, and neuropsychiatric/behavioural characteristics, Table 5.2 specifies the cohort's profiles of insight into health condition, memory, social cognition and performances in ADL.

There were no statistically significant differences across groups in terms of age ($F_{(2, 60)} = 2.64$, $p = 0.085$), years of education ($F_{(2, 60)} = 1.50$, $p = 0.24$) and sex (Chi-square = 3.92, df = 2, $p = 0.14$).

Concerning neuropsychological profiles, both FTD and AD groups exhibited lower scores than the HC groups in tests of global cognitive function (Figure 5.1) (MoCA: $F_{(2, 60)} = 25.50$, $p<0.001$, Figure 5.1a; ECAS: $F_{(2, 60)} = 27.68$, $p<0.001$, Figure 5.1b), attention (TMT Part A: $F_{(2, 60)} = 13.02$, $p<0.001$), memory (CVLT-II SF: $F_{(2, 60)} = 60.58$, $p<0.001$), naming and semantic knowledge regarding language abilities (SYDBAT [Naming: $F_{(2, 60)} = 20.36$, $p<0.001$; Semantic Knowledge: $F_{(2, 60)} = 12.55$, $p<0.001$]), executive function (FES: $F_{(2, 60)} = 16.26$, $p<0.001$; TMT Part B: $F_{(2, 60)} = 21.25$, $p<0.001$) and social cognition (Mini-SEA: $F_{(2, 60)} = 20.50$, $p<0.001$). In contrast, no significant differences were observed for repetition and comprehension in terms of language (SYDBAT [Repetition: $F_{(2, 60)} = 4.38$, $p=0.018$; Comprehension: $F_{(2, 60)} = 9.03$, $p=0.0004$]), and visuospatial skills (ECAS Visuospatial Sub-Scale: $F_{(2, 60} = 4.67$, $p=0.013$) across diagnostic groups. Post-hoc analyses suggested that both FTD and AD groups exhibited lower scores than the HC group in global cognition (Figure 5.1), attention, memory,

naming, semantic knowledge, executive functions and social cognition measures ($p<0.05$). Comparatively, FTD and AD groups did not show differences over their performances on such cognitive domains ($p>0.05$). Unanticipated results were encountered in naming, semantic knowledge and visuospatial skills, whereby patients with FTD, AD and HC did not present statistically significant differences of performance in these domains (Table 5.1).

In terms of neuropsychiatric symptoms, mood and apathy, statistically significant differences were observed across diagnostic groups (CBI-R Total: $F_{(2, 60)} = 26.82$, $p<0.001$; CBI-R Mood: $F_{(2, 60)} = 9.13$, $p<0.001$ and AES: $F_{(2, 60)} = 18.67$, $p<0.001$). Post-hoc analyses suggest the presence of statistically significant larger numbers of neuropsychiatric and apathetic symptoms in both FTD and AD groups compared to HC ($p<0.05$). Low mood was significantly worse in AD patients compared to HC ($p<0.05$); however, no significant differences were seen in depressive symptoms between FTD patients and HC and between AD and FTD patients ($p>0.05$) (Table 5.1).

Lastly, statistically significant differences were also encountered across groups in functionality in ADL (DAD: $F_{(2, 60)} = 21.38$, $p<0.001$). Patients with FTD and AD presented significantly impaired performances in ADL compared to HC ($p<0.05$); however, no significant distinctions were identified here between both patients' groups ($p>0.05$).

Table 5.1 Demographic and clinical characteristics of the sample

Parameter	**Descriptive statistics per group**			**Comparisons‡**
	FTD (*n* = 15)	**AD (*n* = 12)**	**HC (*n* = 34)**	
Age*	65.87 ± 10.80	74.30 ± 10.31	72.93 ± 9.43	*ns*
Years of Education*	12.89 ± 2.57	13.00 ± 3.54	14.88 ± 3.18	*ns*
Sex¥ **%Women(*n*)** **%Men(*n*)**	 33.33%(5) 66.67%(10)	 33.33%(4) 66.67%(8)	 58.82%(20) 41.18%(14)	*ns*
MoCA	18.54 ± 7.33	17.18 ± 6.90	27.24 ± 2.31	*FTD<HC*** *AD<HC*** *FTD~AD***
ECAS	71.33 ± 32.14	67.83 ± 37.13	114.82 ± 8.63	*FTD<HC*** *AD<HC*** *FTD~AD***
TMT A	112.50 ± 109.88	127.90 ± 97.92	27.18 ± 8.14	*FTD>HC*** *AD>HC*** *FTD~AD*
CVLT-II SF	3.20 ± 2.57	1.75 ± 2.56	7.91 ± 1.22	*FTD<HC*** *AD<HC*** *FTD~AD***
SYDBAT				
Naming	19.37 ± 9.21	18.11 ± 5.16	27.91 ± 2.07	*FTD<HC*** *AD<HC*** *FTD~AD***
Repetition	26.15 ± 8.36	29.89 ± 0.33	29.94 ± 0.24	*FTD~AD~HC*
Comprehension	23.31 ± 8.47	24.22 ± 5.21	29.12 ± 1.36	*FTD~AD~HC*
Semantic Knowledge	20.54 ± 10.40	20.11 ± 6.92	28.42 ± 1.75	*FTD<HC*** *AD<HC*** *FTD~AD***

ECAS Visuospatial Sub-scale	9.60 ± 4.94	9.33 ± 3.50	11.82 ± 1.09	*FTD~AD~HC*
FES	4.92 ± 3.07	6.09 ± 2.98	9.85 ± 2.83	*FTD<HC* AD<HC* FTD~AD**
TMT B	191.86 ± 104.94	203.70 ± 109.45	66.70 ± 39.05	*FTD>HC** AD>HC** FTD~AD***
Mini-SEA	15.58 ± 7.14	17.75 ± 5.83	24.35 ± 2.03	*FTD<HC** AD<HC** FTD~AD***
CBI-R Total	64.64 ± 50.73	66.00 ± 27.17	7.90 ± 7.30	*FTD>HC* AD>HC* FTD~AD***
CBI-R Mood	3.36 ± 3.59	4.30 ± 3.50	0.83 ± 1.26	*FTD~HC* AD>HC* FTD~AD**
AES	48.90 ± 12.24	43.67 ± 8.15	60.60 ± 5.18	*FTD<HC* AD<HC* FTD~AD*
DAD	24.69 ± 12.63	28.33 ± 10.28	40.00 ± 0.00	*FTD<HC* AD<HC* FTD~AD**

Results are expressed as Mean ± Standard Deviation. FTD = frontotemporal dementia; AD = Alzheimer's disease; HC = cognitively healthy controls; MoCA = Montreal Cognitive Assessment; ECAS = Edinburgh Cognitive and Behavioural ALS Screen; TMT A = Trail Making Test Part A; CVLT-II SF = California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall); SYDBAT = Sydney Language Battery; Naming = SYDBAT Naming Sub-scale; Repetition = SYDBAT Repetition Sub-scale; Comprehension = SYDBAT Comprehension Sub-scale; Semantic Knowledge = SYDBAT Semantic Knowledge Sub-scale; FES = Frontier Executive Screen; TMT B = Trail Making Test Part B; Mini-SEA = Mini-Social Cognition and Emotion Assessment; CBI-R = Cambridge Behavioural Inventory - Revised; CBI-R Mood = Cambridge Behavioural Inventory - Revised Mood Sub-scale; AES = Apathy Evaluation Scale; DAD = Disability Assessment for Dementia.

ŧAll comparisons were made with one-way ANOVA tests except for the variable sex.

¥Comparisons for the variable sex were conducted through Chi-square tests. For this case, non-significant differences were observed across diagnostic group at p>0.044 (p value obtained here was equal to 0.05).

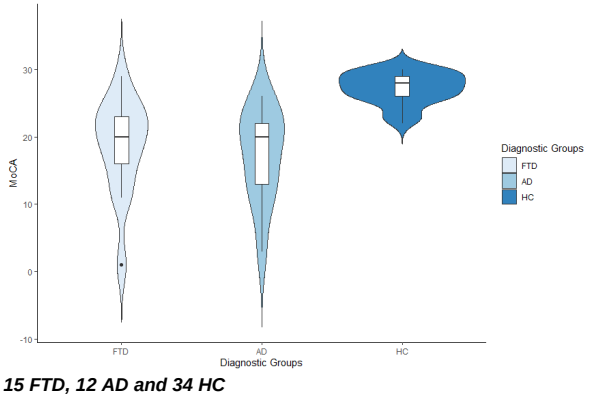
ns = Non-significant differences (p>0.05).

*Significant differences (p<0.05) according to a one-way ANOVA test and Tukey's tests for post-hoc analysis.

**Significant differences (p<0.05) in accordance with one-way ANOVA test and Games-Howell tests for post-hoc analysis.

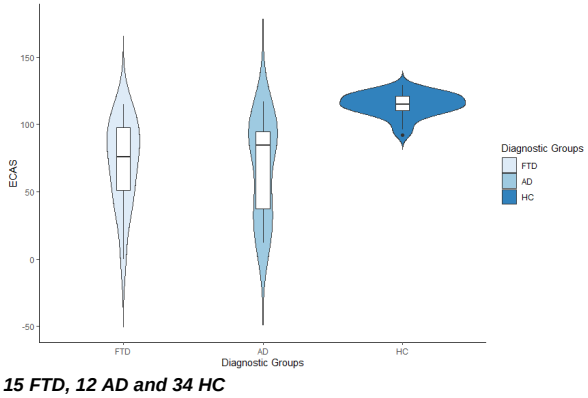
Figure 5.1 Cohort's cognitive profiles according to the Montreal Cognitive Assessment (MoCA) and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

Figure 5.1a



15 FTD, 12 AD and 34 HC
FTD<HC and AD<HC (p<0.05), FTD~AD (p>0.05)

Figure 5.1b



15 FTD, 12 AD and 34 HC
FTD<HC and AD<HC (p<0.05), FTD~AD (p>0.05)

5.4.2 Profiles of insight across the sample

Statistically significant differences across diagnostic groups were observed over measures of participant-informant level of agreement (Figure 5.2) in terms of insight into memory and insight into performances in ADL (CBI-R Memory DS: $F_{(2, 60)} = 3.10$, p=0.03, and CBI-R Everyday Skills DS: $F_{(2, 60)} = 6.97$, p=0.002 respectively) (Table 5.2). Post-hoc analyses across measures indicated that, while insight into memory was significantly decreased in AD patients compared to HC (p<0.05), no significant differences in this form of insight were observed between FTD patients and HC or FTD and AD patients (p>0.05). Regarding insight into functionality in ADL, FTD patients exhibited a statistically significant impairment compared to HC (p<0.05), whereas comparisons between AD patients and HC or FTD and AD patients did not exhibit significant results. Conversely, no significant differences were found between FTD patients and HC, AD patients and FTD patients or AD and FTD patients in accordance with insight into health condition and insight into social cognition (p>0.05).

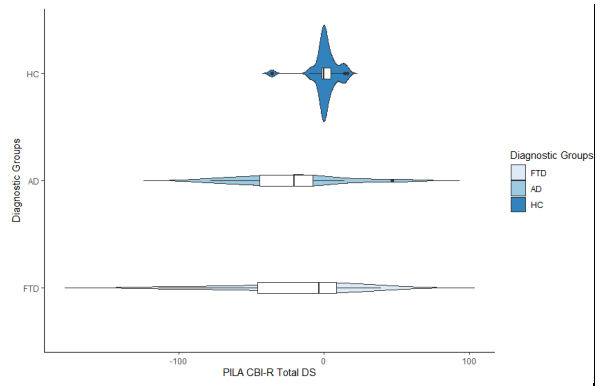
Table 5.2 Cohort's profiles of insight into health condition, memory, social cognition and functionality in activities of daily living, along with sample's performances on global metacognition, metamemory and metacognition about social cognition and executive functions

			Parameters Descriptive statistics per group			Comparisons
			FTD (*n* = 15)	AD (*n* = 12)	HC (*n* = 34)	
Insight	Participant-informant level of agreement	CBI-R Total	-18.71 ± 45.58	-22.30 ± 36.45	0.57 ± 9.11	*ns*
		CBI-R Memory	-3.14 ± 13.65	-7.00 ± 9.31	0.27 ± 3.08	*FTD~HC* AD<HC* FTD~AD***
		CBI-R Abnormal Behaviour	-4.33 ± 8.62	-1.50 ± 6.53	0.47 ± 1.71	*ns*
		CBI-R Everyday Skills	-4.13 ± 6.07	-2.83 ± 5.72	0.09 ± 0.29	*FTD<HC* AD~HC* FTD~AD**

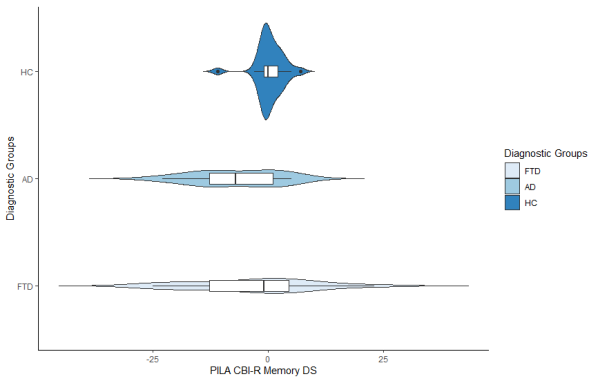
Results are expressed as Mean ± Standard Deviation. FTD = frontotemporal dementia; AD = Alzheimer's disease; HC = cognitively healthy controls; CBI-R Total = Cambridge Behavioural Inventory - Revised Total; CBI-R Memory = Cambridge Behavioural Inventory - Revised Memory Sub-scale; CBI-R Abnormal Behaviour = Cambridge Behavioural Inventory - Revised Abnormal Behaviour Sub-scale; CBI-R Everyday Skills = Cambridge Behavioural Inventory - Revised Everyday Skills Sub-scale.
ns = Non-significant differences (p>0.05).
*Significant differences (p<0.05) according to a one-way ANOVA test and Games-Howell tests for post-hoc analysis.

Figure 5.2 Sample's profiles of insight into health condition, memory, social cognition and functionality in activities of daily living, along with cohort's performances on global metacognition, metamemory and metacognition about social cognition and executive functions

Insight into health condition | **Insight into memory**

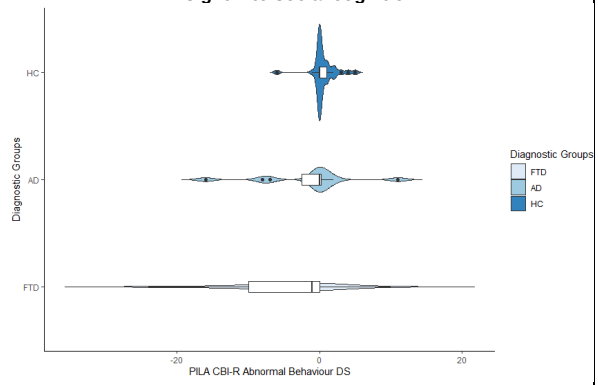


15 FTD, 12 AD and 34 HC
FTD~HC, AD~HC and FTD~AD (p>0.05)



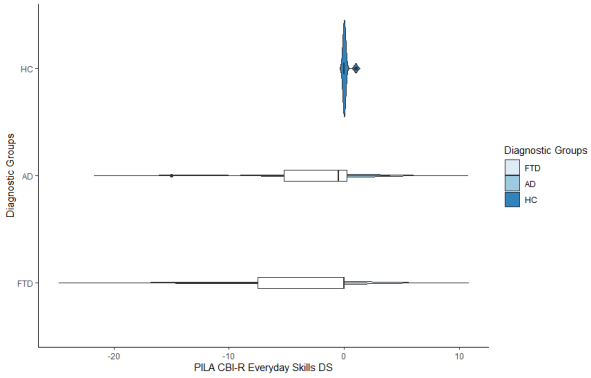
15 FTD, 12 AD and 34 HC
FTD~HC (p>0.05), AD<HC (p<0.05) and FTD~AD (p>0.05)

Insight into social cognition



FTD = 15 subjects, AD = 12 subjects and HC = 34 subjects
FTD~HC, AD~HC and FTD~AD (p>0.05)

Insight into functionality in ADL



FTD = 15 subjects, AD = 12 subjects and HC = 34 subjects
FTD<HC (p<0.05), AD~HC and FTD~AD (p>0.05)

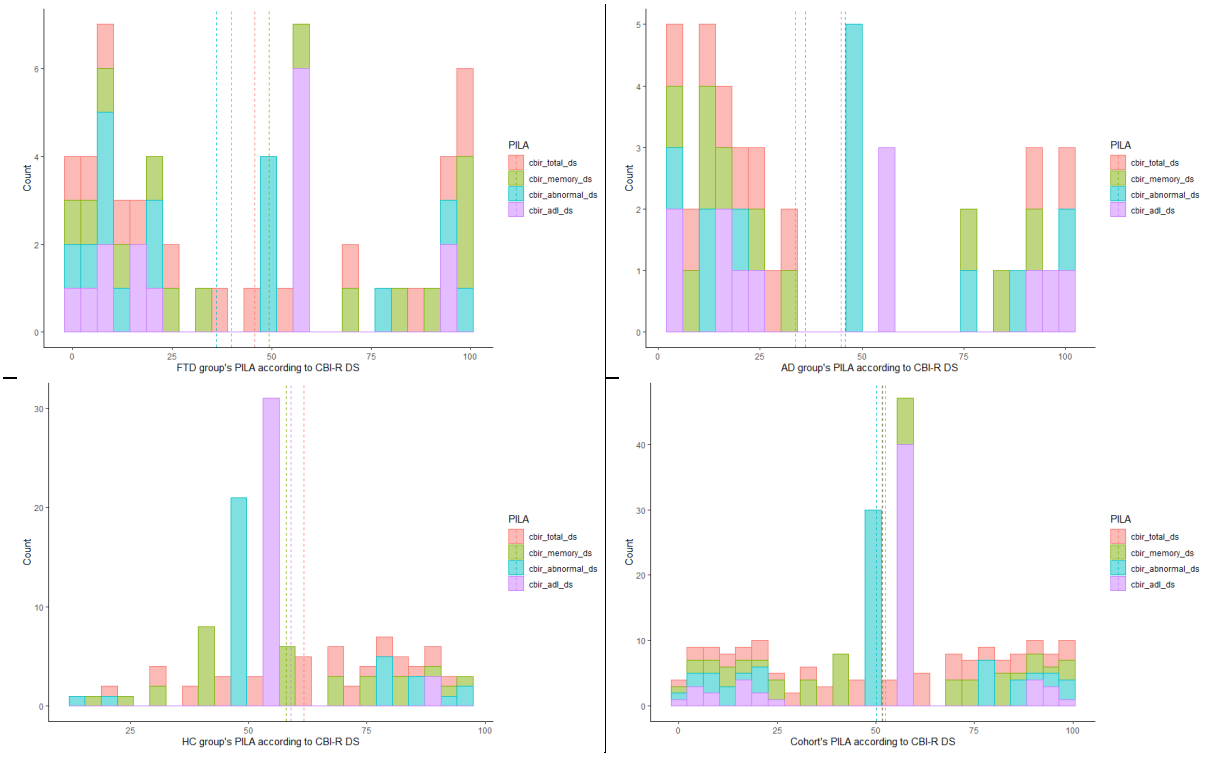
5.4.3 Configuration of insight as a unified or modular concept

Distributions represented by histograms overlaid onto the same axes across charts organised by groups (FTD, AD and HC groups) and the entire sample were generated with homogenized scores taken from participant-informant level of agreement (Figure 5.3). Homogenized scores were obtained transforming CBI-R DS into percentile ranks. These conversions were conducted on measures of insight into health condition, memory, social cognition and functionality in ADL (CBI-R Total DS, CBI-R Memory Sub-scale DS, CBI-R Abnormal Behaviour Sub-scale DS and CBI-R Everyday Skills Sub-Scale DS correspondingly).

Participant-informant level of agreement assessment method revealed through visual inspection that distributions of different modalities of insight (insight into health condition, memory, social cognition and functionality in ADL assessed by CBI-R DS) were shaped considerably different across the FTD group, AD group, HC group and the entire cohort separately (Figure 5.3). Unexpectedly, paired-samples T-tests showed statistically significant differences (p>0.05) only between the means extracted from insight into memory and insight into social cognition (CBI-R Memory and CBI-R Abnormal Behaviour respectively, $t_{(11)}$ = -2.53, p=0.032) in the AD group, as well as between insight into global health condition and insight into memory (CBI-R Total and CBI-R Memory accordingly, $t_{(60)}$ = -2.16, p=0.035) and insight

into global health cognition and insight into social cognition (CBI-R Total and CBI-R Abnormal Behaviour correspondingly, $t_{(60)} = -2.17$, $p<0.035$) in the entire sample.

Figure 5.3 Histograms representing profiles of different modalities of insight according to participant-informant level of agreement for patients with frontotemporal dementia, patients with Alzheimer's disease, cognitively healthy controls and the entire cohort



Distributions of insight into health condition, memory, social cognition and functionality in activities of daily living. PILA = Participant-informant level of agreement; CBI-R DS = Cambridge Behavioural Inventory - Revised Discrepancy Scores; cbir_total_ds = Cambridge Behavioural Inventory - Revised Total Discrepancy Scores; cbir_memory_ds = Cambridge Behavioural Inventory - Revised Memory Sub-scale Discrepancy Scores; cbir_abnormal_ds = Cambridge Behavioural Inventory - Revised Abnormal Behaviour Sub-scale Discrepancy Scores; cbir_adl_ds = Cambridge Behavioural Inventory - Revised Everyday Skills Sub-scale Discrepancy Scores

5.4.4 Neuropsychological predictors of insight

Results yielded by all the generated models indicated that the assumptions for multiple linear regressions were not met when analysing the data of the patients (FTD and AD groups), the HC (HC group) and the entire sample separately. On the one hand, all models failed at providing normality of residuals, where values tended to deviate from the diagonal reference line of the P-P plots (exhibiting a wavy or "snake" shape) instead of the desired straight line that should be observed placed over such a reference line. On the other hand, several models did not present the requirement of homoscedasticity across the scatterplots of standardized predictors against standardized residuals (elliptical-like shapes were not observed in the distribution of results). Consequently, there was no solid evidence to identify neuropsychological predictors for the insight modalities under study here among all the

variables entered in the hierarchical multiple linear regressions performed (attention -TMT-A, memory -CVLT-II-, language -SYDBAT Nomination, Repetition, Comprehension and Semantic Knowledge Sub-scales-, visuospatial abilities -the ECAS Visuospatial Sub-scale-, executive functions -FES- or social cognition -Mini-SEA-).

5.4.5 Neuropsychiatric/behavioural predictors of insight

As occurred with the neuropsychological domains assessed in this investigation, the models created to predict insight using neuropsychiatric/behavioural predictors did not meet the assumptions for multiple regressions (models generated also failed at finding normality of residuals and homoscedasticity) in the groups of patients (FTD and AD groups), the HC (HC group) and the whole cohort separately. Likewise, no statistical evidence was found to identify potential neuropsychiatric/behavioural predictors among the variables entered into the hierarchical multiple linear regressions undertaken (results from the Abnormal Behaviour, Mood, Beliefs, Eating, Sleep, Stereotypic Behaviours, Motivation, Self-care and Everyday Skills CBI-R Sub-scales and the AES).

5.4.6 Caregiver burden: differences between patients groups and possible predictors

As expected, compared to the HC group, caregiver burden assessed by the ZBI was significantly higher in both the FTD group and the AD group ($p>0.05$) (Table 5.3). Differently, no statistically significant differences in terms of this variable were found between FTD and AD ($p<0.05$).

Regarding depression, anxiety or stress evaluated through the DASS21 in carers, no significant differences were observed in these 3 symptoms between the FTD group and the HC group or between the FTD and AD groups ($p>0.05$) (Table 5.3).

Finally, models generated through multiple linear regressions to identify what modalities of insight could have best predicted levels of caregiver burden or those estimated to figure out what variables among insight, neuropsychological and neuropsychiatric/behavioural domains could have better accounted for caregiver burden did not satisfy the criteria required by the assumptions for multiple regressions (especially the requirements of normality of residuals and homoscedasticity) in the FTD and AD groups separately. Thus, it was not possible to suggest insight, neuropsychological or neuropsychiatric/behavioural predictors of caregiver burden with these analyses.

Table 5.3 Carers' burden, depression, anxiety and stress in patient groups

Parameters Descriptive statistics per group			Comparisons
FTD	**AD**	**HC**	

	(*n* = 15)	(*n* = 12)	(*n* = 34)	
ZBI	22.67±20.16	19.17 ± 18.12	1.62 ± 3.60	*FTD>HC** *AD>HC** *FTD~AD**
DASS21 Depression	2.80 ± 5.89	3.00 ± 5.12	0.32 ± 1.30	*FTD~HC** *AD~HC** *FTD~AD**
DASS21 Anxiety	2.33 ± 4.84	1.67 ± 3.06	0.09 ± 0.29	*FTD~HC** *AD~HC** *FTD~AD**
DASS21 Stress	4.73 ± 6.79	4.33 ± 5.61	0.88 ± 1.89	*FTD~HC** *AD~HC** *FTD~AD**
DASS21 Total	9.87 ± 17.23	9.00 ± 13.38	1.29 ± 2.84	*FTD~HC** *AD~HC** *FTD~AD**

Results are expressed as Mean ± Standard Deviation. FTD = frontotemporal dementia patients' carers; AD = Alzheimer's disease patients' carers; HC = cognitively healthy controls' reliable informants; ZBI = Zarit Burden Interview; DASS21 = Depression, Anxiety and Stress Scale.
*Significant differences ($p<0.05$) according to a one-way ANOVA test and Games-Howell tests for post-hoc analysis.
~ = Non-significant differences ($p>0.05$).

5.5 DISCUSSION

The present chapter addressed 2 theoretical issues which are crucial for the understanding of insight from a clinical perspective in FTD, in particular, and in different types of dementias, in general. Firstly, the insight's structure as a unified or fractionated phenomenon was examined in a cohort of FTD patients, AD patients, HC and the entire sample combined. Additionally, possible neuropsychological and neuropsychiatric/behavioural predictors of insight were examined for the same sample across diagnostic groups and the entire cohort. Secondly, the potential consequences of impaired insight on caregiver burden were explored.

In relation to insight's structure, diverse statistical evidence was found to confirm that insight is a fractionated clinical phenomenon spread across different objects of insight in patients with neurodegenerative conditions, which can be broad or specific. The conceptualization of insight as a relational term targeted at different objects in dementia (Markova & Berrios, 2011), whether they are broad like diagnosis or health condition or specific like neuropsychological or behavioural symptoms (Munoz-Neira et al., 2019), have already been discussed elsewhere (David et al., 2012; Markova & Berrios, 2000, 2011; Markova, Clare, Wang, Romero, & Kenny, 2005; Munoz-Neira et al., 2019). In the same line, the fragmentation of insight can be pictorially supported here by the considerable differences observed in the resulting shapes of the histograms of insight into global cognition, memory, social cognition and functionality in ADL plotted onto the same axes across different charts for the FTD, AD and HC groups, as well as

for the entire cohort (Figure 5.3). Since all the scores taken from the insight measures under analysis were homogenized for further contrasts where necessary, the differences seen among those distributions cannot be explained by intrinsic differences relative to the ratings employed. Counterintuitively, T-tests for paired-samples comparisons conducted over pairs of different modalities of insight (6 comparisons in total: i. insight into health condition versus insight into memory, ii. insight into health condition versus insight social cognition, iii. insight into health condition versus insight into functionality in ADL, iv. insight into memory versus insight into social cognition, v. insight into memory versus insight into functionality in ADL and vi. insight into social cognition versus insight into functionality in ADL) did not show statistically significant differences for all the cases. This fact could be understandable when considering that such contrasts compare means and not exactly the shapes of distributions. All the same, statistically significant differences were encountered between insight into health condition and insight into social cognition ($p<0.05$) in AD, as well as insight into health condition and insight into memory, and insight into health condition and insight into social cognition in the entire sample ($p<0.05$) (Figure 5.3). These findings may be suggesting that there are different modalities of insight in dementia which would be dissociated among them. Congruently, insight would be a parcelled clinical phenomenon and does not correspond to a unitary concept. At the same time, these conclusions are coherent with results from previous studies on the matter. For example, a differentiation between awareness of cognitive symptoms and awareness of behavioural disorders has been already reported in in AD (Starkstein et al., 1996). In addition, it has been also highlighted that insight is fragmented and spread across several modalities such as insight into memory or insight into non-memory problems (executive functions and activities of daily living -ADL-) also in AD (Valera-Bermejo, De Marco, Mitolo, McGeown, & Venneri, 2020). Complementary, other findings have already suggested a conceptual and neuroanatomical differentiation of insight across objects such as diagnosis and treatment, social cognition, language and motivation in AD and FTD (Hornberger et al., 2014).

Concerning the profiles of insight observed across the sample, while FTD patients showed a significantly greater impairment in insight into functionality in ADL in comparison with HC ($p<0.05$), comparisons for this variable between AD patients and HC or FTD and AD patients did not suggest statistically significant. Additionally, AD patients showed significantly lower levels of insight into memory compared to HC ($p<0.05$), whereas no significant differences in this insight modality were found between FTD patients and HC or FTD and AD patients ($p>0.05$), Unexpectedly insight into health condition and insight into social cognition did not differ significantly between FTD patients and HC, AD patients and FTD patients or AD and FTD ($p>0.05$). These findings seem to be in discrepancy with other studies where, when

comparing FTD and AD patients, FTD patients present with greater impairments in different forms of insight (Hornberger et al., 2014) or larger failures in distinct metacognitive compared to AD patients (Eslinger et al., 2005). Also, from an observational point of view on the volunteers enrolled in this study, all the FTD patients were clearly presenting with considerably a greater decline in global insight (or insight into memory, social cognition or behavioural changes as well) compared to AD patients, which is not reflected by the just reported comparisons of profiles of insight in the sample.

Regarding the neuropsychological predictors of different forms of insight, the models generated for this purpose failed at meeting the assumptions for multiple linear regressions (mainly due to an absence of normality of residuals and homoscedasticity) in the patients groups (FTD and AD patients), HC and in the total sample. Likewise, it was not possible to suggest cognitive domains that could account for insight with the data analysed in this chapter. A possible explanation for such results may be the inclusion of a sample with small groups (15 FTD, 12 AD and 34 HC). Alternatively, having used hierarchical multiple regressions with confounding variables such as cognition, depression and apathy (which had already presented correlations with insight as discussed in the previous chapter of this PhD thesis) at their first level may have left less possibilities for the other variables entered into the regressions. An alternative approach intended to filter the large number of variables handled in the present chapter could have been undertaken examining potential neuropsychological functions and their relationships with insight through a factor analysis and a principal component analysis, which are aimed at identifying clusters of variables simplifying data sets that have high loads of multicollinearity (Field, 2013).

An identical situation took place when attempting to identify neuropsychiatric/behavioural predictors of insight with hierarchical multiple linear regressions as all the predictive models created did not meet the assumptions for multiple linear regressions patients groups (FTD and AD patients), HC and in the whole cohort (mostly due to an absence of normality of residuals and homoscedasticity). Thus, it was not possible to suggest neuropsychiatric/behavioural variables that could shape insight.

The impossibility to propose neuropsychological or neuropsychiatric/behavioural predictors that could account for levels of insight should not be interpreted as definitive considering that associations between these elements have been already reported in the literature. For example, the critical role played by memory in the formation of clinical insight has been already put forward in MCI and AD (Orfei et al., 2010). Furthermore, studies conducted with AD patients have argued that episodic memory is the cornerstone of insight, where lack of disease awareness corresponds to a ‘petrified self’ and should be explained by constant failures when processing/updating key personal information (Lenzoni, Morris, & Mograbi, 2020; Mograbi,

Brown, & Morris, 2009). In relation to the important contribution of language to insight in dementia, semantic aspects also related to the proper formation of one's personal knowledge have been discussed in connection with the impaired insight into language problems that patients with lvFTD often experience (Savage, Piguet, & Hodges, 2015). Aside from these neuropsychological domains, salient effects of executive functions have been described on insight loss in FTD (Eslinger et al., 2005). Moreover, failures of specific metacognitive functions that entail self-monitoring processes have been suggested to be key in clinical insight in FTD and associated syndromes (O'Keeffe et al., 2007). Regarding behavioural aspects, similar neuropsychiatric symptoms labelled as apathy or as frontal behaviours have been strongly associated with lack of insight in MCI and AD (Spalletta, Girardi, Caltagirone, & Orfei, 2012; Vogel et al., 2005).

Finally, this chapter reported no statistically significant differences between caregiver burden or symptoms of depression, anxiety and stress experienced by carers of patients with FTD and caregivers of patients with AD. These results are contrary to other studies in which carers of patients with FTD exhibited greater burden in contrast with that observed in other neurodegenerative diseases like AD or Creutzfeld-Jacob disease (Uflacker et al., 2016). Moreover, it was not possible to identify predictors of caregiver burden in patients with AD or FTD among different modalities of insight, neuropsychological domains or neuropsychiatric/behavioural symptoms through the multiple linear regressions carried out here as they did not satisfy the assumptions for linear regressions either. These results should not be taken as conclusive since abnormal behaviours have already proven to be highly overwhelming for carers of FTD-ALS patients and have been stressed as key predictors of caregiver burden in FTD (Uflacker et al., 2016), producing unfortunately even more stress overload than physical symptoms in ALS (Burke et al., 2015; Hsieh et al., 2016; Lillo et al., 2012).

The main limitation of this study was the use of a subsample that combined bvFTD and lvFTD, which in ideal conditions should be avoided grouping patients with FTD separately according to their variants. Also, it is thought that the utilization of a highly sophisticated statistical analysis method (such as multiple linear regressions) to find predictors for an enormously complex symptom in a small sample (15 FTD, 12 AD and 34 HC) should be probably reconsidered starting by the exploration of other simpler alternatives (like a factor analysis or a principal component analysis) which could also permit the identification of elements that could account for insight in dementia.

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Chapter 6: STRUCTURAL NEURAL CORRELATES OF BROAD AND SPECIFIC OBJECTS OF INSIGHT IN FRONTOTEMPORAL DEMENTIA

6.1 ABSTRACT

The challenging conceptualization of insight from a clinical perspective as well as the wide variability implemented in the assessment and brain imaging methods used to study this symptom have hampered the examination of its neuroanatomical substrates in frontotemporal dementia (FTD). The objective of this chapter is to explore the neural correlates of altered insight in FTD in order to determine whether broad and specific objects of insight are underpinned by the same or different anatomical brain areas. Altered insight into health condition (broad object) as well as insight into memory, social cognition and functionality in activities of daily living (ADL) (specific objects) were assessed across 10 FTD patients, 8 patients with Alzheimer's disease (AD) and 26 healthy controls (HC). 3 Tesla Magnetic Resonance Imaging (MRI) brain scans were acquired from all the participants. A voxel-based morphometry (VBM) analysis was performed to find neural correlates of altered insight into those broad and specific objects in gray matter across the cohort. Inconclusive results were found to support that broad and specific objects of insight are underpinned by different brain areas in FTD, although a suggestive potential differentiation of distinct modalities of insight across different brain regions in HC was observed. Interestingly, a trend seen in the data collected suggested that global insight may be correlated with multiple frontotemporal and parietal regions when combining the FTD, AD and HC groups.

6.2 INTRODUCTION

Frontotemporal dementia (FTD) is a devastating neurodegenerative disease that results from both frontal and temporal lobes brain pathology (Hodges, 2013). The expression of its characteristic symptomatology depends on whether the behavioural-, language- or motor-related variant of FTD predominates the formation of the observed clinical picture (Finger, 2016). Likewise, a wide range of symptoms can present with this disorder including impaired social tact, disinhibition, impulsivity, apathy, agitation, speech articulatory problems, semantic errors and/or muscular weakness or rigidity, among others (Cycyk & Wright, 2008). In addition, FTD and amyotrophic lateral sclerosis (ALS), which is a form of motor neuron disease (MND), share genetic (Neumann et al., 2006), neuropathological (Kertesz, 2011; Lillo, Mioshi, et al., 2012), neuropsychological and behavioural (Lillo, Savage, Mioshi, Kiernan, & Hodges, 2012)

features that makes them belong to a spectrum of diseases lately named ALS-FTD continuum (Strong et al., 2009).

Patients with FTD's difficulty to identify/recognize their own condition and/or its symptoms has been put forward as one of the hallmarks of this disease since it was first coined as such (The Lund and Manchester Groups, 1994). In contrast, this lack of clinical insight was not explicitly described in the neuropsychiatric syndromes formerly labelled as 'Pick's disease' (PiD) (Constantinidis, Richard, & Tissot, 1974), which was the preceding terminology that later evolved to the modern concept of FTD (Kertesz, 2007). Although both the original (The Lund and Manchester Groups, 1994) and current diagnostic criteria (Gorno-Tempini et al., 2011; Neary et al., 1998; Rascovsky et al., 2011) of FTD have highlighted impaired insight as a critical symptom for its early detection, especially in the behavioural variant of bvFTD (bvFTD) (Neary et al., 1998; Rascovsky et al., 2011), its neural correlates seem to be underexplored in the literature (Hornberger et al., 2014; Markova & Berrios, 2011; Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019).

The elusive nature of the term altered insight (Markova & Berrios, 2000) has apparently led to a certain irregularity in its conceptualization (Markova & Berrios, 2011) and variability in the assessment methods (Alexander, Martyr, Savage, Morris, & Clare, 2020; Clare, Markova, Verhey, & Kenny, 2005) and brain imaging techniques (Zamboni & Wilcock, 2011) employed to thoroughly examine the origin of this clinical phenomenon in dementia. Although this situation has hampered the finding of the neuroanatomical underpinnings of insight loss (Markova & Berrios, 2000), certain conclusions on their respective function-structure interactions can be still drawn. Insight seems to be both conceptually and neuroanatomically differentiated in accordance with studies conducted on patients with Alzheimer's disease (AD) (Markova & Berrios, 2000; Zamboni & Wilcock, 2011) and FTD (Munoz-Neira et al., 2019). As a relational concept, it is addressed towards different broad or specific objects, whether they are a general health condition or particular neuropsychological/behavioural symptoms respectively (Munoz-Neira et al., 2019). For example, disease unawareness appears to be mainly mediated by right frontal areas in AD (Harwood et al., 2005) and FTD (Mendez & Shapira, 2005). In contrast, insight into memory (Bastin et al., 2012) and insight into social cognition (Sollberger et al., 2014) have not only been correlated with frontal lobes but also with the anterior cingulate cortex and the limbic system respectively. Comparatively, insight into functionality in activities of daily living (ADL) has been linked with areas over the prefrontal cortex, cingulate, insula, cuneus and even the cerebellum in FTD (Amanzio et al., 2016). A further discussion on these findings can be found in 'Chapter 3: Neural correlates of altered insight in frontotemporal dementia, a systematic review'.

Fractionating insight into broad and specific objects can facilitate the search of their respective neuroanatomical underpinnings in dementia (Markova & Berrios, 2011; Munoz-Neira et al., 2019). The objective of this chapter then is to explore the neural correlates of altered insight from such an approach to determine whether broad and specific objects of insight are mediated by the same or different areas in FTD. Likewise, the neural substrates of 4 different modalities of insight are inspected here across the same sample of patients with FTD, Alzheimer's disease (AD) and cognitively healthy controls (HC). These forms of insight include insight into health condition (broad object) as well as insight into memory, social cognition and performances in ADL (specific objects) assessed through participant-informant level of agreement, which is a procedure that showed more appropriate psychometric properties in the evaluation of this clinical phenomenon in dementia compared to self-appraisal accuracy and clinical judgement as discussed in 'Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia'.

Bearing in mind the literature revised on the brain areas associated with impaired insight in FTD and other neurodegenerative disease (Munoz-Neira et al., 2019), it is hypothesized that distinct types of insight are mediated by different neural underpinnings in FTD. To the best knowledge of this thesis' author, there are no other reported studies which have investigated specifically whether the same or different brain areas underlie several distinct types of insight over the same cohort of patients with dementia and HC.

Studying impaired insight in neurodegenerative disorders has clinical implications due to its proximity with other clinical factors such as the presence of mood changes, apathy, anxiety and other psychiatric symptoms, loss of autonomy performing everyday tasks, caregiver burden and worsening dementia syndromes (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005; Aalten et al., 2006). In addition to contributing to cognitive neuroscience with the neurocognitive analysis of self-referential processes, finding brain imaging markers for impaired insight in FTD may be of high clinical and research relevance due to the potential connection that exists between this symptom and the prompt identification and report of cognitive/behavioural symptoms characteristic of early onset dementia (Zamboni & Wilcock, 2011).

6.3 METHODS

6.3.1 Participants

Part of the cohort analysed in 'Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia and associated syndromes', which was a convenience sample, and 'Chapter 5: Insight and neuropsychological outputs in frontotemporal dementia'

was used for the purposes specified in this section. Patients with MND/ALS and subjects who did not have brain scans were excluded from the analyses conducted in the present chapter. A smaller sample made up of 44 participants then was divided into 3 groups: an FTD group of 10 patients with FTD (7 with bvFTD and 3 with language variants of FTD -lvFTD-), an AD group of 8 patients with AD, and a cognitively healthy control (HC) group of 26 individuals. Details on the specific criteria utilized to categorize these subjects as such can be found in 'Chapter 2: General Methods'. In brief, patients met diagnostic criteria widely used in research and clinical settings to define their respective clinical pictures. Whilst bvFTD patients presented with the characteristic insight loss and impaired social cognition observed in this disease (Rascovsky et al., 2011), lvFTD patients exhibited mainly speech/semantic problems (Gorno-Tempini et al., 2011). AD patients showed important memory disorders along with impairments in other cognitive domains (Lam, Masellis, Freedman, Stuss, & Black, 2013). In contrast, HC were individuals with normal cognition, autonomy when performing activities of daily living (ADL), and no clinical history of neurological or psychiatric disease.

6.3.2 Assessments and materials

Groups were assessed with an extensive battery of neuropsychological tests and insight assessments. Data on subjects' insight and behavioural changes were collected from self-administered and informant-based questionnaires. Several measures of cognitive function, neuropsychiatric symptoms and functionality in ADL were included in this evaluation.

6.3.2.1 Demographic data

Age, years of education and sex were recorded across the sample to report the demographic characterization of the groups arranged for the present chapter.

6.3.2.2 Neuropsychological assessment

Multiple neuropsychological tests were administered to the sample to assess and later characterize the cognitive profiles of the groups. Global cognitive function was measured through the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Additionally, whilst attention was evaluated with the Trail Making Test - A (TMT-A) (Reitan, 1958; Tombaugh, 2004), language was assessed with the Sydney Language Battery (SYDBAT) and memory with the California Verbal Learning Test - Second Version Short Form (CVLT-II SF) (Delis, Kramer, Kaplan, & Ober, 2000). Lastly, executive functions and social cognition were evaluated with the Frontier Executive Screening (FES) (Leslie et al., 2016) and the Mini - Social and Emotional Assessment (Mini-SEA) (Bertoux et al., 2012) respectively.

6.3.2.3 Behavioural assessment

Reliable informants, who were defined with details as such in 'Chapter 2: General Methods', completed informant-based questionnaires for the assessment of subjects' behavioural symptoms. Depressive symptoms were examined with the CBI-R Mood Sub-scale (Wear et al., 2008), whereas apathy was evaluated through the Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991). Furthermore, other neuropsychiatric/behavioural symptoms and functional capacity in ADL were assessed with the CBI-R (Wear et al., 2008) and the Disability Assessment for Dementia (DAD) (Gelinas, Gauthier, McIntyre, & Gauthier, 1999) correspondingly.

6.3.2.4 Insight assessment

4 different modalities of insight were assessed in the sample employing participant-informant level of agreement and clinical judgement: insight into health condition (broad object) and insight into memory, social cognition and performances on ADL (specific objects). Participant-informant discrepancy scores (DS) obtained from the self-administered and informant-based versions of the Cambridge Behavioural Inventory - Revised (CBI-R) (Hornberger et al., 2014; Wear et al., 2008) were used to these effects considering that this insight assessment approach presented better psychometric properties than those exhibited by self-appraisal accuracy and clinical judgement according to the analyses undertaken in 'Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia'.

6.3.2.5 Imaging acquisition

Magnetic Resonance Imaging (MRI) brain scans were acquired from all the subjects of the sample analysed here at the Clinical Research Imaging Centre of the University of Bristol (CRICBristol) using a 3 Tesla Siemens Magnetom Skyra MRI scanner with a parallel transmit body coil and a 32-channel head receiver array coil. The present investigation used an imaging protocol similar to that previously described elsewhere (Wearn et al., 2020) employing a sequence of 3D T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) with the following parameters: coronal, whole-brain, repetition time (TR) = 2200 ms, echo time (TE) = 2.42 ms, inversion time (TI) = 900 ms, flip angle = 9°, acquired resolution = 0.68 × 0.68 × 1.60 mm, acquired matrix size = 152 × 320 × 144, reconstructed resolution = 0.34 × 0.34 × 1.60 mm (after twofold interpolation in-plane by zero-filling in k-space), reconstructed matrix size = 540 × 640 × 144, GRAPPA factor 2, total acquisition time = 5:25 min.

6.3.3 Procedures

Insight, neuropsychological and behavioural assessments carried out on the subjects of the sample took roughly 2.5 hours spread over 1 or 2 sessions. Small breaks of no longer than 5

minutes were given to patients or HC whenever required. Self-administered and informant-based scales were taken home and completed independently by participants and their informants in no more than 20 minutes. Participants underwent MRI brain scans in the first or second visit, which included both structural and no-task functional images and took roughly 30 minutes. Once data collection was finalized, statistical and brain imaging analyses were conducted.

6.3.4 Data analysis

6.3.4.1 Demographic, insight, neuropsychological and behavioural data

All statistical analyses were carried out at a level of significance (p value) lower than 0.05 ($p<0.05$; two-tailed) using the IBM Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., 2016). Plots were generated with the RStudio Integrated Development Environment for R (RStudio Team, 2016). Demographic variables concerning age and years of education were compared across the diagnostic groups under study with a one-way ANOVA test. Post-hoc analyses considered Tukey's tests if equal variances were assumed or Games-Howell's tests if equality of variances was not assumed. Differently, comparisons among groups regarding sex were carried out with Chi-square tests. Prior to examining function-structure correlations across the subjects' brains of the sample, variables under analysis (levels of insight, metacognition, neuropsychological domains, neuropsychiatric symptoms and functional ability in ADL) were tested for normality through Kolmogorov-Smirnov tests. Comparisons across groups with one-way ANOVAs and post-hoc analyses as just described were conducted for variables normally distributed, whereas Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests were used for variables which did not exhibit normal distributions.

6.3.4.2 Structural brain imaging analysis

A voxel-based morphometry (VBM) analysis (Ashburner & Friston, 2000) was performed with the software Statistical Parametric Mapping 12 (SPM12) (Friston et al., 2007) running on MATLAB version R2019a Update 8 (The MathWorks Inc., 2019) in a workstation equipped with an operational system based on Linux. Raw images taken from the MRI brain scans of the sample (DICOM files) were transformed into compiled images (NIfTI files) through the tool dcm2nii (Rorden, 2007). Converted images were entered into SPM12 to proceed with the VBM analysis, which requires several steps prior to seeking structural brain differences between groups with different conditions and correlations between brain structures and neuropsychological functions. VBM normalizes brain images' contents to the same stereotactic space at first instance to perform then a nonlinear registration of them into predefined template (Ashburner & Friston, 2000). The procedure is followed by a

fragmentation of the brain tissue into gray matter, white matter and cerebrospinal fluid (Ashburner & Friston, 2000). This segmentation continues with the smoothing of the gray matter separated from the brains under analysis in combination with a Gaussian Kernel (Ashburner & Friston, 2000). Lastly, a logit transformation of every voxel in the smoothed image segments precedes the statistical analyses conducted with VBM. Those voxels, which represent local concentrations of tissue (between 0 and 1), are statistically processed through a general linear model to detect brain regions significantly correlated to the effects under study (Ashburner & Friston, 2000). To the ends of this study, images were normalized to the Montreal Neurological Institute (MNI) space and smoothed with an 8mm full width at half maximum (FWHM) filter considering a mask with an absolute threshold of 0.05. Segmentation was conducted with the Computational Anatomy Toolbox 12 (CAT12) (Gaser & Dahnke, 2016; Gaser, Dahnke, Kurth, & Luders, 2020) installed on SPM12 as an extension tool. A two-sample T-test model was used to compare structural brain differences between the FTD and HC groups and the AD and HC groups. Neural correlates of altered insight into health condition (broad object of insight) and insight into memory, social cognition and performances in ADL (specific objects of insight) were explored by entering such variables and the processed images into general linear models. Total intracranial volume (TIV), age, years of education and severity of dementia according to MoCA scores were also entered into such models as confounding covariates. Significant correlations between levels of insight into different objects and gray matter volumes were calculated for patients with FTD only, patients with AD only, HC only and the whole sample wherever statistically significant differences across groups were observed in the outcomes of the insight assessment methods used here. Correlations between insight into health condition, memory, social cognition and activities of daily living, and gray matter volumes were explored starting from the assumption that the greater the failures of insight, the smaller the gray matter volumes. Hence, only negative correlations were examined with one-tailed T tests. Identification and labelling of potentially significant brain areas associated to insight measures was carried out with the Neuromorphometrics brain atlas found in SPM12. Lastly, in terms of statistical power, strict and less conservative approaches were adopted for both the comparisons of brain structures across diagnostic groups and the correlations estimated between insight measures and gray matter volumes. At first instance, all these analyses were performed in the entire brains restricting the results to Family-Wise Error corrected (FWE_{corr}) or False Discovery Rate (FDR) p values smaller than 0.05 ($p_{FWEcorr}<0.05$ or $p_{FDR}<0.05$) at the cluster-level or at the peak-level. In case such levels of significance were not reached, uncorrected p values smaller than 0.001($p_{uncorr}<0.001$) at the cluster-level or at the peak-level were considered after entering the expected voxels per cluster as thresholds in the analyses. It should be noticed that a less lenient interpretation of

the statistical power (i.e. if results that only survived statistical significance at $p_{uncorr}<0.001$ were found) may only express trends in the respective brain-function associations examined.

6.3.5 Ethics approval

University of Bristol's sponsorship and ethical approval from London - Surrey Research Ethics Committee (REC) and NHS Health Research Authority (HRA) allowed the author of this thesis to conduct this study at CRICBristol and Southmead Hospital (North Bristol Trust facilities). Participant and informants were asked whether they had any questions related to the data collection or the entire research project before confirming their participation. Once doubts were resolved, informed consent was acquired from them in accordance with good clinical and research practices instructed by the Declaration of Helsinki, which were closely followed throughout the implementation of this investigation.

6.4 RESULTS

6.4.1 Demographic and clinical characterization of the sample

The total sample of the present study was made up 44 subjects (25 men, 19 women). This cohort was divided and arranged into 3 diagnostic groups: an FTD group of 10 patients with FTD (7 individuals with bvFTD and 3 with language variants of FTD), an AD group of 8 patients with AD, and a HC group of 26 participants. Table 6.1 displays a summary of the demographic, neuropsychological, and neuropsychiatric/behavioural characteristics of the cohort and Table 6.2 specifies their profiles of insight into health condition, memory, social cognition and performances in ADL according to participant-informant level of agreement.

Statistically significant differences in age and years of education were observed across diagnostic groups ($F_{(2, 43)} = 7.22$, $p<0.05$ and $F_{(2, 43)} = 6.67$, $p<0.05$ respectively). Concerning age, although FTD patients were significantly younger than AD patients and HC ($p<0.05$), AD patients and HC were matched in terms of this variable ($p>0.05$). Regarding levels of education, no statistically significant differences were appreciated between FTD patients and HC or FTD patients and AD patients, whereas the AD group had statistically significant lower values on this variable compared to HC. In contrast, FTD, AD and HC groups were matched according to sex (Chi-square = 3.892, df = 2, $p>0.05$).

Concerning neuropsychological testing, FTD, AD and HC groups exhibited statistically significant differences in scores yielded by assessments of global cognitive function (MoCA: Kruskall-Wallis $Test_{(2, 43)} = 23.44$, $p<0.001$) (Figure 6.1), memory (CVLT-II SF: Kruskall-Wallis $Test_{(2, 43)} = 26.62$, $p<0.001$), executive function (FES: Kruskall-Wallis $Test_{(2, 43)} = 11.13$, $p=0.004$) and social cognition (Mini-SEA: Kruskall-Wallis $Test_{(2, 43)} = 18.59$, $p<0.001$). Post-hoc analyses suggested that both FTD and AD groups performed significantly worse than the

HC group in global cognition (Figure 6.1), memory, executive functions and social cognition assessments ($p<0.05$). Conversely, FTD and AD groups did not show statistically significant differences in their performances across those neuropsychological domains ($p>0.05$) (Table 6.1).

Concerning the presence of behavioural symptoms, significant differences were observed in depression, apathy and neuropsychiatric symptoms across the diagnostic groups of this study ($p<0.05$) in accordance with the CBI-R Mood Sub-scale, the AES and the entire CBI-R respectively (Table 6.1) (CBI-R Mood Sub-scale: Kruskall-Wallis $Test_{(2, 43)} = 9.49$, $p=0.009$; AES: Kruskall-Wallis $Test_{(2, 43)} = 13.73$, $p=0.001$; CBI-R Total: Kruskall-Wallis $Test_{(2, 43)} = 18.51$, $p<0.001$ correspondingly). Post-hoc analyses revealed no statistically significant differences between FTD patients and HC or between FTD patients and AD patients in terms of levels of depression and apathy ($p>0.05$), although both symptoms were significantly lower in the AD group compared to the HC group ($p<0.05$). Additionally, while no significant differences between both FTD and AD groups were seen regarding neuropsychiatric symptoms, both patients groups showed significantly larger v in this variable compared to HC ($p>0.05$) (Table 6.1).

Lastly, statistically significant differences were also found in functionality in ADL across groups (DAD: Kruskall-Wallis $Test_{(2, 43)} = 21.51$, $p<0.001$), where post-hoc analyses suggested that FTD and AD groups exhibited statistically significant worse performances in ADL compared to HC ($p<0.05$) and no statistically significant differences between both patients' groups ($p>0.05$).

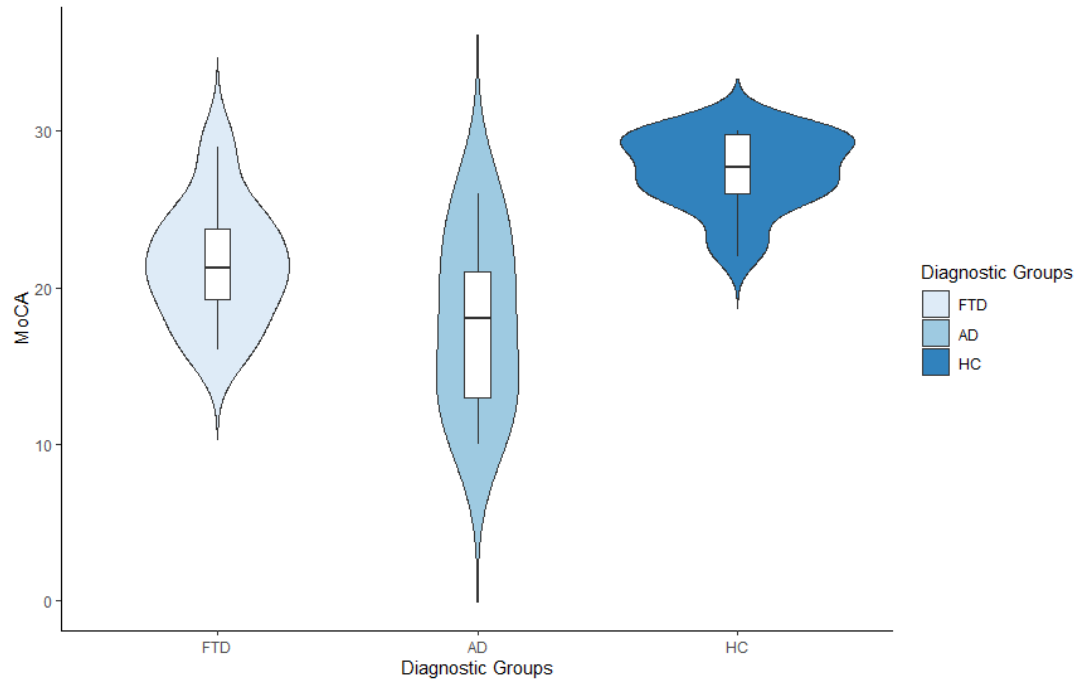
Table 6.1 Demographic and clinical characteristics of the sample

Parameter	Descriptive statistics per group			Comparisons‡
	FTD (*n* = 10)	**AD (*n* = 8)**	**HC (*n* = 26)**	
Age	61.70 ± 8.74	70.86 ± 9.40	71.80 ± 5.83	*FTD<HC* *AD~HC* *FTD~AD*
Years of Education	13.57 ± 2.05	12 ± 2.45	15 ± 2.02	*FTD<HC* *AD<HC* *FTD~AD*
Sex **%Women(*n*)** **%Men(*n*)**	 40%(4) 66%(6)	 12.5%(1) 87.5%(7)	 53.85%(14) 46.15%(12)	*ns*
MoCA	21.56 ± 3.89	17.75 ± 5.68	27.44 ± 2.38	*FTD<HC** *AD<HC** *FTD~AD**
CVLT-II SF	4.20 ± 2.39	1.88 ± 2.80	7.96 ± 1.18	*FTD<HC** *AD<HC** *FTD~AD**
FES	6.11 ± 2.52	6.38 ± 3.16	9.68 ± 3.00	*FTD<HC** *AD<HC** *FTD~AD**

Mini-SEA	18.23 ± 4.96	19.45 ± 4.98	24.40 ± 2.19	*FTD<HC* AD<HC* FTD~AD**
CBI-R Mood	3.33 ± 3.71	3.71 ± 2.63	0.86 ± 1.21	*FTD~HC AD<HC* FTD~AD*
AES	49.83 ± 13.50	44.57 ± 8.96	59.94 ± 4.81	*FTD~HC AD<HC* FTD~AD*
CBI-R Total	57.44 ± 53.39	67.86 ± 28.77	8.64 ± 8.20	*FTD>HC* AD>HC* FTD~AD**
DAD	28.50 ± 11.72	29.69 ± 10.57	40.00 ± 0.00	*FTD<HC* AD<HC* FTD~AD**

Results are expressed as Mean ± Standard Deviation. FTD = frontotemporal dementia; ND = neurodegenerative disorders; HC = cognitively healthy controls; MoCA = Montreal Cognitive Assessment; CVLT-II SF = California Verbal Learning Test - Second Version Short Form (Raw Long Delay Recall); FES = Frontier Executive Screen; Mini-SEA = Mini-Social Cognition and Emotion Assessment; CBI-R Mood = Cambridge Behavioural Inventory - Revised Mood Sub-scale; AES = Apathy Evaluation Scale; CBI-R Total = Cambridge Behavioural Inventory - Revised Total Score; DAD = Disability Assessment for Dementia.
ŧAll comparisons were carried out with nonparametric statistics including Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests, except for the variable sex which was contrasted across groups with Chi-square tests.
ns = Non-significant differences (p>0.05).
*Significant differences (p<0.05) according to Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests.
~ = Non-significant differences (p>0.05).

Figure 6.1 Cohort's cognitive profiles according to the Montreal Cognitive Assessment (MoCA)



10 FTD, 8 AD and 26 HC
FTD<HC, AD<HC (p<0.05) and FTD~AD (p>0.05)

6.4.2 Profiles of insight across the different diagnostic groups of the sample

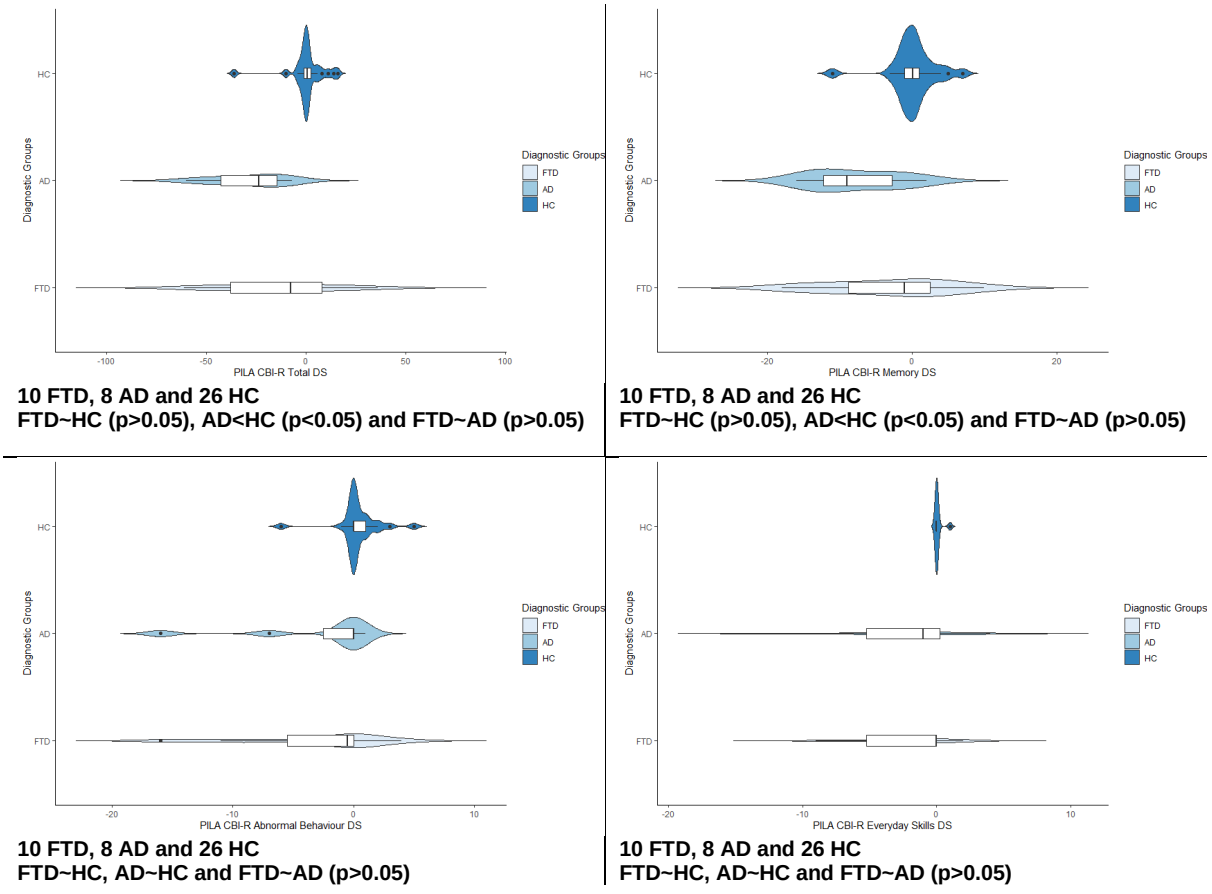
Statistically significant differences in certain modalities of insight assessed through participant-informant level of agreement were found. Concerning, Statistically significant differences in levels of insight across the diagnostic groups under analysis were found only in insight into health condition and insight into memory assessed through participant-informant level of agreement using discrepancy scores calculated with the CBI-R (CBI-R Total DS: Kruskall-Wallis $Test_{(2, 43)}$ = 14.25, p=0.001 and CBI-R Memory DS: Kruskall-Wallis $Test_{(2, 43)}$ = 8.58, p=0.014 respectively). Although the AD group presented significantly worse scores in these insight modalities compared to the HC group (p<0.05), no statistically significant differences in such objects of insight were observed between FTD patients and HC groups or between patients' groups (p>0.05) (Table 6.2, Figure 6.2). In relation to insight into social cognition and insight into functionality in ADL assessed from this approach employing the CBI-R DS, no statistically significant differences across diagnostic groups were found (p>0.05) (Table 6.2, Figure 6.2). Regarding clinical judgment evaluated by the CIRS, diagnostic groups presented statistically significant differences in terms of insight into health condition (CIRS Total: Kruskall-Wallis $Test_{(2, 43)}$ = 23.76, p<0.001), memory (CIRS Memory: Kruskall-Wallis $Test_{(2, 43)}$ = 13.45, p=0.001), social cognition (CIRS Social Cognition: Kruskall-Wallis $Test_{(2, 43)}$ = 25.33, p<0.001), and functional capacity in ADL (CIRS ADL: Kruskall-Wallis $Test_{(2, 43)}$ = 8.10, p=0.017). More precisely, compared to the HC group, FTD patients had significantly greater levels of impairment over such objects of insight (p<0.05). In contrast, comparisons between AD patients and HC showed statistically significant differences only in global insight (p<0.05). Lastly, FTD patients exhibited statistically significant lower levels of insight into social cognition compared to AD patients (p<0.05) in accordance with this assessment approach (Figure 6.2b, Table 6.2).

Table 6.2 Profiles of insight into health condition, memory, social cognition and functionality in activities of daily living across the different groups of the sample

		Parameters Descriptive statistics per group			Comparisons‡
		FTD (*n* = 10)	**AD (*n* = 8)**	**HC (*n* = 26)**	
Insight – **Participant-informant level of agreement**	**CBI-R Total DS**	-13 ± 31.90	-28.50 ± 18.62	0.28 ± 9.27	*FTD~HC* AD<HC* FTD~AD**
	CBI-R Memory DS	-3.21 ± 8.84	-7.75 ± 6.27	0.12 ± 3.19	*FTD~HC* AD<HC* FTD~AD**
	CBI-R Abnormal Behaviour DS	-3.10 ± 6.23	-2.87 ± 5.87	0.35 ± 1.79	*ns*
	CBI-R Everyday Skills DS	-2.20 ± 3.61	-2.50 ± 5.01	0.08 ± 0.27	*ns*

Results are expressed as Mean ± Standard Deviation. FTD = frontotemporal dementia; AD = Alzheimer's disease; HC = cognitively healthy controls; CBI-R DS Total = Cambridge Behavioural Inventory - Revised Discrepancy Scores Total; CBI-R DS Memory = Cambridge Behavioural Inventory - Revised Discrepancy Scores Memory Sub-scale; CBI-R DS Abnormal Behaviour = Cambridge Behavioural Inventory - Revised Discrepancy Scores Abnormal Behaviour Sub-scale; CBI-R DS Everyday Skills = Cambridge Behavioural Inventory - Revised Discrepancy Scores Everyday Skills Sub-scale; CIRS Total = Clinical Insight Rating Scale Total; CIRS Memory = Clinical Insight Rating Scale Memory Sub-scale; CIRS Social Cognition = Clinical Insight Rating Scale Social Cognition Sub-scale; CIRS ADL = Clinical Insight Rating Scale Activities of Daily Living Sub-scale.
ǂAll comparisons were carried out with nonparametric statistics including Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests.
ns = Non-significant differences (p>0.05).
*Significant differences (p<0.05) according to Kruskal-Wallis tests and post-hoc analyses adjusted by Bonferroni corrections for multiple tests.
~ = Non-significant differences (p>0.05)

Figure 6.2 Sample's profiles of insight into health condition, memory, social cognition and functionality in activities of daily living according to participant-informant level of agreement in patients with frontotemporal dementia, patients with Alzheimer's disease and healthy controls



10 FTD, 8 AD and 26 HC
FTD~HC (p>0.05), AD<HC (p<0.05) and FTD~AD (p>0.05)

10 FTD, 8 AD and 26 HC
FTD~HC (p>0.05), AD<HC (p<0.05) and FTD~AD (p>0.05)

10 FTD, 8 AD and 26 HC
FTD~HC, AD~HC and FTD~AD (p>0.05)

10 FTD, 8 AD and 26 HC
FTD~HC, AD~HC and FTD~AD (p>0.05)

6.4.3 Structural brain differences across groups

No statistically significant differences in gray matter densities were observed between the FTD and HC groups, the AD and HC groups, and the FTD and AD groups when considering $p_{FWEcorr}<0.05$ or $p_{FDR}<0.05$ at the cluster-level or the peak-level. Differently, statistically

significant differences in gray matter volumes were seen across diagnostic groups when taking into account $p_{uncorr}<0.001$ at the peak-level and not at the cluster level.

6.4.3.1 FTD and HC groups

Compared to HC, patients with FTD exhibited smaller volumes of gray matter across right hippocampal, parahippocampal and entorhinal areas, the fusiform gyrus, amygdala and ventral dorsal cortex as well as the temporal pole and inferior frontal gyrus regions bilaterally ($p_{uncorr}<0.001$ at the peak-level) (Table 6.3, Figure 6.3a).

6.4.3.2 AD and HC groups

In comparison with HC, patients with AD showed significant reductions of gray matter volumes in areas surrounding the right thalamus and caudate, left precentral and postcentral gyri, left superior and middle frontal gyri and the middle temporal gyrus ($p<0.05$, FWE_{corr} at the cluster-level) (Table 6.3, Figure 6.3b).

Table 6.3 Structural differences across patients with frontotemporal dementia, patients with neurodegenerative diseases and healthy controls

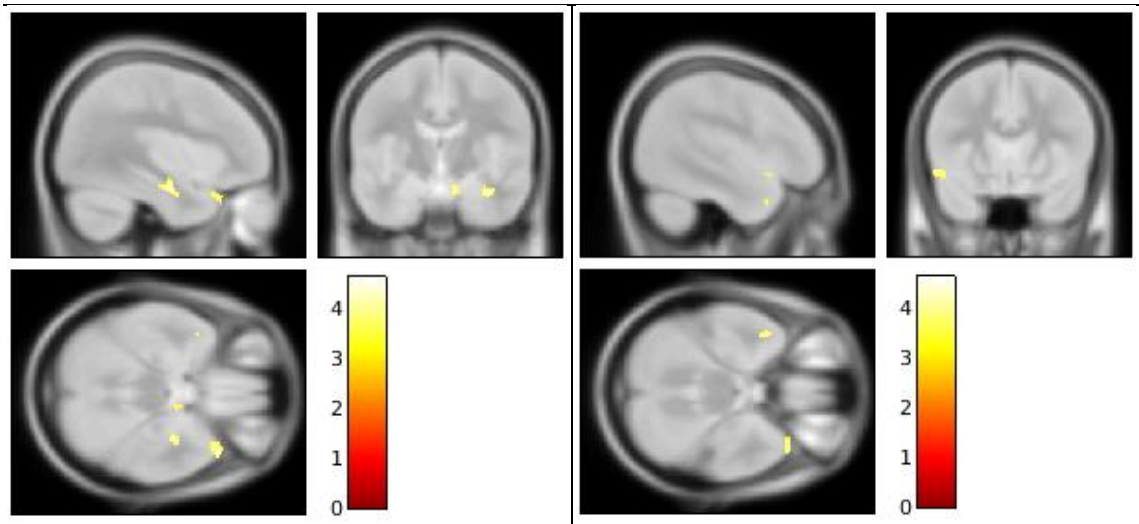
Contrast	Side (hemisphere)	Structure	%	Types of significance									MNI coordinates		
				Cluster-level				Peak-level							
				$pFWE_{corr}$	$qFDR_{corr}$	k_e	p_{uncorr}	$pFWE_{corr}$	$qFDR_{corr}$	T	Z_e	p_{uncorr}	mm	mm	mm
HC group > FTD group															
				0.662	0.937	174	0.130	0.491	0.889	4.62	3.98	0.000	36	-9	22
	Right	Cerebral white matter	70.6												
	Right	Hippocampus	15.9												
	Right	Fusiform gyrus	4.9												
	Right	Inferior lateral ventricle	3.6												
	Right	Amygdala	3.2												
	Right	Inferior temporal gyrus	1.1												
	Right	Planum polare	0.7												
	Right	Parahippocampal gyrus	0.1												
	Right	Posterior insula	0.1												
				0.299	0.937	335	0.042	0.700	0.889	4.35	3.80	0.00	28	24	-34
	Right	Right temporal pole	24.2												
	Right	Cerebral white matter	0.1												

			67.0	0.847	0.937	109	0.224	0.736	0.889	4.30	3.77	0.00	-52	18	10
	Left	Temporal pole	21.7												
	Left	Inferior frontal gyrus	7.5												
	Left	Frontal opercupum	3.4												
	Left	Anterior insula	0.1												
				0.814	0.937	121	0.201	0.788	0.889	4.23	3.72	0.00	9	-8	-21
	Right	Ventral dorsal cortex	25.1												
	Right	Hippocampus	6.1												
	Right	Parahippocampal gyrus	5.5												
	Right	Amygdala	5.1												
	Right	Brain Stem	3.9												
	Right	Entorhinal area	1.3												
	Right	Optic chiasm	0.3												
				0.772	0.937	136	0.177	0.936	0.889	3.96	3.52	0.000	-42	10	-28
	Left	Temporal pole	67.3												
	Left	Cerebral white matter	28.8												
	Left	Planum polare	0.4												
	Left	Middle and superior temporal gyrus	0.3												
AD group > HC group				0.396	0.377	212	0.025	0.968	0.990	4.33	3.76	0.000	-51	-16	45

Left	Postcentral gyrus	57												
Left	Precentral gyrus	20.5												
Left	Supramarginal gyrus	0.2												
			0.894	0.842	97	0.112	0.997	0.990	4.07	3.57	0.000	14	-26	0
Right	Thalamus	70.7												
Right	Ventral Dorsal Caudate	15.6												
	Brain stem	5.8												
	CSF	1.5												
Right	Parahippocampal gyrus	0.7												
Right	Hippocampus	0.1												
			0.996	0.884	44	0.275	1.000	0.990	3.85	3.42	0.000	-16	22	42
Left	Superior frontal gyrus	19.1												
Left	Middle frontal gyrus	4.5												
Left	Supplementary motor cortex	2.1												
			0.986	0.884	58	0.212	1.000	0.990	3.84	3.42	0.000	-57	42	-8
Left	Middle temporal gyrus	60.4												
Left	Inferior temporal gyrus	2.0												

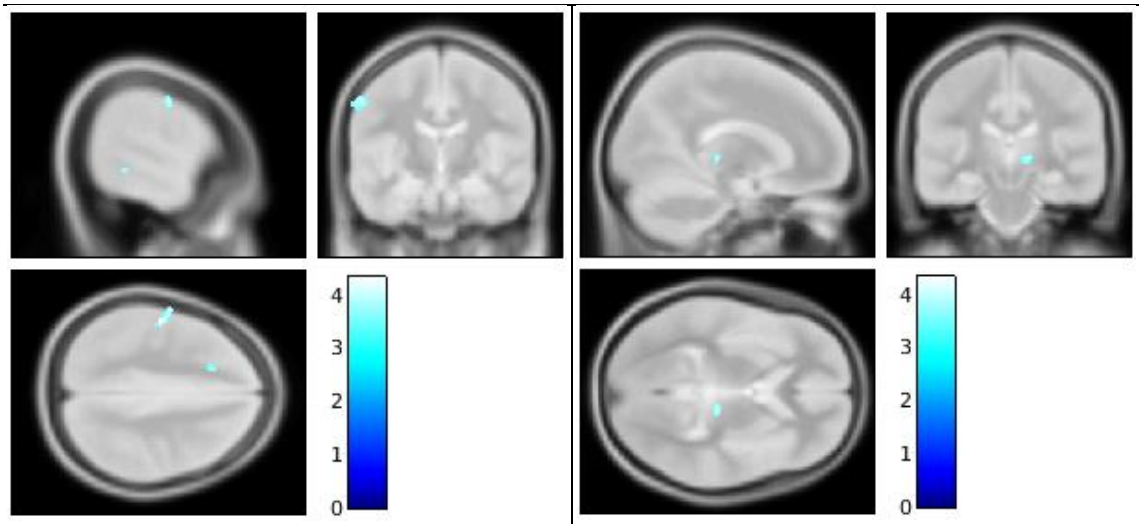
Figure 6.3 Structural brain differences between patients with frontotemporal dementia, patients with Alzheimer's disease and healthy controls

Figure 6.3a. Healthy controls > patients with frontotemporal dementia



p_{uncorr}<0.001 at the peak-level **p_{uncorr}<0.001 at the peak-level**

Figure 6.3b. Healthy controls > patients with Alzheimer's disease



p_{uncorr}<0.001 at the peak-level **p_{uncorr}<0.001 at the peak-level**

6.4.4 Neural correlates of insight into broad and specific objects

As occurred with structural comparisons between the diagnostic groups of this study, correlations between measures of insight and gray matter densities in the FTD group, the AD group, the HC group and the entire cohort did not reach statistical significance when employing $p_{FWEcorr}$<0.05 or p_{FDR}<0.05 either at the cluster-level or the peak-level. Differently, statistically significant differences in gray matter volumes were seen across diagnostic groups when considering p_{uncorr}<0.001 at the peak-level and not at the cluster-level.

6.4.4.1 Insight into health condition

Results suggested certain trends considering a less conservative statistical interpretation, where statistically significant correlations (p_{uncorr}<0.001 at the peak-level) between insight into health condition evaluated through participant-informant level of agreement and different brain areas were found only when considering the HC group only and the entire sample separately in the analyses conducted. Global insight covaried with gray matter volumes in left areas located at the bottom of the frontal lobe, the left temporal pole, and parietal regions bilaterally in HC (p_{uncorr}<0.001 at the peak-level) (Table 6.4, Figure 6.4a). In contrast, changes in this modality of insight correlated with densities of gray matter across the left anterior cingulate, left medial frontal cortex and middle frontal gyrus, left middle and inferior temporal gyrus and the left precentral gyrus when combining FTD patients, AD patients and HC (p_{uncorr}<0.001 at the peak-level) (Table 6.4, Figure 6.4b). There were no statistically significant results with this less conservative approach (p_{uncorr}<0.001) at the cluster-level or at the peak-level for the FTD group or the AD group separately.

Table 6.4 . Neural correlates of insight into health condition

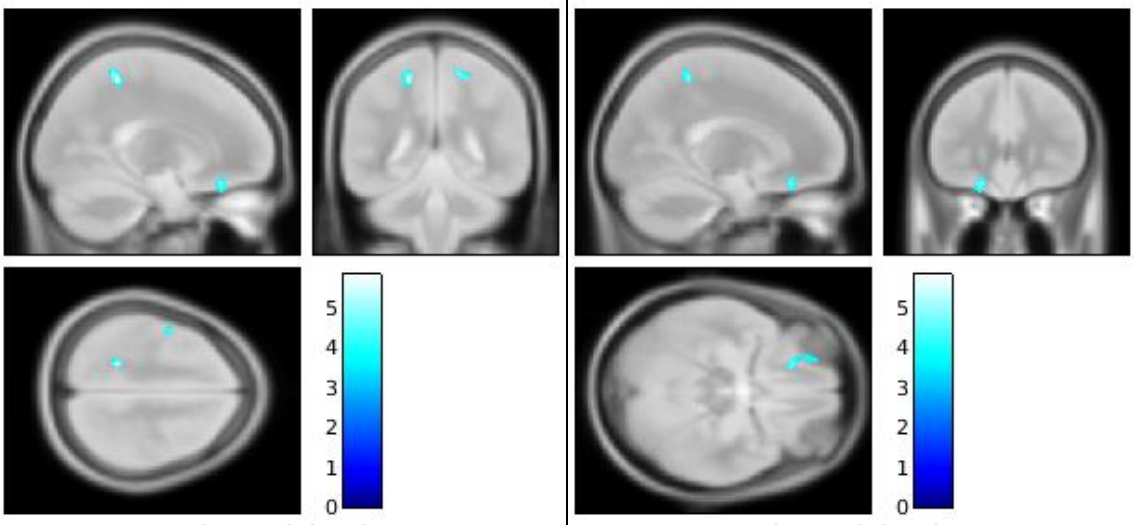
Contrast	Side (hemisphere)	Structure	%	Types of significance									MNI coordinates		
				Cluster-level				Peak-level							
				$pFWE_{corr}$	$qFDR_{corr}$	k_e	p_{uncorr}	$pFWE_{corr}$	$qFDR_{corr}$	T	Z_e	p_{uncorr}	mm	mm	mm
HC group - CBI-R Total DS															
				0.723	0.830	143	0.119	0.202	0.667	5.84	4.41	0.000	20	-44	56
	Left	Cerebral white matter	72.0												
	Left	Superior parietal lobule	10.2												
	Left	Postcentral gyrus	7.4												
	Left	Precuneus	5.6												
	Left	Postcentral gyrus medial segment	4.6												
	Left	Precentral gyrus medial segment	0.2												
				0.826	0.905	113	0.162	0.746	0.709	4.80	3.87	0.000	15	-45	63
	Right	Cerebral white matter	47.9												
	Right	Superior parietal lobule	23.1												
	Right	Precuneus	13.4												
	Right	Postcentral gyrus	9.5												
	Right	Postcentral gyrus medial segment	5.5												

			0.551	0.830	193	0.074	0.783	0.709	4.73	3.83	0.000	-18	32	-20
Left	Medial orbital gyrus	43.7												
Left	Cerebral white matter	35.4												
Left	Posterior orbital gyrus	7.0												
Left	Gyrus rectus	3.5												
Left	Anterior orbital gyrus	0.2												
			0.659	0.830	161	0.100	0.918	0.709	4.45	3.67	0.000	-60	4	-9
Left	Superiortemporal gyrus	21.7												
Left	Temporal pole	13.0												
Left	Cerebral white matter	6.2												
Left	Planum polare	5.3												
Left	Middle temporal gyrus	1.7												
Left	Central operculum	0.3												
Left	Frontal operculum	0.1												
			0.705	0.830	148	0.113	0.941	0.709	4.38	3.62	0.000	-44	-4	58
Left	Precentral gyrus	46.8												
Left	Middle frontal gyrus	4.6												
Left	Cerebral white matter	2.3												
Left	Postcentral gyrus	0.2												

Entire cohort - CBI-R Total DS															
				0.081	0.096	609	0.011	0.198	0.448	4.88	4.27	0.000	-10	28	-12
	Left	Cerebral white matter	65.5												
	Left	Anterior cingulate gyrus	20.9												
	Left	Medial frontal cortex	8.2												
	Left	Gyrus rectus	3.2												
	Left	Medial orbital gyrus	1.6												
	Left	Caudate	0.6												
	Left	Lateral ventricle	0.2												
				0.285	0.191	353	0.043	0.516	0.658	4.40	3.93	0.000	-54	-8	-30
	Left	Middle temporal gyrus	49.6												
	Left	Cerebral white matter	23.4												
	Left	Inferior temporal gyrus	18.2												
				0.597	0.345	200	0.115	0.622	0.658	4.28	3.84	0.000	-45	-3	50
	Left	Precentral gyrus	62.7												
	Left	Cerebral white matter	17.4												
	Left	Middle frontal gyrus	9.1												

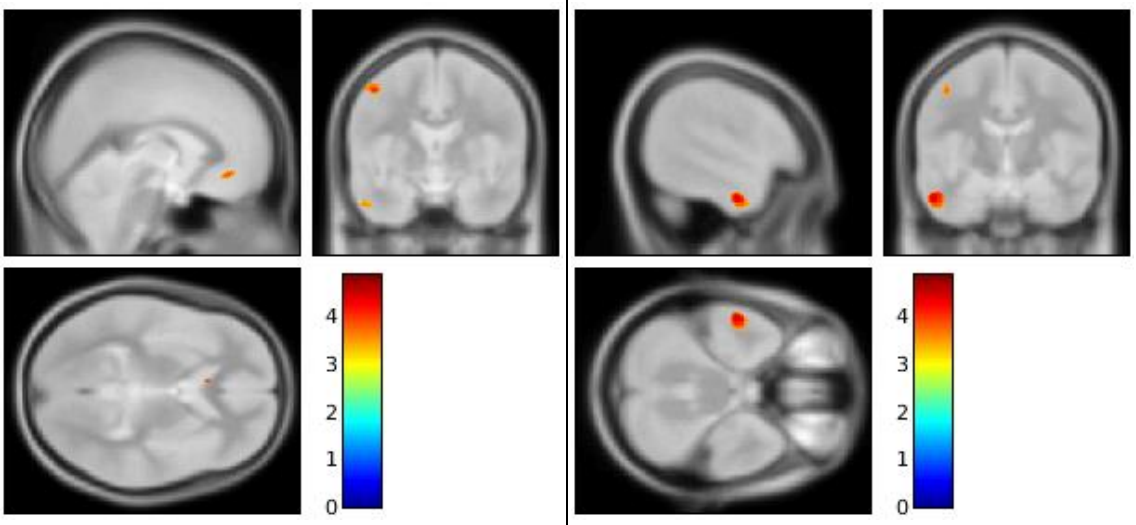
Figure 6.4 Neural correlates of insight into health condition in healthy controls and the entire sample under study (patients with frontotemporal dementia, patients with Alzheimer's disease and healthy controls) according to participant-informant level of agreement

Figure 6.4a. Neural correlates of insight into health condition in healthy controls



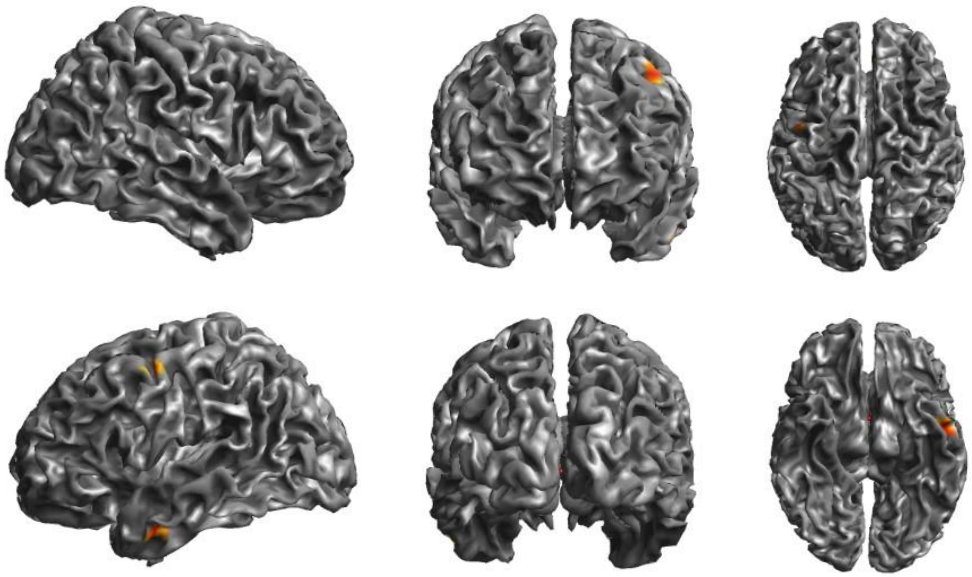
p_{uncorr}<0.001 at the peak-level **p_{uncorr}<0.001 at the peak-level**

Figure 6.4b. Neural correlates of insight into health condition in the entire sample under study (patients with frontotemporal dementia, patients with Alzheimer's disease and healthy controls)



p_{uncorr}<0.001 at the peak-level **p_{uncorr}<0.001 at the peak-level**

Figure 6.4b. Neural correlates of insight into health condition in the entire sample under study (patients with frontotemporal dementia, patients with Alzheimer's disease and healthy controls)



p_{uncorr}<0.001 at the peak-level

6.4.4.2 Neural correlates of insight into memory

In line with the aforementioned outcomes, other trends concerning correlations between insight into memory and brain volumes were found in patients with FTD and HC separately with less lenient statistical interpretation (p_{uncorr}<0.001 at the peak-level). Impaired insight into memory correlated with reductions of gray matter in the left caudate in patients with FTD (p_{uncorr}<0.001 at the peak-level) (Table 6.5, Figure 6.5a)., whereas this form of insight covaried with right occipital areas, left orbital regions and the inferior temporal gyrus bilaterally in HC (p_{uncorr}<0.001 at the peak-level). No statistically significant outcomes with this less lenient approach (p_{uncorr}<0.001) at the cluster-level or the peak-level were observed for the AD group or the entire cohort (FTD, AD and HC combined) separately.

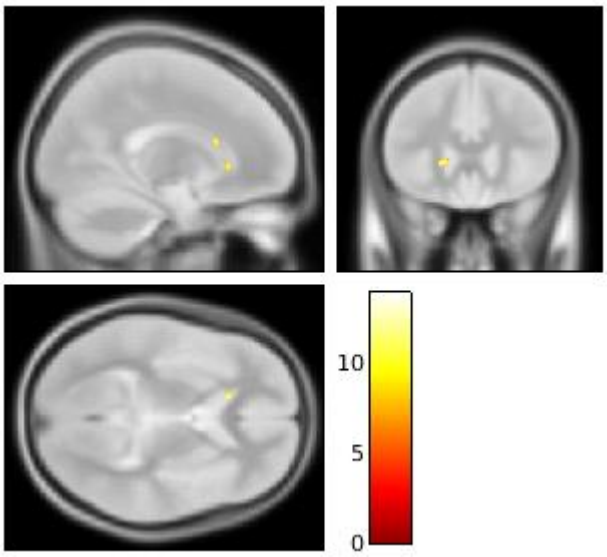
Table 6.5 Neural correlates of insight into memory

Contrast	Side (hemisphere)	Structure	%	Types of significance									MNI coordinates		
				Cluster-level			Peak-level								
				$pFWE_{corr}$	$qFDR_{corr}$	k_e	p_{uncorr}	$pFWE_{corr}$	$qFDR_{corr}$	T	Z_e	p_{uncorr}	mm	mm	mm
FTD -CBI-R Memory DS															
				0.999	0.853	26	0.247	1.00	0.980	13.91	3.78	0.000	-18	16	16
	Left	Cerebral white matter	71.9												
	Left	Caudate	17.8												
		Lateral ventricle	10.3												
HC - CBI-R Memory DS															
				0.995	0.926	64	0.290	0.951	0.995	4.33	3.59	0.000	39	-66	3
	Right	Cerebral white matter	78.9												
	Right	Inferior occipital gyrus	17.9												
	Right	Middle occipital gyrus	2.7												
	Right	Inferior temporal gyrus	0.6												

			0.946	0.926	69	0.272	0.967	0.955	4.26	3.55	0.000	-20	32	-21
Left	Medial orbital gyrus	43.7												
Left	Cerebral white matter	23.0												
Left	Posterior orbital gyrus	10.2												
Left	Gyrus rectus	1.9												
Left	Anterior orbital gyrus	0.6												
			0.950	0.926	67	0.279	0.977	0.955	2.20	3.51	0.000	-46	3	46
Left	Temporal pole	17.2												
	Inferior temporal gyrus	15.5												
	Middle temporal gyrus	2.9												
	Cerebral white matter	0.1												

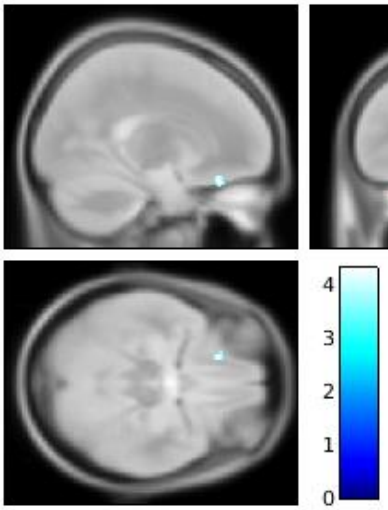
Figure 6.5 Neural correlates of altered insight into memory in patients with frontotemporal dementia and healthy controls according to clinical judgement

Figure 6.5a. Neural correlates of altered insight into memory in patients with frontotemporal dementia

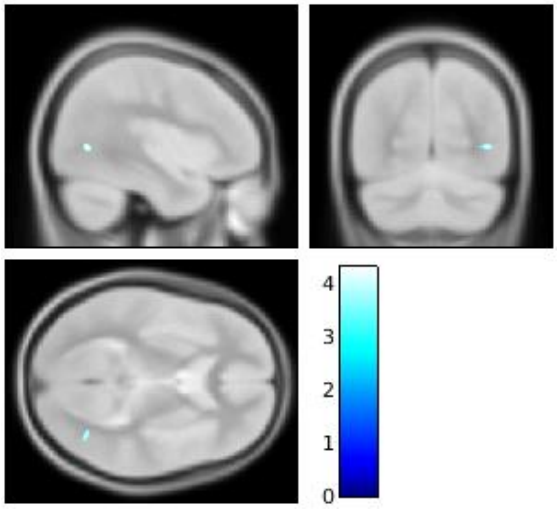


p_{uncorr}<0.001 at the peak-level

Figure 6.5b. Neural correlates of insight into memory in healthy controls



p_{uncorr}<0.001 at the peak-level



p_{uncorr}<0.001 at the peak-level

6.5 DISCUSSION

The present chapter was aimed at exploring the neural correlates of altered insight in FTD in order to determine whether insight into broad (like health condition) and insight into specific objects (such as memory, social cognition and functionality in ADL) are underpinned by the same or different brain areas in this type of dementia. More precisely, it was expected that different forms insight would be underpinned by distinct neuroanatomical correlates in FTD.

The results obtained from the VBM analyses conducted in this study suggest that there is insufficient evidence to support such a hypothesis. This situation is reflected by the fact that it was not possible to identify statistically significant correlations between gray matter densities over different brain regions and insight into health condition (broad object of insight) or insight into memory, social cognition and performances in ADL (specific object of insights) in patients with FTD when employing a conservative level of significance ($p_{FWEcorr}<0.05$ or $p_{FDR}<0.05$).

The outcomes of this investigation differ from those provided by other studies on the matter. For example, neuroanatomical substrates of failures of insight into health condition/diagnosis have been consistently associated with right frontal lobes dysfunction in FTD (McMurtray et al., 2006; Mendez & Shapira, 2005; Miller et al., 1997), which was not corroborated through the results reported here. Conversely, the VBM analysis undertaken in this investigation revealed an absence of significant correlations between reduced gray matter density in right frontal regions (or other brain areas) in FTD employing either strict or more flexible statistical interpretations ($p_{FWEcorr}<0.05$ and $p_{FDR}<0.05$ or $p_{uncorr}<0.001$ respectively at the peak-level or at the cluster-level). It should be noticed that the studies which have stressed the critical role of the right frontal lobe in insight in FTD have used methods that are importantly less robust than VBM (including only visual judgement of PET images) and weak statistical analyses (McMurtray et al., 2006; Mendez & Shapira, 2005; Miller et al., 1997). Concerning self-knowledge of memory problems in FTD, patients' autonoetic consciousness assessed by a feeling-of-knowing task have exhibited hypofunctions across regions adjacent to the anterior medial prefrontal cortex and left dorsolateral prefrontal cortex, along with reduced activations over parietal areas and the posterior cingulate cortex, play a critical role for this metacognitive process (Bastin et al., 2012). Differently, impaired insight into memory in the FTD patients studied here did not show statistically significant correlations with any particular brain are using a conservative statistical interpretation ($p_{FWEcorr}<0.05$ and $p_{FDR}<0.05$ at the peak-level or at the cluster-level), whereas the left caudate was put forward as key for this object of insight according to a less conservative statistical interpretation ($p_{uncorr}<0.001$ at the peak-level) (Figure 6.5a).

Although the hypothesis formulated in this investigation was not confirmed by the results of the VBM analysis conducted, other interesting outcomes across the cohort under study which did survive a less stringent statistical interpretation ($p_{uncorr}<0.001$ at the peak-level) indicate certain suggestive trends that should be discussed. For example, a potential neuroanatomical differentiation for different modalities of insight was observed in the HC group. Global insight correlated with left regions surrounding the bottom of the frontal lobe and the temporal pole, and parietal areas bilaterally in HC ($p_{uncorr}<0.001$ at the peak-level) (Figure 6.4a), whereas insight into memory correlated with right occipital areas ($p_{uncorr}<0.001$ at the peak-level), left

orbital regions and the inferior temporal gyrus bilaterally in the same subjects (Figure 6.5b). Additionally, when further examining the entire cohort under analysis combined, both FTD and AD patients in conjunction with HC revealed correlations between changes of global insight and gray matter over left areas close to the anterior cingulate, medial frontal cortex, middle frontal gyrus, middle and inferior temporal gyrus and the precentral gyrus ($p_{uncorr}<0.001$ at the peak-level) (Figure 6.4b). Such results may partially coincide with those postulated to mediate different self-referential process along cortical midline structures, especially the anterior cingulate and medial prefrontal cortices (Northoff et al., 2006). Concerning the AD group, not having encountered statistically significant results between different types of insight and particular brain areas is conflicting with the diverse literature that supports links between a distorded self-knowledge of diagnosis/symptoms and decreased gray matter over different brain areas in this type of dementia. To mention a few, AD patients tend to show associations between impaired global insight and hypofunction in the right lateral frontal cortex (Harwood et al., 2005), reduced insight into memory deficits and hypoperfusion in the orbital cortex and anterior cingulate (Hanyu et al., 2008) or hippocampal volumes (Tomaszewski Farias et al., 2013) and self-appraisal accuracy measures and medial temporal lobes (Tondelli et al., 2018).

The inconclusive results obtained in this study may be explained by the size of the sample analysed, which reached 10 FTD patients, 8 AD patients and 26 controls. Contrary to expectations, FTD patients and HC did not differ significantly from HC in terms of global insight and insight into memory ($p>0.05$), although AD patients did ($p<0.05$). Furthermore, both FTD and AD patients did not show significantly worse insight into social cognition and performances in ADL in comparison with HC ($p>0.05$). These results are in opposition with what evidence indicates, where FTD patients tend to present consistently with significantly lower levels of insight compared to AD (Hornberger et al., 2014) or HC (Eslinger et al., 2005; O'Keeffe et al., 2007) as it was also revised in ‘Chapter 4: Psychometric properties of insight assessment methods in frontotemporal dementia and associated disorders’ and ‘Chapter 5: Insight, neuropsychological and behavioural characteristics of frontotemporal dementia’ with a slightly larger sample size (15 FTD patients, 12 AD patients and 34 HC). It is thought that the introduction of certain measures of dementia severity alternative to the MoCA as confounding variables across the analyses undertaken could have improved the neuropsychological/insight results and their respective neuroanatomical outcomes. Assessments such as the Clinical Dementia Rating (CDR) (Morris, 1997) or the Frontotemporal Dementia Rating Scale (FRS) (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010), which were not included in this investigation, would have enormously benefited the findings of this investigation.

Another point which attracted attention was the possible influence of the types of groups analysed on the particular neural substrates that may mediate different forms of insight. This

can be appreciated when observing the distinct neuroanatomical outcomes suggested for altered insight into health condition and insight into memory for the HC group only (p_{uncorr}<0.001 at the peak-level) (Table 6.4, Figure 6.4a and Table 6.5, Figure 6.5b correspondingly).

To the best of the author of this thesis' knowledge, there is only one previous study that reported neuroanatomical substrates for different types of insight over the same cohort of patients with AD and FTD (Hornberger et al., 2014). Consequently, this is the second investigation that address this issue reflecting on the need to consider a conceptual and neuroanatomical differentiation across different modalities of insight mediated by different neural correlates. The conceptual specialization of insight considered as a relational clinical phenomenon in dementia, that is to say, its distribution across different targeted objects (either broad like a diagnosis or a global health condition, or specific such as memory, social cognition and functionality in ADL, among other neuropsychologica/behavioural deficits) have been profoundly argued in the literature (Markova & Berrios, 2000, 2001, 2011; Markova, Clare, Wang, Romero, & Kenny, 2005; Markova et al., 2014). Nonetheless, evidence on the neuroanatomical differentiation that underlie distinct modalities of insight in FTD is scarce (Munoz-Neira et al., 2019). In view of this, although the findings of the present investigation are inconclusive, they still have a high scientific value.

The main limitation of this study concerns the size and configuration of the sample under analysis. In relation to its size, the cohort included here can be considered small (44 participants in total), especially bearing in mind that the number of subjects of the FTD group (10 participants). Functional MRI studies have suggested that roughly 25 participants are required to achieve 80% power at the single voxel level for typical activations with thresholds correcting for multiple comparisons (Almutairi, Langley, Crawley, & Thai, 2020; Desmond & Glover, 2002). Equivalently, accurate structural MRI results estimated with FTD patients with approximately 90% of sensitivity and specificity for volumes of interests can be achieved with at least 26 subjects (McMillan et al., 2014). All the same, another study similar to this proposed the right ventromedial prefrontal cortex as the main neuroanatomical correlate for multidomain self-appraisal accuracy in a mixed sample of patients with different neurodegenerative disease (patients with ALS, FTD, AD and corticobasal syndrome) and HC with even smaller numbers than those used here (39 participants in total) (Rosen et al., 2010). Regarding the configuration of the sample included in this study, its FTD group had a mixture of both bvFTD (7 patients) and lvFTD (3 patients), which could have affected the neural outcomes obtained from the VBM analysis conducted. Several studies have been published with clear neuropsychological and behavioural symptomatology for the different forms of FTD, including distinctive diagnostic criteria specific to each one of them FTD (Gorno-Tempini et al., 2011; Hodges, 2013; Piguet,

Hornberger, Mioshi, & Hodges, 2011; Rascovsky et al., 2011). This situation may suggest that there should be specific profiles of impaired insight across the different variant of FTD with their respective different neural correlates. Nevertheless, a considerable heterogeneity has been consistently reported in the etiopathogenetic aspects of the different variants of FTD (Cairns et al., 2007; Giannini et al., 2017; Kovacs, 2016; Mackenzie et al., 2010), which may to a certain extent even permit the utilization of groups with combined pathology in research. Another limitation of this study deals with the levels of significance used to report the results, which only reached uncorrected p values at the peak-level. Although a further discussion on this issue goes beyond the scope of the present thesis, the outcomes reported here should be cautiously interpreted because of this reason and considered as trends.

Future studies should ideally reproduce the methodological aspects of this investigation with a much larger sample triangulating diverse insight assessment methods (such as participant-informant level of agreement and clinical judgement) in order to examine their effects on the results and provide more definitive evidence. An interesting line of research may be pursued by distinguishing different neural correlates of distinct forms insight across the different types of FTD, including for instance bvFTD, progressive non-fluent aphasia (PNFA) and semantic dementia (SD), or frontal AD and traditional AD. In addition, further work needs to be carried out to establish the neural correlates of different modalities of insight in dementia employing functional neuroimaging.

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Chapter 7: GENERAL DISCUSSION

7.1 OVERVIEW

Exploring the neuroanatomical underpinnings of impaired insight in frontotemporal dementia (FTD) poses multiple theoretical and research challenges. Consequently, investigating this scientific problem leads to a wide array of interesting questions, some of which were partially addressed in the present doctoral thesis. A general discussion on the main findings of this research project is presented in this chapter. More precisely, aspects related to the conceptualization of insight as a relational clinical phenomenon, the psychometric properties of different insight assessment methods, and the main neural correlates that may mediate insight, among other issues, are discussed here.

7.2 SCIENTIFIC QUESTION, OVERARCHING GOAL AND MAIN HYPOTHESIS OF THE PRESENT INVESTIGATION

The present thesis intended to offer an answer to the scientific question of what neuroanatomical foundations underpin impaired insight in frontotemporal dementia (FTD). More precisely, the overarching goal of this PhD research project was to explore the neural correlates of altered insight in FTD in order to determine whether distinct forms of insight (insight into broad or specific objects) are underpinned by different or the same brain areas. According to a body of literature that covered studies carried out in patients with Alzheimer's disease (AD) (Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996), FTD (Hornberger et al., 2014), vascular dementia (Bisiach, Vallar, Perani, Papagno, & Berti, 1986; Starkstein, Sabe, Vazquez, et al., 1996), traumatic brain injury (TBI) (Prigatano, 2005; Schmitz, Rowley, Kawahara, & Johnson, 2006) and schizophrenia (SCZ) (Xavier & Vorderstrasse, 2016) just to name a few (see Chapters 1 and 3), it was hypothesized that distinct modalities of insight are differentiated in FTD, that is to say, insight into broad objects like diagnosis or health condition, and insight into specific objects such us memory, social cognition and functionality in activities of daily living (ADL), are distributed across different and separate neural substrates in the brain in FTD. This statement corresponded to the main hypothesis of the present research project and was tested analysing data collected through an extensive battery of insight, neuropsychological and behavioural assessments and 3 Tesla Magnetic Resonance Imaging (MRI) brain scans. Voxel-based morphometry analyses were carried out in a sample of patients with FTD and AD along with cognitively healthy controls (HC) in order to confirm or discard such a hypothesis (see Chapter 6). It should be noticed that no particular neuroanatomical correlates were hypothesized beforehand as underpinnings of either broad

or specific objects of insight in FTD given the considerable diversity in the terminology and methodologies used in the literature to further study the brain-function relationships of this clinical phenomenon in different brain disorders. In addition to the necessity to thoroughly revise this matter through a systematic review (see Chapter 3), such a scenario led also to analyse the conceptualization of insight, the psychometric properties of different insight assessment methods, and insight's structure and its possible neuropsychological and behavioural predictors before exploring its neural substrates directly.

7.3 INSIGHT IN DEMENTIA AND ITS HIGHLY COMPLEX CONCEPTUALIZATION

7.3.1 Diversity in the conceptualization of insight in dementia

The terminology used to characterize subjects' reduced capacity to properly recognise their own diagnosis, global health condition or symptoms has importantly varied in dementia, including concepts such as anosognosia, unawareness or denial, among others (David, Bedford, Wiffen, & Gilleen, 2012; Gilleen, Greenwood, & David, 2010; Markova & Berrios, 2011). The conceptualization chosen in this investigation to address this clinical phenomenon was 'altered or impaired insight'. From this approach, insight is understood as an accurate self-knowledge of a clinical manifestation or object in the presence of a genuine disease, whether this is a diagnosis/global health condition (broad object) or a particular symptom (specific object) such as a neuropsychological impairment or a behavioural disorder (Markova & Berrios, 2011; Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019). The relational nature of the concept is highlighted in this theoretical perspective since there must always be an object to have insight into (it is not possible to have insight into nothing), or in other words, insight can only be understood considering its relation to something , either pathological or non-morbid, as "one cannot have insight without there being something to have insight about" (Markova & Berrios, 2011, p. 426). Pursuing this line of reasoning, altered or impaired insight was understood here as an inaccurate or distorted self-knowledge of a clinical manifestation/object, either broad or specific, within the context of an actual disease (Munoz-Neira et al., 2019). It is highly valuable to notice that this conceptualization for clinical insight was judged as highly appropriate (concerning its clarity, pertinence and sufficiency/adequacy) by a committee of experts who mostly rated it with 8-10 (65-70% of the panel) or 6-7 (15% of the panel) points according to a scale ranging from 0 (poor) to 10 (excellent) (Chapter 4). Also, it is deeply thought that proposing the use of such definition of insight in dementia research and/or clinical settings is a contribution of this doctoral thesis to the field. Likewise, failures of insight in this research project were labelled as altered or impaired insight into health condition (broad object of insight) or altered insight into memory, social cognition or functionality in ADL

(specific objects of insight) bearing in mind that the conceptualization chosen also presents certain advantages compared to others seen in the literature.

7.3.2 Altered or impaired insight in dementia should be the preferred terminology compared to others

Unlike the use of the term anosognosia, considering impaired insight into certain object permits determining what particular type of clinical phenomenon is being analysed. A considerable number of articles seem to have extrapolated anosognosia for particular symptoms in dementia to a global form of unawareness with no explicit distinction of the specific neurological/neuropsychological deficit that are being involved by a distorted self-knowledge, which can be misleading. For example, this problem can be observed when a specific insight deficit is mistaken for broader notions of incapability to identify a diagnosis or a global health condition, as is the case with studies that actually report neural substrates for impaired insight into memory in AD (Shibata, Narumoto, Kitabayashi, Ushijima, & Fukui, 2008; Vogel, Hasselbalch, Gade, Ziebell, & Waldemar, 2005) or insight loss into frontal behaviours in FTD and associated syndromes (Zamboni, Grafman, Krueger, Knutson, & Huey, 2010) instead of neural foundations for a unitary global form of anosognosia.

Although it appears to be that the comprehension of the term anosognosia has recently evolved into considerations that entails “a lack of subjective experience for a wide range of neurological or neuropsychological disturbances” (Prigatano, 2009, p. 606), it should be noticed that its original definition meant something different. Dr Joseph Babinski firstly coined this neologism (lack of knowledge about a disease in Greek language) to account for unawareness of hemiplegia (paralysis of one side of the body) after observing patients who had exhibited left-sided hemiplegia secondary to right hemispheric strokes (Langer & Levine, 2014). Thus, the initial conception of anosognosia entailed an encapsulated sign rather than a flexible approach as the term is being used nowadays (Prigatano, 2009). Taking these details into consideration, it is highly advisable to specify the object in reference when employing the concept anosognosia to avoid clinical misunderstandings in dementia practice.

Discussions addressed in the literature on the employment of the notion of disease/symptoms unawareness exhibited by different patients with brain disorders appear to be inconclusive. On the one hand, all of them tend to treat unawareness as imperception of illness (Zanetti et al., 1999). On the other, this concept has been used interchangeably not only with lack of insight (McGlynn & Schacter, 1989), but also with anosognosia (Mullen, Howard, David, & Levy, 1996). Additionally, it seems to be that unawareness has been commonly understood to mean global insight loss without directly specifying the clinical manifestation/object that is being encompassed by such an unawareness, which prevents health care professionals from

a complete understanding of the clinical picture provoked by the type of impaired insight in reference. Furthermore, using the term ‘awareness’ may be automatically connected with the concept ‘consciousness’, which requires a wholly different debate.

As with different forms of impaired insight, metacognitive disorders also entail failures of self-perception. Metacognition can be broadly defined as a self-reflection on one’s cognition, emotions and behaviours (Frith & Frith, 2012). Furthermore, it has also been suggested that this term can be targeted at several diverse objects as takes place with insight (David et al., 2012). To illustrate this, it can be mentioned that metacognition about memory is currently known as metamemory (Pannu & Kaszniak, 2005). From this point of view, metacognition may even become synonymous with insight; however, metacognition might be more directed towards cognitive domains as implied by its etymology, which conceives it as “cognition about cognitions” (Krueger et al., 2011, p. 741), whereas insight can refer to either diagnosis, general health condition, specific neuropsychological domains or behavioural/neuropsychiatric symptoms (Munoz-Neira et al., 2019). This understanding of insight may coincide with the definitions of attributive metacognition and strategic metacognition given that, even though both types of metacognition are devoted to overseeing cognitive functions, the former comprises a self-knowledge of one’s beliefs/desires and the latter involves monitoring and control of cognitive abilities on ongoing mental activity/plans (David et al., 2012).

According to psychodynamic theories, denial means negating the presence of an actual disease or deficit as an answer to the intolerable situation that could trigger such a pathological condition (Gainotti, 2018). From this approach, this response is considered as a defence mechanism that appears to protect the integrity of the self from acknowledging an unacceptable heath state that could be devastating (Ecklund-Johnson & Torres, 2005). Refusing the existence of an illness or its symptoms may involve a certain degree of conscious/explicit knowledge of the health issue in reference (Ecklund-Johnson & Torres, 2005), which does not match with how clinical insight has been conceptualized in the present investigation in the face of a genuine disease (Munoz-Neira et al., 2019). All the same, bearing this consideration in mind, the relation between denial and lack of insight turns into a highly thought-provoking issue from philosophical and psychological points of view; however, elucidating the link between both phenomena requires further investigation and is out of the scope of the present doctoral thesis.

7.4 PSYCHOMETRIC PROPERTIES OF INSIGHT ASSESSMENT METHODS IN DEMENTIA

7.4.1 Participant-informant level of agreement presents good psychometric properties

Participant-informant level of agreement proved to have highly acceptable psychometric properties (validity and reliability) in accordance with the analyses conducted in this research project (see Chapter 4). These findings support one of the hypotheses formulated earlier in this doctoral thesis (H_2 in Chapter 1). Its content-related validity was considered excellent as an entire impartial panel of experts on dementia care agreed that this insight approach is adequate, clear and sufficient assessments for the assessment of clinical insight in dementia as conceptualized here. Its construct-related validity (convergent validity) was respectable in these types of evaluations for insight. A significant positive correlation (Spearman's correlation coefficient of ~0.3, $p<0.05$) was found in this research project between the total participant-informant discrepancy scores obtained from the Cambridge Behavioural Inventory - Revised (CBI-R) (Wear et al., 2008) and from the Insight Questionnaire (Hornberger et al., 2014) in both patients and the entire sample (Figure 4.3). Also, levels of insight into health condition, memory, social cognition and performances in ADL according to participant-informant level of agreement (discrepancy scores taken from the CBI-R) exhibited significant negative correlations with the scores of their corresponding modalities of impaired insight measured by clinical judgement according to the Clinical Insight Rating Scale CIRS (Lichtenberg, 2010; Ott & Fogel, 1992) (Spearman's correlation coefficients ranging between -0.3 and -0.46, $p<0.05$) (Figure 4.3). Divergent validity was considerably less solid for this insight assessment given its significant correlations found with other measures of cognition and neuropsychiatric symptoms ($p<0.05$). Good criterion-related validity (discriminability) was also observed in participant-informant level of agreement as indicated by their capacity to discriminate between patients with bvFTD, lvFTD, AD, MND/ALS and HC (Table 4.2). Lastly, this insight assessment method showed excellent indexes of reliability with Cronbach's alphas larger than 0.8 in patients and the entire sample separately. These results are considered as a highly relevant contribution since the publication of robust indicators of validity and reliability for insight assessment methods appeared to have been neglected in the literature.

7.4.2 Clinical judgment may also be an insight assessment method with acceptable psychometric properties

Clinical judgement assessed through the CIRS (see Chapter 4) also presented adequate psychometric properties; however, this statement should be taken cautiously, as the author of

this PhD thesis was not blind to the diagnoses of the patients enrolled in this research project when completing this evaluation. All the same, it is worth noticing that roughly 80% of an impartial committee of experts on dementia care agreed on accepting that clinical judgment is sufficient to assess dementia patients' insight, which supports the existence of a hight content-related validity in this insight assessment method. Construct- (Figures 4.3 and 4.4) and criterion-related evidence of validity (Table 4.2) as well as reliability for this insight approach were similar as those observed in participant-level of agreement.

7.4.3 Self-appraisal accuracy is more suitable for the assessment of different forms of metacognition

Psychometric properties of self-appraisal accuracy (see Chapter 4) are respectable in according to certain findings of this investigation. In relation to its content-related validity, only 60% of a committee of experts on dementia agreed that self-appraisal accuracy assessed through the Insight Task (Rosen et al., 2010; Williamson et al., 2010) is an appropriate measure of insight understood as a relational concept focused on broad or specific objects. This assessment method seems to be more compatible with and useful for the definition of metacognition, which refers to those reflections that a person can have on their own cognitive status/activity (David et al., 2012). As a consequence, while self-appraisal accuracy has a weaker content-related validity for the evaluation of clinical insight (compared with that reported for participant-informant level of agreement and clinical judgement), this assessment approach might have an acceptable content-related validity to measure metacognition. Regarding construct-related validity (convergent validity), self-appraisal accuracy into health condition, memory, social cognition and executive functions did not correlate significantly ($p>0.05$) in patients and the entire sample with their paired measures of participant-informant level of agreement (which may suggest proper divergent validity for this measure) (Figure 4.3), even though such types of self-appraisal accuracy did correlate significantly ($p<0.05$) with their paired objects measured through clinical judgement in patients (Figure 4.3). Self-appraisal accuracy exhibited a good criterion-related validity as indicated by its proper discriminatory capacity to significantly differentiate ($p<0.05$) across different diagnostic groups and HC (Table 4.2). Additionally, external reliability for self-accuracy into global cognitive function, memory and executive function was acceptable according to test-retest reliability (intraclass correlation coefficients -average measures higher than 0.6 in patients and the entire cohort) (see Chapter 4). To the best of the author of this thesis's knowledge, explicit indicators of validity and reliability for the Insight Task has not been reported in the literature of disease/symptoms awareness in dementia, therefore, the analysis of this issue is a contribution of the present doctoral thesis.

7.5 CLINICAL INSIGHT IN DEMENTIA IS RATHER A FRACTIONATED CONCEPT, NOT A UNITARY TERM

7.5.1 Unitary versus fractionated configuration of insight in dementia

Everyday clinical practice in dementia reveals that dementia syndromes can present with lack of insight into certain problems but not others. A patient with AD can exhibit clear insight into their diagnosis but not necessarily into their possible memory problems, or vice versa. A similar situation can occur in a patient with FTD, who might express of their memory problems but unaware of their behavioural disorders or specific diagnosis. Accordingly, evidence indicates that insight into cognitive functions and insight into behavioural disorders are dissociated in patients with AD (Starkstein, Sabe, Chemerinski, et al., 1996). Similarly, different modalities of insight, namely overall insight or insight into diagnosis/treatment (broad objects), or insight into social cognition, motivation, and language (specific objects) have been broken down in patients with FTD and AD with FTD have shown (Hornberger et al., 2014). Thus, research on this issue suggests that insight as a clinical phenomenon has a fractionated structure, which contradicts its conception as a unified term.

As in previous studies carried out in patients with AD (Starkstein, Sabe, Chemerinski, et al., 1996; Valera-Bermejo, De Marco, Mitolo, McGeown, & Venneri, 2020) and FTD (Banks & Weintraub, 2009), statistical evidence was found which partially corroborates the fragmentation of insight as clinical phenomenon spread across different objects (see Chapter 5). Thus, employing participant-informant level of agreement, this investigation reported dissociations among different modalities of insight. Once all the respective scores were homogenized, these differences were clearly observed in the resulting shapes of the histograms of insight into global cognition, memory, social cognition and functionality in ADL plotted onto the same axes across different charts for groups of patients with FTD only, AD only, HC only and the entire sample (Figure 5.3). Complementary, statistically significant differences were found between means of insight into significant differences were encountered between insight into health condition and insight into social cognition ($p<0.05$) in AD, as well as insight into health condition and insight into memory, and insight into health condition and insight into social cognition in the entire sample ($p<0.05$) (Figure 5.3).

7.5.2 Profiles of insight levels in patients with frontotemporal dementia and Alzheimer's disease

It was not possible to figure out whether bvFTD patients had a genuine significantly greater impaired insight than lvFTD patients in different forms of insight in the sample under study, although certain significant differences between them were seen employing nonparametric

comparisons ($p<0.05$) (Table 4.2 and Figure 4.5) (see Chapter 4). Consequently, there was no sufficient evidence to confirm another hypothesis of the present PhD research project (H_3 in Chapter 1). Unexpectedly, levels of insight into health condition and social cognition did not significantly differ between FTD and AD patients, FTD patients and HC or AD patients and HC ($p>0.05$) (Table 5.2 and Figure 5.2) (see Chapter 5). These outcomes are not in accordance with studies which have reported a milder decline in insight (Hornberger et al., 2014) and metacognitive abilities (Eslinger et al., 2005) in AD patients in comparison with FTD patients. In contrast, compared to HC, insight into functionality in ADL was significantly impaired in FTD, whereas insight into memory was significantly reduced in AD ($p<0.05$). From a qualitative perspective, all the FTD patients tested did have lower levels of insight into different objects than those observed in AD patients.

7.5.3 Neuropsychological and neuropsychiatric predictors of insight in patients with dementia

Results from the data analysed did not permit to fit any robust model to identify neuropsychological or neuropsychiatric/behavioural predictors of insight in the sample studied here. Unfortunately, the assumptions for multiple linear regressions were not met by the models generated (mainly because of a lack of normality of residuals and homoscedasticity) (see Chapter 5). These findings should not be judged as conclusive given the close connections that other investigations have reported between insight and memory (Maria Donata Orfei et al., 2010) and apathy or frontal behaviours (Spalletta, Girardi, Caltagirone, & Orfei, 2012; Vogel et al., 2005) in MCI and AD, language problems in lvFTD (Savage, Piguet, & Hodges, 2015) and executive functions in FTD (Eslinger et al., 2005)

7.5.4 Impact of dementia patients' impaired insight on caregiver burden

Different from other studies where FTD patients' carers had a considerably greater burden compared to that observed in AD or Creutzfeld-Jacob disease (Uflacker, Edmondson, Onyike, & Appleby, 2016), non-statistically significant differences were found between the caregiver burden associated to patients with FTD and AD (Table 5.3). Predictors of caregiver burden in AD or FTD patients considering different modalities of insight, neuropsychological domains or neuropsychiatric/behavioural symptoms were not encountered with the multiple linear regressions undertaken as they also failed to meet the assumptions for linear regressions.

7.6 NEURAL CORRELATES OF ALTERED INSIGHT IN FRONTOTEMPORAL DEMENTIA

7.6.1 Fractionating insight into broad and specific objects may facilitate the exploration of its neural correlates

Despite the fact that lack of insight is a prominent symptom in FTD (Neary et al., 1998; The Lund and Manchester Groups, 1994), especially in its behavioural variant (bvFTD) (Rascovsky et al., 2011), the study of its neuroanatomical foundations in this disease is underexplored (Hornberger et al., 2014). The high complexity of the clinical pictures associated with FTD clearly challenges its timely detection and appropriate diagnosis. Exploring the neural correlates of altered insight in FTD is both clinically and theoretically relevant due to the potential contributions that this scientific problem can make to the understanding of the disease and to the identification. At the same time, it can also contribute to the finding of neuroimaging biomarkers for a symptom that is prominent in FTD and critical in the diagnosis of bvFTD (Munoz-Neira et al., 2019). A greater understanding of the neuroanatomical underpinnings of insight may aid both the prognosis and progression of the disease.

The high complexity involved in proposing a precise definition for altered insight can probably account for the wide array of terms employed by diverse authors to refer to this clinical phenomenon in dementia (Markova & Berrios, 2011, 2014; Markova, Clare, Wang, Romero, & Kenny, 2005). This considerable variability coincides with the broad selection of methods employed to assess this clinical phenomenon, which ranges from patients versus informants discrepancy scores to clinical judgments, among others (Alexander, Martyr, Savage, Morris, & Clare, 2020; Clare, Markova, Verhey, & Kenny, 2005). At the same time, multiple brain imaging techniques, including structural and functional neuroimaging, have been incorporated in the study of this symptom in dementia (Munoz-Neira et al., 2019; Zamboni & Wilcock, 2011). Altogether, this scenario may have hampered the appropriate examination of the neuroanatomical substrates of altered insight in dementia. As previously discussed elsewhere (Markova & Berrios, 2000) and argued here (see Chapter 3), relating insight to a specified object, either broad or particular, aids the search for its neural correlates in different neurodegenerative and neuropsychiatric conditions.

7.6.2 Neural correlates of altered insight into broad and specific objects in frontotemporal dementia

The VBM analysis conducted (see Chapter 6) revealed that it was not possible to identify statistically significant correlations between gray matter densities over different brain regions and insight into health condition (broad object of insight) or insight into memory, social cognition and performances in ADL (specific object of insights) in FTD patients using conservative level of significance ($p_{FWEcorr}<0.05$ or $p_{FDR}<0.05$). Likewise, there was insufficient evidence to support a neuroanatomical differentiation for distinct insight modalities in FTD,

which leads to reject the main hypothesis of the present investigation (H_1 in Chapter 1). These findings are contradictory to others which have stressed the relevance of the right frontal lobe in insight in FTD employing a less solid method than VBM (only visual judgement of PET images) (McMurtray, Chen, et al., 2006; Mendez & Shapira, 2005; Miller et al., 1997). Additionally, a form of metamemory has been associated with the anterior medial prefrontal cortex and left dorsolateral prefrontal cortex, parietal areas and the posterior cingulate cortex in FTD (Bastin et al., 2012).

The systematic review conducted in this investigation (see Chapter 3) questioned whether insight assessment methods may influence the results yielded by the pertinent analyses conducted (Munoz-Neira et al., 2019). It was not possible to observe whether the use of different insight assessment would yield distinct neural outcomes since only participant-informant level of agreement was considered as a measure of insight for the VBM analysis. Congruently, one of the hypothesis formulated for this PhD research project was not tested investigation (H_4 in Chapter 1).

7.6.3 Neural correlates of insight in a combined sample of patients with frontotemporal dementia, Alzheimer's disease and healthy controls

Outcomes obtained from the VBM analysis (see Chapter 6) did not show statistically significant correlations between volumes gray matter and different forms of insight employing a stringent statistical approach ($p_{FWEcorr}<0.05$ or $p_{FDR}<0.05$). Nonetheless, a suggestive trend was observed combining both FTD and AD patients as well as HC. Levels of global insight and gray matter densities correlated significantly with a less conservative statistical approach ($p_{uncorr}<0.001$ at the peak-level) in regions surrounding over left close to the anterior cingulate, medial frontal cortex, middle frontal gyrus, middle and inferior temporal gyrus and the precentral gyrus (Figure 6.4b). These results may be in accordance to a certain extent with those brain regions that are though to underpin different self-referential process along cortical midline structures, especially the anterior cingulate and medial prefrontal cortices (Northoff et al., 2006).

7.7 LIMITATIONS OF THE PRESENT PHD RESEARCH PROJECT

The main limitations of this investigation were previously discussed in every chapter. In brief, the most salient was the small size and configuration of the sample recruited (15 FTD, 12 AD 6 MND/ALS and 34 HC, which turned into 10 FTD, 8 AD and 26 HC for the brain imaging analyses). Unfortunately, the COVID-19 contingency made the author of this doctoral thesis stop the recruitment of participants in March 2020 (see COVID-19 Statement). Having a specialist blind to the diagnoses of the recruited volunteers to complete the measure of clinical

insight would have been ideal for Chapter 4. In Chapter 5, the use multiple linear regressions to find predictors of insight could have been replaced by alternative procedures such as a factor analysis or a principal component analysis. Furthermore, all the analyses conducted in Chapters 4, 5 and 6 would have benefited from the inclusion of a measure of dementia severity such as the Clinical Dementia Rating (CDR) (Morris, 1997) or the Frontotemporal Dementia Rating Scale (FRS) (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010). Concerning the size of the sample for the VBM analysis in Chapter 6, functional (Desmond & Glover, 2002) and structural (McMillan et al., 2014) MRI studies have indicated that roughly 25 participants at least are required to achieve robust results carrying out analyses at voxel or volumetric levels.

7.8 COMPLEMENTARY REFLECTIONS RELATED TO THE CONCEPTUALIZATION OF INSIGHT IN DEMENTIA

7.8.1 Emergence of self-concepts in human beings' early life and their potential relationships with the self and clinical insight

There seems to be a clear association between human beings' self-perceptions and insight understood from a clinical perspective. Self-perceptions correspond to mental representations of one's own characteristics (Asendorpf, 2002), which should be essential conditions for the identification of one's own diagnosis/symptoms entailed by clinical insight (Landi, Marazziti, Rutigliano, & Dell'Osso, 2016). This reasoning leads inevitably to the necessity to examine the notion of 'self-concept' understood as how one perceives oneself and a part of the 'self' (Sebastian, Burnett, & Blakemore, 2008). At the same time, such considerations transport the argumentation back to Willian James's contributions, who was one of founders of Psychology as a scientific discipline (Tagini & Raffone, 2010). With the purpose of determining certain facets of the self, James discussed a distinction between the conceptions of 'I' and 'me' almost 130 years ago in 1892. According to this author, while 'I' implies a subjective sense of self as knower, thinker and actor, 'me' entails an objective sense of self as creator of self-perceptions, self-images and/or self-concepts with characteristics distinguishable from others' traits (Harter, 2008; Howe, 2004).

It is thought that human beings' capacity to build self-concepts or self-images into their minds may originate in early life when 15- to 24-month-old infants become capable of recognising themselves (Amsterdam, 1972; Anderson, 1984; Tagini & Raffone, 2010), or in other words, once 'self-awareness' emerges by the age of two years (Morrison & Reiss, 2018). This type of self-recognition is preceded by the development of multiple complex behaviours, such as an increase of attention and responsiveness to diverse stimuli since the age of 3 months, and

the manifestation of the ability to interact with reflections when facing a mirror since the age of 8 months, among others (Howe, 2004; Tagini & Raffone, 2010). Later, generally at the age of 22 months, infants tend to be already capable of identifying themselves in pictures, videos and/or mirrors (Howe, 2004; Tagini & Raffone, 2010).

The capacity of self-recognition acquired by the second year of life unfolds parallelly with the prototypical development of self-evaluation, empathy, altruism, and synchronic imitation, as well as the understanding of object permanence, playing, and the important advent of language, all of them also achieved at this age approximately (Howe, 2004). It should be noticed that mirror self-recognition has been used in developmental and evolutionary sciences as an indicator of emerging self-awareness, which is a behaviour observed in only few species, including, in conjunction with human beings, great apes, dolphins, elephants and magpies (Morrison & Reiss, 2018). In the case of human beings, it has been argued that it is precisely this critical moment represented by the consolidation of self-recognition when infants may manage to configure their first version of a 'me' as defined by James (Asendorpf, 2002; Howe, 2004).

7.8.2 Development of the ability to construct self-concepts and its relationships with the self and clinical insight across the lifespan

It should be reasonable to argue that the capability to construct self-concepts ought to be crucial for the configuration of one's self and a requirement to have insight into diagnosis/symptoms when having an actual disease. The capacity to build a self-concept appears to begin to develop in early life and continue to evolve across the entire lifespan with increasing levels of complexity. Likewise the 'I' and the 'me' aspects of the self seem to be forged by different variables as the infant grows up and turns into a child (since the age of 4 years approximately), an adolescent (since the age of roughly 10 years), and then into an adult (since the age of 18 years onwards) (Côté, 2009; Harter, 2008). Such variables encompass the influence of normative changes, early socialisation, and caregiver changes according to neo-Piagetians, psychodinamic and contemporary attachment theorists respectively (Côté, 2009; Harter, 2008). Additionally, authors from social and personality traditions have put forward the effect of those psychosocial factors which accentuate differences in individuals' self-perceptions, especially in adults (Côté, 2009; Harter, 2008). Altogether, it is highly likely that self-concepts, the self and insight evolve whilst a human being interact with significant others and their environments throughout the course of their lives.

7.8.3 Self and clinical insight

A useful approximation to comprehend the notion of self requires to relate it to individuality, singularity, personhood (Damasio, 2003a) or sense of personal identity (Mograbi, Brown, & Morris, 2009). Once such associations have been made, it is important then to clarify what is meant by being conscious or consciousness, which may be understood as a persons' continuous subjective world (Schacter, 1989) that configures the domain where the self is settled (Damasio, 2003a). Bearing in mind these considerations, the self refers to a "stable representation of individual continuity which serves as a mental reference for the organism within the conscious mind" (Damasio, 2003a, p. 254). Also, a much simpler definition of the self encompasses a structured body of personal representations (or mental constructs), personality traits and attitudes that guide a person's inner world, behaviour and a particular style to establish personal interactions with oneself and social interactions with others (Orfei, Robinson, Bria, Caltagirone, & Spalletta, 2008).

A consensual view of the self embraces then a person's identity together with the sense of one's own being and the entire system of qualities which differentiate their mind from others' (Damasio, 2003b). It also considers self-concepts as crucial elements that form the main structure of the self (Sebastian et al., 2008). Likewise, it can be theorized that clinical insight may operate as a mechanism that feeds self-concepts across the lifespan, and consequently, the self. In such a case, although the interactions among these elements can vary in a person's life trajectory making them change, certain aspects of the self remain stable over time. In fact, despite the extremely difficult endeavour involved in the conceptualization of self, most researchers working in the field agree that the notion of self corresponds to "the individuality and continuity of a living organism" (Damasio, 2003b, p. 227). Furthermore, when considering the implications that the definition of self may have, it turns out possible to state that this construct may be certainly shaped by the levels of insight one has into personal abilities and disabilities. Congruently, exploring the neurobiological bases of insight can also pave the way to the study of the underlying neural mechanisms of the self itself (Mograbi et al., 2009).

Bearing in mind that both clinical insight and the self require perceptions of one's own conditions, the apparently tight connection that exists between both concepts becomes much clearer, especially when the self is broken down into its experiential (autobiographical self) and body (core self) aspects. On the one hand, the autobiographical self arises when retrieving memories and historical events of one's life event, including thus personal information and personality traits (date and place of birth, memories of the University graduation ceremony, modesty, diligence, solidarity, etc.) (Araujo, Kaplan, Damasio, & Damasio, 2015). On the other, the core self creates a record on one's ongoing body status, which may incorporate

interoceptive or exteroceptive body changes (hunger, thirst, pressure exerted on superior or inferior limbs, etc.) (Araujo et al., 2015).

Another point of agreement among authors that is worth noting may be the consideration of the self as a cognitive product as well as a social construction (Côté, 2009; Harter, 2008; Howe, 2004). In terms of a cognitive product, several brain and high order intellectual/cognitive processes need to be mature enough to sustain a theory of self at distinct levels (Harter, 2008), which can be reached in different stages throughout the lifespan. These foundations will serve not only to organise reality, but also to configure an inner world of subjective experiences, including self-perceptions (Harter, 2008). As a social construction, individuals' self-representations are shaped in their lifetimes by socialisation with peers, friends, parents and family members, carers, teachers, significant others, and the symbols of their own culture, particularly during the childhood (Harter, 2008; Howe, 2004).

7.8.4 Memory may play a key role in clinical insight in patients with dementia

The key role of episodic memory in clinical insight has been already pointed out in patients with MCI and AD (M. D. Orfei et al., 2010). Other studies have also argued that memory is critical for the construction of self-perceptions/self-images proposing models like the Self-Memory System (SMS) (Conway, 2005). Complementary, investigations carried out with AD patients have also stressed that episodic memory is the cornerstone of insight, where lack of disease awareness may be explained by a 'petrified self' constructed by constant failures when processing/updating key personal information (Lenzoni, Morris, & Mograbi, 2020; Mograbi et al., 2009). All the same, a critical review of the literature on the possible interactions existing between episodic memory and the self in patients with AD and FTD has indicated that memory decline should not necessarily led to a complete disintegration of the self. Likewise, the impact of the characteristic memory loss observed in different forms of dementia on the self may be attenuated by helping patients re-experience significant autobiographical events that could provide them with a sense of continuity to improve then their wellbeing (Strikwerda-Brown, Grilli, Andrews-Hanna, & Irish, 2019).

7.8.5 The prompt identification of frontotemporal dementia is highly challenging and impaired insight may affect its diagnostic process

Although FTD has been considered as a rare brain disorder (Gupta, Fiertag, & Warner, 2009), it is the third cause of dementia after vascular dementia (VD) and AD correspondingly in both young-onset dementia (YOD) -subjects younger than 65 years of age- and late-onset dementia (LOD) -subjects aged 65 or older- (Harvey, Skelton-Robinson, & Rossor, 2003;

McMurtray, Clark, Christine, & Mendez, 2006; Ratnavalli, Brayne, Dawson, & Hodges, 2002). Approximated figures indicate that FTD represents ~10.2% and ~2.7% of all dementia cases within YOD and LOD groups respectively, where males have a higher risk of being diagnosed with this disease compared to females (52.5% versus 47.5%) (Hogan et al., 2016). This scenario turns FTD into a highly salient brain disorder which should be bear in mind in clinical practice for a timely diagnosis when emerging early signs could suggest its presence. Nonetheless, early detection of FTD is challenging due to several circumstances. Symptoms exhibited by patients with FTD may be mistaken by the characteristic clinical manifestations of frontal AD (Johnson, Head, Kim, Starr, & Cotman, 1999; Padovani et al., 2013), the typical presentation of AD, VD, dementia with Lewy bodies (DLB) (Brzezicki, Kobetic, Neumann, & Pennington, 2019) and/or ALS (Strong et al., 2017). Furthermore, FTD can even resemble psychiatric disorders like SCZ or a bipolar disorder (BD) (Galimberti, Dell'Osso, Altamura, & Scarpini, 2015). In addition, the overall time from symptoms onset to diagnosis of FTD is roughly 6.1 years, which exceeds roughly twice that of AD (3.6 years) and VD (3.1 years) (van Vliet et al., 2013). These factors can certainly complicate the identification and diagnostic process of FTD. In fact, evidence suggest that an accurate diagnosis of FTD can take up to 5 clinical appointments over 2.5 years, whereby the diagnosis can be modified 6-8 times approximately (Brzezicki et al., 2019). Such an adverse scene may lead to wonder whether there is a relationship between the pathognomonic lack of insight observed in FTD (Neary et al., 1998; Rascovsky et al., 2011; Wedderburn et al., 2008; Wilson, Sytsma, Barnes, & Boyle, 2016) and the difficulties and delays observed in its the timely detection and diagnosis. Unfortunately, this enquiry was not examined in this research project in spite of its potential great scientific value. Nevertheless, considering that a fairly simple definition of insight from a clinical perspective refers to a capability to identify and report symptoms (Zanetti et al., 1999), failures of insight in dementia should evidently affect the diagnostic procedures required by the high clinical complexity of FTD.

The worrisome everyday life consequences that can be triggered by insight loss in dementia justifies the neuroanatomical and conceptual scrutiny of this symptom and turns it into a highly relevant clinical phenomenon to be further investigated in FTD. Impaired insight can be hard to handle by patients, their relatives or patients' carers, and health care professionals probably because of its associations with low mood, loss of functionality in ADL, decreased quality of life and high caregiver burden (Aalten, Van Valen, Clare, Kenny, & Verhey, 2005). Moreover, insight loss can interfere the timely detection of cognitive impairment and dementia (Iliffe et al., 2005; Koch, Iliffe, & project, 2010) and delay its diagnosis (van Vliet et al., 2013). Patients with FTD can perform risky behaviours such as cooking, doing the shopping, driving or others when they are no longer autonomous. These unsafe behaviours are likely to occur due to the

lack of insight that characterises the disease (Neary et al., 1998; Rascovsky et al., 2011; Wedderburn et al., 2008; Wilson et al., 2016), which implies an incapability to judge one's own capabilities and a consequent impaired ability to recognise and report symptoms (Markova et al., 2005; McGlynn & Schacter, 1989; Mullen et al., 1996). At the same time, the lack of insight shown by patients with FTD can elicit refusal of clinical examinations, poor adherence to treatment, untimely follow-ups and late presentations to clinical services. Altogether, these problematic situations associated with impaired insight in dementia and especially in FTD were not directly studied in the present research project and certainly require further investigation.

7.9 FUTURE DIRECTIONS

The systematic review conducted in this project may be turned into a meta-analysis employing the software GingerALE (GingerALE, 2021) which would be of great scientific value. Concerning all the statistical analyses undertaken, future studies similar to this investigation should ideally reproduce its methodology with a much larger sample to reach conclusive results. This challenging objective might be addressed using The Alzheimer's Disease Neuroimaging Initiative (ADNI) (ADNI, 2021), which claims to have neuropsychological data and brain scans collected from at least 150 healthy older adults, 100 early MCI, 150 late MCI and 150 AD in one of its stages (ADNI-2). Participant-informant level of agreement as an index of insight may be assessed here with the self-administered and informant-based versions of the Everyday Cognition (ECog) (Tomaszewski Farias et al., 2008). Other interesting lines of research may be focused on the study of the neuroanatomical underpinnings of different modalities of insight and metacognition in FTD using functional brain imaging analysis. Also, a further examination of the underlying neural mechanisms of overestimation ('polishers') and underestimation ('tarnishers') of capabilities across the different variants of FTD, AD or other brain disorders may be of great interest (Shany-Ur et al., 2014).

7.10 CONCLUSION

Understanding how insight is expressed in dementia in both clinical and research settings is highly challenging due to the elusive nature of the term. Literature argues that insight in dementia is conceptually and neuroanatomically differentiated, although this situation has been concluded employing a considerably high methodological diversity. Conceptualizing insight in dementia as a relational concept is an enormously useful approach to refer to those difficulties experienced by patients to recognize their own diagnosis/symptoms. Likewise, insight can be defined as self-knowledge of broad (diagnosis/health condition) or specific objects (memory or behavioural problems). Participant-informant level of agreement proved to have better psychometric properties (validity and reliability) to assess insight as conceptualized here than clinical judgment or self-appraisal accuracy. Using participant-

informant level of agreement to evaluate insight into health condition (broad objects) and insight into memory, social cognition and activities of daily living (specific objects), statistically insufficient information was found to support that distinct modalities of insight are underpinned by different neuroanatomical correlates in FTD. Further research is needed to elucidate what brain areas support broad and specific objects of insight not only in FTD, but also in other types of dementias such as AD or other brain disorders. It is thought that the use of such an approach can facilitate the identification of brain imaging markers for impaired insight in dementia, which is scientifically and clinically relevant.

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Chapter 8: APPENDIX

8.1 SUPPLEMENTARY MATERIAL 1

8.1.1 Background on the methodology of data collection

8.1.1.1 Systematic review

8.1.1.1.1 Information tsunami

It is certainly hard to deny that most of researchers tend to face an 'information tsunami' given the progress that science has reached nowadays (Erren, Cullen, & Erren, 2009). This scenario obliges scientists not only to filter irrelevant information (Maier, 2013), but also to consider strategies useful to find out what robust scientific findings entail (Collins & Fauser, 2005). In parallel, information era seems to raise a need for summarised state-of-the-art knowledge and accurate conclusions (Erren et al., 2009), especially provided that "review and synthesis are central to good scientific and clinical practice" (Collins & Fauser, 2005, p. 103).

8.1.1.1.2 Systematic reviews versus narrative reviews

Excluding research of weak scientific bases or out of the required scope when summarizing findings within a context of abundant information of diverse quality poses a challenging task (Erren et al., 2009; Greenhalgh, 1997). Systematic reviews offer an ideal resolution to such a dilemma (Collins & Fauser, 2005; Pae, 2015). Unlike narrative reviews, systematic reviews make use of unbiased, structured, more objective and explicit methods predefining a protocol to critically assess and summarize the literature available on a particular subject (Collins & Fauser, 2005). Narrative reviews instead are more flexible and depend on researchers' subjective decisions to select what type of literature is convenient to analyse (Pautasso, 2013), which can inevitably result in several forms of biases, and therefore, in inaccurate findings (Pae, 2015).

Systematic reviews seek to thoroughly scrutinize scientific databases through the appropriate design of a search strategy. Thus, they can allow researchers to test hypotheses by contrasting the pertinent publications found (Pae, 2015; Pautasso, 2013). Systematic reviews can even take a further step and turn into meta-analyses if statistical analyses are employed to reach conclusions (Greenhalgh, 1997). On the contrary, narrative reviews are intended to integrate and describe common ideas from different sources identified at the convenience of the researcher (Pautasso, 2013). Furthermore, narrative reviews have been criticised for being intuitive, selective and little rigorous to propose good quality scientific information (Pae, 2015); however, there is still wider subjects in health sciences which can be covered by an

unstructured approach with predetermined rules of revision and synthesis (Collins & Fauser, 2005).

8.1.1.1.3 PRISMA statement and PROSPERO

Systematic reviews are the desirable starting point for researchers to obtain a scientifically robust update overview of the field they intend to explore (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). It is also the necessary cornerstone of the design, proposal and implementations of new studies due to its scientific rigor (Collins & Fauser, 2005). In spite of this, it appears to be that scientific journals on health care related matters have mostly tended to publish reviews lacking in transparent methods, clarity on the reported results and evidence critically appraised during roughly the last 30 years (Liberati et al., 2009; Moher et al., 2009). In an effort to tackle this problem, experts on research methods and reviews of scientific literature recently published the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement/protocol with aim of spreading a standardised procedure to conduct both systematic reviews and meta-analysis thoroughly minimizing the risk of bias (Liberati et al., 2009; Moher et al., 2009). It should be noted that health care scientific journals are prioritizing the publication of reviews conducted according to standard methods as those proposed by PRIMA statement (Pae, 2015). Complementary, an international prospective register of systematic reviews (PROSPERO) has been created with the purpose of keeping a record of the systematic reviews being undertaken and preventing researchers from repetitions or redundant targets (Booth et al., 2012).

8.1.1.2 Neuropsychological assessment

8.1.1.2.1 Neuropsychology, clinical neuropsychology and neuropsychological assessments

Neuropsychology is a discipline aimed at exploring the existing relationships between brain, cognitive activity, emotions and behaviour from a perspective based on neurosciences (Lezak, Howieson, Bigler, & Tranel, 2012). Consequently, clinical neuropsychology intends to understand how those domains vary in healthy subjects and people with brain disorders, with a particular focus on the development of procedures for the assessment of neurocognitive and behavioural symptoms as well as non-pharmacological interventions to treat such deficits (Lezak et al., 2012).

In line with the purpose of clinical neuropsychology, neuropsychological assessment is a tool which enables the collection of clinically relevant information through interviews with the patient and their reliable informant, cognitive tests administered to the patient, behavioural self-administered scales completed by the patient, and neuropsychiatric and functional

informant-based questionnaires filled in by their reliable informant (Flores & Munoz-Neira, 2017; Hodges, 2018). Through such a procedure, neuropsychological assessments can yield a systematic description of the consequences of a brain disorder in terms of patients' global cognitive functioning, their attentional abilities, language, episodic memory, visuospatial skills, executive functions, presence of neuropsychiatric symptoms and functional capacity in ADL (Hodges, 2018; Kipps & Hodges, 2005).

8.1.1.2.2 Relevance of neuropsychological assessments in dementia

Several reasons justify the implementation of neuropsychological assessments on patients with cognitive decline and dementia. Tangible evidence of cognitive impairment, which can be detected by neuropsychological assessments, is required for the accurate diagnosis of mild cognitive impairment, which is currently widely recognised as a prodromal stage of dementia syndromes, and different types of dementia according to their diagnostic criteria (Alvarez-Linera & Jimenez-Huete, 2019; Gorno-Tempini et al., 2011; Hort et al., 2010; Lam, Masellis, Freedman, Stuss, & Black, 2013; Petersen, 2016; Rascovsky et al., 2011). Moreover, early stages of dementia typically present with particular patterns of neuropsychological dysfunctions that may suggest a particular neuroanatomical involvement (Hort et al., 2010). For instance, the remarkable episodic memory disorder observed in AD is a widely known sign of hippocampal and temporal medial shrinkage/dysfunction, whereas disinhibition and failures of social cognition in bvFTD is generally accounted for by prefrontal cortex pathology. Such cognitive profiles and/or behavioural disorders can be properly tracked by a thorough neuropsychological assessment (Flores & Munoz-Neira, 2017).

Other further contributions can be attributed to neuropsychological assessments. They can provide relevant clinical information for differential diagnosis and define cognitive profiles of neuropsychological dysfunction or preserved cognitive abilities (Flores & Munoz-Neira, 2017; Hodges, 2018). Neuropsychological assessments can also aid the design of interventions or treatments for neuropsychiatric patients, document neurocognitive changes resulting in brain disorders and assess the impact of cognitive impairment on functional capacity in daily life tasks (Kipps & Hodges, 2005; Lezak et al., 2012).

8.1.1.3 Brain imaging

Brain imaging, also known as neuroimaging, refers to a group of medical techniques used to picture the anatomy or activity of the brain tissue directly or indirectly (Ward, 2015). Broadly speaking, brain imaging can be either structural or functional. Whilst structural brain imaging focuses on measuring the spatial configuration of the different types of brain tissues found in the brain (mainly skull, grey matter, white matter and cerebrospinal fluid), functional brain imaging reflects patterns of functioning of neural networks (Ward, 2015).

8.1.1.3.1 Structural brain imaging

The most popular modalities of structural neuroimaging used in dementia are computed tomography (CT) and magnetic resonance imaging (MRI) (Mortimer, Likeman, & Lewis, 2013). MRI tends to be the preferred alternative chosen by specialists (Alvarez-Linera & Jimenez-Huete, 2019), probably due to its much higher spatial resolution as compared to CT (Ward, 2015). The physics behind the acquisition of these types of brain scans account for such a difference. Whilst CT images are generated by X-rays, MRI scans require the use of massively powerful magnetic fields (Ward, 2015).

MRI is a non-invasive and in vivo structural brain imaging technique which has enormously contributed to the differential diagnosis of dementia (Bhogal et al., 2013; de Souza, Lehericy, Dubois, Stella, & Sarazin, 2012). MRI brain scans can picture the presence of abnormal neuroanatomical structures, for example, showing widespread involvement of different brain areas secondary to multiple strokes in VD, predominant medial temporal atrophies in AD or pronounced frontotemporal shrinkages in FTD (Alvarez-Linera & Jimenez-Huete, 2019; Filippi et al., 2012; Mortimer et al., 2013).

8.1.1.3.1.1 Physics of structural magnetic resonance imaging

Some considerations must be bear in mind to understand the complex physics of MRI. On the one hand, skull, brain tissue (i.e. grey matter and white matter), cerebrospinal fluid, and the other tissues surrounding the brain have different physical properties (Ward, 2015). Human beings, and therefore, all their tissues, are made up by roughly 70% of water at least (Knight, McCann, Kauppinen, & Coulthard, 2016). Water is the main element required to generate brain images through a series of highly complex process. Water molecules have two parts of hydrogen (H+) and one part of oxygen, where nuclei of H+ can act as microscopic magnets that can interact with the magnetic fields emanated by MRI scanners (Jenkinson & Chappell, 2018). On the other hand, MRI scanners are giant coils that can generate 1.5 Tesla (T), 3 T or greater magnetic fields (Knight et al., 2016), where 1.5 T equates to roughly 30,000 times the strength of the magnetic field created by the earth (Ward, 2015). Additionally, MRI scanners have other coils attached to them, which can release or capture radio frequencies. It is exactly those interactions established among the H+ nuclei of the water that forms part of the brain tissue, the extremely powerful magnetic fields generated by MRI scanners, and those radio frequencies released and received also by MRI scanners what will construct later static maps of the physical structure of the brain, i.e. brain images (Jenkinson & Chappell, 2018; Ward, 2015).

The process involved in the creation of brain images requires several steps. Firstly, the subject is placed into MRI scanner's main coil. Then, the magnetic field generated by the MRI scanner

forces the alignment of brain's nuclei of H+. This situation configures a 'relaxation state' in which nuclei of H+ are mostly positioned pointing towards the same direction that the magnetic field generated by the MRI scanner does (although few of them can also be placed pointing in the opposite direction across the same axis) (Jenkinson & Chappell, 2018; Ward, 2015). Later, MRI scanner's gradient coils release short pulses of radio frequencies in different directions that make nuclei of H+ resonate. Once these external pulses are stopped, nuclei of H+ return to their 'relaxation state' releasing energy. MRI scanner's receiver coil (most of the times the head coil) capture and measure such amounts of energy turning them into signals. Finally, these signals undergo a Fourier transformation that leads to the construction of multiple brain images (Jenkinson & Chappell, 2018; Ward, 2015).

8.1.1.3.1.2 Voxel based morphometry

Voxel based morphometry (VBM) is a brain imaging technique useful to examine differences in local gray matter densities between diagnostic groups (Jenkinson & Chappell, 2018). VBM can also be employed to find regions in the brain where amounts of local gray matter correlate to other parameters of interest such as scores obtained in neuropsychological tests or questionnaires for behavioural changes, among others (Jenkinson & Chappell, 2018). Consequently, VBM is a useful method to estimate structure-function relationships across the whole brain even without having predefined hypotheses on what structures one should look into (Leube et al., 2008; Meyer et al., 2013). Likewise, VBM analysis permits to plot significant correlations between particular brain areas that suggest the presence of gray matter changes in brain disorders like dementia and measures of performances on specific neuropsychological domains, behavioural disorders or the degree of severity of a particular neuropsychiatric symptom (Leube et al., 2008).

The appropriate pipeline to carry out an appropriate VBM analysis encompasses several complex steps (Ashburner & Friston, 2000; Jenkinson & Chappell, 2018). The commonest software packages used to handle them are Statistical Parametric Mapping (SPM) (The FIL Methods Group Wellcome Neuroimaging, 2016, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and FSL (Douaud et al., 2007, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM). Firstly, brain must be removed from skull (brain extraction) and normalised/aligned into a template (normalisation/registration). Once these procedures are completed, brain is properly fractionated into different tissues, namely gray matter, white matter and cerebrospinal fluid (segmentation), and modulated to correct for structural size, position and orientation (modulation). Thereafter, brain images are blurred to decrease the influence of noise and alignment errors and improve the statistical sensitivity (smoothing). Lastly, in accordance with the study design in reference, statistical contrasts are conducted to seek for brain areas of significant structural differences between diagnostic

groups or significant correlations with neuropsychological/behavioural parameters of interest. These types of statistical analyses are mostly based on the general linear model, where variables are entered into a matrix that makes possible to perform the respective contrasts (Ashburner & Friston, 2000; Jenkinson & Chappell, 2018).

8.1.1.3.2 Functional brain imaging

Functional brain imaging is based on functional MRI (fMRI). There are primally two overarching objectives in functional brain imaging research, which are: investigating task-related neural activity using task fMRI or exploring functional network connectivity through rsfMRI with no tasks entailed (Jenkinson & Chappell, 2018).

8.1.1.3.2.1 Physics of functional magnetic resonance imaging

fMRI starts from a couple of assumptions one should take into account. Firstly, it has been estimated that human's brain consumes up to 20% of the body's oxygen uptake. Brains do not store oxygen and keep little glucose. Thus, it is actually blood supply the responsible of covering brain's oxygen and its energetic needs (Ward, 2015). Secondly, there is a strict relation between neural activity and metabolic responses, where increased neural activation requires higher metabolic activity and therefore increased blood supply to the respective region to meet the demand. fMRI is a hemodynamic method, that is to say, a technique which is sensitive to fluctuations in the concentrations of oxygen in the blood flow (Ward, 2015).

fMRI physics are compatible with those that mediate traditional structural MRI. Nevertheless, the principal difference between both techniques is the microscopic structure that interacts with the magnetic field generated by the MRI scanner to create brain images (Jenkinson & Chappell, 2018). Unlike MRI, which makes use of H+, fMRI interacts with deoxyhaemoglobin. Haemoglobin is a microscopic structure present in blood cells that carries oxygen. Physiological respiration adheres oxygen to haemoglobin turning it into oxyhaemoglobin. On the contrary, neural activity metabolizes oxyhaemoglobin reducing it into deoxyhaemoglobin. Given that deoxyhaemoglobin is paramagnetic, MRI scanners can distort it and make it trigger signals, either performing of a task (traditional fMRI) or mediating spontaneous activity (rsfMRI). Concentrations of deoxyhaemoglobin in the blood flow and their potential distortions when interacting with the uniform magnetic field generated by MRI scanners can be measured, processed and converted then into brain images. Such a procedure has been coined as blood oxygen-level-dependent contrast (BOLD), which is an index of vascularization. Also, the hemodynamic response function (HRF) corresponds to the progression of BOLD signals over time as a result of an increase of neural activity (Ward, 2015).

8.1.1.3.2.2 Functional resting state magnetic resonance imaging

rsfMRI allows researcher to measure functional connectivity between different brain areas (Jenkinson & Chappell, 2018). It is expected that different groups of neurons across the brain switch on or off synchronously in front of the same task. Similarly, spontaneous neural activity, i.e where there is no task involved, would be mediated then by synchronized activations or deactivations of different brain areas that are functionally connected. Likewise, rsfMRI captures haemodynamic fluctuations without the necessity of having specific stimuli triggering brain changes (Zhou, Liu, Ng, & Wang, 2017).

rsfMRI is a rather novel technique to explore connections between neural networks in both cognitively healthy subjects and patients with brain disorders (Irish, Piguet, & Hodges, 2012; Jenkinson & Chappell, 2018; Zhou et al., 2017). Seed-based correlation analysis (SCA), Independent Component Analysis (ICA) and Graph Theoretical Approach (GTA) are 3 methodologies that have gained special interest in rsfMRI analysis nowadays (Irish et al., 2012).

SCA starts with an a priori approach (Irish et al., 2012), in which intrinsic connectivity networks are identified by estimating correlations between BOLD signals of a 'seed' region with other particular targeted regions or the rest of the brain (Zhou et al., 2017). More precisely, regions of functional connectivity are plot once a time course of BOLD signal from a seed region of interest is paired through correlations with time courses of BOLD signals from every voxel of the brain (Irish et al., 2012). A resulting map of brain areas that share patterns of compatible neural activity is obtained then conducting a SCA (Irish et al., 2012).

In ICA, BOLD signals from all voxels of the brain are fractionated into multiple components and then clustered together according to regions that showed significant correlations. As a consequence, ICA can plot spatially unique maps that include such correlations (Irish et al., 2012).

GTA is a promising method useful to, on the one hand, model the entire brain as a single network and explore its properties, and on the other, identify functional subnetworks (Irish et al., 2012). In GTA, regions of interest are considered as 'nodes', whereas the functional connectivity between paired regions or interest represent an 'edge' (Zhou et al., 2017). Nodes and edges can be grouped together or segregated to the extent that nodes can be part of the same or different networks, while edges can suggest within-network or between-network connectivity (Zhou et al., 2017). Recent findings have proposed that GTA can assist differential diagnosis in dementia distinguishing different forms of dementia, for example, discriminating between early AD and FTD (Irish et al., 2012).

8.1.2 Definitions of variables under study

8.1.2.1 Main variables

8.1.2.1.1 Altered insight into broad and specific objects

8.1.2.1.1.1 Conceptual definition

The term 'insight' is conceptually used throughout this thesis, from a clinical approach to refer to a self-knowledge into an object, whether this object is a diagnosis, a global health status or specific neuropsychological or behavioural/neuropsychiatric symptoms (Markova & Berrios, 2011). Thus, 'altered insight' is defined here as an inaccurate or distorted self-knowledge into health problems, which can be split into broad or specific objects (Munoz-Neira, Tedde, Coulthard, Thai, & Pennington, 2019). Likewise, altered insight can be broken down into 2 parts:

- ✓ Altered insight into broad objects: this term is conceptually defined as an inaccurate or distorted self-knowledge into ample objects of insight such us a diagnosis, a global health status or general health problems awareness. It is possible to distinguish 2 notions with this definition:
  - ➢ Altered insight into diagnosis: inability to appropriately identify/recognise/report the clinical label (diagnosis) assigned by the specialist.
  - ➢ Altered insight into health status: inability to appropriately identify/recognise/report a general health condition configured by several components.
- ✓ *Altered insight into specific objects:* this term is conceptually defined as a rather focused imprecise self-knowledge into particular objects of insight, or in other words, into bounded particular domains, such as neuropsychological impairments or behavioural disorders (functional impairment in ADL or specific neuropsychiatric symptoms). Altered insight into memory problems, social cognition and functional impairment in ADL were of particular interest in this investigation.
  - ➢ *Altered insight into memory problems:* inaccurate self-knowledge of difficulties to remember auto-biographical events (impaired metamemory).
  - ➢ *Altered insight into social cognition:* inaccurate self-knowledge of deficient empathy, social tact, and impaired abilities to interact with others smoothly.
  - ➢ *Altered insight into functional capacity in ADL:* inaccurate self-knowledge of loss of autonomy/self-sufficiency to perform ADL.

8.1.2.1.1.2 Operational definition

From an operational point of view, 'altered insight' refers to the scores obtained by the participants of this study across the insight assessment methods used here. Such assessment methods were applied according to both forms of insight mentioned previously, that is to say, altered insight into broad objects as well as altered insight into specific objects. Thus, operational definitions once altered insight is broken down are as follow:

- ✓ *Altered insight into broad objects:* this concept corresponds operationally to the scores obtained by the participants of this investigation in the tools aimed at assessing altered insight into diagnosis (disease awareness) or a global health condition. Altered insight into health condition was of special concern in this investigation.
  - ➢ Altered insight into health condition: total discrepancy scores obtained between participant and informant versions of the Cambridge Behavioural Inventory - Revised (CBI-R) (Wear et al., 2008) and the Insight Questionnaire (Hornberger et al., 2014) corresponded to altered insight into health condition assessed through the participant-informant level of agreement method. Multi-domain averaged scores estimated by combining altered insight into several neuropsychological measures (executive functions and social cognition, language and memory) represented the self-appraisal accuracy approach (Rosen et al., 2010; Williamson et al., 2010). Additionally, total scores obtained in the Clinical Insight Rating Scale (CIRS) (Lichtenberg, 2010; Ott & Fogel, 1992) reflected altered insight into diagnosis/global health condition according to clinical judgement.
- ✓ Altered insight into specific objects: this concept corresponds operationally to the scores observed in the insight assessment methods used across the bounded specific insight modalities, based on either neuropsychological or behavioural objects/domains. The following forms of altered insight into specific objects with their respective operational definitions were considered as relevant:
  - ➢ Altered insight into memory problems: in conformity with the participant-informant level of agreement, discrepancy scores calculated between the self-administered and informant-based versions of the CBI-R Memory sub-scale (Wear et al., 2008). Regarding the self-appraisal accuracy approach, scores estimated in accordance with the California Verbal Learning Test - Second Version Short Form (CVLT-II SF) (Delis, Kramer, Kaplan, & Ober, 2000) and the Insight Task focused on this neuropsychological domain (Rosen et al., 2010; Williamson et al., 2010). In terms of clinical judgement, scores on the CIRS Memory sub-scale (Lichtenberg, 2010; Ott & Fogel, 1992) were considered.

- Altered insight into social cognition: in conformity with the participant-informant level of agreement, scores calculated between the self-administered and informant-based versions of the CBI-R Abnormal behaviours sub-scale (Wear et al., 2008). Regarding the self-appraisal accuracy approach, scores estimated in accordance with the Mini - Social and Emotional Assessment (Mini-SEA) (Bertoux et al., 2012) and the Insight Task focused on this neuropsychological domain (Rosen et al., 2010; Williamson et al., 2010). In terms of clinical judgement, scores obtained on an adapted version of the CIRS Social cognition sub-scale (Lichtenberg, 2010; Ott & Fogel, 1992) were considered.
- Altered insight into performance on ADL: in conformity with the participant-informant level of agreement, discrepancy scores calculated between the self-administered and informant-based versions of the CBI-R Everyday skills sub-scale (Wear et al., 2008). In terms of clinical judgement, scores on the CIRS ADL sub-scale (Lichtenberg, 2010; Ott & Fogel, 1992) were considered.

8.1.2.2 Other variables: neuropsychological functions

8.1.2.2.1 Global cognitive functioning

8.1.2.2.1.1 Conceptual definition

Although it appears to be that cognitive functioning has not been explicitly defined in the literature, this construct is understood to mean a global cognitive status resulting from the combination of different thinking skills such as attention, memory, language, visuospatial abilities, executive function, and any other related to cognition (Borson, 2010).

8.1.2.2.1.2 Operational definition

Scores obtained in the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) or the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) (Abrahams & Bak, 2013).

8.1.2.2.2 Attention

8.1.2.2.2.1 Conceptual definition

Attention can be defined as a set of cognitive mechanisms that enable human beings to process relevant stimuli while ignoring irrelevant inputs at the same time (Gazzaniga, Ivry, & Mangun, 2014). Pursuing this line of reasoning, attention entails several critical functions required for thinking abilities, namely encoding, focusing, executing, stabilizing, sustaining and shifting, among others (Koziol, Joyce, & Wurglitz, 2014). More precisely, attention as a higher cognitive function embraces different attentional components such as arousal, selective attention, sustained attention and divided attention (Hodges, 2018). Whilst arousal refers to level of alertness (general state of responsivity and wakefulness), selective attention concerns

highlighting or focusing on one input supressing other competing stimuli (focusing) (Hodges, 2018). Sustained attention instead is a state of vigilance or the capability of maintaining mental activity throughout a determined period of time (sustaining) (Hodges, 2018). Lastly, divided attention entails a capacity to alternate between different tasks responding appropriately to more than one stimulus at once (shifting) (Hodges, 2018).

8.1.2.2.2.2 Operational definition

Scores obtained in the Trail Making Test - Part A (TMT-A) (Reitan, 1958; Tombaugh, 2004).

8.1.2.2.3 Episodic memory

8.1.2.2.3.1 Conceptual definition

Episodic memory is the neuropsychological declarative function responsible for maintaining auto-biographical events in mind. Thus, it enables people to remember personal experiences in space and time (Tulving, 1993, 2002). Also, it should be notice that memory is a highly complex cognitive mechanism based on remembering, which entails encoding, storage/consolidation and retrieval of multiple types of information (Tulving, 1984).

8.1.2.2.3.2 Operational definition

Scores obtained in the CVLT-II SF (Delis et al., 2000).

8.1.2.2.4 Social cognition

8.1.2.2.4.1 Conceptual definition

Social cognition refers to those neuropsychological mechanisms that emerge from interactions with other peers or objects (Amodio & Frith, 2006). Processes such as reward learning, imitation, tracking other's intentions and emotion recognition, among others, have been placed under its umbrella and observed in human beings and certain animals (Frith & Frith, 2012). In humans, social cognition encompasses those cognitive abilities required to understand how to behave with a proper tact in interpersonal situations. Thus, this cognitive process should mainly lead to 'mentalizing' or having a 'theory of mind', which refers to the capacity of inferring cognitive or emotional states in others (Amodio & Frith, 2006; Frith & Frith, 2012).

8.1.2.2.4.2 Operational definition

Scores obtained in the Mini-SEA (Bertoux et al., 2012).

8.1.2.2.5 Executive function

8.1.2.2.5.1 Conceptual definition

Executive function is an umbrella term understood to refer to those skills that Alexander Luria proposed to be essential to cope with problem-solving, which includes the higher cognitive

functions of anticipating, planning, executing and monitoring (Luria, 1966). Muriel Lezak (Lezak et al., 2012) coined the concept of executive function as such and also expanded it adhering emotional processes and interpersonal interactions to the construct (Lezak et al., 2012). Likewise, executive functions have been referred to processes eminently cognitive such as sequencing appropriately goal-directed tasks or behaviours, shifting or flexibility when facing new information, decision-making and inhibitory control (Elliott, 2003; Grafman & Litvan, 1999), on the one hand, as well as to those behaviours required to sticking to social rules, understanding punishment and reward, and handling personal and interpersonal emotion processing (Elliott, 2003; Grafman & Litvan, 1999), on the other.

8.1.2.2.5.2 Operational definition

Scores obtained in the Frontier Executive Screen (FES) (Leslie et al., 2016) and the Trail Making Test - Part B (TMT-B) (Reitan, 1958; Tombaugh, 2004).

8.1.2.2.6 Language

8.1.2.2.6.1 Conceptual definition

Speech or body of non-verbal signs used to communicate thoughts. System of spoken or written communication used in self-referential processes and interactions with others (Oxford English Dictionary, 2020). Within the context of dementia care, language problems are commonly assessed by observing naming, repetition, comprehension, and semantic knowledge (Savage et al., 2013).

8.1.2.2.6.2 Operational definition

Scores obtained in the Sydney Language Battery (SydBat) (Savage et al., 2013).

8.1.2.3 Other variables: behavioural signs

8.1.2.3.1 Depression

8.1.2.3.1.1 Conceptual definition

Depression is a mental condition characterized by a high load of psychological distress and the presence of low mood, sadness, irritability, lack of energy, anhedonia and other cognitive or behavioural symptoms, which altogether are important enough to affect significantly the individual's ability to function in everyday life (World Health Organization, 2018).

8.1.2.3.1.2 Operational definition

Scores obtained in the DASS21 Depression sub-scale (Lovibond & Lovibond, 1995).

8.1.2.3.2 Apathy

8.1.2.3.2.1 Conceptual definition

Apathy has been traditionally defined as an absent or reduced capacity to have purposeful interests/concerns and experience pertinent emotions/ feelings (R. Levy & Dubois, 2006). Apathy differs from depression as the former is clinically understood to mean absence or lack of motivation, whereas the latter is rather referred to low mood and psychological distress (M. L. Levy et al., 1998). Lately, apathy has been conceptualized as a quantitative reduction of adaptive behaviour implying then a deficit in the implementation of voluntary actions (i.e. purposeful, internally generated' or goal-directed behaviours) (R. Levy, 2012). Additionally, it has been argued that apathy seems to have underlying neurocognitive mechanisms that configure 3 different modalities of this symptom, including an emotional/affective component, a purely cognitive form and an auto-activation domain (behavioural and referred to thoughts) (R. Levy & Dubois, 2006).

8.1.2.3.2.2 Operational definition

Scores obtained in the Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991).

8.1.2.3.3 Anxiety

8.1.2.3.3.1 Conceptual definition

Anxiety is mental condition configured by mindsets impregnated with feelings of worry and future danger, which can turn into reiterative beliefs of unfortunate development and conclusion of personal experiences, general distress and/or somatic symptoms of tension (World Health Organization, 2018).

8.1.2.3.3.2 Operational definition

Scores obtained in the Depression Anxiety Stress Scales (DASS21) Anxiety sub-scale (Lovibond & Lovibond, 1995).

8.1.2.3.4 Neuropsychiatric symptoms

8.1.2.3.4.1 Conceptual definition

Neuropsychiatric symptoms are psychiatric symptoms resulting from organic diseases, or in other words, psychiatric clinical manifestations caused by brain disorders, including mood changes, apathy, hallucinations, impulsivity, disinhibition, stereotypical behaviours and others (Miyoshi & Morimura, 2010).

8.1.2.3.4.2 Operational definition

Scores obtained in the CBI-R (Wear et al., 2008).

8.1.2.3.5 Performance on activities of daily living

8.1.2.3.5.1 Conceptual definition

Performance on ADL can be defined as a degree of independence or functionally shown at performing everyday tasks. Such tasks can be divided into 3 domains, namely basic ADL (basic physiological and self-maintenance needs like eating, toileting and getting dressed), instrumental ADL (necessary to maintain independent and community life living like managing finances, shopping and using public transport or driving) and advanced ADL (voluntary and complex, but not essential for independency, like using technology, going on holidays and practising hobbies) (Slachevsky et al., 2019).

8.1.2.3.5.2 Operational definition

Scores obtained in the Disability Assessment for Dementia (DAD) (Gelinas, Gauthier, McIntyre, & Gauthier, 1999).

8.1.2.3.6 Caregiver burden

8.1.2.3.6.1 Conceptual definition

Psychological distress associated with providing care to mentally impaired older people, in this case, people living with dementia. This condition can be affected by multiple factors, such as patients' considerable severity of the disease, presence of a debilitating cognitive impairment and behavioural disorders, decreased levels of independence when performing basic or instrumental ADL, and the number of family visits made to the patients in reference, among others (Zarit, Reever, & Bach-Peterson, 1980). It is also understood as those carers' perceptions about how their emotions, physical health, social interactions, and finances are negatively impacted as a consequence of taking care of a person (Zarit, Todd, & Zarit, 1986).

8.1.2.3.6.2 Operational definition

Scores obtained in the Zarit Burden Interview (ZBI) (Whitlatch, Zarit, & von Eye, 1991).

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8.2 SUPPLEMENTARY MATERIAL 2

8.2.1 Search strategies used in the systematic review of this thesis (Chapter 3: Neural correlates of altered insight in frontotemporal dementia, a systematic review).

Medline Search Strategy (23.08.19)

1. Frontotemporal Lobar Degeneration/
2. tauopathy/ or Tauopathies/ or tauopath*.mp.
3. "FTLD Tau".mp.
4. "Pick Disease of the Brain"/ or "Pick's disease".mp.
5. ("GGT" or "globular glial tauopathy").mp.
6. ("CBD" or "corticobasal degeneration").mp.
7. ("PSP" or "progressive supranuclear palsy").mp. or Supranuclear Palsy, Progressive/
8. tdp-43 proteinopathies/ or amyotrophic lateral sclerosis/

9. ("FTDP 17T" or "Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the MAPT tau gene").mp.
10. "FTLD TDP".mp.
11. "FTLD MND TDP".mp.
12. ("aFTLD U" or "atypical frontotemporal lobar degeneration with ubiquitinated inclusions").mp.
13. ("NIFID" or "neuronal intermediate filament inclusion disease").mp.
14. ("BIBD" or "basophilic inclusion body disease").mp.
15. ("FTLD UPS" or "FTLD with inclusions immunoreactive only for the components of the ubiquitine proteasome system").mp.
16. ("FTLD ni" or "FTLD no inclusion specified").mp.
17. frontotemporal dementia/ or primary progressive nonfluent aphasia/
18. ("bvFTD" or "behavioural variant frontotemporal dementia").mp.
19. ("nfFTD" or "PNFA" or "nonfluent variant progressive primary aphasia" or "nonfluent variant frontotemporal dementia" or "agrammatic variant progressive primary aphasia" or "agrammatic variant frontotemporal dementia" or "progressive nonfluent aphasia").mp.
20. ("semantic dementia" or "semantic variant frontotemporal dementia" or "agrammatic variant frontotemporal dementia" or "semantic variant progressive primary aphasia" or "agrammatic variant progressive primary aphasia").mp.
21. ("logopenic aphasia" or "logopenic variant progressive primary aphasia" or "logopenic variant frontotemporal dementia").mp.
22. ("insight" or "lack of insight").mp.
23. anosognosi*.mp.
24. Awareness/ or unawareness.mp.
25. aware*.mp.
26. "self appraisal".mp.
27. Metacognition/ or metacognit*.mp.
28. "meta cognit*".mp.
29. "neural correlate*".mp.
30. ("neural bas*" or "neural foundation*").mp.
31. ("neuroanatomical bas*" or "anatomical bas*").mp.
32. ("cognitive marker" or "neurocognitive marker").mp.
33. "neuropsychological marker".mp.
34. MRI.mp. or nuclear magnetic resonance imaging/
35. "brain imaging".mp. or Neuroimaging/
36. Magnetic Resonance Imaging/
37. Tomography, X-Ray Computed/
38. ("structural neuroimaging" or "structural brain imaging" or "functional brain imaging").mp. or Functional Neuroimaging/
39. ("functional mri" or "structural mri").mp.
40. Magnetic Resonance Spectroscopy/
41. "DTI".mp. or Diffusion Tensor Imaging/ or Neural Pathways/ or Nerve Fibers/
42. ("PET" or "positron emission tomography").mp. or Positron-Emission Tomography/ or Cerebrovascular Circulation/
43. ("SPECT" or "single photon emission computed tomography").mp. or Tomography, Emission-Computed, Single-Photon/
44. "resting state".mp.
45. EEG.mp. or electroencephalogram/
46. Histological Techniques/

47. Postmortem Changes/ or postmortem.mp.
48. "post mortem".mp.
49. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
50. 22 or 23 or 24 or 25 or 26 or 27 or 28
51. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
52. 49 and 50 and 51
53. limit 52 to (english language and humans and yr="1980 -Current")

Embase Search Strategy (23.08.19)

1. frontotemporal dementia/ or "frontotemporal lobar degeneration".mp.
2. tauopathy/ or tauopath*.mp.
3. "FTLD Tau".mp.
4. Pick's disease.mp. or Pick presenile dementia/
5. ("GGT" or "globular glial tauopathy").mp.
6. "CBD".mp. or corticobasal degeneration/
7. "PSP".mp. or progressive supranuclear palsy/
8. amyotrophic lateral sclerosis/ or TDP 43 proteinopathy/
9. ("FTDP 17T" or "Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the MAPT tau gene").mp.
10. "FTLD TDP".mp.
11. "FTLD MND TDP".mp.
12. ("aFTLD U" or "atypical frontotemporal lobar degeneration with ubiquitinated inclusions").mp.
13. ("NIFID" or "neuronal intermediate filament inclusion disease").mp.
14. ("BIBD" or "basophilic inclusion body disease").mp.
15. ("FTLD UPS" or "FTLD with inclusions immunoreactive only for the components of the ubiquitine proteasome system").mp.
16. ("FTLD ni" or "FTLD no inclusion specified").mp.
17. ("bvFTD" or "behavioural variant frontotemporal dementia").mp. or frontal variant frontotemporal dementia/
18. ("nfFTD" or "PNFA" or "nonfluent variant progressive primary aphasia" or "nonfluent variant frontotemporal dementia" or "agrammatic variant progressive primary aphasia" or "agrammatic variant frontotemporal dementia" or "progressive nonfluent aphasia" or "primary progressive nonfluent aphasia").mp. or progressive nonfluent aphasia/
19. ("semantic variant frontotemporal dementia" or "agrammatic variant frontotemporal dementia" or "semantic variant progressive primary aphasia" or "agrammatic variant progressive primary aphasia").mp. or semantic dementia/
20. ("logopenic aphasia" or "logopenic variant progressive primary aphasia" or "logopenic variant frontotemporal dementia").mp.
21. (insight or "lack of insight").mp.
22. anosognosia/ or anosognosi*.mp.
23. awareness/ or aware*.mp. or unawareness.mp.
24. "self appraisal".mp. or self evaluation/
25. metacognition/ or metaconit*.mp. or "meta cognit*".mp.
26. "neural correlate*".mp.

27. ("neural bas*" or "neural foundation*").mp.
28. ("neuroanatomical bas*" or "anatomical bas*").mp.
29. ("cognitive marker" or "neurocognitive marker").mp.
30. "neuropsychological marker".mp.
31. MRI.mp. or nuclear magnetic resonance imaging/
32. "magnetic resonance imaging".mp.
33. "brain imaging".mp. or neuroimaging/
34. x-ray computed tomography/ or brain tomography/
35. ("structural neuroimaging" or "structural brain imaging" or "functional brain imaging" or "structural mri" or "functional mri").mp. or functional neuroimaging/
36. nuclear magnetic resonance spectroscopy/
37. "DTI".mp. or diffusion tensor imaging/
38. PET.mp. or positron emission tomography/
39. SPECT.mp. or single photon emission computed tomography/
40. "resting state".mp.
41. EEG.mp. or electroencephalogram/
42. "histological techniques".mp. or histology/
43. postmortem change/
44. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
45. 21 or 22 or 23 or 24 or 25
46. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
47. 44 and 45 and 46
48. limit 47 to (human and english language and yr="1980 -Current")

PyscInfo Search Strategy (23.08.19)

1. "frontotemporal lobar degeneration".mp.
2. ("tauopathy" or "tauopathies").mp.
3. "FTLD Tau".mp.
4. "pick's disease".mp. or exp Picks Disease/
5. ("GGT" or "globular glial tauopathy").mp.
6. CBD.mp. or exp Corticobasal Degeneration/
7. exp Progressive Supranuclear Palsy/ or PSP.mp.
8. exp Amyotrophic Lateral Sclerosis/ or "tdp 43 proteinopathies".mp.
9. ("FTDP 17T" or "Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the MAPT tau gene").mp.
10. "FTLD TDP".mp.
11. "FTLD MND TDP".mp.
12. ("aFTLD U" or "atypical frontotemporal lobar degeneration with ubiquitinated inclusions").mp.
13. ("NIFID" or "neuronal intermediate filament inclusion disease").mp.
14. ("BIBD" or "basophilic inclusion body disease").mp.
15. ("FTLD UPS" or "FTLD with inclusions immunoreactive only for the components of the ubiquitine proteasome system").mp.
16. ("FTLD ni" or "FTLD no inclusion specified").mp.
17. ("frontotemporal dementia" or "bvFTD" or "behavioural variant frontotemporal dementia").mp.

18. ("nfFTD" or "PNFA" or "nonfluent variant progressive primary aphasia" or "nonfluent variant frontotemporal dementia" or "agrammatic variant progressive primary aphasia" or "agrammatic variant frontotemporal dementia" or "progressive nonfluent aphasia").mp.
19. exp Semantic Dementia/ or ("semantic variant frontotemporal dementia" or "agrammatic variant frontotemporal dementia" or "semantic variant progressive primary aphasia" or "agrammatic variant progressive primary aphasia").mp.
20. ("logopenic aphasia" or "logopenic variant progressive primary aphasia" or "logopenic variant frontotemporal dementia").mp.
21. exp INSIGHT/ or "lack of insight".mp.
22. exp ANOSOGNOSIA/ or anosognosi*.mp.
23. exp AWARENESS/ or unawareness.mp.
24. aware*.mp.
25. exp Cognitive Appraisal/ or exp Self-Evaluation/ or exp Self-Concept/ or exp Self-Perception/ or "self appraisal".mp.
26. exp METACOGNITION/ or metacognit*.mp.
27. "meta cognit*".mp.
28. "neural correlate*".mp.
29. ("neural bas*" or "neural foundation*").mp.
30. ("neuroanatomical bas*" or "anatomical bas*").mp.
31. ("cognitive marker" or "neurocognitive marker").mp.
32. "neuropsychological marker".mp.
33. MRI.mp. or exp Magnetic Resonance Imaging/
34. exp Neuroimaging/ or "brain imaging".mp.
35. exp TOMOGRAPHY/
36. ("structural neuroimaging" or "structural brain imaging" or "functional brain imaging").mp. or exp Functional Magnetic Resonance Imaging/
37. ("functional mri" or "structural mri").mp.
38. "magnetic resonance spectroscopy".mp.
39. "DTI".mp. or exp Diffusion Tensor Imaging/
40. "PET".mp. or exp Positron Emission Tomography/
41. "SPECT".mp. or exp Single Photon Emission Computed Tomography/
42. "resting state".mp.
43. "EEG".mp. or exp Electroencephalography/
44. exp HISTOLOGY/
45. ("posmortem" or "post mosterm").mp.
46. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
47. 21 or 22 or 23 or 24 or 25 or 26 or 27
48. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
49. 46 and 47 and 48
50. limit 49 to (human and english language and yr="1980 -Current")

Web of Science Search Strategy

44 #43 AND #42 AND #41

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

43 #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

42 #24 OR #23 OR #22 OR #21 OR #20

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

41 #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

40 (TS=("histolog*" or "postmortem changes" or "postmortem" or "post mortem")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

39 (TS=("EEG" or "electroencephalogra*")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

38 (TS=("resting state")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

37 (TS=("SPECT" or "single photon emission computed tomography")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

36 (TS=("PET" or "positron emission tomography")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

35 (TS=("DTI" or "diffusion tensor imaging")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

34 (TS=("magnetic resonance spectroscopy")) AND LANGUAGE: (English) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

33 (TS=("functional mri" or "structural mri")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

32 (TS=("structural neuroimaging" or "structural brain imaging" or "functional neuroimaging" or "functional brain imaging")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

31 (TS=("CAT" or "brain computed axial tomography")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

30 (TS=("brain imaging" or "neuroimaging")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

29 (TS=("MRI" or "nuclear magnetic resonance imaging" or "magnetic resonance imaging")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

28 (TS=("cognitive marker" or "neurocognitive marker" or "neuropsychological marker")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

27 (TS=("neuroanatomical bas*" or "anatomical bas*")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

26 (TS=("neural bas*" or "neural foundation*")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

25 (TS=("neural correlate*")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

24 (TS=("metacognition" or "metacognit*" or "meta cognit*")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

23 (TS=("self appraisal")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

22 (TS=("awareness" or "unawareness" or "aware*" or "unaware*")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

21 (TS=(anosognosi*)) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

20 (TS=("insight" or "lack of insight")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

19 (TS=("logopenic aphasia" or "logopenic variant progressive primary aphasia" or "logopenic variant frontotemporal dementia")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

18 (TS=("semantic dementia" or "semantic variant frontotemporal dementia" or "agrammatic variant frontotemporal dementia" or "semantic variant progressive primary aphasia" or "agrammatic variant progressive primary aphasia")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

17 (TS=("nfFTD" or "PNFA" or "nonfluent variant progressive primary aphasia" or "nonfluent variant frontotemporal dementia" or "agrammatic variant progressive primary aphasia" or "agrammatic variant frontotemporal dementia" or "progressive nonfluent aphasia")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

16 (TS=("bvFTD" or "behavioural variant frontotemporal dementia")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

15 (TS=("frontotemporal dementia" or "primary progressive nonfluent aphasia")) AND LANGUAGE:

(English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

14 (TS=("FTLD ni" or "FTLD no inclusion specified")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

13 (TS=("FTLD UPS" or "FTLD with inclusions immunoreactive only for the components of the ubiquitine proteasome system")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

12 (TS=("BIBD" or "basophilic inclusion body disease")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

11 (TS=("NIFID" or "neuronal intermediate filament inclusion disease")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

10 (TS=("aFTLD U" or "atypical frontotemporal lobar degeneration with ubiquitinated inclusions")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

9 (TS=("FTLD TDP" or "FTLD MND TDP")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

8 (TS=("FTDP 17T" or "Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by mutations in the MAPT tau gene")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

7 (TS=("tdp 43 proteinopath*" or "ALS" or "amyotrophic lateral sclerosis")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

6 (TS=("PSP" or "progressive supranuclear palsy")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

5 (TS=("CBD" or "corticobasal degeneration")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

4 (TS=("GGT" or "globular glial tauopathy")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

3 (TS=("PiD" or "Pick's disease")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

2 (TS=("tauopath*" or "FTLD Tau")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

1 (TS=("frontotemporal lobar degeneration")) AND LANGUAGE: (English)

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1980-2019

BIOSIS Search Strategy (23.08.19)

# 44 #43 AND #42 AND #41
Indexes=BCI Timespan=1980-2019

# 43 #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25
Indexes=BCI Timespan=1980-2019

# 42 #24 OR #23 OR #22 OR #21 OR #20
Indexes=BCI Timespan=1980-2019

# 41 #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
Indexes=BCI Timespan=1980-2019

40 (TS=("histolog*" or "postmortem changes" or "postmortem" or "post mortem")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

39 (TS=("EEG" or "electroencephalogra*")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

38 (TS=("resting state")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

37 (TS=("SPECT" or "single photon emission computed tomography")) AND LANGUAGE: (English) AND TAXA
NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

36 (TS=("PET" or "positron emission tomography")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

35 (TS=("DTI" or "diffusion tensor imaging")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

34 (TS=("magnetic resonance spectroscopy")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

33 (TS=("functional mri" or "structural mri")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

32 (TS=("structural neuroimaging" or "structural brain imaging" or "functional neuroimaging" or "functional brain imaging")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

31 (TS=("CAT" or "brain computed axial tomography")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

30 (TS=("brain imaging" or "neuroimaging")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

29 (TS=("MRI" or "nuclear magnetic resonance imaging" or "magnetic resonance imaging")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

28 (TS=("cognitive marker" or "neurocognitive marker" or "neuropsychological marker")) AND LANGUAGE:
(English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

27 (TS=("neuroanatomical bas*" or "anatomical bas*")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

26 (TS=("neural bas*" or "neural foundation*")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

25 (TS=("neural correlate*")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

24 (TS=("metacognition" or "metacognit*" or "meta cognit*")) AND LANGUAGE: (English) AND TAXA NOTES:
(Humans)

Indexes=BCI Timespan=1980-2019

23 (TS=("self appraisal")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

22 (TS=("awareness" or "unawareness" or "aware*" or "unaware*")) AND LANGUAGE: (English) AND TAXA
NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

21 (TS=(anosognosi*)) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

20 (TS=("insight" or "lack of insight")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

19 (TS=("logopenic aphasia" or "logopenic variant progressive primary aphasia" or "logopenic variant frontotemporal dementia")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

18 (TS=("semantic dementia" or "semantic variant frontotemporal dementia" or "agrammatic variant frontotemporal dementia" or "semantic variant progressive primary aphasia" or "agrammatic variant progressive primary aphasia")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

17 (TS=("nfFTD" or "PNFA" or "nonfluent variant progressive primary aphasia" or "nonfluent variant frontotemporal dementia" or "agrammatic variant progressive primary aphasia" or "agrammatic variant frontotemporal dementia" or "progressive nonfluent aphasia")) AND LANGUAGE: (English) AND TAXA
NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

16 (TS=("bvFTD" or "behavioural variant frontotemporal dementia")) AND LANGUAGE: (English) AND TAXA

NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

15 (TS=("frontotemporal dementia" or "primary progressive nonfluent aphasia")) AND LANGUAGE:

(English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

14 (TS=("FTLD ni" or "FTLD no inclusion specified")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

13 (TS=("FTLD UPS" or "FTLD with inclusions immunoreactive only for the components of the ubiquitine

proteasome system")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

12 (TS=("BIBD" or "basophilic inclusion body disease")) AND LANGUAGE: (English) AND TAXA NOTES:

(Humans)

Indexes=BCI Timespan=1980-2019

11 (TS=("NIFID" or "neuronal intermediate filament inclusion disease")) AND LANGUAGE: (English) AND

TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

10 (TS=("aFTLD U" or "atypical frontotemporal lobar degeneration with ubiquitinated inclusions")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

9 (TS=("FTLD TDP" or "FTLD MND TDP")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

8 (TS=("FTDP 17T" or "Frontotemporal dementia and parkinsonism linked to chromosome 17 caused by

mutations in the MAPT tau gene")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

7 (TS=("tdp 43 proteinopath*" or "ALS" or "amyotrophic lateral sclerosis")) AND LANGUAGE: (English) AND

TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

6 (TS=("PSP" or "progressive supranuclear palsy")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

5 (TS=("CBD" or "corticobasal degeneration")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

4 (TS=("GGT" or "globular glial tauopathy")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

3 (TS=("PiD" or "Pick's disease")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

2 (TS=("tauopath*" or "FTLD Tau")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

1 (TS=("frontotemporal lobar degeneration")) AND LANGUAGE: (English) AND TAXA NOTES: (Humans)

Indexes=BCI Timespan=1980-2019

ProQuest Dissertations & Theses Global Search Strategy (23.08.19)

Set#	Searched for	Databases	Results
S1	("lack of insight" AND "frontotemporal dementia" AND "neural correlates") AND la.exact("English") AND pd(>19801231)	ProQuest Dissertations & Theses Global	32°

° Duplicates are removed from your search and from your result count.

8.3 SUPPLEMENTARY MATERIAL 3

8.3.1 Newcastle - Ottawa Quality Assessment Scale used for the systematic review of this thesis (Chapter 3: Neural correlates of altered insight in frontotemporal dementia, a systematic review)

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability*

*This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review ***"Neural correlates of altered insight in frontotemporal dementia: a systematic review".***

Selection

1) Representativeness of the sample of patients with frontotemporal dementia and/or its associated syndromes:
   a) truly representative group of typical patients with frontotemporal dementia and/or any of its associated syndromes in the community; patients diagnosed with published criteria for either research purposes or clinical settings; patients recruited through consecutive sampling ★
   b) truly representative group of typical patients with frontotemporal dementia and/or any of its associated syndromes in the community; patients diagnosed with published criteria for either research purposes or clinical settings; patients recruited through convenience sampling ★
   c) somewhat representative group of patients with frontotemporal dementia and/or any of its associated syndromes
   d) no description of the origin of the group
2) Selection of the cognitively healthy controls
   a) drawn from the same community as the group of patients with dementia ★
   b) drawn from a different source
   c) no inclusion of control group or no description of the origin of the control group
3) Ascertainment of diagnosis of the neurological condition/cognitively healthy status
   a) clinical history, laboratory tests and brain imaging analysis for the cases of neurological conditions and cognitive screening for the cases of cognitively ★
   b) clinical history, laboratory tests and brain imaging analysis in case only neurological conditions have been included ★
   c) clear procedure followed to categorize/diagnose the patients; however unclear method used to assess the cognitively healthy controls
   d) unclear procedure followed to categorize/diagnose the patients or the patients and the controls or no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes ★
   b) no

Comparability

1) Comparability of groups based on the design or analysis
   a) study controls for the assessment and comparison of insight performance with patients ★

b) study controls for the pertinent brain imaging analysis aimed at exploring the neural correlates of altered insight ★

c) comparisons between groups of patients instead of group of patients and controls ★

d) no comparison or no description

Outcome

1) Unbiased assessment of outcomes

a) explicit confirmation that researchers who conducted the insight/neuropsychological assessment were blind to the diagnosis and blind to the brain images in reference before the neuropsychological assessment was conducted ★

b) clear confirmation of the independency between the researchers who rated insight and those who conducted the brain imaging analysis ★

c) researchers who assessed insight also analysed the brain imaging data

d) no description about the independency between the researchers who rated insight and those who conducted the brain imaging analysis

2) Duration of the follow-up for altered insight to occur in patients with a neurological condition

a) enough (well established/well defined diagnostic criteria according to published guidance for research of clinical purposes; where applicable and possible, at least one year of duration of the diagnosis) ★

b) not enough or no explicit description

3) Results (neural substrates of altered insight) obtained through adequate methods

a) use of a valid approach to assess insight along with a robust statistical procedure to analyse the neuropsychological/behavioural outcomes and their respective relationship with brain images (tool to assess insight validated in dementia cohorts and published in peer-reviewed journals plus a direct method to measure the correlation between insight outcomes and their respective potential neural correlates) ★

b) use of a questionable approach to assess insight or a weak statistical analysis to correlate the neuropsychological/behavioural outcomes with their respective brain areas

c) suggestion of introduction of bias due to any methodological aspect (number of dropouts for example)

d) no description

8.4 SUPLEMENTARY MATERIAL 4

8.4.1 Complementary Tables of the systematic review of this thesis (Chapter 3: Neural correlates of altered insight in frontotemporal dementia, a systematic review)

Table 8

Quality assessment for the papers included in the present systematic review according to Crombie's items

Paper	Appropriateness of design to meet the aims	Adequate description of the data	Report the response rates	Adequate representativeness of the sample to total	Clearly stated aims and likelihood of reliable and valid measurements	Assessment of statistical significance	Adequate description of statistical methods	Total points (out of 7)*
Amanzio et al. (2016)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Bastin et al. (2012)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
García-Cordero et al. (2016)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Hornberger et al. (2014)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Ichikawa et al. (2013)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Levy et al. (2018)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Massimo et al. (2013)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
McMurtray et al. (2006)	Yes	Yes	No	Unclear	Yes	Unclear	No	4
Mendez & Shapira (2005)	Yes	Yes	No	Unclear	Yes	Unclear	No	4
Miller et al. (1997)	Yes	Yes	No	Yes	Yes	Unclear	No	4.5
Rosen et al. (2010)	Yes	Yes	No	No	Yes	Yes	Yes	5
Ruby et al. (2007)	Yes	Yes	No	Yes	Yes	Yes	Yes	6

Shany-Ur et al. (2014)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Sollberger at al. (2014)	Yes	Yes	No	Yes	Yes	Yes	Yes	6
Zamboni et al. (2010)	Yes	Yes	No	Yes	Yes	Yes	Yes	6

*****For each item, "Yes" corresponds to 1 point, "Unclear" to 0.5 point and "No" to 0 point

Table 9

General overview of the quality assessment for the papers included in the present systematic review

Paper	Quality summary
Amanzio et al. (2016)	Aims, participant characteristics, and outcomes were clearly described. Patients were recruited from the Neurological Unit of the Department of Neuroscience of the University of Torino (Italy) after an extensive clinical, neuropsychological, neuroradiological and neurogenetic examination. Patients were diagnosed with bvFTD according to Rascovsky et al. (2011) criteria. Controls were cognitively healthy subjects with MMSE >25 and normal in terms of neurological and psychiatric evaluations; however, the location where they were recruited from was not reported. The inclusion and exclusion criteria were appropriately defined. Patients and their carers completed scales useful to assess functional capacity on instrumental ADL. No dropouts were reported.
Bastin et al. (2012)	Aims, participant characteristics, and outcomes were clearly described. The inclusion and exclusion criteria were properly explained and any patient exclusion from analysis was clearly justified. The patients showed a clinical diagnosis of FTD (according to McKhann et al., 2001) that was confirmed after 2 years of follow-up. Several neuropsychological test were assessed to increase the quality of the diagnosis. Through an interview with each participant and a close relative, it was ensured that control participants had no psychiatric or neurological problems, were free of medication that could affect cognitive functioning, and were in good health. However, the location where they were recruited from was not reported.
García-Cordero et al. (2016)	Aims, participant characteristics, and outcomes were clearly described. Recruitment locations were not reported. bvFTD patients were diagnosed using Rascovsky et al. (2011) criteria, AD using NICDS-ADRDA criteria and stroke patients after MRI brain scan visualization. Controls matched by sex, age and education level, however the location where they were recruited from was not reported either. All the same, the inclusion and exclusion criteria were appropriately defined. Participants performed several interoceptive tasks and then they rated how good/bad they thought their performances were. No dropouts were reported.
Hornberger et al. (2014)	Aims, participant characteristics, and outcomes were clearly described. Patients were sourced from the FRONTIER Dementia Clinic (Sydney, Australia) and INECO Dementia and Memory Clinic (Buenos Aires, Argentina) databases. FTD patients met current consensus FTD criteria (Rascovsky et al., 2011). Additional neuropsychological tests were assessed to increase the quality of the diagnosis. No dropouts were reported.

Ichikawa et al. (2013)	Aims, participant characteristics, and outcomes were clearly described. The inclusion and exclusion criteria were properly explained and any patient exclusion from analysis was clearly justified. Diagnosis of ALS was based on El Escorial revised criteria for probable or definite ALS, while two patients were autopsied and the diagnosis of ALS was also confirmed neuropathologically. The severity of ALS was graded using the revised ALS functional rating scale (ALSFRS-R). Dementia was determined based on FTLD criteria (Neary et al., 1998). Several neuropsychological tests (MMSE, FAB) were assessed to increase the quality of the diagnosis. Controls were randomly recruited. However, the location where they were recruited from was not specified. No dropouts were reported.
Levy et al. (2018)	Aims, participant characteristics, and outcomes were clearly described. Patients were recruited from the Cognitive Neuroscience Section of the National Institute of Neurological Disorders and Stroke (NINDS) from 2001 to 2009. Patients' diagnoses were made by a neurologist and a neuropsychologist until reaching consensus once neurological, behavioural, neuropsychological and neuroimaging assessments were conducted. bvFTD was diagnosed according to Neary et al. (1998) criteria and nfPPA with Gorno-Tempini et al.(2011) On the other hand, CBS diagnoses were based on Boeve (2004). The inclusion and exclusion criteria were appropriately defined. Cognitively healthy control subjects were not included in this study. Patients and their carers completed scales useful to assess awareness into dysexecutive behaviours. Clinicians rated patient's levels of anosognosia. No exclusions or dropouts were reported in this study.
Massimo et al. (2013)	Aims, participant characteristics, and outcomes were clearly described. Patients with bvFTD were diagnosed according to Rascovsky et al. (2011) criteria, whereas patient with AD through McKhann et al., *(2011). Diagnoses were made after a clinical history was taken and a detailed neurological and mental status evaluation were carried out by an experienced cognitive neurologist from the Department of Neurology at University of Pennsylvania. Diagnoses were confirmed by at least two other experts. Patients were assessed with a neuropsychological battery focused on the assessment of language and memory and later asked to self-appraise their performances. No dropouts were reported.
McMurtray et al. (2006)	Aims, participant characteristics, and outcomes were clearly described. Patients were recruited from university-affiliated speciality clinics in dementing disorders. Patients underwent a comprehensive neurobehavioural evaluation, laboratory tests and MRI brain scans and then were diagnosed with frontal FTD (bvFTD) according to Neary et al. (1998) criteria. Patients were followed-up for at least 2 years to confirm diagnoses remained. No control subjects were included in this study. The inclusion and exclusion criteria were appropriately defined. The authors completed a scale to assess patient's neuropsychiatric symptoms characteristic of

	FTD. No exclusions or dropouts were reported as this study selected participants from a larger cohort of patients.
Mendez & Shapira (2005)	Aims, participant characteristics, and outcomes were clearly described. Patients were recruited from the University of California Los Angeles (UCLA) Focal-type Dementia Clinic. Patients were diagnosed with FTD (bvFTD) according to Neary et al. (1998) criteria. Diagnoses were confirmed by the presence of frontal or anterior temporal predominant changes on functional brain imaging. No control subjects were included in this study. Inclusion and exclusion criteria were not extensively described. The authors rated patient's level of insight loss according to questions extracted from CERAD. No exclusions or dropouts were reported in this study.
Miller et al. (1997)	Aims, participant characteristics, and outcomes were clearly described. Patients were studied in the UCLA Alzheimer's Disease Center. All patients received a comprehensive neurobehavioral evaluation. Patients were classified as FTD based on SPECT. Additional neuropsychological test were assessed to increase the quality of the diagnosis. However, the location where they were recruited from was not reported. The inclusion and exclusion criteria were appropriately defined. No dropouts were reported.
Rosen et al. (2010)	Aims, participant characteristics, and outcomes were clearly described. FTD patients were diagnosed using published criteria (McKhann et al., 1984; Neary et al., 1998; Brooks et al., 2000; Petersen et al., 2001; Boeve et al., 2003) after a comprehensive evaluation at the UCSF Memory and Aging Center including neurological history and examination, nursing evaluation, laboratory evaluation, and a neuropsychological assessment of memory, executive function, language, and mood. Several neuropsychological test were assessed to increase the quality of the study. However, the location where they were recruited from was not reported. No dropouts were reported.
Ruby et al. (2007)	Aims, participant characteristics, and outcomes were clearly described. Any patient exclusion from analysis was clearly justified. Patients with fvFTD (13 men and 8 women) were selected according to recent consensual diagnostic criteria (Neary et al., 1998). Additional neuropsychological tests were assessed to increase the quality of the diagnosis. However, the location where patients and controls were recruited from was not reported.

Shany-Ur et al. (2014)	Aims, participant characteristics, and outcomes were clearly described. Patients were recruited from a Memory Clinic or external clinics. Patients' diagnoses were determined by a team of neurologists, neuropsychologists and nurses, following thorough neurological, behavioural, neuropsychological and neuroimaging assessments. AD was diagnosed with NINDS-ADRDA criteria, bvFTD with Neary et al. (1998) criteria, right-temporal variant FTD with Josephs et al. (2009) criteria, and svPPA nfPPA with Gorno-Tempini et al. (2011) criteria. Control subjects were recruited through recruitment talks and local advertisements. Controls had an unremarkable neurological exam and MRI scan, and no functional or cognitive deficits. The inclusion and exclusion criteria were appropriately defined. Patients and their carers completed scales useful to assess awareness into cognitive decline, functional impairment and behavioural disorders. No exclusions or dropouts were reported in this study.
Sollberger at al. (2014)	Aims, participant characteristics, and outcomes were clearly described. 28 patients met the research diagnostic criteria for behavioral variant frontotemporal dementia (bvFTD) (Rascovsky et al. 2011), 16 met criteria for semantic variant primary progressive aphasia (svPPA) (Gorno-Tempini et al. 2011), 4 met criteria for non-fluent variant primary progressive aphasia (nfvPPA) (Gorno-Tempini et al. 2011) and 12 met criteria for corticobasal syndrome (CBS) (Boxer et al. 2006). However, the location where they were recruited from was not reported. Nineteen normal controls were recruited through advertisements in local newspapers and talks at local senior community centers. All subjects underwent neuropsychological testing. The inclusion and exclusion criteria were appropriately defined. No dropouts were reported.
Zamboni et al. (2010)	Aims, participant characteristics, and outcomes were clearly described. Patients were recruited from the Cognitive Neuroscience section at the National Institute of Neurological Disorders and Stroke (NINDS). Patients were clinically classified as bvFTD, aphasic variant of FTD or CBS. Diagnoses were determined after clinical and neuropsychological assessments during a single 1-week visit. FTD diagnoses were made according to McKhann et al. (2001) criteria and CBS diagnoses with Boeve et al. (2003) criteria. Reference to the location where the control subjects were recruited from was not reported. Controls had no history of neurological or psychiatric disorders and were examined by Neurologists through clinical evaluation and a brain MRI scan. The inclusion and exclusion criteria were appropriately defined. Patients and their carers completed a scale useful to assess the progression of dysexecutive symptoms in order to estimate discrepancy scores among them later. No exclusions or dropouts were reported in this study.