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A multimodal approach to the study of self and others' awareness in prodromal to mild Alzheimer's disease

By

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Abstract

Patients in the early stage of Alzheimer's disease (AD) can manifest disorders of cognitive awareness such as a lack of/limited self-awareness of their own cognitive deficits (anosognosia) or as a reduction in the ability to be aware of others, i.e., social cognition; more specifically in the ability to recognise emotions or attribute mental states to others (also known as Theory of Mind, ToM). The present thesis intended to explain the behavioural, brain neuroanatomical, structural connectivity and resting-state functional relationship between the presence of multi-domain alterations of self-awareness/anosognosia and others awareness/social cognition to understand the cognitive and neural substrates that shape conscious awareness in early AD.

Behavioural findings evidenced an association between the presence of anosognosia and reduced ToM. Individually, memory anosognosia was associated with memory proxies and total anosognosia with visuospatial abilities, while social cognition was associated with language, memory, attention and most importantly, executive functions. Neuroanatomical structural findings of non-memory and total anosognosia showed reduced grey matter volume in the anterior cingulate cortex (ACC), fusiform, lingual and precentral gyri. Conversely, ToM showed reduced grey matter volume also in the ACC, but reduction extended to encompass temporoparietal junction, orbitofrontal, superior temporal and cerebellar cortices. The ACC showed a statistical shared neural overlap between self-other awareness. At the functional level, both anosognosia and social cognition were associated with reduced internetwork connectivity between the default mode network (DMN) and the executive frontoparietal network (FPN), as well as higher connectivity between the DMN and the salience network, in which the insula seems to have an essential role. Subcortical contributions to large-scale network connectivity were also found.

We propose that medial frontal executive mechanisms, such as those subserved by the ACC, might support awareness in the presence of an inherently damaged DMN in early-AD. Functional adaptive reorganisation of network dynamics might increase the strain to salient system hubs (ACC) by redirecting network traffic of executive resources to cope with the progressive decline of conscious awareness.

Declaration

I, the author, confirm that the Thesis is my own work. I am aware of the University's Guidance on the Use of Unfair Means (www.sheffield.ac.uk/ssid/unfair-means). This work has not previously been presented for an award at this, or any other, university.

Publications arising from this thesis:

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List of abbreviations

AAL: Automated Anatomical Labelling; **ACC**: anterior cingulate cortex; **AD**: Alzheimer's disease; **Aff-Tom**: affective Theory of Mind; **aMCI**: amnesic mild cognitive impairment; **APOE**: Apolipoprotein-E; **APP**: Amyloid precursor protein; **BA**: Brodmann area; **BET**: Brain Extraction Tool; **BMI**: body mass index; **BOLD**: blood oxygen-level dependent; **bvFTD**: Behavioural variant frontotemporal dementia; **CAA**: Cerebral amyloid angiopathy; **CAM**: Cognitive Awareness Model; **CAS**: Conscious awareness system; **CSF**: cerebrospinal fluid; **Cog-ToM**: Cognitive Theory of Mind; **dIPFC**: dorsolateral prefrontal cortex; **DM2**: Diabetes Mellitus type 2; **DMN**: default mode network; **DTI**: diffusion tensor imaging; **FA**: fractional anisotropy; **FDT**: FMRIB's Diffusion Toolbox; **FOFB**: first order false belief; **FPN**: Fronto-parietal network; **fMRI**: functional magnetic resonance imaging; **FSL**: FMRIB software library; **FWE**: family-wise error; **GM**: grey matter; **HC**: healthy controls; **ICA**: independent component analysis; **ICBM**: International Consortium for Brain Mapping; **IPL**: Inferior parietal lobe; **IWG**: International Working Group; **LATE**: Limbic-predominant age-related TDP-43 encephalopathy; **MAS**: Metacognitive Awareness System; **MCI**: mild cognitive impairment; **MD**: mean diffusivity; **MMSE**: Mini-Mental State Examination; **MNI**: Montreal Neurological Institute; **mPFC**: medial prefrontal cortex; **MRI**: magnetic resonance imaging; **MTL**: medial temporal lobe; **NFT**: neurofibrillary tangles; **NIAA**: National Institute of Aging-Alzheimer's Association; **NINCDS**: National Institute of Neurological and Communicative Disorders and Stroke; **NPS**: neuropsychiatric symptoms; **OFC**: orbitofrontal cortex; **PCA**: posterior cortical atrophy; **PCC**: posterior cingulate cortex; **PET**: positron emission tomography; **PPA**: primary progressive aphasia; **rCBF**: Regional cerebral blood flow; **REST**: Resting-State fMRI Data Analysis Toolkit; **RMET**: reading the mind in the eyes test; **ROI**: region of interest; **SOFB**: second order false belief; **SPECT**: single photon emission computed tomography; **SPM**: Statistical Parametric Mapping; **SPSS**: Statistical Package for the Social Sciences; **STS**: superior temporal sulcus; **TBSS**: tract-based spatial statistics; **ToM**: Theory of Mind; **TPJ**: Temporoparietal junction; **TIV**: total intracranial volume; **UK**: United Kingdom; **VBM**: voxel-based morphometry; **VD**: Vascular dementia; **WM**: white matter; **WAIS**: Wechsler Adult Intelligence Scale.

Chapter 1

Alzheimer's Disease Overview

The improvement of worldwide healthcare options has led to a gradual increase in the overall population lifespan. As a result, the increase in the number of the elder population has created a sociological phenomenon defined as demographic transition ([Mercer, 2018](#)). The latter can be explained as an ongoing contraction of the global younger population as a direct consequence of an overall decline in birth rates due to adverse socioeconomic determinants that are seen across the lifestyle factors that accompany modern globalisation ([Bongaarts, 2009](#)). Paradoxically, this improvement in the world health systems has impacted in a considerable reduction of transmittable diseases such as infections, but has given place to non-transmittable conditions, such as metabolic diseases, neoplastic conditions or neurodegenerative syndromes that manifest with a higher prevalence in the later stages of life. Consequently, the incidence of neurodegenerative diseases such as those resulting in dementia will exhibit an overwhelming upsurge in the upcoming decades ([Prince & Acosta, 2006](#)).

In this context, Alzheimer's disease (AD) continues to be the leading cause of irreversible dementia worldwide, with an estimated number of 50 million people affected globally by the disorder ([Guzman-Martinez et al., 2021](#)). In a clinical setting, AD can be described as a neurological syndrome characterised by a progressive impairment of higher cognitive functions such as memory, attention, language, executive functions, visuospatial abilities, behaviour and personality, that will ultimately

restrain affected individuals' potential to accomplish independently activities of the daily life (Weller & Budson, 2018).

1.1 Epidemiology

Results from the World Alzheimer Report 2015 outlined a global prevalence of 36 million people living with dementia in 2010, doubling its numbers every 20 years, to 66 million by 2030 and 115 million by 2050 (Prince et al., 2014). On the other hand, the age-related incidence of AD has also increased, doubling with every 5.9 years increase in age. Resultantly, the incidence numbers point to 3.1/1000 new cases of dementia at age 60-64, to 175/1000 persons per year at age 95 and above. Distinctly, high-income countries display higher incidence rates (doubling every 5.8 years, from 3.4/1000 per year to 202.2/1000 per year) in comparison to low or middle-income countries (doubling every 6.7 years, from 2.9/1000 per year to 99.4/1000 per year) (Prince et al. 2014). Therefore, the most consistent determinant related to disease incidence is age; however, the accuracy of calculating incidence numbers relies on the correct characterisation of the disease's age of onset, in concomitance with the correct identification of the population that does not display the disease. The latter proves to be challenging as the decisive diagnosis relies on histopathological hallmarks that can only be evidenced in *post-mortem* tissue. Luckily, improvements in diagnostic clinical criteria and comprehensive methodological standardisation have optimised the global prevalence and incidence statistics that can rely on more trustworthy rates (Mayeux & Stern, 2012).

Based on the Dementia UK update report (2014), in the United Kingdom (UK) alone, the prevalence of dementia was estimated in around 850,000 people living with

the disease in 2015. In a similar pattern to the global numbers, based on the 2020 report of the Lancet Commission on dementia prevention, intervention and care (2020), by 2040 over 1.2 million people will have this form of disease and eventually doubling by 2050. Notably, approximately one in every three patients with dementia in the UK has AD. These numbers are directly associated with the progressive rise in healthcare system costs. Just in England, the estimated cost of dementia in 2015 was £24.2 billion, with an individual cost ranging from £24 400 to £46 050, depending on the stage of the disease (Wittenberg et al. 2019). Lastly, mortality has also shown an alarming growth, as in 2016 dementia was the fifth leading cause of death globally (Nichols et al. 2019). Notably, due to prevention measures of risk factors and novel treatments, the overall incidence of all cause dementia worldwide has seen a decrease (Matthews et al., 2016; Wolters et al., 2020); although, for AD it does not seem to be the case, particularly in eastern countries where there is an increase in numbers of AD incidence (Gao et al., 2019).

1.2 Risk factors

There is yet no conclusive evidence that specifies a causal constituent for AD onset. To this extent, the main focus of current research in this area is to elucidate the main risk factors that play a pivotal role, among other variables, in triggering the progressive brain-parenchymal alterations that will eventually establish the disease.

The literature has pointed out age as the most consistent risk finding associated with AD (Alzheimer's Association, 2021; Dubois et al., 2021). The age of occurrence for sporadic AD is usually after 65 years, when comorbidity, senescence and health-related features interact more closely than in younger populations (Livingston et al.

2017). Additionally, age-related comorbidities, which have been proposed to be significant risk factors for AD, have also been proposed to interact as probable causal factors; more specifically, increased levels of fasting-blood-sugar, high body mass index (BMI) and smoking habits (Nichols et al. 2019). Furthermore, supplementary research has highlighted the presence of metabolic disorders, such as obesity, dyslipidaemia, hypertension and diabetes, to be consistent precursors for dementia onset (Mayeux & Stern, 2012).

1.2.1 Modifiable Risk Factors

The contributions that research has offered to identify modifiable risk factors fostering the appearance of AD in vulnerable populations has led to an improvement in the overall rates of disease occurrence. Strategies based on public health have targeted these risk factors resulting in positive outcomes, especially in countries with a higher public expense directed to health prevention campaigns, where the incidence of dementia has reasonably dropped (Stephan et al. 2018).

As mentioned previously, vascular disease has been proposed to be one of the essential risk factors for AD appearance. In this sense, vascular damage is present in approximately 10-20% of patients with dementia and manifests itself, at histological levels, as the presence of atherosclerosis, arteriosclerosis, macro and microvascular ischemic lesions and cerebral amyloid angiopathy (CAA) (Kapasi & Schneider, 2016). This pathological spectrum can be manifested within certain etiological syndromes namely, cerebrovascular disease, systemic arterial hypertension and diabetes. Furthermore, some mechanisms have been proposed to support the interaction between AD and vascular dysfunction; for instance, brain tissue lesions in post-stroke

patients reveal destruction of neurons in vital regions such as the thalamus that could, in turn, potentiate amnesic disorders (Mayeux & Stern, 2012). Subsequently, a second mechanism of cerebrovascular comorbidity in AD has been explained through the presence of hypoxia and ischemia that leads ultimately to neural hypoperfusion (Wen et al., 2007; Wen et al., 2008). These negative changes dysregulate the expression of proteins like p25/cdk5, a macromolecule that triggers a disproportionate expression of the amyloid precursor protein (APP), resulting in a greater accumulation of amyloid plaques (Wen et al., 2007; Wen et al., 2008). Moreover, vascular disease as a risk factor has been suggested to increase the occurrence of dementia by almost three times (Kapasi & Schneider, 2016).

Hypertension, with a concomitant risk of stroke, has been shown to have a strong association with vascular dementia (VD) (Sierra, 2020); however, high systolic blood pressure has been demonstrated to also affect patients with AD (Lennon et al., 2019). In this context, the mechanistic pathway in which hypertension, in the absence of post-stroke neural injury, affects the brain of AD individuals may be explained possibly by the presence of white matter lesions that result in cognitive impairment. Nevertheless, the exact way by which this occurs is still yet poorly understood (Tzourio, 2007).

Type 2 diabetes (DM2) is one of the most robust risk factors for the appearance of AD dementia, due primarily to unhealthy lifestyles actions; for instance, malnutrition and low physical activity (Alzheimer's Association, 2021). In this context, the presence of hyperinsulinemia (a direct consequence of chronic insulin resistance) and hyperglycaemia, which are the inherent outcomes of the pathophysiological setting of this metabolic disease, would produce a synergic detrimental effect on neurons targeted also by AD. These mechanisms are unspecific and a wide range of

pathological processes has been proposed. For example, excessive glycation deposition in structural cellular components could promote microvascular lesions (including of the blood-brain barrier). Additionally, oxidative stress, accumulation of detrimental amyloid by-products, mitochondrial alterations and sustained neuroinflammation, that also characterises the pathological spectrum of DM2, would lead ultimately to cumulative neurodegeneration and deterioration of higher cognitive domains (Lee et al., 2018).

Among the modifiable risk factors, smoking has also been linked to increased AD risk. This risk is almost 1.7 times greater than in non-smokers and depends largely on the cumulative effects of chronic inhalation of cytotoxic particles. Also, oxidative stress has been postulated to contribute to the development of dementia. These oxygen-dependent-by-products interact with the APP cleavage process by increasing the activity of the β -secretase that could potentiate the detrimental processes that foster the onset of AD (Durazzo, Mattsson & Weiner, 2014).

Lastly, research on social engagement has demonstrated this to be one of the most relevant modifiable risk factors for AD dementia. A longitudinal study followed up non-demented elderly people over a period of 4 years. Results showed that socially isolated individuals increased substantially their risk of developing AD more than twice. Additionally, these individuals exhibited faster cognitive decline and displayed more AD-typical histopathological alterations *post-mortem* (Wilson et al., 2007). Similarly, a large cohort study followed participants up for 10 years and revealed an increased risk of developing dementia of 40% in a population experiencing loneliness, regardless of factors such as genetics, education, gender or race (Sutin et al., 2018). Distinctively, social isolation could lead possibly to depression that, by itself, has already be shown to be a significant risk factor for AD (1.9-2.0 odds ratio, OR) (Ownby et al., 2006).

Lastly, research on animal models has pointed out that loneliness has detrimental effects at a cellular level that can be explained mechanistically with synaptic plasticity alterations, by internalisation of AMPA glutamatergic receptors in susceptible AD neurons ([Hsiao, Chang & Gean, 2018](#)).

1.2.2 Non-Modifiable Risk Factors

Non-modifiable risk factors for AD can be defined as attributes that are intrinsic to an individual's lifespan, regardless of any effort to alter them. The effect of these factors is inevitable; however, their prompt detection could increase the chances for personalised targeted therapy or intervention strategies to tackle the disease before the onset of brain damage or clinical manifestations ([Loeffler, 2021](#)).

1.2.2.1 Genetic factors

Currently, genetic characteristics are known as the most relevant non-modifiable risk factors for AD, as they play an essential role in its development. In this regard, distinctive cases of AD occurrence result as a causal effect of mutations in three genes that express high penetrance namely, APP, PSEN1 and PSEN2, that code for amyloid Precursor Protein (APP), Presenilin 1 and Presenilin 2 proteins, respectively ([Bekris et al., 2010](#)). The specific pathophysiological role of these proteins relies on the increased synthesis of amyloid-beta proteins in the brain (more details will be given in further sections in this introductory chapter). Moreover, the pattern of inheritance of these genes is autosomal dominant, and manifests with a very low incidence of less than 1% of all AD cases. These individuals are defined clinically as early-onset AD (with a development of disease in individuals who are < 65 years old that accounts for

nearly 5-10% of all cases of AD), in a form of disease known as familial AD (Harvey, Skelton-Robinson & Rossor, 2003; Dai et al., 2018). Moreover, pioneering research into the genetics of individuals with trisomy 21 (Down Syndrome) has shown a higher risk of early-onset AD due to the presence of a triplicate APP gene locus coded on chromosome 21, that interacts with amyloid formation and higher neuroinflammation (Castro, Zaman & Holland, 2017).

In contrast, late-onset AD has been characterised as a sporadic and multifactorial-causal disease, with a considerable genetic component related to its development. The most consistent finding throughout the literature has revealed the Apolipoprotein-E (APOE) gene as the main genetic risk factor for AD in people older than 65 years (Strittmatter et al., 1993; Bekris et al., 2010). This gene, located on chromosome 19q12, is responsible for the synthesis of a protein that acts as a mediator for cholesterol transport, neural development and regeneration, and immunomodulation. Moreover, three main genetic variants are produced depending on the allele in a single locus ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) that result in specific isoforms named as ApoE2, ApoE3 and ApoE4 (Van Cauwenbergh et al. 2015). Of these, APOE- $\epsilon 4$ has been shown to increase the risk of developing AD by triplicate in heterozygotes (OR=3.2) and almost fifteen times in homozygotes (OR=14.9) (Farrer et al., 1997; Bertram et al., 2007). Furthermore, the presence of the $\epsilon 4$ allele has been shown to be also associated with an early onset of disease (Gomez-Isla et al., 1996). Clinically, the presence of the ApoE4 isoform has been associated with cognitive impairment and faster progression from the prodromal stages to AD dementia and the ApoE2 isoform has been associated with a global lower risk of decline in AD; nonetheless, there is yet no conclusive evidence that these specific alleles are associated with the disease in a causal manner (Martins et al., 2005). Current research into genomics has identified additional genes that play a

crucial role in the clinical evolution of AD; for example, ADAM10, ACE, BIN1, CLU, PICALM, SS4A2, ECHOC3, SORL1, ABCA7, CR1, HLA-DRB1 and TREM2 (Kunkle et al., 2019). Lastly, due to the genetic complexity that is involved in modulating the clinical expression of AD in its late-onset form, polygenic risk score models have been devised with the purpose of taking into consideration the aggregate detrimental effect attached to the multiple genetic contributions responsible of AD onset (Zhou et al., 2021). These genetic models have the objective to improve the predictability of the disease and the therapeutic options through individualised risk management (Escott-Price et al., 2017).

1.3 Protective Factors

1.3.1 Physical activity

Exercise and general physical activity, commensured to a patient's age and personal capacities, has shown a consistent protective effect on altering the inherent progression of AD. In this context, research has shown that exercising more than three times a week for at least 15 minutes a day, significantly decreases the risk of conversion to AD dementia in mildly cognitively impaired patients (Larson et al. 2006). Additionally, it seems that these protective effects are enhanced when physical activity is based on sport-related rather than work-related exercise (Stephen et al., 2017). Ultimately, current research has found that people who do moderate-intensity walking on a daily basis, for approximately 20-30 minutes, have a 40% less chance of AD occurrence in contrast to sedentary matched individuals (Santos-Lozano et al., 2016).

1.3.2 Nutritional factors

A substantial amount of research about diet in patients with AD has shed light into the protective factors that come along with adherence to a Mediterranean-type diet, that has demonstrated a significant reduction of AD risk in large prospective cohort studies ([Scarmeas et al., 2009](#); [Sofi et al., 2010](#)). Furthermore, everyday foods rich in vitamins, antioxidants and polyunsaturated fats, in addition to low intake of alcohol (more importantly wine, due to antioxidant properties), has been shown to be beneficial for patients at risk of developing AD ([Letenneur, 2004](#); [Hu et al., 2013](#)).

1.3.3 Cognitive reserve

With regard to the severity of the symptoms in AD, cognitive reserve has been identified as an essential protective factor that can be, as a consequence, one of the fundamental non-pharmacological treatment approaches in neurodegenerative conditions. In this context, Katzman et al. ([1988](#)) found, in a *post-mortem* study, that some patients with preserved cognitive functionality during lifetime manifested pathology comparable to a definitive diagnosis of moderate AD. This was initially explained as a possible higher preservation of a reserve of neuronal populations. Subsequently, Fratiglioni and Wang ([2007](#)) proposed that lifetime factors such as education, leisure activities, professional challenges and social functioning could directly interact with an increased resilience of the brain parenchyma to structural damage. Therefore, preservation of neuronal tissue could have a direct effect on the conservation of networks and, hence, on the adaptability of cognitive performance in the presence of neuronal damage (an occurrence that is now known as cognitive reserve). Lastly, brain reserve and cognitive reserve could potentiate brain plasticity

and serve as crucial protective factors for AD development. Likewise, potential cognitive therapeutical interventions toward these factors would be a great way to approach treatment when pharmacological compounds are not effective ([Stern et al. 2018](#)).

Lastly, social context has been shown to be a key aspect of everyday life interactions in dementia-susceptible people. In most circumstances, activities of daily life rely heavily on the interaction with family and carers. Research into patients' social cognition could give valuable suggestions into how the patient-carer relation begins to slowly diverge, a change that, in turn, increases caregiver's burden, risk of institutionalisation and onset of neuropsychiatric symptoms ([Cosentino et al., 2014](#)).

1.4 Physiopathology

The constant interaction of risk and protective factors during the lifetime of a person will eventually trigger the physiopathological cascade that delineates the natural history of AD. However, although substantial research has been produced in this matter, the causal explanation of the pathological manifestations of this disease is still poorly understood. Since the discovery of the disease, almost a century ago, the hallmark histological features of the disease have been recognised as the accumulation and brain deposition of amyloid protein or neuritic plaques and neurofibrillary tangles (constituted of hyperphosphorylated tau protein), primarily in neocortical structures and medial temporal lobe, respectively. Nevertheless, current research has expanded in the detrimental effect of other factors that also contribute to the progression of this neurodegenerative disorder. Therefore, to create research

models and elucidate the biological mechanisms of disease, several hypotheses have been proposed to this day ([Knopman et al. 2019](#)).

In the literature, the amyloid hypothesis is still recognised as the main physiopathological entity that explains, at a cellular level, the main manifestations of AD. The conceptualisation of this hypothesis, as proposed by Hardy and Higgins ([1992](#)), suggested that the abnormal accumulation of the amyloid-beta protein could be defined as the core causal agent for the presentation of AD. This would consequently lead to further neuronal loss, production of neurofibrillary tangles and, ultimately, dementia ([Hardy & Higgins, 1992](#)).

The amyloid cascade starts with a glycoprotein embedded in the neuronal membrane termed as amyloid precursor protein (APP) that possesses an intracellular and extracellular component, a feature that defines it as a transmembrane protein. In a physiological context, APP has been proposed to help in neuronal growth and regeneration after neuronal damage; however, its specific function is yet to be determined. This physiological non-amyloidogenic cycle eventually leads to cleavage of the APP, after it has fulfilled its biological function within the cell, which is to have macromolecules and essential amino acids ready to be used for other intracellular processes. The enzymes in charge for this cleavage are α -secretase and γ -secretase (that contains an active site of either Presenilin 1 or 2) in charge of the creation of soluble protein by-products. A third enzyme named β -secretase (and more importantly, the β -site-APP-cleaving enzyme 1, BACE1) can interact also with APP. The latter cleavages the protein into a monomeric proteolytic by-product known as amyloid-beta ($A\beta$) that, in conjunction with the γ -secretase splitting process, forms two main residual protein isoforms namely, $A\beta_{40}$ and $A\beta_{42}$ (the most common form in AD) ([Chow et al., 2010](#); [Gu & Guo, 2013](#)). As a consequence, the neuronal injury of $A\beta$ pathology relies

not on the neurotoxicity of the molecule itself, but on the balance between its creation and clearance in the brain. Therefore, the amyloidogenic pathway results from an extracellular accumulation of chemically “sticky” A β 42 monomers that are highly susceptible to bind with each other to form more stable A β 42 oligomers. This will lead, as a result, to the formation of diffuse insoluble amyloid plaques. In this setting, the accumulation and further deposition of these plaques will induce mechanisms that favour synaptotoxicity and neuronal death (Hardy & Selkoe, 2002). Conspicuously, although extensive research has portrayed the amyloid hypothesis as the core hallmark of AD pathobiology, the current literature does not support that amyloid deposition solely is sufficient enough to account for the complex aetiopathological changes that precede AD dementia, at least in sporadic cases of AD (Hardy, 2009). Furthermore, other neurodegenerative diseases, which may also lead to mild cognitive impairment (MCI) and later dementia, have been shown to rely on non-amyloidogenic pathways, leading to complications in the overall medical examination and denoting the importance of proper assessments for differential diagnosis (Caroli et al., 2015).

For this reason, tau deposition has been proposed to be a synergic key feature in the histopathological development of AD (Wood et al., 1986). Tau can be characterised as a protein associated with a family of scaffolding proteins called microtubules that constitute part of the cytoskeletal complex, generally in mature neurons. Its function is mainly the specific assemblage of tubulin into microtubules that, in addition, grants cellular structural stabilisation (Iqbal et al., 2010). In AD, two isoforms of tau (3R and 4R) may aggregate in a hyperphosphorylated state that provokes cytopathological inclusions in the neuronal body referred to as neurofibrillary tangles (NFT) (Espinoza et al., 2008).

The accumulative effect of the previously mentioned distinctive neuropathology (most importantly, tauopathies and amyloidosis) could interact in three important domains, namely, synaptic disruption, neuroinflammation and amyloid angiopathy (DeTure & Dickson, 2019). Synaptic dysfunction has been proposed as one of the essential biological lesions in AD. In this context, the cholinergic hypothesis stipulates that selective damage of cholinergic neurons in structures and nuclei such as the amygdala, hippocampus, frontal cortex, nucleus basalis and medial septum modulates the clinical expression of AD. These alterations, mediated by AD proteinopathies, have shown a decrease in substrate uptake (choline), subsequent neurotransmitter release into the synaptic cleft and downregulation of receptor expression (Francis et al., 1999; Sanabria-Castro et al., 2017; Hampel et al., 2019). Similarly, glutamate transmission and NMDA receptors are compromised in AD starting in the entorhinal cortex, spreading to the hippocampus, amygdala and later frontal and parietal cortices, where neuronal increased excitability can lead to neuronal death and neurodegeneration (Mohandas, Rajmohan & Raghunath, 2009; Wang & Reddy, 2017). Notably, significant research has pointed out that dopaminergic degeneration in rich areas such as the Ventral Tegmental Area (VTA) in the midbrain may happen in the earliest stages of AD (or preclinical stage) and could affect the mesocorticolimbic dopaminergic pathway projecting to the amygdala, nucleus accumbens, hippocampus and prefrontal cortex (Iaccarino et al., 2020). As a consequence, chronic dopamine downregulation would affect ultimately functions involved in plasticity, reward and memory consolidation (De Marco & Venneri, 2018; Krashia, Nobili & D'Amelio, 2019). The vital association of synaptic dysregulation and symptomatic expression has shed light into pharmacological treatments indicating that, in the absence of current demonstrably

effective disease-modifying therapies, neurotransmitter modulators are still the best available treatment option for AD ([Kandimalla & Reddy, 2017](#)).

Neuroanatomical progression of AD pathology also depends on its characteristic histopathological hallmarks, namely, β -amyloidosis and neurofibrillary tauopathy. In this sense, amyloid progression generally constitutes five stages of disease progression. The first stage affects diffuse cortical areas of association and later overall neocortical regions (stage A and B respectively of Braak and Braak); stage 2 affects the entorhinal cortex, hippocampal formation, amygdala, insula and cingulate cortices; stage 3 presents with a spread of pathology to diencephalon and subcortical nuclei (such as the basal forebrain cholinergic nuclei and thalamus); stage 4 is characterised by the involvement of brainstem structures that includes the substantia nigra and tectum colliculi; lastly, in stage 5 (stage C of Braak and Braak) A β spread deposits in the pons (reticulo-tegmental nuclei, dorsal tegmental nucleus, raphe nuclei and locus coeruleus) and molecular layer of the cerebellum ([Braak and Braak, 1991](#); [Thal et al., 2002](#)).

On the other hand, Braak and Braak ([1995](#)) also clustered the anatomical dissemination of NFT spread pathology in AD. Stage I and II stipulates an initial deposition of tau in the transentorhinal region (the medial region of the perirhinal cortex) in the temporal mesial cortices ([Taylor & Probst, 2008](#)); stage III shows involvement of the entorhinal region (with extended damage in the pre-alpha layer); stage IV displays dissemination of NFT in proximal hippocampal regions (CA1) and mildly to subiculum, limbic regions, basal nuclei, thalamus and neocortex; stage V has a high compromise of the hippocampus and neocortex; lastly, stage VI shows NFT deposition extension to the extrapyramidal system and overall cortical regions ([Braak & Braak, 1991](#); [Braak et al., 2006](#)).

If one extrapolates the neuroanatomical sequence of pathological hallmarks of AD with the clinical manifestations, the amyloid hypothesis loses strength, as the initial symptomatic manifestations move in parallel with those found in relation to a decline in hippocampal functionality. The most plausible overlap of pathological alterations that are associated tightly with the symptomatic spectrum is with NFT deposition. In relation to this, synaptotoxicity can be mediated by tau deposition, and this could explain the close connection between this proteinopathy and the clinical signs ([Pooler, Noble & Hanger, 2014](#)). In this sense, research efforts are currently focusing on therapeutical approaches targeting tauopathies. This line of evidence could also explain, to some extent, the failure of anti-amyloid disease-modifying treatments in showing an effect on symptoms, despite successful clearance of amyloid deposits from the brain ([Mullane & Williams, 2020](#)).

Synaptic research is currently concentrating on other satellite mechanisms that are involved in synaptoplasticity. For example, ApoE proteins are expressed by several nervous system cell-lines such as neurons, astrocytes and microglia. This protein acts as a cholesterol transporter, a ligand for endocytosis of lipoprotein molecules and is the leading apolipoprotein in circulating brain high-density lipoprotein (HDL). Consequently, released cholesterol may be essential for structural synaptogenesis and synaptic performance ([Kim, Basak & Holtzman, 2009](#)).

The vascular hypothesis of AD stipulates that small vessel dysfunction could result in a reduction of AD pathology clearance in the brain. Additionally, the compromise of the blood-brain barrier and endothelial damage may also lead to extravasation of plasmatic elements, in which an abnormal accumulation could contribute to neural toxicity ([Janota, Lemere & Brito, 2016](#)). Finally, it is noteworthy to mention that AD may have its neurodegenerative aetiology in ageing itself, which is

already the main risk factor. The integrative process of this disease includes nine progressive interwoven senescence mechanisms, namely, DNA instability, telomere contraction, epigenetic changes, mitochondrial dysfunction, cellular biological ageing, impaired nutrient intake, stem cell decline, altered cellular communication and loss of proteostasis (which leads to abnormal protein metabolism, an essential trait of neurodegenerative disorders) (Hou et al., 2019). These age-related processes, in addition to a gradual decrease in cellular regenerative mechanisms, could trigger the onset of characteristic microstructural features typical of AD and other types of age-related neurodegeneration processes (Hou et al., 2019).

In conclusion, research in the aetiology of AD has shed light into the conjoined but independent detrimental effects of amyloid and tau proteinopathies in susceptible brains that could find their foundations in altered APP metabolism. Nonetheless, other aetiological factors such as the interaction of ApoE (Gomez-Isla et al., 1996), vascular contributions (Govindpani et al., 2019), neuroinflammation, oxidative stress and calcium dysregulation could all interplay into explaining the causality of AD, that could activate complex cellular detrimental mechanisms resulting in neuronal death and brain degeneration (Tönnies & Trushina, 2017).

1.5 Diagnosis

The characteristic pathological traits of AD will have a detrimental effect on the neurophysiology of brain cells and concomitant cellular mechanisms. Therefore, physiopathological alterations such as neuroinflammation, synaptic disruption and non-programmed neuronal death will eventually lead to the decline of specific brain-associated functions that may be interpreted as distinctive behavioural and cognitive

symptoms. The definitive diagnosis of AD is accomplished by confirming the characteristic pathological markers in *in vivo* brain tissue. Nevertheless, there is still no practical non-invasive technique available to achieve this; therefore, gold-standard definitive diagnosis is established in *post-mortem* tissue (Weller & Budson, 2018). As a result, the internationally accepted current diagnostic research (Jack et al., 2018; Dubois et al., 2021) and clinical (McKhann et al., 2011) criteria rely primarily on three core components that could identify the disease during the lifetime of the patient, namely: clinical spectrum, neuroimaging patterns and molecular biomarkers. The most current understanding towards a diagnosis of AD requires a clinical-biological approach through the use of biomarkers and a characteristic phenotype (Jack et al., 2018; Dubois et al., 2021); however due to cost-effectiveness or invasiveness, clinical-neuroimaging diagnosis continues to prevail as a reliable diagnostic method.

1.5.1 Classification

Current evidence reveals that asymptomatic patients with late-onset AD already have a high load of pathological markers in their brain decades before they seek medical advice (Vos et al., 2013). Therefore, the heterogeneity of the clinical spectrum in which detrimental and protective factors (such as cognitive reserve) are in constant interaction translates into substantial differences in the clinical profile at an individual level. For this reason, patients can be classified into three critical diagnostic entities defined as preclinical, prodromal and dementia stages of AD. The objectivity that characterises the classification of these nosological entities depends mainly on the presence (A+) or absence (A-) of a biomarker of abnormal brain amyloid accumulation evidenced by A β 42 in cerebrospinal fluid (CSF) or amyloid-PET imaging. Secondly,

the presence (T+) or absence (T-) of tau protein aggregation in the form of NFT evidenced by phosphorylated tau in CSF or tau-PET imaging. Lastly, a process of neurodegeneration can be present (N+) or absent (N-) when evidenced by anatomical detrimental changes with MRI, metabolic positron emission tomography (PET) imaging or the total amount of tau-CSF ([Jack et al., 2018](#)).

1.5.1.1 Preclinical stage

Preclinical AD has been defined as a stage in which patients lack a consistent clinical spectrum of MCI or dementia but have already developed build-up of brain characteristic proteinopathies (more specifically of diffuse amyloid accumulation) decades before the clinical features are compatible with cognitive decline ([Sperling et al., 2011b](#); [Villemagne et al., 2013](#); [Vos et al., 2013](#)). The inconsistency of the anatomopathological signatures with distinctive symptomatic manifestations in some patients might be explained as a result of the continual interaction of protective factors, for instance, cognitive reserve or healthy lifestyle activities that take part in the modulation of the preclinical stage timeline or evolution ([Soldan, Pettigrew & Albert, 2018](#)).

The International Working Group (IWG) and the National Institute on Aging-Alzheimer's Association (NIAA) have further classified this stage into individuals who are 1) asymptomatic at risk and 2) presymptomatic AD. The latter can be characterised as subjects who would inevitably develop AD due to genetic predisposition, such as those with early-onset AD. In the asymptomatic-at-risk stage 1, patients should exhibit positive AD biomarkers based on *in vivo* measures of amyloidosis. Consequently, stage 2 exposes further evidence of a neurodegenerative process. To deliver a

diagnosis of preclinical AD, a range of objective clinical assessments should be used, such as CSF or brain imaging based on positron emission tomography (PET) with A β -based ligands as substrates. Lastly, stage 3 can be distinguished with the presence of subtle cognitive alterations, in an established process of amyloidosis and neurodegeneration that is identified in more challenging assessments of complex mental processes, a stage that precedes closely the MCI stage (Sperling et al., 2011b; Dubois et al., 2016). The preclinical stage (biomarker positive) may take up to 20 to 30 years to develop into MCI or AD dementia; however, some patients may potentially take even longer or never shift (Sperling et al. 2011b).

The presented diagnostic approaches have now considered neuropsychological profiling as a supplementary component for classification of the preclinical staging of the disease that currently relies primarily on molecular objective measurements. However, targeted neuropsychological profiling has shed light into cognitive changes that can even be detected early in the preclinical stage of the disease. In this context, a meta-analysis performed by Duke and colleagues (2017) has shown subtle but significant differences in cognitive performance in preclinical patients that expressed positive biomarkers, in comparison to healthy elderly controls. As an example, decline of semantic memory in preclinical AD has been found to be a diagnostic novel approach in the very early stages of the disease, even preceding the established role of episodic memory decline as one of the first incipient changes to define mild cognitive impairment, which is an essential attribute for cognitive profiling (Venneri et al., 2016). On the premise that pathological changes caused by NFT have demonstrated to have a strong correlation with cognitive decline, the neuroanatomical progression of NFT could clarify the global patterns that would model the clinical spectrum of a person with AD. Therefore, direct extrapolation of grey matter loss (due to the neurodegenerative

cascade associated with NFT) in the initial medial perirhinal cortices, which are in charge of the modulation of declarative memory and semantic processing, could provide insight into the initial cognitive domain affected by the disease ([Hirni et al., 2013](#)).

Moreover, deficits in essential higher cognitive abilities, such as self-awareness and metacognition, have also been associated with the preclinical stage of AD. The capacity of introspection that grants awareness of cognitive changes has proven to be a more useful clinical instrument in the pre-MCI stage than subjective memory complaint, as it associates more closely with amyloid burden ([Cacciamani et al., 2017](#)). Therefore, this concept has partially established the foundations of the project in this thesis involving the study of cognitive awareness (self-awareness and awareness of others) across the MCI to early dementia stages.

1.5.1.2 Mild Cognitive Impairment

The prodromal stage of dementia or MCI has been defined by Petersen and colleagues ([1999](#)) as a decline in cognitive performance (and more essentially, memory in the case of AD dementia) in relation to people of the same age and education that do not fulfil diagnostic criteria for dementia. In this sense, it bridges, in a global clinical perspective, the stage of normal cognitive ageing with dementia. It can be further classified as amnesic MCI (aMCI) (affecting the memory domain) and non-amnesic MCI (naMCI). The natural history progression pathway generally shifts aMCI into AD dementia, while naMCI may evolve into any type of dementia, which could also include AD ([Fischer et al., 2007](#); [Bora & Yener 2017](#)). Furthermore, some authors have put forward the term “mild behavioural impairment” as a new label for patients whose initial

dysfunction involves behavioural symptoms and display relative preservation of cognitive functionality, with an accompanying risk of progressing to dementia (Taragano et al., 2009; Rosenberg et al. 2013; Ismail et al. 2017).

1.5.2 Symptomatic spectrum of AD

The clinical diagnostic criteria for patients with the prodromal stage of AD or MCI due to AD are based on the National Institute on Aging-Alzheimer's Association (NIAA) workgroups diagnostic guidelines for AD (Albert et al., 2011). Setting aside the subtle cognitive changes in the preclinical stage, the starting clinical hallmark of AD relies on changes in prospective cognitive performance in relation to a previous time of optimal function (Bilgel et al., 2018). This can be evidenced with alterations namely in memory, attention, executive functions, visuospatial abilities or language. In this context, memory disturbances continue to be the most notable highlight of decline in the initial clinical stages; and more importantly, the alteration in the ability to consolidate accurately declarative episodic memories (everyday life experiences) and autobiographical memories (Gallagher & Koh, 2011; Sperling et al., 2011b; Bature et al., 2017). Secondly, an essential trait that patients must present to be classified as MCI is the maintenance of overall independence in activities of daily living (Petersen et al., 1999). Therefore, patients in the prodromal stage of AD would not fulfil criteria for a diagnosis of any form of dementia.

The clinical features of a probable AD diagnosis depend initially on the chronic progression of the disease, in which symptoms worsen over time. Secondly, the amnesic presentation is the most frequently related to progression to AD type dementia, defined as a decline in the ability to learn and memorise recently acquired

information ([Petersen & Negash, 2008](#); [Csukly et al., 2016](#)). Thirdly, this decline is accompanied by impairment in at least one more cognitive domain (other than memory) such as executive functioning, visuospatial skills (and topographical memory), language (word-finding problems) or the appearance of neuropsychiatric symptoms (NPS) ([McKhann et al., 2011](#)). On the other hand, the non-amnesic form can express dysfunctions that could impact, as its fundamental clinical manifestation, on cognitive domains such as language, visuospatial or executive functions. In the case of mixed pathobiological backgrounds, which may be compatible with other types of dementia or atypical symptomatology, the diagnostic outcome should rely upon a definition of possible AD ([McKhann et al., 2011](#); [Warren, Fletcher & Golden, 2012](#)).

Neuropsychiatric or behavioural symptoms are a paramount concept to help clinicians approach any type of dementia or neurodegenerative disorder. An overall consistent pattern of NPS expression will affect 98% of the patients with dementia at any point of the disease course depending on the neurodegenerative aetiology, and has served as an important assessment instrument for neurological differential diagnosis ([Müller-Spahn, 2003](#)). A first essential concept that can be defined when approaching this cluster of symptoms is their possible early-onset. Patients in prodromal, and even preclinical stages, may display a certain degree of behavioural manifestations ([Rosenberg et al., 2013](#); [Ng et al., 2017](#)) with depression (30%), sleep disturbances (18%) and apathy (15%) being the most frequent ([Kohler et al. 2016](#)). Secondly, these symptoms seem to modulate the overall natural history of the disease, that may include a faster progression and conversion to dementia, increased risk of institutionalisation and caregiver burden, deterioration of quality of life and eventually death ([Aalten et al., 2005a](#)).

The most prevalent NPS in dementia are apathy, depression, irritability and anxiety (Mega et al. 1996; Lyketsos et al. 2002; Zhao et al. 2016). Notably, each type of dementia displays a different spectrum of behavioural manifestations. For example, the most common NPS in AD is apathy (Mega et al. 1996; Palmer et al. 2011; Zhao et al. 2016); apathy and depression are the most common symptoms in vascular dementia (Fernandez-Martinez et al. 2008), hallucinations and delusions in Lewy Body Dementia (Ballard et al. 2013), and loss of insight and apathy in frontotemporal dementia (Snowden & Neary, 1999).

In conclusion, the progressive symptomatic manifestations that are characteristic of AD have shown to be more closely associated with damaged areas harbouring tauopathies rather than diffuse amyloidopathy. Therefore, tau deposition could serve as a biological mediator between the diffuse proteinopathy spread and the clinical continuum (Bennett et al., 2004; Hanseeuw et al., 2019). Patients who show progression to AD dementia display, as one of the first clinical hallmarks, the incapacity to perform activities of their everyday life properly, which in turn, affects directly their global status of independence. This notion is the pillar conceptual framework that supports the differentiation of the MCI stage from dementia. Lamentably, the spreading damage of cognitive domains will continue to enlarge the symptomatic spectrum of cognitive dysfunction in these patients, in conjunction with a more evident demonstration of neuropsychiatric symptoms (Jack et al., 2018).

Diagnosis based solely on clinical characteristics is currently not recommended, as almost one in every three patients diagnosed with “AD spectrum”, using only clinical criteria, will manifest a different neurological aetiological entity, for example, vascular lesions, hippocampal sclerosis or Limbic-predominant Age-related TDP-43 encephalopathy (LATE) (an amnesic syndrome associated with dementia that mimics

the clinical expression of AD) (Masters et al., 2015; Nelson et al., 2019). For this reason, definitive diagnosis should also be supported by biochemical and neuroimaging markers.

1.5.3 Atypical symptoms of AD

Typical clinical manifestations of AD can be construed as a cognitive multi-domain syndrome with a predominant amnesic component. However, atypical syndromic variants of AD may display diverse symptomatology that is consequential to initial neurodegeneration in distinct regions other than the hippocampus (Galton et al., 2000). The main atypical forms of AD reported in the literature include a visual variant defined as posterior cortical atrophy (PCA), a language-temporal variant termed logopenic aphasia and a frontal variant of AD (Warren, Fletcher & Golden, 2012; Dickerson et al., 2017).

In more depth, PCA is characterised clinically by early visuospatial dysfunction due to parieto-occipital grey matter reduction, which is progressive and displays an insidious onset. Visual alterations can include impairment of space and object perception, oculomotor or limb apraxia, visual agnosia, alexia, constructional dyspraxia or defects in the visual field (Benson, Davis & Snyder, 1988; Crutch et al., 2017).

Logopenic aphasia is a type of primary progressive aphasia (PPA) that can be distinguished symptomatically as a language disorder that exhibits a specific dysfunction in naming and repetition that includes single-word retrieval and phonologic deficits and that causes a slow-down of speech production (Henry & Gorno-Tempini, 2010; Gorno-Tempini et al., 2011). The AD-type pathological substrates trigger

macroscopic alterations that were firstly described in the left posterior perisylvian area ([Mesulam, 1982](#)), with additional cortical atrophic changes in inferior parietal regions ([Beber et al., 2014](#)).

Lastly, the frontal (behavioural or dysexecutive) variant of AD can be defined phenotypically as the presence of prominent decline in executive function and NPS that are compatible with AD pathology, more specifically predominant NFT accumulation in frontal regions ([Johnson et al., 1999](#)); paradoxically, overall grey matter reduction can be observed in temporoparietal regions, a characteristic of typical AD, rather than frontal atrophy ([Ossenkoppele et al., 2016](#)).

The significant challenge of AD clinical diagnosis, when atypical variants play as confounding variables in the clinician's judgement, has pushed worldwide consensus criteria to develop other tools based on biomarkers to assure certainty of diagnosis, in which disease-modifying treatments could be beneficial if initiated in the earliest stages.

1.6 Neuroimaging

Brain imaging has gradually become an indispensable tool required for the diagnosis of AD as the machinery behind it undergoes a process of constant technological sophistication. The historic shift from clinical visual estimations to objective measures of quantification brain loss has relied fundamentally on the use of neuroimaging tools, as a foundation concept for current non-invasive diagnosis ([Johnson et al., 2012](#)).

1.6.1 Structural Imaging

Physics behind the functionality of Magnetic Resonance Imaging (MRI) starts at the anatomical level, specifically in the hydrogen atoms of water molecules (H₂O) that compose approximately 60% of the human body mass. MRI employs magnetic fields and radio frequencies, in contrast to ionising radiation used by other methods of imaging such as x-rays or computerised tomography. The strength of the magnetic field is measured in Teslas, in which the machine operates generally at 1.5, 3, 7 or 11 Teslas (T), providing an improved signal-to-noise ratio detection for better visual resolution. This potent magnetic field interacts with the magnetic properties of hydrogen atoms in body organs to produce images. The primary magnetic field, referred to as the static permanent field, aligns the hydrogen atoms in a phenomenon called longitudinal magnetisation, in the long axis of the magnetic field. Additionally, the hydrogen nucleus displays a spinning property around its axis that has been defined as magnetic momentum. These spinning nuclei can show excitability when a second magnetic force is applied in the form of radio frequencies. The immediate consequence of this process is the release of energy and, depending on the amount of energy released, it will take a specific amount of time to realign all atoms to the same direction. Subsequently, these differences of alignment emit different radiofrequency signals that are measured by the MRI machine and depend on the specific head tissue. This translates in an output image of the differently acquired brain intensities. Therefore, from a clinical perspective, clinicians will be able to assess *in vivo* structural intracranial tissue with precision to evaluate and diagnose relevant neurological alterations ([Grover et al., 2015](#)).

In the theoretical construct of neurodegenerative diseases, structural imaging is one of the most commonly used methods to support diagnosis in dementia. One of

the distinctive attributes that portrays AD, and that is measured through structural MRI, is the visual evidence of progressive brain atrophy that can be interpreted biologically as a macroscopic reduction of brain tissue due to neuronal death, secondary to pathobiological processes ([Whitwell et al., 2010](#)). The clinical advantages for the systematic use of structural imaging rely on the strong association with NFT deposition and topological-associated neuropsychological decline. Therefore, it has been currently established as a strong marker of neurodegeneration ([Frisoni et al., 2010](#)). The specific pattern of atrophy clusters predominantly in global atrophy of the hippocampus ([Gosche et al., 2002](#)) and middle temporal lobe regions, with a higher predominance of left-hemispheric structures that is concurrent with cognitive alterations in memory-based domains ([Scheltens et al., 1992](#); [Scahill et al., 2002](#)). Hence, in the initial stage, it is crucial to perform differential diagnosis with normal cognitive ageing; the latter shows a typical pattern of grey matter reduction in prefrontal neocortices as the first feature of grey matter decline ([Tromp et al., 2015](#)). Moreover, a comparative study conducted in AD and healthy elderly individuals demonstrated almost twice as many atrophic cortical changes in AD patients in comparison with normal cognitive ageing ([Bakkour et al., 2013](#)). Conversely to the ageing process, the initial point of atrophic changes in the very early preclinical stage of AD is a reduction of the entorhinal cortex, a region that longitudinal studies have evidenced to be indispensable for predicting disease progression ([Killiany et al., 2002](#)). Furthermore, the presence of medial temporal lobe atrophy has also been indicated as a predictive factor for conversion to dementia ([DeCarli et al., 2007](#)). Chronicity of atrophic changes in AD can be fairly traced back in time, as the rate of hippocampal atrophy per year is approximately 3.5% - 4.5%, and it means that macroscopic brain damage is present years or even decades before the appearance of symptoms ([Barnes et al., 2009](#)).

Clinicians' visual rating of medial temporal reduction in structural imaging has shown a sensitivity and specificity of 80% to 85% for diagnosis, percentages that support its use for differential examination among people with normal cognitive ageing, aMCI, naMCI and AD (Duara et al., 2008). In contrast, one study has not found validity for the regular implementation of this method after accounting for important variables such as APOE status and episodic memory performance (Persson et al., 2017). Therefore, automated segmentation of pathognomonic regions linked to disease could help improve the diagnostic specificity and sensitivity of structural MRI methods, in addition to a reduction of the clinician's time to formulate a diagnosis and overall increase in cost-effectiveness (Amoroso et al., 2018; Ledig et al., 2018).

In a general overview, the topological progression of AD will affect, in a second stage, neocortical areas by involving possible synaptic hippocampal connecting pathways to temporal-frontal-parietal regions, for instance, the posterior cingulate in the parietal cortex and the subgenual frontal cortex. Targeted fronto-temporo-parietal grey matter loss exposes a more remarked exhibition of detrimental outcomes in executive functions, language and visuospatial abilities (Frisoni et al., 2009). Lastly, continuous disease spread would eventually alter sensory-motor cortices, subcortical regions and white matter tracts (Whitwell, 2010; Pini et al., 2016).

1.6.2 Metabolic Imaging

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have shown to be an important clinical aid to a clinician's diagnostic judgement, with additional advantage for research purposes. For this reason, this method is now considered one of the core biomarkers for AD diagnosis. The most

common approach of PET imaging in AD relies upon the measurement of local brain glucose metabolism that is an indirect representation of synaptic activity, through a marked radioactive tracer called fludeoxyglucose (FDG or 18F-FDG) (Marcus, Mena & Subramaniam, 2014). Areas that exhibit reduced glucose metabolism have revealed a notable overlap with the functional correlates of the default mode network, one of the main brain large-scale networks that modulates cognition in humans (Bressler & Menon, 2010). This evidence validates PET imaging as a pragmatic tool that measures a proxy of functional brain activity (Watabe & Hatazawa, 2019). Patterns of hypometabolism will converge primarily in the posterior cingulate cortex, precuneus and middle temporal structures, showing a sensitivity of 94% and specificity of 73% (as other types of dementia can present a similar pattern of hypometabolism) (Ossenkoppele et al., 2013; Tripathi et al., 2014).

More recently, amyloid and tau *in vivo* tracers for molecular imaging have been incorporated into the core clinical criteria, because of their potential applicability as diagnostic biomarkers for (A+) and (T+), respectively (Jack et al., 2018). Through the use of amyloid tracers such as the Pittsburgh Compound B (PiB), F-florbetapir-46, Flutemetamol and F-florbetaben, *in vivo* amyloid identification has bestowed advantages for differential diagnosis (for example, normal cognitive ageing and other dementias) in the very early stages of the disease (Ossenkoppele et al., 2015). Therefore, these tracers have been established to be practical tools to detect AD-related pathologic changes and consequently classify a patient as being on the Alzheimer's continuum, with a sensitivity of 94% and a sensitivity of 79% (Morris et al., 2016; Jack et al., 2018). Nevertheless, this clinical approximation has not reported a consistent association with cognitive measures or neurodegeneration status, a finding that provides limited diagnostic applicability in the later prodromal stages (Iaccarino et

al., 2017). In the clinical framework, the pragmatism of amyloid imaging demonstrates that, regardless of the aetiopathological background, positive results can be evidenced decades before the onset of clinical symptoms, and this grants valuable time for pharmacological and non-pharmacological therapeutic interventions (Jansen et al., 2015).

Tau-PET has been one of the latest *in vivo* imaging techniques to be developed as a result of the protein biochemical complexity that has consequently slowed down the synthesis of selective tracers that can bind with a high affinity (Villemagne & Okamura, 2014). Anatomical imaging distribution of tau-related proteinopathy has shown compatibility with the Braak-tau staging of histopathological regions generally affected by AD such as the medial temporal lobe (entorhinal cortex, parahippocampal gyrus) and at a later point in the disease course, the inferior temporal and frontoparietal lobes (Cho et al., 2016, Schöll et al., 2016). More importantly, tau-tracers uptake also demonstrates a significant overlap with cognitive deterioration and synaptic dysfunction typical of AD that flows in concurrence with tau evolution (Ossenkoppele et al., 2016). Tau-PET has a meaningful higher specificity to detect AD than amyloid imaging that enables it to be used as a useful differential diagnostic marker for other types of dementia or atypical variants of AD (Dronse et al., 2017).

In summary, PET imaging has great applicability in the AD diagnostic framework; however, it also relies profoundly on a clinician's understanding, as every molecular tracer has a different diagnostic purpose in the context of a patient's clinical history. Hence, the usage of PET imaging operates in parallel with the pathobiological spectrum of disease progression, in which amyloid-PET grants insights for the stratification of the disease on the amyloid continuum with a presentation of dispersed deposition of whole-brain amyloid, regardless of clinical performance. Secondly, tau-

PET has higher specificity to differentiate nosological neurodegenerative entities, with the disadvantage of lower tracer binding strength, a consequence of current tracer biochemical properties. Lastly, FDG-PET, as a representation of synaptic dysfunction, has shown greater accuracy for AD diagnosis, and should be acquired ideally in relation to amyloid, tau and other molecular tracers ([Perani et al, 2016](#); [Dronse et al., 2017](#); [Iaccarino et al., 2017](#)).

1.6.3 Functional Imaging

Localised structural degeneration of regions that are intrinsically connected to the medial temporal lobe has validated the use of functional magnetic resonance imaging (fMRI) as an invaluable instrument to study brain activation and connectivity dysfunction in AD. The biological basis of fMRI is dependent of blood-oxygen homeostatic properties to create the blood-oxygen-level-dependant (BOLD) signal. The latter is constituted of the hemodynamic response to blood volume changes, regional flow and oxy-deoxyhemoglobin ratio ([Glover, 2011](#)). This can be transposed into a non-invasive indirect proxy of neuronal activity ([Logothetis et al., 2001](#)). In this context, there are two ways brain function can be estimated by fMRI: firstly, the individual undergoes a neuropsychological “task” that, at a neurobiological level, increases the ratio of oxygenated-deoxygenated blood in specific areas that require a higher metabolic cellular demand when performing the specified task. As a consequence, an area of activation will be contrasted to a control condition as a way to compare the different patterns of activation ([Sperling, 2011a](#)).

A second methodological approximation can be implemented based on the analysis of intrinsic brain connectivity, a neurophysiological trait of neuronal network

communication when an individual is at rest during the time the scan is acquired. This method has been denominated as resting-state fMRI (rs-fMRI) and has the potential of measuring whole or targeted network disruptions in patients with neurodegenerative disorders (Smitha et al., 2017). In the context of AD, the most consistent finding related to rs-fMRI is a decrease of connectivity in the posterior cingulate cortex and precuneus in the medial parietal lobe; these are regions that compose the posterior segment of a vital human network described as the default mode network (DMN). This is followed by compensatory increased connectivity of the anterior frontal DMN and the salience network (Vemuri, Jones & Jack, 2012). In this context, the progression of the disease will eventually impact on compensatory hyper-connected networks, displaying a pattern of typical disconnection across all the components of the DMN (Bai et al., 2011). The DMN has been found to be the most commonly affected network in AD (Greicius et al., 2004; Badhwar et al., 2017) and comprises functional topological interconnected areas such as the posterior cingulate cortex (PCC), precuneus, ventral and dorsal medial prefrontal cortex, inferior lateral parietal cortex and medial temporal regions (Buckner, Andrews-Hanna & Schacter, 2008). This large-scale network is made of smaller resting-state-associated interconnected regions that are active in a task-free status. The functional physiology of the DMN has shown to be responsible for the modulation of complex brain functions involving: 1) self-referential processes, namely, past autobiographical acquisition, self-prospection of future scenarios and self-projective simulation states, 2) social-cognitive skills that include inferential thoughts about others' beliefs and thinking (known as mentalising or Theory of Mind), and 3) undefined thoughts that are not associated with response to an external demand (Mével et al., 2011; Buckner & DiNicola, 2019). Lately, rs-fMRI has been proposed to be used systematically as a supportive diagnostic biomarker in the clinical field;

however, restrictions such as difficulties in the systematic analysis at a single-subject level or the widespread utilisation of a functional connectivity atlas still need to be overcome ([Damoiseaux, 2012](#)).

1.7 Biomarkers

In a biological perspective, the core methodological approximations for AD diagnosis namely, clinical, neuroimaging and molecular analysis compose, by their own conceptual definition, a biomarker. However, biomarkers are generally referred, in the current clinical criteria, as objective biological indicators of a physiological, pathological or biological process that, translated into the AD medical profile, are denoted to as neuroimaging and molecular diagnostic assessments ([Dubois et al., 2021](#)). In the context of this thesis, the discussed biomarkers in this section will be based on molecular assays of cerebrospinal fluid (CSF) and blood. As previously mentioned, the implications of current biomarker application in AD are sustained with the evidence of *in vivo* accumulation/deposition of amyloid (A+) and tau (T+) that, consequently, will produce a neurodegenerative process (N+) ([Jack & Holtzman, 2013a](#); [Jack et al., 2018](#)).

CSF biomarkers dynamics are based on CSF A β 42 or A β 42/A β 40 ratio. A decrement of CSF A β 42 levels has been adopted as a medical marker across neurology-based memory clinics with levels < 500pg/ml compared to healthy matched controls. Total tau protein in CSF has also been shown to be a valuable biomarker with levels ranging from > 450 – 600pg/ml in AD patients after the fifth decade of life ([Jack et al., 2011](#); [Sharma & Singh, 2016](#)). Phosphorylated tau may be one of the best molecular biomarkers for AD diagnosis with a specificity of 75% and sensitivity > 85%

([Hampel et al., 2004](#)). Lastly, Tau/A β 42 ratio is utilised as a suitable proxy as decrement of CSF amyloid is coincident with the progressive increase of tau and has been demonstrated to be a worthy biomarker in the preclinical stages ([Fagan et al., 2007](#)). The biggest limitation of CSF biomarkers, in comparison to other biological proxies, is the invasiveness of the lumbar puncture technique approach to obtain CSF that could lead to severe adverse effects if performed by inexperienced hands.

Notably, differential diagnosis using CSF biomarkers has shown valuable cues. Frontotemporal dementia patients tend to display higher levels of A β 42 with low tau. On the other hand, Parkinson's disease and vascular dementia patients have low levels of both, CSF amyloid and tau, in association with cognitive performance ([Skillbäck et al., 2015](#)).

Blood-based biomarkers hold the advantage to be less invasive than CSF. However, reproducibility and clinical applicability have hampered the applicability of blood biomarker analysis ([Shi et al., 2018](#)). The current efforts aim into adopting this lab-based approach for screening purposes, as it would significantly increase the sensitivity of the diagnostic profiling sequence and consequentially improve medical care through more trustworthy cost-effective follow-up procedures. In this setting, the use of plasma A β 42/A β 40 ratio, when controlled for APOE- ϵ 4 status and age, has been compared positively with the amyloid PET status of patients with AD ([Schindler et al., 2019](#)). Also, current studies have found that neurofilament light (a light-chained polypeptide) appears to be a suitable plasma biomarker for AD ([Mattsson et al., 2019](#)). Conversely, plasma tau has currently shown a weak association with AD, when used in multicentre studies ([Mattsson et al., 2016](#)).

In essence, diagnostic clinical, neuroimaging and molecular biomarkers need to be combined to increase their overall diagnostic sensitivity and specificity. Clinical

precision balance depends initially on highly sensitive tools to screen precisely the population-at-risk that already carries a build-up of pathological particles (or a defective genetic code alteration that will inevitably lead to it) in a setting where symptomatology may be absent. Consequently, a highly specific biomarker would serve as a proxy for definitive etiological diagnosis that could be potentially treated with disease-modifying interventions (Gaugler et al., 2013). Time is a crucial factor to establish an adequate treatment in the very early stages of the disease that will, in turn, increase patients' quality of life. To this end, it is relevant to have the most precise diagnosis in relation to the individuals' clinical stage and the progression of the disease natural history; any misdiagnosis could lead to severe adverse consequences in a person's life (Jack et al., 2013b)

1.8 Treatment

The efforts in treatment development have found its main historical foundations in research on the amyloid hypothesis cascade. However, consistent failure in developing an anti-amyloid treatment has given insight, not only in the urge of targeting other possible etiological factors but also in the complex pathobiological interactions that promote neuronal synaptic dysfunction and later neurodegeneration (Mullane & Williams, 2020).

1.8.1 Pharmacological Therapeutics

At present, the current core treatment of AD is based mainly on mitigating the symptomatic manifestations that are detrimental to the patients' quality of life. In this

respect, therapeutic approaches can be classified as, namely, 1) therapies that modulate synaptic communication, 2) treatments that prevent amyloid deposition, 3) treatments that target tau accumulation, 4) treatments that decrease an oxidative response, 5) intracellular targets (for mitochondrial degeneration, electrolytic balance and additional cellular processes) and 6) treatments that target neuroinflammation (Anand, Gill & Mahdi, 2014; Huang, Chao & Hu, 2020).

Synaptic modulators are currently used in a wide number of memory clinics, in the light of the physiological relevance that synaptic communication has in cognitive performance (Greenwood & Parasuraman, 2010). As discussed in previous sections, synaptotoxicity in acetylcholinergic neurons induces impairment on cognitive functions such as learning and memory. Therefore, the inhibition of acetylcholinesterase (an enzyme in charge of degrading the biochemical components of acetylcholine, namely, acetyl-coenzyme A and choline) has demonstrated to be beneficial for AD symptomatic improvement and is currently the gold standard for AD therapy. Research findings have pointed out that irreversible (Metrifonate), pseudo-reversible (Rivastigmine, Eptastigmine and Physostigmine) and reversible (Donepezil, Galantamine and Tacrine) acetylcholinesterase inhibitors have a limited but significant overall improvement in global cognition that translates into an additional improvement in activities of daily living (Burns et al., 1999; Imbimbo, 2001; Wilkinson et al., 2004; Cummings & Winblad, 2007; Razay & Wilcock, 2008; Yiannopoulou & Papageorgiou, 2020). Furthermore, targeted treatments to prevent glutamate excitotoxicity led to the synthesis of Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist (a calcium-dependent inotropic receptor that binds to glutamate and induces neuronal excitability) that has confirmed to be advantageous for the modulation of synaptic plasticity and memory (van Marum, 2009). This mildly useful medication is prescribed to patients in

moderate to severe stages of AD and is generally combined with inhibitors of acetylcholinesterase (McShane et al., 2019). Lastly, this treatment has shown additional support in controlling positive NPS during the later stages of AD (Wilcock et al., 2008).

Therapeutics based on prevention of amyloid formation has prompted the creation of pharmacological compounds that target the enzymes responsible for the pathological outcomes. In this setting, inhibitor compounds that target BRACE1 (the main beta-secretase) and presenilin (a major component of gamma-secretase) have shown negative outcomes in clinical trials. The reason for this is that the enzymatic proteolysis is not particular to APP cleavage but also of a substantial amount of proteins, that includes synaptic components (Gouras, Olsson & Hansson, 2015). To this end, clinical trials of anti-amyloid compounds have failed in phase III trials, possibly due to the administration of these compounds in the later stages of disease. This finding remarks the necessity of starting drug administration in the extensive preclinical stage, where inhibition of amyloid build-up may slow down or even terminate the onset of pathological mechanisms that are conjoined to cognitive decline (Grossberg et al., 2019). Pharmaceutical compounds based on tackling amyloid deposition are based on BACE-1 inhibition, γ -secretase inhibition and modulation, amyloid aggregation inhibition and, the most promising, based on active (vaccination) and passive (monoclonal antibodies) immunotherapy (Vaz & Silvestre, 2020). Most recently, aducanumab has been approved as one of the first disease modifying therapeutics against beta amyloid oligomers and fibrils accumulation (Alexander, Emerson & Kesselheim, 2021), although evidence of its clinical efficacy is still lacking.

On the other hand, anti-tau treatments were originally produced to target namely, the abnormal deposition of the protein, inhibit kinases, acetylation,

deglycosylation and phosphodiesterase-4 processes and stabilisation of cytoskeletal components. However, these approaches have shown negative results; hence, current approaches through immunotherapy (active and passive immunisation) aim to block tau spread when symptoms are almost unidentifiable through active vaccination and antibody therapeutics ([Congdon & Sigurdsson, 2018](#); [Vaz & Silvestre, 2020](#)).

There is yet no available methodology that can predict accurately the trigger of progression from MCI to dementia, in addition to the type of dementia that is inherent to the natural history of a patient's disease. A meta-analysis has shown that the rate of progression from MCI to dementia is approximately 5-10% in a 10 year follow up ([Mitchell & Shiri-Feshki, 2009](#)). The critical relevance of dementia progression and of accurate diagnosis are closely linked to the requirement for disease-modifying therapies that could prevent, delay, block, or even reverse the pathological processes before the continuous clinical deterioration leads to functional disability and ultimately, death. Improvements into diagnostic methods that are now acknowledged as biomarkers, can be beneficial for a coextending formulation of disease-modifying molecules that could become available in the near future ([Cummings & Fox, 2017](#), [Dubois et al., 2021](#)).

1.8.2 Non-Pharmacological Therapies

The requirement for a comprehensive holistic approximation for therapeutic purposes has generated non-pharmacological treatment approaches that are as essential for the in-clinic management of the disease as any drug-based therapy. The main aim of these therapies, as alternative approaches of treatment, is to delay the onset of symptoms or worsening of the pre-existing ones. Resultantly, treatments can

be focused on the amelioration of cognitive symptoms or improvement of declined mental abilities that are inherent to AD; with an additional focus of the highly detrimental NPS that would inescapably co-occur with the disease. These evidence-based treatments are classified namely in: auditory stimuli rehabilitation (music therapy, personalised family sounds or binaural stimulation within relaxing environments), carer-based training (psychoeducation and behavioural change-related interventions), other sensory therapy (aromatherapy, pet or light therapy) and cognitive rehabilitation (cognitive stimulation, reminiscence therapy, validation therapy, reality orientation and targeted recreational activities) ([Berg-Weger & Stewart, 2017](#); [Loi et al., 2018](#)). Lastly, physical exercise and a balanced diet (high in proteins and low in carbohydrates) have reported positive outcomes in the reduction of behavioural symptoms ([De Oliveira et al., 2015](#)). The discussed treatments have shown evidence-based validity and efficacy when used in combination with the established pharmaceutical medications; therefore, patients in low-income households have an available option to enhance the positive outcomes of disease therapeutics ([Olazaran et al., 2010](#)).

1.9 Conclusions

To summarise this theoretical framework, the necessity of highly sensitive and specific diagnostic non-invasive and cost-effective methods has shown that neuropsychological measures are still valuable instruments in the field of dementia research and clinical management. To this end, the presence of neuropsychiatric or behavioural symptoms (NPS) have shown to be inherent, not only to all stages of the AD spectrum but also to the modulation of the overall clinical profile ([Lyketsos, 2015](#)).

Consequently, the definition of a definitive diagnosis can be hampered, as these NPS are also extremely prevailing in other types of neurodegenerative conditions. For this reason, new cost-effective neuropsychological techniques based, for example, on the patients' ability to be aware of their self and social abilities could be advantageous for the overall diagnosis in very early stages of any neurodegenerative disease (Cacciamani et al., 2017). To this end, diagnostic efforts to spot brain functional changes in these early stages could eventually permeate the spread of pharmacological therapeutics that have previously failed due to late diagnosis.

Functional brain changes will initiate with synaptic dysfunction that precedes brain micro and macro-structural damage reflected in the integrity of brain interconnected networks. In AD, the DMN disconnection has been confirmed to be one of the earliest indirect markers to foreshadow cognitive decline. In this perspective, the functional neuroanatomy of the regions connected within the DMN extrapolates into critical complex brain capacities based on self-awareness and social-cognitive skills. With this in mind, objective cognitive measures of self-awareness and social cognition skills could provide a neuropsychological signature of DMN integrity, in addition to how this network might interplay with other large-scale networks. These measures of cognitive awareness could firstly help predict the onset of other NPS inherent to the AD spectrum and secondly, serve as a valuable inexpensive tool that could improve accuracy of diagnosis in the preclinical stage, where potential disease-modifying therapies could interact positively with the pathobiological processes.

Chapter 2

The complex interplay of cognitive awareness of the self and others in the Alzheimer's continuum

The study of awareness requires a precise definition among terms that share conceptual similarities. In a first instance, human consciousness can be referred to as an objective state of wakefulness that is distinct from other mental states such as sleep or coma. A second conceptual subjective approximation to the study of consciousness is through awareness. In everyday human activity, a state of wakefulness would also generally imply that we are not only conscious, but conscious of something. This notion has been widely recognised as conscious awareness ([Zeman, 2006](#)). For the purpose of this thesis, we will refer to cognitive awareness as a conscious state of mind that allows the perception and appraisal of internal and external stimuli in order to produce specific behavioural reactions ([Ortinski & Meador, 2004](#)). This state of awareness seems to rely on a constant combination of complex cognitive capacities that allows the recognition of internal sensations, thoughts, feelings, memory or perceptions and external intentions, beliefs or emotions ([Zeman, 2005](#)). Therefore, the domains that define cognitive awareness can be broadly distinguished between internally mediated self-awareness and externally mediated awareness of others ([Zeman, 2005](#)).

2.1 Overview of cognitive awareness

The study of self-awareness can be traced back not only to humans, but to other types of high-order animals that share biological and brain resemblance with humans.

In this sense, three domains of self-awareness have been recognised, namely bodily self-awareness, social self-awareness and introspective awareness (DeGrazia, 2009). For example, bodily self-awareness refers to the ability to recognise body parts and bodily indicators (e.g., interoceptive signals), recognise one's own spatial location (i.e., where I am positioned in relation to space) and first-person perspective (e.g., the ability to experience the world through an internal representation) (Blanke, 2012). Social self-awareness has been recognised as the ability to create self-centred internal mental representations about others' attitudes, beliefs, intentions or emotional states, a cognitive framework that significantly overlaps with a human neurocognitive domain defined as social cognition (Northoff et al., 2006).

Lastly, introspective awareness relies on self-referential thinking as a reflection of the ability to generate a conscious judgment of our own behaviours, skills and mental functions (McClelland, 2015; Lou, Changeux & Rosenstand, 2017). Human self-awareness has been construed as a multi-layered construct that relies on the specific internal domain we are consciously aware of, including ourselves (Lacerda, et al., 2021). For example, we can be aware of our skills such as memory function, emotional states or motor capacities; this capability of thinking about our own thinking has been recognised as metacognition, an extension of the overall capacity of self-monitoring and, ultimately, of self-awareness (Samsonovich et al., 2008).

The neurocognitive domain that entails the ability to be aware of others is defined as social cognition. This domain includes the ability to recognise, process and integrate thoughts, intentions, beliefs and emotions of our social sphere (Arioli, Crespi & Nicola, 2018). Additionally, a way to approach the study of awareness of others is through the ability to shift from first-self to third-others perspective as a reflection of

the ability to put ourselves in the context of others ([Vogeley et al., 2004](#)). More details of this social domain are discussed in further sections within this chapter.

The interaction between self-awareness and others-awareness is so intertwined that current research is still debating as to whether social cognition is an extension of the ability for self-awareness, based on social-awareness and self-referential mechanisms within the social environment ([Happe, 2003](#); [Northoff et al., 2006](#)), or whether self-awareness is a prerequisite of social cognition, where internal self-directed mental processes serve as the foundation to produce inferences about other people's minds ([Van Overwalle, 2009](#); [Bradford et al., 2015](#)). Therefore, it has been postulated that awareness of the self and others might share neural representations in similar functional and anatomical territories ([Decety & Summerville, 2003](#)). Consequently, some neurological disorders, such as neurodegenerative diseases, including some forms of dementia, could manifest a concomitant decline of self-awareness along with deficits in social awareness ([Shany Ur et al., 2014](#)).

There is substantial evidence that patients with Alzheimer's disease (AD) may manifest dysfunction of cognitive awareness, specifically in the already discussed domains of self-awareness ([Mondragon, Maurits & De Deyn, 2019](#)) and others awareness ([Bora & Yener, 2017](#)). Furthermore, in the clinical neurological setting and throughout this thesis, the presence of impairment in self-awareness of cognitive deficits has been classically termed anosognosia ([Mograbi & Morris, 2018](#)). Regarding the natural history of these symptoms, it seems that deficits of self-awareness may be detectable as early as the preclinical stage of neurodegenerative conditions such as AD ([Cacciamani et al., 2017](#); [Hanseeuw et al., 2020](#)). In contrast, awareness of others, which will be referred to throughout this thesis as social cognition, seems to be relatively preserved until the later stages of the disease ([Christidi et al., 2018](#)). In

further sections of this chapter, there will be a conceptual dissection of the essential current psycho-biological perspectives that characterise self-awareness deficits (anosognosia) and changes in others' awareness (social cognition) within the AD continuum.

2.2 Anosognosia/self-awareness deficits

Deficits in awareness were first described by Babinski after the introduction of the word “anosognosia” (Babinski, 1914), or a deficit of perception (loss of insight) of one's own disease (Aalten et al., 2005b). Concisely, it refers to the impaired ability of self-perception in relation to one's internal capacity (insight) or one's state of mind (metacognition) (Cova et al., 2017). Awareness of our personal capacities appears part of a complex functional system of cognitive mechanisms that allows us to perform effectively by the constant acknowledgement of our own personal limitations, in a constantly changing physical and socioemotional environment. For this reason, metacognitive functions are strongly related to the sense of self-awareness (Bertrand, Landeira-Fernandez & Mograbi, 2016), social awareness (Happe, 2003) and, to some extent, to the study of consciousness (Koriat, 2007). Therefore, functional neural deficits, which clinically translate into anosognosia, will reflect profoundly on to a person's performance and perception of reality.

The mechanisms that intend to explain the presence of anosognosia are still poorly understood. Some theoretical perspectives have interpreted this symptom as a disorder of awareness of the self (Gil et al., 2001). In this context, the essential differences of how this clinical symptom manifests among the neurological syndromes depend on the specific mental concept patients are not aware of, or the domain of

awareness (e.g. cognitive functions, motor abilities or disease signs). Patients may lack the ability to recognise their own symptomatic manifestations or the severity of expression; however, the constellation of diverse clinical displays can also be manifested as lack of awareness for objects, places, people or even their own body parts (Feinberg & Keenan, 2005).

As mentioned before, anosognosia is a symptom commonly found in a significant proportion of neurological and psychiatric diseases that may affect, as part of their clinical expression, one's capacity for self-reflection. Moreover, its presence in a wide spectrum of neuropsychiatric diseases reflects the complexity of the neural mechanism breakdowns involved in this symptom. For example, patients who suffer from asomatognosia tend to create a mental dissociation of their own limb from the rest of the body representation and refer to it as a completely different entity, showing with it, disengagement with reality between discrepancies of internal and external perceptions (Feinberg et al., 2010; Feinberg & Venneri, 2014). The brain structures affected when anosognosia for hemiplegia is present have a right hemisphere predominance, essentially involving fronto-temporo-parietal structures. Notably, the presence of subcortical damage (basal ganglia and thalamic regions) seems to be critical for anosognosia for motor disorders to emerge (Pia & Conway, 2008; Besharati et al., 2016).

The overall incidence of this symptom across numerous neurological disorders seems to share a characteristic anatomical imprint on right hemispheric regions. This recurrent predominance points at the main neuroanatomy underlying the capacity for self-appraisal and the functional areas that define, at least in part, our own consciousness. Anosognosia in other etiological entities has already been associated with strong foundations in specific neural substrates based on the frontal lobe.

Comparably, the study of anosognosia in dementia has also shown to have similar pathophysiological mechanisms to those recognised in awareness decline in other acute conditions, although there is more brain variability in the findings of the anatomical deficits underpinning the appearance of this symptom in neurodegenerative conditions. Additionally, the vital detrimental impact of this symptom on the early stages of neurodegeneration is based on the impaired ability for self-appraisal of cognitive functions or metacognitive abilities (Sunderaraman & Cosentino, 2017).

2.2.1 Anosognosia in Alzheimer disease

In the context of AD, anosognosia can be defined as the inability of the patient to be aware of the decline of their own cognitive functions (such as memory, language or executive functions), the severity of the disorder or the presence of it (Mograbi & Morris, 2018). Nevertheless, the behavioural manifestations of anosognosia at the individual level tend to be highly heterogeneous (Starkstein, 2014). As a result, this neuropsychiatric symptom can be commonly displayed as unawareness of other critical cognitive functions aside from just lack of awareness of memory decline (Tagai et al., 2020). As a matter of fact, the level of self-reflection about one's own memory ability (or metamemory) is independent of global memory performance in AD (Amanzio et al., 2013; Avondino & Antoine, 2016). Consequently, deficits of awareness appear to confer a higher clinical risk of earlier deterioration, in addition to placing a higher burden upon the family and caregivers (Kelleher, Tolea & Galvin, 2016). As a result, patients who are not aware of their personal limitations can often experience injuries, resist pharmacological treatment, decline psychological intervention or be prone to

developing other types of neuropsychiatric symptoms such as apathy, depression or anxiety (Aalten et al., 2005b).

The clinical onset of anosognosia can be observed even in the prodromal or mild cognitive impairment (MCI) stage of the disease (Vogel et al., 2004; Vannini et al., 2017a). Although other types of dementia can also express this prodromal stage and manifest clinically with distinctive cognitive symptoms, in this thesis the term MCI will refer to non-demented individuals for whom the aetiological entity is represented by underlying AD pathophysiology (Albert et al., 2011). Most importantly, as mentioned in the previous chapter, deficits of self-awareness have been evidenced not only in the prodromal stage, but even earlier at the preclinical stage (Cacciamani et al., 2017; Hanseeuw et al., 2020).

It may look like a paradoxical phenomenon that one of the core clinical criteria for MCI diagnosis is awareness of memory deficits, generally determined as a subjective memory complaint. In this context, a patient performs a critical evaluation of their own cognitive functions (or metacognitive assessment). Consequently, the concern of even a slight malfunction generally motivates individuals to seek medical attention. Subsequently, these individuals are referred to neurology units or memory clinics for full neuropsychological and medical assessments. However, not all MCI patients will exhibit this capacity of accurate self-evaluation. As a result, dysfunction of metacognitive abilities will have a negative effect on early diagnosis and treatment (Roberts, Clare & Woods, 2009). Subsequently, a vast number of people, who already harbour AD pathology, are unaware of their cognitive dysfunction until this is noticed by a caregiver (Silva et al., 2016). Studies that have investigated this symptom through the use of *in-vivo* and *post-mortem* techniques have revealed that the presence or absence of this neuropsychiatric trait is linked directly to the degree of deposition of

the abnormal proteins that explains the histopathological aetiology of AD (Marshall et al., 2004; Vannini et al., 2017b).

In summary, the clinical expression of anosognosia has a significant variability among patients and across different stages of the disease. The high heterogeneity of this symptom, therefore, explains its vital clinical relevance and the diverse findings of the literature on its neurophysiological and neural substrates (Vogel et al., 2004). Diagnostic criteria for AD generally ignore the presence of cognitive unawareness that may affect overall cognitive functioning in people with AD. Most importantly, disease evolution can be modified significantly by the presence of unawareness, reflecting on a patient's activities of daily life and socioemotional interactions. Lastly, the high prevalence of this symptom translates into an urge for better medical and therapeutic conduct for patients with this symptomatic manifestation, that can happen as early as the preclinical stage of this disease.

2.2.2 Domains of self-awareness characterising anosognosia

The study of anosognosia in neurodegeneration can be interconnected with a wide variety of clinical symptoms, and every one of them has its own distinct brain representation as part of a process of continual metacognitive evaluation of cognitive functions (Schacter, 1990). For this reason, research on anosognosia tends to classify assessment techniques of awareness of disease-related deficits into specific independent domains. Therefore, pioneering research on anosognosia in AD has proposed two big domains of study, based on the independence of the underlying functional brain mechanisms and in parallel with the descriptions that emerged from the initial theoretical models. These two domains, in synchrony with the clinical criteria,

were named initially as awareness of cognitive deficits and awareness of behavioural problems (Starkstein et al., 1996). The “cognitive domain” was then broadly divided into two subcomponents, namely awareness of memory and of executive functions (Agnew & Morris, 1998). Subsequently, additional domains have been progressively suggested as target for the evaluation of anosognosia during clinical examination and these include awareness of competency in activities of daily living and awareness of socioemotional interactions, in which conscious self-other awareness might overlap (Leicht, Berwig, & Gertz, 2010; Clare et al., 2012a).

In AD, the most common domain of awareness affected by the disease is the memory one, and it is usually the most explored in the literature, given that memory decline is a typical symptomatic manifestation paralleling the progression of the disease. However, as the disease follows its inherent progressive pathological pathway, additional functional domains of awareness might be damaged, accumulating to the clinically observed deterioration (Vasterling et al., 1997). Therefore, as a result of a more comprehensive assessment and in conjunction with the conceptual evolution of the cognitive psychopathological models, current research has established that AD manifests as a multi-domain dysfunction of self-awareness (Leicht, Berwig & Gertz, 2010). With this in mind, current practice for clinical examination tends to differentiate the domain affected by anosognosia as the most consistent methodological approach for diagnosis (de Ruijter et al., 2020). As a result, the dysfunction of one or several domains of awareness seems to follow how the cognitive mechanisms interact with each other providing an explanation to the complexity and heterogeneity that characterise this condition.

2.2.3 Theoretical models of anosognosia

As mentioned previously, the variability in the clinical expression of awareness deficits at an individual level, regardless of the severity of the disease, has led to conflicting research in the quest for the most reasonable neuropsychological model to explain the presence of this symptom (Avondino & Antoine, 2016). Multi-domain assessment is the most accepted method to quantify the clinical degree of anosognosia in patients with AD (de Ruijter et al., 2020). The reason for this is that the functional substrate for the expression of this symptom is still unknown. Therefore, the core concepts that explain the framework of anosognosia in AD are established on complex multi-dimensional processes of selective mental dysfunction. Specific cognitive alterations could lead to selective outcomes on the ability to recognise one's own mental dysfunctions. Furthermore, integrative theoretical frameworks have been proposed in order to explain this complex transition between normal self-evaluation (metacognitive monitoring) and the emergence of anosognosia as a symptom based on the damage of multidimensional neural mechanisms.

One of the first models was proposed by Schacter (1990). In his model, this author formulated the concept of a Conscious Awareness System (CAS), a modular representation that starts with a sensory input in the medial and lateral parietal regions (parietal perception) that is then brought to consciousness as a result of the activation of other functional domains within each cognitive module (knowledge, memory and learning). Then, this piece of information is projected to an executive system associated with the frontal cortex, in charge of processing and performing a response as a metacognitive output. Consequently, anosognosia would be explained as the result of the disruption of one or more of the modules connecting to the CAS or the executive unit, leading to a domain-specific anosognosia.

Based on the CAS, a decade later Agnew and Morris (1998) developed the Cognitive Awareness Model (CAM) with an important focus on the role of memory and executive mnemonic comparators on the capacity of cognitive awareness. The core concept of this theory is founded on the mental ability to perform a continuous self-evaluation to update a personal database of episodic and semantic memories, as new information enters the senses continuously. This piece of information is received by short-term memory and perceived as such. Subsequently, it is transferred to long-term memory by experiencing a second event of awareness. The information is then compared, with the support of a mnemonic comparator, within the frontal executive system, with a database of personal experiences containing semantic portrayals of the individuals' own capacities (for example, I know my name and where I live without having to look at an official identification every day). This information is subsequently updated in the Metacognitive Awareness System (MAS). The simple retrieval of memories from the personal knowledge database is not sufficient for an individual to acknowledge the information learned from each memory, as an efficient and effective executive system is a requirement to achieve complete appraisal and awareness. This system contributes to gaining consciousness and modelling an adequate response in relation to previously formed experiences. At this level, the occurrence of anosognosia is explained as the result of an information mismatch between personal knowledge and sensory information received requiring a metacognitive evaluation (e.g., this new information about myself does not match with who I am or the experiences I have stored). Subsequently, information update does not occur, and the patient fails to accomplish an accurate self-appraisal (in contrast to the appraisal perceived by the social sphere), that will eventually show a delay in semantic updates, with a higher risk

of being unable to recognise conditions that could pose potential health risks ([Agnew & Morris, 1998](#)).

In concordance with the previous mechanisms, two types of anosognosia were postulated, namely: primary anosognosia, as the result of damage in the CAS itself (with more severe clinical manifestations related to global anosognosia); and secondary anosognosia that can be divided further into executive anosognosia (a result of intrinsic damage within the mnemonic comparators) and memory anosognosia (with difficulties in semanticisation processes of memory update into the metacognitive output). Other models based on memory dysfunction have shown that anosognosia in AD is not only due to lack of memory update of the personal database but is also a result of a detriment in the recollection and consolidation of semantic knowledge about the self in a conceptual framework defined as the “petrified self” or an outdated version of an individual’s self-representation ([Mograbi, Brown & Morris, 2009](#)).

Within the CAM conceptual framework, Rosen ([2011](#)) established that emotions are a critical notion that can influence metacognitive processes, as they reflect heavily on the sense of “self”, result of personal motivations connected to each level of self-monitoring. The degree of success and failure in each of an individual’s performance displays an emotional attachment in the semantic representation of one’s capacities. The degree of this emotional attachment depends on the level of significance given by an individual’s standards. Consequently, a process of evaluation and judgement is required for each mnemonic representation ([Clare et al., 2011](#)). Finally, anosognosia would manifest as a result of the alteration of any of both, over or underestimations about the self, related with the external physical or social environment. Hence, this could explain in part the concomitant existence of other neuropsychiatric symptoms

that are closely interconnected with a patient's emotional state, such as depression or apathy (Jacus, 2017).

Lastly, a more recent theory has proposed that anosognosia would manifest not only as a dysfunction of episodic or semantic memory, but also as a result of lack of acquisition of self-perspective due to deficits in visuospatial memory (Serino & Riva, 2017). This phenomenon results in an alteration of one's personal perspective that also spreads into acknowledging the perspective of others, or mentalising abilities (i.e., loss of Theory of Mind). Finally, as a way to explain anosognosia with this theory, some patients have difficulties to perform self-assessments of their own deficits, though they are aware of the impairments of others; or of themselves seen through a third-person perspective (Vogeley et al., 2004; Ruby et al., 2009).

In conclusion, the theoretical frameworks used to explain anosognosia are based on the alterations of conjoined processes that utilise complex brain resources to achieve adequate cognitive functionality (**Fig 2.1**). However, although these flawed cognitive traits in neurodegeneration appear to be dependent on mnemonic functions, the brain-function complexity of self-awareness deficits seems to find its foundation in the dysfunction of executive mechanisms that oversee continual comparisons and synchronisations between mental representations about the past-self and present-self. Consequently, the patient's everyday progressive underperformance of essential mental abilities such as memory, visuospatial skills, attention and reasoning, that characterises patients with AD, will be eventually unrecognised. Failure in self-monitoring predisposes to an inability to achieve a proper update of how cognitive abilities are performing in everyday life activities. This reflects negatively on an individual's metacognitive functionality and, therefore, manifests clinically as an altered capacity for self-recognition.

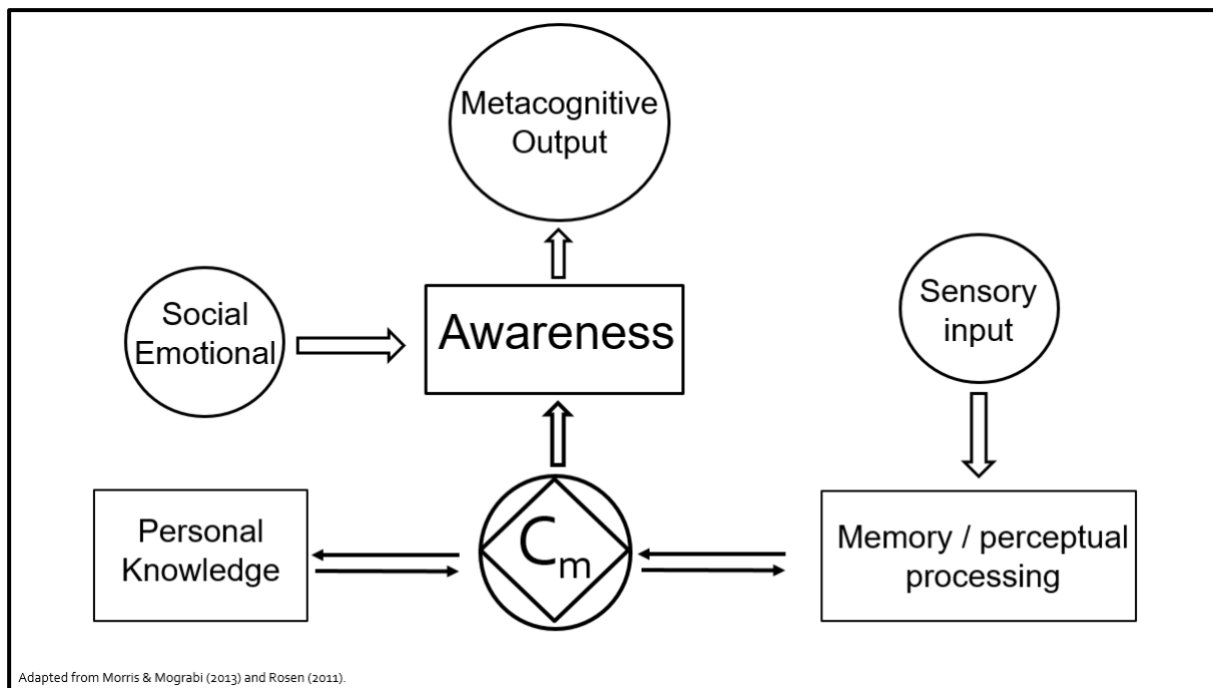


Figure 2.1. Visual representation of the theoretical model of awareness. Cm = Comparator mechanism.

2.2.4 Clinical assessment of anosognosia

The multifaceted theoretical background involved in explaining poor awareness as a metacognitive dysfunction of the self limits a homogeneity of consensus about the most appropriate form of clinical assessment to detect this symptom (de Ruijter et al., 2020). Therefore, there is still no “gold standard” instrument for a sensible and specific diagnosis (Starkstein, 2014; Piras et al., 2016).

Three approaches have been generally used throughout the literature to measure deficits of self-awareness. The first one relies on the judgment given by clinicians in charge of the assessment. A clinical review of medical records, neuropsychological outcomes or a brief structured or semi-structured interview is completed in order to classify clinically the level of anosognosia and the domains affected by it. The main advantages of this method are essentially the depth in which each topic can be assessed, and the detail of the qualitative information obtained. Nevertheless, the disadvantages tend to be bigger since this method tends to be

inherently biased due to lower intra-observer reliability, as the diagnosis relies purely on the clinicians' judgment. Moreover, the large variance in the qualitative methodological approach significantly reduces the replicability of the findings. Lastly, there is a tendency for patients to show the clinician that their overall cognitive functioning has not changed (i.e., defensive denial) and this could be misleading in the analysed data (Clare, 2004; Ecklund-Johnson & Torres, 2005).

The second method relies on a comparison based on a subjective self-assessment in contrast with the objective outcomes from the neuropsychological assessment. This association between the objective-subjective tests would give a prediction about one's metacognitive performance. The pragmatic convenience of this method relies on the elimination of the influence of an external evaluator (researcher or carer). Consequently, there is a rise in the objectiveness of the test through a decrease in replicability flaws. However, the standardisation of a method that can compare objectively the performance on neuropsychological testing and awareness outcomes may be influenced by the personal beliefs of the examiners (Starkstein, 2014).

Lastly, the third and most used method of assessment is one that uses discrepancy scores. A specific or multiple awareness domain questionnaire is applied to the patient and a caregiver. A discrepancy score is obtained when comparing patient-carer answers. Importantly, the reliability of this measurement is based on the assumption that the rating given by the carer is always trustworthy. It would seem that this method relies on two subjective ratings that can be both unreliable and lack scientific validity; nevertheless, the greatest benefit is displayed by the motivational and affective bond between the two individuals that the subjective-objective assessment methodology might lack. There are limitations as well; however, the same

emotional and motivational factors (presence of caregiver burden reflecting on a false overestimation or underestimation) may impact the ratings given by the patient or the carer (de Ruijter et al., 2020). Regardless of the apparent limitations, standardised discrepancy assessments continue to be the most reliable and accurate method of assessment of anosognosia and have shown to predict strongly the progression from prodromal stages to dementia (Carr et al., 2000; Tabert et al., 2002; Ecklund-Johnson & Torres, 2005). Moreover, most neuroimaging studies have applied this clinical approach to elucidate the neuroanatomical underpinnings of anosognosia. For all these reasons, we have selected the discrepancy assessment methodology for our data throughout the present thesis.

A last and relatively new type of assessment has been used through a perspective-taking approach in accordance with some of the newest conceptual frameworks. Essentially, the proposition is based on a theoretical visuospatial and attentional model proposed by Bertrand and colleagues (2016) where patients are able to assess correctly the limitations of non-related individuals who suffer from a similar symptomatology. Their findings showed that, although capable of doing this task, they were incapable of performing an accurate self-reflection on their own overall cognitive abilities. In this context, Clare and collaborators (2012b) developed a visual technique where patients were able to assess a fictional character that displayed the typical dementia symptomatic spectrum of AD in a short scenario centred on vignettes. Consequently, some patients were able to identify spontaneously their own cognitive deficits. This type of methodology has shown to be a reliable procedure and it has already been used with positive therapeutic results (Au et al., 2020). Nonetheless, more work is needed before this type of methodology can be used widely across diverse research centres. Lastly, this third-person perspective assessment could

explain the patient's inability of putting themselves in the context of others, an inability that extends not only to self-awareness but to others-awareness as well, where a patient might be incapable of differentiating the thoughts of others from their personal ones (Morris & Mograbi, 2013).

Although the variability in methodological approaches for clinical assessment seems a disadvantage and could explain in part the heterogeneity of the clinical expression of anosognosia in AD, there has been an ongoing research effort into the creation of new methodologies or in modifying the standardised tools used in everyday research (Aalten, et al., 2005b). A multi-domain approach of awareness should be fundamental in every assessment regardless of the methodology used. The reason for this is that the type of metacognitive function assessed significantly changes depending on the individual mental status in relation to the domain tested. In other words, awareness can only be defined in relation to the object someone can be aware of; a concept defined by Markova et al. (2001) as the "object of awareness" that in AD generally refers to cognitive functions. On the other hand, research should also consider a patient's ability to perform accurately the distinction between their own functional abilities and those of other individuals.

For the purpose of the present project a discrepancy score method was used, due to this method being extensively used in clinical settings currently (de Ruijter et al., 2020). A standardised questionnaire known as the Measurement of Anosognosia Questionnaire was adopted (Stewart et al., 2010). The Measurement of Anosognosia Questionnaire consists of 15 questions; 9 that assess the memory domain and 6 that assess the executive and everyday life activities domain. For the purpose of the present project, this latter domain was referred to as non-memory domain (for assessment and scoring details please refer to section 4.1.2.2). The selected

instrument has been standardised for assessment with patients with AD. In this context, a normative overall discrepancy score of 3 (SD of 2.74) was considered as the cut-off score for normal performance ([Stewart et al., 2010](#)).

2.2.5 Neural correlates of anosognosia in Alzheimer's disease

In line with the theoretical models discussed in the section above, the neural correlates of anosognosia in AD have been associated with functional areas recognised classically to control memory, executive tasks and spatial representations in the brain; more specifically, the frontal, temporal and parietal lobes ([Zamboni & Wilcock, 2011](#); [Mondragon, Maurits & De Deyn, 2019](#)). Currently, there is a reasonable amount of structural and functional brain imaging studies that have highlighted the neural correlates of anosognosia in AD. The neuroimaging studies centred on self-awareness deficits in AD available at time of writing are summarised in **Table 2.1**. The wide variability of clinical manifestations and methods of assessment, even in patients with the same level of disease severity, has led to divergent conclusions. This characteristic heterogeneity that defines the clinical presentation of anosognosia in AD seems to be also present in the regions that define it, as there is not yet a consensus of the neuroanatomy involved. Nevertheless, there appears to be a certain pattern in the overall results that demonstrates the involvement of frontal lobe structures, particularly with right hemispheric predominance, regardless of the neuroimaging methodology ([Rosen, 2011](#)).

Table 2.1. Review of neuroimaging studies of brain changes underpinning anosognosia in AD.

Study	Subjects	Awareness domain and assessment	Regions involved with anosognosia	Results and theoretical model to explain anosognosia
PET				
Harwood et al., 2005	41 AD	Multi-domain (Cognitive and functional). Clinician ratings.	Right lateral and dorsolateral PFC.	Hypometabolism in right frontal regions.
Salmon et al., 2006	209 AD	Multi-domain. Discrepancy scores and objective-subjective scores.	left OFC, right parahippocampus and left TPJ.	Hypometabolism in fronto-temporo-parietal regions. General multi-domain model, executive update dysfunction.
Jedidi et al., 2014	37 AD 25 HC	Personality domain. Discrepancy scores, objective-subjective scores, perspective chance scores.	dorso-medial PFC.	Hypometabolism in frontal regions. Perspective taking model explains better anosognosia for personality.
Perrotin et al., 2015	23 AD 30 HC	Memory domain. objective-subjective scores.	OFC, precuneus and PPC.	Hypometabolism in fronto-parietal regions. Mnemonic model (PPC) and self-reference mechanisms (OFC).
Gerretsen et al., 2017	499 MCI 191 AD 372 HC	Multi-domain. Discrepancy scores.	PPC, right angular gyrus.	Predictive study. Hypometabolism in specific brain areas predicts. Anosognosia predicts dementia progression.
Vannini et al., 2017b	31 aMCI 251 HC	Memory domain. Discrepancy scores.	PPC, hippocampus.	Hypometabolism in regions in charge of memory and self-processing. Mnemonic model and self-reference mechanisms.
Therriault et al., 2018	468 MCI	Multi-domain. Discrepancy scores.	PPC (baseline), left basal forebrain, bilateral medial temporal lobes, right lateral temporal lobe (24-months follow up).	Predictive study. Hypometabolism in specific brain areas predicts DMN impairment. Anosognosia predicts dementia progression.

Guerrier et al., 2018	30 AD 16 HC	Multi-domain. Discrepancy scores.	ACC	Hypometabolism and atrophy in the ACC were associated with anosognosia.
SPECT				
Reed et al., 1993	20 AD	Memory domain. Clinician rating.	Right dorsolateral PFC.	Reduced cerebral blood flow in right frontal regions. Frontal dysfunction may be involved in memory anosognosia.
Starkstein et al., 1995	24 AD	Cognitive and Behavioural. Discrepancy scores.	right inferior OFC and right superior PFC.	Reduced cerebral blood flow in right frontal regions. Anosognosia results in only frontal lobe impairment.
Ott et al., 1996	40 AD	Cognitive (memory) and disease. Clinician rating.	right temporal and occipital cortex.	Reduced cerebral blood flow in right temporal and occipital regions. Probable disconnection of a long transcortical temporo-frontal network.
Derouesne et al., 1999	78 AD	Multi-domain. Clinician rating and discrepancy scores.	Right frontal lobe.	Reduced cerebral blood flow in the frontal lobe. Anosognosia is correlated with NS (apathy).
Vogel et al., 2005	30 MCI 36 AD 33 HC	Memory domain. Discrepancy scores.	Right inferior frontal gyrus.	Reduced cerebral blood flow in frontal regions. Anosognosia is correlated with NS (Apathy, disorganisation and aspontaneity). No executive dysfunction correlates.
Mimura & Yano, 2006	24 AD 16 HC	Memory domain. Objective-subjective scores.	medial cortical structures, right precuneus and right inferior frontal gyrus.	Reduced cerebral blood flow fronto-parietal regions. Self-reference mechanisms.
Shibata et al., 2008	29 AD	Memory domain. Discrepancy scores.	Left OFC.	Reduced cerebral blood flow in frontal regions.

Hanyu et al., 2008	38 AD	Memory domain. Discrepancy scores.	Bilateral lateral and medial PFC, bilateral ACC and PCC, and left inferior parietal lobe.	Reduced cerebral blood flow in fronto-parietal regions. Self-monitoring mechanisms.
Sedaghat et al., 2010	42 AD	Cognitive and functional domain (ADL). Discrepancy scores.	Right PFC, inferior parietal and bilateral medial temporal cortex.	Reduced blood flow in fronto-temporo-parietal regions. Executive function model.
Structural MRI (VBM)				
Ford et al., 2014	65 MCI 55 HC	Multi-domain(ADL, cognitive and non-cognitive). Discrepancy scores.	right (predominant) and left medial frontal gyrus.	GM reduction in frontal region. It is not advised to do awareness assessment as a routine clinical evaluation.
Hornberg et al., 2014	15 AD	Multi-domain (Social, emotion, disease, language and motivation). Discrepancy scores.	bilateral OFC, right frontopolar cortex, parahippocampus, middle temporal gyrus and amygdala.	GM reduction in fronto-temporal regions. General multi-domain model; social (OFC, parahippocampal, right middle temporal gyrus, right amygdala), motivation (OFC, ACC, frontopolar cortex).
Spalletta et al., 2014	36 MCI	Multi-domain cognitive (GF, Memory, language, EF). Discrepancy scores.	ACC, right inferior frontal cortex, cerebellar vermis and left superior-middle temporal lobe.	Predictive study. MCI who converted showed more anosognosia. GM reduction in fronto-cerebellar areas of MCI that progressed to dementia. General multi-domain model (cerebellar); Mnemonic (ACC, Inferior frontal cortex) and language (middle temporal lobe).

Shany-Ur et al., 2014	AD 35 HC 46	Multi-domain (ADL, social, cognitive and emotional). Discrepancy scores.	Right predominance; Superior-middle PFC, OFC, insula, putamen, fusiform gyrus, thalamus, caudate, midbrain, pons.	GM reduction in frontal and subcortical regions. General Multi-domain model; ADL (right frontal regions, thalamus, insula, putamen, caudate, medial-lateral temporal regions and pons), cognitive (middle temporal gyrus, middle frontal gyrus), emotional (OFC, insula, PFC) and social (putamen, fusiform gyrus).
Fujimoto et al., 2017	49 AD	Memory domain. Discrepancy scores.	Left superior frontal gyrus.	GM reduction in frontal region. Mnemonic model.
Tondelli et al., 2018	15 MCI 12 AD	Cognitive (memory and EF). Discrepancy scores	Hippocampus, supramarginal gyrus and precentral gyrus.	GM reduction in medial temporal lobe and hippocampus. Mnemonic and executive model.

Functional MRI

Ries et al., 2007	16 MCI 16 HC	Personality domain. Discrepancy scores.	Medial PFC, PCC.	Connectivity study in frontal regions. Self-awareness tasks reflect on cortical midline structures. General cognitive model.
Ruby et al., 2009	14 AD 34 HC	Personality domain. Discrepancy scores.	Bilateral intra parietal sulcus and right OFC.	Self-awareness activates fronto-parietal regions. Perspective taking model.
Amanzio et al., 2011	29 AD	Multi-domain (Cognitive, executive, language).	Right ACC, frontopolar PFC, right poscentral gyrus, right TPJ, left temporal gyrus, striatum and cerebellum.	Lower connectivity in cortical-subcortical regions.
Zamboni et al., 2013	17 MCI 17AD 17 HC	Multi-domain (Cognitive, behavioural and physical). Discrepancy scores.	medial PFC, Medial temporal lobe.	Lower connectivity in frontal-temporal regions. Medial PFC is involved in self-reference mechanisms.

Perrotin et al., 2015	23 AD, 30 HC	Memory domain. Objective-subjective scores.	OFC, PCC, hippocampus.	Lower connectivity in frontal-temporal regions. DMN specific disconnection explains anosognosia. Mnemonic model (PPC) and self-reference mechanisms (OFC).
Vannini et al., 2017b	31 MCI, 251 HC	Memory domain. Discrepancy scores.	PCC, OFC, bilateral IPL.	Lower connectivity in fronto-parietal regions. Disconnection between left and right hippocampus. Mnemonic model and self-reference mechanisms.
Mondragon et al., 2021	92 MCI, 18 AD, 33 HC	Memory domain. Discrepancy scores.	ACC.	Increased connectivity in the ACC.

Histopathology

Marshall et al., 2004	26 AD	Multi-domain. Clinician ratings.	Superior and middle frontal gyrus, superior temporal lobe, hippocampus (prosubiculum) and entorhinal cortex	Higher amyloid plaque deposition in patients with anosognosia in the Prosubiculum. This region seems a critical point for connection with other fronto-temporal regions.
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ACC: Anterior cingulate cortex; AD: Alzheimer Disease; ADL: Activities of the daily life; DMN: Default mode network; EF: Executive functions; fMRI: Functional magnetic resonance imaging; GF: General functions; GM: Grey matter; HC: Healthy controls; IPL: Inferior parietal lobe; MCI: Mild cognitive impairment; NPS: Neuropsychiatric symptoms; OFC: Orbitofrontal cortex; PCC: Posterior cingulate cortex; PET: Positron emission tomography; PFC: Prefrontal cortex; PPC: Posterior parietal cortex; SPECT: Single-photon emission computed tomography; TPJ: Temporoparietal junction; VBM: Voxel-based morphometry

2.2.5.1 Perfusion and metabolic neuroimaging

The pioneer neuroimaging studies that delimited the brain regions involved with anosognosia in AD were based on the use of single-photon emission computed tomography (SPECT). This technique measures regional cerebral blood flow (rCBF)

and compares the radioactive uptake (through the use of radioactive tracers and gamma-ray detection) within designated regions of interest (Royal, Hill & Holman, 1985). The overall results of studies of cerebral blood flow alterations associated with the presence of anosognosia in AD have emphasised the role of the dorsolateral and inferior orbital areas (part of the prefrontal cortex) and cingulate cortex, both part of the frontal lobe, as the most consistent areas of reduced regional cerebral blood flow that correlated with the presence of cognitive anosognosia (predominantly in the memory domain) (Reed, Jagust & Coulter, 1993; Starkstein et al., 1995; Derouesne et al., 1999; Vogel et al., 2005; Mimura & Yano, 2006; Shibata et al., 2008; Hanyu et al., 2008; Sedaghat et al., 2010). Moreover, alterations in parietal structures, namely the precuneus and inferior parietal cortex were also associated with this symptom (Mimura & Yano, 2006; Hanyu et al., 2008; Sedaghat et al., 2010).

In addition, through the use of positron emission tomography (PET), brain metabolism studies have pointed out that the main regions underlying the presence of multi-domain anosognosia also suggest a key role for frontal, temporal and parietal areas, with higher predominance of the prefrontal cortex (PFC) (Harwood et al., 2005; Salmon et al., 2006; Jedidi et al., 2014; Perrotin et al., 2015), cingulate cortex (Perrotin et al., 2015; Gerretsen et al., 2017; Vannini et al., 2017b; Therriault et al., 2018), hippocampus (Vannini et al., 2017b), parahippocampal gyrus (Salmon et al. 2006) and temporoparietal junction (Salmon et al., 2006; Gerretsen et al., 2017). Notably, recent studies have pointed out the involvement of the posterior cingulate cortex as a structure responsible for anosognosia, within a broader dysfunction of the default mode network (DMN) (Therriault et al., 2018).

Within the context of a normally functioning brain, the functional substrates of the cingulate cortex, precuneus and PFC have already been associated with mechanisms

of self-reference ([Northoff et al., 2006](#)). Therefore, the presence of hypoperfusion and hypometabolism in targeted cortical brain regions that are affected by AD pathology may be the cause of the inability to achieve proper conscious self-awareness since an early stage within the AD pathological continuum.

2.2.5.2 Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) in anosognosia shows consistency with the findings from brain metabolism and perfusion studies, discussed in the section above. Task-based fMRI studies have shown activation of fronto-parietal ([Ruby et al., 2009](#)), fronto-cingular ([Ries et al., 2007](#); [Amanzio et al., 2011](#)) and fronto-temporal ([Zamboni et al., 2013](#)) networks during activities based on self-reflection and perspective-changing, with fewer clusters of significant activation located in posteromedial parietal regions ([Amanzio et al., 2011](#)). Conversely, evidence from resting-state fMRI showed reduced intrinsic connectivity of the orbitofrontal, posterior cingulate, medial temporal ([Perrotin et al., 2015](#)) and inferior parietal cortices ([Vannini et al., 2017b](#)); translating into reduced connectivity within some of the structures that constitute the DMN. The most recent study regarding the functional neural substrates of anosognosia showed an essential involvement of the anterior cingulate cortex ([Mondragon et al., 2021](#)). Notably, regardless of the methodology applied, all task-based and resting-state functional studies displayed the involvement of the frontal lobe as an essential region involved in intrinsic connective functions of multi-dimensional awareness and self-appraisal abilities ([Ries et al., 2007](#); [Amanzio et al., 2011](#); [Zamboni et al., 2013](#); [Perrotin et al., 2015](#); [Vannini et al. 2017b](#); [Mondragon et al., 2021](#)).

2.2.5.3 Neuroanatomical structural imaging

The neuroanatomical bases of anosognosia investigated through structural magnetic resonance imaging (MRI) and the application of a voxel-based research methodology (Voxel-based morphometry, VBM) has associated multiple-domain anosognosia with a more varied set of neural structures than the studies reviewed in the earlier sections. These studies showed atrophy in the PFC ([Ford et al., 2014](#); [Hornberger et al., 2014](#); [Shany-Ur et al., 2014](#); [Spalletta et al., 2014](#); [Fujimoto et al., 2017](#), [Guerrier et al., 2018](#)), cingulate cortex ([Spalletta et al., 2014](#)), medial temporal lobe ([Hornberger et al., 2014](#); [Spalletta et al., 2014](#); [Tondelli et al., 2018](#)), subcortical structures ([Shany-Ur et al., 2014](#)) and cerebellum ([Spalletta et al., 2014](#), [Guerrier et al., 2018](#)). Almost all studies except one showed consistency with grey matter reduction in the frontal lobe when assessing cognitive and non-cognitive anosognosia. In addition to this region, the second territory that is most commonly affected was the medial temporal lobe. The use of VBM techniques in order to uncover the neural underpinning of awareness of cognitive and non-cognitive deficits has shown promising results, as the focus of analysis is centred on bigger regions than metabolic or perfusion studies, where these latter studies generally tended to use a region of interest analysis ([Zamboni & Wilcock, 2011](#)).

In summary, histopathological ([Marshal et al., 2004](#)) and brain imaging techniques have demonstrated to be essential tools to define the functional and neuroanatomical abnormalities involved in the genesis of anosognosia in AD. For that reason, the main objective of these studies has been to assemble the brain regions emerging from studies using diverse methodologies so that the results would reflect the backbones of the proposed theoretical models, as a way of evidencing the pathophysiological bases behind this symptom ([Mondragon, Maurits & De Deyn, 2019](#)).

Remarkably, the study of anosognosia, as a widespread clinical phenomenon at a population level has found a certain degree of consistency in the cerebral areas that when dysfunctional would result in unawareness, regardless of the domain explored. The role of the right frontal lobe could be the necessary evidence to define, finally, not only the neural mechanisms underlying anosognosia, but also the scaffolds of self-reflection abilities and the fundamental interaction among other metacognitive processes.

2.2.6 Demographics and neuropsychology of anosognosia

A recent meta-analytical study has reported that the prevalence of anosognosia in AD ranges between 40 and 91% depending on the severity of the disease. In detail, awareness of cognitive decline is significantly poorer in mild AD than in amnesic MCI and, ultimately, than cognitively healthy controls ([Cacciamani et al., 2021](#)). Research into the relationship between single epidemiological variables and anosognosia in AD has pointed out no overall relevant associations. Studies have shown inconsistent results regarding the influence of age of onset, duration or severity of disease and sex ([Clare, 2004](#)). Importantly, awareness of deficits of cognitive functions can also be observed in healthy ageing. One study linked alterations of perceptual and mnemonic abilities (metacognition and metamemory) in a geriatric population; however, no association was found with executive functions ([Palmer, David & Fleming, 2014](#)). In this respect, targeted alterations in the awareness executive system could support an effective distinction between changes that might be due to abnormal ageing in MCI and cognitive changes due to healthy ageing. Additionally, these results point out that the accuracy of metacognitive performance relies on age-dependent resources, in

addition to the presence of an underlying pathological process. Not surprisingly, disease severity remains the most consistent clinical correlate of the degree of unawareness; although studies that obtained null results justified the outcomes with inadequately small sample sizes ([Aalten et al., 2005b](#)).

The neuropsychological correlates of anosognosia could be of assistance in explaining the mechanisms of this symptom based on the proposed theoretical models and the findings of neuroimaging studies. Nevertheless, assessments based on subjective self-reflection of cognitive functions (i.e., metacognition) have shown no correlation with the objective measurement of that cognitive function (e.g., the presence of anosognosia for memory functions might not be directly linked to memory impairment) ([Clare, 2004](#)). In fact, objective memory testing in MCI and AD has shown no association with unawareness in that domain (metamemory deficits) ([Avondino & Antoine, 2016](#)).

Furthermore, research in this area has broken down the cognitive correlates of unawareness based on their relevance in the theoretical models; specifically, about associations with the memory, executive functions and attentional domains. In this sense, executive dysfunction has shown the highest association with anosognosia in AD ([Starkstein 2014](#)). Nevertheless, not all studies show convergent findings ([Agnew & Morris, 1998](#); [Clare, 2004](#); [Hannesdottir & Morris, 2007](#); [Amanzio et al., 2013](#)).

In conclusion, overall descriptive and cognitive studies in patients with AD (at different disease stages) seem to show no consistent association between levels of awareness and neuropsychological traits across the current literature. Therefore, cognitive measures alone seem unsuitable to clarify the substrate of unawareness associated with specific or multi-domain anosognosia. The neuroanatomical and cognitive conceptual patterns point out that alterations of executive functioning,

mediated by the frontal lobes, have an impact on the levels of self-awareness in AD. This could be explained in part due to the extensive complex construct of the individual components that comprise executive abilities (i.e., reasoning, inhibition, monitoring, planning, attention or judging) that are intrinsically involved in the ability of self-appraisal and conscious awareness.

2.3 Social cognition and awareness of others

The ability to be aware of others relies substantially on the neurocognitive domain defined as social cognition. This field of study derives from social psychology and can be defined as a group of mind mechanisms that enable humans to manage and understand relations with others and adapt to these interactions in order to perform properly in an established society (Frith, 2008). The neuropsychological independent domains in which research has focused the study of social cognition are based namely on the domains of emotion perception, attributional style, theory of mind, empathy, social knowledge, emotional awareness and alexithymia. In addition to the study of specific neuropsychological aspects, the theoretical constructs to elucidate the study of social cognition have been classified into information that requires low or high-level mental processing. Subsequently, this piece of information can be further divided into the amount of cognitive or affective processing that is required for social processing (Etchepare & Prouteau, 2018). In a more pragmatic context, and within the research based on neurological conditions, social cognitive processing relies on three sequential domains, starting with the ability to perceive others as human beings that possess distinctive emotional features, namely, the ability to recognise facial affective gestures and body language (i.e. emotion recognition). Once a human being has been perceived and acknowledged, a second mechanism established as social comprehension is engaged. This mechanism relies on the capacity to create attributions about the beliefs, intentions or emotions of others (a concept defined as theory of mind, ToM). Lastly, the third domain comprises the ability to modulate higher-order mental decisions and response behaviours based on social inspiration that results from mutual self-other understanding (Arioli, Crespi & Canessa, 2018).

2.3.1 Social cognition in Alzheimer's disease

Impairment in the ability to be consciously aware of the social surroundings has attracted the attention of neuroscience since it was first associated with frontal lobe injury in the Phineas Gage case over a century ago (Kihlstrom, 2010). The Diagnostic and Statistical Manual of Mental Disorders (DSM V) has established that the predominant cognitive domains that affect patients with established major neurocognitive disorders present selective dysfunctions in the spheres of attention, executive functions, learning and memory, language, perceptual-motor functions and social cognition. Of these, AD continues to be the most representative neurocognitive syndrome that affects the elder population. Notably, it was not until the last version of the DSM that social cognition was included as part of the essential domains affected by neurocognitive dysfunction in this population, since an impairment of this sphere can also contribute to overall brain function decline in neurocognitive diseases (Van Assche, Persoons & Vandenbulcke, 2014; Arioli, Crespi & Nicola, 2018).

As a starting point of how changes in social cognition are closely intertwined with ageing and dementia, minor decline of social cognition has been evidenced even during healthy ageing (Castelli et al., 2011; La Salvia & Chemali, 2011). Social cognitive decline has been also evidenced in MCI patients who manifest impairments in emotion recognition and ToM tasks (Bora & Yener, 2017; Kessels, Elferink & van Tilborg, 2021), probably due to overall higher cognitive burden. With the progression of MCI to AD dementia, global social cognition declines progressively (Elferink, van Tilborg & Kessels, 2015; Moreau et al., 2015). Most of the research performed on social cognition and AD has focused on the domain of theory of mind that will be discussed in more detail in the sections below.

2.3.2 Emotion Recognition

Affective recognition develops from childhood, starting first with the ability to attribute emotional signalling or affective arousal (associated with structures of the OFC, amygdala and hypothalamus); secondly, the acquisition of an emotional understanding that is associated with structures within the medial prefrontal cortex, ventro medial prefrontal cortex and temporoparietal junction, TPJ; and finally with the development of emotional regulation (associated with structures of the orbitofrontal cortex, medial prefrontal cortex and dorsolateral prefrontal cortex) (Decety, 2010). Specifically, the amygdala projects a mental description in two phases: first, face recognition and then emotional understanding (Adolphs, 2006).

Dementia and MCI individuals who have progressive deterioration of the relevant cortical structures have shown difficulty in completing emotion recognition assessments (Christidi et al., 2018). In fact, amnesic MCI patients who have difficulties in recognising emotions through facial expressions experience faster progression to AD (Spoletini et al. 2008; Bediou et al. 2009). There is growing evidence that suggests that emotion recognition might be impaired in the AD continuum, specifically during the prodromal and early dementia stage (Elferink, van Tilborg & Kessels, 2015). This impairment might partially reflect an overall cognitive dysfunction of executive, attention, and visuospatial abilities (Christidi et al., 2018; Torres et al., 2019).

2.3.3 Empathy

Empathy refers to the capacity to understand (i.e., cognitive empathy) and share (i.e., affective empathy) the personal experience of others, by being able to construct an

internal image and relate to the subjective emotional thinking of other individuals (Decety, 2011; Kemp et al., 2012; Dermody et al., 2016). This social cognition attribute activates in three stages, namely emotional sharing, others perspective taking and emotion assimilation (Decety & Jackson, 2004). Moreover, it also depends on the context of the social interaction in which a fronto-temporal and insular network might be activated (Ibanez & Manes, 2012; Melloni, Lopez & Ibanez, 2014). In contrast to AD, empathy and moral judgment are often lost in patients with behavioural variant frontotemporal dementia, in which impairment of these abilities seems to be a determinant diagnostic feature that characterises this type of dementia (Eslinger et al., 2007; Eslinger et al., 2011; Baez et al., 2014; Oliver et al., 2015).

2.3.4 Theory of Mind

Theory of mind is defined as the ability to construct an internal meta-representation about other individuals, to predict, attribute and understand their internal states of mind and behavioural displays (Premack & Woodruff, 1978; Baron-Cohen, Leslie & Frith, 1985).

Two types of ToM have been recognised across the current literature. Firstly, cognitive ToM (cog-ToM) refers to the ability to attribute intentions, beliefs and general thoughts to others. Secondly, affective ToM (aff-ToM) relies on the ability to comprehend and further mentalise emotional states. The latter component of ToM can further overlap with empathetic mechanisms in which aff-ToM and cognitive empathy, mentioned above, share the same neuropsychological attributes (Dodich et al., 2016; Oliver et al., 2015). Impairment of cognitive empathy or affective ToM may be displayed as an incapacity to understand the feelings of others, reflecting on how the

individual might behave in a social context. This has been shown to be an essential ability greatly compromised in patients with autism ([Baron-Cohen, Leslie & Frith, 1985](#)). Finally, a third social construct, recognised as emotional empathy, allows people to assimilate and experience these emotions transmitted to them within a particular social sphere ([Kalbe et al., 2010](#); [Shamay-Tsoory, 2011](#)). For example, when a person observes another one crying in anguish or grief, that person might experience sadness for seeing someone else in suffering.

2.3.4.1 Theory of Mind assessment

In a clinical setting, ToM abilities can be assessed in various ways; for example, cog-ToM can be assessed by the False Belief test ([Baron-Cohen, Leslie, & Frith 1985](#)), structured to understand simple and complex mental constructs by correctly differentiating the way one thinks compared to others. This test can be divided into two independent assessment domains, depending on their degree of difficulty, namely recognition of a first-order false belief (FOFB) that is simply intended to adopt the perspective of others (character A thinks that...), and a more complex second-order false belief (SOFB) that relies on metacognitive constructs, based on two different individual perspectives, concomitantly (Character A thinks that Character B thinks...) ([Baron-Cohen, Leslie, & Frith, 1985](#)). Theory of mind skills can also be assessed through the *Faux pas* test ([Bottiroli et al., 2016](#)), where patients recognise Cog-ToM in an initial phase and then aff-ToM by the identification and internalisation of affective states based on inappropriate social interactions ([Bottiroli et al., 2016](#)).

Due to the nature of dementia, adaptive social cognition assessments have been constructed with the aim of reducing the overall cognitive burden that is inherent

to the disease, by rather depending on non-verbal visual depictions. For example, the ability to recognise emotions through photographs portraying character facial expressions (Ekman 60-face test) (Ekman & Friesen, 1976; Diehl-Schmid et al., 2007; Dodich et al., 2014), or the ability to recognise intentions through the gaze reflected in photographs of characters' eye expressions (Reading the Mind in the Eyes Test, RMET) (Baron-Cohen et al., 2001). Also, the use of simple cartoon-vignette pictures to depict easy stories regarding everyday social situations can help a patient infer the thinking of others without having to process and remember a substantial amount of information (Happe, 1995; Dodich et al., 2015). For this reason, these social cognitive assessments, which do not rely significantly on cognitive burden, were used throughout this thesis, as they tend to demand fewer overall cognitive resources from the patients; hence, improving the reliability of data and allowing the interpretations to be associated with true changes in the social cognition domain. A more detailed description of each of the tests can be found in the materials and methods section of the specific experimental chapter regarding social cognition (section 5.1.2.2).

2.3.4.2 Theory of Mind in Alzheimer's disease

As mentioned previously, an overall cognitive assessment of dementia should include a social cognition component; not only for its comprehensive neuropsychological value, but for its intrinsic value as a cost-effective clinical tool for differential diagnosis among different types of dementia and neurodegenerative syndromes (Dodich et al., 2016). A recent meta-analytical approach has shown that patients with AD may manifest an impairment in both cog-ToM and aff-ToM compared to controls (Demichelis et al., 2020). However, this impairment seems to be restricted predominantly to complex

tasks such as SOFB detection or the *Faux pas* test (Cuerva et al. 2001; Koff et al., 2004; Zaitchik et al., 2004; Fernandez-Duque, Baird & Black, 2009; Castelli et al., 2011; Laisney et al., 2013; El Haj, Gely-Nargeot & Raffard, 2015). In this context, it was initially proposed the existence of a dissociation between executive functions in relation to ToM (Gregory et al., 2002; Moreau et al., 2016), with the statement that possibly a neural social network, independent of other cognitive networks, might serve as a substrate for social processing (Cosentino et al., 2014), in which cognitive burden would not impact negatively on mentalisation tasks (Fernandez-Duque, Baird & Black, 2009; Youmans & Bourgeois, 2010; Castelli et al., 2011; Freedman et al., 2013; Shany-Ur et al., 2012). However, more recent contrasting findings have postulated a counterpoint in which ToM in AD might rely predominantly on higher-cognitive functions, such as executive functions (Fliss et al., 2016; Ramanan et al., 2017; Dos Santos et al., 2020; Lucena et al., 2020) or working memory (Shany-Ur et al., 2012; Le Bouc et al., 2012; Laisney et al., 2013; Sandoz, Demonet & Fossard, 2014; Dodich et al., 2016; Fliss et al., 2016; Poveda et al., 2017; Chainay & Gaubert, 2020). Therefore, the support of overall cognitive functions to social performance could partially explain why ToM is relatively preserved in the earliest stages of the AD continuum (Choong & Doody, 2013; Poletti, Enrici & Adenzato, 2012). Preserved executive-attentional networks, therefore, could support ToM performance in the presence of damage to the brain social systems. Consequently, it has been hypothesised that preserved ToM in the early stages of AD could be explained through adaptive compensatory cognitive mechanisms that could have the potential role of serving as a potential “social reserve” (Fliss et al., 2016).

2.3.5 Neuroimaging of social cognition and Theory of Mind

Neuroimaging mapping has highlighted the role of predominantly frontotemporal cortices and limbic regions in supporting social cognition skills. ToM abilities rely upon these complex neural circuits, including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), temporal poles (TP), superior temporal sulcus (STS), temporoparietal junction (TPJ) and insula (Saxe & Wexler, 2005; Amodio & Frith, 2006; Frith & Frith, 2006; Abu-Akel & Shamay-Tsoory, 2011; Shany-Ur & Rankin, 2011; Schurz et al., 2014). In more detail, the medial PFC inhibits self-mentalising constructs to adopt others' viewpoints. Subsequently, the TPJ infers external thoughts through mentalising and belief recognition (Le Bouc et al., 2012). Additionally, the posterior medial PFC is involved in high-order processes of attention, decision making and reasoning, and the orbitofrontal cortex (OFC) is associated with complex social analysis and emotion acknowledgement (Amodio & Frith, 2006; Choong & Doody, 2013; Bora, Walterfang & Velakoulis, 2015). Finally, Cog-ToM is related to the TPJ and dorsolateral PFC, while Aff-ToM is associated with the TPJ and ventromedial PFC (Kalbe et al., 2010; Abu-Akel & Shamay-Tsoory 2011; Poletti, Enrici & Adenzato, 2012).

Emotion recognition mapping includes the occipital, fusiform and lingual gyri (involved in visual identification); amygdala and insula (for emotion perception); STS and OFC (involved in emotion adaptation and expression, respectively); and the overall contributions of the medial PFC and cerebellum (Adolphs, 2006; Carrington & Bailey, 2009; Fusar-Poli et al., 2009; Shany-Ur & Rankin, 2011). Subsequently, once affective recognition structures have been recruited, the neural substrate of empathy is added through the contributions of the ACC, temporal poles, TPJ, subcallosal gyrus and fusiform gyrus (Gregory et al., 2002; Cerami et al., 2014b; Caminiti et al., 2015). Finally, the dorsolateral and ventromedial PFC are related to harm differentiation in

relation to empathetic processes ([Davidson & Irwin, 1999](#); [Lamm, Batson & Decety, 2007](#)).

Functional resting-state studies have delimited the cooperation of three overlapping large-scale functional brain networks that appear to play a role in social cognition tasks, namely, the default mode network (DMN), the salience network and the central executive fronto-parietal network. These networks have been recognised to be involved in mediating cognition ([Bressler & Menon, 2010](#)). In addition, social cognition has shown to be supported by the additional involvement of a frontotemporal-insular network (or social context network model) and the Mirror Neuron System ([Rizzolatti & Craighero, 2004](#); [Seeley et al., 2007](#); [Baez, Garcia & Ibanez, 2017](#)).

The DMN (active during the absence of external stimuli) shows prefrontal, temporal, parietal and ACC activation, converging in the PCC and anterior mPFC ([Grieder et al., 2018](#); [Alves et al., 2019](#)). There is evidence of substantial overlap between the functional hubs of the DMN and the known territories that support social cognition, with significant predominance of ToM functions ([Andrews-Hanna, 2012](#); [Mars et al., 2012](#); [Schurz et al. 2014](#)). Most importantly, it has been extensively recognised that patients with AD show an impairment of the DMN from an early stage in the disease process ([Greicius et al., 2004](#)). On this note, early amyloid accumulation has been found in core hubs of the DMN that may lead to network hypoconnectivity, while brain volume and glucose metabolism are still relatively preserved ([Palmqvist et al., 2017](#)). Therefore, it is sensible to hypothesise the existence of ToM deficiencies even in the very early stages of the disease if there is a dysfunctional DMN; however, in the clinical setting, this might seem paradoxical as social cognitive functions stay preserved until later stages of the disease. Hence, this might raise the question of

possible functional compensatory mechanisms that are active in the presence of an early downregulation of the DMN in early AD.

The salience network is recognised as a system in charge of directing attention to internal self-centred or external relevant stimuli with the purpose of shifting mental resources between the internal state of mind and the external physical and social environment (Uddin, 2015). The central nodes of the salience network are found predominantly in the anterior cingulate and frontal insular cortices (Uddin, Yeo & Spreng, 2019). Indeed, there is evidence that the salience network is also affected in MCI patients, suggesting an impairment in the ability to regulate transit of information between the DMN and the frontoparietal network (Chand et al., 2017).

The central executive fronto-parietal network is crucial to perform high-order cognitive tasks. It shows activation during tasks based on working memory, decision making and problem-solving, in the context of goal-achieving behaviour (Menon, 2011). The central nodes that define the frontoparietal network are centred predominantly on the dorsolateral prefrontal cortex and the posterior parietal cortex (Bressler & Menon, 2010).

In the social cognition framework, the salience network mediates self-related brain representations centred on a temporally tagged remembrance of social interactions and the recognition of external social prompts (Melloni, Lopez & Ibanez, 2014). Also, some of the salience network hubs have been found to overlap with empathetic processes (Kennedy & Adolphs, 2012). The frontal (OFC, superior orbital sulcus), temporal (amygdala, hippocampus, perirhinal and parahippocampal cortices) and insular networks, which involve a significant proportion of salience system territories, are involved in the recognition of specific social contexts and empathetic

responses (Melloni, Lopez & Ibanez, 2014). Finally, the mirror neuron system has been proposed to support cognitive and social networks involved in the processing of affective and mentalising abilities through social imitative learning and visual mimicry (Sperduti et al. 2014).

2.3.5.1 Neuroimaging of social cognition and Theory of Mind in dementia

Due to the distinctive nature of social cognition decline in the behavioural variant of frontotemporal dementia, the majority of research regarding the neural substrates of social cognition in dementia is based on evidence from patients with this particular type of dementia (Christidi et al., 2018). In this setting, the neural substrates of social cognition deficits in neurodegenerative diseases have been broadly associated with medial frontotemporal and anterior frontal regions (Shany-Ur & Rankin, 2011; Poletti, Enrici & Adenzato, 2012; Strikwerda-Brown, Ramanan & Irish, 2019). Disruption of these brain regions has been shown to result in detriment is function related to moral judgement (Baez et al., 2014), empathy (Dermody et al., 2016) and ToM (Baglio et al., 2012), even at the prodromal stages of neurodegeneration. There is evidence that patients with amnesic prodromal MCI may have degeneration in the medial PFC (Poletti & Bonuccelli, 2013) with alterations of the mirror neuron system network (Baglio et al., 2012; Moretti, 2016) resulting in impairment of social cognitive abilities. Few studies exist that have investigated social cognition specifically in the AD continuum. These studies are detailed in **Table 2.2**. The specific revision and critical analysis of these studies will be presented in chapter 5 in relation to the experiments based on awareness of others and social cognition. Despite the small number of studies, a pattern of shared damage areas can be detected and shows mainly

involvement of the left TPJ (Le Bouc et al., 2012; Dermody et al., 2016) and cerebellum (Baglio et al., 2012; Synn et al., 2018). Interestingly, executive functions and social cognition share network components such as the OFC and PFC; with an additional involvement of executive-independent sub-cortical regions (Couto et al. 2013; Cosentino et al. 2014).

Table 2.2 Review of neuroimaging studies of brain changes in relation with social cognition in AD.

Study	Subjects	Social cognition domain and assessment	Social Cognition results	Neuroimaging Findings
VBM				
Dermody et al. 2016	24 bvFTD 25 AD 22 HC	Empathy: Interpersonal reactivity index	AD showed empathy impairments possibly due to cognitive dysfunction	AD displayed left TPJ atrophy associated with perspective-taking deficits in addition to the left fusiform and temporal cortex
Kumfor et al. 2017	25 bvFTD 23 AD 25 HC	Emotion perception and ToM: Awareness of Social Inference Test (TASIT)	AD showed no difference with HC after controlling for cognitive function.	Reduced GM in the right middle and inferior temporal gyrus, right temporo-occipital, operculum and left parahippocampal gyrus.
Synn et al. 2018	18 AD 18 bvFTD 25 HC	ToM: Frith-Happe animations	ToM deficits are present in AD and seem to be mediated by cognitive dysfunction.	GM loss in the bilateral cerebellum and right hippocampus
PET				
Le Bouc et al. 2012	11 bvFTD 12 AD 20 HC	ToM: first-second order false belief	AD impairment in belief inference.	AD showed hypometabolism in the left TPJ junction (Belief inference).
SPECT				
Takenoshita et al. 2020	63 AD	ToM: Sally-Anne Test (false belief)	Comparison between impaired ToM (n= 34) vs non impaired (n=29)	Cerebral blood flow difference in the bilateral PCC.
fMRI				

Baglio et al. 2012	16 MCI 15 HC	ToM: eye directions, RMET, first-second order false belief	aMCI, impairment in complex ToM tasks. Neuropsychological tests and RMET no difference with HC.	Activation of fronto-temporal cortex (middle & inferior frontal, left superior & bilateral middle temporal and temporo-occipital gyri) and bilateral cerebellum .
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AD: Alzheimer disease; bvFTD: behavioural variant frontotemporal dementia; fMRI: functional magnetic resonance imaging; GM: grey matter; HC: healthy controls; MCI: mild cognitive impairment; PCC: Posterior cingulate cortex; PET: Positron emission tomography; RMET: Reading the mind in eyes test; SPECT: Single-photon emission computed tomography; ToM: Theory of Mind; TPJ: Temporoparietal junction; VBM: Voxel-based morphometry.

2.4 Conclusions

In this chapter, the basic theoretical framework of the neuropsychological and imaging foundations of cognitive awareness were established by reviewing the available evidence on self-awareness deficits (anosognosia) and changes of awareness of others (social cognition) in healthy population and disease. In AD, it seems that global cognitive awareness impairments might be partially driven by impairments in overall cognitive functions. In this context, interesting neuropsychological patterns emerged throughout this chapter where significant contributions of executive-related abilities seem to modulate the onset and overall clinical manifestations not only of self-awareness deficits ([Bradford, Jentzsch & Gomez, 2015](#); [Ramanan et al., 2017](#); [Lacerda et al., 2021](#)), but also changes of social cognitive skills ([Torres et al., 2019](#); [Dos Santos et al., 2020](#); [Chainay & Gaubert, 2020](#)), as a reflection of the ability to be aware of others.

Executive functions are recognised as a group of complex high-order mental abilities that allows cognitive control. They depend on behaviours focused on specific goal-associated purposes ([Cristofori, Cohen-Zimmerman & Grafman, 2019](#)). Three core

domains have been established for this function namely: self-inhibition, working memory and cognitive flexibility (or mental shifting). These complex skills allow the mastering of abilities such as planning, problem solving and reasoning ([Diamond, 2013](#)). Within the manipulation of these complex high-order mental resources there might be what constitutes the cognitive substrates of awareness, and given that these high order abilities are associated with frontal structures, the frontal lobe seems to be the anatomical leading contributor ([Ardila, 2016](#)). Therefore, cognitive awareness as a global entity of cognition and consciousness should be associated with function in a particular set of regions in the brain in which the two main domains that compose conscious awareness i.e. self-awareness and others-awareness, might have shared neural substrates ([Decety & Summerville, 2003](#)). It seems that, in healthy ageing, these shared substrates of conscious awareness reside primarily in territories outlining the DMN ([Mars et al., 2012](#); [Davey, Pujol & Harrison, 2016](#)). However, patients in the early stages of AD experience a downregulation of this network ([Greicius et al., 2004](#)) due to the inherent pathophysiological process that could consequently promote adaptive responses of other core functional large-scale networks, in the effort to sustain conscious awareness, at least in the earliest stages of AD neurodegeneration.

Chapter 3

Aims and objectives

There is a golden thread that explains the intentions behind the present project. The neuropsychological and neural correlates that underpin cognitive awareness have been studied in Alzheimer's disease (AD); however, the focus of this research was inclined more on a comprehensive approach to deficits in self and others awareness, as there is scarce information focused in elucidating the neural substrates that outline the ability to be aware of others (social cognition) in the early AD continuum. Detrimental changes of conscious awareness have a significant negative impact on the overall prognosis of the disease by increasing the risk of conversion to dementia (Therriault et al., 2018) in addition to caregiver burden, global costs and leading to early institutionalisation, accumulating to the overall load of public health systems worldwide (Starkstein, 2014). Social cognitive tools have already been shown to be important predictors of progression and appear to have also a significant discriminative power among dementias (Christidi et al., 2018). In this context, Theory of Mind (ToM) and emotion recognition assessment could serve as a useful tool for the impact and progression of AD within the context of a comprehensive neuropsychological examination that includes assessments of all the other established neurocognitive domains (Henry et al., 2016).

The logic behind this thesis work relied on the novel investigation of the relationship that exist between the multiple domains that define awareness deficits in AD; self-awareness through anosognosia and awareness of others through social

cognition changes in the early stages of the disease. The theoretical framework for this project was constructed firstly through the most consistent neuropsychological premise in AD in which self-awareness and social cognition might be driven by high-order cognitive skills such as executive/attentional functions (Starkstein, 2014; Ramanan et al., 2017). However, existing findings remain still contradictory as they do not cover the complex interplay of multiple domains of awareness with the global neurocognitive profile. Secondly, the neuroimaging studies associated with the study of self and others awareness in AD have pinpointed the frontal lobe as one of the most representative brain territories responsible of harbouring self-others conscious awareness, both in healthy participants (Amodio & Frith, 2006; Northoff et al., 2006; Schurz et al., 2014) and in AD (Hallam et al., 2020; Baglio et al., 2012). Furthermore, the interplay of functional large-scale networks that could underpin unawareness in AD is yet unknown.

Once established the cognitive and brain biological framework, the specific aims and objectives can be dissected by chapters. On the whole, the methodological experimental approach for the present work was based on six cross-sectional cognitive and multi-modal neuroimaging experiments based on three separate constructs that served as the main dependant variables of cognitive awareness, through the independent outcomes of 1) multi-domain anosognosia and self-awareness deficits, 2) social cognition and changes in other's awareness and 3) the intrinsic relationship of self and other's awareness domains in the early AD continuum. To our knowledge, the present work is the first to explore awareness in AD through a comprehensive multi-modal approach. Most importantly, this work is the first to provide a detailed approach to the cognitive and neural substrates of social cognition in the early AD continuum.

Each experimental chapter was comprised of two independent comprehensive multi-modality experiments. In the first experiment within each chapter, the methodological approach intended to clarify the association of the neuropsychological assessments alongside the structural connectivity and neuroanatomy related with the specific domain of awareness (self, other, or both). The second experiment within each experimental chapter intended to elucidate the functional neural correlates of awareness through resting-state large-scale and seed-based regional functional models. Therefore, the main objective in the second experimental stage was to investigate how specific dysfunctions of self-awareness and social cognition traits may be a negative reflection of disrupted connectivity among global networks within the brain, in addition to how the variables of self and others awareness were associated to damage to similar regions responsible for the independent modulation of these domains, a direct reflection of possible shared neural substrates that underpin conscious awareness.

The novel approach to the field of self-awareness deficits in AD in the present work was through exploration of the different domains that entails self-awareness; in this case, memory anosognosia, non-memory anosognosia (a proxy of activities of daily living and executive functions) and total anosognosia. The majority of studies have focused only on memory anosognosia ([Avondino & Antoine, 2016](#)), so our methods allowed us to explore a more comprehensive panorama that delineates self-awareness in AD. Furthermore, social cognition was also explored through a multi-domain assessment that assessed the social spheres of emotion recognition and cognitive and affective Theory of Mind. The logical reason for using a multi-domain examination of awareness relies on the complex neural adaptive mechanisms that might interplay differently depending on the clinical manifestations of awareness in the

AD continuum, where they might display subtle to mild impairments in different domains related to self-awareness decline in contrast to how they might manifest more preserved social cognition and awareness of the thoughts, intentions and emotions of other individuals. To give more depth, the specific objectives of the current PhD research project were:

1. To investigate the structural, functional and behavioural associations of multi-domain and domain-specific anosognosia in patients in the early AD continuum, as a direct reflection of their level of insight and self-awareness.

The first study intended to explain the relation between the existence of anosognosia for memory and functional abilities, and the reduction of grey matter volume in specific brain regions among patients diagnosed with prodromal and early mild AD dementia. Several brain regions have already been identified as associated with deficits of awareness of metacognitive functions, such as metamemory; however, the neuroanatomical foundations behind its development are yet to be clarified as a way to reconcile current brain imaging findings of anosognosia in AD and consolidate the theoretical models that try to give a comprehensive explanation. We intended to clarify the biological substrates of domain-specific unawareness as an independent phenomenon from an impairment in the cognitive domain itself (i.e., the presence of unawareness for a neurocognitive domain does not necessarily mean an impairment of the explored domain).

The first aim of this study was to examine the neuropsychological differences in relation to patients that manifested clinical multi-domain anosognosia, in the domains that control awareness for memory, activities of the daily life and executive functions. Secondly, we aimed to associate the regional patterns of grey matter volumetric loss

and structural connectivity with the individual scores of overall anosognosia, and consequently, with each subdomain level (memory and non-memory-related activities). Based on neuroimaging and theoretical conceptual settings we hypothesised that:

- **Domain-specific anosognosia would reflect the detrimental effects of grey matter loss in frontal lobe regions that support the performance of a mnemonic comparator system and associated cognitive functions.**

At the functional level, a resting state analysis was performed with the aims to explore the connectivity variations of different networks that could interact to result in awareness deficiencies in early AD patients. By this means, our hypothesis proposed that:

- **Participants with total or domain-specific anosognosia will show connectivity alterations mainly in frontal regions and within the default mode network that would also reflect changes in regional and large-scale network dynamics.**

The rationale and findings of these experiments will be presented in chapter 4.

2. To investigate the structural, functional and behavioural correlates of social cognition deficits in early AD patients, as a direct reflection of the level of insight and awareness of others.

There is some evidence that social cognition abilities can also be compromised from an early stage in the disease course in AD. Additionally, the neural underpinnings that define social cognition deficits in AD patients are still poorly understood. The study of the neural correlates of social cognition in healthy participants has pinpointed areas of the brain including the prefrontal cortex, temporo-parietal cortex and temporal poles within the default mode network territory as the neural substrates of this ability ([Mars](#)

et al., 2012; Schurz et al., 2014). The first aim of this study was to investigate the brain anatomical areas and structural connectivity associated with changes in social cognition. The second aim intended to clarify the behavioural associations between social cognition and overall cognitive performance, as a way to evidence the connection of global cognition and possibly executive functions as an essential foundation for social performance. There is evidence that social cognition is relatively preserved in early-AD; therefore, we did not intend to explore the presence or absence of true dysfunction of social cognition in our sample, but rather to clarify which alterations in neural territories directly modulate changes in social performance. In this experiment, we hypothesise that:

- **Changes in social cognition are related to brain grey matter reductions along with structural connectivity changes in frontal regions known to support social cognition skills in healthy individuals in association with frontally-mediated cognitive functions.**

In the brain functional setting, a resting-state connectivity study was performed with the aim to investigate the integrity of the networks involved in Theory of Mind and emotion recognition. In the presence of a hampered default mode network, a network known to modulate social cognition, functional large-scale and regional connectivity alteration dynamics might provide an explanation of why social cognitive skills are relatively preserved in the early stages of the disease. Therefore, our hypothesis proposed that:

- **Social cognition alterations in patients with AD will have large-scale and regional connectivity alterations associated with the changes in activity of the default mode network, as defined by the social cognition studies in**

healthy individuals, and relative preservation of these skills at an early stage will reflect adaptive dynamics of other cognitive functional networks.

The rationale and findings of these experiments will be presented in chapter 5.

3. To investigate the structural, functional and behavioural relationship between self-other awareness in early AD patients.

As a follow up of the research completed in healthy participants, our aims were to study the neural relation of self-other awareness through the conjunction analysis of independent measurements of multi-domain anosognosia and social cognition. The main aim was to understand if there exist a behavioural and neural interaction between the two main domains that encompass cognitive awareness. Hence, the first main hypothesis for this experiment was that:

- **The presence of anosognosia parallels poorer performance in social cognition.**

Additionally, it was hypothesised that:

- **Deficits of self and others awareness will be associated with shared structural and functional neural territories, specifically in medial frontal cortical regions, where neural associations with conscious awareness have been detected in healthy people.**

The rationale and findings of these experiments will be presented in chapter 6.

The specific role that I took in the development of this research started with the formulation of the research questions and research hypotheses. Imaging data had been acquired as part of a EU funded initiative (the VPH-DARE@IT project). The behavioural data on which this PhD is based were acquired as part of an ancillary

project to the parent project. Once acquired, I was given access to both imaging and behavioural data. I was then in charge of processing of all raw neuroimaging and cognitive data. This data was firstly processed for group-level analyses. After several pre-processing steps, the neuroimaging data were ready to be modelled and analysed. I designed the methodology of all statistical modelling in relation to the project's hypotheses and theoretical background. After t statistical modelling, data outcomes were interpreted and further *post-hoc* models planned and implemented to test the experimental hypotheses. Lastly, results were discussed and drafted in the form of this thesis and several research articles written up for publication. This project also included a prospective study that I had designed and that had received ethical approval. This prospective study could not be carried out as data acquisition could not be done because of the restrictions on clinical research imposed by government health authorities to contain the 2020 COVID-19 pandemic.

Chapter 4

Neuroanatomical, functional connectivity and behavioural correlates of self-awareness impairment in early Alzheimer's disease

4.1 Experiment 1 | Behavioural, neuroanatomical and structural connectivity correlates of domain-specific anosognosia in early Alzheimer's disease

4.1.1 Introduction

Introduced more than one century ago ([Babinski, 1914](#)), the term “anosognosia” can be recognised as a neurological symptom that is characterised by lack of self-awareness of the presence of a disorder or disability such as disease-associated deficits, cognitive alterations or behavioural changes ([Mograbi & Morris, 2018](#)). Anosognosic patients are unaware of their neurological impairments or are unable to judge how severe these are ([Morris & Mograbi, 2013](#)). It is a common symptom in Alzheimer's disease (AD), with an onset frequently observable at the prodromal mild cognitive impairment stage ([Vannini et al., 2017a](#); [Vogel et al., 2004](#)) and prevalence rates ranging from 20% to 80% ([Starkstein, 2014](#)).

In AD patients, anosognosia is associated with the deposition of amyloid peptides in the brain ([Marshall et al., 2004](#); [Vannini et al., 2017a](#)) and tends to affect awareness of memory dysfunction in parallel with other symptomatic manifestations, such as behavioural changes ([Sunderaraman & Cosentino, 2017](#)). However, with

disease progression, multiple domains may become affected by an anosognosic trait (often in an unpredictable way), resulting in considerable clinical heterogeneity (Gambina et al., 2015; Avondino & Antoine, 2016). Notably, the presence of low cognitive awareness has been demonstrated to serve as a potential preclinical marker of AD (Cacciamani et al., 2017).

Anosognosia in AD can be described according to clinical or theory-informed approaches (de Ruijter et al., 2020). Clinical classifications focus on the various domains of clinical relevance that can be affected by an anosognosic trait, i.e., awareness of behavioural problems vs. awareness of cognitive deficits (Starkstein et al., 1996). The latter can be further divided into a memory and an executive sub-component (Agnew & Morris, 1998) and additional domains have been proposed, e.g., awareness of skill in activities of daily living or in socioemotional interactions (Clare et al., 2012a). It is well-established today that dysfunction of awareness in AD is a multi-domain phenomenon (Leicht, Berwig, & Gertz, 2010). The aetiology of domain-specific dysfunction can be traced back to the modular theoretical model of anosognosia discussed in chapter 2. Selective impairment of the Conscious Awareness System (CAS) or mnemonic executive comparators leading to anosognosia would be the result of disruption of one or more modules along the computational pathway that links the outcome of aware processing to the executive unit (Schachter, 1990; Agnew & Morris, 1998).

The conceptual elements laid out by both clinical evidence and theoretical models of anosognosia have led to the exploration of the neurological mechanisms responsible for this highly disruptive symptom. Since AD is a neurodegenerative disease characterised by widespread brain atrophy, the neuroanatomical correlates are of particular interest. Significant associations have been found between the

presence of symptoms of anosognosia and grey matter volumes in a set of regions that include the prefrontal cortex (Ford et al., 2014; Fujimoto et al., 2017; Hornberger et al., 2014; Shany-Ur et al., 2014; Spalletta et al., 2014), cingulate cortex (Guerrier et al., 2018; Hanyu et al., 2008; Spalletta et al., 2014), medial temporal lobe (Hornberger et al., 2014; Spalletta et al., 2014; Tondelli et al., 2018), subcortical structures (Shany-Ur et al., 2014) and cerebellum (Guerrier et al., 2018; Spalletta et al., 2014). The majority of these studies highlights an association between anosognosia in AD and the volume of the forebrain (prefrontal and antero-limbic regions) (Mondragon, Maurits & De Deyn, 2019; Hallam et al., 2020). Accordingly, the cognitive domain in which dysfunction is most distinctively associated with anosognosia in AD is executive functioning (Starkstein, 2014); however, there is no consistency of findings within the literature and disorders of memory may be associated with the presence of this symptom (Orfei et al., 2010; Clare et al., 2013, Senturk et al., 2017).

The evidence emerging from neuroimaging studies aligns with the existing theoretical models. Prefrontal regions such as the anterior cingulate or the medial prefrontal cortex may serve as a core hub in support of the executive comparator system and dysfunctional connections in these pathways may result in executive anosognosia (Guerrier et al., 2018). Similarly, other studies postulate that anosognosia for memory deficits could find its pathological substrates in regions responsible for autobiographical conceptual memory such as medial temporal lobe structures that are impaired by the characteristic pathophysiology of AD (Morris & Mograbi, 2013; Chavoix & Insausti, 2017; Tondelli et al., 2018). This latter argument, however, is difficult to sustain since there is evidence that anosognosia for memory disturbance in AD is not necessarily associated with volume loss in mediotemporal structures, but rather with volume loss in the left superior frontal cortex (Fujimoto et al., 2017). In addition,

evidence from patients with focal lesions in mediotemporal structures that cause severe amnesia shows that amnesia does not inevitably lead to anosognosia (Shimamura & Squire, 1986; Amanzio et al., 2013; Avondino & Antoine, 2016). It follows that for anosognosia to appear, following either a focal lesion or as a result of neurodegeneration in mediotemporal structures, the contribution of additional dysfunctional mechanisms/regional damage is necessary. In neurodegenerative conditions, the clinical manifestations of memory or executive anosognosia are said to be associated with degeneration of densely interconnected fronto-temporal structures that are thought to be responsible for the integrity of the cognitive awareness system (Chavoix & Insausti, 2017).

Moreover, since anosognosia in AD can be expressed in multiple clinical domains, it is unknown whether the mechanisms are the same for each domain affected by the trait. In this respect, the current study explored anosognosia in two clinical domains: memory and non-memory (i.e., including activities of daily living and executive functioning). Specifically, we studied the association between global and domain-specific anosognosia and: 1) cognitive profiles, 2) voxel-based volumetric properties of the brain and 3) structural white matter connectivity. Therefore, based on neuroimaging and theoretical frameworks we hypothesised that domain-specific anosognosia would reflect the detrimental effects of grey matter loss and white matter tract alterations in frontal lobe regions that support the mnemonic comparator system performance and associated cognitive functions.

4.1.2 Methods and Materials

4.1.2.1 Participants

Fifty-four candidate patients were initially enrolled. All candidates had received either a clinical diagnosis of AD, $n = 25$, following the National Institute of Aging criteria (McKhann et al., 2011; Jack et al., 2018) or a diagnosis of MCI due to AD, $n = 29$, (Albert et al., 2011) as part of a sole continuum of AD severity that served as the central inclusion criteria for patient recruitment in this study. Longitudinal follow-ups in patients labelled as MCI for at least four years showed a clinical course supportive of an AD aetiology (Figure 4.1). This study was ancillary to a major EU funded initiative and recruitment was carried out from participants in the EU-funded Virtual Physiological Human – DementiA Research Enabled by IT (VPH-DARE@IT) initiative, a multicentre project clinically coordinated by the Department of Neuroscience, University of Sheffield, UK. The main inclusion criteria defined by the VPH-DARE initiative for the parent study were as follows:

For healthy controls, normal cognitive function evidenced by no memory complaints, an overall score of the Clinical Dementia Rating (CDR) scale of 0 or a score on the Mini-Mental State Examination test above 27/30. Inclusion criteria for MCI patients were defined as patients with age ranging between 50 and 85 years, with evidence of cognitive impairment established following clinical referral to a memory clinic and fulfilment of the amnesic and non-amnesic MCI criteria developed by Petersen, 2004 and Petersen and Morris, 2005. Inclusion criteria for mild AD specified patients with age ranging between 50 and 85 years fulfilling criteria for a clinical diagnosis of probable mild AD according to the NINCDS-ADRDA diagnostic criteria (McKhann et al., 2011). VPH-DARE exclusion criteria included: the presence of

obvious brain, systemic or psychiatric disorders that could potentially affect cognitive functions inclusive of stroke, severe depression or endocrine disorders; the presence of any other type of dementia not compatible with AD was also included as an exclusion determinant. For control participants and MCI, the presence of dementia according to the DSM-IV criteria at baseline was also specified as an exclusion criterion.

All eligible patients for the VPH-DARE initiative at our sites were also approached to take part in this ancillary study. All patients were recruited consecutively, and all were approached only if they also met the eligibility criteria for this additional study, i.e., having a reliable informant.

The expanded main set of exclusion criteria for this particular study consisted of other significant neurological conditions such as: acute or chronic cerebrovascular disease or history of transient ischaemic attacks (TIA), uncontrolled brain seizures or history of epilepsy, peripheral neuropathy disorders, presence of substantial behavioural symptoms or diseases compatible with brain MRI diagnosis not in accordance with this study; cardiovascular and gastroenterological conditions such as: sick-sinus syndrome or peptic ulcer; metabolic disorders namely, abnormal levels of B12, folates or thyroid-stimulating hormone; major pharmacological interventions such as treatment with memantine/cholinesterase inhibitors, psychotropic medication, pharmacological components displaying important organic adverse effects or medications used in other research protocols; and the presence of overall major disabilities that could impact negatively on cognitive or everyday life functions. All participants who had chronic treatment for other severe non-neurological diseases were on a stable treatment regime during data acquisition. Moreover, since the main predictor was dependent on the score obtained in a questionnaire administered to

patient-caregiver dyads, participants were not approached if no reliable informant was available. Each informant was briefly screened to rule out neurological or psychological factors that would prevent them from answering all study questions in a reliable way. One dyad was excluded due to incomplete testing, giving a final sample of 53 patients ([Table 4.1](#)).

Ethical approval was granted by the Yorkshire and Humber Regional Ethics Committee for the Sheffield arm of the study (Ref No: 12/YH/0474) and by the Joint Ethics Committee of the Health Authority Venice 12 and the IRCCS Fondazione Ospedale San Camillo for the Venice arm of the study (Protocol number 2014.08). Written informed consent was obtained from all participants.

4.1.2.2 Anosognosia and neuropsychological assessment

Levels of self-awareness were measured with the Measurement of Anosognosia Instrument ([Stewart et al., 2010](#)). This questionnaire consists of 15 binary “yes-no” questions assessing cognitive performance in daily-life settings. All questions need to be answered independently by the patient and by the informant. By doing so, two scores are obtained: that provided by the informant as a “standard-of-truth” objective assessment of the patient’s abilities and that provided by the patient as a self-evaluative measure. The Measurement of Anosognosia Instrument explores two functional domains of awareness: “memory” (9 questions) and “non-memory” (inclusive of executive functioning and activities of daily living; 6 questions). The informant-based and the patient-based responses were compared to quantify the number of discrepant answers provided by the patient. Discrepancy scores were used to quantify the presence of anosognosia across three domains: “memory”, “non-memory”, and “total” (the sum of both domains) ([Migliorelli, 1995](#); [Stewart et al., 2010](#)).

Finally, each participant underwent a comprehensive neuropsychological examination to obtain a cognitive profile. The assessment battery included the Mini-Mental State Examination (MMSE) to test for overall cognitive status, the Raven's Coloured Progressive Matrices test to assess for visual perception and abstract reasoning, the Token test for language comprehension, the Digit Span Forward for short-term memory and the WAIS Similarities test for verbal reasoning. Furthermore, in consistency with the conceptual background, tests of experimental interest related to cognitive awareness were chosen to assess the behavioural association of anosognosia with memory (Category Fluency test for semantic memory and Prose Memory delayed recall test for long-term memory), executive functions (Letter Fluency test and Stroop test for cognitive inhibition) and Visuospatial abilities (Rey–Osterrieth Complex Figure Test) (Morris et al., 1989; Wakefield et al., 2014) (Table 4.2).

4.1.2.3 MRI acquisition

A three-dimensional T1-weighted MRI scan was obtained for each participant. MRI scans were acquired and analysed following a shared protocol with the acquisition and modelling steps set up by the VPH-DARE@IT consortium for Philips scanners (<http://www.vph-dare.eu/index.php/project/work-packages/WP2>). T Turbo Field Echo T1-weighted images ($n= 33$) were acquired on a Philips Achieva 1.5 scanner with the following parameters: voxel size: $1.1 \times 1.1 \times 0.6$ mm; repetition time 7.4 ms; echo delay time 3.4 ms; flip angle 8° ; field of view 250 mm; matrix size $256 \times 256 \times 124$ and on a Philips Ingenia 3T scanner T1-weighted images ($n=20$) with the following parameters: voxel size: $0.94 \text{ mm} \times 0.94 \text{ mm} \times 1.00 \text{ mm}$; repetition time: 8.2 s; echo delay time: 3.8 s; flip angle 8° ; field of view: 256 mm; matrix size: $256 \times 256 \times 170$. Structural T1-MRI

multicentre protocol data merging followed standardised parameters used in research, already repeatedly used in the AD population ([Jack et al., 2008](#); [Marchewka et al., 2014](#); [Schmitter et al., 2015](#)).

Diffusion tensor imaging (DTI) scans acquired on the cohort scanned with a Philips Achieva 1.5T scanner were single-shot echoplanar diffusion-weighted (DW) SENSE images with the following parameters: TR = 8.28 s, TE = 70 ms, b factor = 600 s/mm², resolution = 1.67 × 1.67 × 3 mm³, matrix = 96 × 96, slice thickness = 3 mm, no gap. Diffusion-weighted echo planar scans acquired on the cohort scanned with a Philips Ingenia 3T scanner had the following acquisition parameters: TR = 3 s, TE = 98 ms, diffusion-encoding gradients b = 0 and 1000 s/mm², directions = 32, slices = 48, slice thickness = 2.5 mm, matrix size = 96 × 94, field of view = 240 × 240 mm²).

4.1.2.4 Voxel-based morphometry pre-processing

The voxel-based morphometry (VBM) neuroimaging automated technique provides objective information about specific structural brain changes in grey matter and white matter volumes by means of an unbiased voxel-based approximation. This technique performs individual statistical analysis across each of the voxels (a three-dimensional element equivalent to a computational pixel that represents a specific point in space on a regular matrix composed by them) from the whole brain with the objective to identify volumetric differences between the samples to be compared ([Ashburner & Friston, 2000](#)). VBM pre-processing and analyses were carried out using the most updated standard VBM routine included in the Statistical Parametric Mapping (SPM) software 12 (Wellcome Centre for Human Neuroimaging, London, UK) running in MATLAB R2014a, version 8.3 (The MathWorks, Inc, Natick, Massachusetts).

MRI scans require pre-processing steps in order to be analysed by a voxel-wise approach. This process is composed of several steps that consist essentially of orientation, spatial normalisation, segmentation, modulation and smoothing. All images were manually aligned to the same anatomical reference landmark, namely the anterior commissure of the brain. Firstly, spatial normalisation comprises a process in which the MRI scans are matched together in the same three-dimensional space so that the specific positions in one individual scan can be a common coordinate space among all the other scans within the sample. In order to achieve this process, the software takes into account the complexity of inter-individual anatomical differences among the individuals' head dimensions and position taken during image acquisition. Consequently, a coordinated image was registered to a common template ([Whitwell, 2009](#)). This standard template is registered on a shared background space defined as the Montreal Neurological Institute (MNI) Space, which is based on the brain's average from a normalised sample composed of hundreds of healthy participants. As a result, this common space confers a better representation at the group level ([Chau & McIntosh, 2005](#)). A second normalisation space is commonly used in the literature and is based on the Co-Planar Stereotaxic Atlas of the Human Brain, also known as the Talairach space ([Talairach, 1988](#)). This latter space is used at the end of the analytic process to identify specific anatomical landmarks.

After the normalisation step, data underwent a process called segmentation. This procedure consists of the creation of distinctive fragmented images of brain tissues defined by specific intracranial densities, namely grey matter, white matter and cerebrospinal fluid (CSF). By this means, statistical analysis can be carried out separately on the grey or white matter segments, to contrast the aetiopathological cascade of the same disease that might affect different tissues ([Ashburner & Friston,](#)

2000). Furthermore, intracranial tissues and CSF volumes were quantified by using the *get_totals* script (http://www0.cs.ucl.ac.uk/~staff/g.ridgway/vbm/get_totals.m) within SPM12 to compute total intracranial volumes and account for overall head size differences among participants (Peelle, Cusack, & Henson, 2012).

Subsequently, a modulation procedure takes into account the differences in volume change after the normalisation process is completed. This method intends to preserve local volumetric properties in which the voxel density may also represent the volume (Radua et al., 2014). Subsequently, the images were smoothed through a process that involves the application of an 8mm full-width half-maximum isotropic Gaussian kernel. In essence, this step allowed the scans intensities to be transformed into weighted averages of the nearby voxels. Additionally, smoothed scans tend to overlook data outliers; therefore, this information becomes more normally distributed, in accordance with the statistical parametric tests used in further steps. The final output of the pre-processing steps was that of a statistical parametric map that was used for further statistical analyses (Radua et al., 2014). Volumetric grey matter tissue maps were chosen as the substrate of analyses throughout this chapter because the literature involving anosognosia and deficits in self-awareness points at a more extended damage to grey matter cortical territories (Mondragon, Maurits & De Deyn, 2019; Hallam et al., 2020).

4.1.2.5 Diffusion tensor imaging pre-processing

A sub-sample of 38 patients underwent diffusion tensor imaging (DTI) in which 20 scans were acquired through a 3T MRI scanner and 18 by means of a 1.5T. Images were pre-processed using the FMRIB Software Library (FSL) v5.0.9

(<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). The first step of data processing involved the correction of head motion and eddy current distortion through the FSL integrated Diffusion Toolbox (FDT). The resulting corrected images were extracted through the Brain Extraction Toolbox (BET) with a threshold of fractional intensity of 0.5 as a way to eliminate non-brain related voxels and obtain a cerebral outline. In this context, a binary brain mask is created and overlapped with the diffusion tensor model to generate maps of fractional anisotropy (FA) at the individual level.

Tract-based spatial statistics (TBSS) was used on the FA images resulting from DTI pre-processing to align voxel-wise data for group-level statistical analysis (Smith et al., 2006). The analysis is computed by means of initial spatial registration of all subject FA maps to each other to find the most representative image of the sample. This subject map is selected by showing the least amount of neural distortion in relation to the other subjects. Subsequently, non-linear spatial registrations aligned the rest of the FA images into the subject-derived template, affined-aligned and averaged into a common MNI space. The averaged FA map served as a base for the creation of a skeleton mask, a space that only accounts for voxels related to white matter tracts that will serve for statistical analysis. Lastly, a binary skeleton map is created from the skeletonised FA image to avoid non-WM related tissue being included in the analysis. A threshold of 0.2 was found to be ideal for this type of analysis (Smith et al., 2006).

4.1.2.6 Statistical analyses

Three sets of inferential models were devised to test the association between measures of anosognosia and indices of cognitive functioning, brain structure and structural connectivity. To define these associations, statistical models, including all further experiments in this thesis, were corrected for a series of confounding factors.

First, age was used to control for the decrease of grey matter volume due to normal ageing (Fox & Schott, 2004). Second, education levels (in years) were included as a proxy of cognitive reserve (Fratiglioni & Wang, 2007). Third, normalised hippocampal volumes (Jorge Cardoso et al., 2013) were used as an objective way to control for disease severity, given the extensive disease-dependent atrophy this structure is subjected to in AD. This index was obtained by dividing the extracted hippocampal volume by the total grey matter volume within the MNI space to observe the disease-related variance of grey matter tissue between the hippocampus and the rest of the cortex; thus, allowing the differentiation of the AD continuum from age-related cortical atrophy.

Neuropsychological data were analysed with IBM SPSS Statistics 26 software for Windows (SPSS Inc., Chicago, IL, USA). After carrying out normality tests in all variables, coefficients of non-linear partial correlation were run between the three indices of memory, non-memory and total anosognosia and the selected neuropsychological scores (Spearman's rho, ρ). The statistical threshold to define the significance of these associations was set to $p < 0.007$ (Bonferroni correction of $p < 0.05/7 = 0.007$) to account for multiple comparisons.

Regression models were carried out to infer the linear association between voxel-by-voxel maps of grey matter and levels of anosognosia in SPM 12. An initial structural VBM whole brain t-test analysis was performed between the present early-AD sample and a healthy control group matched for sex, age and years of education, as a way to contrast the overall grey matter differences that confer our sample the classification of early AD (given that a great proportion of the sample fulfilled criteria for MCI due to AD pathology). Total intracranial volumes were included as a fourth covariate in brain models to account for inter-individual variability found in head size

([Peelle, Cusack, & Henson, 2012](#)) and its relation to brain reserve ([van Loenhoud et al., 2018](#)). Generally, the null hypothesis assumption in all the analyses suggests the absence of volumetric differences between the chosen brain tissues (grey matter in this case) and the compared groups. Voxel visualisation will occur when the null hypothesis rejection overpasses the p-value threshold selected by the researcher. An uncorrected $p < 0.005$ was selected as a cluster-forming threshold for this experiment as an appropriate threshold for this sample size that decreases the probability of appearance of false-negative results, related to a high conservative threshold, or false-positive results with less conservative thresholds ([Whitwell, 2009](#)). In this analytic approach an independent statistical model is performed in each of the independent voxels across the whole brain; therefore, increasing the probability of false-positive results due to multiple comparisons. For this reason, a correction method was applied. The three types of correction methods used typically are the family-wise error (FWE), the false discovery rate (FDR) correction and the small volume correction. These corrections rely on the premise that voxels are dependently conjoined to the contiguous ones and therefore, by taking this factor into account, the ultimate outcome displays a reduction of false-positive observations ([Whitwell, 2009](#)). In the current study, clusters surviving a FWE correction of $p < 0.05$ were considered significant. In addition, only significant clusters surpassing 100 voxels ($k > 100$) were considered. Peak stereotactic coordinates were converted to the Talairach atlas space using the *mni2tal* Matlab function. Coordinates in the Talairach space were interpreted using the Daemon Client ([Lancaster et al., 1997](#); [Lancaster et al., 2000](#)).

Multiple regression models were devised to examine the relation between domain-specific and total anosognosia outcomes and FA of WM tissue controlling for the same covariates mentioned in the section above. Non-parametric TBSS statistical

analysis was performed using the “randomise” toolbox available in FSL where 5000 permutations were computed for both, positive and negative statistical correlations (Smith et al., 2006). Multiple comparison control was performed through the Threshold Free Cluster Enhancement (TFCE) correction of $p < 0.05$ in which contiguous voxel forming patterns are highlighted as significant for this specific analysis (Smith & Nichols, 2009). Significant peak region coordinates were obtained in MNI space and visualised with the John Hopkins University International Consortium of Brain Mapping (JHU ICBM-DTI-81) white-matter labels and JHU white-matter tractography atlases (Wakana et al., 2007; Hua et al., 2008; Mori et al., 2008). Independent analyses were performed in relation to the magnetic field strength of the subsample.

4.1.2.7 *Post hoc volumetric grey matter region of interest analyses*

A supportive *post hoc* analysis was performed where volumes for specific grey matter regions of interest were extracted in relation to our specific hypothesis based on the current literature in combination with the volumetric result outcomes that arose from the VBM structural study. Independent grey matter regions were selected through the human atlas within the Wake Forest University (WFU) PickAtlas tool for SPM12. The Automated Anatomical Labelling (AAL) tool was chosen to create masks for the individual structural parcellations (Tzourio-Mazoyer et al., 2002). Grey matter volumes were extracted from the pre-processed T1-weighted MRI images described in the previous section. The *get_totals* script was used to compute all bilateral volumes from the chosen regions of interest from each of the participants. Due to the distribution of the outcomes, partial non-parametric correlations were performed between the region of interest grey matter volumes and levels of memory, non-memory and total

anosognosia outcomes in SPSS 24. In consistency with the VBM analysis, all volumetric analyses were controlled for age, years of education, total intracranial volume and hippocampal ratio. The statistical threshold of significance was chosen as $p < 0.002$ after accounting for multiple comparisons.

The selected specific regions computed for this set of analyses included bilateral structures from the frontal lobe, namely the anterior cingulate cortex, medial orbitofrontal cortex, medial prefrontal cortex and precentral gyrus; parietal lobe that included the posterior cingulate cortex and precuneus. From the temporal lobe the lingual gyrus, fusiform gyrus and hippocampus. Lastly, two subcortical structure volumes, namely the cerebellum and thalamus, were extracted for this analysis.

4.1.3 Results

4.1.3.1 Demographical characteristics

Patients labelled as MCI had longitudinal follow-ups for at least four years. Comparison with scans of healthy controls matched for demographic characteristics (age mean 74.74, SD 6.96, $p < 0.44$ and years of education mean 9.94, SD 4.00, $p < 0.38$), showed lower grey matter volumes in bilateral middle temporal cortices, supportive of an AD aetiology, are shown in **Fig. 4.1**. In the aMCI sample ($n=29$), 13 patients displayed single domain memory anosognosia (mean 2.69 / SD 0.95), 9 non-memory anosognosia (mean 2.67 / SD 0.87), 12 total anosognosia (summation of both numerical scores) (mean 4.42 / SD 2.07), and 6 were impaired in both memory and non-memory domain (determined by the cut-off score of diagnosis). On the other hand, in the mild AD sample ($n=24$), 14 patients displayed memory-anosognosia (mean 3.64

/ SD 1.55), 11 non-memory anosognosia (mean 3.18 / SD 1.08), 17 total anosognosia (mean 5.41 / SD 2.94) and 8 were independently impaired in both domains. Descriptive characteristics of the raw scores are described in [table 4.2](#). A summary of demographics and neuropsychological scores of the patient sample are shown in [table 4.1](#) and [table 4.3](#).

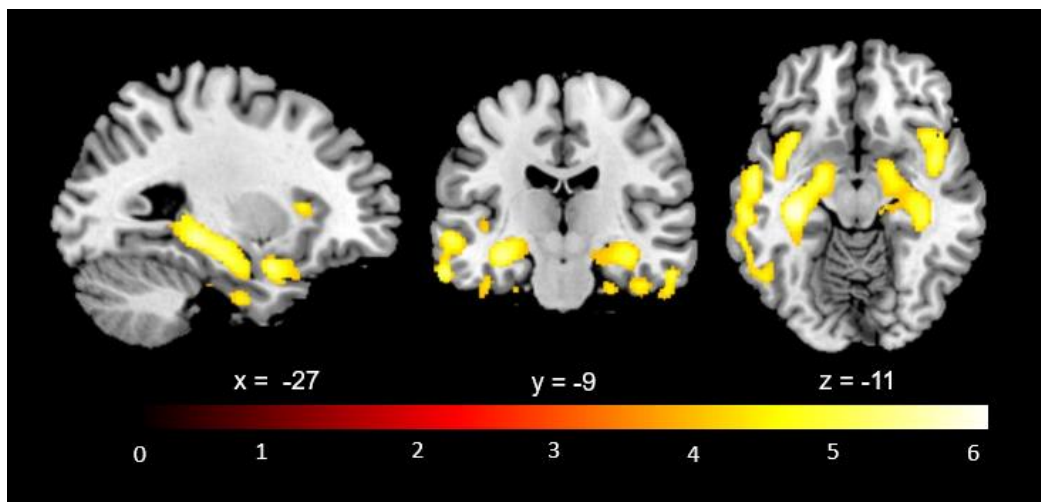


Figure 4.1. Statistical whole-brain grey matter volumetric comparison between the participant sample ($n= 53$) and a control group ($n= 53$) matched for sex, age and education shows atrophy in medial temporal lobe structures consistent with the AD aetiology.

Table 4.1. Demographic characteristics and cognitive profile of the selected sample ($n= 53$). Means (standard deviation), median and range are shown

Variable	Early-AD ($n=53$)	Healthy Controls ($n=34$)	p-value
	Mean / (SD)	Mean / (SD)	
Demographic data			
Gender, n (%)	27 Male (51%): 26 Female (59%)	16 Male (47%): 18 Female (53%)	0.63
Age (years)	71.68 (10.2)	74.74 (6.96)	0.44
Years of Education	10.62 (4.06)	9.94 (4.00)	0.38
Neuropsychological data			
MMSE	23.38 (3.77)	28.73 (1.39)	0.001*
Letter Fluency	25.27 (11.86)	32.70 (11.23)	0.006*
Category Fluency	25.52 (12.08)	36.64 (8.89)	0.001*
Prose Memory Immediate	5.63 (3.50)	9.91 (3.30)	0.001*

Prose Memory Delayed	5.25 (4.94)	12.79 (4.68)	0.001*
Rey Figure Copy	24.16 (8.73)	32.23 (3.19)	0.001*
Rey Figure Recall	5.39 (5.09)	13.42 (5.33)	0.001*
Digit Span Forward	5.38 (0.97)	5.70 (0.90)	0.040*
Digit Span Backwards	3.69 (1.09)	3.85 (0.82)	0.294
Digit Cancellation	39.83 (11.82)	50.26 (7.14)	0.001*
Similarities	14.08 (5.42)	19.82 (4.47)	0.001*
Paired Associates Learning	7.74 (4.81)	11.63 (3.44)	0.001*
Confrontation Naming	16.71 (3.38)	18.38 (2.01)	0.009*
Token Test	30.79 (2.96)	34.12 (1.98)	0.001*
Raven's Progressive Matrices	22.90 (6.85)	28.44 (4.0)	0.001*

* Non-parametric Mann-Whitney U and Chi-squared significant results reported as $p < 0.05$.

Table 4.2. Descriptive profile of the number of patients with early-AD that manifested single-domain or multi-domain anosognosia.

Anosognosia domain	aMCI ($n=29$) Mean / SD	Mild AD ($n=24$) Mean / SD	p-value
Single memory	$n=13 / 2.69 (0.95)$ Range: 2 – 5	$n=14 / 3.64 (1.55)$ Range: 2 – 6	0.07
Single non-memory	$n=9 / 2.67 (0.87)$ Range: 2 – 4	$n=11 / 3.18 (1.08)$ Range: 2 – 5	0.25
Total summation score	$n=12 / 4.42 (2.07)$ Range: 2 – 9	$n=17 / 5.41 (2.94)$ Range: 2 – 10	0.29
Memory & Non-memory (count)	$n=6$	$n=8$	-

Table 4.3. Clinical profiling and test of experimental interest. Mean, median, range and test cut-offs are displayed.

Cognitive test	Sample Mean / n	Median / n	Range (min-max)	Cut-off (Z scores)
Clinical Profiling				
Raven	22.9 / $n = 50$	23.5 / $n = 50$	9 - 35	-1.51
Token	30.8 / $n = 53$	31 / $n = 53$	21 - 36	-2.43
Similarities	14.1 / $n = 53$	13 / $n = 53$	4 - 26	-1.85
Experimental Interest				
Mini-Mental State Examination	23.4 / $n = 53$	24 / $n = 53$	15-30	-3.07

Letter Fluency	25.3 / n = 52	23.5 / n = 52	6 - 59	-1.06
Stroop Test Error	8.1 / n = 53	5 / n = 53	0 - 30	15.47
Category Fluency	25.5 / n = 52	25 / n = 52	10 - 72	-1.96
Prose Memory delayed recall	5.3 / n = 52	3.5 / n = 52	0 - 20	-8.44
Rey-Osterrieth complex Figure Copy	24.2 / n = 52	27.5 / n = 52	3 - 36	-2.46
Rey-Osterrieth complex Figure Recall	5.4 / n = 52	4 / n = 52	0 - 19	-1.72

4.1.3.2 Association with neuropsychological functioning

The index of total anosognosia was associated with scores on the following tests: delayed recall of the Prose Memory test ($\rho = -0.467$, $p = 0.002$), the copy and recall of the Rey-Osterrieth complex figure ($\rho = -0.424$, $p = 0.005$; $\rho = -0.419$, $p = 0.006$, respectively), the Category Fluency test ($\rho = -0.492$, $p = 0.001$) and the Mini-Mental State Examination ($\rho = -0.525$, $p = 0.001$). The index of memory anosognosia was associated with the scores achieved on the Prose Memory Test ($\rho = -0.429$, $p = 0.005$) and Category Fluency Test ($\rho = -0.449$, $p = 0.003$) and on the Mini-Mental State Examination ($\rho = -0.563$, $p = 0.001$). Finally, the index of non-memory anosognosia showed no significant associations with scores on any of the neuropsychological tests in the battery ([Table 4.4](#)).

Table 4.4. Domain-specific anosognosia correlations with cognitive tests of experimental interest. Correlation rho and p values are reported.

Cognitive test of experimental interest	Memory Anosognosia Correlation / p value	Non-Memory Anosognosia Correlation / p value	Total Anosognosia Correlation / p value
MMSE	$\rho = -0.563$ / $p = 0.001^*$	$\rho = -0.327$ / $p = 0.035$	$\rho = -0.525$ / $p = 0.001^*$
Letter Fluency	$\rho = -0.2836$ / $p = 0.067$	$\rho = 0.104$ / $p = 0.512$	$\rho = -0.114$ / $p = 0.471$
Stroop Test error	$\rho = 0.405$ / $p = 0.008$	$\rho = 0.222$ / $p = 0.157$	$\rho = 0.352$ / $p = 0.022$

Category Fluency	$\rho = -0.449 / p = 0.003^*$	$\rho = -0.364 / p = 0.018$	$\rho = -0.492 / p = 0.001^*$
Prose Memory delayed recall	$\rho = -0.429 / p = 0.005^*$	$\rho = -0.386 / p = 0.012$	$\rho = -0.467 / p = 0.002^*$
Rey-Osterrieth complex Figure copy	$\rho = -0.292 / p = 0.061$	$\rho = -0.379 / p = 0.013$	$\rho = -0.424 / p = 0.005^*$
Rey-Osterrieth complex Figure recall	$\rho = -0.385 / p = 0.012$	$\rho = -0.316 / p = 0.042$	$\rho = -0.419 / p = 0.006^*$

*A p value < 0.007 was selected as significant after correction for multiple comparisons. Associations were controlled for age, years of education and hippocampal fraction as covariates of no interest. MMSE: Mini-mental state examination

4.1.3.3 Association with brain structure

Firstly, a significant negative association was found between the total anosognosia score and volumes of the bilateral anterior cingulate cortex, left thalamus ($k=3430$, $p=0.001$), left lingual and left fusiform gyri ($k=1803$, $p=0.021$). Likewise, a significant negative association was found between the non-memory anosognosia score and volumes of the bilateral anterior cingulate cortex ($k=1964$, $p=0.014$), left precentral gyrus ($k=1769$, $p=0.023$), bilateral lingual ($k=3379$, $p=0.001$) and bilateral fusiform gyri ($k=3320$, $p=0.001$), right superior frontal gyrus and right postcentral gyrus ($k=1832$, $p=0.019$) (Table 4.5; Figure 4.2). No significant associations were detected between memory anosognosia scores and grey matter volumes.

Table 4.5. Grey matter clusters of significant correlation for multi-domain and non-memory anosognosia.

Cognitive test	Cluster Voxel Extent	FWE-corrected p -value	T score	Side	Peak-based localisation	MNI coordinates		
						x	y	z
Multi-domain Anosognosia	3430	0.001	3.70	R	Anterior cingulate	4	27	-10
			3.69	L	Anterior cingulate	0	-22	-2
			3.76	L	Thalamus	-4	-30	6
	1803	0.021	4.42	L	Lingual gyrus	-15	-66	-9
			4.42	L	Fusiform gyrus	-21	-50	-15

Non-Memory Anosognosia	3320	0.001	4.09	L	Fusiform gyrus	-24	-41	-13
			5.30	L	Fusiform gyrus	-28	-40	-22
			5.02	L	Fusiform gyrus	-32	-54	-16
			4.89	L	Fusiform gyrus	-26	-48	-15
	1769	0.023	4.53	L	Precentral gyrus	-21	-22	57
			4.20	L	Precentral gyrus	-33	-20	64
			4.16	L	Precentral gyrus	-45	-16	32
	1964	0.014	4.44	R	Anterior cingulate	4	27	-10
			3.83	R	Anterior cingulate	9	40	-10
			3.78	L	Anterior cingulate	-2	20	0
	3379	0.001	4.44	R	Fusiform gyrus	28	-38	-22
			4.41	R	Lingual gyrus	20	-68	-6
3.96			R	Lingual gyrus	36	-74	-12	
1832	0.019	4.38	R	Superior frontal gyrus	9	-18	68	
		3.83	R	Precentral gyrus	38	-16	63	
		3.47	R	Postcentral gyrus	42	-22	48	

L: left; MNI: Montreal Neurological Institute; R: right

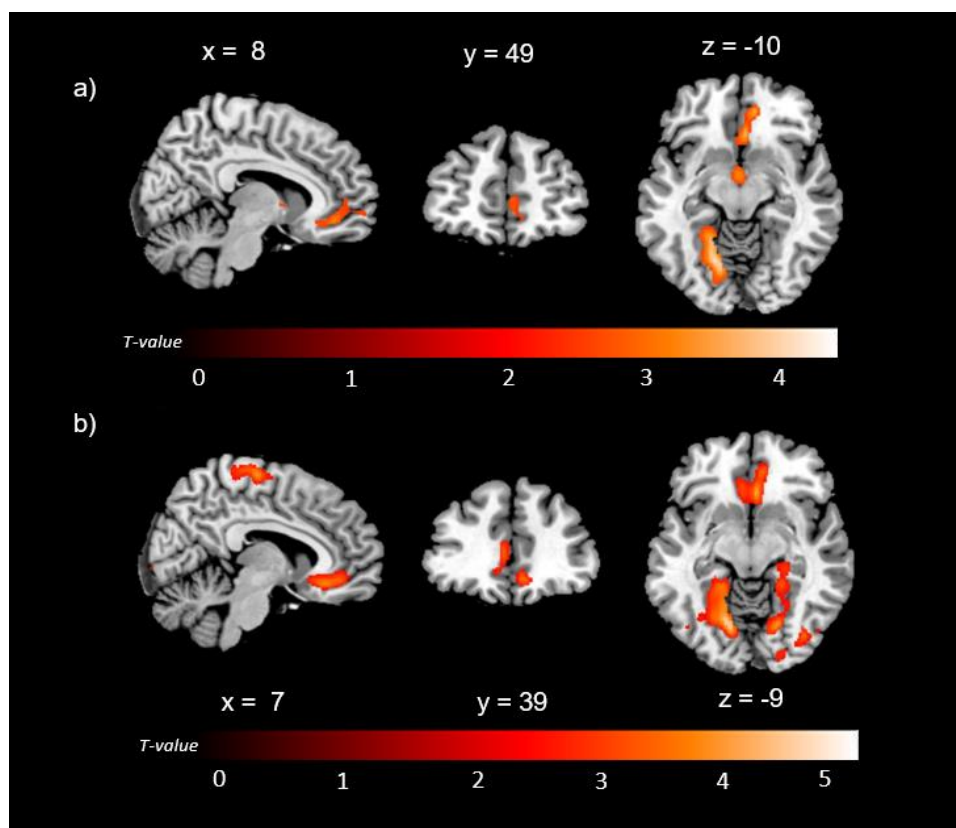


Figure 4.2. Regions of significant negative correlation between a) non-memory anosognosia scores and b) total anosognosia scores and grey matter volume values; clusters are shown at $p < 0.05$ FWE corrected.

4.1.3.4 Associations with brain structural connectivity

No significant results were found in the TBSS analyses performed in DTI images from the 1.5T sample ($n=18$) or the 3T sample ($n= 20$).

4.1.3.5 Post Hoc grey matter volumetric results

Post Hoc structural analyses are summarised in [table 4.6](#). The region of interest analyses showed a significant negative association of the left fusiform gyrus and scores for non-memory anosognosia after correction for multiple comparisons ($\rho = -0.431$, $p = 0.002$, accounting for age, years of education, TIV and hippocampal ratio ([figure 4.3](#)). Notably, an association approaching significance level was also found in the right fusiform gyrus ($\rho = -0.393$, $p = 0.005$). Several frontotemporal and subcortical regions showed associations at a threshold level of $p<0.05$ but did not survive correction for multiple comparisons.

Table 4.6. Region of interest associations between grey matter volumes extracted from selected brain areas (in mm^3) and memory, non-memory and total anosognosia indices. Mean, standard deviation and rho (ρ) values are reported.

Region of Interest	Side	Mean (SD) n=53	Correlation values (ρ)		
			Memory Anosognosia	Non-Memory Anosognosia	Total Anosognosia
ACC	L	9.26 (1.49)	-0.227	-0.329*	-0.308*
	R	9.53 (1.42)	-0.217	-0.323*	-0.297*
mOFC	L	2.01 (0.31)	-0.234	-0.266	-0.270
	R	2.41(0.36)	-0.280	-0.329*	-0.329*
mPFC	L	5.82 (0.94)	-0.271	-0.344*	-0.344*
	R	6.05 (0.88)	-0.254	-0.357*	-0.333*
Precentral gyrus	L	6.97 (1.20)	-0.224	-0.214	-0.247
	R	6.25 (1.19)	-0.222	-0.305*	-0.306*
PCC	L	1.09 (0.20)	-0.070	-0.290*	-0.204
	R	0.66 (0.13)	-0.088	-0.261	-0.191
Precuneus	L	8.27 (1.51)	-0.027	-0.294*	-0.177

	R	7.86 (1.44)	-0.044	-0.278	-0.175
Lingual gyrus	L	5.98 (1.10)	-0.216	-0.315*	-0.317*
	R	6.26 (1.18)	-0.233	-0.355*	-0.356*
Fusiform gyrus	L	8.19 (1.26)	-0.148	-0.431***	-0.327*
	R	8.61 (1.26)	-0.172	-0.393**	-0.334*
Hippocampus	L	2.09 (0.40)	-0.282	-0.307*	-0.351*
	R	2.18 (0.41)	-0.256	-0.240	-0.264
Cerebellum	L	37.92 (5.34)	-0.294*	-0.308*	-0.345*
	R	37.73 (5.12)	-0.263	-0.315*	-0.339
Thalamus	L	2.06 (0.37)	-0.361	-0.286	-0.361
	R	2.12 (0.40)	-0.263	-0.272	-0.298

*** Significant values that survived Bonferroni multiple comparison correction of $p < 0.002$ ($0.05/22$)

** Significant values of $p < 0.01$ that did not survive multiple correction

* Significant values of $p < 0.05$ that did not survive multiple correction

All models were controlled for age, years of education, TIV and hippocampal ratio

ACC: anterior cingulate cortex; mOFC: medial orbitofrontal cortex; mPFC: medial prefrontal cortex; PCC: posterior cingulate cortex; TIV: total intracranial volume.

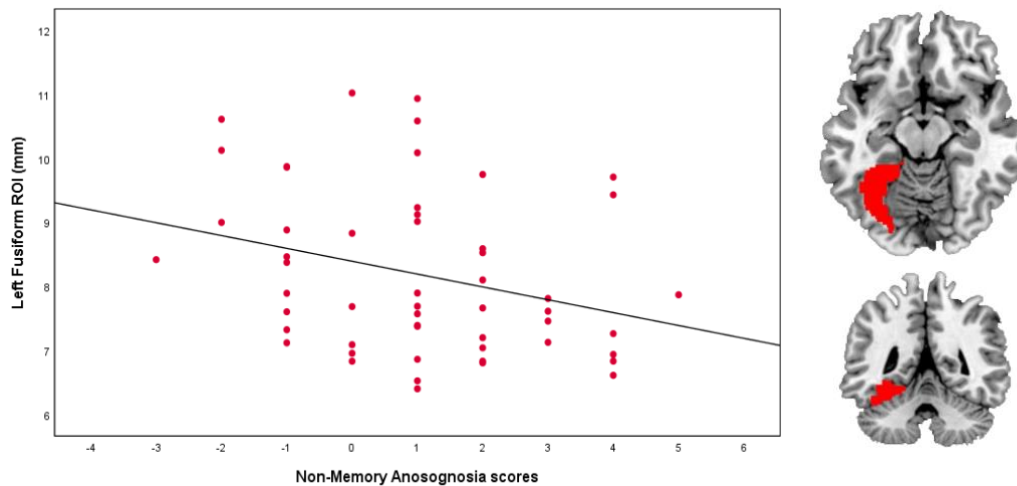


Figure 4.3. Scatterplot displaying the significant negative correlation of non-memory anosognosia scores and the extracted grey matter volume of the left fusiform gyrus after controlling for multiple comparisons and covariates of no interest.

4.1.4. Discussion

The purpose of this study was to characterise the neuropsychological and neurovolumetric correlates of anosognosic profiles in the early stage of AD, differentiating between memory and non-memory anosognosia. Lack of associations

of structural connectivity might translate into anosognosia being a symptom most commonly associated with grey matter alterations and not with white matter integrity.

4.1.4.1 Association between anosognosia and neuropsychological functioning

Total anosognosia was associated with a series of measures of episodic memory, semantic memory and visuoconstructive skills. Overall, we cannot rule out the possibility that total-anosognosia scores were driven by the distribution of scores on the non-memory section of the test (hence, the similar pattern of findings). However, the total score was significantly associated with both memory and non-memory sub-scores (both r scores > 0.8) suggesting equal dependence on both sub-scores. After splitting the construct into its two components, memory anosognosia showed an association with the Category Fluency Test (a measure of semantic memory) and the Prose Memory Test. This latter is a test of episodic memory based on the retrieval of material characterised by semantic relatedness (Carlesimo et al., 1998; Venneri et al., 2019). Semanticisation processes are an essential trait for the integration of episodic autobiographical memory (Westmacott et al., 2004; Morris & Mograbi, 2013). This domain has a significant influence on the representation of the self. In this respect, patients with anosognosia constantly try to reorganise their self-representation without success, and this leads to a progressive deterioration of their own identity (Mograbi, Brown & Morris., 2009; Toffle & Quattropiani, 2015). On the other hand, deficits in episodic memory are central clinical hallmarks in AD and are associated with disease severity (Reitz et al., 2009). Notably, these results are consistent with those of other studies focusing on anosognosia in AD (Orfei et al., 2010; Clare et al., 2013; Senturk et al. 2017). In line with our results, Gambina et al., (2014) characterised anosognosia

patients using a quantitative-qualitative method in which unawareness of memory deficits was particularly visible at the initial clinical stages of disease, while later clinical stages were characterised more distinctively by executive unawareness, displaying dissociation with the cognitive performance in the memory and executive domain, respectively. To minimise the likelihood of obtaining spurious results, all of the inferential models involving neuropsychological tests were controlled for normalised hippocampal size, an established measure of neuronal injury in AD ([Jack Jr et al., 2018](#)).

Total anosognosia was also associated with performance on visuospatial skills. Visuoconstructive abilities are an essential trait of self-awareness, in that they enable the individual to shift from a first-person to a third-person perspective ([Vogelely et al., 2004](#)). These abilities would also serve to update information processing by projecting allocentric (object-to-object) and egocentric (self-to-object) spatial representations, prerequisite components of global awareness ([Serino & Riva, 2017](#)). Based on this view, our findings indicate that patients with total anosognosia would be less able to achieve this “mental frame syncing”; or, in other words, the ability to update properly previously experienced scenarios stored in episodic memory. Therefore, these patients may not be able to understand the mental scenarios of their first-person orientation, a difficulty that could lead to unawareness of the perceived space in contrast with the one remembered.

Lastly, overall cognitive severity of disease was associated with total and memory anosognosia. This finding has been reported in the literature ([Migliorelli et al., 1995](#); [Derouesne et al. 1999](#); [Harwood, Sultzer & Wheatley, 2000](#); [Leicht, Berwig & Gertz, 2010](#)) and may reflect the direct detrimental effects of the proteinopathies on the awareness system through the progression of the disease ([Vannini et al., 2017a](#)).

However, the scientific literature indicates that there is no well-defined link between severity of disease and anosognosia, with studies that support a link (such as those referenced in the section above) and studies that do not ([Reed, Jagust & Coulter, 1993](#); [Weinstein, Friedland & Wagner, 1994](#); [Almeida & Crocco, 2000](#), [Gambina et al., 2014](#)). The AD pathophysiological progression may impact directly on the severity of the disease but is not an essential variable for the onset of anosognosia; this explains the heterogeneity between disease stage and the initial symptomatic expression of anosognosia that displays worsening with disease progression characterised initially by memory disconnection ([Avondino & Antoine, 2016](#)).

4.1.4.2 Association between anosognosia and brain structure

Total anosognosia was associated with volume in the anterior cingulate cortex (ACC). This region has been linked with disease awareness in other studies involving AD patients ([Hanyu et al., 2008](#); [Amanzio et al., 2011](#); [Spalletta et al., 2014](#); [Guerrier et al., 2018](#)). Progressive neuronal loss in the anterior cingulate leads to a decline of executive metacognitive processes that involve cognitive regulation ([Cohen, Botvinick, & Carter, 2000](#)) through continual internal error processing and monitoring ([Van Veen & Carter, 2002](#); [O'Connell et al., 2007](#); [Amanzio & Palermo, 2014](#)). In this study, the ACC was associated with both total and non-memory domain anosognosia, the latter consisting mostly of decreased awareness on activities dependent on executive functions. Likewise, [Amanzio et al. \(2011\)](#) showed decreased activation of the ACC in a task-based fMRI study consisting of a paradigm based on a response-inhibition go/no-go task, proposing anosognosia as a dysfunction of the executive system in charge of abilities such as self-monitoring. Lastly, [Guerrier et al. \(2018\)](#) found, in a

structural and metabolic study, alterations of the ACC related to anosognosia, interpreting it as an area involved in executive processing and self-monitoring affecting the comparator mechanisms of mnemonic functions.

The involvement of the ACC can be interpreted as that of a gateway region sustaining conflict resolution within the framework of the Cognitive Awareness Model (Agnew & Morris, 1998). The ACC is a region responsible for the integration of cognitive and emotional stimuli (Bush, Luu, & Posner, 2000) and is also a major hub of the salience network, a functional circuit responsible for processing and integrating external and internal inputs for decision making (Seeley et al., 2007). In coherence with the Cognitive Awareness Model (CAM), the ACC may provide the executive resources necessary to the mnemonic comparator to verify the authenticity of the processed information.

Scores in the total and non-memory anosognosia domain also showed a significant association in the fusiform gyrus and lingual gyrus. Moreover, the fusiform gyrus showed an additional volumetric association in the region of interest grey matter analyses. The involvement of the fusiform gyrus in anosognosia does not come as a novel finding (Guerrier et al. 2018). Dysfunction in this area is linked to awareness deficits for bodily representations. In fact, hemiplegic patients with lesions extending to the fusiform gyrus show impaired mentalisation of the body (Besharati et al. 2016). Moreover, the pathway linking the fusiform gyrus with the ACC was found to be abnormally upregulated in patients with amnesic MCI (Cai et al., 2015). Atrophy of a set of regions including the lingual gyrus is linked to a faster decline in AD dementia (Kinkingnéhun et al., 2008), suggesting a plausible link between anosognosia and faster disease progression.

The non-memory anosognosia domain showed additional significant negative associations with the precentral, postcentral and superior frontal gyrus, results that run in parallel with the findings of other studies related to the field of AD. The precentral gyrus was found to be associated with anosognosia of executive functions in a structural MRI study (Tondelli et al., 2018). In this context, Morita and colleagues (2008) proposed the precentral gyrus to serve as a key region of self-recognition of facial features. The postcentral gyrus showed less activation in a comparative analysis of aware vs unaware AD patients based on a response-inhibition go/no-go task (Amanzio et al., 2011). Lastly, the superior frontal gyrus was also associated with anosognosia in another structural study (Fujimoto et al., 2017), a region that has shown to be essential in self-awareness (Goldberg, Harel & Malach, 2006). Therefore, we argue that specific frontal regions could serve as crucial components for the modulation of executive-function-related awareness processes.

Despite the importance of executive resources in this process, however, no association was found between indices of anosognosia and measures of executive functioning. Arguably, however, a dysfunctional comparator may result in subtle executive deficits that will not necessarily emerge with standardised executive tests.

A number of published structural and functional neuroimaging studies found that anosognosia was associated with medial temporal structures (e.g., Chavoix & Insausti, 2017; Tondelli et al., 2018). To this end, Salmon and colleagues (2006) suggested that the mediotemporal hypometabolism seen in anosognosic patients may result in impaired comparison mechanisms, highlighting a primary role of memory functions based on these structures, and not executive resources for this comparator function. Our findings, however, seem not to support this suggestion, since no association was found between hippocampal volume and anosognosia scores.

Associations between anosognosia and semantic and episodic memory were identified in the current study, but these associations did not appear to be mediated by hippocampal volume. In this respect, the findings by Avondino and colleague (2016) highlight memory as a supportive element in anosognosia rather than the prime cause. Therefore, we argue that mediotemporal structures most likely provide a supportive mnemonic input to the structures that provide comparative resources, and it is possible that this link could be spurious and driven by disease severity that is known to affect this part of the brain. Based on our findings, comparative resources would be more consistently linked with the ACC instead.

The mismatch found between anatomical findings and behavioural outcomes could be due to the inherent relation of unawareness to the functional domain controlled by it. The consistency of association of visuospatial abilities with the behavioural and neuroimaging outcomes sheds light on the essential role of these functions in global awareness. Dissecting anosognosia study by domains in the very early stages of the disease could lack any evident association between the broad neuronal anatomical conformation and the specific function mediated by that region.

4.1.5 Conclusions

Our findings highlight the ACC as the main structure associated with total and non-memory anosognosia in patients with early AD. Additionally, volume in the fusiform and lingual gyri were also associated with total and non-memory anosognosia. The precentral gyrus, postcentral gyrus and superior frontal gyrus show further involvement in non-memory anosognosia. Behavioural findings foregrounded the role played by semantic memory, episodic memory and visuospatial abilities. All in all, these findings

indicate that anosognosia is a complex symptom in which executive resources seem to play a crucial role. Moreover, and as pointed out by previous research ([Chapman et al., 2018](#)), different theoretical elements appear to be at play depending on the cognitive domain affected by anosognosia in AD.

4.2 Experiment 2 | Resting-state functional brain network connectivity of multi-domain anosognosia in early Alzheimer's disease

4.2.1 Introduction

Resting-state fMRI (rs-fMRI) research in AD has shown its potential reliability as a biomarker for early diagnosis evidenced by intrinsic connectivity network disruptions ([Sorg et al., 2007](#)). Specifically, current data suggest that an early breakdown of the default mode network (DMN) is closely associated with cognitive decline, the main symptomatic feature in AD patients ([Greicius et al., 2004](#); [Badhwar et al., 2017](#); [Grieder et al., 2018](#)). In parallel, there are proposals that the functional hubs composing the DMN are heavily implicated in self-awareness abilities in healthy individuals ([Northoff et al., 2006](#); [Davey, Pujol & Harrison, 2016](#)). Therefore, AD patients displaying early-dysfunction of the DMN should consequently experience difficulties of self-awareness or symptoms related to anosognosia from an early disease stage. An integrative perspective with the theoretical cognitive awareness model (CAM) that explains self-awareness deficits in AD may imply a metacognitive involvement of the CAM and executive-related comparator mechanisms within a fronto-temporo-parietal-network that heavily relies upon the integrity of the DMN ([Tagai et al., 2020](#)). This association has been consistently found in the existing literature in which anosognosia seems to reflect connectivity alterations resulting from

disruption of neural integrity within the DMN (Zamboni & Wilcock, 2011; Antoine et al., 2019; Mondragon, Maurits & De Deyn, 2019). Most importantly, the presence of anosognosia has been found to predict hypometabolism of the DMN and an increased risk of dementia progression (Therriault et al., 2018). However, the global interplay of other large-scale networks is yet poorly understood. Moreover, an understanding of what type of perturbation in the physiological equilibrium of whole brain network dynamics may account for domain-specific anosognosia could provide valuable insights into the mechanisms underpinning alteration of self-awareness in this type of population.

Task-related functional imaging studies of self-awareness detriments in AD have shown activation of fronto-parietal (Ruby et al., 2009), fronto-cingulate (Ries et al., 2007; Amanzio et al., 2011) and fronto-temporal (Zamboni et al., 2013) networks during tasks based on self-reflection and perspective-changing, with lower levels of activation of posteromedial parietal regions (Amanzio et al., 2011). Rs-fMRI research of early-stage AD participants has demonstrated reduced intrinsic connectivity mainly in regions comprising the DMN (Buckner et al., 2008). More specifically, Berlingeri et al. (2015) found reduced connectivity within this network, the temporal cortex and between the hippocampus and the insula. Perrotin and colleagues (2015) found reduced connectivity between the orbitofrontal cortex and both the posterior cingulate and the medial temporal lobe. Data from research performed by Vannini's team (2017b) showed reduced connectivity between the precuneus and the inferior parietal lobe, left posterior cingulate and orbitofrontal cortex, and in the hippocampus with the fusiform gyrus. Lastly, Mondragon's and collaborators (2021) showed that increased connectivity of the bilateral ACC was associated with anosognosia. Notably, regardless of the applied methodology, all task-based and rs-fMRI studies displayed a

partial or greater involvement of the frontal lobe cortex as an essential region involved in multi-dimensional awareness and self-appraisal abilities (Ries et al., 2007; Amanzio et al., 2011; Zamboni et al., 2013; Perrotin et al., 2015; Vannini et al., 2017b; Mondragon, Maurits & De Deyn, 2019; Mondragon et al., 2021).

Based on the literature and the premise of the involvement of an executive comparator in unawareness symptoms, our hypothesis is that resting-state large-scale and seed-to-brain intercommunications will provide evidence of frontal-centred connectivity alterations to other structures known to be associated with multi-domain anosognosia in the early AD continuum. We also hypothesise a higher intercommunication among structures supporting the central-executive networks and the DMN.

4.2.2 Methods

4.2.2.1 Participants

This study included the same number of early AD participants ($n= 53$) as the previous experiment (Experiment 1). Demographic details and characteristics of the sample can be found in [section 4.1.3.1](#), [table 4.1](#).

4.2.2.2 Anosognosia assessment

In consistency with experiment 1, the present study used the same questionnaire discrepancy scores to calculate memory, non-memory and total anosognosia. More details on the questionnaire and calculation methodology can be found in [section 4.1.2.2](#).

4.2.2.3 Functional MRI image acquisition

Neuroimaging acquisition and analysis followed the shared protocol set by the VPH-DARE@IT consortium for Philips MRI scanners (<http://www.vph-dare.eu/index.php/project/work-packages/WP2>). Functional MR images were acquired at rest with a 3.T Phillips Achieva scanner with the following parameters: 35 axial slices, reconstructed in-plane voxel dimensions= 1.8x1.8 mm², slice thickness= 4.0 mm, repetition time= 2.6sec, echo time= 35ms, number of temporal dynamics=125. Also, resting-state functional images were acquired with a Philips Achieva 1.5 T scanner with the following parameters: voxel size: 3.28 × 3.28 × 6.00 mm³ voxel dimension, 64 × 64 matrix size, 230 mm field of view, 2 s TR, 50 ms TE and 90° flip angle. All scans had at least 200 volumes and each volume consisted of 20 slices acquired axially and contiguously, in ascending order. Each participant was asked to remain still with their eyes closed for the entire duration of the acquisition (5-7 minutes in average)

4.2.2.4 functional MRI pre-processing

Functional brain images were processed using the Statistical Parametric Mapping (SPM12) software through a standardised pipeline of fMRI data computation (Postema et al., 2019). The first step of functional data processing consisted of slice-timing as a result of the sequence of 2D slice acquisition occurring at different time points in relation to the actual BOLD signal; this phenomenon may generate temporal inconsistencies among sequential slices. This can be compensated through a process

named temporal data interpolation; a method that corrects timing differences by using the same middle slice in each participant as a reference point. Therefore, this method is a way to standardise single-subject time discrepancies in relation to the MRI repetition time (TR) ([Sladky et al., 2011](#)).

Secondly, an automated realignment process was applied to all scans (and independent sessions), to control for head motion and noise parameters related to physiological dynamics that inevitably occur during the acquisition process ([Maknoja et al., 2019](#)). A 4th Degree B-Spline interpolation option was chosen for more accurate estimation and intra-subject registration. Visual outcomes from the realignment process were displayed as graphical data plotted in relation to the number of volumes (120 volumes for scans acquired at 1.5T and 125 volumes for scans acquired at 3T) and the head's linear distance of movement (measured in mm³) in the three-separate x, y and z spatial axis, plus an additional rotational graph that included the three possible types of head rotation (defined as pitch, roll and yaw). Visual evaluations of the graphed movement parameters were performed independently (and in each session) to discard scans that showed more than $\pm 3\text{mm}$ and $\pm 3^\circ$ of motion that could produce artefact related changes. In this step, there were no images excluded because of increased noise related to the previously mentioned motion parameters.

The third step is based on the spatial normalisation of images to an echo-planar imaging (EPI) template within the MNI space to allow inter-subject comparison. In a similar way as for structural images, spatial normalisation corrects for differences in head size and creates voxel-wise spatial alignment (2mm x 2mm x 2mm) within each individual ([Qing et al., 2019](#)). Subsequently, images were filtered with the REST (Resting-state fMRI Data Analysis Toolbox) software ([Song et al., 2011](#)) using an amplitude of low-frequency fluctuation (ALFF) low-to-high band-pass filters to quantify

oscillations in the range of 0.01hz – 0.1hz (full frequency band), as a way to reduce noise-associated artefacts that are not explained by regional neural activity (Zou et al., 2008; Li et al., 2017). Lastly, the previously filtered images were smoothed (in consistency with the previous structural experiment) with a 6mm full-width at half-maximum Gaussian kernel (FWHM = 6mm) to increase the overall signal-to-noise ratio.

4.2.2.5 Independent Component Analysis

Pre-processed resting-state fMRI images were used for an Independent Component Analysis (ICA) to extract functional large-scale network connectivity maps. The GIFT toolbox (v1.3i; mialab.mrn.org/software/gift) running within the SPM12 software was used to carry out this analysis. An Infomax algorithm was chosen with the number of components to be extracted set at 20, as a reliable number that includes the fundamental resting-state human connectivity networks (Wang & Li, 2015). This data-driven method is based on a computational deconstruction of conjoined multivariate MRI signals (BOLD activity) to recreate independent non-correlated spatial maps of coordinated neural activity. Connectivity maps are displayed as z scores that result from the association between the brain's network mean-time and single-voxel time-series (Calhoun et al., 2001).

Second-level inferential analyses were performed with the manually selected (hypothesis-driven) independent component maps for each of the five extracted networks of interest; namely, the anterior Default Mode Network (aDMN), posterior Default Mode Network (pDMN), left Fronto-Parietal Network (l-FPN), right Fronto-Parietal Network (r-FPN), also known as Executive Control Networks, and Salience Network. Connectivity maps were analysed independently in relation to domain-

specific (memory and non-memory) and total anosognosia scores, as a way to test the associations between the behavioural outcomes and resting-state connectivity indices at the voxel level.

4.2.2.6 ICA Statistical Analysis

Multiple regression analyses were carried out at the group level. By this approach, each of the five resting-state network maps were correlated independently with the memory, non-memory and total anosognosia. In consistency with the previous experiment, the selected threshold for significance was set at $p=0.005$ uncorrected (Whitwell, 2009). Clusters were considered as significant only if they survived a FWE corrected threshold of $p < 0.05$. The statistical models were controlled for age, years of education, TIV and hippocampal volume ratio as variables of no interest (see section 4.1.2.6 for details). MNI-based peak regions were identified and transformed into Talairach coordinates for identification of anatomical regions through the Talairach Daemon Client version 2.4.3 (<http://www.talairach.org/client.html>) (Lancaster et al., 2000)

4.2.2.7 Seed extraction and first level analysis

Region of interest (ROI) analyses were carried out to elucidate the association of a brain region (seed) with the rest of the brain as a reflection of the existent functional connectivity between those structures. Seed-based analysis relies on the association between the time-series in the selected seed region with the rest of the brain that can be translated as the areas that are communicating with each other. Selected seeds

were based on the structural VBM outcomes of experiment 1, in addition to characteristic regions that have been shown as strongly associated with anosognosia and functional connectivity in the current literature ([Mondragon, Maurits & De Deyn, 2019](#)).

Cytoarchitectonic anatomical seed structures were extracted through the WFU PickAtlas toolbox (<https://www.nitrc.org>) ([Maldjian et al., 2003](#)). A second step was applied in order to extract the time courses from the previously obtained ROIs at the individual level, through the use of the SPM-based MarsBar toolbox (<http://marsbar.sourceforge.net/>) ([Brett et al., 2002](#)).

A first-level analysis is based on a linear model of correlation between the seed average time-courses to predict each independent voxel time-course at the single-subject brain level. Individual data were computed by taking into account physiological and motion parameters that were included as covariates for signal denoising purposes, namely: the white matter and cerebrospinal fluid BOLD signal maps transformed through principal component analysis and 24 movement parameters, defined as, 1) six original motion and rotation parameters, 2) six squared original movement outcomes 3) six calculated first-order time derivatives and 4) six squared outcomes of the previously obtained time derivatives, that were extracted by the mp/diffpow.sh command in SPM12 ([Muschelli et al., 2014](#)). This method also allowed for functional scans to address the differences in magnetic field strength as it has been stipulated that signal extent and intensity are not affected by this effect; however, signal-to-noise ratio may variate depending on the magnetic field-strength ([Voss, Zevin & McCandliss, 2006](#)).

In this particular study the rationale behind the extracted seeds was based:

1) On the neuroanatomical findings obtained from experiment 1 (see **table 4.5** and **figure 4.2**). Therefore, the ACC, fusiform gyrus, lingual gyrus and precentral gyrus were selected as functional hubs of study.

2) On the theoretical background of functional regions that could harbour deficits in self-awareness. Thus, a priori hypothesis-driven selected regions included in this experiment were the orbitofrontal cortex, medial prefrontal cortex, precuneus, posterior cingulate and hippocampus.

Empirical evidence has found differences that depend on hemispheric laterality in the clinical outcome of this symptom, as in several other neuropsychiatric symptoms. Therefore, all seed regions were extracted bilaterally and modelled in an independent manner. Selected seed regions are displayed in **figure 4.4**.

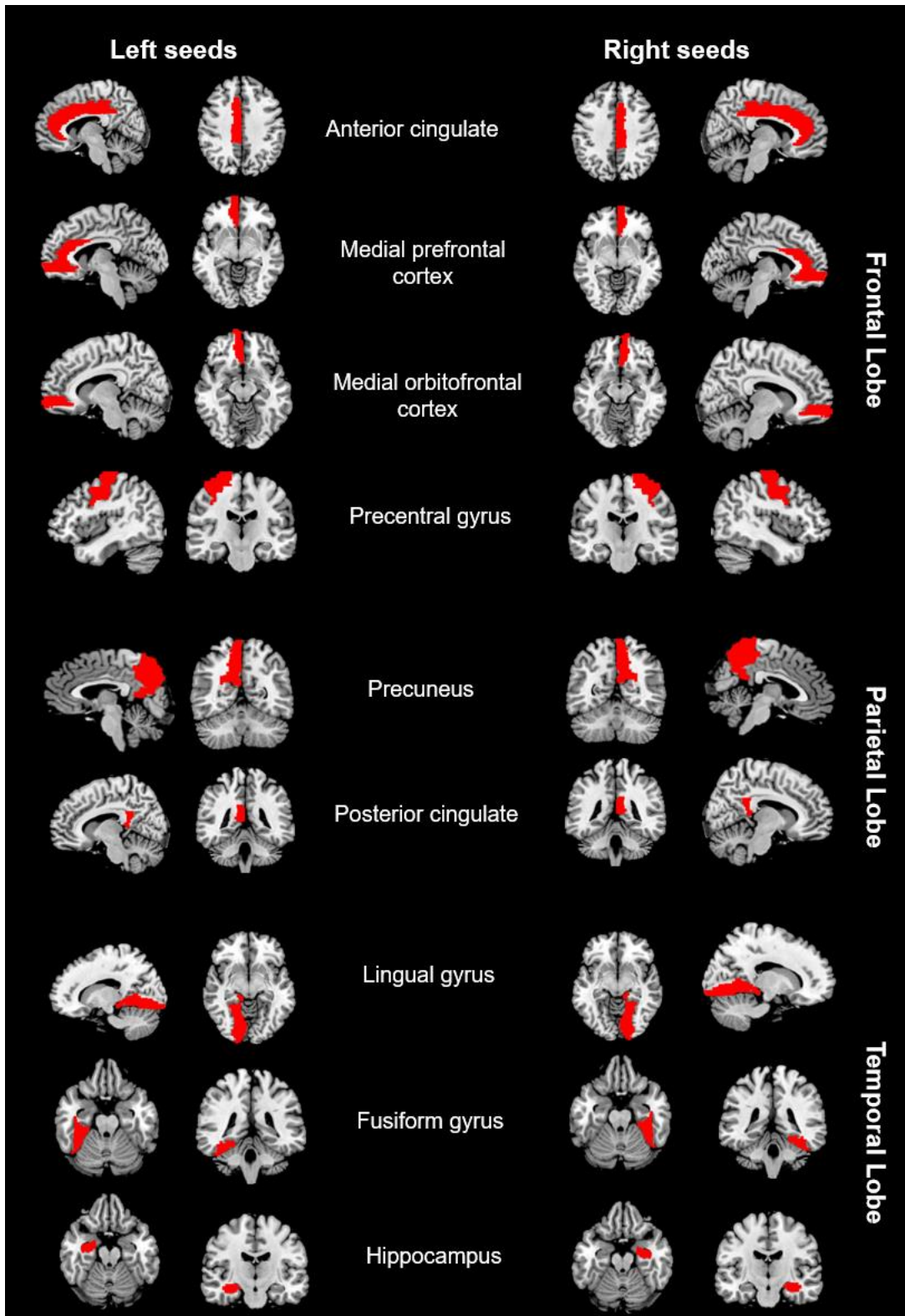


Figure 4.4. *A priori* selected seed regions used for resting-state fMRI domain-specific anosognosia analyses.

4.2.2.8 Seed-based Statistical Analysis

A second-level analysis was carried out at the group-level to find differences across the sample for each individual bilateral ROI outcome. All models were controlled for age, years of education, total intracranial volume and hippocampal volume ratio. Independent multiple regression models were carried out for each seed region at the group level. In consistency with the previous experiments, the significance level was set at $p=0.005$ uncorrected (at the set level) and clusters were considered as significant if they survived a FWE corrected threshold of $p < 0.05$. Significant peaks labels were chosen in the same way as described in [section 4.1.2.6](#).

4.2.3 Results

4.2.3.1 Independent Component Analysis Results

Significant correlations emerged from the models performed between multi-domain anosognosia scores and connectivity clusters (k) in the whole-brain functional maps within each of the extracted networks. The left fronto-parietal network showed a significant negative association with outcomes of memory anosognosia ($k=298$, $p=0.02$) and total anosognosia ($k=375$, $p=0.006$) in the left lingual gyrus (BA 18) and left posterior cingulate (BA 30), respectively ([table 4.7](#) and [figure 4.5](#)). Conversely, the right fronto-parietal network showed a significant positive association with total anosognosia scores ($k=264$, $p=0.036$) in the left lingual gyrus (BA 18) and left inferior occipital gyrus (BA 19) ([table 4.8](#) and [figure 4.6](#)). Similarly, the anterior default network displayed a significant positive association with non-memory anosognosia scores ($k=263$, $p=0.038$) in the bilateral culmen within the cerebellum and total

anosognosia ($k=261$, $p=0.039$) in the right anterior cingulate (BA 32 & 33) (table 4.9 and figure 4.7). No significant associations were found among anosognosia measures and the salience or posterior default mode networks.

Table 4.7. Independent component analyses showing significant clusters of negative correlation between memory and total anosognosia outcomes and functional connectivity in the left fronto-parietal network.

Behavioural test	Cluster extent	FWE P-value	T Score	HS	Peaked-based localisation	BA	MNI coordinates		
							x	y	z
<i>Left fronto-parietal network (l-FPN)</i>									
Memory	298	0.02	4.70	L	Posterior cingulate	30	-20	-62	8
Anosognosia			4.59	L	Lingual gyrus	-	-22	-68	-4
			3.05	L	Lingual gyrus	18	-16	-70	-12
Total	375	0.006	5.22	L	Lingual gyrus	-	-22	-68	-4
Anosognosia			4.49	L	Posterior cingulate	30	-24	-62	4
			3.75	L	Posterior cingulate	30	-14	-66	4

* Threshold of significance defined at $p= 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute.

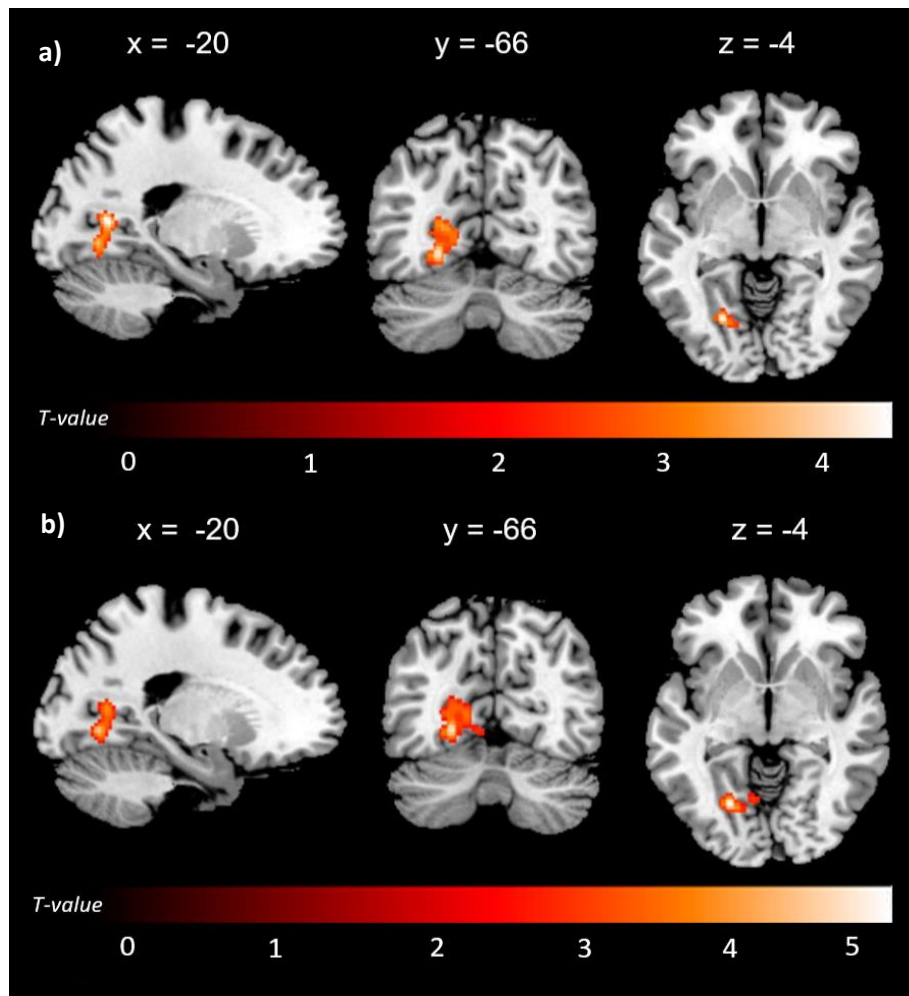


Figure 4.5. Negative correlations between functional connectivity of the left fronto-parietal network (l-FPN) and a) memory and b) total anosognosia; clusters are shown at $p < 0.05$ FWE corrected.

Table 4.8. Independent component analysis showing clusters of significant positive correlation between total anosognosia outcomes and functional connectivity in the right fronto-parietal network.

Behavioural test	Cluster extent	FWE P-value	T Score	HS	Peaked-based localisation	BA	MNI coordinates		
							x	y	z
<i>Right fronto-parietal network (r-FPN)</i>									
Total Anosognosia	264	0.036	4.89	L	Inferior occipital	19	-40	-74	-14
			4.50	L	Inferior occipital	19	-36	-80	-10
			3.36	L	Lingual gyrus	18	-16	-84	-12

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute.

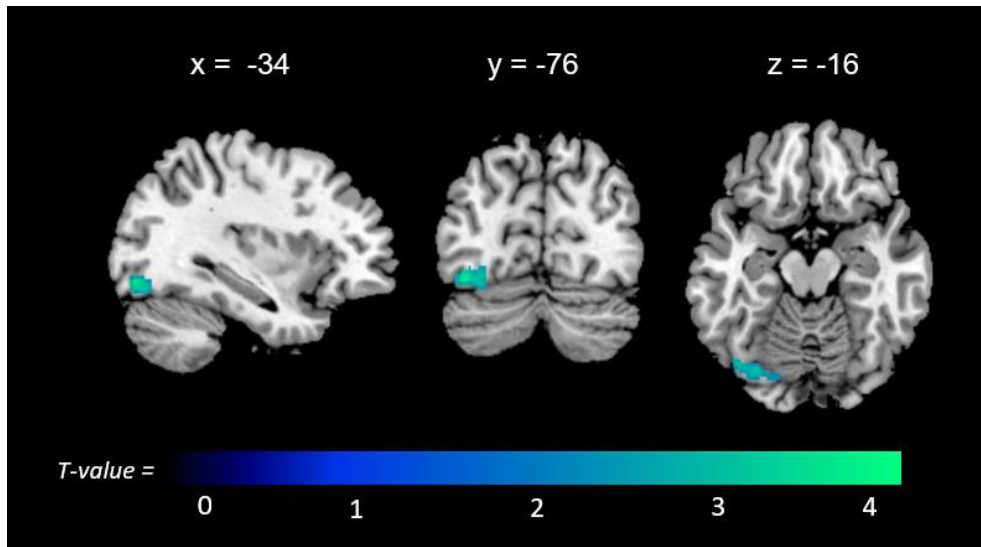


Figure 4.6. Positive correlations between functional connectivity of the right fronto-parietal network (r-FPN) and total anosognosia; clusters are shown at $p < 0.05$ FWE corrected.

Table 4.9. Independent component analyses showing clusters of significant positive correlation between non-memory and total anosognosia outcomes and functional connectivity in the anterior default mode network.

Behavioural test	Cluster extent	FWE P-value	T Score	HS	Peaked-based localisation	BA	MNI coordinates		
							x	y	z
<i>Anterior default mode network (aDMN)</i>									
Non-memory	263	0.038	5.21	L	Cerebellum	-	-12	-48	-14
Anosognosia			4.94	R	Cerebellum	-	4	-52	-14
			3.49	L	Cerebellum	-	-6	-36	-8
Total	261	0.039	4.35	R	Anterior cingulate	24	10	18	20
Anosognosia			3.70	R	Anterior cingulate	24	16	28	16

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute.

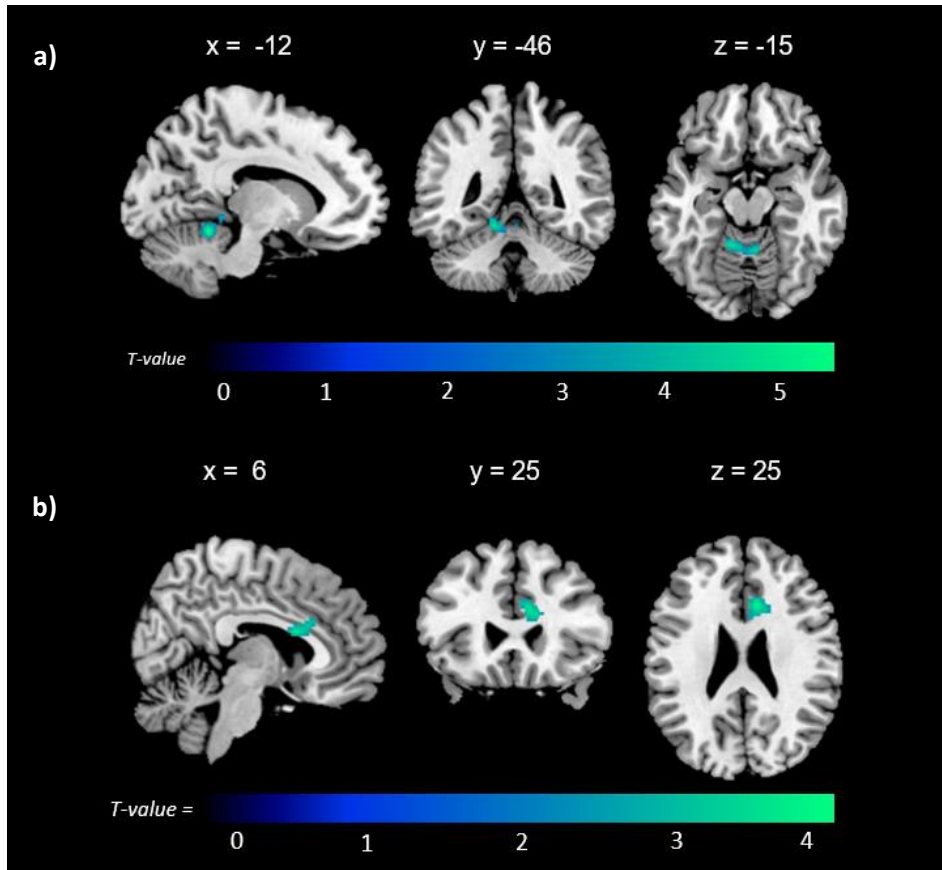


Figure 4.7. Positive correlations between functional connectivity of the anterior default mode network (aDMN) and a) non-memory and b) total anosognosia; clusters are shown at $p < 0.05$ FWE corrected.

4.2.3.2 Seed-based Results

Memory anosognosia outcomes were significantly negatively associated (decreased connectivity) with right-hemispheric seed regions and cerebral clusters, namely the right anterior cingulate cortex seed with decreased connectivity in the right fusiform gyrus (BA 20) and caudate ($k=383$, $p=0.025$), and the right hippocampus seed with the bilateral caudate and right thalamus ($k=394$, $p=0.016$). Left-sided decreased connectivity was found between the left hippocampus seed and the right dorsolateral prefrontal cortex (BA 9 & 46) ($k=333$, $p=0.040$). Conversely, memory anosognosia scores on right-sided seeds showed a positive association (increased connectivity) of the precuneus seed and the left fusiform and lingual gyri (BA 20 & 37) ($k=358$, $p=0.028$), while the right posterior cingulate seed was positively associated with the

right inferior occipital gyrus (BA 19) and cuneus (BA 17) ($k=407$, $p=0.025$). Similarly, left-sided regions of interest showed increased connectivity between memory anosognosia scores in the left anterior cingulate cortex seed and the precentral and postcentral gyri (BA 3 & 4) ($k=346$, $p=0.029$). These results are displayed and summarised in **table 4.10** and **figure 4.8**.

Non-memory anosognosia outcomes showed decreased connectivity in right-side regions, namely the right lingual seed with the right dorsolateral prefrontal cortex (BA 9) ($k=590$, $p=0.002$) and the right precuneus seed with the right transverse gyrus (BA 41), caudate and thalamus ($k=802$, $p=0.001$). On the other hand, left-sided seed regions displayed increased connectivity with non-memory anosognosia, namely the left anterior cingulate and medial prefrontal cortex seed with the right dorsolateral prefrontal cortex (BA 9) ($k=434$, $p=0.012$; $k=318$, $p=0.048$, respectively) and the left hippocampus seed with the caudate and insula ($k=354$, $p=0.031$) (**table 4.11** and **figure 4.9**).

Lastly, total anosognosia scores were associated with the left hippocampal seed where decreased connectivity was found in the right dorsolateral prefrontal cortex (BA 9,6 & 46) ($k=457$, $p=0.009$), and increased connectivity was found in the body of the left caudate nucleus ($k=330$, $p=0.042$), as shown in **table 4.12** and **figure 4.10**.

Table 4.10. Clusters of significant correlation detected in the functional connectivity analysis between memory anosognosia outcomes and signal in unilaterally selected seed-regions.

Memory Anosognosia									
Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI coordinates			
						x	y	z	
Decreased Connectivity									
<i>Right anterior cingulate cortex (ACC) seed</i>									
383	0.025	3.96	R	Caudate	-	30	-34	6	
		3.76	R	Fusiform gyrus	20	42	-36	-16	
		3.54	R	Fusiform gyrus	20	48	-12	-20	
<i>Right hippocampus seed</i>									
394	0.016	4.11	R	Caudate	-	12	14	8	
		3.73	R	Thalamus	-	4	-4	4	
		3.57	L	Caudate	-	14	18	-2	
<i>Left hippocampus seed</i>									
333	0.040	4.78	R	Middle frontal gyrus	46	46	34	28	
		4.38	R	Middle frontal gyrus	9	34	38	38	
		3.68	R	Middle frontal gyrus	9	46	26	38	
Increased Connectivity									
<i>Right precuneus seed</i>									
358	0.028	4.57	L	Fusiform gyrus	37	-48	-44	-14	
		4.42	L	Fusiform gyrus	20	-44	-36	-16	
		4.05	L	Lingual gyrus	-	-26	-66	-4	
<i>Right posterior cingulate cortex (PCC) seed</i>									
407	0.025	4.15	R	Posterior cingulate	30	30	-66	6	
		3.41	R	Inferior occipital gyrus	19	34	-74	-6	
		3.39	R	Cuneus	17	22	-76	2	
<i>Left anterior cingulate cortex (ACC) seed</i>									
346	0.029	4.52	L	Postcentral gyrus	3	-38	-32	58	
		4.08	L	Precentral gyrus	4	-30	-32	66	
		3.85	L	Postcentral gyrus	3	-22	-36	60	

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute; R: Right.

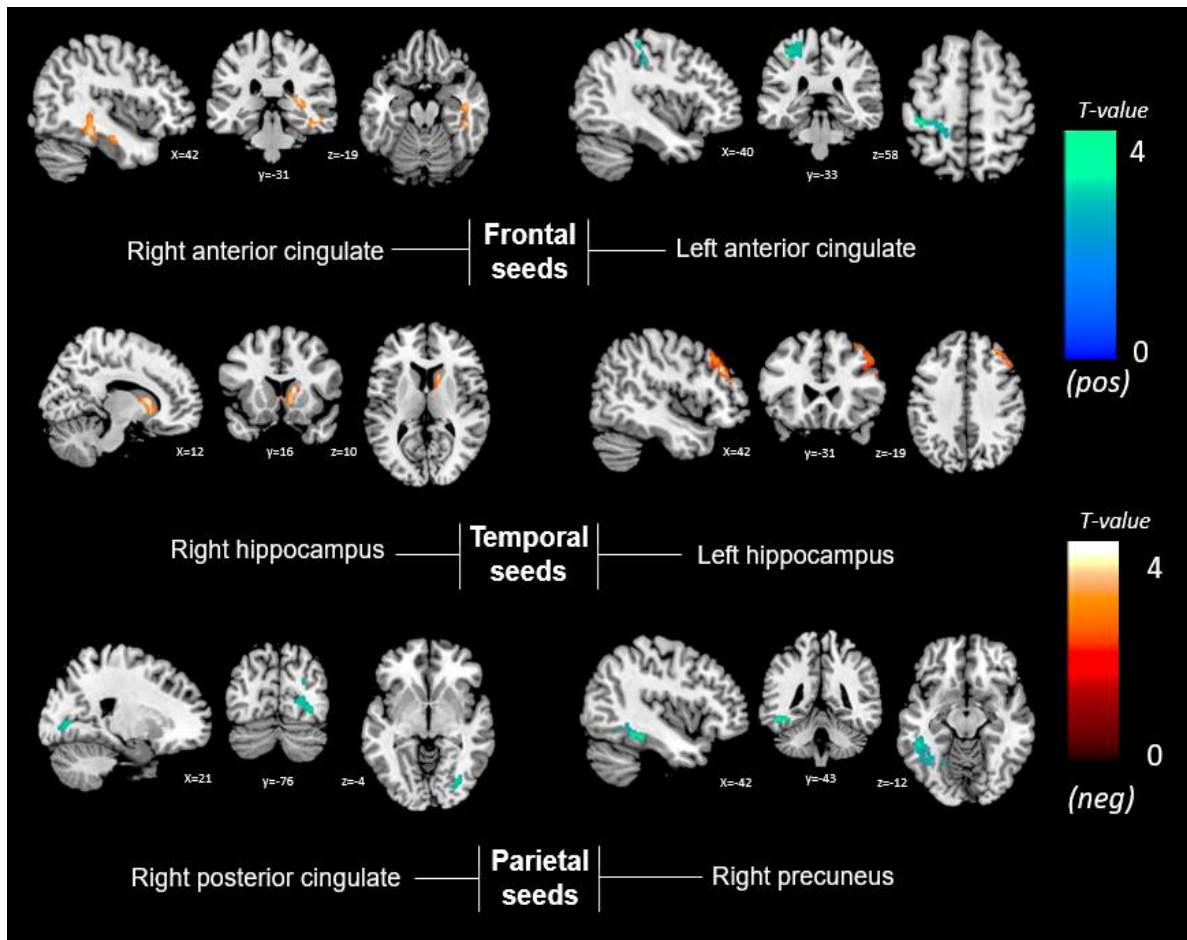


Figure 4.8. Positive (blue) and negative (red) correlations between brain functional connectivity of selected unilateral seed regions and memory anosognosia outcomes; clusters are shown at $p < 0.05$ FWE corrected.

Table 4.11. Clusters of significant correlation detected in the functional connectivity analysis between non-memory anosognosia outcomes and signal in unilaterally selected seed-regions.

Non-memory Anosognosia									
Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI coordinates			
						x	y	z	
Decreased Connectivity									
<i>Right lingual seed</i>									
590	0.002	5.26	R	Middle frontal gyrus	9	32	44	30	
		4.50	R	Middle frontal gyrus	9	24	54	22	
		3.38	R	Superior frontal gyrus	10	12	54	32	
<i>Right precuneus seed</i>									
802	0.001	4.98	R	Transverse gyrus	41	40	-32	10	
		3.99	R	Thalamus	-	24	-24	16	
		3.99	R	Caudate	-	22	-36	10	

Increased Connectivity									
<i>Left anterior cingulate cortex (ACC) seed</i>									
434	0.012	4.35	R	Superior frontal gyrus	10	20	58	18	
		3.88	R	Middle frontal gyrus	9	40	46	20	
		3.63	R	Middle frontal gyrus	9	28	40	32	
<i>Left medial prefrontal cortex (mPFC) seed</i>									
318	0.048	4.59	R	Middle frontal gyrus	9	26	36	22	
		3.71	R	Middle frontal gyrus	9	30	44	30	
		3.26	R	Superior frontal gyrus	9	20	50	20	
<i>Left hippocampus seed</i>									
354	0.031	3.88	L	Caudate	-	-16	-38	20	
		3.25	L	Insula	13	-26	-36	24	

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute; R: Right.

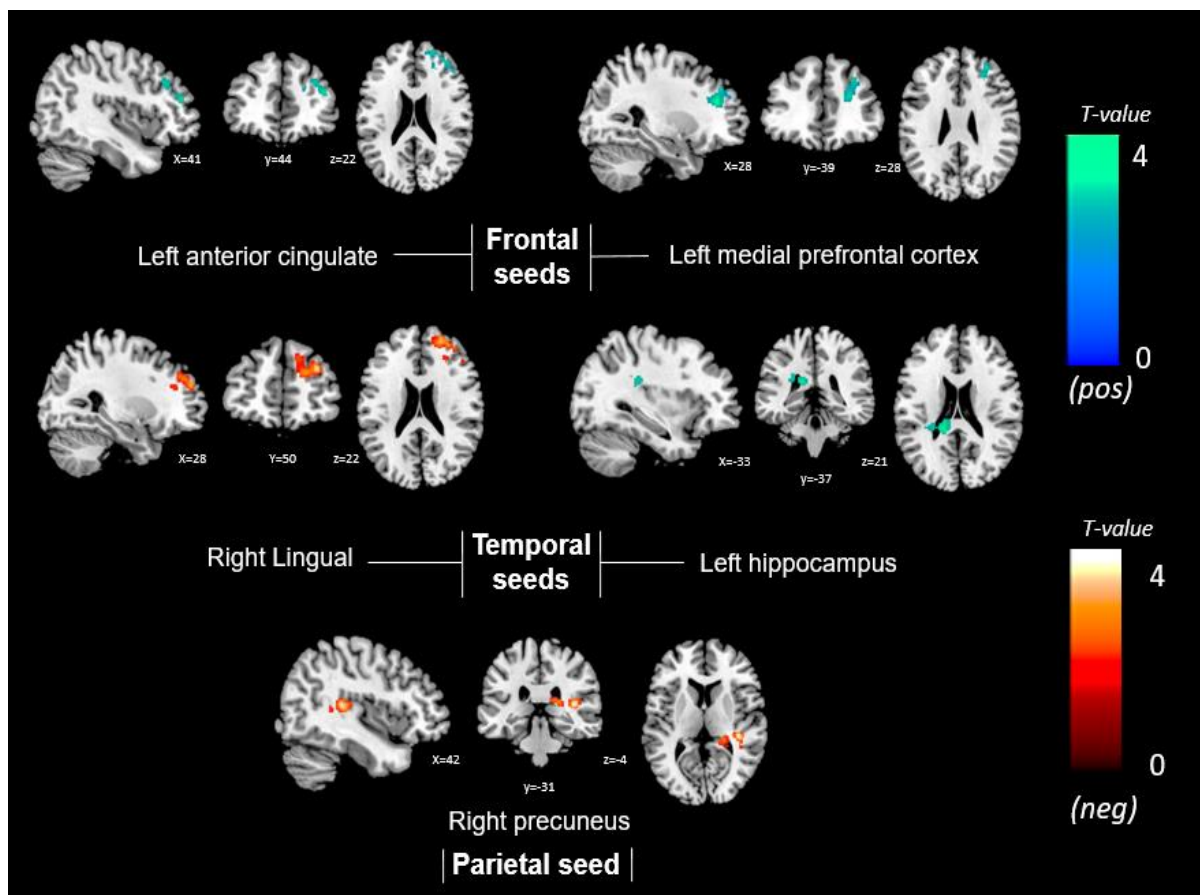


Figure 4.9. Positive (blue) and negative (red) correlations between brain functional connectivity of selected unilateral seed regions and non-memory anosognosia outcomes; clusters are shown at $p < 0.05$ FWE corrected.

Table 4.12. Clusters of significant correlation detected in the functional connectivity analysis between total anosognosia outcomes and signal of unilaterally selected seed-regions.

Total Anosognosia									
Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI coordinates			
						x	y	z	
Decreased Connectivity									
<i>Left hippocampus seed</i>									
457	0.009	4.91	R	Middle frontal gyrus	46	48	32	28	
		4.70	R	Middle frontal gyrus	9	36	36	40	
		4.35	R	Middle frontal gyrus	6	28	60	60	
Increased Connectivity									
<i>Left hippocampus seed</i>									
330	0.042	3.71	L	Caudate	-	-16	-38	18	
		3.57	L	Caudate	-	-22	-30	26	

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute; R: Right.

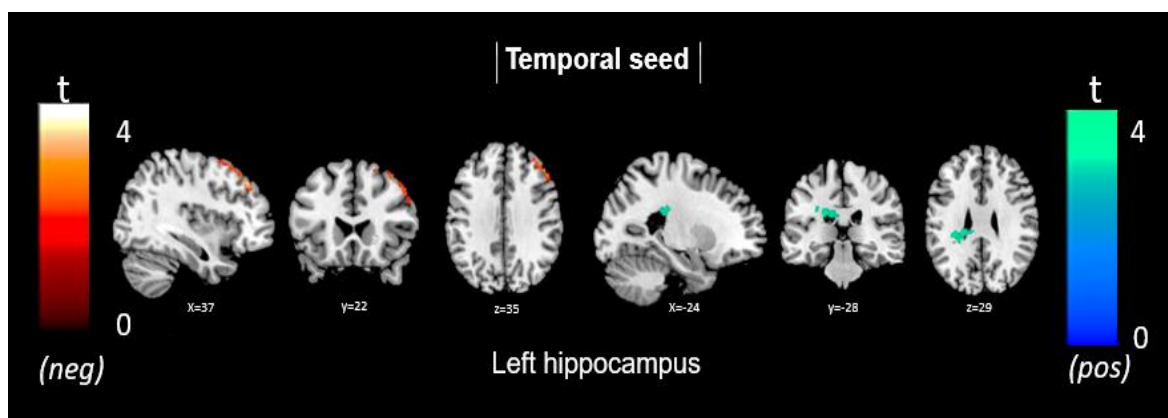


Figure 4.10. Positive (blue) and negative (red) correlations between brain functional connectivity of selected unilateral seed regions and total anosognosia outcomes; clusters are shown at $p < 0.05$ FWE Corrected.

4.2.4 Discussion

The present experiments had the objective to consolidate the functional neural substrates that delineate multi-domain anosognosia in early-AD with particular attention to discover what type of alteration in the brain functional network dynamics

may account for unawareness of memory, executive and everyday life functions in early AD. A better understanding of the functional substrates of domain-specific anosognosia might provide insights into how disconnection of structures supporting functions involved in the cognitive awareness model (CAM) translates into different mechanisms leading to cognitive unawareness.

4.2.4.1 Functional connectivity associated with memory anosognosia

Unawareness of memory deficits was linked to functional brain connectivity changes affecting large-scale neural networks and region-to-brain intercommunication. Memory anosognosia was linked mainly with reduced functional connectivity between the fronto-temporal cortex, but increased connectivity with parieto-temporal structures. In more detail, network-to-brain linear correlations showed that memory anosognosia was associated with lower intrinsic connectivity between the central executive I-FPN and the left lingual gyrus and posterior cingulate. Similarly, seed-to-brain communication displayed reduced connectivity between right-predominantly frontal and bilateral temporal structures, namely between the right anterior cingulate seed and the right fusiform, and the right dorsolateral prefrontal cortex with the left hippocampus seed. Additionally, subcortical lower connectivity was found in the right caudate and the right anterior cingulate seed and right hippocampal seed. Conversely, memory anosognosia was associated with increased parieto-temporal connectivity between the right precuneus seed and the left lingual and fusiform gyrus and the left anterior cingulate seed and left postcentral gyrus. The significant contribution of temporal cortical structures in early-AD patients presenting with higher memory anosognosia and functional connectivity alterations is consistent with the pathophysiological

manifestations of clinical AD. In this context, degeneration of the medial temporal lobe induces cognitive detriments centred on memory performance that may extend to reduced self-awareness regarding memory performance (Chavoix & Insausti, 2017). A histopathological study showed that unaware AD patients showed greater amyloid plaque density in the hippocampal presubiculum *post-mortem* (Marshall et al., 2004). However, this particular change could have been related to severe detrimental pathological changes affecting the medial temporal lobe regions in the final stages of the disease. In our study, the main affected temporal regions were the fusiform and lingual gyrus. These structures were also associated with non-memory anosognosia scores and grey matter changes in experiment 1. Functional alterations of the fusiform (Vannini et al., 2017b) and lingual gyrus (Mitelpunkt et al., 2020) have been found to be associated with anosognosia in AD and seem to be closely linked with a network delineating cognitive awareness.

Pioneer studies that explored the functional neural substrates of memory anosognosia through single-photon emission computerised tomography (SPECT) (Reed et al., 1993; Starkstein et al., 1995; Derouesne et al., 1999; Hanyu et al., 2008) or positron-emission tomography (Harwood et al., 2005; Jedidi et al., 2014) have consistently demonstrated that AD patients manifest reduced brain function predominantly in right frontal cortical structures. AD patients showed decreased fronto-temporal brain activation in relation to self-awareness in a study performed by Zamboni et al. (2013), the findings of which show consistency with the fronto-temporal connectivity results at the resting-state level in the present study. Increased frontal and parietal communication were found by a functional task-based MRI study that showed higher activation in the prefrontal cortex of healthy controls in relation to AD patients

when engaging in self-awareness tasks, while AD patients displayed higher activation of the parietal cortex (Ruby et al., 2008).

4.2.4.2 *Functional connectivity associated with non-memory anosognosia*

Anosognosia related to executive and everyday life functions was significantly positively associated with the connectivity of the aDMN and the cerebellum, i.e., higher connectivity in the presence of more severe anosognosia. Similarly, positive seed-based linear analyses showed increased connectivity of left medial prefrontal seeds (ACC and mPFC) to the right dorsolateral prefrontal cortex. Likewise, the left hippocampus seed showed higher connectivity with the left insular cortex and caudate. Conversely, significant negative associations were obtained in the region-to-brain connectivity analyses and non-memory anosognosia outcomes, namely between greater non-memory anosognosia and lower functional connectivity of the right lingual seed and the right dorsolateral prefrontal cortex and right precuneus seed with right subcortical regions (caudate and thalamus). Results from this experiment demonstrate the compelling involvement of the right dorsolateral prefrontal cortex in modulating self-awareness, with this region displaying higher connectivity with the left frontal lobe while lower intercommunication with the right temporal cortex. Notably, the central nodes of the central executive FPN are anchored to the dorsolateral prefrontal cortex and posterior parietal cortex (Bressler & Menon, 2010). The former has been associated with executive functions and working memory and has been found to display selective age-related vulnerability in the elder population (MacPherson, Phillips & Della Sala, 2002). More importantly, the right dorsolateral prefrontal cortex involvement in AD patients presenting with anosognosia has been evidenced in the

current literature regardless of the neuroimaging methodological approach used ([Reed et al., 1993](#); [Starkstein et al., 1995](#); [Ries et al., 2012](#)). This region has been proposed as part of an executive control network that, in conjunction with the ACC, coordinates behaviour related to accomplishing life-related objectives ([Cohen, Botvinick & Carter, 2000](#); [Amanzio et al., 2011](#); [Xu et al., 2020](#)). In addition, the contribution of the dorsolateral frontal cortex to declarative memory has been established in AD ([Kumar et al., 2017](#); [Turriziani et al., 2019](#)), as this structure may serve as a mnemonic structure related to working memory for manipulation and update of conscious information that works in close relation with a central executive system ([Funahashi, 2017](#)). Furthermore, the executive control network has shown to rely on cerebro-cerebellar intercommunication that could act as a supportive structure in executive decline ([Xu et al., 2020](#)). Dorsolateral prefrontal dichotomous contrasting connectivity of increased communication to contralateral frontal structures and reduced communication to ipsilateral temporal regions might provide foundations for the role this region has with adaptive cognitive control for abilities such as attention ([Gbadeyan et al., 2016](#)). Involvement of the left dorsolateral prefrontal cortex has been proposed to serve in the maintenance and direction of attentional resources while the same contralateral structure has been found to be associated with resolving attentional-related conflict ([Vanderhasselt et al., 2009](#)).

Increased connectivity of the aDMN to the cerebellar cortex could contribute to improve intercommunication with higher networks that are involved in higher cognitive functions as it has been shown that structures in the cerebellum provide substantial contributions to cognition, for example to executive functions ([Nowrangi et al., 2016](#); [Xu et al., 2020](#)). The DMN-subcortical findings in our study stress the relevance of

contributions of subcortical structures to the DMN connectivity, including the cerebellum (Buckner et al., 2011; Alves et al., 2019).

Findings in the insula have shown consistency with those available in the literature centred on the neuroscience of self-awareness (Lou, Changeux & Rosenstand, 2017). One study that highlighted grey matter volumetric changes centred in left insular-hippocampal regions was carried out by Sanchez-Benavides and colleagues (2018) who found that individuals self-assessed as unaware of cognitive decline had higher grey matter insular volumes compared to individuals displaying subjective cognitive decline. Additionally, informant-related reports of cognitive changes (unrelated to self-awareness status) were associated with lower overall grey matter volume in the left hippocampus. This study provides valuable insights about neural insular-hippocampal changes present in a healthy psychometrically normal ageing sample displaying cognitive alterations consistent with the preclinical phase of AD in the same regions we found showing higher connectivity in our early-AD sample manifesting non-memory anosognosia. While we found higher connectivity between the left hippocampus and insula related to non-memory anosognosia, Berlinger and team (2015) found reduced connectivity between these same structures for memory anosognosia. Insulo-temporal connectivity dissociations might be related to domain-specific awareness in which the insula might serve as a supporting system in the presence of more complex unawareness for executive and daily life functions while a mnemonic hub might relate to memory unawareness. Moreover, the insula has been found to be concomitantly active alongside the prefrontal cortex and anterior cingulate to achieve self-referential processing where the insula might be involved in self-awareness (Craig, 2009; Modinos, Ormel & Aleman, 2009). This evidence provides further support that anosognosia at its initial onset might stem from early dysfunction

of structures interconnected to an executive control system, such as the insular cortex, rather than depending entirely on the decline of medial temporal lobe regions inherent to the aetiopathological cascade of AD.

4.2.4.3 Functional connectivity associated with total anosognosia

Early-AD patients displaying total anosognosia symptoms displayed large-scale network alterations, namely lower functional connectivity of the left FPN to the left posterior cingulate and increased connectivity of the right FPN to the left inferior lingual gyrus and adjacent inferior occipital cortex, while increased connectivity with the right ACC. Similarly, the aDMN showed increased connectivity with the right ACC. Region of interest seed-based resting-state functional analyses yielded significant connectivity differences in the left hippocampal seed by detecting lower intercommunication with the right dorsolateral prefrontal cortex and increased connectivity with the left subcortical caudate nucleus. Large-scale executive fronto-parietal communication with the lingual gyrus runs in line with our hypothesis of frontally mediated control of unawareness symptoms. The lingual gyrus is a region essential for visual perception (Yang et al., 2015b), but it also plays an executive role, as shown in a study that reported activation during a divergent thinking paradigm (Zhang et al., 2016). These findings provide higher support that reduced fronto-temporal connectivity could define the aetiology of multi-domain anosognosia in this particular population as a result of extensive damage to frontal executive comparator mechanisms. Lastly, as total anosognosia can be the outcome of memory or non-memory unawareness, particular details of these findings have already been discussed in the previous sections.

A comprehensive overview of the results in the present study indicates that the anterior cingulate cortex seems to have a strong involvement in the overall clinical manifestation of multi-domain anosognosia. Structural changes, which are seen later than functional changes in the disease course, showed grey matter alterations of the ACC related to non-memory and total anosognosia while rs-fMRI findings demonstrated the involvement of this structure in all anosognosia domains. Regardless of the methodological approach, this structure has been shown to be heavily implicated in unawareness symptoms in the early AD continuum ([Hanyu et al., 2008](#); [Amanzio et al., 2011](#); [Zamboni et al., 2013](#); [Guerrier et al., 2018](#); [Mondragon et al., 2021](#)).

These results show consistency with the premise that midline structures are essential for self-awareness and self-referential processing ([Northoff & Bermpohl, 2004](#); [Lou, Changeux & Rosenstand, 2017](#)). The neural structure and function of the ACC could play a major role within an executive supporting system. On this note, executive impairment was shown to be associated with the ACC in patients with prodromal AD, patients who also had a lower amyloid burden ([Yoon et al., 2019](#)). Notably, the ACC has been found to be highly involved in the manifestation of neuropsychiatric symptoms in AD ([Boublay et al., 2016](#)), where anosognosic symptoms are also included as part of a behavioural disorder spectrum that affects this clinical population ([Tagai et al., 2020](#)). Therefore, the ACC is considered a core region that modulates behaviour through reward, motivation and initiation ([Devinsky, Morrell & Vogt, 1995](#)). This could result in patients presenting with self-awareness deficits experiencing higher behavioural alterations when losing their sense of self.

Subcortical selective decrease and increased connectivity patterns were also associated with multi-domain anosognosia. In the light of our findings, memory

anosognosia displayed lower fronto-temporal connectivity with the bilateral caudate and right thalamus. On the other hand, non-memory anosognosia was linked with increased interconnectivity between the cerebellum and aDMN, and between the left hippocampus and left caudate. The latter pattern of results was replicated with total anosognosia scores. Decreased connectivity was observed between the right precuneus and right thalamus and caudate. Subcortical contributions to anosognosia in AD have been found in the literature ([Ries et al., 2012](#)). For example, there is a great subcortical contribution when overestimating overall cognitive functions and emotional control in dementia patients ([Shany-Ur et al., 2014](#)). In this context, subcortical regions are associated with the dopaminergic system involved in reward actions based on self-centred attention, resulting from everyday life accomplishments ([Shany-Ur et al., 2014](#)). Dopaminergic activity has been proposed to enhance paralimbic structures in charge of self-referential processing in which subcortical contributions might support medial frontal cortical regions in self-awareness ([Lou, Changeux & Rosenstand, 2017](#)). Therefore, structural and functional alterations might derive from a redirection of dopaminergic resources to cope with symptoms related to unawareness.

4.3 Limitations

Limitations might arise from the choice of instrument to measure anosognosia. In fact, failing to acknowledge the presence of symptoms or poor performance could in part be due to a defensive mechanism of denial, triggered by individual socioemotional factors ([Ecklund-Johnson & Torres, 2005](#)). This possibility, however, is an intrinsic factor in this type of measurement and would affect any questionnaire/scale. On this note, it is desirable to confirm each diagnosis of anosognosia with a clinical qualitative

judgment. Secondly, the use of discrepancy scores depends on the answers given by both patient and informant. Caregiver burden may inadvertently shift the perception of the patient's abilities into an over/underestimation. To rule out this possibility, we chose to rely on a robust instrument that has undergone methodological validation; but acknowledge that there are other ways to assess anosognosia, such as the discrepancy between estimation and actual performance on a task. Lastly, although the total anosognosia score was strongly correlated with both the memory ($r = 0.895$) and non-memory ($r = 0.818$) sub-scores, we cannot completely rule out the possibility that one of the two subscales may have had a larger impact on the total score than the other. The lack of findings in structural connectivity might also derive from a low sample size that lacked the power to delineate neural correlates of fractional anisotropy. Multi-centre sample pooling was not possible for this study as there is no published research of combining different magnetic fields for DTI analysis. Therefore, separate analyses were the optimal choice for this particular arm of the study, but in so doing statistical power was considerably reduced, leading to potentially underpowered analyses.

4.4 General discussion

An integrative perspective of the experiments carried out in this chapter provides evidence that anosognosia is not a homogeneous concept and a multi-domain approach is further required for its study not only in AD, but also in other neurodegenerative conditions. Results arising from the present structural and functional experiments reinforce the fundamental contribution of the right-sided frontal cortex and limbic-associated structures to the neuroscience of self-awareness deficits in the early AD continuum ([Mondragon, Maurits & De Deyn, 2019](#); [Hallam et al., 2020](#)),

with a particular involvement of the ACC across all the implemented neuroimaging modalities. In addition, temporal structures, such as the lingual and fusiform gyrus, seem to have a secondary substantial involvement in multi-domain unawareness.

Following a domain-specific perspective, memory anosognosia was found to be associated with both semantic and episodic memory, to have fronto-temporal and parieto-temporal connectivity alterations while no major involvement of grey matter volumes was found. On the other hand, non-memory related to executive and everyday life anosognosia seems to have a greater impact in early-AD with brain structural and functional connectivity changes mainly involving volumes of the ACC, fusiform, lingual and precentral gyri, and connectivity of the dorsolateral prefrontal cortex. Brain laterality differences in the present research showed consistency with the prevalent premise of a right-sided frontal dominance controlling self-awareness and anosognosia ([Keenan & Gorman, 2007](#)).

A broader neuroimaging-based perspective suggests that damage to frontal-circuitry precedes loss of grey matter, and this would account for how the clinical symptoms present in relation to multi-domain anosognosia ([Mondragon, Maurits & De Deyn, 2019](#)). The present functional large-scale and seed-based connectivity findings provide evidence of a reduced network coupling between the DMN and central executive frontoparietal system in relation to memory and total anosognosia. In contrast, multi-domain anosognosia showed extended increased connectivity of the DMN with the cerebellum and the ACC. According to this view, reduced connectivity of the default mode network (DMN), seen in the early phases of AD ([Klaassens et al., 2017](#)), may act as a marker of progression associated with anosognosia ([Therriault et al., 2018](#)). In fact, the bases of impaired self-awareness and anosognosia have been heavily intertwined with the functionality of the DMN in AD ([Antoine et al., 2019](#);

[Mondragon, Maurits & De Deyn, 2019](#)) and other neurological conditions, such as anosognosia for hemiplegia ([Pacella et al., 2019](#)). On these grounds, the dysfunction of the DMN could be conceived as a translational construct to justify routine assessment of awareness even at the preclinical stage of AD ([Cacciamani et al., 2017](#)). In turn, damage to the DMN could then hinder other frontal pathways of connectivity that would lead to a dysfunctional use of the central executive comparator and other neuronal systems such as those associated with attention or emotional processing ([Shany-Ur et al., 2014](#)). Cingulate and subcortical interconnections to the DMN might suggest a global brain circuitry that modulates cognitive awareness in the early AD continuum.

Mechanistic approaches might provide explanations for our results. In the context of selective damage to the executive-comparator mechanism within the conscious awareness model (CAM), affected fronto-cingulate regions could modulate cognitive multi-domain awareness, where executive dysfunction might extend to temporal regions and thus explaining an incapacity to update self-centred memories ([Amanzio et al., 2020](#)). Therefore, hampered fronto-temporal intercommunication might originate in the dysfunction of a frontal-based central executive system rather than a consequential manifestation of the aetiopathological cascade affecting middle temporal lobe structures. This could explain why the neural functional and structural correlates for non-memory anosognosia were more extensive than the memory domain. We propose that independent pathological mechanisms surrounding anosognosia onset might explain the heterogeneous clinical expression in comparison to the rest of cognitive symptoms that characterise patients in early-AD. As a consequence, the study of awareness has already provided valuable insights to act as

a robust non-invasive and cost-effective clinical biomarker for diagnosis as early as the preclinical stage of AD ([Cacciamani et al., 2017](#); [Vannini et al., 2020](#)).

Chapter 5

Neuroanatomical, functional connectivity and behavioural correlates of social cognition and Theory of Mind in early Alzheimer's disease

5.1 Experiment 3 | Behavioural, neuroanatomical and structural connectivity correlates of social cognition and Theory of Mind in early Alzheimer's disease

5.1.1 Introduction

Social cognition constitutes one of the five major neurocognitive domains proposed by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defined as a group of brain mechanisms required to establish everyday human interactions ([Sachdev et al., 2014](#)). This type of social processing relies on complex neural dynamics that allow individuals to perceive, understand and adapt their internal state of mind in relation to others ([Adolphs, 2009](#)). To achieve this, self-originated inferences regarding other people's intentions, beliefs and emotions guide decision making and modulate behaviour in accordance with the established social standards in a concept defined as Theory of Mind (ToM) ([Baron-Cohen, Leslie & Frith, 1985](#)). ToM has been recognised as the most representative component of social cognition and can be further divided into dyad domains namely, cognitive ToM (inferences based on intentions and beliefs) and affective ToM (inferential thoughts based on emotional attributes) that are said to be controlled by independent neural systems ([Kalbe et al., 2010](#); [Abu-Akel & Shamay-](#)

Tsoory, 2011; Kemp et al., 2012; Poletti, Enrici & Adenzato, 2012). Moreover, the affective component of ToM seems to contain shared functional processes that integrate an initial first step of emotion recognition or social perception and subsequent attribution of emotional states (social understanding), also defined as cognitive empathy (Mier et al., 2010; Dvash & Shamay-Tsoory, 2014; Arioli, Crespi & Canessa, 2018).

Impairment of ToM and other social cognition abilities have been evidenced in the AD continuum (Hargrave, Maddock & Stone, 2002; Miller et al., 2012; Freedman et al., 2013; Moreau et al., 2016; Torres et al., 2019; Chainay & Gaubert, 2020; Kessels, Elferink & van Tilborg, 2020; Demichelis et al., 2020). However, it is significantly less severe when compared to other neurocognitive domains such as memory (Dodich et al., 2016). Furthermore, it has been well established that patients with AD experience significantly milder ToM decline compared with other forms of neurodegeneration, such as Lewy body dementia (Heitz et al., 2015) or the behavioural variant of frontotemporal dementia (Bora, Walterfang & Velakoulis, 2015; Dodich et al., 2018), in which deterioration of social components of behaviour is a fundamental clinical feature for clinical diagnosis (Rascovsky & Grossman, 2013). Longitudinal studies have revealed that deterioration of social cognition in AD occurs in concomitance, and as a possible consequence, of progressive neurodegeneration (Cosentino et al., 2014, Torres et al., 2015). Furthermore, increasing reported evidence indicates that this deterioration in AD may originate early and may be already detectable at the prodromal stage (Elferink, Tilborg & Kessels 2015; Bora & Yener, 2017, Yildirim et al., 2020).

Theory of Mind, as a separate neurocognitive domain, may be controlled by independent neural mechanisms that are not shared by other domains modulating general cognition (Cosentino et al., 2014, Moreau et al., 2016). This could partially

explain why ToM and other social cognition skills are preserved mostly until the later stages of the disease (Kumfor et al., 2014). Nevertheless, the prevailing conceptual framework suggests that detriments of ToM in AD are inherently intertwined as a secondary outcome of the inherent overall cognitive dysfunction, with higher predominance on the executive domain (Shany-Ur et al., 2012; Dodich et al., 2016; Ramanan et al., 2017; Christidi et al., 2018; Torres et al., 2019). As a result, cognitive and affective ToM impairment would initiate in complex functions, that rely heavily on attention, reasoning or decision-making (e.g., detection of second-order false beliefs), with later deterioration of more basic social functions (e.g first-order false belief, recognition of emotions or basic facial expressions) (Gregory et al., 2002; Castelli et al., 2011; Garcia-Rodriguez et al., 2012). Executive/attentional mechanisms prompt decision-making processes relying on semantic processing of visual cues and verbal descriptions that allow labelling and assimilation of others' affective mental states (Phillips et al., 2010; Circelli, Clark & Cronin-Golomb, 2013).

The neural substrates that modulate ToM abilities in AD remain poorly understood. Extensive literature involving healthy individuals has shed light on the possible regions that harbour this type of social processing. A multiple-dynamic network comprising of a neuroanatomical backbone that includes the medial prefrontal cortex (mPFC), temporoparietal junction (TPJ), posterior superior temporal sulcus (pSTS) and precuneus has been identified as the core set of anatomical/functional neural systems responsible for ToM performance (Gallagher & Frith, 2003; Frith & Frith, 2012; Schurz et al., 2014). Brain lesion studies have investigated the role of distinctive neural regions that contribute to social cognition processing, in which selective damage to the right occipito-temporal cortex (face recognition), left temporal poles (semantic naming of others), bilateral amygdala (recognition of fear), right ventral

mPFC (emotion decision-making and affective ToM), insula (empathy) and right somatosensory cortex (emotion labelling) has shown different degrees of social cognitive impairment ([Shamay-Tsoory et al., 2005](#); [Kennedy & Adolphs, 2012](#)).

Research focused on other types of neurodegeneration has provided evidence about the areas in which dysfunction could impact negatively mechanisms of social processing. More specifically, the limited neuroimaging evidence elucidating the neural underpinnings of ToM in AD has found consistent neural deficits in similar areas as those found in the healthy population ([Strikwerda-Brown, Ramanan & Irish, 2019](#)). Le Bouc and colleagues ([2012](#)) demonstrated that AD patients display hypometabolism in the left TPJ (others' mind inference) and right mPFC (self-perspective inhibition) in relation to ToM tasks. In addition, Synn and collaborators ([2018](#)) found brain structural associations of ToM with the hippocampus and cerebellum. On this note, cerebellar contributions to social cognition and ToM in healthy subjects have been widely demonstrated, mainly through brain functional imaging research ([Van Overwalle et al., 2014](#)).

Although the vast majority of research on AD has focused on grey matter changes and associated functions, impairment of white matter tracts has also been evidenced in AD, and it is characterised by selectively decreased fractional anisotropy in vulnerable regions ([Sexton et al., 2011](#)), in particular the fornix, cingulum and corpus callosum ([Acosta-Cabronero & Nestor, 2014](#)); the latter structures also found affected in the MCI stage ([Chua et al., 2008](#)). This mechanism of disease could be explained potentially as diffuse axonal Wallerian degeneration ([Sexton et al., 2011](#)). Understandably, although detrimental white matter changes have been found in AD, it does not seem to be linked closely with cognitive performance ([Mayo et al., 2019](#)). The evidence of white matter changes associated with social cognition in the healthy

population has shown that the inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF) are closely related with social facial perception, while the superior longitudinal fasciculus (SLF) has been linked to mirroring abilities, and the SLF, arcuate and cingulum seem to delineate intercommunicating structures in charge of mentalising and ToM. These interconnected pathways serve as backbone elements that outline parts of the default mode network (DMN) (Wang et al., 2018).

As the most commonly accepted premise in AD is that there is no major impairment of social cognition in the early stages in contrast to other cognitive domains (Goodkind et al., 2015; Fliss et al., 2016), this aspect of cognition has been considered as a good clinical marker for differential diagnosis with other types of dementia (Bertoux et al., 2016. Dodich et al., 2018). However, the presence of subtle changes in social cognition skills in early-AD could indicate an underlying pathology that eventually could spread into substantial damage to the social cognitive sphere. Therefore, the rationale behind the present experiment was to measure these subtle changes initially in those behavioural tasks and brain structures that have been associated with social cognition and ToM functioning by earlier studies in healthy people. Hence, correlation models were preferred for this study with specific control for covariates that could cause spurious effects in our statistical analytical models. Based on the vast literature available on ToM in the healthy population and the very limited one on neurodegeneration of the Alzheimer type, we hypothesised that ToM performance, at the neurocognitive level, would be more closely associated with executive/attentional functions. At the brain structure level, early-AD will manifest grey matter reduction of core ToM regions established in healthy individuals delimited to specific frontal (PFC), parietal (TPJ), temporal (temporal sulcus and poles) and subcortical (cerebellum) structures, and white matter tracts associated with these

regions. The evidence provided in this experiment on the neural correlates of social cognition and ToM in early-stage AD could provide insights into how the social neurocognitive domain might longitudinally decay in later disease stages. To our knowledge, this is the first comprehensive study to encompass the behavioural and multi-modal neural substrates of emotion recognition and cognitive and affective ToM performance in AD.

5.1.2 Methods

5.1.2.1 Participants

A sample of 46 patients who met clinical criteria for a diagnosis of prodromal or early-stage AD (9 AD and 37MCI) (Albert et al., 2011) was included in this experiment. Patients were recruited among service users of the neuropsychology service of the outpatient memory clinic of the IRCCS San Camillo Hospital, in Venice, Italy. The age of the selected group ranged between 57 and 89 years (mean 75.33, SD 7), 17 males (37%) and 29 females (63%) were part of the final sample. All patients underwent full general cognition assessment with the Mini-Mental State Examination (MMSE) as a measure of overall cognitive functioning and their scores ranged from 21 to 30 (mean 25.95, SD 2.61).

MCI clinical diagnosis was reached following the diagnostic criteria set by Petersen et al. (1999) and Albert et al. (2011). A clinical diagnosis of AD dementia was formulated using the National Institute of Neurological and Communicate Disorders and Stroke and the Alzheimer's Disease Related Disorders Association (NINCDS/ADRDA) criteria by McKhann et al. (2011), in concordance with Jack et al. (2018) criteria and the support of an MRI profile (Fig. 5.1). Main exclusion criteria

consisted of participants with other neurological conditions such as acute or chronic cerebrovascular disease or history of transient ischaemic attacks (TIA), uncontrolled brain seizures or history of epilepsy, peripheral neuropathy disorders, presence of substantial neuropsychiatric symptoms or diseases compatible with brain MRI diagnosis not in accordance with this study; cardiovascular and gastroenterological conditions such as sick sinus syndrome or peptic ulcer; metabolic disorders such as abnormal levels of B12, folates or thyroid-stimulating hormone and pharmacological interventions such as treatment with memantine/cholinesterase inhibitors, psychotropic medication, pharmacological components displaying important organic adverse effects or medications used in other research protocols; and the presence of overall major disabilities that could impact negatively on cognitive or everyday life functions. All participants who had chronic treatment for other severe non-neurological diseases were in control levels during data acquisition.

Ethical approval was granted by the Joint Ethics Committee of the Health Authority Venice 12 and the IRCCS Fondazione Ospedale San Camillo (Protocol number 2014.08). Written informed consent was obtained from all participants.

5.1.2.2 Social cognition and neuropsychological assessment

Multi-domain social cognition skills were assessed using three instruments. Firstly, the **Ekman 60 Faces (Ek-60F)** test that evaluates a participant's ability to recognise basic human emotions; more specifically, happiness, sadness, anger, disgust, fear and surprise. Participants are firstly asked to provide a sentence to recognise semantically each of the different emotions (e.g., "Please give an example of a situation in which you feel sad"). Secondly, the assessment consists of 60 black and white pictures from

the series of Picture and Facial Affect (Ekman & Friesen, 1976) with the faces of 4 male and 6 female characters displaying the six emotions mentioned previously. The global score is calculated as one point for every correct answer, for a total score of 60 points. A sub-score can be calculated to obtain the specific outcome in each of the emotion parameters. Each picture is displayed for 5 seconds, after a trial example of six images (one for each emotion). A cut-off value of 37 has been established in a previously selected and standardised normative sample, representative of the present population (Dodich et al., 2014). In the context of AD, the Ekman test has been the most consistently used tool to measure emotion recognition (Torres et al., 2019), but this test is also considered a valid test that measures the initial affective component of ToM (Heitz et al., 2016).

The second task was the **Reading the Mind in the Eyes Test (RMET)** that consists of 36 photographs focusing on the eye region of 17 female and 19 male real-life characters. The participant is asked to choose properly among four words that best match the emotion or thinking process reflected in the eye's expression. The main aim of this test is to measure the participant's ability to shift their own perspective into the perspective of others by inferring their state of mind. Therefore, this test assesses cognitive (mental states attributions) and affective (facial expression and emotional identification) ToM through the employment of diverse social cognitive resources (Baron-Cohen et al., 2001). The score is calculated by giving one point to every correct answer (for a total of 36 items). This test has already been standardised in a sample representative of the present study population (Vellante et al., 2013). Both, the Ekman test and RMET are the most consistently used assessments in people with neurological disorders, as performance on these tests depends on visual features that

present lower cognitive burden when used in patients with dementia ([Henry et al., 2016](#)).

Lastly, the **Story-based Empathy Task (SET)** was the third clinical tool used for cognitive and affective ToM assessment as it reflects cognitive empathy abilities that are shaped by both domains of ToM ([Dodich et al., 2016](#)). It is a non-verbal cartoon vignette task designed to assess the abilities to attribute a character's intentions (Intention Attribution, SET-IA), in relation to cognitive ToM, and to attribute properly a character's emotional state (Emotion Attribution, SET-EA), as a proxy of affective ToM. Lastly, the third part of this assessment serves as a control task, intended to examine the inference of causal actions between object and human interactions in the physical world (Causal Inference, SET-CI). The whole battery is composed of a total of 18 trials; 6 for every condition assessed, with the requirement to predict the correct ending for each story. The vignettes consist of three upper positioned cartoons depicting the chronological sequence of a story and three lower cartoons showing different possible endings to that specific story. The participant must select the best possible story conclusion in relation to their own social cognition skills. One point is given when the participant picks the correct vignette for the correct ending. The global score is calculated by summing the scores for all tasks, with a possible global score of 18. A trial run example of a causal inference story will precede the assessment, to clarify the instructions to the participant. A cut-off value of 13 has been applied from a normative standardised sample to establish impairment in ToM ([Dodich et al., 2015](#)).

Additionally, each participant completed a comprehensive neuropsychological testing battery for a detailed profiling of cognitive performance. The cognitive battery, included the following: memory functioning was assessed with the Prose Memory Test (immediate and delayed) for long-term memory; Digit Span (forward and backward)

for short-term and working memory; Category Fluency test for semantic memory; and the Verbal Paired Associates Learning Task for episodic and semantic memory; executive functions were examined through the Stroop test to assess inhibition and attention; Rey-Osterrieth Complex Figure for visuospatial abilities; WAIS Similarities subtest for verbal reasoning; Boston Naming Test for language skills; Token test for language comprehension; Raven's Coloured Progressive Matrices test for visual perception and abstract reasoning and the Digit Cancellation Test for visual selective attention (Morris et al., 1989; Wakefield et al., 2014). A comprehensive executive function profile was drawn using scores of reasoning abilities tasks and comprised the Stroop task, Letter Fluency, Similarities and the Raven's test.

5.1.2.3 MRI Acquisition

Scans were acquired with a Philips Achieva 1.5 T scanner. Turbo Field Echo T1 images were acquired with the following parameters: voxel size: $1.1 \times 1.1 \times 0.6$ mm; repetition time 7.4 ms; echo delay time 3.4 ms; flip angle 8° ; field of view 250 mm; matrix size $256 \times 256 \times 124$. The diffusion tensor imaging scan was acquired using a single-shot echoplanar diffusion-weighted (DW) SENSE sequence with the following acquisition parameters: TR = 8.28 s, TE = 70 ms, b factor = 600 s/mm^2 , resolution = $1.67 \times 1.67 \times 3 \text{ mm}^3$, matrix = 96×96 , slice thickness = 3 mm, no gap.

5.1.2.4 Voxel-based morphometry pre-processing

A Voxel-Based Morphometry (VBM) methodology was selected to elucidate structural associations, employing a multiple regression model and controlling, in consistency

with the previous studies, for years of education, age, total intracranial volume (TIV) and normalised hippocampal ratio (defined as the product from the division between each participant's extracted normalised hippocampal volume and the total grey matter volume within the MNI space) as variables of no interest. Images were analysed with SPM12 using pre-processed MRI T1 weighted 3D structural scans. In a similar way as the previous experiments, scans were reoriented, using the brain's anterior commissure as an anatomical landmark, to accommodate scans broadly in the same space allocation, after correction for head position and regular acquisition variances. Secondly, a normalisation process was performed, with the registration of the scans into a common (as defined by the Montreal Neurological Institute, MNI) space standard template, based on a European population. Thereafter, images were segmented into grey matter, white matter and cerebrospinal fluid density maps. Following this, modulation and smoothing processes were applied in order to preserve overall volumes and homogenise voxels consistency, respectively. The processed images were smoothed with an 8mm full-width half-maximum (FWHM) Gaussian kernel.

5.1.2.5 Diffusion tensor imaging pre-processing

A sub-sample of 26 patients underwent DTI brain scanning. Images were pre-processed with FSL v5.0.9 (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). In a similar way as the previous experiment, images were computed to obtain an individual fractional anisotropy map. For more details refer to [section 4.1.2.5](#).

5.1.2.6 Statistical Analyses

Demographics, neuropsychological testing, social cognition assessments and region of interest volumes were analysed with IBM SPSS Statistics 26 software for Windows (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test for normality was performed on the variables of interest to evaluate their overall distribution. In a similar way as experiment 1, an initial structural VBM whole brain t-test analysis was performed between the present sample and a healthy control group matched for sex, age and years of education, to demonstrate that our sample is composed by participants with early-stage AD. A first correlation model was performed among the social cognition assessments global scores to establish the degree of relationship among these tasks, to justify the selected tests as reliable measurements of cognitive and affective ToM. Significant results were considered if they survived threshold of $p < 0.017$, after correction for multiple comparisons ($0.05/3$). Subsequently, non-parametric partial correlation analyses were performed between these three different social cognition assessments and all other neuropsychological outcomes. The p-value was set to $p < 0.05$ with a Bonferroni correction ($p = 0.05/n$) for multiple comparisons defined as $p = 0.003$ ($0.05/15$). All behavioural association models were controlled for age, years of education and normalised hippocampal volume ratio, in consistency with the previous experiments (refer to [section 4.1.2.6](#) for details).

Statistical volumetric associations of grey matter and ToM were obtained by performing whole-brain VBM multiple regression models. In concordance with the previous experiment, a cluster defining threshold of $p = 0.005$ was chosen ([Whitwell, 2009](#)). Significant clusters were retained if they survived a FWE corrected $p < 0.05$. Peak region coordinates were transformed from MNI space to Talairach with the Talairach client software and Lancaster transformation method ([Lancaster et al., 1997](#);

Lancaster et al., 2000). An initial analysis was performed simultaneously using the three tests measuring different components of ToM as main predictors together. Two subsequent *post-hoc* analyses were created at an uncorrected threshold of $p = 0.01$ for the Ekman test (to increase the statistical power for detection of potential significant clusters of association at a less conservative threshold) and $p = 0.0001$ uncorrected for the RMET, to isolate the clusters that displayed the strongest association with this task.

Multiple regression models were devised to test for the association of the ToM tests and fractional anisotropy of white matter diffusivity maps controlling for the same covariates mentioned before. Analysis and visualisation details can be found in [section 4.1.2.6](#).

5.1.2.7 Post-hoc volumetric grey matter region of interest analyses

As a way to provide a different approach to the results obtained in the VBM arm of this experiment, a structural brain *post-hoc* analysis was performed in selected grey matter regions resulting from the VBM outcomes and based on the literature underpinning the neural substrates of ToM (Schurz et al., 2014). Bilateral regions of interest were selected from the AAL human brain atlas (Tzourio-Mazoyer et al., 2002) and extracted from the individual grey matter tissue maps used for the VBM analyses. The individual extracted brain volumes (in mm^3) served as a continuous variable and were correlated with the three ToM neuropsychological outcomes through a non-parametric model, due to the non-normal distribution of data in this sample. A p -value of $0.05/n$ was chosen, where n was the selected number of regions ($n=14$), to account for multiple comparisons ($p < 0.004$). In consistency with the previous structural analyses, the

statistical model was controlled for age, years of education, total intracranial volume and hippocampal ratio. For further details please refer to [section 4.1.2.6](#).

Selected bilateral regions computed for this set of analyses included the anterior cingulate cortex, medial prefrontal cortex, insula, precuneus, temporo-parietal junction (which included the extracted regions of the angular gyrus, BA 39; superior temporal gyrus, BA 22 and supramarginal gyrus, BA 40), temporal poles and cerebellum.

5.1.3 Results

5.1.3.1 Demographical characteristics

Whole brain comparison of baseline structural scans of patients labelled as MCI (who had their clinical status confirmed with longitudinal follow ups for at least four years) with structural scans of matched controls (age mean 74.74, SD 6.96, $p < 0.73$ and years of education mean 9.94, SD 4.00, $p < 0.60$), showed lower grey matter volumes in bilateral middle temporal cortices, supportive of an AD aetiology, are shown in [Fig. 5.1](#). A summary of demographics of the patient sample are shown in [table 5.1](#).

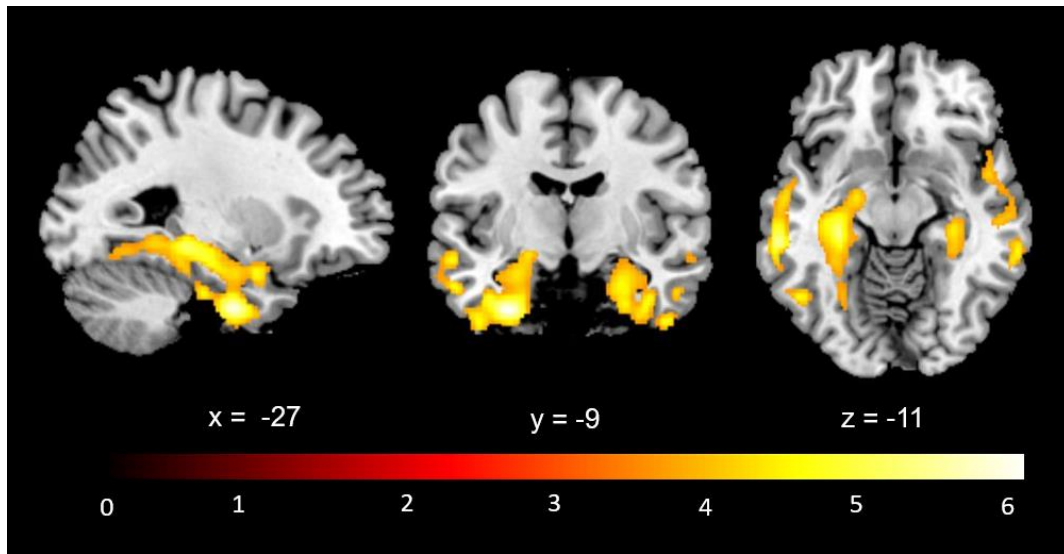


Figure 5.1. Statistical whole-brain grey matter volumetric comparison between the participant sample ($n= 46$) and a control group ($n= 46$) matched for sex, age and education shows atrophy in medial temporal lobe structures consistent with an AD aetiology.

Table 5.1. Demographic characteristics and cognitive profile of the selected sample ($n= 46$). Means (standard deviation), median and range are shown.

Variable	Early-AD ($n=46$)	Healthy Controls ($n=34$)	p-value
	Mean / (SD)	Mean / (SD)	
Demographic data			
Gender, n (%)	17 Male (37%): 29 Female (63%)	16 Male (47%): 18 Female (53%)	0.52
Age (years)	75.33 (7)	74.74 (6.96)	0.73
Years of Education	9.54 (3.86)	9.94 (4)	0.60
Neuropsychological data			
MMSE	25.95 (2.61)	28.73 (1.39)	0.001*
Letter Fluency	26.65 (12.24)	32.70 (11.23)	0.023*
Category Fluency	27.61 (12.33)	36.64 (8.89)	0.001*
Prose Memory Immediate	6.61 (3.69)	9.91 (3.30)	0.001*
Prose Memory Delayed	7.09 (5.20)	12.79 (4.68)	0.001*
Rey Figure Copy	25.27 (9.07)	32.23 (3.19)	0.001*
Rey Figure Recall	6.15 (4.87)	13.42 (5.33)	0.001*
Digit Span Forward	5.33 (0.84)	5.70 (0.90)	0.05*
Digit Span Backwards	3.66 (0.99)	3.85 (0.82)	0.20

Digit Cancellation	42.65 (9.99)	50.26 (7.14)	0.001*
Similarities	14.85 (4.66)	19.82 (4.47)	0.001*
Paired Associates Learning	8.05 (3.85)	11.63 (3.44)	0.001*
Confrontation Naming	16.58 (3.33)	18.38 (2.01)	0.004*
Token Test	31.43 (2.70)	34.12 (1.98)	0.001*
Raven's Progressive Matrices	23.67 (5.97)	28.44 (4.0)	0.001*

* Non-parametric Mann-Whitney U and Chi-squared significant results reported as $p < 0.05$.

5.1.3.2 Associations with neuropsychological functioning

The first model of correlations among the ToM scores were all associated with each other, supporting the validity of the selected tests as measures of overall ToM performance. These results are summarised in [table 5.2](#). Results from the second model of neuropsychological associations are shown in [table 5.3](#). Overall cognitive performance, measured through the MMSE, was positively correlated with the RMET ($\rho = 0.518$, $p = 0.001$) and the Ekman test ($\rho = 0.554$, $p = 0.001$). The RMET also correlated with performance on the Letter Fluency test ($\rho = 0.607$, $p = 0.001$), Category Fluency test ($\rho = 0.631$, $p = 0.001$), Digit Cancellation test ($\rho = 0.577$, $p = 0.001$), Raven's Coloured Progressive Matrices ($\rho = 0.450$, $p = 0.002$), WAIS Similarities test ($\rho = 0.491$, $p = 0.001$), the Digit Span Backward ($\rho = 0.447$, $p = 0.003$) and the Confrontation Naming test ($\rho = 0.486$, $p = 0.001$). The Ekman test was positively correlated with the Letter Fluency test ($\rho = 0.442$, $p = 0.003$), Digit Cancellation test ($\rho = 0.551$, $p = 0.001$), Digit Span Backward ($\rho = 0.439$, $p = 0.003$) and with the Token test ($\rho = 0.496$, $p = 0.001$). Finally, none of the SET scores showed significant correlations with neuropsychological performance.

Table 5.2. Non-parametric correlations of the social cognition measurements. P and rho (ρ) values are reported.

Social cognition inter-domain correlates				
	Mean/(SD)	RMET	Ekman test	SET-GS
RMET	19.89 / (5.86)	-		
Ekman Test	39.80 / (8.95)	$\rho = 0.672 / p < 0.001^*$	-	
SET – GS	13.48 / (3.55)	$\rho = 0.348 / p < 0.012^*$	$\rho = 0.493 / p < 0.001^*$	-

* Significant results are reported as $p(0.05/3) = 0.017$ after Bonferroni correction for multiple comparisons. MMSE: Mini-mental test examination; RMET: Reading the Mind in the Eyes Test; SET-GS: Story-based Empathy Task Global Score. Correlation models are controlled for age, years of education and normalised hippocampal volume ratio.

Table 5.3. Non-parametric correlations between social cognition assessments and neuropsychological measures. P and rho (ρ) values are reported.

Social cognition correlations				
	Mean / (SD)	RMET	Ekman test	SET-GS
MMSE	25.95 / (2.61)	$\rho = .518 / p = .001^*$	$\rho = .554 / p = .001^*$	$\rho = .404 / p = .007$
Letter Fluency	26.65 / (12.2)	$\rho = .607 / p = .001^*$	$\rho = .442 / p = .003^*$	$\rho = .361 / p = .017$
Category Fluency	27.61 / (12.3)	$\rho = .631 / p = .001^*$	$\rho = .301 / p = .050$	$\rho = .333 / p = .029$
Prose Memory Immediate	6.61 / (3.69)	$\rho = .193 / p = .215$	$\rho = .043 / p = .786$	$\rho = .251 / p = .105$
Prose Memory Delayed	7.09 / (5.20)	$\rho = .345 / p = .023$	$\rho = .246 / p = .112$	$\rho = .167 / p = .283$
Rey-Osterrieth complex figure Copy	25.27 / (9.07)	$\rho = .400 / p = .008$	$\rho = .197 / p = .205$	$\rho = .218 / p = .160$
Rey- Osterrieth complex figure Recall	6.15 / (4.87)	$\rho = .187 / p = .230$	$\rho = .057 / p = .715$	$\rho = .011 / p = .946$
Digit Span Forward	5.33 / (0.84)	$\rho = .299 / p = .052$	$\rho = .399 / p = .008$	$\rho = .361 / p = .017$
Digit Span Backwards	3.66 / (0.99)	$\rho = .447 / p = .003^*$	$\rho = .439 / p = .003^*$	$\rho = .425 / p = .004$
Digit Cancellation	42.65 / (9.99)	$\rho = .577 / p = .001^*$	$\rho = .551 / p = .001^*$	$\rho = .388 / p = .010$

Similarities	14.85 / (4.66)	$\rho = .491 / p = .001^*$	$\rho = .330 / p = .031$	$\rho = .245 / p = .113$
Paired Associates	8.05 / (3.85)	$\rho = .199 / p = .200$	$\rho = .077 / p = .624$	$\rho = .054 / p = .732$
Naming	16.58 / (3.33)	$\rho = .486 / p = .001^*$	$\rho = .338 / p = .027$	$\rho = .247 / p = .110$
Token	31.43 / (2.70)	$\rho = .383 / p = .011$	$\rho = .496 / p = .001^*$	$\rho = .209 / p = .178$
Raven	23.67 / (5.97)	$\rho = .450 / p = .002^*$	$\rho = .273 / p = .076$	$\rho = .299 / p = .051$

* Significant results are only reported as $p(0.05/15) < 0.003$ after Bonferroni correction for multiple comparisons. The SET test or sub-tests showed no significant correlations. MMSE: Mini-mental test examination; RMET: Reading the Mind in the Eyes Test. Correlation models are controlled for age, years of education and normalised hippocampal volume ratio.

5.1.3.3 Association with brain structure

An initial multiple regression analysis was performed using the three ToM tests as predictors and controlling for the same covariates; a positive association was found between the three tests and grey matter volume of the right side precuneus (BA 19), superior occipital gyrus (BA 19) and middle temporal gyrus (BA 39) ($k=1694$, $p=0.015$) (Table 5.4, Fig. 5.2).

Table 5.4. Grey matter clusters of concomitant significant correlation for the Ekman, RMET and SET-GS.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI Coordinates		
						x	y	z
1694	0.015	4.85	R	Precuneus	19	42	-80	38
		4.43	R	Superior occipital gyrus	19	44	-82	27
		4.36	R	Middle temporal gyrus	39	54	-72	20

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute; RMET: Reading the Mind in the Eyes test; SET-GS: Story-Based Empathy task global score.

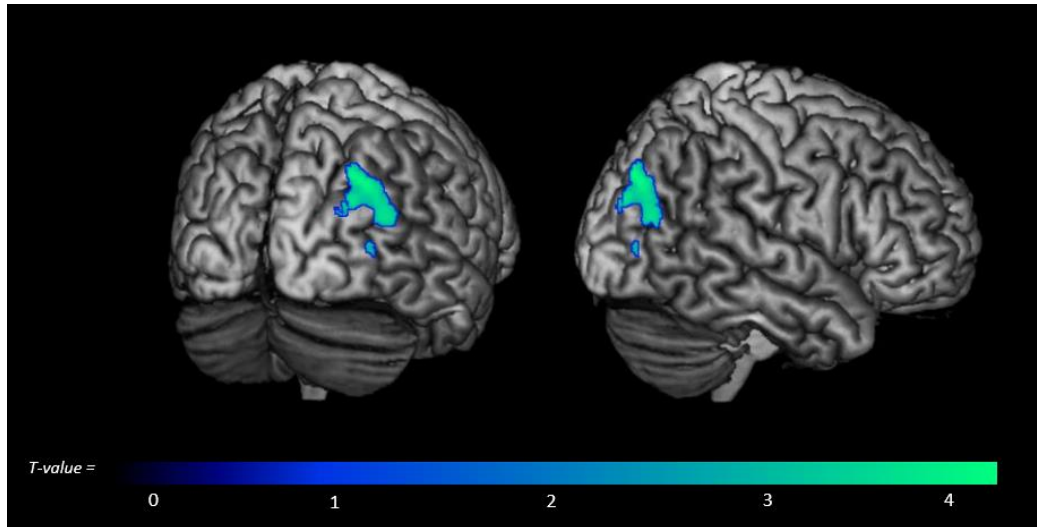


Figure 5.2. Regions that displayed changes in grey matter volume that showed a positive correlation with the Ekman, RMET and SET-GS outcomes concurrently; clusters are shown at $p < 0.05$ FWE.

Three independent multiple regression models were implemented to investigate the relation between grey matter volumes and levels of ToM performance. Results show a significant positive correlation between lower scores of the RMET and reduced grey matter volumes in the right angular gyrus (TPJ, BA 39), superior occipital gyrus (BA 19) ($k=3918$, $p=0.001$), left ACC (BA 32), left rectal gyrus (orbitofrontal cortex, BA 11), right inferior lateral frontal cortex (BA 45) ($k=6854$, $p=0.001$), right middle temporal gyrus (superior temporal sulcus, STS, BA 21) and inferior temporal gyrus (BA 20) ($k=1750$, $p=0.009$), left middle temporal (BA 22) and occipital gyri (BA 37), and left cerebellum ($k=2473$, $p=0.002$), left thalamus and caudate ($k=1554$, $p=0.013$) (**Table 5.5, Fig. 5.3**). Secondly, the total scores of the SET showed no significant results with the methodology employed; however, the Emotion Attribution (SET-EA) sub-test showed a significant association with grey matter changes, mainly in left cerebellar regions ($k=2167$, $p=0.004$), (**Table 5.6, Fig. 5.4**). The Ekman test showed a positive pattern of association nearing significance ($p < 0.056$) in the left ACC at the FWE

cluster correction level. All structural statistical models were controlled for age, years of education, total intracranial volume and normalised hippocampal ratio.

Table 5.5. Grey matter clusters of significant correlation with the RMET.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI Coordinates		
						x	y	z
6854	0.001	5.26	L	Anterior cingulate cortex	32	-20	21	-30
		5.20	R	Inferior frontal gyrus	45	58	33	4
		4.75	L	Rectal gyrus	11	-10	22	-28
1750	0.009	5.11	R	Middle temporal gyrus	21	69	-28	-21
		4.27	R	Inferior temporal gyrus	20	62	-44	-27
		3.63	R	Inferior temporal gyrus	21	63	-54	-8
3918	0.001	5.11	R	Superior occipital gyrus	19	42	-82	27
		4.89	R	Angular gyrus	39	48	-72	32
		4.66	R	Middle temporal gyrus	19	52	-80	6
2473	0.002	4.45	L	Middle temporal gyrus	22	-69	-44	0
		4.19	L	Cerebellum culmen	-	-51	-42	-33
		3.94	L	Middle occipital gyrus	37	-54	-66	-12
1554	0.013	4.14	L	Thalamus	-	-14	-33	4
		3.72	L	Caudate	-	-12	9	10

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute.

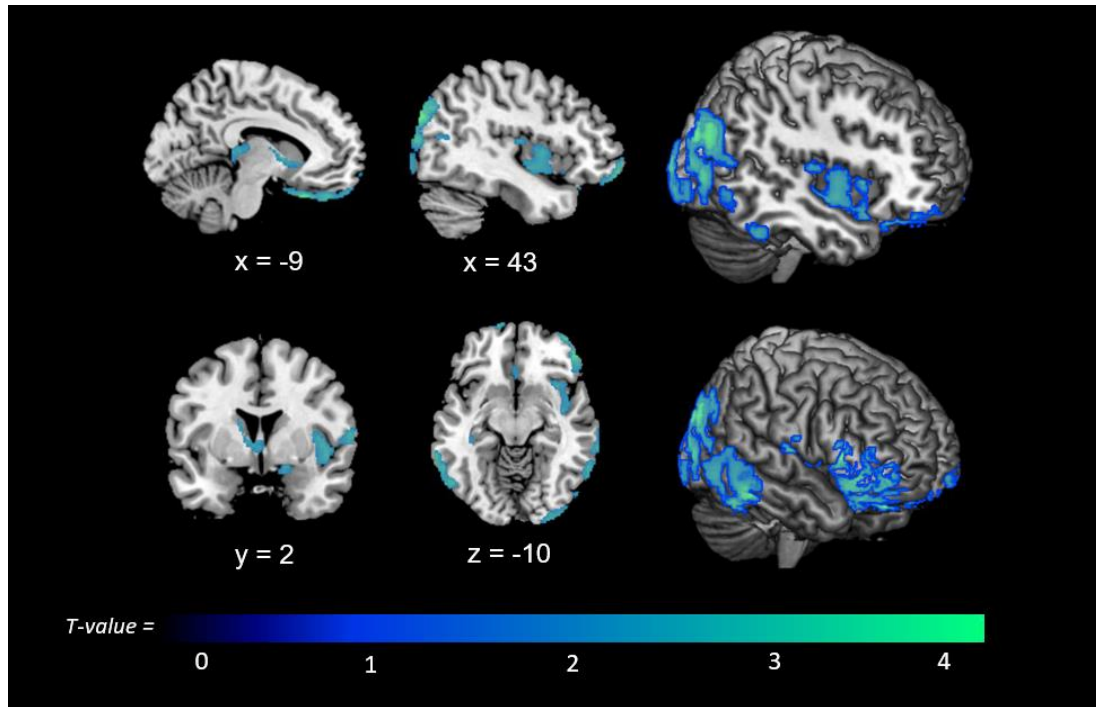


Figure 5.3. Regions that displayed changes in grey matter volume that showed a positive correlation with the RMET outcomes; clusters are shown at $p < 0.05$ FWE.

Table 5.6. Grey matter clusters of significant correlation for the SET-EA.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	MNI Coordinates		
					x	y	z
2167	0.004	5.99	L	Cerebellum: Uvula	-20	-86	-33
		3.69	L	Cerebellum: Declive	-33	-78	-28
		2.81	L	Cerebellum	-28	-75	-52

* Threshold of significance defined at $p = 0.005$. BA: Brodmann area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute; SET-EA: Story-based Empathy Task – Emotion attribution sub-scores.

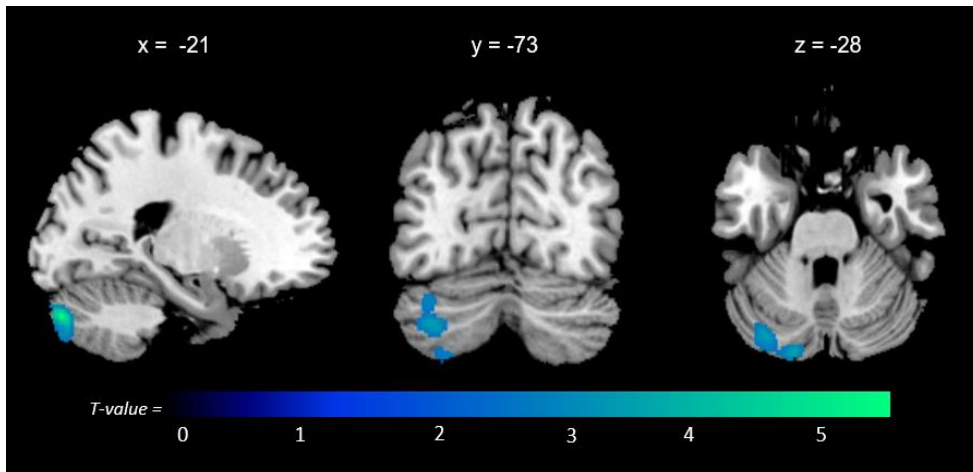


Figure 5.4. Regions that displayed changes in grey matter volume that showed a positive correlation with the SET-EA scores; clusters are shown at $p < 0.05$ FWE.

5.1.3.4 Associations with brain structural connectivity

Tract-based analysis of white matter microstructural architecture showed significant positive associations of the Ekman test and fractional anisotropy (FA) in right-sided white matter tracts, i.e., the cingulum, forceps minor, anterior thalamic radiation, inferior fronto-occipital fasciculus and superior corona radiata. Similarly, the RMET showed positive associations with the bilateral inferior fronto-occipital fasciculus, the right forceps minor and right corona radiata. Neither the SET global score nor any of its sub-tests showed significant results in TBSS analyses. Results are reported in **Table 5.7** and **Fig. 5.5**.

Table 5.7. Significant clusters of positive association between FA and the Ekman test and RMET.

Social cognition	Cluster extent	T Score	HS	Peak-based localisation	MNI Coordinates		
					x	y	z
Ekman	169	4.73	R	Forceps Minor	18	33	11
		4.47	R	Forceps Minor	18	33	8
		3.96	R	Forceps Minor	17	31	14
		3.87	R	Anterior thalamic radiation	20	31	13
		3.85	R	Forceps Minor	18	31	12
	160	3.53	R	Anterior thalamic radiation	20	25	20
		3.34	R	Cingulum	17	35	28
		3.29	R	Anterior thalamic radiation	24	27	26
		3.25	R	Anterior thalamic radiation	23	25	26
		3.23	R	Inferior fronto-occipital fasciculus	18	31	33
	95	3.01	R	Superior Corona Radiata	22	25	28
		4.15	R	Superior Corona Radiata	20	11	36
		4.12	R	Superior Corona Radiata	17	10	34
		3.46	R	Superior Corona Radiata	20	8	38
		3.42	R	Superior Corona Radiata	17	6	39
RMET	41871	3.22	R	Superior Corona Radiata	18	6	37
		3.10	R	Superior Longitudinal fasciculus	18	14	31
	7.66	R	Inferior fronto-occipital fasciculus	-37	-20	-8	
	7.24	R	Forceps Minor	18	34	10	
	6.55	R	Superior Corona Radiata	20	11	33	
	6.39	R	Inferior fronto-occipital fasciculus	37	-20	-7	
	6.38	L	Inferior fronto-occipital fasciculus	-10	37	43	
	5.76	R	Superior Corona Radiata	20	12	36	

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute.

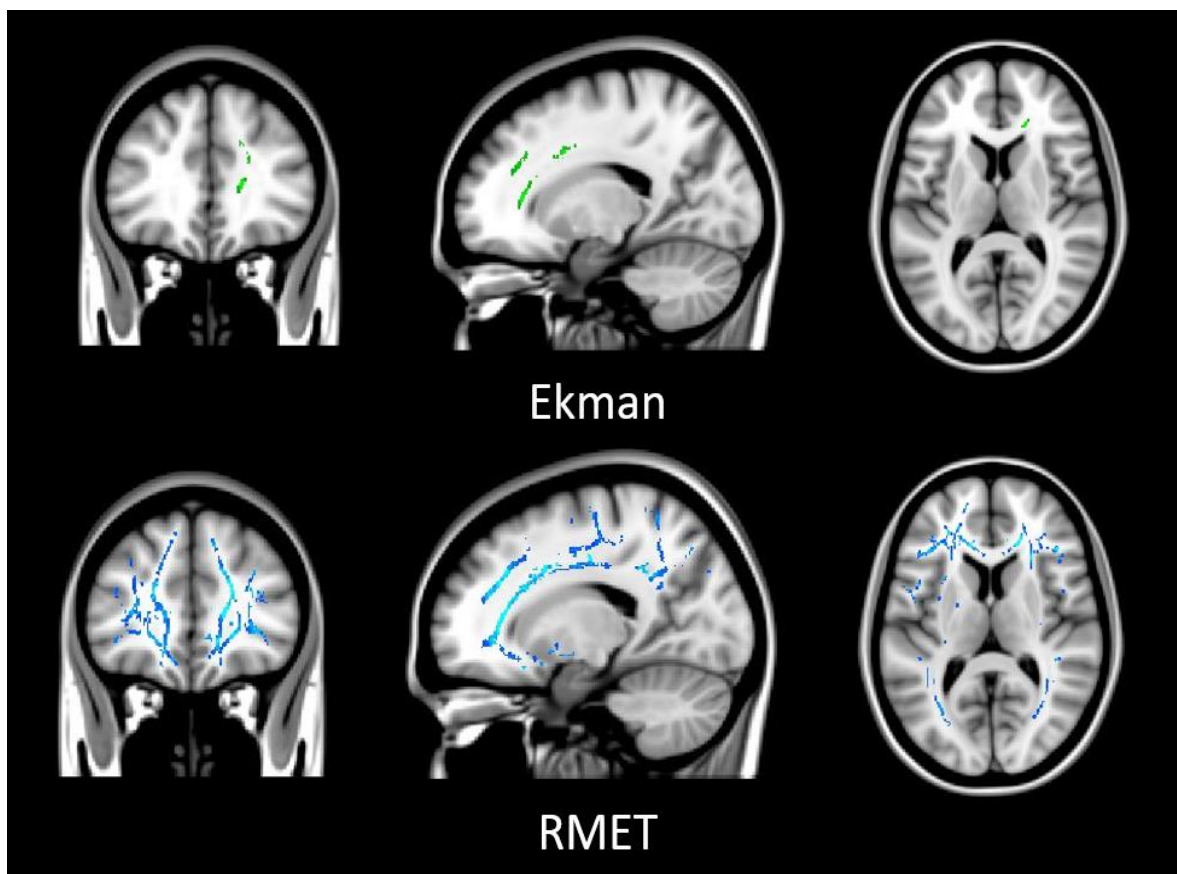


Figure 5.5. Positive correlation patterns between FA and the Ekman test and RMET scores.

5.1.3.5 Voxel-based morphometry post-hoc results

Two additional *post-hoc* analyses were performed on the Ekman Test and RMET. The results for the Ekman test are displayed in **Table 5.8** and **Fig. 5.6**. Significant positive correlations were found between this test and grey matter volume of the left anterior cingulate (BA 24) and dorsolateral prefrontal cortex (BA 9) ($k=2301$, $p=0.029$), at a less conservative threshold of $p = 0.01$. The RMET results are displayed in **Table 5.9** and **Fig. 5.7**. Positive correlations were found between this ToM test and grey matter loss in the superior occipital gyrus and temporo-parietal junction ($k=349$, $p=0.004$), after applying a more conservative threshold ($p = 0.0001$), in an attempt to isolate the most closely associated voxels with the ToM test.

Table 5.8. *Post-hoc* grey matter clusters of significant correlation for the Ekman Test.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI Coordinates		
						x	y	z
2301	0.029	3.91	L	Anterior Cingulate	24	0	22	22
		3.30	L	Middle Frontal Gyrus	9	0	42	28
		3.21	L	Anterior cingulate	24	-2	39	6

* Threshold of significance defined at $p = 0.01$. BA: Brodmann area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute.

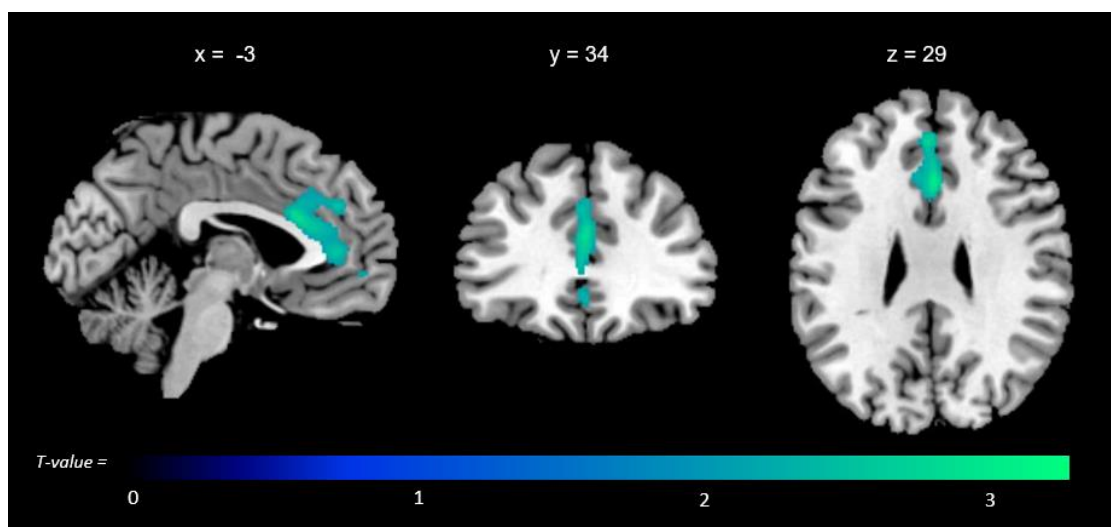


Figure 5.6. Regions that displayed a reduction of grey matter volume that showed a positive correlation with Ekman's test scores, using a less conservative threshold of significance ($p = 0.01$); clusters are shown at $p < 0.05$ FWE.

Table 5.9. *Post-hoc* grey matter clusters of significant correlation for the RMET.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI Coordinates		
						x	y	z
349	0.004	5.11	R	Superior occipital gyrus	19	42	-82	27
		4.89	R	Angular gyrus	39	48	-72	32

* Threshold of significance defined at $p = 0.0001$ uncorrected. BA: Brodmann area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute; R: Right; RMET: Reading the Mind in the Eye Test.

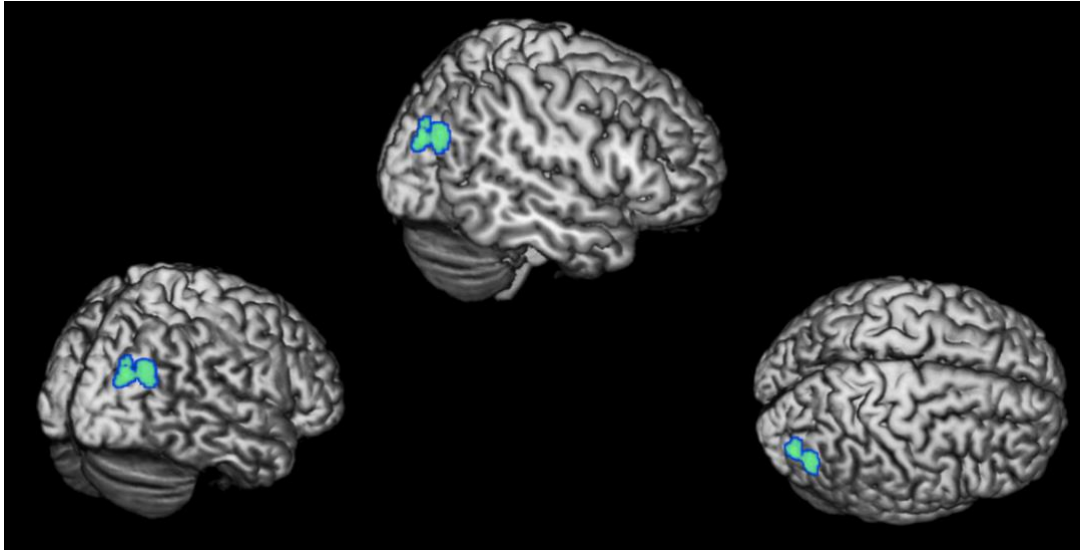


Figure 5.7. Regions that displayed a reduction of grey matter volume that showed a positive correlation with the RMET test scores, using a conservative threshold of significance; clusters are shown at $p < 0.05$ FWE.

5.1.3.6 Post-hoc region of interest grey matter volumetric results

Post-hoc analyses are summarised in **Table 5.10**. In concordance with the structural VBM model results, the region of interest analyses showed a significant positive association of the SET emotion attribution scores and the left ($\rho = 0.430 / p = 0.004$) and right ($\rho = 0.430 / p = 0.004$) cerebellar grey matter, after Bonferroni correction for multiple comparisons and accounting for age, years of education, TIV and hippocampal ratio (**Fig. 5.8**). Notably, a significant association was also found in the bilateral anterior cingulate cortex and insula for the Ekman test and the bilateral insula and left TPJ for the RMET test; however, these results did not survive correction for multiple comparison.

Table 5.10. *Post-hoc* region of interest associations between grey matter volumes extracted from selected brain areas (in mm³) and RMET, SET-EA, SET-IA, SET-GS and Ekman test scores. Mean, standard deviation and rho (ρ) values are reported.

Region of Interest	Side	Mean (SD)	Correlation values (ρ)				
			RMET	SET-EA	SET-IA	SET-GS	Ekman
ACC	L	9.03 (1.11)	0.261	0.223	0.060	0.153	0.329*
	R	9.28 (1.10)	0.276	0.236	0.082	0.182	0.322*
mPFC	L	5.76 (0.76)	0.195	0.189	0.047	0.141	0.216
	R	5.95 (0.76)	0.155	0.231	0.092	0.199	0.214
Insula	L	5.51(0.68)	0.314*	0.112	0.044	0.093	0.326*
	R	5.07 (0.67)	0.384*	0.152	0.130	0.119	0.262
Precuneus	L	8.05 (1.15)	0.150	0.075	0.148	0.071	0.049
	R	7.65(1.09)	0.192	0.141	0.200	0.186	0.139
TPJ	L	11.51 (1.45)	0.313*	0.062	-0.030	0.090	0.297
	R	15.83 (2.03)	0.272	0.177	0.135	0.216	0.201
TP	L	4.54 (0.78)	0.176	0.086	0.116	0.145	0.118
	R	5.33 (0.80)	0.300	0.154	0.089	0.137	0.162
Cerebellum	L	35.76 (3.38)	0.103	0.430**	0.079	0.339	0.071
	R	35.84 (3.44)	-0.002	0.430**	0.167	0.351	0.021

**Significant values that survived Bonferroni correction for multiple comparison at $p < 0.004$ (0.05/14)

* Significant values of $p < 0.05$ that do not survive correction for multiple comparisons

All models are controlled for age, years of education, TIV and hippocampal ratio

ACC: anterior cingulate cortex; EA: emotion attribution; GS: global score; IA: intention attribution; L: Left; mPFC: medial prefrontal cortex; R: Right; SD: standard deviation; SET: Story-based Empathy Task; TIV: total intracranial volume.

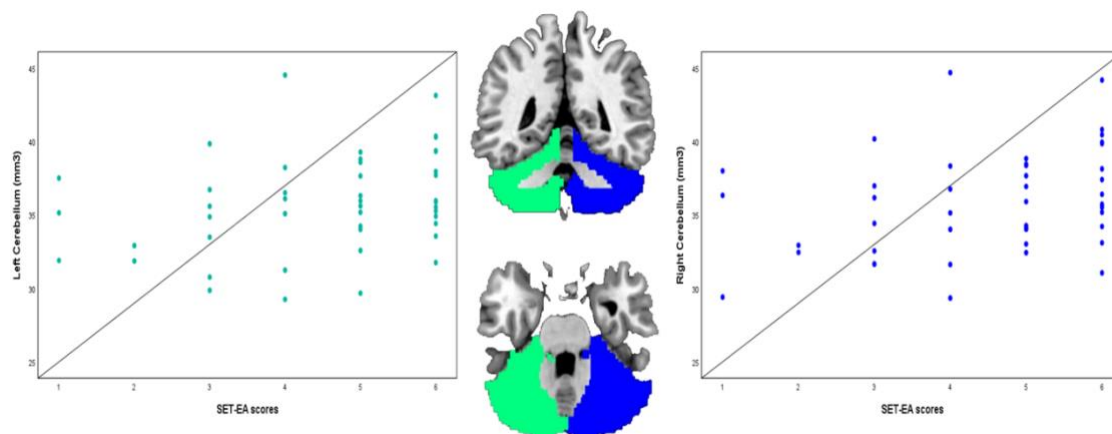


Figure 5.8. Scatterplots displaying the significant positive correlation of SET-EA scores and the extracted grey matter volumes of the left (green) and right (blue) cerebellum after controlling for multiple comparisons and covariates of no interest.

5.1.4 Discussion

The main purpose of the present study was to investigate the neuropsychological, neurovolumetric and structural white matter connectivity associations that characterise changes in affective and cognitive ToM performance in patients with early-AD, with the aim to identify the brain structures and cognitive domains that support residual social cognition performance in this patient population.

5.1.4.1 Associations between social cognition and neuropsychological profiling

Our data illustrate consistency with other cognitive studies focused on investigating the neuropsychological correlates of the ToM profile in AD patients and healthy individuals. Scores on the Ekman test and on the RMET showed parallel associations with selective attention (digit cancellation), executive functions (letter fluency), working memory (digit backwards) and overall cognition (MMSE). Individually, the Ekman test also correlated with verbal comprehension (Token test), while the RMET showed associations with proxies of semantic memory, visuospatial abilities, language and executive functions (verbal fluency and verbal and abstract reasoning). In the context of our results, measuring affective ToM through the RMET may be considered a first step of emotion recognition through facial attributes and a subsequent second step of attribution of intentions reflected in the expression centred in the eye region, explaining, therefore, the overlap between our results of this test with other tests based on emotional recognition ([Vellante et al., 2013](#)). Although there is substantial literature that has defined this tool as a reliable measure of ToM abilities, some authors have proposed that it could be more suited to assess the first component of social perception ([Oakley et al., 2016](#)). Therefore, a consolidation point in the present data states that

the Ekman test and the RMET can be considered good proxy measures of affective ToM, which relies on the summation of both, emotion recognition abilities and attribution of affective mental states (Valle et al., 2015).

Social cognition functionality is significantly influenced by overall cognitive alterations. Both social cognitive scores (Ekman-RMET) demonstrated associations with the MMSE in parallel with other neurodegenerative studies that have also found this link in affective recognition (Phillips et al., 2010; Torres et al., 2015), ToM (Cuerva et al., 2001) or both (Freedman et al., 2013). This association supports the most accepted premise stating that social cognition in AD is sustained primarily by cognition and not by an independent social network (Shany-Ur et al., 2012; Dodich et al., 2016; Ramanan et al., 2017; Christidi et al., 2018; Torres et al., 2019). Reason for which we actively controlled the influence of disease severity with proxies of hippocampal integrity, to isolate the influence of cognitive decline in our models, an intrinsic parameter that interacts negatively with social cognition performance.

Our results also shed light on the association of social cognition (Ekman-RMET) with other signatures of cognition, such as selective attention. Selective attention is central to social cognition, as it supports decision-making, elicited by processing of verbal information that is typical of social interactions and by visual recognition and labelling of facial expressions that is central to the activation of affective connotations (Hot et al., 2013; Phillips et al., 2010; Garcia-Rodriguez et al., 2012; Circelli et al., 2013). Therefore, selective attention modulates responses arising from mental representations, including those of others (Leslie, Friedman & German, 2004). Moreover, memory decline in AD may dictate a need for increased supply of attentional and executive resources that would have to be channelled towards independent

cognitive processes occurring concomitantly during ToM tasks ([Garcia-Rodriguez et al., 2012](#); [Laisney et al., 2013](#)).

Executive functions have been considered to be the most closely associated cognitive parameter related to detrimental changes in ToM in the AD population ([Ramanan et al., 2017](#); [Lucena et al., 2020](#)). The similarities test can be considered as a proxy of verbal reasoning and conceptualisation, intrinsic abilities that are supported by executive processes ([Woo et al., 2010](#)). In this context, verbal reasoning has been linked with affective ToM in healthy subjects ([Miguel et al., 2017](#)) and in patients with autism (integrated into a verbal IQ composite score) ([Golan et al., 2006](#)). In the AD population, studies have found associations of executive verbal reasoning with ToM scores, specifically when solving complex tasks that rely on understanding false beliefs ([Koff et al., 2004](#); [Takenoshita et al., 2018](#)). An overall executive decline may contribute to verbal reasoning deficits in AD; specifically, language and verbal processing are prerequisite functions that identify and label adequately the emotional states of others ([Miguel et al., 2017](#)). Similarly, abstract reasoning has also been used as a bridging concept of executive processing in AD ([Ambra et al., 2016](#)). Conjoined functions derived from reasoning and attention may modulate internal perceptual thoughts to create further social inferential representations that could bind self-awareness ([Demetriou et al., 2018](#)).

In parallel with our study, affective ToM has already been shown to be associated with performance on verbal fluency tests in non-clinical young and elder populations ([Saltzman et al., 2000](#); [Ahmed & Stephen, 2011](#)) and in individuals with AD ([Laisney et al., 2013](#); [Yildirim et al., 2020](#)). Fluency tests have been commonly defined as measures of executive functioning and found to be predictive of ToM performance ([Chainay & Gaubert, 2020](#); [Yildirim et al., 2020](#)), but these tests also have

intrinsic properties of verbal skills, overlapping with both domains ([Henry & Crawford, 2004](#)). Notably, a behavioural study based on AD patients' performance displayed significant deficiencies in ToM tests, but also in tasks related to abstract reasoning, verbal reasoning, language and verbal memory ([Cuerva et al., 2001](#)). Our data also showed that language performance was associated with performance on social cognition tests through the naming test. At a first glance, this could reflect the usage of verbal skills and language to understand and answer the items in the ToM tests ([Olderbak et al., 2015](#)). On the other hand, semantic memory (as measured by the semantic fluency and similarities tests) in ToM mechanisms has been proposed to be essential for retrieval of conceptual representations of unknown characters, to allow proper recognition and attribution of mental states within an unfamiliar environment ([Ciaramelli, Bernardi & Moscovitch, 2013](#)). On this note, a decline of cognitive and affective ToM has been already evidenced in semantic dementia, a condition characterised by a progressive degenerative impoverishment of semantic resources ([Duval et al., 2012](#)).

The behavioural associations of language, verbal semantic memory, phonemic and verbal reasoning with social cognition in our study may indicate a fundamental construction of the brain social mechanisms as early substrates of communication evidenced early on in childhood cognitive development ([Miller, 2006](#)). These results come as no surprise, as the inherent nature of communication itself is essentially intertwined with the social need to interact with others for the benefit of society and culture ([Falk & Bassett, 2017](#)). The close relation between recognising emotional attributes (a proxy of non-verbal communication) and verbal communication could underlie the starting point of disconnection between the interaction of the individual with the social environment. Therefore, a patient's verbal and non-verbal deterioration

may manifest initially with miscommunication features among their caregivers that might lead to progressive increase in caregiver burden and additional decline of a patient's social neurocognitive domain ([Martinez et al., 2018](#)).

Lastly, the cognitive and affective components of social cognition have been found to be impaired in early AD ([Teng, Lu & Cummings, 2007](#); [Spoletini et al., 2008](#); [Poletti & Bonuccelli, 2013](#); [Bora & Yener, 2017](#); [Yildirim et al., 2020](#)); however, the specific aims of the present study intended to uncover subtle changes associated with social cognitive performance among the behavioural domains most commonly affected in this type of patients, independently of the presence or absence of true ToM impairment in this sample.

5.1.4.2 Association between social cognition and brain structure

The structural voxel-based neurovolumetric arm of this study showed a positive association of cognitive and affective ToM scores with volumes in the left ACC (BA 32), orbitofrontal cortex (BA 11), middle occipital gyrus (BA 37), cerebellum, thalamus and caudate; right TPJ (BA39), inferior lateral frontal cortex (BA 45) and superior occipital gyrus (BA 19); and bilateral superior temporal sulcus (STS) (BA 21). Remarkably, our data displayed a substantial overlap with the neuroanatomical ToM core regions already evidenced in the healthy population ([Abu-Akel & Shamay-Tsoory, 2011](#); [Frith & Frith, 2012](#); [Schurz et al., 2014](#), [Van Overwalle et al., 2014](#)).

Firstly, the left ACC was associated with scores on both the RMET and Ekman test (*post-hoc* analysis). This region has shown higher functional activation during ToM task performance in an MCI population ([Baglio et al., 2012](#)). At this stage, the ACC could serve as a compensatory area supporting complex cognitive processes ([Duncan](#)

& Owen, 2000), including ToM mechanisms. In fact, the ACC has been shown to be spared in AD patients that displayed higher levels of cognitive reserve (Serra et al., 2011). Furthermore, this region has also been established to be linked to self-awareness deterioration in early-AD (Amanzio et al., 2011; Mondragon, Maurits & De Deyn, 2019) and might be a supporting structure that modules self-other brain representations, in which a two-point disconnection could provide cognitive insights of conscious awareness in neurodegeneration (Amodio & Frith, 2006). In the context of other neurodegenerative diseases, both the ACC and fronto-insular cortices were found to act as key regions associated with affective ToM in patients with amyotrophic lateral sclerosis (Cerami et al., 2014a). This could translate into possible similar mechanisms of social neural degeneration based on limbic prefrontal networks, impoverishment of which appears to characterise ToM deterioration across different neurodegenerative conditions.

In addition to the left ACC (BA24), a *post-hoc* voxel-based analysis in the present study showed an additional significant association of affective ToM with the adjacent dorsal mPFC (BA9). Similarly, Hornak and colleagues (2003) described the presence of significant affective alterations that hampered profoundly the activities of daily life, in patients that underwent unilateral surgical excision specifically of the medial BA9/ACC. A strong involvement of the prefrontal cortex in ToM has been evidenced in other neurodegenerative dementias, such as dementia with Lewy bodies (Heitz et al., 2016) and behavioural variant frontotemporal dementia (Cerami et al., 2014b; Brioschi Guevara et al., 2015). In the context of early-AD, a volumetric quantification study performed by Sapey-Triomphe and collaborators (2015) showed also a positive correlation between the volumes of the left ACC, in addition to the right medial orbital cortex, with proxies of affective identification. Lastly, Pernigo et al. (2015)

found the mPFC closely associated with proxies of emotional discrimination in MCI patients. Regions of the mPFC/ACC (BA9/32) have been established to provide vital inputs in ToM processing by sustaining regions that mediate executive-related reasoning during the assimilation of other's beliefs (Gallagher & Frith, 2003; Schurz et al., 2014). The current theoretical construct of the neural basis of the dyad ToM domains has proposed that the dorsolateral and ventromedial PFC are the frontal systems that enable cognitive and affective ToM, respectively (Poletti, Enrici, & Adenzato, 2012).

Our data supported the contribution of the TPJ to ToM in early AD. This demonstrated a high consistency with the current social neuroscience literature, as the right TPJ has been postulated to be a core structure for ToM abilities (Saxe & Wexler, 2005; Perner et al., 2006; Aichhorn et al., 2009; Schurz et al., 2014) and more specifically right-lateralised (Krall et al., 2016). The integrity of the right TPJ, a key node of the default mode network (DMN), seemed to predict performance on ToM tasks in relation to ageing (Hughes et al., 2019). In neurodegeneration, Dermody and collaborators (2016) showed that grey matter reduction in the left TPJ in AD patients was predictive of their performance when engaged in perspective-taking empathy tasks. Likewise, Kumfor and colleagues (2017) found similar fronto-temporo-parietal structural results, including clusters within the left TPJ, when evaluating emotional processing in a voxel-based morphometry study in AD patients. Reliably, existing evidence of the metabolic substrates of ToM in AD demonstrated selective hypometabolism in the TPJ (left-lateralised) in contrast to brain metabolism of subjects with frontotemporal dementia (Le Bouc et al., 2012). In the present study, an additional *post-hoc* analysis isolated the right TPJ and superior occipital gyrus as the areas that displayed the strongest correlation with ToM. Moreover, hypometabolism of the TPJ in

amnesic MCI could highlight a supplementary metabolic signature of brain degeneration (Meyer et al., 2019). Although it has been established that the initial neural neurodegeneration in AD involves structures comprising or closely connected to the DMN, a functional study found that hippocampal volumes could be predictive factors of DMN integrity in the right TPJ in healthy, MCI and AD populations (De Marco, Ourselin & Venneri, 2019). Lastly, the TPJ has also been remarked to act along with an attentional network in which connections with the PFC could mediate salient stimuli (Corbetta, Patel & Shulman, 2008). Finally, a neurocognitive and structural integrative approach of our results may rely on the TPJ additional support to general verbal abilities, in which ToM performance could differ according to culture and language differences (Perner & Aichhorn, 2008). Moreover, this region also contributes to cognitive attention, visuospatial abilities and executive reasoning, implying the stated strong involvement of ToM in overall cognition (Seghier, 2013).

In line with our data, both the TPJ and the PFC have been proposed as the two most vital regions for ToM (Saxe & Wexler, 2005; Schurz et al., 2014). This dynamic interaction may be explained with the mPFC providing an initial inhibition of self-generated beliefs, to adopt others perspective; then, the TPJ provides cognitive reasoning that integrates external perceptions into inferential processes and belief recognition (Saxe & Kanwisher, 2003; Le Bouc et al., 2012). In this setting, patients with specific frontal lobe and temporo-parietal lesions have been shown to underperform substantially during social cognition and ToM tasks (Rowe et al., 2001; Samson et al., 2004). The strong cognitive and neural overlap of executive functions and ToM in this study denotes the connection between these processes and their probable interplay within their underlying fronto-parietal structures.

Associations with the occipital cortex have been evidenced during ToM performance ([Otti, Wohlschlaeger & Noll-Hussong, 2015](#)) and it may reflect initially on the visual nature of the ToM tasks that, based on our population of interest, did not put excessive demands on memory or extensive verbal outlines; this could also explain partially the behavioural association of ToM with visuospatial abilities already found in dementia ([Heitz et al., 2016](#)) and in our results. Visual attributes are an essential trait to initiate ToM, as recognition of human affective states is inherently linked to visual perceptual capacities.

Subcortical bilateral volumetric associations of the cerebellum and affective ToM (SET) arose from both the VBM and *post-hoc* volumetric analysis. These results provide insights into the cumulative research that demonstrates the substantial contribution of cerebellar cortices to the social cognition domain ([Schmahmann, 2019](#)) and to executive functioning ([Stoodley & Schmahmann, 2009](#)), a contribution that seems to be crucial for high-level abstraction, mirrored-based motor tasks and executive processing ([Van Overwalle et al., 2014](#)). In AD patients, a VBM study linked the bilateral cerebellum to ToM functions, as a structure that supports cognitive coordination when alternating self-other mental states concurrently ([Synn et al., 2018](#)). This structure was also found to be activated bilaterally in a task-based functional study in aMCI patients, indicating that this is a reliable structure implicated with decline of a social cognition network even in the prodromal stage of the disease ([Baglio et al., 2012](#)). Overall, this finding only highlights the heavy involvement of executive functions and supporting regions of this function in the syndromic characterisation that relates to a declining ToM.

Additional subcortical contributions to ToM in our data (caudate and thalamus) have been pointed out also in the existing literature ([Abu-Akel & Shamay-Tsoory,](#)

2011). Activation of the caudate nucleus was evidenced in healthy participants when performing tasks related to emotional attribution of positive and negative affective states (Carretié et al., 2009). Patients displaying lesions in the caudate have shown alterations of affective and cognitive ToM as symptomatic manifestations consequence of a disconnection between frontal-subcortical networks (Kemp et al., 2012). Lastly, patients with thalamic stroke have displayed ToM deficits, suggesting the contribution of this structure to the mentalising network (Wilkos et al., 2015).

5.1.4.3 Associations between social cognition and white matter tracts

Our study is the first of its kind that explored white matter tract changes associated with social cognition and ToM in early-AD. In this context, positive association findings from white matter integrity analyses associated with social cognition performance showed a significant involvement majorly of right-sided pathways. Specifically, better performance on the Ekman-RMET tests was associated with higher fractional anisotropy (FA) in the inferior fronto-occipital fasciculus (IFOF), corpus callosum (forceps minor) and superior corona radiata. Additionally, the Ekman test also showed associations with the anterior thalamic radiation, superior fronto-occipital fasciculus and cingulum. In consistency with our findings, it has been demonstrated that the IFOF has a particular role in facial recognition and affective facial processing (Unger et al., 2016; Wang et al., 2018). The cingulum, including the corpus callosum, is considered a fundamental structure within a mentalising network as its axonal pathways construct the skeletal architecture of the default mode network (van den Heuvel et al., 2008). Although cingulum findings were associated with the Ekman test, this provides supporting evidence of the cingulate gyrus displaying higher involvement of social

perception and face recognition skills in mentalising abilities within an integral interconnected large-scale social network. In relation to AD and disease, reduced fractional anisotropy in the corona radiata, thalamic radiation, superior-inferior longitudinal fasciculus and cingulum has been found in patients with AD compared to controls (Mayo et al., 2017). Likewise, lower FA in the corpus callosum, corona radiata and thalamic radiation has also been found in patients with schizophrenia (Peng et al., 2020), while reduced FA was found in the left cingulum and superior longitudinal fasciculus in relation to ToM performance in patients presenting with first-episode psychosis (Kim et al., 2021). The anterior thalamic radiation, associated with affective recognition in our study, has been associated with reduced fractional anisotropy in emotion recognition impairment in patients with frontotemporal dementia (Downey et al., 2015). It has been widely demonstrated that reduced FA in AD involves white matter pathways (Sexton et al., 2011; Acosta-Cabronero & Nestor, 2014; Mayo et al., 2017). However, our patients' performance on social cognitive tasks was found to be associated with increased FA in structures commonly affected by AD and with social cognition. These findings are supportive of the premise that compensatory mechanisms might come into play to counteract social cognition decline in the early AD continuum, with increased axonal resource diffusivity along interconnected social networks.

Lastly, it has been proposed that in a similar way as patients with neurodegenerative diseases display a type of cognitive reserve derived from education and profession, a social reserve might help mitigate the effects of damage to the brain-social networks. Therefore, humans, characterised as closely socially engaged creatures, could show less impairment of the social neurocognitive domain until the later stages of neurodegeneration (Fliss et al., 2016). This social reserve may be

supported and nurtured by executive resources that could provide the foundations to support the strong relation between executive functions and ToM detected in our data and in the literature based on social neuroscience.

5.2 Experiment 4 | Resting-state functional brain network connectivity correlates of social cognition and Theory of Mind in early Alzheimer's disease

5.2.1 Introduction

A wide range of neurological disorders will display, to a variable extent, a detrimental impact on the neurocognitive domain known as social cognition that further extends to subdomains such as affective recognition or Theory of Mind (ToM). Progressive disruptions of a network dedicated to the attribution of mental states to others may be explained through pathophysiological alterations that depend on genetic abnormalities, synaptic degeneration and neuroanatomical atrophy ([Abu-Akel & Shamay-Tsoory, 2011](#)). Regions that delineate the proposed “Theory of mind network” have been consistently found in functional MRI (fMRI) studies based on a healthy population in which the prefrontal cortex (PFC), temporal regions, temporoparietal junction (TPJ) and subcortical cerebellar-striatal functional inputs seem to be the most closely associated to this network's performance during social cognition and ToM tasks in healthy individuals ([Schurz et al., 2014](#), [Saxe & Wexler, 2005](#); [Van Overwalle et al., 2014](#)), and extending to dementia patients ([Rankin, 2020](#)). Demarcation of cognitive and affective ToM neural components have proposed a partial dissociation of independent regions sub-serving each function ([Abu-Akel & Shamay-Tsoory, 2011](#)). Specifically, the TPJ evaluates self-other representations that are modulated by the cingulate cortex and subcortical structures that define the affective or cognitive components of ToM from an overlapping communicating structure harboured within the medial PFC to the inferior lateral frontal cortex or the dorsal PFC, corresponding to affective or cognitive social processing ([Abu-Akel & Shamay-Tsoory, 2011](#)). A

broader perspective into social neuroscience has proposed the interaction of three independent functional networks for social cognition processing named the facial perception network, the mirror network and the mentalising network (Yang et al., 2015a).

An integrative panorama of the functional substrates of ToM sheds light in dynamic multiple network intercommunications (Thye et al., 2018), characterised mainly by the contributions of the default mode network (DMN) (Schilbach et al., 2008; Mars et al., 2012; Li, Mai & Liu, 2014; Rankin, 2020) and supported by an executive controlling network that may confer resources to cognitive processes controlled by both networks when engaging in affective processing (Wade et al., 2018). The integrity of the DMN has been shown to have a strong intrinsic relation to ToM in ageing (Hughes et al., 2019). The DMN comprises functional topological interconnected areas such as the posterior cingulate cortex (PCC), precuneus, ventral and dorsal medial prefrontal cortex, inferior lateral parietal cortex and medial temporal regions (Schurz et al., 2014) and extending to subcortical areas such as the cerebellum (Alves et al., 2019). This large-scale network is made of smaller interconnected arrangements that are particularly active during a task-free or resting state. The functional physiology of the DMN has shown to be responsible for the modulation of complex brain functions including: 1) self-referential processes (past autobiographical acquisition, self-prospection of future scenarios and self-projective simulation states), 2) social-cognitive skills, including cognitive and affective ToM, and 3) undefined thoughts that are not associated with response to an external demand (mind-wandering) (Mével et al., 2011; Mars et al., 2012; Buckner & DiNicola, 2019). Early dysfunction of this network is a distinguishable pathophysiological hallmark of MCI and early-AD individuals (Greicius et al., 2004; Zhang et al., 2012; Badhwar et al., 2017). Resting-

state fMRI evidence has found decreased connectivity in the posterior segment of the DMN network that includes the posterior cingulate cortex/precuneus. In a compensatory attempt, increased connectivity of the anterior frontal DMN and salience network intends to support progressive systemic brain-failure (Vemuri, Jones & Jack, 2012). Notably, these findings seem to be directly linked to the deposition of abnormal proteins (amyloid, at the initial stage) related to the characteristic aetiopathological cascade of AD (Sperling et al., 2009; Koch et al., 2015). As a result, insights into disease progression show compensatory hyper-connected networks that parallel the typical pattern of disconnection across particular components of the DMN (Bai et al., 2011). Therefore, it is sensible to hypothesize that a clear disruption of this network, highly involved in the AD spectrum, could accentuate the presence of early ToM and social cognitive deficits that may occur concomitantly (De Marco, Ourselin & Venneri, 2019). In fact, AD patients that failed complex first-order false belief ToM tests showed lower brain blood flow in the posterior cingulate in a SPECT study (Takenoshita et al., 2020). In the context of early-AD, task-based fMRI research found activation of networks located in fronto-temporal and subcortical (cerebellar) regions, a finding that has shed light into the functional neural substrates of ToM (Baglio et al., 2012).

Possibly, the later onset of symptomatic manifestations that accompany ToM decay in AD might be explained as the result of positive effects conferred by cognitive reserve (Castelli & Baglio, 2016), in which social processing might be sustained by other types of cognitive (executive/attentional) resources through the upregulation of networks interconnected to the DMN. Another possibility would be that performance is sustained by a completely different type of neural resources that prevents social skills decline and that could act as a social reserve, acquired through an individual's lifespan (Fliss et al. 2016). Furthermore, it is logical to hypothesize that accompanying

supportive intercommunication of other large-scale networks, such as the fronto-parietal (central executive) network or salience network, might be able to handle complex cognitive outcomes in the context of a degenerating DMN, and provide insights on an explanation to the robust association of cognitive and affective ToM with executive functions in behavioural studies ([Ramanan et al., 2017](#)). Moreover, it has also been suggested that there is an interplay between the executive fronto-parietal network and social perspective-alternation processes ([Corbetta, Patel & Shulman, 2008](#)). Similarly, the salience network has been said to provide valuable computing resources to social mechanisms, as it mediates critical behavioural performance based on attention and cognitive control, derived from recurrent sensorial input ([Menon & Uddin, 2010](#)). Neural hubs within these triad large-scale networks (fronto-parietal network, salience and DMN) seem to overlap considerably in the so-called “ToM or mentalising network”.

Individually, clustering functional cores from large-scale networks indicate that the posterior cingulate cortex (PCC), precuneus, dorsal and ventral mPFC, inferior parietal cortex and medial temporal lobe structures are enclosed within the DMN, displaying the highest overlay of subsystems in the global ToM and mentalising system ([Buckner, Andrews-Hanna & Schacter, 2008](#); [Spreng, Mar & Kim, 2009](#)). Likewise, the central executive system (fronto-parietal network) includes the dorsolateral PFC, posterior parietal cortex and subcortical areas, and provides neural computing resources such as working memory, decision-making, cognitive control and attentional resources and has been shown to be closely related to the functionality of the DMN as a supporting system, also within a general mentalising network ([Sridharan, Levitin & Menon, 2008](#); [Menon, 2011](#)). Lastly, the anterior cingulate cortex (ACC) and insular structures seem to control processes involving salient stimuli that confer cognitive

regulation in which there is also significant intersection with ToM processing ([Seeley et al., 2007](#)). The intercommunication of these conformational triad networks seems to show that overall cognition, which also incorporates ToM, relies on the synergistic activity between internal self-processing mediated by the DMN and externally-driven stimuli mediated by the executive FPN, where both networks are fundamentally controlled by the regulatory outputs of the salience network ([Chiong et al., 2013](#)).

Lack of resting-state functional connectivity studies to uncover the functional network correlates of ToM in AD provides novelty foundations for this study. The specific aims of the present experiments were to investigate the brain functional connectivity correlates of core regions serving ToM through two methodological approaches. Firstly, a large-scale network independent component analysis (ICA) was performed with the objective to provide an understanding of the overall role of large-scale network dynamics within or outside the correlated components of these systems related to social cognition and ToM. Subsequently, seed-based analyses were devised to elucidate the specific connectivity patterns that derive from the most commonly known functional hubs associated with ToM performance, with the intention to investigate patterns of functional connectivity related to changes in social cognitive skills in patients with early-AD. These experiments were not designed to evidence the degree of true decline of ToM in the different stages of the disease, as it has been previously stated that AD individuals in the early stages may not display substantial detrimental changes in social cognition. Our objectives were focused on elucidating the neural substrates and connectivity patterns derived from subtle changes of the different domains that support social cognition performance. Therefore, correlational models on a pooled sample of diagnosed prodromal and mild AD patients were selected as a way to provide insights on the functional alterations in ToM skills

occurring in early-AD. Therefore, in concordance with the provided evidence, our hypothesis states that patients with early AD will display functional connectivity alterations in core ToM regions defined by the social neuroscience literature and in consistency with the structural results from experiment 3. Furthermore, we propose that detrimental changes of social cognition and ToM are supported by multi-systemic dynamic interplays of regional and large-scale networks in which a distinctive pattern of intercommunication may explain the overall performance of social cognition and ToM in this population at an early stage of neurodegeneration. To our knowledge, this is the first resting-state multi-modal functional study to be carried out in an AD population in relation to the functional network underpinning social cognition and ToM skills.

5.2.2 Methods

5.2.2.1 Participants

The sample consisted of the same 46 early AD patients recruited and portrayed in experiment 3. For a more comprehensive description of the sample see [section 5.1.2.1](#). Each patient completed a resting-state functional MRI scan. Inclusion and exclusion criteria were applied in the same way as in [section 5.1.2.1](#). Ethical approval was granted by the Joint Ethics Committee of the Health Authority Venice 12 and the IRCCS Fondazione Ospedale San Camillo (Protocol number 2014.08). All patients provided written consent to participate in this study.

Data processing and further analysis was developed in a replicated method as the functional MRI study in experiment 2 (see [section 4.2.2.3](#) and [4.2.2.4](#) for more details). Statistical models were performed through independent component analyses (ICA)

and seed-based fMRI connectivity experimental models to discover subtle functional connectivity patterns associated with ToM variance in performance across the sample.

5.2.2.2 Theory of Mind assessment

In consistency with experiment 3, the present study used the same three tests of emotion recognition and cognitive and affective ToM. As stated before, the emotion recognition test also served as a proxy of affective ToM serving as a reflection of the first phase performance of ToM ability when identifying emotional features that will allow the assignment of affective attributions. For more details on the social neurocognitive battery please refer to [section 5.1.2.2](#).

5.2.2.3 fMRI image acquisition

Neuroimaging acquisition and analysis followed the shared protocol set by the VPH-DARE@IT consortium for the MRI scanners (<http://www.vph-dare.eu/index.php/project/work-packages/WP2>). Resting-state functional MRI scans were also acquired for each participant with a Philips Achieva 1.5 T. All scans had at least 200 volumes and each volume consisted of 20 slices acquired axially and contiguously, in an ascending order. The parameters of acquisition were: 3.28 × 3.28 × 6.00 mm³ voxel dimension, 64 × 64 matrix size, 230 mm field of view, 2 s TR, 50 ms TE and 90° flip angle.

5.2.2.4 Resting-state functional MRI analysis

Images were pre-processed following an in-house pipeline procedure (Postema et al., 2019). Details for each step of data processing can be found in section 4.2.2.4.

5.2.2.5 Independent Component Analysis

Pre-processed resting-state fMRI images were used in an Independent Component Analysis (ICA) to extract functional connectivity patterns reflecting large-scale networks (Beckmann et al., 2005). The GIFT toolbox (v1.3i; mialab.mrn.org/software/gift) within the SPM software was used to carry out the ICA. An Infomax algorithm was chosen with the number of components to be extracted set at 20, as a reliable number that includes the fundamental resting-state human connectivity networks (Wang & Li, 2015). This data-driven method is based on a computational deconstruction of conjoined multivariate MRI signals (BOLD activity) to recreate independent non-correlated spatial maps of coordinated neural activity. Connectivity maps are displayed as z scores that result from the association between the brain's network mean-time and single-voxel time-series (Calhoun et al., 2001).

Second-level inferential analyses were performed with the manually selected (hypothesis-driven) independent component maps for each of the five extracted networks of interest, namely: the anterior Default Mode Network (aDMN); posterior Default Mode Network (pDMN); left Fronto-Parietal Network (l-FPN), right Fronto-Parietal Network (r-FPN), also known as Executive Control Networks; and salience Network. Connectivity maps were analysed independently in relation to social cognition total scores, as a way to test the associations between the behavioural outcomes and resting-state connectivity indices at the voxel level.

5.2.2.6 ICA Statistical Analysis

Multiple regression analyses were performed at the group level. By this means, each of the five resting-state network maps were correlated independently with the Ekman test, RMET and SET scores. The selected threshold for significance was set at $p=0.005$ uncorrected. Significant clusters were only chosen if they survived a multiple comparison FWE corrected threshold set to $p < 0.05$. In consistency with the previous structural and behavioural statistical analyses (see [section 4.1.2.6](#)), statistical models were controlled for age, years of education, TIV and hippocampal ratio as variables of no interest. MNI-based peak regions were identified and transformed into Talairach coordinates for identification through the Talairach Client version 2.4.3 (<http://www.talairach.org/client.html>) ([Lancaster et al., 2000](#)).

5.2.2.7 Seed extraction

ROI were devised to investigate the relation between a targeted extracted signal from an *a priori* selected brain region (seed) and the rest of the brain in relation to its connection with ToM outcomes. Cytoarchitectonic bilateral anatomical seed structures were extracted through the WFU PickAtlas toolbox (<https://www.nitrc.org>) ([Maldjian et al., 2003](#)). A second step was applied in order to extract the time courses from the previously obtained ROIs at the individual level, through the use of the SPM-based MarsBar toolbox (<http://marsbar.sourceforge.net/>) ([Brett et al., 2002](#)).

First level analysis was performed in the same way as described in experiment 2, [section 4.2.2.7](#). This step accounts for the decrease in signal-to-noise ratio by correcting for 18 parameters including motion and other intracranial tissues in close association with the grey matter. The rationale for seed region selection and extraction

was based on the cortical neuroanatomical results found in the VBM arm of experiment 3 and the known literature of the regions underpinning ToM in healthy individuals. Notably, these regions (findings of experiment 3) overlapped significantly with the known regions that correspond to ToM found in the literature. Therefore, the selected seeds for this experiment were the anterior cingulate cortex, medial prefrontal cortex, precuneus, posterior cingulate, temporo-parietal junction, temporal poles, hippocampus and insula (**Fig. 5.9**). All regions were extracted bilaterally and computed independently to investigate hemispheric differences that could account for the statistical outcomes.

5.2.2.8 Seed-based Statistical Analysis

Second-level analysis was performed at the group level to find differences across the sample for each individual bilateral ROI outcome. Independent multiple regression models were carried out for each seed region at the group level. In consistency with all brain-related experiments, significance level was set at $p=0.005$ uncorrected (at the set level) and clusters were retained if they survived a FWE corrected threshold level of $p < 0.05$. Significant peak labels were chosen in the same way as described in section **4.1.2.6**. All statistical neural models were controlled for age, years of education, TIV and hippocampal ratio.

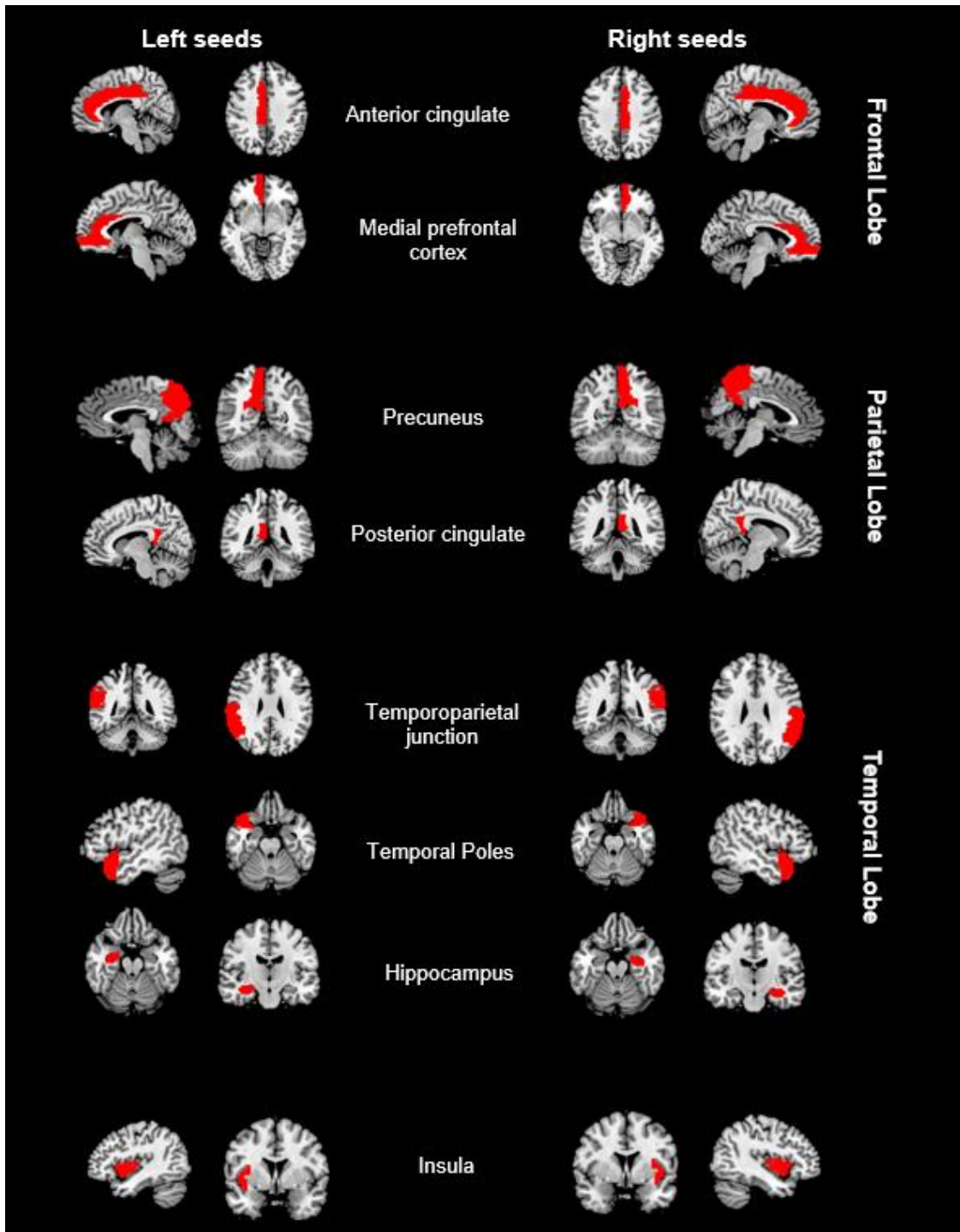


Figure 5.9. *A priori* selected seed regions used for resting-state fMRI social cognition analyses.

5.2.3 Results

5.2.3.1 Resting-state ICA results

Outcomes from the multiple regression models between large-scale network connectivity maps and ToM scores are displayed in **Table 5.11** and **Figure 5.10**. Firstly, the Ekman test showed a significant positive association with the strength of functional connectivity of the right fronto-parietal network (r-FPN) in the right insula (BA13) and TPJ (BA39/40) ($k=243$, $p=0.049$). In contrast, scores on this test were negatively associated with connectivity of the salience network in the left posterior parietal cortex (BA40) ($k=275$, $p=0.024$) and of the pDMN in the left precentral gyrus (BA6) ($k=507$, $p=0.001$) and dorsolateral prefrontal cortex (BA 9) ($k=411$, $p=0.002$). Similarly, a negative association was found between scores on the RMET and functional connectivity of the aDMN in the right anterior prefrontal cortex (BA9/10) ($k=256$, $p=0.040$) and of the salience network in the left precentral gyrus (BA6), insula (BA13) and claustrum ($k=342$, $p=0.007$). The SET or any of its subtests showed no significant results in this arm of the study.

Table 5.11. Clusters of significant correlation between social cognition assessment scores and functional connectivity of the aDMN, I-FPN and salience network.

Social cognition Task	Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	B A	MNI coordinates		
							x	y	z
<i>Right Fronto-Parietal Network (positive)</i>									
Ekman Test	243	0.049	5.40	R	Inferior parietal lobe	40	66	-36	32
			3.89	R	Angular gyrus	39	54	-62	26
			3.65	R	Insula	13	50	-38	22
<i>Anterior Default Mode Network (negative)</i>									
RMET	256	0.040	4.55	R	Middle frontal gyrus	9	24	34	24
			4.14	R	Superior frontal gyrus	10	22	58	20
			4.10	R	Middle frontal gyrus	9	22	42	20
<i>Posterior Default Mode Network (negative)</i>									
Ekman Test	507	0.001	6.05	L	Precentral gyrus	4	-48	-12	42
			4.12	L	Precentral gyrus	6	-50	-6	34
			3.61	L	Precentral gyrus	6	-34	-16	38
	411	0.002	5.72	L	Superior frontal gyrus	10	-20	52	28
			5.37	L	Middle frontal gyrus	9	-28	44	18
<i>Salience Network (negative)</i>									
Ekman Test	275	0.024	4.24	L	Supramarginal gyrus	40	-50	-48	36
			3.89	L	Supramarginal gyrus	40	-44	-42	34
			3.89	L	Inferior parietal lobe	40	-48	-52	44
RMET	342	0.007	6.32	L	Precentral gyrus	6	-32	-16	34
			5.17	L	Insula	13	-38	-8	26
			3.77	L	Clastrum	-	-30	-6	16

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; RMET: Reading the Mind in the Eye Test.

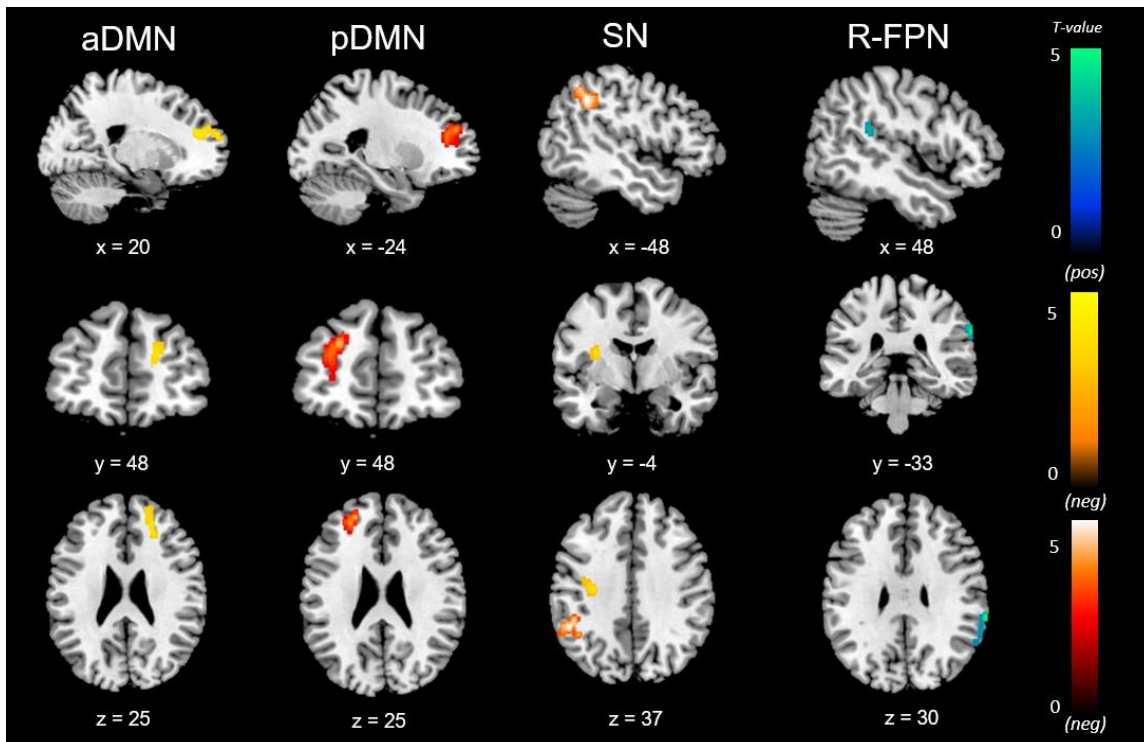


Figure 5.10. Negative (Ekman, red; RMET, yellow), and positive (Ekman, blue) correlations between functional connectivity of the anterior default mode network (aDMN), posterior default mode network (pDMN), salience Network (SN), right fronto-parietal network (R-FPN) and social cognition scores; clusters are shown at $p < 0.05$ FWE corrected.

5.2.3.2 Seed-based analysis fMRI results

Functional seed-based analysis showed statistical significant clusters of increased and reduced connectivity when correlated with social cognition scores (**Table 5.12, Fig. 5.11**). In more detail, the Ekman test scores showed positive associations with connectivity in right-sided seeds, namely the right ACC seed showed increased connectivity with the right superior temporal sulcus (BA 21/22) ($k=364$, $p=0.017$), insula, precentral gyrus ($k=540$, $p=0.002$) and cerebellum ($k=299$, $p=0.042$). The right TPJ showed higher connectivity with the bilateral superior temporal sulcus (BA22), left temporal pole (BA 38), right insula, right precentral gyrus and left inferior frontal gyrus ($k=735$, $p=0.001$; $k=794$, $p=0.001$). The right insular seed displayed higher connectivity with the left ACC and middle frontal cortex (BA6) ($k=343$, $p=0.023$). The right

hippocampal seed showed higher connectivity with the left thalamus and right caudate head ($k=1173$, $p=0.001$). Likewise, left-sided functional seeds showed positive correlations (higher connectivity) with the Ekman test scores namely, the left medial prefrontal cortex seed with the bilateral precuneus (BA 31) ($k=516$, $p=0.002$); the left TPJ with the right insula, right precentral gyrus ($k=742$, $p=0.001$), the left superior temporal sulcus (BA 22) and left temporal pole (BA 38) ($k=622$, $p=0.001$); the left insular seed with the bilateral cerebellum ($k=565$, $p=0.001$) and right temporal cortex (BA 39 & 41) ($k=309$, $p=0.031$); and the left hippocampal seed with the right dorsolateral prefrontal cortex (BA 8/9) ($k=622$, $p=0.001$). In contrast, a negative correlation i.e. lower connectivity with better performance scores on the Ekman test was found between right-side seeds namely, the right TPJ seed and the right insula, thalamus and transverse gyrus (BA 41) ($k=892$, $p=0.001$); the right insular seed with the right PCC ($k=478$, $p=0.004$) and bilateral thalamus ($k=341$, $p=0.023$); the right PCC seed with the right insula, superior temporal cortex (BA 22) and inferior frontal gyrus (BA 47) ($k=449$, $p=0.007$); and the right hippocampus seed with the right Insula ($k=852$, $p=0.001$), caudate ($k=528$, $p=0.002$), temporal cortex (BA 19, 22 & 39) ($k=510$, $p=0.002$; $k=312$, $p=0.029$) and PCC ($k=338$, $p=0.007$). Lastly, the left hippocampal seed showed a negative correlation in the right insula, superior temporal cortex (BA 21), precentral gyrus ($k=463$, $p=0.004$) and left middle temporal cortex (BA 22) and caudate ($k=449$, $p=0.009$).

The RMET scores were positively associated only with bilateral seeds commonly known to be linked with ToM performance (**Table 5.13, Fig. 5.12**). Right-sided seeds that showed higher correlation with RMET scores were the right mPFC seed in the bilateral precuneus and left PCC ($k=607$, $p=0.001$); the right insular seed with the bilateral ACC (BA 24) and right middle frontal cortex (BA 6) ($k=1320$, $p=0.001$);

and the right temporal pole seed with the right TPJ (BA 40) and superior temporal sulcus (BA 22) ($k=338$, $p=0.019$). RMET scores were also positively associated with left-sided seeds, namely the left mPFC seed with the bilateral precuneus ($k=328$, $p=0.026$); the left insular seed with the right anterior and posterior cingulate cortex ($k=502$, $p=0.002$); and the left TPJ seed with the right insula and inferior frontal cortex (BA 44) ($k=308$, $p=0.036$).

The SET global scores showed statistical significant associations with selected ToM seeds as shown in **Table 5.14** and **Fig. 5.13**. Firstly, right hemispheric seeds that displayed a positive association were the right precuneus seed with the right precentral, right postcentral gyrus ($k=427$, $p=0.007$), left precuneus and bilateral PCC ($k=352$, $p=0.019$); and the right hippocampus seed with the left paracentral lobule (BA 5) ($k=368$, $p=0.014$). Left-side seeds were also positively associated; specifically, the left PCC seed with the right fusiform gyrus (BA 37 & 19), right cerebellum ($k=428$, $p=0.009$), right caudate and bilateral thalamus ($k=323$, $p=0.036$). The left precuneus seed showed positive associations with the bilateral PCC ($k=461$, $p=0.004$). Finally, negative associations arose from the right PCC seed with the right insula and precentral gyrus (BA 44) ($k=606$, $p=0.001$); and the left insular seed with the bilateral PCC ($k=423$, $p=0.006$).

Results of the subtests of the SET showed that cognitive ToM (SET-IA) was positively associated with the left PCC seed and the right fusiform gyrus (BA 37), right cerebellum ($k=557$, $p=0.002$) and bilateral thalamus ($k=1428$, $p=0.001$); left insular seed with the right ACC (BA 24 & 32) ($k=521$, $p=0.002$); and right hippocampal seed with the left PCC ($k=353$, $p=0.017$). Lower connectivity with cognitive ToM was found in the left PCC seed and the bilateral PCC, left superior temporal cortex (BA 22) and right precuneus ($k=355$, $p=0.023$; $k=390$, $p=0.015$, respectively). Lastly, the SET-EA,

a proxy of affective ToM, displayed higher connectivity of the right precuneus seed and the right PCC and left precuneus ($k=510$, $p=0.002$), and lower connectivity of the right PCC and the right insula and precentral gyrus (BA 44) ($k=326$, $p=0.033$). Results are displayed in **Table 5.15**, **Fig. 5.14**.

Table 5.12. Clusters of significant correlation of functional connectivity between the Ekman test scores and unilaterally selected seed regions.

Ekman Test								
Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI coordinates		
						x	y	z
Increased Connectivity								
<i>Right anterior cingulate cortex (ACC) seed</i>								
364	0.017	4.62	R	Middle temporal gyrus	21	52	-30	-8
		4.09	R	Middle temporal gyrus	22	48	-42	4
		4.04	R	Middle temporal gyrus	21	60	-34	-8
299	0.042	4.42	R	Cerebellum	-	6	-62	-16
		3.70	R	Cerebellum	-	6	-64	-6
		3.45	R	Cerebellum	-	22	-50	-16
540	0.002	4.39	R	Precentral gyrus	44	56	10	6
		3.95	R	Insula	13	46	-12	4
		3.85	R	Superior temporal gyrus	22	48	4	0
<i>Left medial prefrontal cortex seed</i>								
516	0.002	4.53	R	Precuneus	31	16	-62	18
		4.42	L	Precuneus	31	-14	-66	22
		3.80	L	Precuneus	31	-2	-66	20
<i>Left temporo-parietal junction seed</i>								
742	0.001	5.42	R	Precentral gyrus	44	48	2	8
		4.91	R	Insula	13	42	6	0
		4.66	R	Insula	13	36	10	18
622	0.001	4.55	L	Superior temporal gyrus	22	-52	6	2
		4.34	L	Superior temporal gyrus	22	-48	2	-4
		3.87	L	Superior temporal gyrus	38	-48	10	-10
<i>Right temporo-parietal junction (TPJ) seed</i>								
735	0.001	5.53	L	Superior temporal gyrus	38	-48	10	-10
		4.36	L	Superior temporal gyrus	22	-50	4	-2
		4.14	L	Inferior frontal gyrus	47	-36	18	-6
794	0.001	4.86	R	Superior temporal gyrus	22	48	6	-6
		4.82	R	Precentral gyrus	44	60	8	8
		4.53	R	Insula	13	46	0	0
<i>Left insular seed</i>								
565	0.001	4.92	R	Cerebellum	-	2	-50	-16

		4.21	L	Cerebellum	-	-10	-50	-16
		3.70	R	Cerebellum	-	20	-38	-30
309	0.031	4.13	R	Transverse gyrus	41	40	-36	12
		3.84	R	Superior temporal gyrus	39	40	-50	8

Right insular seed

343	0.023	4.28	L	Anterior cingulate gyrus	24	-6	-18	44
		3.76	L	Middle frontal gyrus	6	0	-22	68
		3.64	L	Middle frontal gyrus	6	-6	-16	68

Right hippocampus seed

1173	0.001	5.49	L	Thalamus		-4	-2	10
		4.81	R	Caudate - head		12	14	2

Left hippocampus seed

622	0.001	5.32	R	Middle frontal gyrus	9	48	30	30
		4.61	R	Superior frontal gyrus	8	22	28	56
		3.86	R	Middle frontal gyrus	6	28	16	58

Decreased Connectivity

Right temporo-parietal junction (TPJ) seed

892	0.001	5.22	R	Insula	13	30	-30	22
		4.54	R	Transverse gyrus	41	38	-34	8
		4.26	R	Thalamus	-	24	-22	12

Right insular seed

341	0.023	4.54	R	Thalamus	-	8	-36	10
		3.50	L	Thalamus	-	-4	-36	4
478	0.004	4.26	R	Posterior cingulate	31	24	-46	24
		4.26	R	Insula	13	26	-36	26
		3.55	R	Insula	13	34	-42	20

Right hippocampus seed

852	0.001	5.52	R	Postcentral gyrus	40	60	-24	22
		4.06	R	Insula	13	36	-10	16
		3.93	R	Postcentral gyrus	42	58	-10	16
528	0.002	5.12	R	Caudate – body	-	20	-6	32
		4.43	R	Caudate – body	-	24	-22	32
		3.74	R	Precentral gyrus	6	32	-4	30
510	0.002	4.48	R	Middle occipital gyrus	19	36	-68	2
		4.44	R	Superior temporal gyrus	39	40	-50	10
		4.22	R	Middle temporal gyrus	19	34	-64	16
312	0.029	4.41	R	Superior temporal gyrus	22	54	-28	-2
		4.21	R	Superior temporal gyrus	22	46	-28	-4
		3.93	R	Caudate – tail	-	38	-16	-17
338	0.007	4.19	R	Posterior cingulate	23	6	-62	18
		3.84	R	Posterior cingulate	30	10	-66	10
		2.84	R	Cuneus	23	4	-74	10

Left hippocampus seed

463	0.004	5.03	L	Middle temporal gyrus	22	-48	-38	0
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		4.11	L	Caudate – tail	-	-32	-26	-8
		3.86	L	Caudate – tail	-	-36	-18	-12
409	0.009	4.89	R	Precentral gyrus	44	58	12	6
		4.33	R	Superior temporal gyrus	21	62	-6	-2
		3.68	R	Insula	13	46	-12	4
<i>Right posterior cingulate cortex (PCC) seed</i>								
449	0.007	4.21	R	Inferior frontal gyrus	47	40	14	-10
		4.16	R	Superior temporal gyrus	22	48	2	2
		3.62	R	Insula	13	44	-4	-2

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute; R: Right.

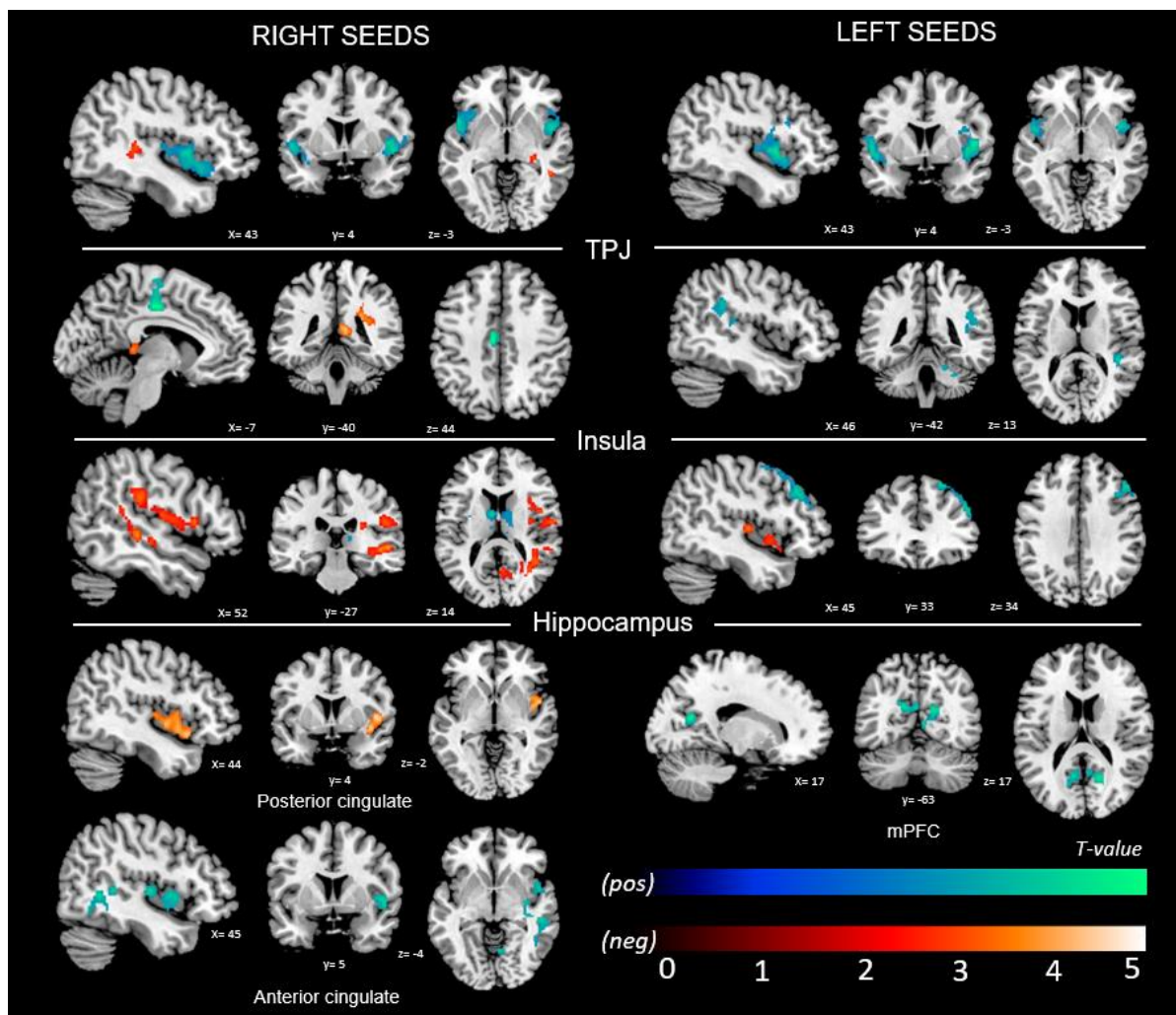


Figure 5.11. Brain positive (blue) and negative (red) correlations between functional connectivity of selected unilateral seed regions and Ekman test scores; clusters are shown at $p < 0.05$ FWE corrected.

Table 5.13. Clusters of significant correlation of functional connectivity between the RMET scores and unilaterally selected seed regions.

RMET Test									
Cluster extent	FWE <i>p</i> -value	<i>T</i> Score	HS	Peak-based localisation	BA	MNI coordinates			
						x	y	z	
Increased Connectivity									
<i>Right medial prefrontal cortex (mPFC) seed</i>									
607	0.001	4.82	R	Precuneus	7	6	-62	30	
		4.34	L	Precuneus	31	-4	-66	20	
		4.18	L	Posterior cingulate	31	-6	-58	20	
<i>Left medial prefrontal cortex (mPFC) seed</i>									
328	0.026	4.34	L	Precuneus	23	-2	-62	20	
		3.62	L	Precuneus	31	-12	-68	20	
		3.41	R	Precuneus	7	4	-62	30	
<i>Right insular cortex seed</i>									
1320	0.001	5.16	L	Anterior cingulate	24	-4	-20	42	
		4.69	R	Anterior cingulate	24	8	-2	50	
		4.65	R	Middle frontal gyrus	6	4	-24	68	
<i>Left insular cortex seed</i>									
502	0.002	4.69	R	Middle frontal gyrus	6	10	-2	54	
		3.97	R	Anterior cingulate	24	4	0	40	
		3.80	R	Posterior cingulate	31	8	-10	46	
<i>Left temporo-parietal junction (TPJ) seed</i>									
308	0.036	3.92	R	Inferior frontal gyrus	44	50	20	22	
		3.86	R	Insula	13	40	4	22	
		3.66	R	Insula	13	44	2	12	
<i>Right temporal pole seed</i>									
338	0.019	4.25	R	Supramarginal gyrus	40	40	-42	30	
		3.68	R	Superior temporal gyrus	22	48	-48	12	

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute; R: Right; RMET: Reading the mind in the Eyes Test.

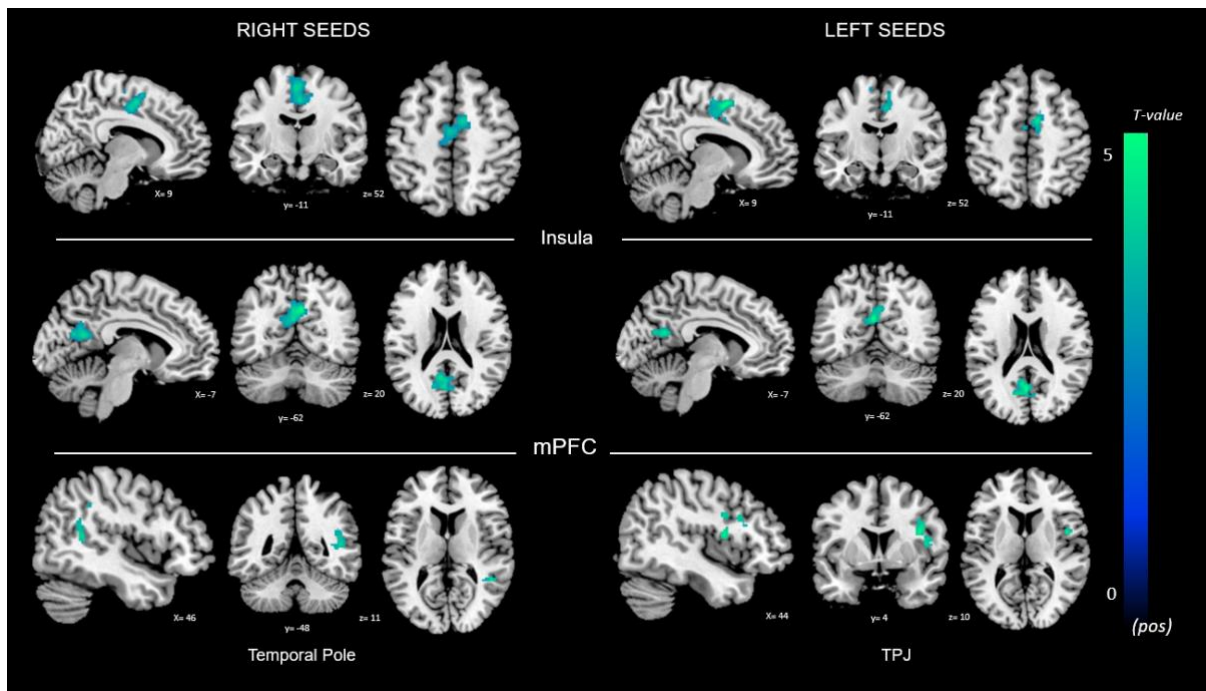


Figure 5.12. Brain positive (blue) correlations between functional connectivity of selected unilateral seed regions and RMET outcomes; clusters are shown at $p < 0.05$ FWE corrected.

Table 5.14. Clusters of significant correlation of functional connectivity between the SET-GS scores and unilaterally selected seed regions.

SET-GS Test									
Cluster extent	FWE p -value	T Score	H S	Peak-based localisation	BA	MNI coordinates			
						x	y	z	
Increased Connectivity									
<i>Left posterior cingulate cortex (PCC) seed</i>									
428	0.009	4.50	R	Cerebellum	-	32	-	-	
		3.98	R	Fusiform gyrus	37	38	-	-	
		3.95	R	Fusiform gyrus	19	28	-	-	
323	0.036	3.97	R	Caudate	-	8	0	16	
		3.82	L	Thalamus	-	-6	-8	18	
		3.68	R	Thalamus	-	10	-	14	20
<i>Right precuneus seed</i>									
427	0.007	4.17	R	Postcentral gyrus	3	20	-	62	
		4.16	R	Precentral gyrus	4	58	-	42	
		3.99	R	Precentral gyrus	4	36	-	60	

352	0.019	3.89	L	Precuneus	31	-4	-	30
		3.88	R	Posterior cingulate	29	4	-	12
		3.88	L	Posterior cingulate	31	-2	-	32
<hr/>								
<i>Left precuneus seed</i>								
461	0.004	4.15	R	Posterior cingulate	31	2	-	24
		4.11	R	Posterior cingulate	30	8	-	10
		4.02	L	Posterior cingulate	31	-4	-	28
<hr/>								
<i>Right hippocampus seed</i>								
368	0.014	4.65	L	Paracentral lobule	5	0	-	52
		4.55	L	Paracentral lobule	5	-16	-	48
		3.92	L	Paracentral lobule	5	-10	-	56
<hr/>								
Decreased Connectivity								
<hr/>								
<i>Left Insular seed</i>								
423	0.006	4.62	L	Posterior cingulate	30	-4	-	6
		3.84	L	Posterior cingulate	23	-4	-	22
		3.71	R	Posterior cingulate	23	4	-	22
<hr/>								
<i>Right posterior cingulate cortex (PCC) seed</i>								
606	0.001	4.20	R	Precentral gyrus	44	44	6	8
		3.60	R	Insula	13	36	2	18

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; L: Left; MNI: Montreal Neurological Institute; R: Right; SET-GS: Story-based Empathy Task global scores.

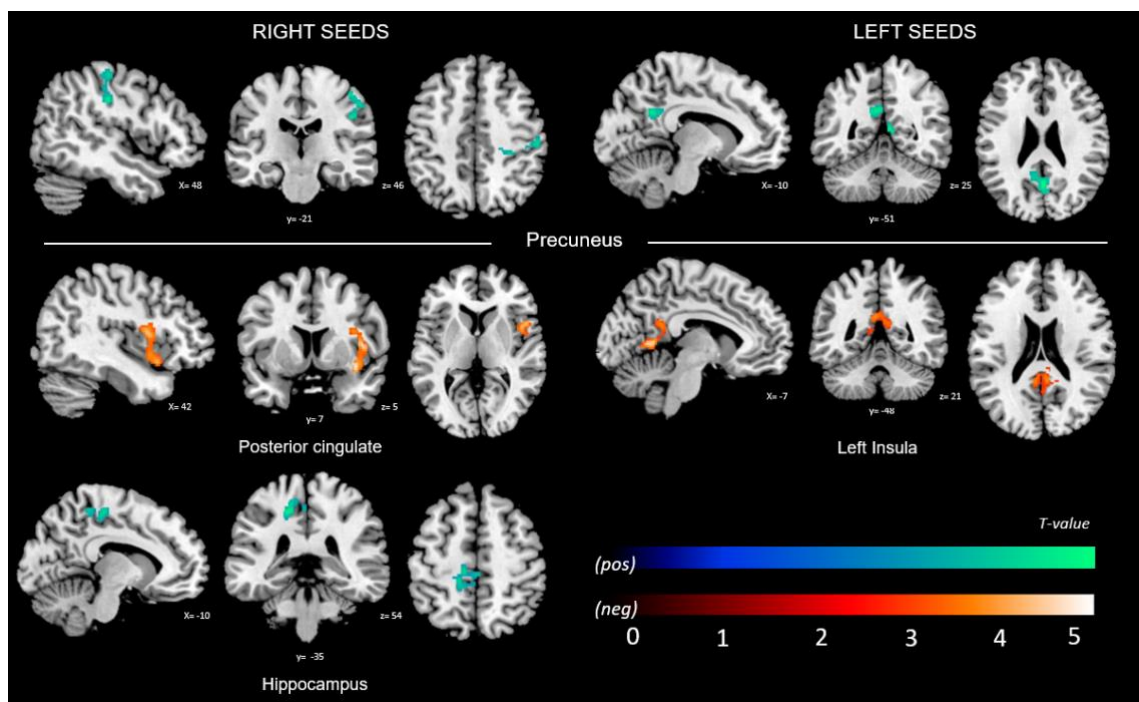


Figure 5.13. Brain positive (blue) and negative (red) correlations between functional connectivity of selected unilateral seed regions and SET-GS outcomes; clusters are shown at $p < 0.05$ FWE corrected

Table 5.15. Clusters of significant correlation of functional connectivity between SET sub-test outcomes and unilaterally selected seed regions.

SET-IA sub-test								
Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI coordinates		
						x	y	z
Increased Connectivity								
<i>Left posterior cingulate cortex (PCC) seed</i>								
557	0.002	4.75	R	Cerebellum	-	32	-	-
		4.41	R	Fusiform gyrus	37	44	-	-
		4.29	R	Cerebellum	-	32	62	16
1428	0.001	4.25	R	Thalamus	-	4	-	6
		4.19	L	Thalamus	-	-12	-	12
<i>Left insular seed</i>								
521	0.002	3.77	R	Anterior cingulate	32	10	22	34
		3.74	R	Anterior cingulate	24	14	18	26
		3.69	R	Anterior cingulate	32	16	28	30
<i>Right hippocampus seed</i>								

353	0.017	4.60	L	Posterior cingulate	31	-20	-	34	46
		4.44	L	Posterior cingulate	31	-6	-	30	48
		3.12	L	Posterior cingulate	31	-6	-	40	58
Decreased Connectivity									
<i>Left posterior cingulate cortex (PCC) seed</i>									
355	0.023	3.60	L	Superior temporal gyrus	22	-34	-	50	16
		3.44	L	Posterior cingulate	30	-30	-	64	14
390	0.015	4.05	R	Posterior cingulate	31	12	-	40	34
		3.93	R	Posterior cingulate	31	10	-	24	36
		3.36	R	Precuneus	7	14	-	52	44
SET-EA sub-test									
Increased Connectivity									
<i>Right precuneus seed</i>									
510	0.002	4.85	L	Precuneus	31	-6	-	54	30
		3.75	L	Precuneus	7	-6	-	64	34
		3.66	R	Posterior cingulate	29	4	-	54	12
Decreased Connectivity									
<i>Right posterior cingulate cortex (PCC) seed</i>									
326	0.033	3.98	R	Precentral gyrus	44	40	14	-	14
		3.31	R	Insula	13	46	6	6	6

* Threshold of significance defined at $p = 0.005$. BA: Brodmann Area; EA: Emotion Attribution; FWE: Family Wise Error; HS: Hemispheric side; IA: Intention attribution; L: Left; MNI: Montreal Neurological Institute; R: Right; SET: Story-based Empathy Task.

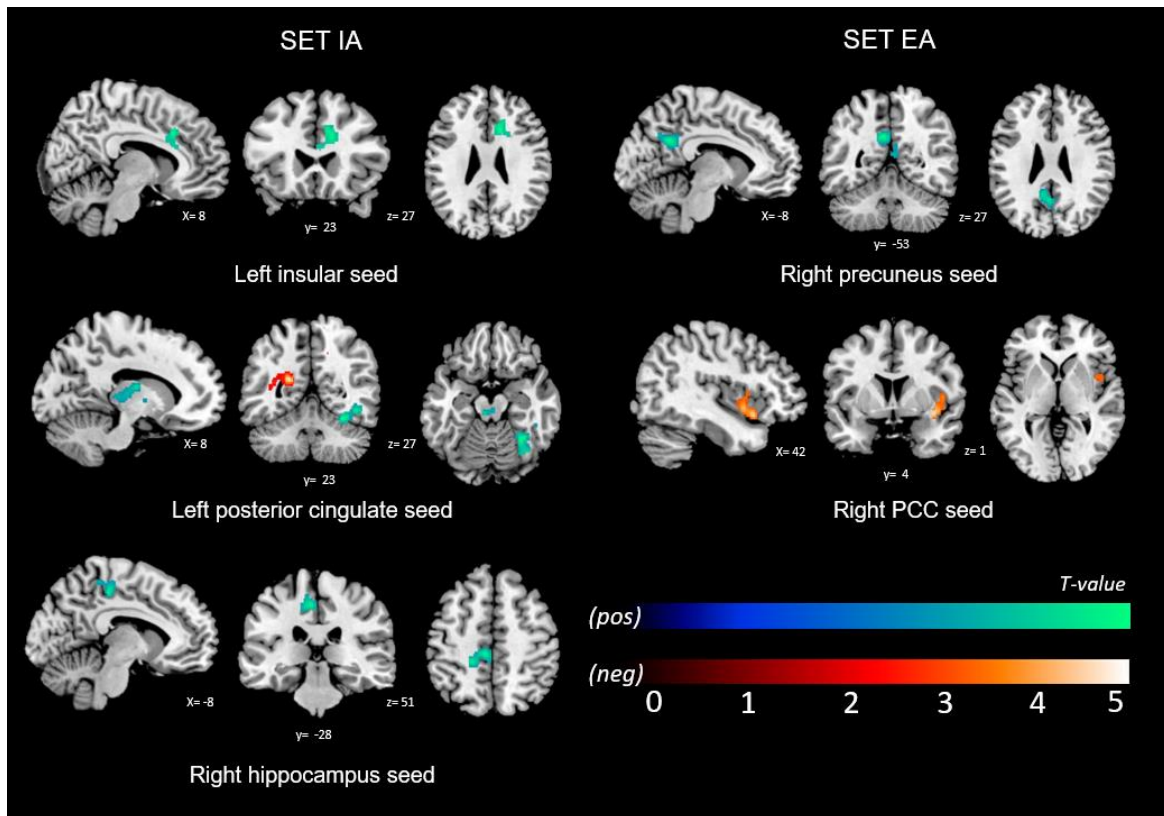


Figure 5.14. Brain positive (blue) and negative (red) correlations between functional connectivity of selected unilateral seed regions and SET-IA and SET-EA sub-test outcomes; clusters are shown at $p < 0.05$ FWE corrected.

5.2.4 Discussion

Findings from the ICA models showed associations among the main large-scale networks that drive cognition, namely the DMN, FPN (central executive) and salience network in relation to cognitive and affective social cognition skills, as measured by the three social neurocognitive tests in the present study. In addition, region-to-region functional analyses also showed clusters of lower and higher connectivity differences and will be discussed in relation to their relationship with the large-scale networks harbouring those structures. This study intended to consolidate the patterns of resting-state connectivity derived from large-scale network dynamics and independent seed-based correlates among clustered functional regions associated with ToM and social cognition performance. In order to interpret connectivity changes in our cohort, it is

important to remark on the most representative nodes that comprise the anatomy of these networks. Firstly, the central nodes of the executive FPN are located in the dorsolateral prefrontal cortex and posterior parietal cortex; the salience network is harboured within the ACC and insular cortex; and the DMN is supported by the precuneus/PCC and mPFC, extending to the hippocampus and cerebellum (Bressler & Menon, 2010; Alves et al., 2019). The organised interconnected processes, derived from the function of these triple networks, have been proposed to serve as the core functional foundations of cognition that eventually encompasses ToM (Bressler & Menon, 2010). In early-AD, the interaction of these networks depends heavily on the evidenced role of a selective pathological vulnerability within the DMN (Greicius et al., 2004; Broyd et al., 2009).

5.2.4.1 Large-scale functional connectivity associated with social cognition

Firstly, scores of emotion recognition and ToM (Ek-60F and RMET) displayed lower strength of functional connectivity of the anterior and posterior DMN in the left and right dorsolateral prefrontal cortex (mPFC), respectively. This region, an important hub of the executive frontoparietal network, has been found to be associated but not essential for ToM abilities in healthy individuals (Otti, Wohlschlaeger & Noll-Hussong, 2015) and in patients with mPFC lesions (Bird et al., 2004). Moreover, the anterior PFC has been shown to contribute to the attentional input needed in the alternation of salient self-other generated thoughts that support ToM abilities (Gilbert et al., 2006; Burgess et al., 2007). On the other hand, the posterior DMN (pDMN) was additionally negatively correlated with the precentral cortex. The precentral gyrus is considered a key hub of motor imitation within the mirror neuron system, a network proposed to be closely

related to social cognition performance ([Rizzolatti & Craighero, 2004](#); [Yang et al., 2015a](#)). In the context of social cognition in early-AD, reduced network coupling of the DMN with bilateral frontal structures such as the executive frontoparietal network could translate into a redirection of network traffic to other systems in charge of salient task shifting that may be relatively preserved, in an effort to cope with complex cognitive social processing in the presence of a hampered DMN.

Secondly, functional connectivity within the salience network showed a negative association with emotion recognition and ToM (Ekman-RMET) in left-sided regions, i.e., the TPJ, precentral gyrus and insula, respectively. Although the right TPJ has been defined as a fundamental region of social cognitive processing ([Saxe & Wexler, 2005](#)), research has shown that the left TPJ displays reduced connectivity during the processing of salient stimuli ([Kucyi, Hodaie & Davis, 2012](#)). Additionally, impairment in the left TPJ has been associated with ToM performance in AD ([Le Bouc et al., 2012](#); [Dermody et al., 2016](#); [Kumfor et al., 2017](#)). Furthermore, the right side TPJ has also been associated with social cognition in AD. In a resting-state functional study, [Multani et al. \(2019\)](#) found a decrease of connectivity in the right opercular, TPJ and temporal cortices. However, in the present sample the left TPJ demonstrated to be more commonly affected.

On the other hand, the insula is a core functional hub of the salience network ([Uddin, 2015](#)). This network is essential in brain-functional organisation of internal/external directed thought processes ([Corbetta, Patel & Shulman, 2008](#)). In the context of our findings, increased resource traffic to the salience network might have a modulatory role in social cognition by downregulating inter-network coupling with the left TPJ to foster functional shifting and facilitate increasing connectivity of other networks to the right TPJ. Therefore, reduced network coupling of the DMN to

structures commonly known to be involved in attentional switching might explain changes of social cognition in our sample ([Ramnani & Owen, 2004](#); [Menon & Uddin, 2010](#)).

Thirdly, affective recognition (Ekman test) displayed stronger connectivity strength of the r-FPN in the right TPJ and right insula. The FPN is commonly associated with executive control functions and goal-directed behaviour ([Menon, 2011](#); [Uddin, Yeo & Spreng, 2019](#)). Bilateral activation of the TPJ and insular regions have been linked to emotion recognition processes ([Fusar-Poli et al., 2009](#)) in addition to ToM and mentalising abilities ([Saxe & Wexler, 2005](#)). Human affective processing might not rely on a rigid anatomical backbone but extend to a broader multi-dynamic social network, at least at the functional level. Therefore, classical regions known to be involved in ToM are also involved in emotion recognition. In this context, the process of emotion recognition can be considered an initial step of social perception, a prerequisite to achieve effective social understanding or ToM, as individuals need to recognise facial emotional features before they can attempt to attribute an affective mental state to others ([Arioli, Crespi & Canessa, 2018](#)).

Our results shed light on the involvement of the TPJ and insular cortex into a network supporting affective recognition and processing during social cognition. Our results showed lower connectivity of the left insula within the salience network, but higher inter-network connectivity of the right insula and the right fronto-parietal network, in relation to social cognition performance. This intercommunication between social and executive networks accentuates the crucial contribution of executive functional resources in support of affective processing.

In the context of neurodegeneration, Chen and colleagues (2019) found stronger functional coupling of the salience and fronto-parietal executive network in MCI patients, alongside decreased connectivity of the DMN and salience (insula) network in participants with lesions in the white matter. In addition, hyper modulation of the executive fronto-parietal network in parallel with salience dysfunction has been found in the MCI population (Chand et al., 2017). Stronger internetwork connectivity between the insular hub of the salience network and the executive FPN may be explained in the context of a dysfunctional DMN in early-AD, where the former has been proposed to serve as a supplementary system ancillary to the DMN responsible for regulation of introspective and self-awareness attributes based on self-centred reasoning regarding complex social representations (Dixon et al., 2018). These modulations in the framework of network dynamics might reflect a combination of concomitant adaptive and maladaptive processes at play in support of a behavioural response in a system grossly depleted by advancing neurodegeneration.

In summary, large-scale analytical findings provide evidence of increased salience-frontoparietal intercommunication, but reduced DMN-frontoparietal network coupling of social cognition performance in early-AD. In healthy individuals, it has been proposed that the salience network has a pivotal role in switching between the executive fronto-parietal and DMN depending on the type of task that needs performing (Sridharan, Levitin & Menon, 2008). However, within the framework of our findings, social cognitive initiation might require a higher load of executive/attentional resources deriving from cognitive control networks to cope with the demands of a hampered DMN by reducing the default network's coupling to an executive compensatory system. The salience network has been evidenced to be downregulated in socio-emotional contexts in other types of dementia, such as fronto-temporal

dementia (Zhou et al., 2010; Seeley, 2019), but seems to be relatively spared in early-AD (Rijpma et al., 2021), thus explaining our results and providing valuable insights for a unique social cognitive profile distinguishing AD from other types of dementia.

5.2.4.2 Seed-based connectivity associated with social cognition

Increased region-to-region connectivity of affective recognition (Ekman) was displayed between the left and right TPJ seeds and the left superior temporal cortex, right precentral gyrus and right insular cortex. The superior temporal cortex is a region highly involved in emotion recognition through portrayal of dynamic representations of facial traits that contributes to facial expression encoding (Adolphs, 2002), while the precentral gyrus is involved in the mirror neuron system that promotes social imitation learning (Rizzolatti & Craighero, 2004). The insula has been found to be associated with emotion recognition via an impairment of modulation of interoceptive factors, as revealed in patients with insular tumours (Motomura et al., 2019). In the context of our findings, the left and right insular seeds displayed increased connectivity with the bilateral cerebellum and the left anterior cingulate and middle frontal cortex, respectively. The left and right hippocampal seeds showed increased connectivity with the right prefrontal cortex and bilateral subcortical regions, respectively, while reduced connectivity of the left hippocampal seed and right insula, and surrounding regions, was also found. The left mPFC showed higher connectivity with the bilateral precuneus and the ACC seed with the right cerebellum, middle temporal cortex, precentral and insular cortex. In consistency with the ICA results, regional seed-based functional patterns displayed increased inter-network point-to-point affinity that could translate in higher salience-frontoparietal connectivity of the right insular seed and left dorsolateral

prefrontal cortex. Conversely, affective recognition yielded reduced region-to-region connectivity associated with lower right-sided DMN-salience coupling, i.e., between two-way right insular seed and right PCC, and right PCC seed and right insula, and right and left hippocampal seeds, intrinsically associated with the DMN (Alves et al., 2019), to the right insula. Nevertheless, increased DMN-salience association was also shown through selective connectivity of the TPJ seeds and the right insula.

Affective ToM (RMET) scores showed only associations of higher functional connectivity, namely of the right and left mPFC seeds with the bilateral precuneus; the left and right insular seeds with the right middle dorsolateral prefrontal cortex and bilateral anterior cingulate; and the left TPJ seed with the right insula and inferior frontal cortex. Lastly, the temporal pole seed was associated with the right TPJ and posterior superior temporal sulcus (pSTS). Activation of the temporal poles and pSTS seems to play a supportive role (but is not essential to ToM) through the retrieval of episodic and personal semantic memory and self-perspective taking, respectively, that allows one to engage in social dynamics (Gallagher & Frith, 2003). These findings suggest that connectivity among hubs of the same network, i.e., default mode and salience network, maintain relative preservation and increase intercommunication during social processing, while coupling between networks shows the higher impairment.

Affective recognition and processing (Ekman-RMET) displayed increased intercommunication between the left TPJ and the right insula. As already mentioned, early-AD patients have shown impairment of the left TPJ while engaging in ToM reasoning (Le Bouc et al., 2012; Dermody et al., 2016; Kumfor et al., 2017). Sustained selective damage of the left TPJ (within the DMN) during ToM performance might induce increased affinity to the right insula (within the salience network) in order to induce cognitive shifting that allows possible adaptive recruitment of high-order brain

resources to cope with complex mentalising abilities. On the other hand, increased connectivity between salience-FPN hubs was evidenced through communication between the right insular seed and lateral prefrontal cortex for both affective recognition and ToM (Ekman-RMET). These findings reinforce the premise that the insular cortex seems to have a paramount role to mitigate social cognitive decline in AD by shifting brain-network modulation from the DMN to a relatively preserved executive fronto-parietal system (Menon & Uddin, 2010).

The SET total scores (ToM) showed increased connectivity of the left PCC seed to bilateral subcortical regions, right precuneus seed to right precentral, postcentral and bilateral posterior cingulate cortices. The left precuneus seed to the bilateral posterior cingulate and right hippocampus seed to the left precentral lobule. Decreased two-way connectivity was found between the left insular seed and posterior cingulate and posterior cingulate seed to the right insula. Findings in the SET sub-tests showed that affective ToM (SET-EA) was associated with increased connectivity of the right precuneus seed and bilateral parietal connectivity but decreased connectivity of the PCC seed and the right precentral and insular cortices. On the other hand, cognitive ToM (SET-IA) was associated with increased connectivity of the left PCC seed to bilateral subcortical regions, left insular seed to right ACC and right hippocampus to left PCC. These findings also display consistency of reduced DMN-salience coupling, i.e., between the insula and posterior cingulate for global ToM, and the PCC and right insula for affective ToM.

Significant findings were shown regarding subcortical involvement with salience-related seeds, where the right anterior cingulate seed and left insular seed displayed stronger connectivity in the bilateral cerebellum in relation to affective recognition. Similarly, seeds related to the DMN (i.e., left PCC) also showed increased

connectivity in relation to global ToM scores. This intercommunication has been well established as the cerebellum has been considered to be closely intertwined to the DMN (Alves et al., 2019). In fact, cerebellar contributions to large-scale connectivity during social and overall cognitive performance is well recognised (E et al., 2014; Van Overwalle et al., 2014). Activation of the cerebellum has been related to affective processing through facial expression recognition and empathetic evaluation in relation to assessing salient emotional traits that require a behavioural response (Habas et al., 2009; Stoodley & Schmahmann, 2009). In a mechanistic view, the cerebellum might have served as a primitive phylogenetic emotional processing structure, and this could explain its active contribution to large-scale network performance. The interconnection of cerebellar and salience-related structures might also provide understandings of limbic control to motor actions (Habas et al., 2009). The latter provides insights into brain-cerebellar circuitry in motor imitation within the context of the mirror system (Van Overwalle et al., 2014). The few studies investigating the neural correlates of social cognition in AD have found a significant involvement of cerebellar regions (Baglio et al., 2012; Synn et al., 2018). In the context of AD, we propose that subcortical and cerebellar contributions to social cognition might derive from executive and semantic support to cognitive networks in charge of sustaining social processes (Van Overwalle et al., 2014). Structural and functional associations of the caudate also proves the substantial contribution of cortico-striatal communication in emotional processing and extended ToM performance (Jung et al., 2014) and the relevant role of subcortical regions arising from our results to the paramount executive support to social cognition in AD (Jacobs et al., 2018).

Results arising from both large-scale network analyses and regional connectivity approximations of resting-state functional brain dynamics in the present

experiment show a consistent display of reduced network coupling between the DMN and salience network, with the exception of increased connectivity between the left TPJ and right insula. This network communication has been proposed to be essential in the brain functional organisation to achieve complex internal-external homeostasis of thought processing (Corbetta, Patel & Shulman, 2008). In the context of early-AD, the interaction of the DMN and salience network in MCI has shown that these dyad systems display reciprocal balance of BOLD-related frequency variability as a possible secondary compensatory process that responds to an early default network breakdown (Zhang et al., 2020). Moreover, antiparallel functional connectivity is shown by other types of dementia such as behavioural variant frontotemporal dementia, that shows increased DMN connectivity with decreased salience activation, whereas AD displays reduced DMN but enhanced salience activation (Zhou et al., 2010; Rijpma et al, 2021). Likewise, Caminiti et al (2015) demonstrated stronger connectivity of the DMN and salience networks with ToM performance in frontotemporal dementia patients. Therefore, the aberrant interrelation between network dynamics of reduced DMN, but increased salience activations, could be a potential large-scale non-invasive biomarker method for differential diagnosis between AD and behavioural variant fronto-temporal dementia in the context of awareness.

Our results support the idea that computational processes derive from a modular “social network” that relies on the coupling of multiple networks that are intercommunicated with one another during the activation of social brain mechanisms (Chiong et al., 2013). Separately, the close association of the reduced DMN-FPN but increased FPN-salience intercommunication may be explained through the alternation of antagonistic endogenous/exogenous cognitive attentional demands, such as ToM (Ahmed et al., 2016). In healthy people, the salience network has been demonstrated

to drive this alternation through brain network switching between the task-free DMN and task-engaging executive FPN (Goulden et al., 2014). In AD, the FPN may serve as a supporting adaptive system to the DMN (Dixon et al., 2018) by reducing its coupling and increasing its communication with the salience network to support complex social functions such as Theory of Mind. Therefore, we suggest that patients in the early stages namely, MCI and mild AD, rely more on independent executive resources to cope with complex functions based on social cognition and theory of mind; providing a possible explanation for which the current literature has not evidenced a substantial decline of social processing at these stages, including our sample.

Brain-network activity may opt to compensate for intricate mentalising abilities, result of the breakdown within the DMN, with a partially unaffected network at an early stage of the disease, responsible to provide attentional/executive substrates that mediate the attribution of complex self-other representations. Subsequent inherent neuropathological spreading of damage to core ToM regions within the DMN may overwhelm compensatory mechanisms and manifest clinically as a more profound impairment of social cognition in the later stages. This might explain the clinical progression of social cognitive impairment from complex to simple social processing tasks (Castelli et al., 2011).

More specifically, our results found a bridging involvement of the insula with large-scale and seed-based alterations in connectivity strength in social cognition performance. We propose that at the initial stage of the disease, functional network changes relying on the insular cortex, an integrative core region of emotional processing and salient modulation, may function as a structure responsible for affective modulation that arbitrates network traffic in the context of an inherent downregulated DMN and a possible compensatory upregulation of the executive

network during social cognition performance ([Sridharan, Levitin & Menon, 2008](#); [Menon & Uddin, 2010](#); [Kurth et al., 2010](#)). Network dissociations of independent systems controlled by the insula and the PFC have been linked to impairment of cognitive and affective ToM, respectively, in stroke patients ([Corradi-Dell'Acqua, et al., 2020](#)). In consistency with our results, laterality could be an influencing factor in social cognition. In healthy individuals, better ToM performance relied on a network with predominance of left-hemispheric nodes, within the frontal and insular cortices, proposed to mediate the cognitive and affective components of ToM, respectively ([Marchetti et al., 2015](#)). Increased insular to left TPJ communication might provide an integrative approximation to a region that is particularly vulnerable in the AD aetiopathological context when engaging in social cognition. Our findings show an enhancement of functional connectivity with the left TPJ in comparison to the right side. However, brain structural findings revealed the right TPJ as the region with the strongest association to ToM performance. Hence, possible adaptive restructuring of brain resources increases network traffic to the left TPJ in an attempt to preserve social functions, while the right side might continue relatively preserved.

A comprehensive consolidation of the results presented in this experiment sheds light on the substantial relevance of executive control networks and the critical role of the insular cortex in modulating attentional and executive resources in the presence of pathological hampering of core structural ToM structures within the DMN in early AD. Executive neural substrates in early-AD have found substantial overlap of temporo-parietal structures that are heavily involved in social cognition ([Habeck et al., 2012](#)). Our results support the conceptual hypothesis of ToM performance mediated by executive/attentional functions. Early decline and downregulation of the ToM network within the DMN could activate a salient system to promote the participation of

an executive network with the objective to fight, at the initial stages, neurodegeneration of ToM regions during performance of complex social cognitive processes based on cognitive and affective mental attribution to others.

5.3 Limitations

A possible limitation may arise from the choice of combining patients with different disease severity levels. However, this pooling was required to observe the widespread variation of social cognition changes among the sample. Furthermore, to account for differences in disease severity, a correction factor was included in the analyses to control for the influence of severity of neurodegeneration, i.e., a proxy of hippocampal integrity. A second potential limitation may be our decision to implement three different social cognitive measures that might not rely on shared neural substrates. The presence of variable results across the three instruments, however, may reflect the heterogeneous nature of affective abilities and ToM, whereby the outcome of the assessments is complementary rather than capturing a single social construct.

5.4 General discussion

The use of social cognitive tools for early-stage neurodegenerative differential diagnosis has shown to be beneficial in the clinical setting ([Dodich et al., 2021](#)). Multi-domains of social cognition were explored through three social cognitive tasks, namely social perception through emotion recognition and social understanding through cognitive and affective ToM reasoning. These variables were explored through five independent methodologies, i.e., neurocognitive, brain structure, structural

connectivity (white matter tracts), resting functional large-scale networks and resting-state functional region-to-region connectivity analyses.

Structural and functional contributions of the frontal (inferior frontal and precentral gyri) and parietal (inferior) cortex in the present chapter overlap with the brain domains that outline the mirror neuron network ([Rizzolatti & Craighero, 2004](#); [Arora, Schurz & Perner, 2017](#)). The mirror neuron network comprises mainly the inferior frontal gyrus, premotor (precentral) cortex (dorsal and ventral part) and inferior and superior parietal lobule; however, supportive regions are also associated with its function such as the occipital cortex and cerebellum ([Molenberghs, Cunnington & Mattingley, 2012](#)). This system has substantial overlap with overall social cognition ([Agnew, Bhakoo & Puri, 2007](#)) and has been found to degrade accordingly in relation to normal ageing, MCI and AD ([Moretti, 2016](#); [Farina et al., 2017](#)). The contributions of the mirror neuron system to social cognitive skills such as ToM and empathy may be crucial to understand the pathological neuronal degradation of evidenced ToM decline in AD patients. In line with the present data, it has been proposed that empathic processes rely on mental representations based on imitation and mirroring that receive limbic input from the insular cortex ([Carr et al., 2003](#)).

Structural and functional overlap of the inferior parietal cortex (including TPJ) denotes its involvement as an essential prerequisite region for the inception of ToM thinking ([Saxe & Kanwisher, 2003](#); [Otti, Wohlschlaeger & Noll-Hussong, 2015](#)). More importantly, this structure has been consistently found involved in the limited neuroimaging research related to social cognition and ToM across the different stages of AD ([Le Bouc et al., 2012](#); [Dermody et al., 2016](#); [Moretti et al., 2016](#)). Close association of AD-related hippocampal reductions with connectivity in the TPJ may flag up an early DMN disconnection and, conceptually, how ToM performance could

be an overlooked predictive factor of the clinical spectrum outcome in the early stages (Moretti et al., 2016; De Marco, Ourselin & Venneri, 2019). Clinical assessment of ToM has already been a valuable approach to differential diagnosis among neurodegenerative dementias (Bertoux et al., 2016; Dodich et al., 2018). Our results point out the relevance of doing comprehensive systematic assessment of social cognition and theory of mind as this potential early hampered neurocognitive domain may reflect a more important role in disease than previously believed.

An integrative panorama of the results presented in this chapter supports the idea that even in the absence of true clinical social impairment, early-AD patients display reduced volumes of core ToM regions in relation to worse performance associated with cognitive and affective ToM (Schurz et al., 2014), evidenced in the brain-structural arm of this chapter. Resting-state functional dynamics demonstrated variances in internetwork coupling strength characterised by reduced DMN-FPN but increased salience-FPN functional coupling. Salience and DMN connectivity seem to show patterns of reduced and increased connectivity, with an important focus in the increased left TPJ to right insula communication.

Affective processing relies on stronger network coupling of a right-sided executive system to key components comprising the salient and default networks. These findings provide evidence of the substantial contribution of executive directed systems to social cognition, and these show consistency with our behavioural findings. The intercommunication between social and executive networks accentuates the crucial contribution of executive functional resources that support affective processing. Furthermore, the salience-insular cortex seems to be actively involved in the modulation of these changes, a region that may be involved in anchoring selective awareness of self-other attributional representations. Subcortical contributions to

social cognition in early-AD point to the significant involvement of the cerebellum, a primitive emotional region that might provide support to affective and social processing as to a motor mirror network of social imitation. Lastly, structural and functional changes in the present study provide a conceptual framework to explain why the neurocognitive correlates of executive/attentional functions show the highest association with social cognition performance. We therefore propose that a frontally mediated high-order cognitive network provides neural resources to cope with functions of cognitive and affective inferential thinking related to others in the early stage of AD.

Chapter 6

Neuroanatomical, functional connectivity and behavioural association of self and others awareness in early Alzheimer's disease

6.1 Experiment 5: The behavioural, neuroanatomical and functional connectivity association of anosognosia and social cognition in early Alzheimer's disease: findings of a preliminary proof of concept study

6.1.1 Introduction

Awareness is an essential cognitive trait for humans, defined as the ability to achieve a rational appraisal related to the feature of one's own condition or perception ([Nelis et al., 2011](#)). One of the most relevant domains within the awareness concept is the ability to evaluate consciously our own functions, skills and behaviours, a trait known as self-awareness ([Lou, Changeux & Rosenstand, 2017](#)). In contrast, the mental ability to process and create attributions of intentions, emotions, beliefs and behaviour of others, as a reflection of the awareness achieved within a social environment, is defined as social cognition ([Belfort et al., 2018](#)). The individual interaction among these concepts is so interweaved that the literature is still debating as to whether social cognition is an extension of the ability for self-awareness, as a result of self-referential processing within a social sphere ([Happe, 2003](#); [Northoff et al., 2006](#)); or self-awareness is a prerequisite of Theory of Mind (ToM), where our internal self-directed

mental states serve as a foundation to create inferences about other people's minds (Van Overwalle, 2009; Bradford et al., 2015). For this reason, it has been proposed that self-others awareness in the brain may have its neural substrates in analogous brain structures (Decety & Summerville, 2003). Consequently, a great number of neurological disorders such as neurodegenerative diseases and various forms of dementia might show a parallel decline of self-awareness along with social awareness (Shany Ur et al., 2014).

In the brain-imaging framework, few studies have aimed to clarify the neural overlap between social cognition and self-awareness, and these studies have been mainly focused on the healthy population. Functional MRI (fMRI) imaging has associated self-awareness to activation of regions based on cortical midline structures, namely the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), posterior cingulate cortex (PCC) and precuneus (Northoff et al., 2006) with higher predominance in the right hemisphere (Feinberg, 2005). Similarly, social cognition, and specifically ToM, shows activation in the mPFC, precuneus and temporoparietal junction (TPJ), along with the temporal poles (Schurz et al., 2014). Amodio and Frith (2006) suggested that the medial prefrontal cortex (that includes the ACC) is an essential area responsible for achieving ToM, perception of others and self-knowledge. A meta-analysis based on fMRI studies focused on facial recognition of self-other and ToM demonstrated that areas of the prefrontal cortex and superior temporal gyrus were involved in performance of both self-awareness and social cognition tasks (Van Veluw & Chance, 2014). In this setting, Reniers et al. (2014) attempted to address self/other awareness in a task-based fMRI study that yielded activation of the prefrontal cortex, frontal poles and orbitofrontal cortex in participants engaging in self-referential thoughts and ToM assessments.

Likewise, Gilbert and Fung (2018) revealed in another task-based fMRI study, using an assignment based on intentions of self and other representations, that structures within the prefrontal cortex, posterior cingulate, superior parietal and occipital cortices may contribute to how we attribute personal and social intentions. As already discussed throughout this thesis, at a large-scale functional level, it seems that the overlapping structural and functional neural substrates that shape self-other thinking outline a substantial involvement of regions within the default mode network (DMN) (Li, Mai & Liu, 2014; Yeshurun, Nguyen & Hasson, 2021). It has been suggested that a mechanistic approach to explaining self-other brain processes can be achieved through the involvement of the mirror neuron system, a neural system that also shares a partial neural overlap with the DMN (Jeon & Lee, 2018). Therefore, the inherent network breakdown of the DMN that characterises AD (Greicius et al., 2004) might also extend to functional hubs of the mirror neuron system (Farina et al., 2017) that could eventually compromise the patients' ability to process cognitive awareness.

An approximation in how to interconnect the concept of self-other thinking in disease has been through the assessment of the patient's ability to create spatial representations based on first to third person perspective, as an extension of the mechanisms that control ToM performance (Vogeley et al., 2001, Ruby & Decety, 2003, Mograbi et al., 2014; Besharati et al., 2016). Current evidence seems to associate this perspective change to mesial cortical structures (Uddin et al., 2007) in accordance with the findings of Northoff and collaborators (2006) who clustered the self in these structures. Accordingly, Vogeley and colleagues (2001) agreed that self-perception is strongly associated with ToM and could find its conjoined neural substrates in structures such as the ACC and TPJ.

In the case of individuals with Alzheimer disease (AD), studies have shown how the presence of anosognosia also influences negatively the patients' socioemotional sphere (Nelis et al., 2011; Leicht, Berwig & Gertz, 2010; Clare et al., 2012a; Belfort et al., 2018). Behavioural insights have suggested that social cognition decline in AD might be a consequence of deficits in self-perspective abilities, in which the presence of anosognosia could be a hampering factor closely intertwined with socio-emotional decline (Le Bouc et al., 2012; Serino & Riva, 2017). However, the brain structural association of social cognition and self-awareness as mental processes that are essentially interweaved has not been investigated comprehensively in AD, although it has been postulated that self-other processing might also rely on shared neural correlates (Zamboni et al., 2013). In this context, Mograbi et al. (2014) tested perspective-taking in performance outcomes of self and others memory tasks, finding overall alterations in awareness that also correlated with pre-morbid personality features. From a neural standpoint, Ruby and colleagues (2009) found activation in the ACC, mPFC, precuneus and inferior parietal lobe in healthy controls and in the intraparietal sulcus and prefrontal cortex in AD patients when engaging in self-other perspective alternation during a task-based fMRI study.

Independent research on self-awareness and others awareness displays a consistent neural activation that overlaps with interconnected regions based on the mPFC, ACC/PCC and the TPJ, brain territories known to shape the DMN (Li, Mai & Liu, 2014). Therefore, the present study intends to extend the existing evidence from research in healthy participants to early AD patients by studying the behavioural and brain structural relationship between self and others awareness using independent measurements of deficits in self-awareness (anosognosia) and social cognition in an early-AD population. The main aim is to elucidate the behavioural and brain interaction

between self-others awareness in this population. Hence, the hypotheses for this proof-of-concept experiment are firstly, that patients' level of anosognosia parallels behavioural impairment in social cognition performance. Secondly, this association reflects a brain structural and functional shared territory, with particular involvement of medial frontal cortical regions. This is the first study of this type that intends to explore the relationship of self-other awareness in patients with prodromal and early AD through a combination of behavioural and multi-modal brain imaging approach.

6.1.2 Methods and Materials

6.1.2.1 Participants

A subsample of twenty-nine participants, taken from the previous studies with a diagnosis of prodromal ($n= 21$) or mild AD ($n= 8$), were included in this preliminary proof of concept experiment. Prodromal AD participants included patients with MCI who had been diagnosed following Petersen et al. (1999) and Albert et al. (2011) criteria, while patients with mild AD were diagnosed following the National Institute of Neurological and Communicate Disorders and Stroke and the Alzheimer's Disease Related Disorders Association (NINCDS/ADRDA) (McKhann et al. 2011) and Jack et al. (2018) criteria. Recruitment was carried out in the same outpatient memory clinic as detailed in previous experiments. The age of the selected group ranged between 57 and 89 (Mean 75.7, SD 7), and the group included 14 males (48.3%) and 15 females (51.7%). All patients underwent a comprehensive neuropsychological profile using a battery of tests (see section 4.1.2.2 for a detailed description of the tests included in this battery) also including the Mini-mental State Examination (MMSE) as a measure of overall cognitive functioning (Mean 25, SD 2.72) (Folstein, 1975). In

consistency with the procedures followed in previous chapters, main exclusion criteria consisted of participants with other neurological, cardiovascular, gastrointestinal or metabolic conditions or pharmacological treatments described in detail in [section 5.1.2.1](#). Ethical approval was granted by the Joint Ethics Committee of the Health Authority Venice 12 and the IRCCS Fondazione Ospedale San Camillo (Protocol number 2014.08). Written informed consent was obtained from all participants.

6.1.2.2 Neuropsychological assessment

All participants underwent measurements to detect self-awareness deficits through the Measurement of Anosognosia Instrument ([Stewart et al., 2010](#)) and others awareness skills through tests of social cognition assessment, namely the Ekman 60 faces test ([Ekman & Friesen, 1976](#)), Reading the Mind in the Eyes Test ([Baron-Cohen et al., 2001](#)) and Story-based Empathy Task (SET) ([Dodich et al., 2015](#)). More specific details about the neuropsychological self-other assessments can be found in [section 4.1.2.2](#) and in [section 5.1.2.2](#), respectively.

6.1.2.3 Behavioural statistical analysis

Neuropsychological and demographical outcomes were analysed with IBM SPSS Statistics 26 Software for Windows (SPSS Inc., Chicago, IL, USA). The main focus of this segment of the experiment was to search for the behavioural association between anosognosia and social cognition, as proxies of deterioration in self-other's cognitive awareness. Tests of normality were used to assess the overall data distribution. Subsequently, statistical models of nonparametric partial correlations

were devised in which independent scores obtained on memory, non-memory and total anosognosia test sections were correlated with the Ekman test, RMET and SET global scores. A pragmatic approach to these associations is based on the complexity of cognitive awareness and how self-awareness and others-awareness can only be explored comprehensively through a multi-domain perspective. These behavioural associations could later allow the discovery of the possible shared substrates of this interaction depending on variance of performance on any selective cognitive awareness domain. All neuropsychological analytical models were Bonferroni corrected for multiple comparisons defined as $p = 0.05/n$ in which n were the number of statistical associations in the individual models (i.e., $p < 0.05/6 = 0.008$). In consistency with the previous experimental models, all cognitive data were controlled for age, years of education and hippocampal ratio as described in [section 4.1.2.6](#).

6.1.2.4 MRI Acquisition

Scans were acquired with a Philips Achieva 1.5 T scanner. Turbo Field Echo T1 images were acquired with the following parameters: voxel size: $1.1 \times 1.1 \times 0.6$ mm; repetition time 7.4 ms; echo delay time 3.4 ms; flip angle 8° ; field of view 250 mm; matrix size $256 \times 256 \times 124$. Resting state functional MR images were acquired following the shared protocol set by the VPH-DARE@IT consortium for the Philips Achieva MRI scanners (<http://www.vph-dare.eu/index.php/project/work-packages/WP2>). Acquisition parameters were as follows: $3.28 \times 3.28 \times 6.00$ mm voxel dimension, 64×64 matrix size, 230 mm field of view, 2 s TR, 50 ms TE and 90° flip angle.

6.1.2.5 Voxel-based morphometry (VBM) analysis

For the structural part of this study, multiple regression models were devised in which grey matter structural maps were extracted from T1-weighted MRI pre-processed scans. MRI scans pre-processing and statistical VBM analyses were performed with the SPM12 software. First, six independent multiple regression analyses were implemented between memory anosognosia, non-memory anosognosia, total anosognosia, Ekman test, RMET and SET total outcomes with whole brain grey matter volumetric maps. Due to a smaller sample size and the preliminary proof of concept nature of this study, the cluster forming threshold of significance was set at $p=0.025$ uncorrected. These models were controlled for age, years of education, total intracranial volume and hippocampal ratio. Characterisation of neural shared substrate patterns was achieved first through a visual intersection of the independent statistical significant cluster maps of anosognosia and social cognition outcomes. Maps were visualised and overlapped through the MRICron (Neuroimaging Tools & Resources Collaboratory NITRE, NIH, Bethesda, Maryland, USA) software for stereotaxic display (Rorden & Brett, 2000). The additive overlay function showed a change in colour when two spatial maps overlapped in the same stereotactic space. Crosshaired MNI coordinates were extracted from this shared neural territory and subsequently converted to Talairach, thus providing a visual proxy of the brain structural underpinnings of self-others awareness (Lancaster et al., 1997; Lancaster et al., 2000).

Statistical models of shared neural underpinnings were explored through two different methodological approaches. Firstly, self and other single domain outcomes were analysed through the conjunction analysis function in SPM12 by selecting both predictors to be analysed concomitantly. A second approach was devised through an

initial VBM multiple-regression analysis for each of the anosognosia self-awareness variables (as described in the section above). The statistical significant clusters arising from this regression were extracted and binary statistical mask maps were created from the areas associated with anosognosia and grey matter volume changes on a whole brain analysis. Subsequently, independent social cognition outcomes were analysed only within the significant cluster territory mask that arose from the anosognosia results. Therefore, statistical significant social cognition outcomes would only be shown if they shared a communal neural territory with grey matter changes also underpinning anosognosia. For the purpose of this study, only clusters of more than 100 voxels and surviving a family-wise error correction (FWE) of $p > 0.05$ at the peak level were retained as significant.

The aim of the present VBM structural analysis was to discover the shared neural substrates of anosognosia and social cognition that overlapped in brain regions that could possibly serve as hubs for conscious awareness. Brain covariates used for this study were consistent with the previous VBM models (more details can be found in [section 4.1.2.6](#)).

6.1.2.6 Post-hoc volumetric analyses

Due to the intrinsic nature of the neuropsychological variables, a higher score in the anosognosia discrepancy questionnaire indicates a higher impairment of self-awareness. Conversely, a higher score in the social cognition assessments establishes a better performance in this neurocognitive domain and less impairment in other's awareness. The different direction indicating impairment of the neuropsychological scoring system may interfere with the conjunction analyses at the

brain level, as significant intersecting results might cancel each other; hence, displaying no significant results with the automated statistical procedures performed by the imaging software. To solve and explore this, we converted the anosognosia discrepancy scoring system by multiplying the score n by -1 . In this way, the variable directionality was transformed, so that a higher discrepancy score meant better performance and therefore, less presence of anosognosia. This method was used only at *post-hoc* level analysis only for the self-other multi-domain variables that showed significant visual and statistical significant intersection in the VBM analysis. Therefore, supplementary VBM multiple regression models were devised in which the inverted anosognosia score and social cognition score were selected concurrently in the statistical model as equivalent predicting variables for grey matter changes that could only be explained by the presence of alterations in both self and others awareness. In consistency with all brain-related experiments, all analyses were controlled for the same covariates used throughout this experimental work. The cluster forming threshold of significance was set as $p < 0.025$ uncorrected at the set-level, and at a FWE corrected threshold of $p < 0.05$ at the peak level, to account for multiple comparisons.

6.1.2.7 Resting-state functional independent component analysis

Pre-processed resting-state fMRI images were used for an Independent Component Analysis (ICA) to extract functional connectivity patterns reflecting large-scale networks (Beckmann et al., 2005). For this purpose, the GIFT toolbox (v1.3j; mialab.mrn.org/software/gift) within SPM was used. An Infomax algorithm of 20 components was used (Wang & Li, 2015). In consistency with the previous functional

experiments, five large-scale networks were extracted, namely the anterior Default Mode Network (aDMN), posterior Default Mode Network (pDMN), left Fronto-Parietal Executive Network (l-FPN), right Fronto-Parietal Executive Network (r-FPN) and Salience Network. In a similar manner as the structural arm of this study, connectivity maps were analysed:

1. Separate multiple regression models were performed for each of the six self and other neuropsychological proxies for each large-scale network. Brain intersections were evidenced through visual overlaps of self and others maps within the same stereotactic space.
2. The conjunction analysis tool within SPM12 was selected.
3. Statistical masked maps were created from the self-awareness results and social cognition variables were analysed only within the boundaries of the significant self-awareness neural territory.
4. A *post-hoc* analysis was performed with the statistical significant results arising from step 2 and 3 through the inversion of self-awareness scores and concomitant analysis of both (anosognosia and social cognition) predictors in the same model.

6.1.3 Results

6.1.3.1 Associations with neuropsychological functioning

Demographical data are displayed in **Table 6.1**. Additionally, after correction for multiple comparisons and accounting for covariates of no interest, the behavioural correlation analysis between anosognosia and the RMET test outcomes showed a

significant negative correlation between Theory of Mind (RMET) and levels of memory ($\rho = -0.623$, $p = 0.001$) non-memory ($\rho = -0.576$, $p = 0.002$) and total anosognosia ($\rho = -0.672$, $p = 0.001$) (Fig. 6.1). Similarly, the scores on the Ekman test displayed a negative association with memory ($\rho = -0.580$, $p = 0.002$) and total anosognosia ($\rho = -0.547$, $p = 0.004$) scores (Fig. 6.2). Non-memory anosognosia scores were negatively associated with the SET-GS scores ($\rho = 0.448$, $p = 0.022$), the SET-IA subtest scores ($\rho = -0.433$, $p = 0.027$) and the Ekman test scores ($\rho = -0.428$, $p = 0.029$); however, significance of these findings did not survive the Bonferroni statistical correction for multiple comparisons.

Table 6.1. Demographic and descriptive characteristics of the selected participants. Means (standard deviation) and range are shown.

Variable	Descriptive statistics
Sex: n (%)	14 Male (48%): 15 Female (52%)
Age	Mean (SD): 75.72 (7.88) Range: 57 to 89
Years of Education	Mean (SD): 9.34 (4.23) Range: 5 to 18
MMSE	Mean (SD): 25 (2.73) Range: 21 to 30

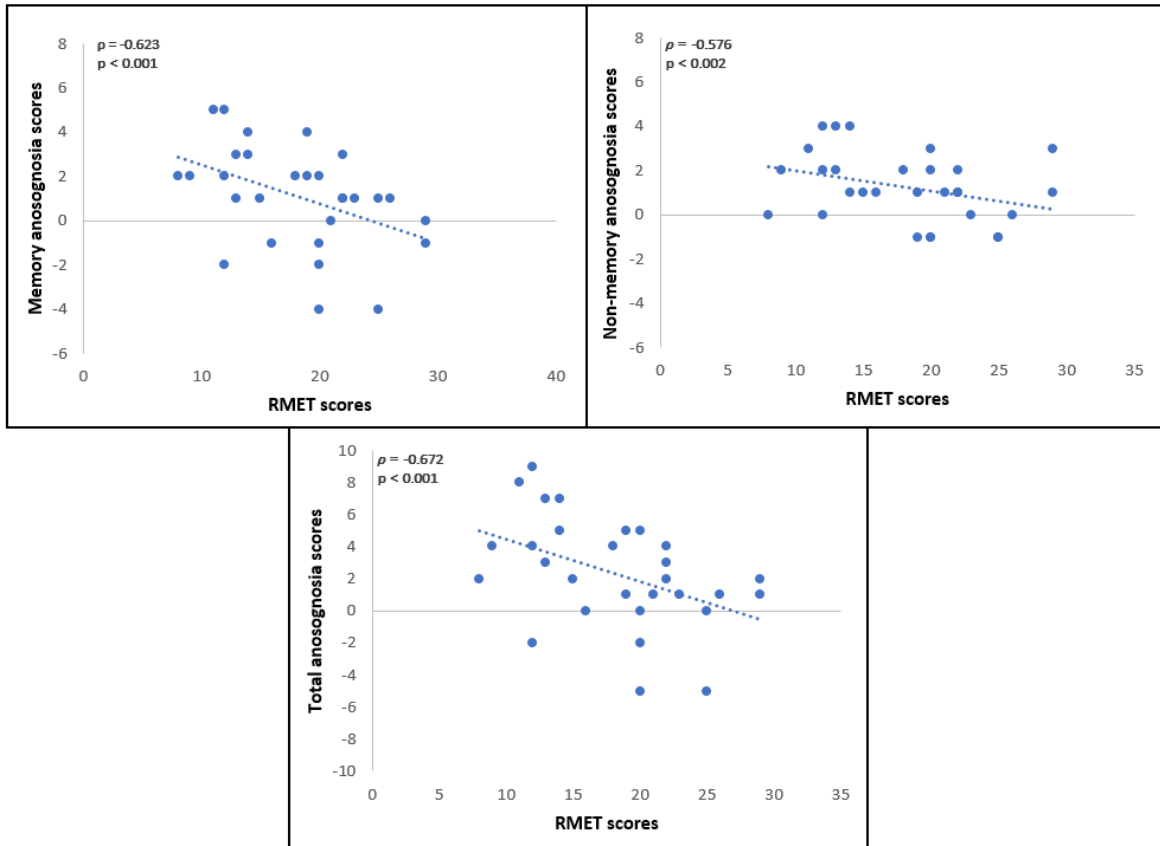


Figure 6.1. Negative correlations between multi-domain anosognosia scores and the RMET scores that survived multiple comparison correction.

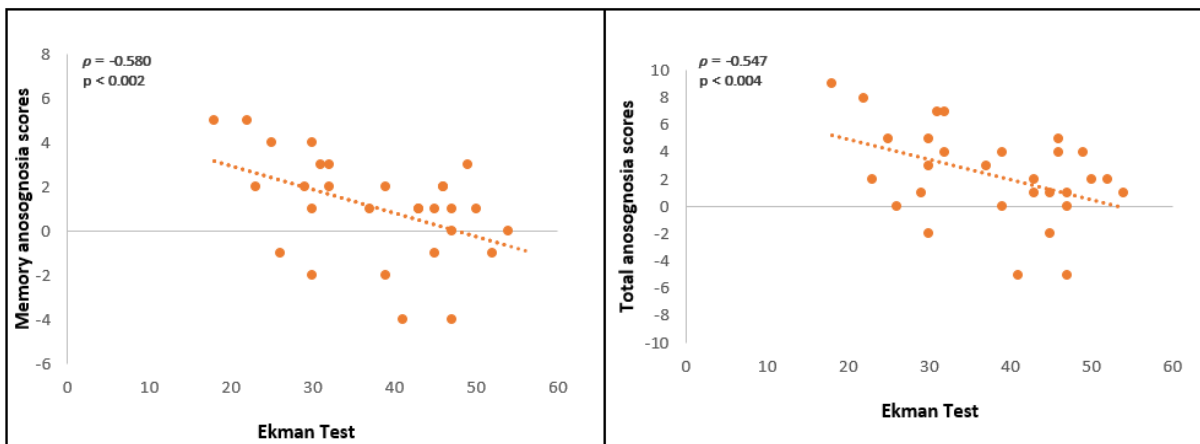


Figure 6.2. Negative correlations between multi-domain anosognosia and the Ekman test scores that survived multiple comparison correction.

6.1.3.2 Intersections of brain structure

Significant VBM negative associations were found between grey matter volumes and all self-awareness measures, while only a positive association was found for ToM (RMET). However, the latter showed a predominant right-sided neural visual overlap with the three measures of multi-domain anosognosia (**Fig. 6.3**). ToM-memory anosognosia neural overlap was found in the ACC ($x= 5, y= 50, z= 5$) and left orbitofrontal cortex ($x= -26, y= 59, z= -16$); ToM-non-memory anosognosia in the thalamus ($x= -2, y= 13, z= 10$), medial prefrontal cortex ($x= -2, y= 45, z= 27$) and ACC ($x= -2, y= 40, z= 2$); and ToM-total anosognosia in the medial prefrontal cortex ($x= -2, y= 45, z= 27$) and ACC ($x= 4, y= 52, z= -4$). Secondly, conjunction analyses found no significant results for any of the models.

Independent significant statistical multi-domain anosognosia maps of grey matter volumes were transformed and masked as a binary map for further analysis of social cognition intersection that shared mutual statistical neural underpinnings. Masked self-other multiple regression models showed a significant statistical positive association ($p < 0.015$ FWE corrected) only for ToM (RMET) - total anosognosia in the ACC and caudate nucleus (**Table 6.2** and **Fig. 6.4**).

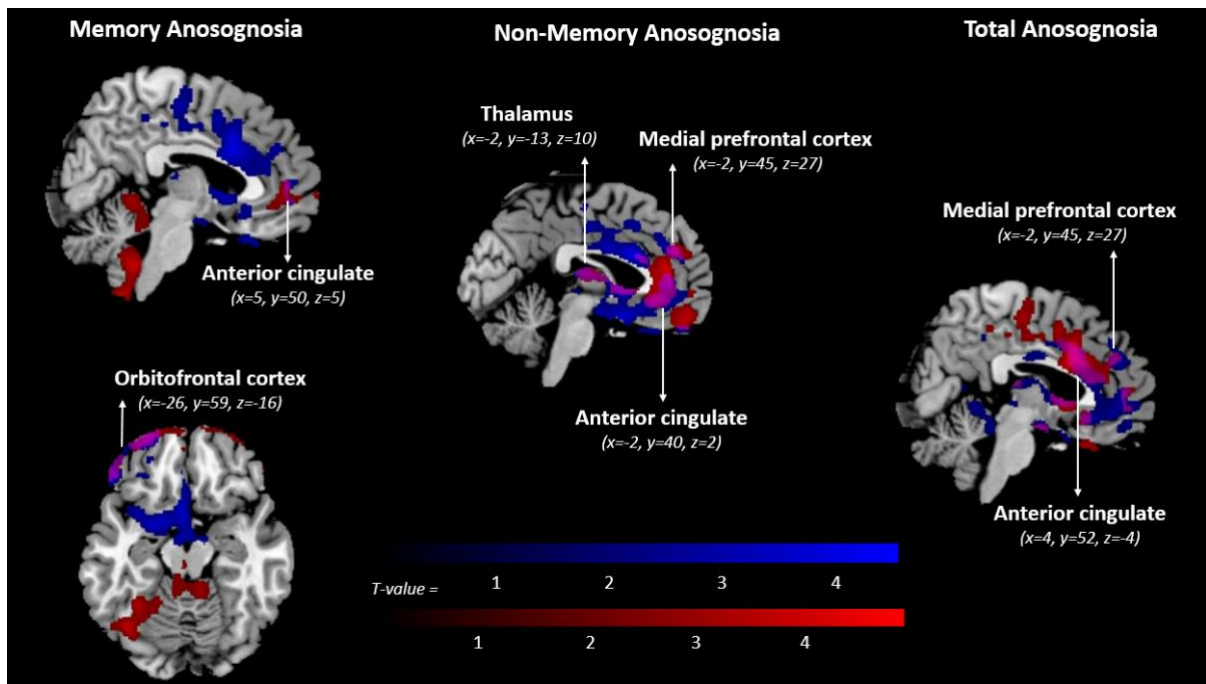


Figure 6.3. Visual brain intersection (magenta) of regions that displayed grey matter changes associated with multi-domain anosognosia (red) and ToM-RMET (blue) significant clusters.

Table 6.2. Significant grey matter clusters of correlation of ToM (RMET) scores within the total anosognosia masked voxel neural territory.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI Coordinates		
						x	y	z
5356	0.015	4.59	R	Anterior cingulate	24	2	14	26
		4.17	R	Anterior cingulate	32	6	16	36
		4.11	L	Caudate - Head	-	-8	6	2

* Threshold of significance defined at $p = 0.025$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute; RMET: Reading the Mind in the Eyes test.

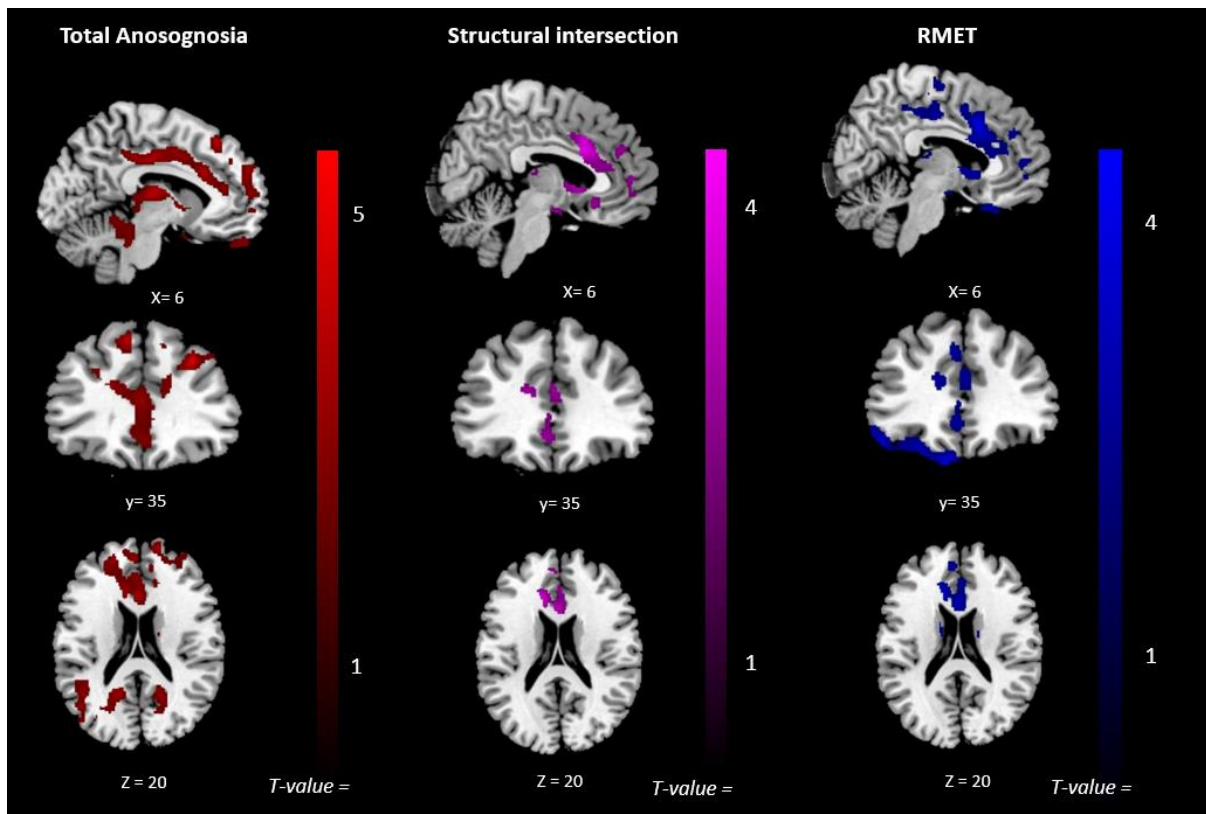


Figure 6.4. Regions that displayed significant changes in grey matter volume that showed a correlation with ToM (RMET) scores within the boundaries of the total anosognosia neural territory; clusters are shown at $p < 0.05$ FEW corrected.

6.1.3.3 Post-hoc intersections with brain structure

Post-hoc analyses were based on the significant results arising from the total anosognosia-RMET masked analysis through applying inverted anosognosia scores ($n \times -1$) and the raw RMET scores in a parallel model where both were included as predictors. A significant positive association was found between total anosognosia-RMET scores and whole-brain grey matter volumes in the bilateral superior and middle frontal gyrus (BA 9), left anterior cingulate (BA 32), left cerebellum, bilateral fusiform gyrus (BA 19/37) and bilateral thalamus ([Table 6.3](#) and [Fig. 6.5](#)).

Table 6.3. Grey matter clusters of significant correlation with the RMET/total anosognosia (inverted) scores parallel predictor model.

Cluster extent	FWE p -value	T Score	HS	Peak-based localisation	BA	MNI Coordinates		
						x	y	z
6741	0.001	5.36	L	Superior frontal gyrus	9	-16	42	39
		4.51	R	Middle frontal gyrus	9	32	33	39
		4.23	L	Anterior cingulate	32	-10	24	28
4600	0.003	4.36	L	Cerebellum	-	-33	-52	-15
		3.77	L	Fusiform gyrus	19	-39	-66	-16
		3.76	R	Fusiform gyrus	37	30	-46	-16
2851	0.042	4.26	L	Thalamus	-	-10	-16	14
		3.77	R	Thalamus	-	14	-10	16

* Threshold of significance set at $p = 0.025$. BA: Brodmann Area; FWE: Family Wise Error; HS: Hemispheric side; MNI: Montreal Neurological Institute.

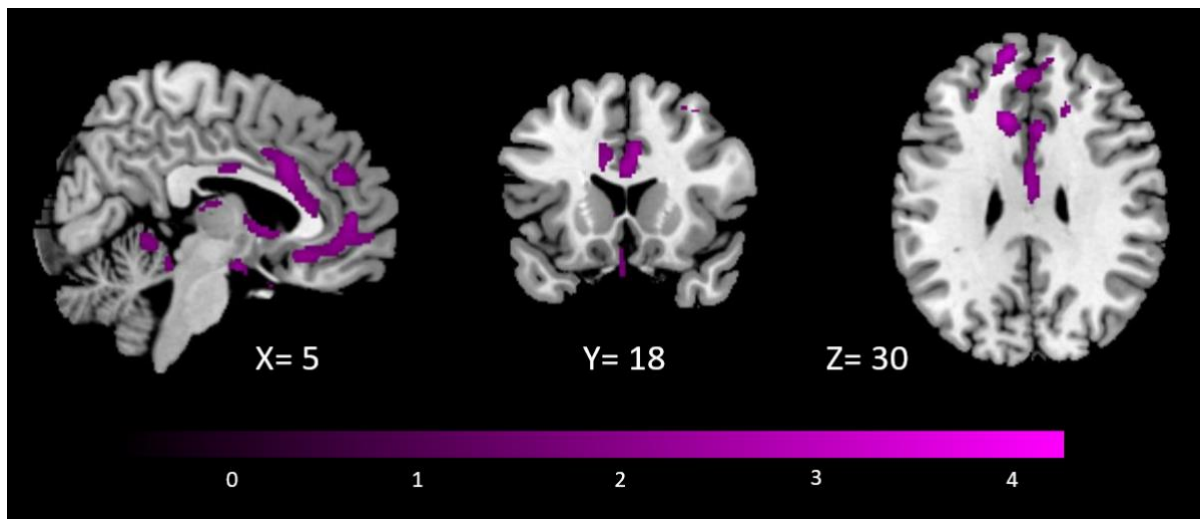


Figure 6.5. Regions that displayed changes in grey matter volume that showed a positive correlation with the RMET and total anosognosia outcomes (inverted) concurrently; clusters are shown at $p < 0.05$ FWE.

6.1.3.4 Intersections with brain function

Significant results were found in association with brain function of large-scale network connectivity and self-other awareness proxies. In this context, only the right FPN and aDMN displayed visual neural overlaps consistent with our methodological approach.

The r-FPN yielded visual brain intersections of decreased connectivity maps underpinning significant clusters of memory anosognosia (negative association) and emotion recognition (positive association) in the right superior temporal gyrus ($x= 56$, $y= 6$, $z= -7$). The aDMN showed an overlap of lower functional connectivity for the RMET (positive) and memory anosognosia (negative) in the inferior occipital gyrus, while higher functional connectivity of the RMET (negative) and non-memory executive anosognosia (positive) was found in the paracentral lobule (**Fig. 6.6**). Lower connectivity could be explained through a parallel negative association with anosognosia (higher anosognosia scores point to lower connectivity) while positive association with social cognition (lower social cognition scores point to lower connectivity). Contrarywise, higher connectivity for self-other awareness would, therefore, translate into a positive correlation of anosognosia in concomitance with a negative social cognition association. Visual intersection findings of the l-FPN, pDMN and salience network showed no clusters of neural overlap. Furthermore, the conjunction and masked territory analyses showed no significant results in any of the large-scale networks.

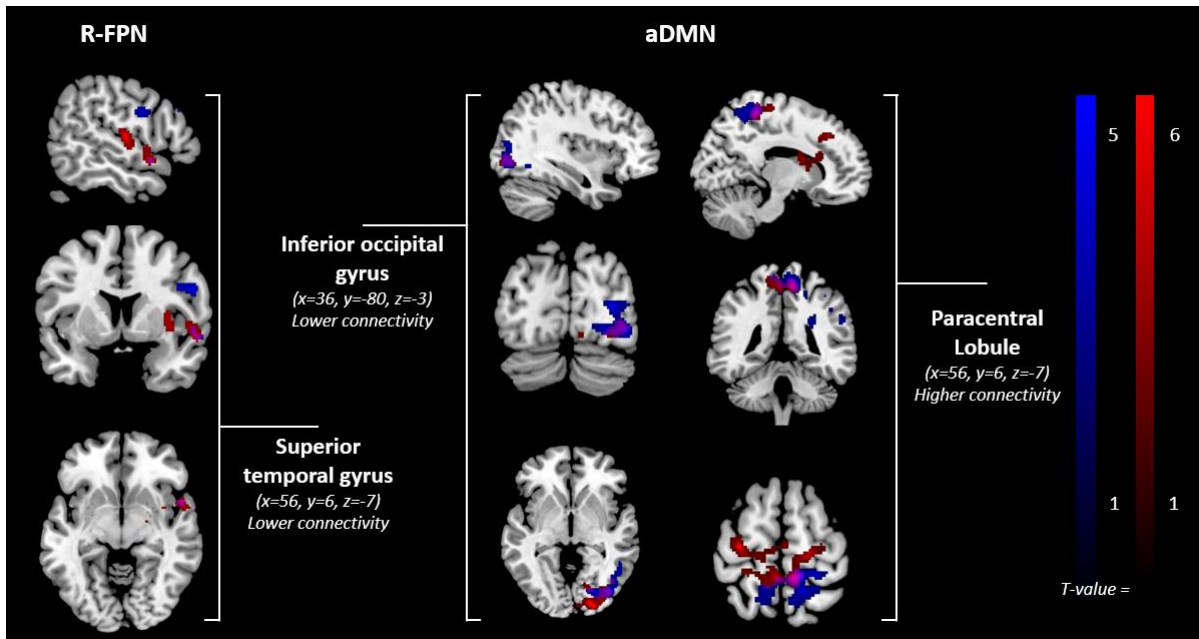


Figure 6.6. Visual brain intersection (magenta) of regions that displayed functional large-scale connectivity differences associated with multi-domain anosognosia (red) and ToM-RMET (blue) significant clusters.

6.1.4 Discussion

The neural correlates of awareness of self and others in early-AD patients show consistency with the independent findings obtained in chapter 4 (self-awareness) and chapter 5 (others-awareness). The present findings provide evidence of a common shared brain territory that underpins cognitive awareness centred in grey matter and functional changes of the self (multi-domain anosognosia) and of one's social surroundings (Theory of Mind, ToM). The essence behind this association relies in the premise that humans who engage in social cognition are employing self-centred neural processes in order to attribute mental states to others (Vogeley et al. 2001).

Firstly, behavioural associations of multi-domain anosognosia and social cognition established a significant negative correlation specifically between affective recognition and processing (ToM) with memory, non-memory and total anosognosia scores. In this context, a higher presence of anosognosia was associated with a

decreased level of proficiency in social cognition in the selected subsample. An initial approach to explore the association of self-other awareness can be observed in patients with alexithymia, or the inability to be self-aware of one's own socio-emotional states. There is evidence that patients with MCI and AD might display unawareness of emotional processing in comparison to controls ([Belfort et al., 2018](#); [Yuruyen et al., 2017](#); [Smirni, Beadle & Paradiso, 2018](#)); however, this impairment is not prominent enough to be featured as a pathognomonic hallmark of AD, but rather an accompanying feature delineating a multi-domain decline of cognitive awareness in the early stage of the disease ([Arroyo-Anllo et al., 2020](#)). As mentioned throughout this thesis, the presence of unawareness follows a domain-specific trajectory. The most prominent feature of unawareness, aligning with the aetiopathological manifestations of the disease, is through reduced self-awareness of decline/deficits within the memory domain. Nevertheless, decline in the socio-emotional sphere seems to be present and linked to other domains of awareness, as demonstrated in the present behavioural correlational models.

A further possible insight on the impact of self-other awareness in early-AD patients is through research based on the patients' ability to extrapolate their own self-perspective to take the perspective of others, an ability that can be altered by other neurological disorders such as hemiplegia ([Ramachandran & Rogers-Ramachandran, 1996](#); [Besharati et al., 2016](#)). Research based on the first-to-third person perspective taking has demonstrated that patients with AD seem to be better at recognising deficits in others than in themselves ([Clare et al., 2012b](#); [Mograbi et al., 2014](#)). Hence, behavioural interventions based on improving perspective-taking abilities have shown to decrease effectively neuropsychiatric symptoms and caregiver burden while

increasing quality of life. These interventions have the aim to enhance self-care through caring for others by strengthening skills based on empathy (Au et al., 2020).

The structural neural overlap of self-others awareness in this study showed that the mPFC and ACC display a spatial brain intersection, sustained by the data findings from three different methodological approaches (visual intersections, masked neural territories and *post-hoc* two predictor analyses). The ACC is proposed to serve as an integrative centre for cognitive monitoring of personal and socioemotional processing (Stevens et al., 2011; Lavin et al., 2013). Therefore, this neural structure may serve as one of the areas regulating decision-making processes about behavioural outputs that depend on social-environmental stimuli. In the context of socio-emotional unawareness, Sturm and Levenson (2011) showed that people with dementia displaying alexithymia had lower grey matter volumes in the right pregenual ACC. This finding was corroborated by the results of a study comparing higher-lower alexithymia in the healthy population, also detecting grey matter changes predominantly in the ACC, amygdala and insula (Ihme et al., 2013). The mPFC (including the ACC) has been established as essential for metacognitive functions, in which self-referential thinking is a fundamental feature that allows high-level representations to align with social functioning (Amodio & Frith, 2006; Uddin et al., 2007). Lower activation in the mPFC was found in a study of patients diagnosed with alexithymia when these latter were compared with controls, and socio-emotional unawareness was attributed to the patients' inability to shift from first-to-third perspectives (Moriguchi et al., 2006). In relation to AD, brain functional activation based on perspective-taking tasks showed higher neural activations of the mPFC and OFC (Ruby et al., 2009; Zamboni et al., 2013). In a task-dependent fMRI study, Finlayson-Short, Davey & Harrison (2020)

found that self-other referential judgements in healthy young individuals activate the dorso-ventral mPFC extending to parts of the ACC, PCC and medial temporal cortices.

Our findings also revealed the role of particular subcortical structures as relevant neural points for self-other's awareness. Specifically, the thalamus showed an association with these skills in the structural arm of this study. This region has shown to support self-other mental processing in studies based on healthy individuals (Finlayson-Short, Davey & Harrison, 2020) and in patients with multiple sclerosis (Czekóová et al., 2019). A brain physiological proposition states that the thalamus may participate in the construction, update and maintenance of mental representations by supporting cognitive functioning, and therefore, the capacity for overall mental awareness (Wolff & Vann, 2019).

Lastly, functional visual intersections of worst self-other performance revealed parallel regions of reduced connectivity of the r-FPN in the superior temporal gyrus and the aDMN in the inferior occipital gyrus. The superior temporal gyrus was found to be an overlapping area of self-other facial recognition in an fMRI meta-analysis based on healthy individuals (van Veluw & Chance, 2014). In this respect, the temporal pole has been recognised as a structure supporting mnemonic processing of self-related information. Hence, this region might serve as an anchoring hub for self-others information by the integration of experiences related to the self that might eventually assist to comprehend the minds of others (Moriguchi et al., 2006). The occipital cortex has also been implicated in self-other functional processing; specifically, this region might help create visual templates for expectations of different behavioural outcomes regarding others, as a way to help predict the behavioural responses of others (Gilbert & Fung, 2018). In this respect, a reduced intercommunication of the DMN with the visual and semantic systems during self-other processing might be a consequential

effect stemming from the detrimental impact of the brain pathological spread to visuospatial and semantic territories that characterises AD. Nonetheless, this could also translate into the redirection of neural resources to more elementary and robust social systems based on social imitation and mimicking, such as the mirror neuron system (Jeon & Lee, 2018). On this note, our experimental findings showed that worst self-other performance yielded increased visual parallel connectivity of the aDMN in the paracentral lobule, a region known to be involved in sensory-motor functions (Lim et al., 1994). This increase of neural resources to motor-related structures might reveal adaptive mechanisms centred on increasing brain load to the mirror neuron system to cope with impaired social performance.

The mirror neuron system has been intrinsically associated with social cognition and imitative behaviour. Hence, an integrative vision to our results based on midline cortical structures (mPFC and ACC) and functional mirror mechanisms relies on the conjunction of a physical-psychological system that facilitates social understanding and learning. The mirror neuron system has been shown to be highly active during self-other representations based on internal to external intention attributions. In a task-based fMRI study, the ACC was active for all tasks involving self-other depictions (Iacoboni et al., 2005). Therefore, the mirror neuron system might provide motor other-to-self mapping and imitation learning, while the midline cortical regions provide high order complex cognitive evaluation and mental state attributions (Uddin et al., 2007).

The perspectives that have been stipulated throughout this current chapter are based solely on the notion that social cognition is an extension of the ability of self-awareness. However, it has also been postulated that self-awareness is an extension of social cognition, where ToM can be divided into two stages that comprise an initial self-perspective inhibition, associated with structures within the frontal cortex, and

subsequent reasoning of beliefs, a process that is essential for correct mental attribution, a trait that could be partially mediated by the superior temporal gyrus ([van der Meer et al., 2011](#)). In this context, Moretti (2016) found cortical thinning in the inferior parietal lobe, supramarginal gyrus and precuneus in MCI patients who eventually progressed to AD during an electroencephalography study, in which it was proposed that a pathological process damaging the mirror neuron system early in the disease course might trigger a transitional pathological shift to dementia.

A mechanistic approximation to the present findings relies on the equilibrium between the neural territories that define cognitive awareness. Independent systems might code semantic information related to the self and others in separate brain spatial domains. However, it seems that, although the separate domains of awareness rely on independent systems, a substantial neural overlap might delineate the processing of cognitive awareness, in relation to the self and social spheres ([Bertrand, Landeira-Fernandez & Mograbi, 2016](#)). In this context, the DMN might be the large-scale brain network implicated in how individuals perceive and process the separate constructs demarcating cognitive awareness ([Yeshurun, Nguyen & Hasson, 2021](#)).

6.1.5 Conclusions

As a concluding remark, the independent findings arising from this chapter and the previous experimental work-frame show a consistent contribution of the frontal cortex (most predominantly of the ACC) to cognitive awareness in early-AD. The transitional state between self-awareness to other-awareness might rely on executive/attentional-related mechanisms that allow the inhibition of self-centred mental states and direct cognitive resources to an external social stimulus that, in turn, promotes mechanisms

of attribution of mental states to others, and that depends considerably on cognitive flexibility. In this case, the prefrontal cortex and ACC might regulate and establish integrative coordination of brain directed resources. In a brain network mechanistic model, large-scale network dynamics might direct attention to self-referential thinking with a subsequent deactivation of the DMN when attention is now drawn to external social stimuli, with the consequent activation of other networks such as fronto-parietal or salience networks ([Buckner, Andrews-Hanna & Schacter 2008](#)). In the presence of a breakdown of systems in charge of cognitive awareness (i.e., the DMN extending to the mirror neuron system), brain network dynamics seem to rely upon a flexible redirection of attentional and executive resources to support and manage cognitive awareness in the context of early AD. Unfortunately, for this specific experiment we did not find widespread results regarding the functional self-other substrates defining large-scale functional networks. This might be a result of a reduced sample size; however, this proof-of-concept study provided valuable insights that helped shape the understanding of conscious awareness in the early AD continuum.

Chapter 7

General Discussion

Patients in the early AD continuum might present with impairments in the different spheres that constitute cognitive awareness. The presence of unawareness can impact substantially a patient's quality of life as it hampers directly the individual's ability to perceive reality. The presence of this symptom eventually leads to an increased risk of faster disease progression, caregiver burden and institutionalisation. The foundation of this experimental thesis was based on the two most important domains that define conscious awareness, namely the capacity for self-awareness and the capacity to be aware of others studied through two concepts of cognitive psychology known as metacognition and social cognition, respectively.

Deficits in self-awareness (metacognition) were studied through the presence and severity of domain-specific and multi-domain anosognosia. In AD, anosognosia is defined as a lack of awareness for cognitive deficits or severity of disease and is a prevalent neuropsychiatric symptom ([Tagai et al., 2020](#)). The onset is highly heterogeneous and can present as early as the preclinical stage ([Cacciamani et al., 2017](#)). Most importantly, it has been shown to be a predictive risk factor of dementia conversion in people with prodromal symptoms ([Therriault et al., 2018](#)). At the brain level, previous studies have highlighted the link between anosognosia and damage to prefrontal functioning ([Mondragon, Maurits & De Deyn, 2019](#)) and the default mode network (DMN) ([Therriault et al., 2018](#)), that extends to dysfunction of frontally mediated abilities such as executive functions ([Ramanan et al., 2017](#)). On the other

hand, deficits in awareness of others might reflect an incapacity to recognise and understand the intentions, beliefs or emotions of other individuals. Likewise, In AD, social cognitive skills might be supported by high-order cognitive functions ([Christidi et al., 2018](#)) and their neural substrates seem to correspond to territories also within the default mode network or structures that have an intrinsic connection with this large-scale functional brain system ([Baglio et al, 2012](#), [Synn et al, 2018](#), [Le Bouc et al., 2012](#); [Kumfor et al., 2017](#); [Takenoshita et al., 2020](#)). Therefore, the main domains that define cognitive awareness (self-other) in AD share two important similarities in the current literature, 1) the possible dependence on high-order executive resources and 2) their relation to the integrity of the DMN.

The main objectives of this thesis were to clarify the substrates that define cognitive awareness in the early AD continuum through the correlates of three pragmatic research proxies, namely 1) a comprehensive neurocognitive profile, 2) grey matter brain structure and 3) brain functional and structural intrinsic connectivity. Dissecting each domain of awareness, experiment 1 and 2 (chapter 4) had the objective to elucidate the neuropsychological, brain structural and functional profile of anosognosia in the early AD continuum with the novel approach of exploring the two main domains that comprise self-awareness in AD: 1) a memory domain and 2) executive/daily life activities domain through a comprehensive behavioural and multi-modal imaging methodology. Similarly, experiment 3 and 4 intended to provide insights into others' awareness and social cognitive functioning (through the domains of emotion recognition and cognitive and affective Theory of Mind). In the setting of early AD and social awareness, the novelty of these experiments relied on the lack of literature regarding the neural substrates of social cognition in this population. Therefore, the results of chapter 5 provided the first insights of a comprehensive brain-

cognitive clinical profile that could be utilised to enhance the differential diagnostic tools between AD and other types of neurodegenerative dementias.

The neuropsychological profile of cognitive awareness demonstrated in a first instance that the proxies of self and others awareness are associated with each other (as shown in chapter 6). In other words, patients presenting with single and multi-domain anosognosia also displayed deficits in social cognition, specifically in Theory of Mind and emotion recognition. The findings from this experiment supported significantly our hypothesis that the presence of anosognosia parallels poorer performance in social cognition. This association raises a critical dilemma, i.e., does the ability for self-awareness modulate social cognition or do social cognition deficits drive the presence of anosognosia? Initially, the former seemed like a more plausible hypothesis. The only way to recognise and acknowledge the state of minds of others requires a judgment based on an introspective comparison relying upon the self. However, the social-cognitive domain seems to have been vastly overlooked in the literature and we seem to neglect that the acquisition of knowledge and learning is based on social skills that are based on imitation and continual social feedback. Therefore, the self might be fundamentally determined by others. More specifically, results arising from experiment 1 showed that self-awareness deficits were associated with proxies of semantic and episodic memory (memory and total anosognosia) and with visuoconstructive skills (total anosognosia). Our hypothesis stated that grey matter loss in frontally mediated structures would also extend to associated cognitive functions. In this respect, we found no specific cognitive deficits related to frontal functioning, i.e. executive/attention functions associated with mnemonic structures in our results. Following the theoretical model of awareness, mnemonic functions such as semantic and episodic memory are the essential foundation to form a healthy

personal database that relies on neural structures supporting memory and extends to impact on the comparator mechanisms. On the other hand, social cognition and others awareness was mainly associated with overall cognitive functioning, language, working memory, semantic memory, selective attention and executive functions, the latter showing the most consistent findings. In this sense, social cognition showed a more widespread association with overall cognition than self-awareness. The findings from cognitive assessment supported our hypothesis stating that impairment in frontal lobe structures would be associated with frontally-mediated cognitive functions, as executive-attentional abilities yielded the highest associations with social cognition tasks. This point could provide an opening explanation regarding the clinical differences of deficits in conscious awareness, in which in AD, social cognition remains preserved until the later stages of the disease supported by higher mental abilities, while self-awareness dysfunction is more prevalent in the early stages and even in the preclinical stage and behave independently of cognitive functions. Selective compensatory mechanisms might preserve social and emotional abilities. The cross-domain variability of the cognitive correlates of these abilities in our results indicates that various computational mechanisms are at play in the presence of alterations of cognitive awareness.

Brain structural findings showed associations of non-memory anosognosia predominantly in fronto-temporal structures, specifically the bilateral anterior cingulate, fusiform, lingual and precentral gyri, where the bilateral fusiform gyrus displayed the higher association through the use of two volumetric methodologies. Similarly, total anosognosia showed negative associations in the bilateral anterior cingulate and left lingual gyrus, fusiform gyrus and thalamus. The result of this structural analysis supported our hypothesis suggesting that domain-specific anosognosia would reflect

the detrimental effects of grey matter loss in frontal lobe regions that support the performance of the mnemonic comparator system; in this case, structures such as the anterior cingulate and precentral gyri were found related to domain-specific self-awareness deficits. On the other hand, Theory of Mind was correlated with grey matter volume in the anterior cingulate cortex, orbitofrontal cortex, temporoparietal junction (TPJ), superior temporal cortex and cerebellum, with the latter displaying the most consistent findings. Our hypothesis stated that social cognition changes were related to grey matter reductions in frontal regions known to support social cognition skills in healthy individuals. In this context, there was a substantial overlap of regions known to be associated with social cognition abilities in healthy individuals in addition to the few regions that have been associated with social cognition deficits in patients with AD. Therefore, not only frontal regions known to be associated with social cognition (cingulate and orbitofrontal cortices) were found involved but also temporo-parietal regions that are essential to social cognition, providing greater support to our hypothesis. Structural connectivity showed positive associations with the inferior fronto-occipital fasciculus, corpus callosum and superior corona radiata. Grey matter reduction of the ACC was evidenced both in relation to multi-domain anosognosia (experiment 1) and theory of mind deficits (experiment 3). Notably, these shared findings were corroborated in experiment 5 in which the ACC was the most representative shared neural territory affected by self-other awareness deficits. Notably, these findings supported our self-other hypothesis in which shared structural neural territories, specifically in medial frontal cortical regions, i.e., the ACC, would be the underlying substrates of impaired conscious awareness in early-AD. These findings come as no surprise, substantial evidence has shown the involvement of the ACC to self and others awareness ([Amodio & Frith, 2006](#); [Lieberman, 2007](#); [Lou,](#)

[Changeux & Rosenstand, 2017](#)). This region has been proposed to be responsible for self-regulation and monitoring of affective states ([Stevens et al., 2011](#)). In addition, the ACC represents a key node of the salience network, a system in charge of modulating the neural outputs of the DMN and of the executive fronto-parietal network in relation to internal and external demands. Furthermore, this structure drives autonomic attention to salient stimuli regarding emotional situations through an increased communication to the insular cortex ([Medford & Critchley, 2010](#)). The cognitive component within the ACC relies on high-order executive-attentional resources that allow for essential functions that lead to cognitive awareness such as inhibition and shifting of self to others perspective and self-related mnemonic update of the personal database. In this context, we argue that specific regions based on the frontal lobe, including the ACC, could contribute to the functioning of the executive mnemonic comparator systems postulated by the theoretical models of anosognosia and to the core mentalising network that anchors the domains of affective and cognitive Theory of Mind. The integrity of the ACC is required not only to perform complex high-order cognitive functions such as awareness but also for the patient to perceive and retain an adequate sense of reality.

Functional connectivity experiments 2 and 4 had the objective to approach the study of cognitive awareness through a reliable non-invasive methodology relying on resting-state fMRI and the study of large-scale brain functional networks that might be associated with conscious unawareness. Brain functional alterations showed a particular pattern of changes in network dynamics that characterised self and others awareness. Domain-specific alterations of conscious awareness were reflected in the intrinsic connectivity among the three main networks that drive brain cognition, namely the default mode network (key nodes relying upon the medial prefrontal cortex and

posterior cingulate/ precuneus), executive fronto-parietal network (main nodes in the dorsolateral prefrontal and posterior parietal cortices) and salience network (key nodes are harboured in the ACC and insula) (Bressler & Menon, 2010).

As a starting point, it is paramount to highlight the most predominant functional connectivity feature seen in AD, in comparison to other dementias, that is an early breakdown of the default mode network (DMN). The explanation of our results can only be approached with the conceptual foundation of a hampered DMN. More importantly, this network has been widely studied in health and disease and there is substantial evidence suggesting that self-awareness and social cognition are inherently mediated by the neural hubs that constitute this brain system. This is mainly due to this network's activation during task-free activities, where the mind can be centred on self-monitoring activities that extend to behaviours within a social environment. However, the global interplay of other large-scale networks in support of these abilities was poorly understood in AD. Moreover, the effect of how distinct domains of unawareness selectively affected the overall brain network architecture provided valuable insights into cognitive awareness performance in this type of dementia.

Our results reflect an overall pattern of reduced DMN-FPN connectivity, but increased DMN-salience intercommunication. Memory anosognosia scores were associated with overall lower fronto-temporal connectivity but increased parieto-temporal connectivity. Conversely, non-memory anosognosia was associated with higher DMN-cerebellar connectivity, and between the left medial prefrontal cortex, including the ACC, and the right dorsolateral prefrontal cortex; while lower connectivity was observed between the right prefrontal cortex and ipsilateral temporal regions. Lastly, total anosognosia displayed large-scale network alterations, namely lower

functional connectivity of the left FPN to the left posterior cingulate and the left hippocampus to the right dorsolateral prefrontal cortex, while increased connectivity between the right FPN to the left inferior lingual gyrus and adjacent inferior occipital cortex; and aDMN to the right ACC. In this setting, the frontal cortex seems to be heavily interconnected to networks and regions involved in multi-domain anosognosia. Memory and total anosognosia correlates displayed a large-scale interconnection among fronto-parieto-temporal regions. On the other hand, non-memory, which includes executive-related anosognosia, shows overall connectivity changes mainly centred in the dorsolateral prefrontal cortex, a key node of the executive frontoparietal network. Subcortical contributions to anosognosia denote the interplay of a broader brain interconnected awareness network outlining these symptoms. Furthermore, these findings support the premise that executive related mechanisms seem to orchestrate the neural findings of domain-specific unawareness in early AD. More importantly, the findings of the present thesis show that memory anosognosia results from reduced network coupling between the DMN and frontoparietal executive network, while non-memory anosognosia appears to be linked with increased connectivity of the frontoparietal executive network to both the DMN and salience network. In this setting, memory anosognosia network dynamics seem to provide support to our hypothesis that a central executive component of the conscious awareness system (CAM) might be malfunctioning during self-reflection of memory abilities and result in the clinical symptom of unawareness of memory deficits. On the other hand, non-memory anosognosia for executive functioning could reinforce adaptive mechanisms to increase resources from the salience network in an attempt to redirect network traffic and compensate for damage of complex high-order metacognitive functions within the DMN.

The experimental approaches of chapter 5 served to elucidate the functional neural substrates of social cognition in early-AD to create a comprehensive clinical profile of social performance. This study sheds light on how multi-network dynamics exhibit particular connectivity dissociation patterns that may characterise up and down-regulation of social processing in AD. Firstly, changes in grey matter show consistency with regions already known to be associated with ToM in healthy individuals. Affective social cognition scores were associated with changes in functional connectivity with the right executive fronto-parietal network, showing higher functional internetwork connectivity in the right TPJ and insula. In contrast, the salience network showed lower internetwork connectivity with the left TPJ and Insula. The aDMN displayed less functional connectivity with the right prefrontal cortex and the pDMN with the left prefrontal and precentral cortices. In other words, large-scale and seed-based connectivity findings demonstrated also patterns of reduced DMN-FPN and increased Salience-FPN network coupling associated with variation in social cognition performance.

Alterations in connectivity coupling of the DMN to executive-attentional networks may cope with ToM-DMN associated decline through the support of independent executive mechanisms and increased network traffic to the salience network to provide compensatory support to awareness mechanisms. The latter may provide insights into an integrative perspective of the brain-to-cognition consolidation that arose from the behavioural findings in which executive functions is the neurocognitive domain most profoundly intertwined with ToM performance in AD.

Overall, the multimodal approach to the study of awareness in AD showed an interesting pattern of results that arose from both the independent functional network correlates that define cognitive awareness in AD in chapter 4 and 5. Both our functional

connectivity hypotheses were supported as they relied on network connectivity changes to/from or within the DMN. It seems that there is clear evidence of reduced network coupling between the DMN-FPN as shown in memory and total anosognosia, in addition to the findings related to emotion recognition and affective Theory of Mind. In contrast, increased network coupling was evidenced between the DMN-salience network in association with the findings of non-memory and total anosognosia and emotion recognition and Theory of Mind analyses **Figure 7.1**.

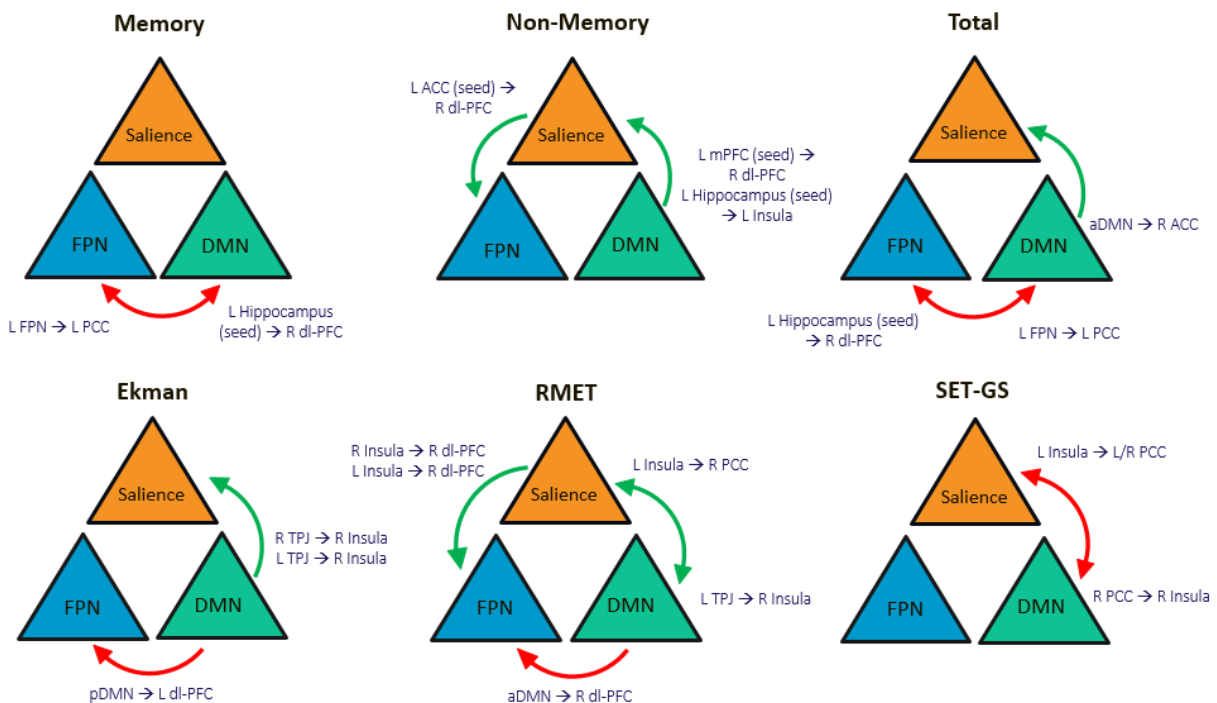


Figure 7.1. Visualisation and summary of significant large-scale and seed-based functional findings of self (anosognosia) and other's (social cognition) awareness variables in the context of the main networks that define cognition.

However, these patterns of results could not be replicated through a statistical conjunction methodology in chapter 6. A possible explanation for the absence of functional overlap might be related to the fact that the functional intercommunication of the triad networks relies on different brain components for self and for others

awareness. The relatively small sample size on which this analysis was carried out, however, could equally explain the lack of significant findings when a conjunction analysis was attempted. Nevertheless, large-scale and seed-based results pointed to these alterations in network dynamics. Our findings point to frontal midline structural changes in the ACC but detected no widespread alterations in this region. As stated before, functional detrimental alterations precede grey matter structural changes. As a way to propose an integrative perspective of our experimental cognition-brain-related findings, it might be suggested that cognitive network dynamics rely on the interplay between a self-centred internal DMN and an externally-mediated executive network. These networks appear to be modulated by a network in charge of regulating traffic of salient internal or external stimuli, within which the ACC is a central computational node (Bressler & Menon, 2010). Therefore, increased intercommunication between the salience network and the DMN might reflect a redistribution of resources in an effort to increase the cognitive demand and attention to internal metacognitive processes in the presence of diminished capacity for awareness in early AD. As a result, a possible maladaptive consequence of this increased demand for network resources might result in heavy strain to nodes responsible for salient control (ACC and insula), resulting in a secondary reduction of grey matter volume evidenced throughout all the structural experiments in this thesis. A critical review of the findings, however, highlight some potential mismatch and overrepresentation of finding pointing at a central role of ACC. The importance given to a more central involvement of the ACC in the present research than to any of the other significant structures from our findings might have been influenced by a trend for publication bias that overrepresents the ACC in previous published work. However, in all experimental studies of self, other and self-other awareness, the ACC was a consistent finding, at least at the structural

neural level. To provide a convincing argument about the contributions of this region to awareness, it is important to refer to the amount of current published clinical data. This structure has been found in several other multimodal neuroimaging studies associated with anosognosia and AD (Amanzio & Palermo, 2014; Guerrier et al., 2018; Mondragon et al., 2021) and self-awareness related abilities in healthy populations (Devinsky, Morrell & Vogt, 1995; Bush et al., 2000; Amodio & Frith, 2006; Medford & Critchley, 2010).

7.1 General limitations

A number of general limitations can be identified throughout this work. Firstly, regarding the sample size; due to the study design, it was not feasible to recruit a larger number of patients to undergo the assessment for both anosognosia and social cognition. This had a negative impact on the structural connectivity and resting-state findings, as some of the trends arising in this thesis may have shown significant results with higher patient numbers or at lower statistical thresholds. Nevertheless, in comparison with the literature focused on the study of anosognosia and social cognition in AD and other neurodegenerative disorders, the studies in this thesis have the largest sample size to date and there was sufficient statistical power to support our hypotheses and findings and to provide mechanistic approximations to how conscious awareness might be affected early in the AD continuum.

The neurocognitive assessments used for testing the different domains of self-awareness and social cognition can also represent a potential general limitation within this project. Unlike other aspects of cognition such as declarative memory or visuospatial abilities, the assessment of conscious awareness might be complex in clinical settings. To begin with, anosognosia is a neuropsychiatric symptom that relies

on the subjective assessment of the patient's ability to perceive reality. In order to detect that there is indeed a change of perceived reality, both the carer and the clinician have to establish a definite standard of truth for comparison in order to establish a mismatch in reality perception. This means that in order to assess self-awareness decline on others a witness must provide a truthful statement of cognitive change in the patient. This is an intrinsic limitation inherent to the assessment of symptoms such as anosognosia that rely on complex mental processes to achieve a proper appraisal of one's own reality. Moreover, the assessment of social cognition requires the patient to have a proper understanding of the social sphere and grasp everyday social interactions. At first, this seems like an inherent human quality, but as cognitive decline begins to affect the patient's everyday life activities, the social construct can be severely hampered leading to a patient's loss of interest in the surrounding social engagements. With all these limitations in mind, a series of neuropsychological tests were constructed in two ways; firstly, they were such that had low cognitive demands using very straightforward questions in the anosognosia questionnaire or predominantly visual assessments, with the objective to reduce the overall burden on memory functions. Secondly, we used the most prevalent methodological approaches across the existing literature that tested anosognosia (through a questionnaire approach based on patient/informant discrepancy scores) and social cognition (emotion recognition and reading the mind in the eyes test). Of course, we cannot rule out the effect of other domains of cognition at the time of assessment, but everything possible was done to minimise the effect of spurious factors on results.

The inclusion in the same sample of patients at different stage of cognitive decline, i.e. mild cognitive impairment and mild probable AD, might also be seen as another

possible general limitation of this project. In a first instance, the current diagnosis of AD relies on molecular biomarkers that were not possible to be obtained due to the retrospective nature of data analysis. The cohort sample was recruited during times in which molecular biomarker sampling was not routine or pragmatic within the research environment. However, the cohorts were diagnosed through three different parameters, namely neuropsychological assessment, neurological testing and structural hippocampal MRI measurements and clinical follow up has been done with these patients for a number of years now, increasing confidence on the accuracy of diagnostic status at time of recruitment. A second possible limitation might be the combination of all patients in one cohort without any stratification by severity. This choice, although maximising statistical power and variance in scores, did not allow a characterisation of how conscious awareness impairment manifests and evolves across different disease stages.

Lastly, neuroimaging data for the participants in this study had been acquired through a multicentre protocol within the VPH-DARE@IT initiative that required distinct scanning protocols depending on the available scanner at each site, resulting in pooling of data from different scanner magnetic field strengths. In an ideal scenario, all patient acquisitions should have been performed with the same scanner at the same magnetic field strength. Acquisition protocols, were however, harmonised and the influence of this potential confound was accounted for in the analyses and minimised by the harmonisation of acquisition parameters. This practice has become increasingly accepted and widespread in multicentre international initiatives. In this context, volumetric and functional data were preprocessed accounting for this potential source of variability in the data and information was homogenised, smoothed and modelled in an appropriate manner at the group level.

7.2 Future directions and impact

This project had the objective of investigating in depth the cognitive and neural correlates of self-other conscious awareness in the early stages of AD. If this project had to be redesigned, we would have included a more comprehensive battery of assessments to address the most representative domains of human awareness, inclusive of spatial awareness (that would have helped elucidate and provide an explanation for the correlates of self-other perspective-changing abilities), time awareness (as a reflection of how a patient perceive not only a static reality but the dynamic shifts of their every-day-changing surroundings) and interoceptive abilities as a proxy of perceptual awareness. With a more comprehensive battery of assessments, a more integrative neurocognitive profile would have been acquired to elucidate how subtle changes related to awareness at all levels might possibly explain the presence of other symptoms normally attributed to other cognitive domains. Secondly, I found a profound interest in social cognitive skills and the perception of a patient's social sphere. With this in mind, I would have tried to dissect all the neuropsychiatric symptoms in relation to how the presence or absence of both positive (delusions, psychosis, confabulations or anosognosia) or negative (apathy, anxiety, depression or agitation) might influence a person's social cognition skills including emotion recognition and, most importantly, cognitive and affective Theory of Mind.

The findings of this project have also a direct clinical impact. First, they suggest an early frontal cognitive degeneration in AD that is not detected by traditional cognitive tasks, but can be detected with the tasks used in this thesis; although middle temporal lobe degeneration is a paramount feature, the findings presented in this thesis indicate that a more globally widespread synaptic dysfunction happens even at the earliest stages of AD neurodegeneration. Our findings revealed a selective vulnerability of

large-scale networks such as the Default Mode Network; this latter network is recognised as a modulator of both self-awareness and social cognition abilities. The present findings provide evidence that other large-scale networks are involved to support abilities and compensate for the decline of this network. Our results point to an increased intercommunication between other large-scale networks and the salience network, a system known to oversee shifting between self-centred thinking and externally driven social stimuli. In the presence of decline of self/other awareness a clinician would be alerted to a potential more widespread functional decline already present and failure of compensatory mechanism that could then potentially lead to early neuropsychiatric manifestations and increased carer burden. Clinical awareness of these potential risks might suggest the implementation of early behavioural interventions to strengthen a patient's ability to reflect and introspect on their own mental abilities (metacognition). This should be essentially accompanied by a reinforcement of a patient's social sphere through selective social interventions in order to reestablish how an individual perceives themselves and their social environment. In turn, this would reduce the anxiety and stress that accompanies the emergence of these alterations and might also result in improvements in other areas of cognition such as memory, attention or executive functions.

7.3 Final conclusions

The present thesis has shed light on the cognitive and neural correlates that define self and others awareness in the early AD continuum. In essence, the findings suggest a substantial contribution of the frontal lobe and associated high-order cognitive functions to the different domains that compose human conscious awareness. The

novel principle of this thesis was that it aimed to elucidate the complex concept of awareness through the investigation of its different independent components and to provide an understanding of the relationships that exist among the interactions of the most predominant domains affecting the AD population. Behavioural, structural and functional changes denoted an overall reduction of neural resources predominantly in midline cortical structures that are part of a territory proposed to be involved in awareness and conscious appraisal ([Amodio & Frith, 2006](#)). The cognitive correlates of self-awareness rely upon mnemonic functions, as a possible reflection of a dysfunction in the ability to update an internal personal database, while social cognition relies heavily on overall cognition with a particular predominance of executive and attentional resources. The latter could provide a possible explanation for the late onset of social cognition decline in early AD. Functional changes showed a reduced intercommunication between the DMN and the executive frontoparietal network, while increased DMN and salience communication in all levels of awareness was also detected. The inherent early dysfunction of the DMN might promote an increase in the contribution of a network in charge of shifting resources in order to compensate for a progressive decline of awareness. Further functional strain to salience network hubs could explain the structural detrimental changes of the medial frontal anterior cingulate cortex observed associated with all levels of domain-specific and multi-domain self-other awareness. This structural decline could eventually translate into damaged frontal lobe mechanisms associated with the executive comparator within the self-awareness model along with the control centre of the mentalisation system in charge of complex processes regarding the intentions and emotions of others. Patients presenting with changes in cognitive awareness should not be overlooked in the clinical setting, a progressive loss of awareness might increase importantly the risk of

dementia progression, caregiver burden and risk of institutionalisation. It seems that several brain structural and functional adaptive mechanisms interplay in restructuring the brain architecture that defines the ability to achieve and sustain a sense of consciousness. Therefore, systematic assessment of social cognition and self-awareness abilities could provide a new avenue for early therapeutics to restore the patients' ability to perceive themselves and others adequately according to current reality, not only in AD but in other neurodegenerative dementias.

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Appendix A. Original research article based on chapter 4, experiment 1.

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Research Report

Neuroanatomical and cognitive correlates of domain-specific anosognosia in early Alzheimer's disease



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ABSTRACT

Anosognosia in Alzheimer's disease (AD) is defined as a lack of awareness for cognitive deficits or severity of disease. Previous studies have highlighted the link between anosognosia and damage to prefrontal functioning, i.e., executive functions. This study investigated the neuropsychological and neurostructural substrates of domain specific anosognosia in early AD.

Fifty-three patients with a clinical diagnosis of early-AD and a reliable informant were administered the Measurement of Anosognosia Instrument, a validated tool to quantify anosognosia. Linear models were devised to test the association between the patient-informant discrepancy scores in the memory and non-memory domains and clinical profiles inclusive of cognitive scores and maps of grey matter.

Total anosognosia scores were associated with episodic memory, semantic memory, visuoconstructive skills and volume of the anterior cingulate cortex (ACC), lingual gyrus, fusiform gyrus and thalamus. Memory anosognosia was associated with episodic memory and visuoconstructive skills. Non-memory anosognosia was associated with episodic and semantic memory and with volume of the ACC, precentral gyrus, superior frontal gyrus, postcentral gyrus, fusiform gyrus and lingual gyrus.

Known as a region responsible for self-regulation and monitoring, reduction of grey matter in the frontal lobe was highlighted as crucial for the presence of anosognosia. Based on our findings, we argue that specific regions based in the frontal lobe could contribute to the functioning of the mnemonic comparator systems postulated by theoretical models of anosognosia. The cross-domain variability of cognitive correlates indicates that various computational mechanisms are at play in the presence of anosognosia.

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1. Introduction

Introduced more than one century ago (Babinski, 1914), the term “anosognosia” can be recognised as a neurological symptom that is characterised by a lack of self-awareness of the presence of a disorder or disability such as disease-associated deficits, cognitive alterations or behavioural changes (Mograbi & Morris, 2018). Anosognosic patients are unaware of their neurological impairments or are unable to judge how severe these are (Morris & Mograbi, 2013). It is a common symptom in Alzheimer’s disease (AD), with an onset observable since the mild cognitive impairment stage (Vannini et al., 2017b; Vogel et al., 2004) and prevalence rates ranging from 20% to 80% (Starkstein, 2014).

In AD patients, anosognosia is associated with the deposition of amyloid peptides in the brain (Marshall et al., 2004; Vannini et al., 2017a) and tends to affect awareness of memory dysfunction in parallel with other symptomatic manifestations, such as behavioural changes (Sunderaraman & Cosentino, 2017). However, with disease progression, multiple domains may become affected by an anosognosic trait (often in an unpredictable way), resulting into considerable clinical heterogeneity (Avondino & Antoine, 2016; Gambina et al., 2015). Notably, the presence of low cognitive awareness has been demonstrated to serve as a potential preclinical marker for AD (Cacciamani et al., 2017).

Anosognosia in AD can be described according to clinical or theory-informed approaches. Clinical taxonomies focus on the various domains of clinical relevance that can be affected by an anosognosic trait, i.e., awareness of behavioural problems vs. awareness of cognitive deficits (Starkstein, Sabe, Chmerinski, Jason, & Leiguarda, 1996). The latter can be further divided into a memory and an executive sub-component (Agnew & Morris, 1998) and additional domains have been proposed, e.g., awareness of skill in activities of daily living or in socioemotional interactions (Clare et al., 2012). It is well-established today that dysfunction of awareness in AD is multi-domain (Leicht, Berwig, & Gertz, 2010).

Theory-informed classifications are instead based on computational models that are characterised by modular information processing. A first framework, the Conscious Awareness System (Schachter, 1990) posits that sensory information processed by higher-order parietal regions would be brought to awareness as a result of the perception of other domains within each cognitive module (i.e., knowledge, memory and learning). This information would then be transmitted to an executive system in charge of computing a metacognitive output. According to this framework, anosognosia would be the result of disruption of one or more modules along the computational pathway that links the outcome of aware processing to the executive unit (Schachter, 1990).

A second framework, the Cognitive Awareness Model, focuses instead on the role played by memory and mnemonic comparators of executive nature (Agnew & Morris, 1998). The rationale of this model is a continuous evaluative processing of episodic and semantic memories, carried out in constant concomitance with the inflow of sensory input. Sensory information would be firstly processed by short-term memory (triggering a first episode of awareness) and would then be

subsequently transferred to long-term memory systems (triggering a second episode of awareness). After that, an executive-based mnemonic comparator would compare memory information with a database of personal experiences containing semantic portrayals of individuals’ own capacities. Following such comparison, finally, the information reaches conscious awareness through the Metacognitive Awareness System (Agnew & Morris, 1998). Based on the Cognitive Awareness Model, therefore, memory retrieval must be supported by executive resources and anosognosia would be the result of a mismatch between the information stored in the personal knowledge database and that resulting from the processing of newly-received sensory information.

Various theory-informed types of anosognosia have been postulated based on these two theoretical frameworks. *Primary anosognosia* would be due to dysfunction of the Conscious Awareness System and would result in severe clinical manifestations affecting multiple cognitive and behavioural domains. *Secondary anosognosia*, on the other hand, would be caused by dysfunction of the Cognitive Awareness System and would result in *executive anosognosia* (when damage is to the comparator system) or *memory anosognosia* (when damage affects the information updating system) (Hannesdottir & Morris, 2007; Morris & Mograbi, 2013).

Other studies, finally, have proposed that anosognosia in AD can also be due to poor/failed recollection and consolidation of semantic knowledge about the self or to an outdated version of an individual’s self-recognition (Mograbi, Brown, & Morris, 2009).

The conceptual elements laid out by both clinical evidence and theoretical models of anosognosia have led to the exploration of the neurological mechanisms responsible for this highly disruptive symptom. Since AD is a neurodegenerative disease characterised by widespread brain atrophy, the neuroanatomical correlates are of particular interest. Significant associations have been found between the presence of symptoms of anosognosia and grey matter volumes in a set of regions that include the prefrontal cortex (Ford et al., 2014; Fujimoto et al., 2017; Hornberger et al., 2014; Shany-Ur et al., 2014; Spalletta et al., 2014), cingulate cortex (Guerrier et al., 2018; Hanyu et al., 2008; Spalletta et al., 2014), medial temporal lobe (Hornberger et al., 2014; Spalletta et al., 2014; Tondelli et al., 2018), subcortical structures (Shany-Ur et al., 2014) and cerebellum (Guerrier et al., 2018; Spalletta et al., 2014). The majority of these studies highlights an association between anosognosia in AD and the volume of the forebrain (prefrontal and antero-limbic regions). Accordingly, the cognitive domain most distinctively associated with anosognosia in AD is executive functioning (Starkstein, 2014); however, this is not a consistent finding within the literature and memory may be associated with the presence of this symptom (Clare et al., 2013; Orfei et al., 2010; Senturk et al., 2017).

The evidence emerging from neuroimaging aligns with the theoretical models previously outlined. Prefrontal regions such as the anterior cingulate and the medial prefrontal cortex may serve as a core hub in support of the executive comparator system and dysfunctional connections in these pathways may result in executive anosognosia (Guerrier et al., 2018). Similarly, other studies postulate that memory anosognosia could find its pathological substrates in regions

responsible for autobiographical conceptual memory such as medial temporal lobe structures that are damaged by the characteristic pathophysiology of AD (Morris & Mograbi, 2013; Tondelli et al., 2018). The clinical manifestations of memory or executive anosognosia are associated with degeneration of densely interconnected fronto-temporal structures which are thought to be responsible for the integrity of the cognitive awareness system (Chavoix & Insausti, 2017).

Moreover, since anosognosia in AD can be expressed in multiple clinical domains, it is unknown whether the mechanisms are the same for each domain affected by the trait. In this respect, the current study explored anosognosia in two clinical domains: memory and non-memory (i.e., including activities of daily living and executive functioning). Specifically, we studied the association between domain-specific anosognosia and total anosognosia scores with: 1) cognitive profiles and 2) voxel-based volumetric properties of the brain. Therefore, based on neuroimaging and theoretical frameworks we hypothesised that domain-specific anosognosia would reflect the detrimental effects of grey matter loss in frontal lobe regions that support the performance of the mnemonic comparator system and associated cognitive functions.

2. Methods and materials

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. No part of the study procedures or analyses was pre-registered in an institutional registry prior to the research being conducted.

2.1. Participants

Study recruitment was carried out as part of the EU-funded Virtual Physiological Human – Dementia Research Enabled by IT (VPH-DARE@IT) initiative, a multicentre project clinically coordinated by the Department of Neuroscience, Royal Hallamshire Hospital in Sheffield, UK (<http://www.vph-dare.eu>). Fifty-four candidate patients were initially enrolled. All candidates had received either a clinical diagnosis of AD, $n = 25$ following the National Institute of Aging criteria (McKhann et al., 2011) or a diagnosis of MCI due to AD, $n = 29$ (Albert et al., 2011) as part of a sole continuum of AD severity. Longitudinal follow ups for at least four years in patients labelled as MCI showed a clinical course supportive of an AD aetiology. The set of exclusion criteria included evidence of other significant neurological conditions (e.g., acute or chronic cerebrovascular disease or history of transient ischaemic attacks), uncontrolled brain seizures or history of epilepsy, peripheral neuropathy, presence of significant behavioural symptoms or radiological evidence which could otherwise account for the symptoms, cardiovascular and gastroenterological conditions (e.g., sick-sinus syndrome or peptic ulcer), metabolic disorders (e.g., abnormal levels of vitamin B12, folates or thyroid-stimulating hormone), major pharmacological interventions (e.g., treatment with psychotropic medication other than AD-related drugs, pharmacological components displaying

important organic adverse effects or medications used in other research protocols) and presence of major disabilities. Moreover, since the main predictor (see Section 2.2) was dependent on the score obtained in a questionnaire administered to patient-caregiver dyads, participants were not approached if no reliable informant was available. Each informant was briefly screened to rule out neurological or psychological factors that would prevent them from answering all study questions in a reliable way. One dyad was excluded due to incomplete testing, giving a final sample of 53 patients (Table 1).

In compliance with the description of data-collection procedures approved by the European Union, local ethical approval was granted by relevant ethics committees at recruitment sites. Written informed consent was obtained from all participants. The conditions of our ethics approval do not permit the sharing of any data supporting this study with any individual outside the author team under any circumstances.

2.2. Anosognosia and neuropsychological assessment

Levels of self-awareness were measured with the Measurement of Anosognosia Instrument (Stewart, McGeown, Shanks, & Venneri, 2010). This questionnaire consists of 15 binary “yes-no” questions assessing cognitive performance in daily-life settings. All questions need to be answered independently by the patient and by the informant. By doing so, two scores are obtained: that provided by the informant as a “standard-of-truth” objective assessment of the patient’s abilities and that provided by the patient as self-evaluative measure. The Measurement of Anosognosia Instrument explores two functional domains of awareness: “memory” (9 questions) and “non-memory” (inclusive of executive functioning and activities of daily living; 6 questions). The informant-based and the patient-based responses were compared to quantify the number of discrepant answers provided by the patient. Discrepancy scores were used to quantify presence of anosognosia across two cognitive domains: “memory” and “non-memory”, with an additional “total” score (the sum of both domains) (Migliorelli, 1995; Stewart et al., 2010).

Finally, each participant underwent a neuropsychological examination to obtain a clinical profile that included the Mini Mental State Examination, the Raven Progressive Matrices test, the Token test, the Digit Span Forward test and the WAIS Similarities test. Furthermore, in consistency with the conceptual background, tests of experimental interest were chosen to assess the behavioural association of anosognosia with

Table 1 – Demographic characteristics of the sample. Means (standard deviation) are shown.

Variable	Mean (SD)/ $n = 53$	Range (min–max)
Age	71.68 (10.2)	48–89
Gender (Male/Female)	27/26	–
Years of education	10.62 (4.05)	5–20
Mini Mental State Examination	23.38 (3.77)	15–30

memory (Category Fluency test and Prose Memory delayed recall test), executive functions (Letter Fluency test and Stroop test) and Visuospatial abilities (Rey–Osterrieth Complex Figure test) (Table 2).

2.3. MRI acquisition and processing

A three dimensional T1-weighted image was obtained for each participant. MRI images were acquired and analysed following a shared protocol with the acquisition and modelling steps set up by the VPH-DARE@IT consortium for Philips scanners (<http://www.vph-dare.eu/index.php/project/work-packages/WP2>): voxel size: 1 mm³, flip angle: 8°, matrix size: 256 × 256, repetition time 7.4 ms; echo delay time 3.4 ms; field of view 250 mm [see Venneri, Mitolo, and De Marco (2017) for details].

A voxel-based morphometry analysis was carried out using the Statistical Parametric Mapping (SPM) software 12 (Wellcome Centre for Human Neuroimaging, London, UK) on processed MRI T1 weighted scans. Scans were initially reoriented and segmented into grey matter, white matter and cerebrospinal fluid tissue maps. These were quantified in volumetric terms (using the `get_totals` script: http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) to compute total intracranial volumes and account for overall head size differences among participants (Peelle, Cusack, & Henson, 2012). Grey

matter maps were then normalised and registered to the Montreal Neurological Institute space. Finally, spatial smoothing (8 mm full-width half maximum Gaussian kernel) was carried out.

2.4. Statistical analyses

Three sets of inferential models were devised to test the association between measures of anosognosia and indices of cognitive functioning and brain structure. To define these associations, all models were corrected for a series of confounding factors. First, age was used to control for decrease of grey matter volume due to normal ageing (Fox & Schott, 2004). Second, education levels (in years) were included as a proxy of cognitive reserve (Fratiglioni & Wang, 2007). Third, normalised hippocampal volumes (Cardoso et al., 2013) were used as a way to control for disease severity, given the extensive disease-dependent atrophy this structure is subjected to in AD.

Neuropsychological data were analysed with IBM SPSS Statistics 24 software for Windows (SPSS Inc., Chicago, IL, USA). Coefficients of non-linear partial correlation were run between the three indices of anosognosia and the neuropsychological scores (Spearman's ρ). The statistical threshold to define significance of these associations was set to $p < .007$ to correct for multiple comparisons.

Regression models were carried out to infer the linear association between voxel-by-voxel maps of grey matter and levels of anosognosia in SPM 12. Total intracranial volumes were included as fourth covariate in these models. This served to account for the inter-individual variability in head size (Peelle et al., 2012) and brain reserve (Van Loenhoud, Groot, Vogel, van der Flier, & Ossenkoppele, 2018). An uncorrected $p < .005$ was selected as cluster-forming threshold. Clusters surviving a Family-Wise Error $p < .05$ were considered significant. Peak stereotactic coordinates were converted to the Talairach atlas space using the `mni2tal` Matlab function. Coordinates in the Talairach space were interpreted using the Daemon Client (Lancaster et al., 1997, 2000).

Table 2 – Clinical profiling and test of experimental interest.

Cognitive test	Sample Mean/n	Range (min–max)	Cut-off (scores)
Clinical Profiling			
Raven	22.9/n = 50	9–35	–1.51
Token	30.8/n = 53	21–36	–2.43
Similarities	14.1/n = 53	4–26	–1.85
Experimental Interest			
Mini Mental State Examination	23.4/n = 53	15–30	–3.07
Letter Fluency	25.3/n = 52	6–59	–1.06
Stroop Test Error	8.1/n = 53	0–30	15.47
Category Fluency	25.5/n = 52	10–72	–1.96
Prose Memory delayed recall	5.3/n = 52	0–20	–8.44
Rey Figure Copy	24.2/n = 52	3–36	–2.46
Rey Figure Recall	5.4/n = 52	0–19	–1.72

Table 3 – Domain specific anosognosia correlations with cognitive tests of experimental interest.

Cognitive test of experimental interest	Memory Anosognosia Correlation/p value	Non-Memory Anosognosia Correlation/p value	Global Anosognosia Score Correlation/p value
MMSE	$\rho = -.563/p = .001^a$	$\rho = -.327/p = .035$	$\rho = -.525/p = .001^a$
Letter Fluency	$\rho = -.284/p = .067$	$\rho = .104/p = .512$	$\rho = -.114/p = .471$
Stroop error	$\rho = .405/p = .008$	$\rho = .222/p = .157$	$\rho = .352/p = .022$
Category Fluency	$\rho = -.449/p = .003^a$	$\rho = -.364/p = .018$	$\rho = -.492/p = .001^a$
Prose Memory delayed recall	$\rho = -.429/p = .005^a$	$\rho = -.386/p = .012$	$\rho = -.467/p = .002^a$
Rey-Osterrieth Complex Figure copy	$\rho = -.292/p = .061$	$\rho = -.379/p = .013$	$\rho = -.424/p = .005^a$
Rey-Osterrieth Complex Figure recall	$\rho = -.385/p = .012$	$\rho = -.316/p = .042$	$\rho = -.419/p = .006^a$

^a A p value $< .007$ was selected as significant after correction for multiple comparisons. Associations were controlled for age, years of educations and hippocampal fraction as covariates of no interest.

3. Results

3.1. Association with neuropsychological functioning

The total anosognosia score was associated with scores on the following tests: delayed recall of the Prose Memory test

($\rho = -.467, p = .002$), the copy and recall of the Rey-Osterrieth complex figure test ($\rho = -.424, p = .005$; $\rho = -.419, p = .006$, respectively), the Category Fluency test ($\rho = -.492, p = .001$) and the Mini Mental State Examination ($\rho = -.525, p = .001$). The index of memory anosognosia was associated with the scores achieved on the Prose Memory test ($\rho = -.429, p = .005$) and Category Fluency test ($\rho = -.449, p = .003$) and on the Mini Mental State Examination ($\rho = -.563, p = .001$). Finally, the index of non-memory anosognosia showed no significant associations (Table 3).

3.2. Association with brain structure

A significant negative association was found between the total anosognosia score and volumes of the bilateral anterior cingulate cortex, left lingual gyrus, left fusiform gyrus and left thalamus. Likewise, a significant negative association was found between the non-memory anosognosia score and volumes of the bilateral anterior cingulate cortex (ACC), bilateral precentral gyrus, bilateral lingual gyrus, bilateral fusiform gyrus, right superior frontal gyrus and right postcentral gyrus (Table 4; Fig. 1). No significant associations were detected between memory anosognosia scores and grey matter volumes.

4. Discussion

The purpose of this study was to characterise the neuropsychological and neurovolumetric correlates of anosognosic profiles in the early stage of AD (prodromal to mild), differentiating between memory and non-memory anosognosia. Cognitive and anatomical analyses performed in the MCI and mild AD samples separately demonstrated similar patterns of results, although in both groups statistical power was low.

Given the similarity in the pattern of findings, these clinical profiles were, therefore, merged to increase statistical power.

4.1. Association between anosognosia and neuropsychological functioning

Total anosognosia scores were associated with a series of measures of episodic memory, semantic memory and visuo-constructive skills. Overall, we cannot rule out the possibility that these total-anosognosia scores were driven by the distribution of scores on the non-memory section of the test (hence, the similar pattern of findings). However, the total score was significantly associated with both memory and non-memory sub-scores (both r scores $> .8$) suggesting equal dependence on both sub-scores. After splitting the construct into its two components, memory anosognosia showed an association with the Category Fluency test (a measure of semantic memory) and the Prose Memory test. This latter is a test of episodic memory based on the retrieval of material characterised by semantic relatedness (Carlesimo et al., 1998; Venneri et al., 2019). Semanticisation processes are an essential trait for the integration of episodic autobiographical memory (Morris & Mograbi, 2013; Westmacott, Black, Freedman, & Moscovitch, 2004). This domain has a significant influence on the representation of the self. In this respect, patients with anosognosia constantly try to reorganise their self-representation without success, and this leads to a progressive deterioration of their own identity (Mograbi, Brown & Morris., 2009; Toffle & Quattropiani, 2015). On the other hand, deficits in episodic memory are central clinical hallmarks in AD and are associated with disease severity (Reitz, Honig, Vonsattel, Tang, & Mayeux, 2009). Notably, these results are consistent with those of other studies focusing on anosognosia in AD (Clare et al., 2013; Orfei et al., 2010; Senturk

Table 4 – Grey matter clusters of significant correlation for total anosognosia score and non-memory anosognosia.

	Cluster Extent (voxels)	FWE-corrected p-value	z score	Side	Peak-based localisation	Talairach Coordinates		
						x	y	z
Total Anosognosia Score	3430	.001	3.70	R	Anterior cingulate	4	26	-10
			3.69	L	Anterior cingulate	0	21	-3
			3.76	L	Thalamus	-4	-29	7
	1803	.021	4.42	L	Lingual Gyrus	-15	-64	-4
			4.42	L	Fusiform Gyrus	-21	-49	-10
			4.09	L	Fusiform Gyrus	-24	-41	-13
Non-Memory Anosognosia	3320	.001	5.30	L	Fusiform Gyrus	-28	-40	-17
			5.02	L	Fusiform Gyrus	-32	-53	-11
			4.89	L	Fusiform Gyrus	-26	-47	-10
	1769	.023	4.53	L	Precentral Gyrus	-21	-19	53
			4.20	L	Precentral Gyrus	-33	-16	60
			4.16	L	Precentral Gyrus	-45	-14	30
	1964	.014	4.44	R	Anterior Cingulate	4	26	-10
			3.83	R	Anterior Cingulate	9	38	-10
			3.78	L	Anterior Cingulate	-2	19	-1
	3379	.001	4.44	R	Fusiform Gyrus	28	-38	-17
			4.41	R	Lingual Gyrus	20	-66	-2
			3.96	R	Lingual Gyrus	36	-72	-6
1832	.019	4.38	R	Superior Frontal Gyrus	9	-14	63	
		3.83	R	Precentral Gyrus	38	-13	59	
		3.47	R	Postcentral Gyrus	42	-19	45	

L:left; R: right.

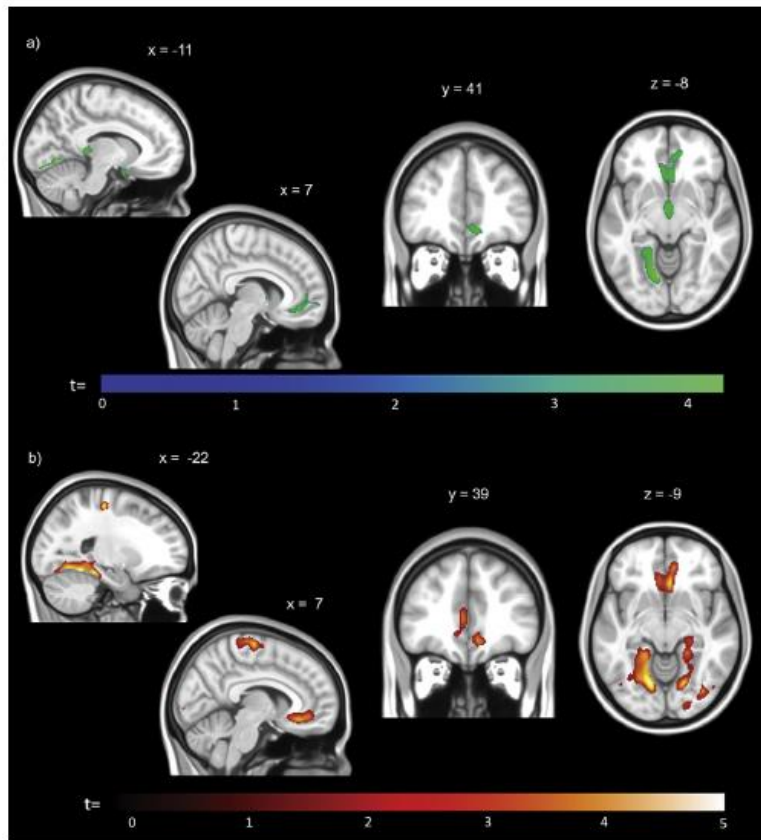


Fig. 1 – Regions of significant negative correlation between a) total anosognosia scores and b) non-memory anosognosia scores and grey matter volume values.

et al., 2017). In line with our results, Gambina et al. (2015) characterised anosognosia patients using a quantitative-qualitative method in which unawareness of memory deficits was particularly visible at the initial clinical stages of disease, while later clinical stages were characterised more distinctively by executive unawareness, displaying dissociation with the cognitive performance in the memory and executive domain, respectively. To minimise the likelihood of obtaining spurious results, all of the inferential models involving neuropsychological tests were controlled for normalised hippocampal size, an established measure of neuronal injury in AD (Jack et al., 2018).

The total anosognosia score was also associated with performance on visuospatial skills. Visuoconstructive abilities are an essential trait of self-awareness, in that they enable the individual to shift from a first-person to a third-person perspective (Vogele, May, Falkai, Zilles, & Fink, 2004). These abilities would also serve to update information processing by projecting allocentric (object-to-object) and egocentric (self-to-object) spatial representations, prerequisite components of

global awareness (Serino & Riva, 2017). Based on this view, our findings indicate that patients with higher total anosognosia scores would be less able to achieve this “mental frame syncing”; or, in other words, the ability to update properly previously experienced scenarios stored in episodic memory. Therefore, these patients may not be able to understand the mental scenarios of their first-person orientation, which could lead to unawareness of the perceived space in contrast with the one remembered.

Lastly, overall cognitive severity of disease was associated with the total anosognosia scores and the memory anosognosia scores. This finding has been reported in the literature (Migliorelli et al., 1995; Derouesne et al., 1999; Harwood, Sultzer, & Wheatley, 2000; Leicht et al., 2010) and may reflect the direct detrimental effects of the proteinopathies on the awareness system through the progression of the disease (Vannini et al., 2017a). However, the scientific literature indicates that there is no well-defined link between severity of disease and anosognosia, with studies that support a link (such as those referenced in the section

above) and studies that do not (Almeida & Crocco, 2000; Gambina et al., 2015; Reed, Jagust, & Coulter, 1993; Weinstein, Friedland, & Wagner, 1994). The AD pathophysiological progression may impact directly on the severity of the disease, but it is not an essential variable for the onset of anosognosia, which explains the heterogeneity between disease stage and the initial symptomatic expression of anosognosia that displays worsening with disease progression characterised initially by memory disconnection (Avondino & Antoine, 2016).

4.2. Association between anosognosia and brain structure

The total anosognosia score was associated with volume in the ACC. This region has been associated with disease awareness in other studies involving AD patients (Hanyu et al., 2008; Amanzio et al., 2011; Guerrier et al., 2018; Spalletta et al., 2014). Progressive neuronal loss in the anterior cingulate leads to decline of executive metacognitive processes that involve cognitive regulation (Cohen, Botvinick, & Carter, 2000) through continual internal error processing and monitoring (Van Veen & Carter, 2002; O'Connell et al., 2007; Amanzio & Palermo, 2014). In this study, the ACC was associated with both total anosognosia scores and non-memory domain anosognosia scores, the latter consisting mostly of decreased awareness of activities dependent on executive functions. Likewise, Amanzio et al. (2011) showed decreased activation of the ACC in a task-based fMRI study consisting of a paradigm based on a response-inhibition go/no-go task, proposing anosognosia as a dysfunction of the executive system in charge of abilities such as self-monitoring. Lastly, Guerrier et al. (2018) found, in a structural and metabolic study, alterations of the ACC related to anosognosia, interpreting it as an area involved in executive processing and self-monitoring affecting the comparator mechanisms of mnemonic functions.

The involvement of the ACC can be interpreted as that of a gateway region sustaining conflict resolution within the framework of the Cognitive Awareness Model (Agnew & Morris, 1998). The ACC is a region responsible for the integration of cognitive and emotional stimuli (Bush, Luu, & Posner, 2000) and is also a major hub of the salience network, a functional circuit responsible for processing and integrating external and internal inputs for decision making (Seeley et al., 2007). In coherence with the Cognitive Awareness Model, the ACC may provide the executive resources necessary to the mnemonic comparator to verify the authenticity of the processed information.

Total anosognosia scores and non-memory anosognosia scores also showed a significant association in the fusiform gyrus and lingual gyrus. The involvement of the fusiform gyrus in anosognosia does not come as a novel finding (Guerrier et al., 2018). Dysfunction in this area is linked to awareness deficits for bodily representations. In fact, hemiplegic patients with lesions extending to the fusiform gyrus show impaired mentalisation of the body (Besharati et al., 2016). Moreover, the pathway linking the fusiform gyrus with the ACC was found to be abnormally upregulated in patients with amnesic MCI (Cai et al., 2015).

The lingual gyrus is instead a region essential for visual perception (Yang, Deng, Xing, Xia, & Li, 2015), but it also plays an executive role, as shown in a study that reported activation during a divergent thinking paradigm (Zhang et al., 2016). Moreover, atrophy of a set of regions including the lingual gyrus is linked to faster decline in AD dementia (Kinkingnehun et al., 2008) suggesting a plausible link between anosognosia and faster disease progression.

The non-memory anosognosia domain showed additional significant negative associations with the precentral, postcentral and superior frontal gyrus that runs in parallel with the findings of other studies related to the field of AD. The precentral gyrus was found to be associated with anosognosia of executive functions in a structural MRI study (Tondelli et al., 2018). In this context, Morita et al. (2008) proposed the precentral gyrus to serve as a key region of self-recognition of facial features. The postcentral gyrus showed less activation in a comparative analysis of aware vs. unaware AD patients based on a response-inhibition go/no-go task (Amanzio et al., 2011). Lastly, the superior frontal gyrus was also associated with anosognosia in another structural study (Fujimoto et al., 2017), a region that has shown to be essential in self-awareness (Goldberg, Harel, & Malach, 2006). Therefore, we argue that specific frontal regions could serve as crucial components for the modulation of executive-function-related awareness processes.

In spite of the importance of executive resources in this process, however, no association was found between indices of anosognosia and measures of executive functioning. Arguably, however, a dysfunctional comparator may result in subtle executive deficits that will not necessarily emerge with standardised executive tests.

A number of published structural and functional neuroimaging studies found that anosognosia was associated with medial temporal structures (e.g., Chavoix & Insausti, 2017; Tondelli et al., 2018). To this end, Salmon et al. (2006) suggested that the mediotemporal hypometabolism seen in anosognosic patients may result in impaired comparison mechanisms, highlighting a primary role of memory functions based on these structures, and not executive resources for this comparative function. Our findings, however, seem not to support this suggestion, since no association was found between hippocampal volume and anosognosia scores. Associations between anosognosia and semantic and episodic memory were identified in the current study, but these associations did not appear to be mediated by hippocampal volume. In this respect, the findings by Avondino & Antoine (2016) highlight memory as a supportive element in anosognosia rather than the prime cause. Therefore, we argue that mediotemporal structures most likely offer a supportive mnemonic input to the structures that provide comparative resources, and it is possible that this link could be spurious and driven by disease severity, which is known to affect harshly this part of the brain. Based on our findings, comparative resources would be more consistently linked with the ACC instead.

A broader neuroimaging-based perspective suggests that damage to frontal circuitry precedes loss of grey matter, and this would account for how the clinical symptoms present in relation to multi-domain anosognosia (Mondragon, Maurits &

Deyn, 2019). According to this view, reduced connectivity of the default mode network (DMN), seen in the early phases of AD (Klaassens et al., 2017), may act as a marker of progression associated with anosognosia (Therriault et al., 2018). In fact, the bases of impaired self-awareness and anosognosia have been heavily intertwined with the functionality of the DMN in AD (Antoine et al., 2019; Mondragón, Maurits, & De Deyn, 2019) and other neurological conditions, such as anosognosia for hemiplegia (Pacella et al., 2019). On these grounds, the DMN could be conceived as a translational construct to justify a routine assessment in the preclinical stage of AD (Cacciamani et al., 2017). In turn, damage to the DMN could then hinder other frontal pathways of connectivity that would lead to a dysfunctional use of the central executive comparator and other neuronal systems such as those in charge of attention or emotional processing (Shany-Ur et al., 2014).

The mismatch found between anatomical findings and behavioural outcomes could be due to the inherent relation of unawareness to the functional domain controlled by it. The consistency of association of visuospatial abilities to the behavioural and neuroimaging outcomes sheds light into the essential role of these functions in global awareness. Dissecting anosognosia study by domains in the very early stages of the disease could lack of evident association between the broad neuronal anatomical conformation to the specific function mediated by that region.

4.3. Limitations

Limitations might arise from the choice of instrument to measure anosognosia. In fact, failing to acknowledge the presence of symptoms or a poor performance could in part be due to a defensive mechanism of denial, triggered by individual socioemotional factors (Ecklund-Johnson & Torres, 2005). This possibility, however, is an intrinsic factor in this type of measurement and would affect any questionnaire/scale. On this note, it is desirable to confirm each diagnosis of anosognosia with a clinical qualitative judgment. Secondly, the use of discrepancy scores depends on the answers given by both patient and informant. Caregiver burden may inadvertently shift the perception of the patient's abilities into an over/underestimation. To rule out this possibility, we chose to rely on a robust instrument that has undergone methodological validation, but acknowledge that there are other ways to assess anosognosia, such as the discrepancy between estimation and actual performance on a task. Lastly, although the total anosognosia score was strongly correlated with both the memory ($r = .895$) and non-memory ($r = .818$) sub-scores, we cannot completely rule out the possibility that one of the two sub-scales may have had a larger impact on the total score than the other.

5. Conclusions

Our findings highlight the ACC as the main structure associated with total scores and non-memory anosognosia scores in patients with early AD. Additionally, volumes in the fusiform and lingual gyri were also associated with the total scores and non-memory anosognosia scores. The precentral

gyrus, postcentral gyrus and superior frontal gyrus show further involvement in non-memory anosognosia. Behavioural findings foregrounded the role played by semantic memory, episodic memory and visuospatial abilities. All in all, these findings indicate that anosognosia is a complex symptom in which executive resources seem to play a crucial role. Moreover, and as pointed out by previous research (Chapman et al., 2018), different theoretical elements appear to be at play depending on the cognitive domain affected by anosognosia in AD.

Authors' contribution

JMVB contributed data analysis and wrote the initial draft of the manuscript;

MDM. contributed to data acquisition, study design, supervised data analysis, and critical revision of the manuscript;

MM contributed to data acquisition and critical revision of the manuscript;

WMG contributed to planning of data analysis and critical revision of manuscript;

AV contributed to acquisition of funding, design and conception of the study, interpretation of data, revision and finalisation of manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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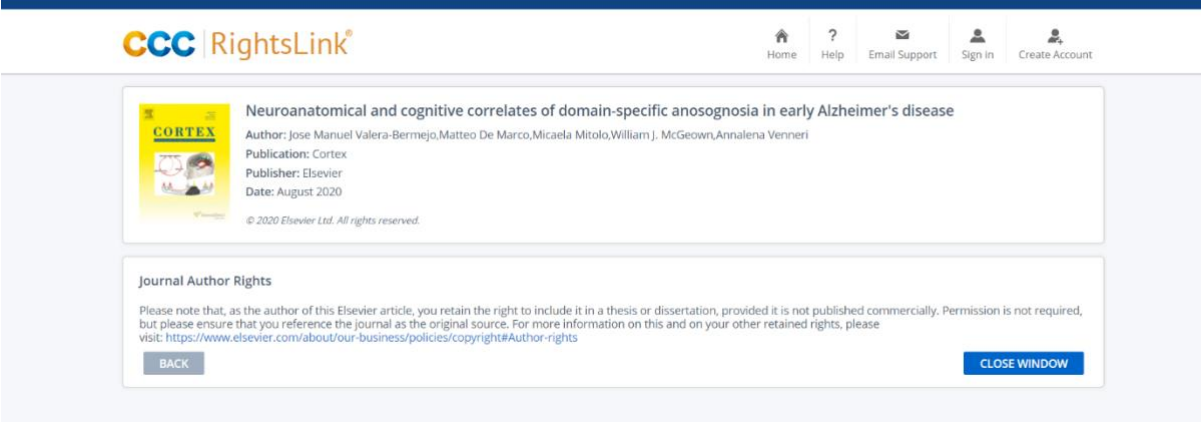
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Appendix B. Permission to use the published paper for thesis/ dissertation purposes.



The screenshot shows the CCC RightsLink interface. At the top, the logo 'CCC RightsLink' is on the left, and navigation links for Home, Help, Email Support, Sign in, and Create Account are on the right. The main content area features a white box with a yellow journal cover thumbnail on the left. The article title is 'Neuroanatomical and cognitive correlates of domain-specific anosognosia in early Alzheimer's disease'. Below the title, the author list is 'Author: Jose Manuel Valera-Bermejo, Matteo De Marco, Micaela Mitolo, William J. McGeown, Annalena Venneri'. Further down, it lists 'Publication: Cortex', 'Publisher: Elsevier', and 'Date: August 2020'. A copyright notice at the bottom of this box reads '© 2020 Elsevier Ltd. All rights reserved.' Below this box is a 'Journal Author Rights' section with a paragraph of text and a URL: 'https://www.elsevier.com/about/our-business/policies/copyright#Author-rights'. At the bottom of the page, there are two buttons: 'BACK' on the left and 'CLOSE WINDOW' on the right.

Appendix C. Measurement of Anosognosia Questionnaire retrieved from Stewart et al., 2010.

Stewart et al.

Assessing anosognosia by calculating discrepancies between self- and informant ratings on a questionnaire has been criticised for assuming that the informant is able to give an accurate and reliable assessment of the participant's residual competence (38). Although the present study used informants who were close to the participant to maximise the likelihood of them providing valid ratings of the participants' abilities, this method is less than ideal to obtain an accurate measure of a person's true level of awareness, and more refined techniques should be developed.

The implications of poor awareness are substantial in terms of patient management and treatment, and any means of improving awareness in this clinical population would greatly benefit the patient and their carers. Some studies have suggested that exposing patients to their memory failures explicitly is one way of facilitating improved awareness (39). If as argued above, however, anosognosia in AD develops after neural damage in areas critical for retaining and updating information about self performance, it seems unlikely that attempts to improve awareness through explicit memory based interventions would succeed. It seems more likely that sustaining awareness of ability in AD might not be achievable without either constant feedback which takes advantage of residual implicit memory abilities, or by guided environmental/carer interventions. For example, family members and professional carers might be encouraged to frame residential environments so that organisational and sensory cues are in place to compensate for explicit memory failures (40). In this way a more accurate ongoing representation of the patient's own abilities might be dynamically maintained or prospectively supported, at least in the earlier stages of the disease.

Appendix 1

Measurement of anosognosia A (patient)	Response	
1. Do you think you have a memory problem?*	Yes	No
2. Is your memory worse than it was 6 months ago? *	Yes	No
3. Do you have difficulty in following conversations?	Yes	No
4. Do you find it easy to remember events that happened in the news in the last 5 years?*	Yes	No
5. Do you often find yourself putting things down (e.g. keys) and then forgetting where you have put them?*	Yes	No
6. If I asked you about details of this questionnaire in 1 month's time, do you think you will be able to remember it well?*	Yes	No
7. Do you find it easy to follow what people are saying to you?	Yes	No
8. Do you often find yourself in the situation where something is 'on the tip of your tongue' but you cannot remember it?*	Yes	No
9. Do you forget to take your medication?*	Yes	No
10. Do you initiate your own showering/bathing routine?	Yes	No
11. Do you find it increasingly difficult to recall memories from your adult life (i.e. a number of years ago)?*	Yes	No

(continued)

Measurement of anosognosia A (patient)	Response	
12. Have you been experiencing difficulties trying to concentrate on activities such as watching a TV programme or reading a book?	Yes	No
13. Do you often forget to turn the lights off when you go out or go to bed?*	Yes	No
14. F:-In the last year have you been less active in housework/cooking/hobbies than you have previously been?	Yes	No
M:- In the last year have you been less active doing gardening/DIY/hobbies than you have previously been?	Yes	No
15. Has your ability to pay attention to what goes on around you changed in recent years?	Yes	No

*The subset of items which investigate anosognosia for memory are marked with an asterisk. F = female, M = male.

Appendix 2

Measurement of anosognosia B (carer)	Response	
1. Does your partner have a memory problem?*	Yes	No
2. Is your partner's memory worse than it was 6 months ago?*	Yes	No
3. Does your partner have difficulty in following conversations?	Yes	No
4. Do they find it easy to remember events that happened in the news in the last 5 years?*	Yes	No
5. Do they often put things down (e.g. keys) and then forget where they have put them?*	Yes	No
6. If I asked your partner about details of this questionnaire in 1 month's time, do you think they would be able to remember it well?*	Yes	No
7. Do they find it easy to follow what people are saying to them?	Yes	No
8. Do they often complain that something is on the tip of their tongue but they cannot remember it?*	Yes	No
9. Do they forget to take their medication?*	Yes	No
10. Do they initiate their own showering/bathing routine?	Yes	No
11. Does your partner find it increasingly difficult to recall memories from their adult life (i.e. a number of years ago)?*	Yes	No
12. Do they appear to have difficulty trying to concentrate on activities such as watching a TV programme or reading a book?	Yes	No
13. Does your partner often forget to turn the lights off when they go out or go to bed?*	Yes	No
14. F:-In the last year have they been less active in housework/cooking/hobbies than they have previously been?	Yes	No
M:-In the last year have they been less active doing gardening/DIY/hobbies than they have previously been?	Yes	No
15. Has your partner's ability to pay attention to what goes on around them changed in recent years?	Yes	No

*The subset of items which investigate anosognosia for memory are marked with an asterisk. F = female, M = male.

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Appendix D. Example of the Ekman 60 faces test extracted from Young et al., 2002 based on Ekman & Friesen, 1976.

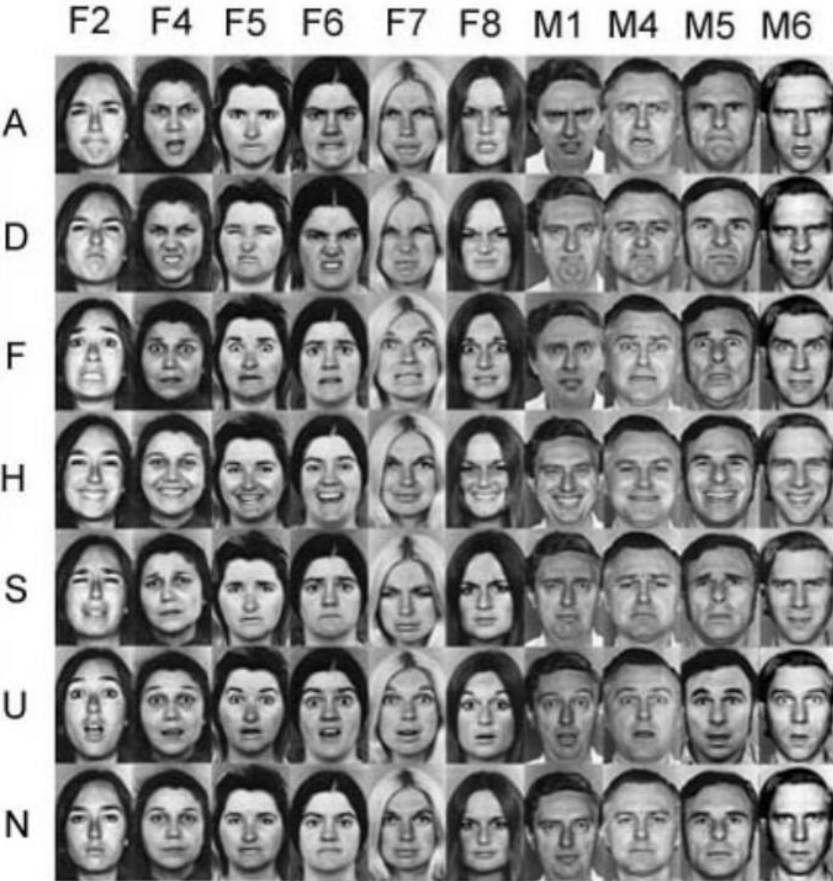


Figure 0.1: Photographs of facial expressions from the Ekman and Friesen (1976) Pictures of Facial Affect used in FEEST. There are emotional expressions of anger (A), disgust (D), fear (F), happiness (H), sadness (S) and surprise (U), and a neutral (N) pose for 6 female and 4 male models. The labels used to identify each of the models locate them in the Ekman and Friesen series (F2 = second female model in the series, M1 = first male model, etc.).

The prototype expressions used in FEEST are shown in Figure 0.1. The identifiers of the facial expressions in the Ekman and Friesen (1976) series are given in Tables 0.1a and 0.1b.

Appendix E. Example of the Reading the Mind in the Eyes test extracted from Baron-Cohen et al., 2001

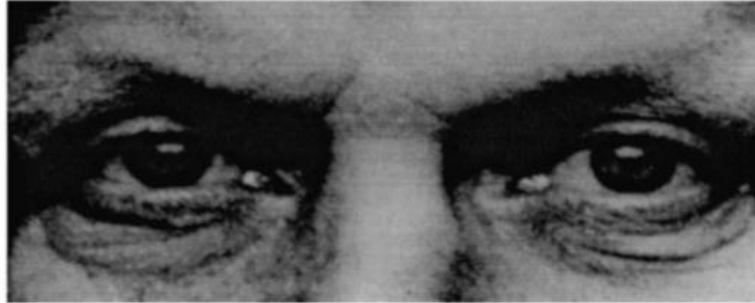


Figure 1. An example of a (male) stimulus used: in the first version word choices were serious (correct) vs. playful. In the revised version the word choices were serious (correct), ashamed, alarmed, and bewildered.



Figure 2. A second (female) example from the Eyes Test: in the first version the word choice was reflective (correct) vs. unreflective. In the revised version the word choice was reflective (correct), aghast, irritated, and impatient.

controls, or adults with a Tourette's syndrome (TS) (a different psychiatric condition, and included as an additional control group). Thus, the adults with HFA or AS scored on average 16.3 out of 25 ($SD = 2.9$), whereas the adults with TS scored on average 20.4 out of 25 ($SD = 2.6$). Although this was only a 4-point difference, it was significant at the $p < .01$ level. The group with TS did not differ significantly on this test from the general population.

Thus, we had succeeded in developing a test of social sensitivity or mind-reading that was able to reveal subtle mind-reading difficulties in adults with HFA or AS. This had been predicted on the basis of more basic mind-reading deficits in younger children with autism (Baron-Cohen, 1995). This was also of interest because it demonstrated that normal adults could judge mental states from even minimal cues (expressions around the eyes alone). Having established that the ability to "read the mind in the eyes" was testable, we considered in what ways the test could be improved.

Problems with the Original Version of the Test

(1) The first version of the task involved a forced choice between only two response options (the two words presented), so chance performance on each trial is $p = .5$. Across the test as a whole one would therefore need to score 17 or above out of 25 to be significantly above chance (Binomial Test). This meant that the range of scores in which the test can reveal individual differences whilst still being above chance is only 9 points (17–25).

This is too narrow. Ideally, a test such as this would have a wider range, in order to be able to identify individual differences with greater power.

(2) When the first version of the test was given to parents of children with AS, they too scored below the general population level (Baron-Cohen & Hammer, 1997). This had been predicted on the basis that they might have the "broader phenotype" (Bailey et al., 1995), since one or both of such parents might be carrying the genes for autism. However, parents scored at a similar level to people with HFA or AS (fathers scoring on average 17.3 out of 25 ($SD = 1.6$), and mothers scoring a mean of 18.9 ($SD = 2.1$), even though they did not have the condition themselves. This highlights that the test has too narrow a range of scores to be able to distinguish between someone with the "lesser variant"/"broader phenotype" (e.g., in a first-degree relative of someone with autism), and someone with the condition itself.

(3) The narrow range of scores that are significantly above chance on the first test can lead to a score in the normal range being close to the ceiling of the test. Ceiling effects are obviously undesirable because one loses power to detect individual differences.

There are two simple modifications we can make to the test to remedy these three limitations: increase the number of items in the test, and increase the number of response options on each trial. In the revised version of the test reported in this paper, we have made both of these modifications: the total number of items (photographs) is increased from 25 to 36, and the number of response options (forced-choice words) is increased from 2 to 4 per trial. This means that chance is $p = .25$ per trial, and that

Appendix F. Example of the Story-Based Empathy Task Vignette Cartoons extracted from Dodich et al., 2015

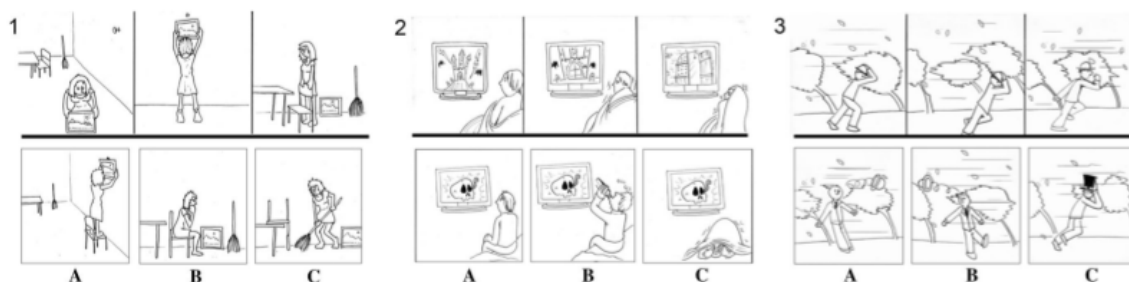


Fig. 1 Vignettes from the Story-based Empathy Task. **1** Intention attribution (SET-IA), **2** Emotion attribution (SET-EA) based on fear, **3** causal inference (control condition—SET-CI). A, B and C represent the possible endings of the story among which subjects must choose the correct one

Table 2 Raw descriptive values of the Story-based Empathy Task global score (GS) and single conditions sub-scores in 136 healthy subjects

	Mean	Standard deviation	Median	Minimum	Maximum	95 % confidence interval
SET-GS	15.73	2.30	16	7	18	15.34–16.12
SET-EA	5.22	1.02	6	1	6	5.05–5.39
SET-IA	5.36	0.94	6	1	6	5.20–5.52
SET-CI	5.14	1.03	5	1	6	4.97–5.32

EA emotion attribution, IA intention attribution, CI causal inference

testing phase. Within the whole sample of 136 subjects, 85 % answered correctly to the trial run, while the other 15 % interpreted correctly the story and the possible endings, even when selecting a wrong one.

The Story-based Empathy task material can be obtained directly from the first author.

Statistical analyses

Based on the performance of 136 subjects, we computed descriptive statistics for SET global (SET-GS) and sub-tasks scores, i.e., SET-IA, SET-EA and SET-CI (see Table 2). Seven different linear regression analyses were performed for each performance score, to establish which demographic variables had to be included in the final model, as the most effective in reducing the residual variance. Adjusted values were calculated by adding (or subtracting) the contribution of each variable for each subject [25]. We derived correction grid to adjust the performance of each newly tested individual for the effect of the demographic variables. Finally, we classified the adjusted SET-GS into five categories, i.e., equivalent scores (ES) ranging from 0 to 4 [25]. The “0” corresponds to scores located below the outer unidirectional non-parametric tolerance limit, with a confidence of the 95 % (the third observation for 136 subjects [26]). The “4” score corresponds to the median and above median values; “1”, “2”, and “3” are intermediate values on a quasi-interval scale calculated with reference to the left half of the

distribution [25]. Statistical analyses were performed with STATISTICA 8 software (<http://www.statsoft.com>).

Results

Descriptive SET raw scores are reported in Table 2. The final model of multiple regression showed age (converted into a logarithm of 100-age) and square root of education in years as the best predictors of both the SET-GS performance [$F(2133) = 28.25, p < 0.001, f^2 = 0.43$] and single sub-task scores [SET-IA = $F(2133) = 8.29, p < 0.001, f^2 = 0.12$; SET-EA = $F(2133) = 14.29, p < 0.001, f^2 = 0.22$; SET-CI = $F(2133) = 22.87, p < 0.001, f^2 = 0.34$], with higher scores for younger and more educated subjects. The correction grids and normative data for each SET sub-task are reported in Tables 3 and 4.

Discussion

In this study, we provide the Italian normative data of the Story-Based Empathy Task (i.e., SET), a novel test for the assessment of intention and emotion attribution. In addition, the task comprises a control condition of physical causality, allowing the evaluation of mentalizing deficits and controlling for the impairment in basic cognitive functions.

The standardization in the Italian population identified age and years of education as predictive variables of all

Appendix G. Copy of Ethics granted for these experiments.



Health Research Authority
NRES Committee Yorkshire & The Humber - Sheffield
Yorkshire and the Humber REC Office
First Floor, Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050128

28 December 2012

Professor Annalena Venneri
Professor of Clinical Translational Neuropsychology
University of Sheffield, Department of Neuroscience
Medical School, N Floor, Rm N130
Beech Hill Road
Royal Hallamshire Hospital, Sheffield
S102RX

Dear Professor Venneri

Study title: Assessment of age and disease related cognitive impairment in normal volunteers and people with degenerative and vascular brain disease and assessment of the potential neuroplastic effect of non pharmacological treatment

REC reference: 12/YH/0474

IRAS project ID: 84442

Thank you for your letter of 19 December 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Rachel Bell, nrescommittee.yorkandhumber-sheffield@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering Letter		18 September 2012
GP/Consultant Information Sheets	1.0	18 September 2012
Investigator CV		
Participant Consent Form: Patient 1	2	19 December 2012
Participant Consent Form: Patient 2	2	19 December 2012
Participant Consent Form: Volunteer 1	2	19 December 2012
Participant Consent Form: Volunteer 2	2	19 December 2012
Participant Information Sheet: Patient 1	2	19 December 2012

Participant Information Sheet: Patient 2	2	19 December 2012
Participant Information Sheet: Volunteer 1	2	19 December 2012
Participant Information Sheet: Volunteer 2	2	19 December 2012
Protocol		
REC application		
Response to Request for Further Information		19 December 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "*After ethical review – guidance for researchers*" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0474	Please quote this number on all correspondence
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We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

With the Committee's best wishes for the success of this project.

Yours sincerely



**Pp Professor Basil Sharrack
Chair**

Email: nrescommittee.yorkandhumber-sheffield@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Ramila Patel, STH Research Department*

**COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DELLA PROVINCIA DI
VENEZIA E IRCCS SAN CAMILLO(CESC)**

SEDUTA del 27/01/2015

Verbale N°18A/CESC

Il giorno 27/01/2015 alle ore 14.30 presso l'aula 145 - Azienda ULSS 12 VENEZIANA - si è riunito il Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS San Camillo, istituito in conformità alle disposizioni del DM 15/07/1997 e nominato con deliberazione del Direttore Generale ULSS12 n. 1803 del 25/09/2013 ai sensi del DM 8/2/2013 e della DGRV n°1066 del 28/6/2013 e che risulta così costituito:

	Componente	
P	Bon Dott. Giuseppe	Esperto in Bioetica
P	Boscolo Bariga Dott. Angelo	Clinico
P	Bova Prof. Sergio	Farmacologo
P	Burlon Dott.ssa Nerina	Farmacista
P	Carraro Dott. Daniele	Medico legale
P	Crovato Avv. Alberto	Esperto in materia giuridica e assicurativa
P	Della Bianca Dott.ssa Simona	Rappresentante del settore infermieristico
P	Ghi Dott.ssa Maria Grazia	Clinico
P	Gobbo Sig. Giorgio	Rappresentante del volontariato
P	Minicuci Dott.ssa Nadia	Biostatistico
A	Penzo Dott. Carlo	Clinico
P	Piccione Dott. Francesco	Clinico
P	Ponzetto Dott. Tiziana	Medico di Medicina Generale
P	Raise Prof. Enzo	Clinico
A	Righetti Dott. Andrea	Pediatra
P	Serino Dott. Francesco Saverio	Clinico
P	Barzan Dott.ssa Daniela	Esperto in dispositivi
P	Agostini Dott.ssa Michela	fisioterapista
P	Stradella Dott. Giovanni	Farmacista

A	Bellometti Dott.ssa Simona Aurelia (sostituita dal Dott. Giovanni Mazzanti)	Direttore Sanitario ULSS 10
P	Fabbri Dott. Alessandro (sostituito dal Dott. Alvisè Spolaor)	Direttore Sanitario ULSS 13
A	Finotto Dott.ssa Rita (sostituita dalla Dott.ssa Lisa Bertoncetto)	Direttore Sanitario ULSS 12
NC	Malatesta Dott. Renzo	Direttore Sanitario P. S.Marco
NC	Cestroni Dott. Adriano	Direttore Sanitario casa di cura Rizzola
NC	Sbrogiò Dott. Luca Gino (sostituito dal Dott. Paolo Venerucci)	Direttore Sanitario ULSS 14
NC	Sattin Dott. Guido	Direttore Sanitario Fatebenefratelli
NC	Veneri Prof. Annalena	Direttore scientifico IRCCS San Camillo
NC	Giron Dott. Giampiero	Direttore Sanitario Villa Salus

P	Anglani Dott.ssa Franca	Esperta in genetica
NC	Semenzato Ing. Mara	Ingegnere clinico
NC	Spinella Prof. Paolo	Esperto in nutrizione
NC	Merenda Prof. Roberto	Esperto clinico per studi di nuove procedure tecniche, diagnostiche e terapeutiche invasive e semiinvasive

Legenda: P=presente A=assente NC=non convocato

La Dott.ssa Michela Zanutti, in qualità di Segretario Scientifico è presente alla seduta.

Riscontrato il numero legale dei componenti si procede alla visione e discussione degli argomenti stabiliti nell'ordine del giorno.

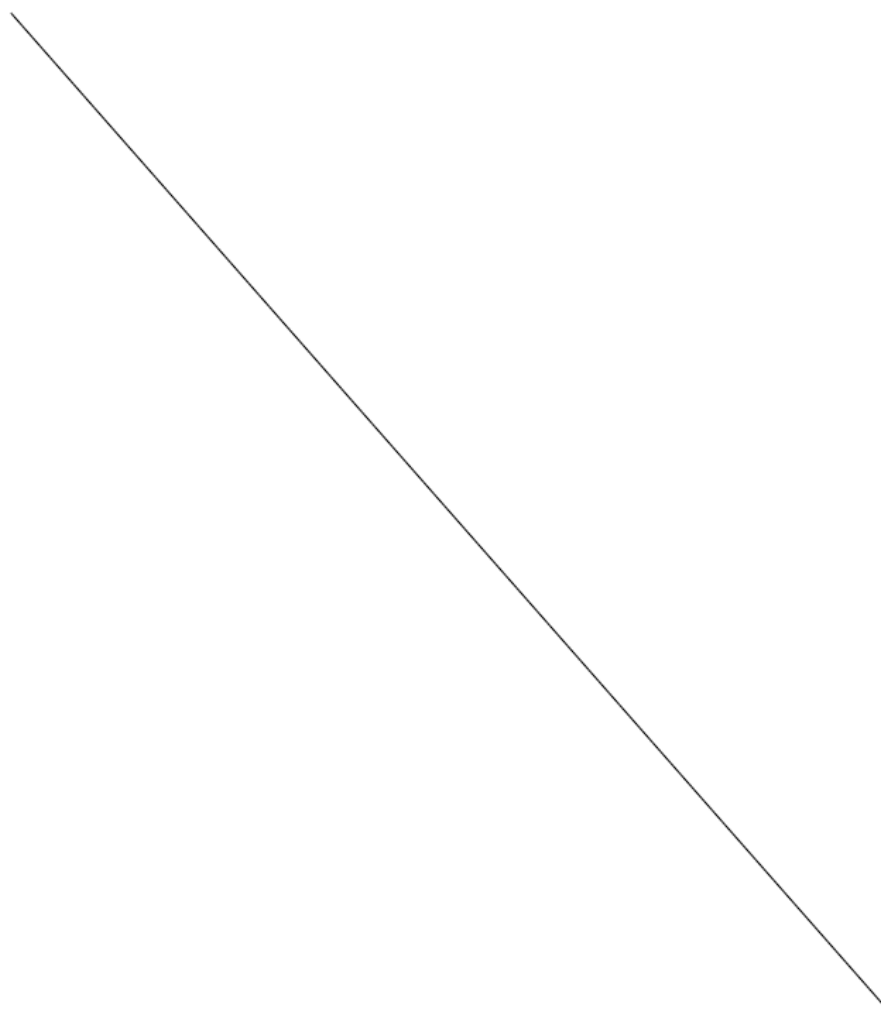
IL COMITATO

valutati tutti gli aspetti inerenti la validità scientifica e l'utilità clinica della ricerca, il protocollo e il disegno sperimentale, la correttezza etica, l'idoneità delle strutture coinvolte e le compensazioni finanziarie;

considerate con particolare attenzione tutte le condizioni di garanzia per i pazienti che partecipano agli studi clinici, dalle modalità di arruolamento alle forme di acquisizione del consenso ed all'eventuale indennizzo;

preso atto che tutti gli aspetti degli studi sono pienamente corrispondenti alle indicazioni contenute ai DGRV n. 1376 del 27/4/1999, DGRV n. 57 del 23/01/2004, n. 3456 del 11/01/2004, n. 4049 del 22/12/2004, n. 4430 del 28/12/2006; DGRV n. 2855 del 7.10.2008, DLgs n. 211 del 24/06/2003 e s.m., Decreto del Ministero della Salute del 12/05/2006 (G.U. n. 194 del 22/08/2006) e successive integrazioni normative, inerenti alla costituzione ed il funzionamento dei Comitati Etici per la sperimentazione clinica dei farmaci.

Procede ad esaminare la seguente documentazione:



[OMISSIS]

**Studio sospeso n. 585/IRCCS San Camillo
Studio osservazionale – no profit
Relatore *Dr. Bariga***

Titolo Studio	VIRTUAL PHYSIOLOGY IN HUMAN DEMENTIA RESEARCH ENABLED BY IT	
Codice Protocollo	VHP-DARE@IT	Eudract
Promotore	IRCCS SAN CAMILLO	CRO
Principio Attivo		
Struttura	UOSD di Riabilitazione neuropsicologica, IRCCS San Camillo	
Sperimentatore	Dott.ssa Francesca Meneghelo	

Documentazione esaminata

Email di chiarimenti del 12/01/2015
Sinossi v.2 del 08/01/2015
Scheda raccolta dati v.2 del 08/01/2015
Protocollo di studio v.2 del 08/01/2015

Esaminata la documentazione, il Comitato esprime il seguente parere:

✓ *Approvata*

[OMISSIS]

VIENE RIBADITO

che questo Comitato Etico dovrà essere informato di ogni successivo emendamento ai protocolli, nonché degli eventi avversi o inattesi registrati nel corso degli studi tali da influire sulla sicurezza dei soggetti o sul completamento degli studi stessi e, a conclusione delle ricerche, dovrà acquisire i risultati finali;

che al responsabile della sperimentazione compete stabilire una procedura di gestione dei medicinali in studio, secondo il D.M. 15 luglio 1997 "Recepimento delle linee guida dell'Unione Europea di buona pratica clinica per la esecuzione delle sperimentazioni cliniche dei medicinali", la D.G.R. del Veneto n. 1376 del 27.4.1999 "Linee guida per la costituzione ed il funzionamento dei Comitati Etici per la sperimentazione clinica dei farmaci" e le successive integrazioni normative, nonché ai sensi del DLgs n. 211 del 24/6/2003 e alle Linee Guida per gli studi osservazionali sui farmaci (determinazione AIFA-20 marzo 2008)

che il Servizio di Farmacia Ospedaliera/Servizio Farmaceutico Territoriale in ogni singola Azienda ULSS consegnerà, nei casi che lo prevedono, i farmaci in unica soluzione al ricercatore il quale, alla chiusura dello studio, dovrà restituire i prodotti inutilizzati al medesimo Servizio per la successiva resa degli stessi allo sponsor;

che i costi della sperimentazione non dovranno gravare sul SSN come previsto art. 20 del D.Legislativo n. 211 del 24 giugno 2003 e al comma 1 art.6 D. M 12/5/2006 e per gli studi No Profit si applica il DM 17/12/2004;

che al responsabile della sperimentazione è demandato, inoltre, l'onere della conservazione degli atti relativi alle ricerche per il tempo e con le modalità previsti dalle disposizioni in vigore.

La seduta si conclude alle ore 18.15

IL RESPONSABILE DELLA
SEGRETERIA SCIENTIFICA
(Dr.ssa Michela Zanutti)

IL PRESIDENTE DEL
COMITATO ETICO
(Prof. Enzo Raise)