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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 trustworthy 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.

Keywords

awareness; mild cognitive impairment; cognition; anterior cingulate;

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 (Gambina et al., 2015; Avondino & Antoine, 2016). 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, Chemerinski, 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 and 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 and 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, Lin, Rosen, Sollberger, Miller & Rankin, 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 highlight 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 (Orfei et al., 2010; Clare et al., 2013, 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 mnemonic comparator system performance 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**).

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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 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 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**).

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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 mm^3, 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 $p < 0.007$ 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, Cusack, & Henson, 2012) and brain reserve (Van Loenhoud, Groot, Vogel, Van der Flier & Ossenkoppele, 2018). An uncorrected $p < 0.005$ was selected as cluster-forming threshold. Clusters surviving a Family-Wise Error $p < 0.05$ 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; Lancaster et al., 2000).

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 ($\rho = -0.467$, $p = 0.002$), the copy and recall of the Rey-Osterrieth 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 (**Table 3)**.

--- Please insert **Table 3** about here ---

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, bilateral precentral gyrus, bilateral lingual gyrus, bilateral fusiform gyrus, right superior frontal gyrus and right postcentral gyrus (**Table 4**; **Figure 1**). No significant associations were detected between memory anosognosia scores and grey matter volumes.

--- Please insert **Table 4** and **Figure 1** about here ---

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 visuoconstructive 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 > 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, Black, Freedman & Moscovitch, 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 & Quattropani, 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., (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 Jr 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 (Vogeley 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 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 (Reed, Jagust & Coulter, 1993; Weinstein, Friedland & Wagner, 1994; Almeida & Crocco, 2000, Gambina et al., 2015). The AD pathophysiological progression may impact directly on the severity of the disease, but 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 anterior cingulate cortex (ACC). This region has been associated 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 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 and 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 amnestic 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 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.

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 and 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 comparatory 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 colleagues (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 comparatory 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, comparatory 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 to the functionality of the DMN in AD (Antoine et al., 2019; Mondragon, Maurits & 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 ($r = 0.895$) and non-memory ($r = 0.818$) 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.

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Disclosure

The authors have no conflict of interest to report.

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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

Table 2. Clinical profiling and test of experimental interest

Cognitive test	Sample Mean / *n*	Range (min-max)	Cut-off (Z 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	**ρ = -0.563 / *p* = 0.001***	ρ = -0.327 / *p* = 0.035	**ρ = -0.525 / *p* = 0.001***
Letter Fluency	ρ = -0.2836 / *p* = 0.067	ρ = 0.104 / *p* = 0.512	ρ = -0.114 / *p* = 0.471
Stroop Test error	ρ = 0.405 / *p* = 0.008	ρ = 0.222 / *p* = 0.157	ρ = 0.352 / *p* = 0.022
Category Fluency	**ρ = -0.449 / *p* = 0.003***	ρ = -0.364 / *p* = 0.018	**ρ = -0.492 / *p* = 0.001***
Prose Memory delayed recall	**ρ = -0.429 / *p* = 0.005***	ρ = -0.386 / *p* = 0.012	**ρ = -0.467 / *p* = 0.002***
Rey Figure copy	ρ = -0.292 / *p* = 0.061	ρ = -0.379 / *p* = 0.013	**ρ = -0.424 / *p* = 0.005***
Rey Figure recall	ρ = -0.385 / *p* = 0.012	ρ = -0.316 / *p* = 0.042	**ρ = -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 educations and hippocampal fraction as covariates of no interest.

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

	Cluster Extent	FWE-corrected *p*-	*z* score	Side	Peak-based localisation	Talairach Coordinates		
						x	y	z
Total Anosognosia Score	3430	0.001	3.70	R	Anterior cingulate	4	26	-10
			3.69	L	Anterior cingulate	0	21	-3
			3.76	L	Thalamus	-4	-29	7
	1803	0.021	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	0.001	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	0.023	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	0.014	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	0.001	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	0.019	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

Figure caption

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