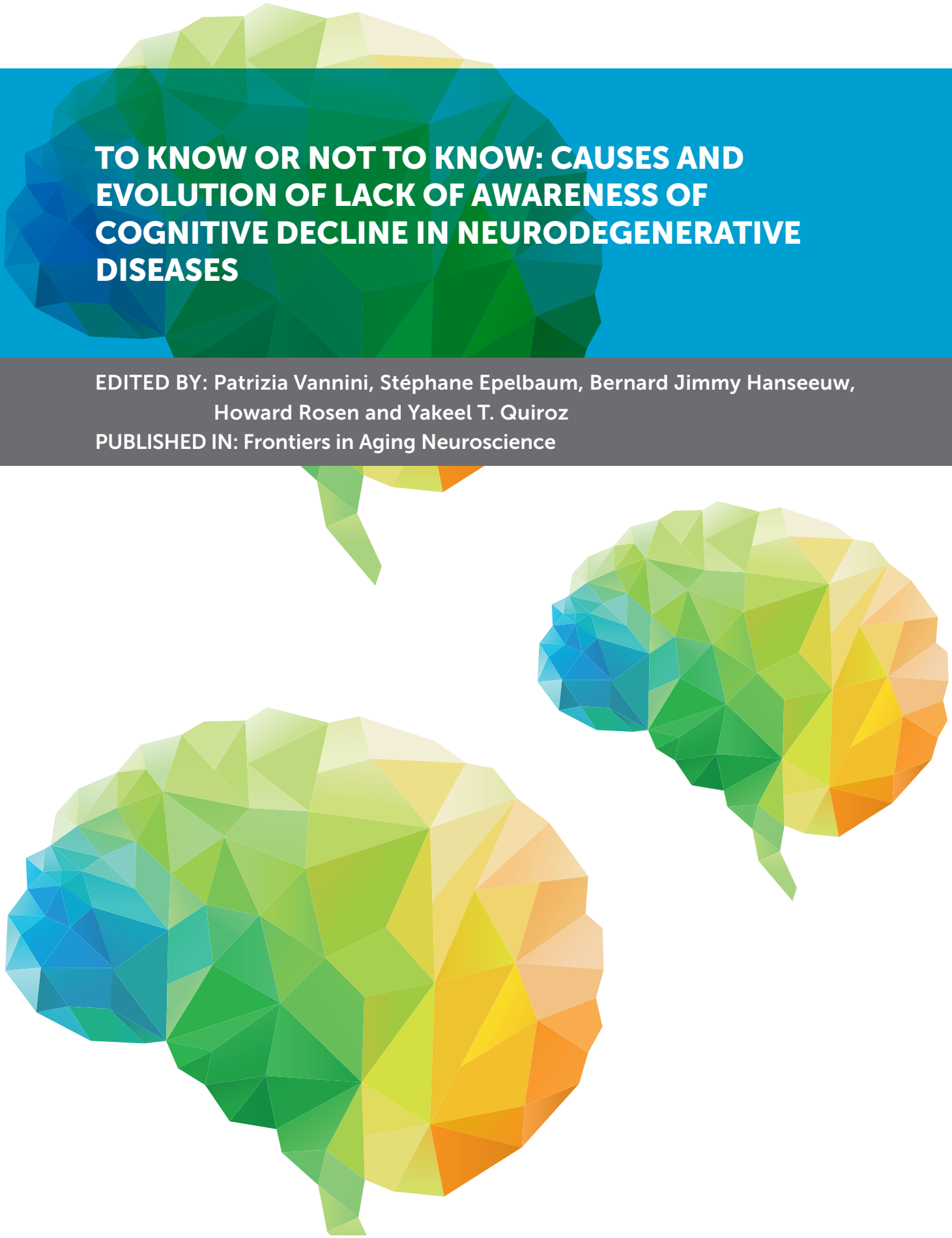
TO KNOW OR NOT TO KNOW: CAUSES AND EVOLUTION OF LACK OF AWARENESS OF COGNITIVE DECLINE IN NEURODEGENERATIVE DISEASES

EDITED BY: Patrizia Vannini, Stéphane Epelbaum, Bernard Jimmy Hanseeuw, Howard Rosen and Yakeel T. Quiroz

PUBLISHED IN: Frontiers in Aging Neuroscience



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-83250-515-1
DOI 10.3389/978-2-83250-515-1

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

TO KNOW OR NOT TO KNOW: CAUSES AND EVOLUTION OF LACK OF AWARENESS OF COGNITIVE DECLINE IN NEURODEGENERATIVE DISEASES

Topic Editors:
Patrizia Vannini, Brigham and Women's Hospital, Harvard Medical School, United States
Stéphane Epelbaum, Hôpitaux Universitaires Pitié Salpêtrière, France
Bernard Jimmy Hanseeuw, Cliniques Universitaires Saint-Luc, Belgium
Howard Rosen, University of California, San Francisco, United States
Yakeel T. Quiroz, Massachusetts General Hospital, Harvard Medical School, United States

Citation: Vannini, P., Epelbaum, S., Hanseeuw, B. J., Rosen, H., Quiroz, Y. T., eds. (2022). To Know or Not to Know: Causes and Evolution of Lack of Awareness of Cognitive Decline in Neurodegenerative Diseases. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83250-515-1

Table of Contents

frontiers in Aging Neuroscience

SYSTEMATIC REVIEW
published: 03 August 2021
doi: 10.3389/fnagi.2021.697234

Awareness of Cognitive Decline in Patients With Alzheimer's Disease: A Systematic Review and Meta-Analysis

Federica Cacciamani[1,2,3,4,5], Marion Houot[1,4,6], Geoffroy Gagliardi[7,8], Bruno Dubois[1,2,3,4,6], Sietske Sikkes[7,9], Gonzalo Sánchez-Benavides[10,11,12], Elena Denicolò[13], José Luis Molinuevo[10], Patrizia Vannini[7,8] and Stéphane Epelbaum[1,2,3,4,5,6]*

[1] Institut du Cerveau, ICM, Hôpital de la Pitié-Salpêtrière, Paris, France, [2] Inserm, U 1127, Paris, France, [3] CNRS, UMR 7225, Paris, France, [4] Sorbonne Université, Paris, France, [5] Inria, ARAMIS-Project Team, Paris, France, [6] Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), ICM, CIC Neurosciences, AP-HP, Department of Neurology, Hôpital de la Pitié-Salpêtrière, Sorbonne University, Paris, France, [7] Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States, [8] Department of Neurology, Center for Alzheimer Research and Treatment, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States, [9] Department of Neurology, Alzheimer Center Amsterdam, Amsterdam Neuroscience, Amsterdam University Medical Center (UMC), Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [10] BarcelonaBeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona, Spain, [11] Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain, [12] Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid, Spain, [13] Department of Biomedical Science and Neuromotor Sciences, University of Bologna, Bologna, Italy

Background: Identifying a poor degree of awareness of cognitive decline (ACD) could represent an early indicator of Alzheimer's disease (AD).

Objectives: (1) to understand whether there is evidence of poor ACD in the pre-dementia stages of AD; (2) to summarize the main findings obtained investigating ACD in AD; (3) to propose a conceptual framework.

Data Sources: We searched Scopus, Pubmed, and the reference lists for studies published up to August 2020. Original research articles must report a measure of ACD and included individuals with AD dementia, or prodromal AD (or MCI), or being at risk for AD.

Data Synthesis: All studies covering preclinical, prodromal, and AD dementia were systematically reviewed. We intended to perform a meta-analysis of empirical studies on preclinical AD or prodromal AD (or MCI), to compare ACD between clinical groups. Due to the paucity of literature on preclinical AD, meta-analysis was only possible for prodromal AD (or MCI) studies.

Results: We systematically reviewed 283 articles, and conducted a meta-analysis of 18 articles on prodromal AD (or MCI), showing that ACD was not significantly different between patients with amnestic and non-amnestic MCI (SMD = 0.09, $p = 0.574$); ACD was significantly poorer in amnestic MCI (SMD = −0.56, $p = 0.001$) and mild AD (SMD = −1.39, $p < 0.001$) than in controls; ACD was also significantly poorer in mild AD than in amnestic MCI (SMD = −0.75, $p < 0.001$), as well as poorer than in non-amnestic MCI (SMD = −1.00, $p < 0.001$). We also discuss key findings on ACD in AD, such as its neural and cognitive correlates.

OPEN ACCESS

Edited by:
Roberto Monastero, University of Palermo, Italy

Reviewed by:
Maria Donata Orfei, IMT School for Advanced Studies Lucca, Italy
Elena Chipi, University of Perugia, Italy

****Correspondence:***
Federica Cacciamani
federica.cacciamani@icm-institute.org

Received: *19 April 2021*
Accepted: *22 June 2021*
Published: *03 August 2021*

Citation:
Cacciamani F, Houot M, Gagliardi G, Dubois B, Sikkes S, Sánchez-Benavides G, Denicolò E, Molinuevo JL, Vannini P and Epelbaum S (2021) Awareness of Cognitive Decline in Patients With Alzheimer's Disease: A Systematic Review and Meta-Analysis. Front. Aging Neurosci. 13:697234. doi: 10.3389/fnagi.2021.697234

Conclusions and Implications: We propose that patients may be complaining of their initial subtle cognitive changes, but ACD would soon start to decrease. The individual would show mild anosognosia in the MCI stage, and severe anosognosia in dementia. The evaluation of ACD (comparing self-report to cognitive scores or to informant-report) could be useful to guide the clinician toward a timely diagnosis, and in trials targeting early-stage AD.

Keywords: awareness, anosognosia, metamemory, hypernosognosia, Alzheimer's disease

INTRODUCTION

Rationale

Over the past two decades, advances in basic and clinical research have provided a better understanding of the natural history of Alzheimer's disease (AD). It is now well-known that years pass before pathophysiological changes (such as the buildup of amyloid plaques and neurofibrillary tangles) lead to cognitive impairment. AD has therefore been reconceptualized as a continuum comprising three phases (Dubois et al., 2010): (i) an initial *preclinical* phase, in which the patient may show a subtle decrease in cognitive efficiency compared to his or her own baseline level, without having normal cognitive scores (*transitional cognitive decline* according to Jack et al., 2018); (ii) an intermediate phase known as *prodromal AD*, during which the patient has mild objective cognitive impairment (MCI) which does not limit his or her autonomy in daily life; and (iii) the term *dementia* indicates the final phase of the disease in which the disorders are more severe, widespread in multiple cognitive domains, and interfering with autonomy. In a recent study (Vermunt et al., 2019), the preclinical phase lasted on average 10 years, the prodromal phase 4 years, and the dementia phase 6 years, in individuals who presented with preclinical AD at 70 years of age.

The search for strategies for timely diagnosis (before patients cross the threshold of dementia) has become one of the key themes in AD research. A timely diagnosis opens up a wide spectrum of possibilities for the patients and their family, but also at the community and societal level, mainly in terms of treatment, decision-making and cost reduction (see Dubois et al., 2016b for a review). The importance of timely diagnosis is underlined by campaigns aimed at the general population, for example within the WHO Global Action Plan on dementia 2017–2025. Their goal is to promote an accurate understanding of AD, increase public knowledge about risk factors, and educate people to recognize early symptoms of AD. This is changing people's attitudes toward the disease (Cations et al., 2018, PLoS ONE).

As a result of this ongoing cultural shift, people are increasingly seeking medical advice for a self-perceived decline in cognition. A growing number of studies are currently investigating whether Subjective Cognitive Decline (SCD) could represent an early (mostly preclinical) indicator of AD. SCD is defined as a self-experienced persistent decline in cognitive capacity in comparison with a previous normal status and unrelated to an acute event, while age-, gender-, and education-adjusted performance on standardized tests is normal (Jessen et al., 2014). The idea that seems to prevail is that the expression of cognitive complaints can represent the first manifestation of AD prior to objective cognitive impairment. Results are rather conflicting but various studies have identified an increased likelihood of biomarker abnormalities consistent with AD pathology in individuals with SCD (e.g., ApoE ε4 allele overrepresentation in Abdulrab and Heun, 2008; abnormal amyloid levels in Wolfsgruber et al., 2015; regional hypometabolism in Mosconi et al., 2008; atrophy in Garcia-Ptacek et al., 2014). According to the most recent criteria of SCD (Jessen et al., 2020), individuals aged 60 years or over, persistently worried by a memory decline for at least 5 years, for which they have sought medical advice, and which is confirmed by an informant, would be more at risk of preclinical AD.

These criteria for SCD are still subject to ongoing validation and refinement, as the authors also stated (Jessen et al., 2020). Some studies in recent years have attempted to go further in describing how patients with early-stage AD experience their progressive cognitive decline. It has recently been proposed that exhibiting a poor awareness of cognitive decline (ACD) could represent an early clinical indicator of the disease (Cacciamani et al., 2017), more specific than SCD, and should encourage more in-depth patient monitoring. The lack of awareness of illness is indeed a known symptom of AD, especially in the dementia phase, in which it goes under the name of *anosognosia*. The term *anosognosia* derives from the Greek α (without), νοσοζ (disease or illness), γνωσιζ (knowledge) (Babinski, 1914, translated by Langer and Levine, 2014).

According to the Dissociable Interactions and Conscious Experience (DICE) theory (McGlynn and Schacter, 1989; Schacter, 1989; McGlynn and Kaszniak, 1991), the activation distinctive cognitive modules representing specific cognitive functions would trigger the Conscious Awareness System, resulting in conscious awareness of the information being processed. Damage to one or more individual modules, or their disconnection from the Conscious Awareness System, due to brain damage, would result in a domain-specific deficit in awareness. The Conscious Awareness System itself could be damaged, resulting in a generalized unawareness. Agnew and Morris (1998) and Mograbi et al. (2009) extended the DICE model, which was renamed *Cognitive Awareness Model*. According to this new model, the Conscious Awareness System, which would be located in the parietal lobe, processes the feedback received after an action has been executed: in this

way, the individual becomes aware of having performed it correctly or not. Then, the mnemonic comparator, located within the executive system, would compare this knowledge with existing information about the individual's abilities. If it does not match with the semantic personal knowledge base, this latter would be updated. Anosognosia in AD dementia has been suggested to arise from a suboptimal ability to detect a mismatch between current performance and past knowledge about the self, and to the inability to recollect and update personal semantics (Graham et al., 2005). Mograbi et al. (2009) added that AD mainly affects recent memories and predominantly spares older information about the self, since the oldest memories are located in the neocortex and therefore less dependent on hippocampus integrity. This amnestic pattern, together with executive dysfunction, would result in a *petrified* self-evaluation based on premorbid abilities (Kalenzaga and Clarys, 2013). Recent studies have provided partial support to the *Petrified-self* theory. Patients with AD dementia may acknowledge their deficient performance shortly after its execution, and use this information to partially and temporarily update their self-knowledge. However, this new knowledge about the self fails to be used and integrated into long-term self-representations (Gil and Josman, 2001; Duke et al., 2002; Ansell and Bucks, 2006; Mimura and Yano, 2006; Hannesdottir and Morris, 2007; Oyebode et al., 2007; Stewart et al., 2010; Silva et al., 2017; Bertrand et al., 2019).

The possibility that poor ACD could serve as an early indicator of AD may seem to run counter to research results on SCD. However, the concepts of *SCD* and *poor awareness* are only apparently opposed since they can coexist in the same individual, as found in the INSIGHT-PreAD cohort (Cacciamani et al., 2017, 2020). This is the case of individuals who complain of a certain degree of cognitive difficulties, still underestimating their severity or impact on daily life (when compared to the assessment made by an informant or using cognitive tests). Studying the degree of ACD in AD continuum helps us to better understand how patients experience the disease, and therefore better characterize the cognitive complaints typical of the patient with AD.

The methods commonly used to assess ACD in the context of AD in research and clinical settings can be categorized as follows.

The first category includes the evaluation of the clinician, who asks the patient more or less structured questions about the reason for the visit or whether he or she perceives cognitive difficulties (e.g., Cova et al., 2017). This is a time-saving method, but its psychometric robustness is not always known.

A second category is performance-based methods, assessing (i) the discrepancy between objective cognition and self-reported cognition (Dalla Barba et al., 2015); and (ii) the accuracy of pre-test predictions or post-test estimates of performance (Graham et al., 2005; Hannesdottir and Morris, 2007; Mograbi et al., 2012). Hannesdottir and Morris for example propose Objective Judgment Discrepancy to measure awareness of memory performance (or memory-monitoring). The clinician or investigator asks the individual to estimate the number of successfully remembered items in a memory test, and then applies the following formula: [(estimated score-actual score) / maximum possible score on measure] × 100. The main difficulty related to these methods is that it could be challenging for an individual to evaluate the performance on unfamiliar cognitive tasks.

The third category of methods includes the discrepancy between the cognitive difficulties perceived by the patient and those reported by an informant (a family member or close friend). This is generally calculated by asking the patient and an informant to separately fill in parallel forms of the same questionnaire that assesses the patient's cognitive functioning (e.g., Edmonds et al., 2018). The discrepancy between these two scores can be treated as a continuum, or a cut-off can be identified to attribute an awareness status to the subject. We describe here the main questionnaires allowing to compute the subject-informant discrepancy. The *Cognitive Change Index* (CCI, Rattanabannakit et al., 2016) is a widely used questionnaire. Two parallel forms are available (one for the patient and one for an informant), in which they assess the severity of recent changes in memory (12 items), in attention and executive functions (5 items), and in language (3 items). The *Everyday Cognition Questionnaire* (Farias et al., 2008), known as E-Cog and also used in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort study (http://adni.loni.usc.edu), asks the patient and an informant to evaluate how much specific domains have changed compared to 10 years ago: everyday memory, language, visuospatial abilities, planning, organization, and divided attention. Another questionnaire used in the literature and of less recent construction is the *Anosognosia Questionnaire-Dementia* (AQ-D) by Migliorelli et al. (1995). It is a 30-question questionnaire that assesses the frequency of cognitive, functional and behavioral changes. The *Healthy Aging Brain Care (HABC) Monitor* is a valid and reliable tool to compare the self- and informant-report of decline. It includes questions relating to the cognitive, functional and psycho-behavioral spheres (Monahan et al., 2012, 2014). Finally, the *Patient Competency Rating Scale* (PCRS) was developed by Prigatano (1987) to evaluate anosognosia following brain trauma. It includes 30 questions covering cognitive, but also behavioral and functional domains. The patient and a person who knows him/her well (a family member or a clinician) use a 5-point Likert scale to assess the degree of difficulty in the aforementioned contexts.

It has two parallel forms for the patient and an informant, thus allowing to calculate the discrepancy between the two reports. The questions ask to assess the frequency of 30 cognitive difficulties or behavioral changes. The subject-informant discrepancy is one of the most used methods in literature to measure ACD. However, few studies explored the psychometric properties of these questionnaires (e.g., Gil and Josman, 2001; Monahan et al., 2012, 2014). The subject-informant discrepancy method assumes that the informant's report is an accurate source of information. However, the possibility that the informant's report could be distorted by factors such as anxiety, depression, burden, personality traits, should also to be taken into consideration. In Cacchione et al. (2003), for instance, the informant's rating significantly predicted his or her actual cognitive decline, and its accuracy was above case even for informants who were not spouses, who did not live with the patient, or who spoke to the patient less than daily, and for patients who were older or less educated.

See Rabin et al. (2015) for a review.

Objectives

We aimed at providing a synthesis of the current state of the art of scientific literature investigating ACD in relation to AD. Qualitative and quantitative methods have been used to describe ACD in AD, to (1) understand whether there is evidence of poor ACD in the pre-dementia stages, and therefore whether it can be used as an early indicator of AD; (2) qualitatively summarize the main results obtained for a better understanding the neural and clinical correlates of ACD in the different stages of the disease; (3) outline a theoretical framework, useful in clinical practice in the context of early AD diagnosis and in research to motivate further studies and to suggest where future research might be best directed.

METHODS

Protocol and Registration

The review and meta-analysis protocol have not been published elsewhere than in this article.

Search Strategy and Study Eligibility Criteria

Studies were identified by searching two electronic databases (PubMed and Scopus). The reference list of the resulting articles was also hand-searched to find additional relevant articles.

Search terms were: "(*Alzheimer disease OR Mild Cognitive Impairment) AND (awareness OR metacognition OR anosognosia*)" (MeSH terms when relevant). We imposed no restrictions in terms of study type (we included original research papers, reviews and meta-analyses) and publication date. In fact, we wanted to include all eligible articles published until August 2020, when the literature search was carried out.

Original research articles must report at least one measure of ACD. Review articles must discuss ACD or anosognosia in relation to AD. Studies that exclusively addressed the awareness of non-cognitive changes (for example, awareness of functional decline, or psycho-behavioral disorders) were excluded.

For the selection of articles, we have taken into account that many diagnostic labels have been proposed over the years and that preclinical AD is a newly formulated concept. Therefore, we have established that subjects must be classified as: (i) cognitively-intact at risk for AD including at least one biomarker for AD and the findings discussed within the scope of preclinical AD; or (ii) subjects classified as having a MCI, with or without *in vivo* evidence of AD pathology, with no restrictions in terms of diagnostic criteria used or type of MCI (e.g., amnestic or non-amnestic); or (iii) individuals diagnosed with AD dementia, regardless of the diagnostic criteria used. We imposed no demographical restrictions.

Articles must be in English or French.

Study Selection

Two authors (FC and GG) reviewed all retrieved records by reading the title and abstract and, if necessary, the body of the article. We checked whether the articles met the eligibility criteria and issued a decision independent of each other. In the case of ineligibility, they recorded the reason. Subsequently, they discussed to reach a common agreement for each article. None of the authors were blind to the study authors, their affiliations, or journal title.

Data Collection Process and Data Items

For all original research articles, we used an uncoded form, along the lines of the Cochrane Data Extraction Form. We pilot-tested it on five randomly-selected studies, and no refinement was needed. For each of these studies, we recorded: (a) aim, (b) sample size, (c) diagnostic classification of the participants, (d) mean age, (e) mean and (f) range of the Mini-Mental State Examination (MMSE) when available, (g) mean years of education, (h) percentage of men, (i) measure used to assess ACD, (j) statistical model performed, and (k) key findings relevant for this review.

We also had additional coded items, to be filled in only if the original research article included at least a subgroup of subjects at risk for AD (or with preclinical AD) or prodromal AD (or MCI), as we decided to perform a meta-analysis (Objective 1). Relevant information to be extracted was determined a priori as follows:

1: Studies treating the measure of ACD as a continuous variable. We extracted (l) mean ACD of each clinical group (i.e., cognitively-normal, amnestic MCI, non-amnestic MCI, mild dementia, moderate dementia, severe dementia), (m) standard deviation (SD) for each clinical group, (n) size of the whole sample, and (o) size of each clinical group being compared in the study. When relevant, continuous measures of ACD were multiplied by −1 so that, for each article, a lower value represented a poorer ACD, and a higher value a higher ACD.

2: Studies treating the measure of ACD as a categorical variable. We extracted the (p) percentage of subjects with impaired ACD of each clinical group, (q) size of the whole sample, and (r) size of each clinical group being compared in the study. In particular, we considered the ACD as impaired when classified by the authors as both shallow or completely lacking, according to an established threshold.

The studies on preclinical AD and on prodromal AD (or MCI) that reported neither mean ACD (and SD) nor percentages of subjects with impaired ACD were systematically reviewed but excluded from the meta-analysis.

In the meta-analysis, the indices of ACD were considered as comparable, even if measured with different methodological approaches.

Regarding past literature reviews, we used a separate uncoded form to extract (a) the number of studies included, (b) search strategy, (c) stage of the disease, and (d) key results.

Data extraction was carried out by three authors (FC and GG independently, then MH for verification of coded items). Any discrepancies between the authors were resolved by discussion.

Planned Methods of Analysis

The review of these articles will be addressed thematically by stage of the disease, which means that we will discuss the degree of awareness of patients in dementia, prodromal (or MCI), and preclinical stages, separately.

We intended to systematically review all the articles and to conduct a meta-analysis only of those including at least a subgroup of subjects at risk of AD (or with preclinical AD), or with prodromal AD (or MCI). Indeed, we wanted to place special

emphasis on the degree of ACD in the pre-dementia stages, which is currently being debated, although we included studies on all three stages to investigate ACD throughout the entire course of AD.

We decided a priori that we would conduct a meta-analysis when at least three articles compared the same pair of clinical groups.

Summary Measures

A random-effect meta-analysis using the inverse variance method was performed for each pairwise comparison. For articles treating the measure of ACD as a continuous variable: we estimated a standardized mean difference (SMD) between clinical groups using Hedges' g method. For articles treating the measure of ACD as a categorical variable: we estimated the odds ratio (Robins et al., 1986) and converted it to Hedges' g estimate (see Borenstein et al., 2009) in order to make these studies comparable to those that treated ACD as a continuous variable.

Heterogeneity was tested using Cochran's Q test and assessed through I^2 and Tau^2 indexes.

Statistical analyses were performed using R 3.6.1. and the meta (V. 4.9-7) package.

Assessment of the Risk of Bias

To ascertain the validity of the included studies, we a priori identified some potential risks of bias and noted them when extracting data from the studies: (i) heterogeneity of study populations (e.g., in terms of age, sex, education); (ii) unclear stage of disease (e.g., inclusion of subjects with a diagnosis of AD dementia without specifying stage of severity); (iii) absence of evidence of abnormal AD biomarkers in case of MCI diagnosis; (iv) heterogeneity in the definition of preclinical AD.

RESULTS

Study Selection

A flow chart showing the selection process and results is provided as **Supplementary Materials**. The bibliographical search yielded 662 citations, published between 1991 and August 2020. Of these, 379 did not meet the eligibility criteria and were excluded. Two hundred and eighty-two articles were systematically reviewed.

Figure 1 shows the number of revised publications per year and stage of the disease addressed.

We systematically reviewed 52 studies including subjects with prodromal AD or MCI. Eighteen of these were eligible for the meta-analysis, as they reported either a mean index of ACD (and SD) or the percentage of subjects with impaired ACD (see **Supplementary Table 1** for more details). These studies compared ACD between clinical groups: controls, amnestic MCI, non-amnestic MCI, mild AD. The group of participants with moderate AD was excluded from the meta-analyses, as they were only compared with subjects with amnestic MCI in 1 article and with mild AD in 1 article.

On the contrary, the meta-analysis of the studies on preclinical AD was not possible, as the articles were too few (<3 articles comparing the same clinical groups).

Characteristics and Key Findings of Studies on AD Dementia

Prevalence of Anosognosia in AD Dementia

The prevalence of anosognosia in AD dementia has been estimated between 40 and 91% based on the study, this range varying according to the severity of dementia, which was found to be the main determinant of anosognosia (Akai et al., 2009; Maki et al., 2013; Turró-Garriga et al., 2016).

Prevalence estimations may also vary according to how the anosognosia was operationalized and measured. In fact, all three studies that identified a lower prevalence of anosognosia in dementia (around 40%) had used the Awareness of Deficit Questionnaire-Dementia (AQ-D; Migliorelli et al., 1995). It consists of 30 questions in which the patient and an informant assess separately the frequency of certain cognitive difficulties, difficulties in everyday tasks, and changes in interests and mood. In contrast, a higher prevalence of anosognosia in dementia was found for instance in Lacerda et al. (2020) using the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (Dourado et al., 2007, 2014). This is a 23-question-semi-structured interview, assessing awareness in the domains of cognition, social functioning, emotional status, and activities of daily living.

Neural Correlates of Anosognosia in AD Dementia

Anosognosia appears to be present in those demented AD patients who have particular frontal and temporoparietal lesions.

More specifically, anosognosic patients with mild to severe AD showed reduced perfusion, glucose metabolism and gray matter volume in the prefrontal cortex (PFC), both dorsolateral and in the anterior cingulate gyrus (Harwood et al., 2005; Hanyu et al., 2008; Jedidi et al., 2014; Fujimoto et al., 2017).

Others found that anosognosia was associated with reduced intrinsic connectivity and functional changes of brain areas known to be involved with self-referential processes, such as the orbitofrontal cortex (OFC), the posterior cingulate cortex (PCC) and the medial temporal lobe. For instance, Kashiwa et al. (2005) found that anosognosic patients had reduced perfusion in the OFC, and a blood flow that was reduced in the right PFC, and increased in the left temporoparietal junction. One study by Therriault et al. (2018), found that anosognosia correlated with a greater amount of amyloid in the PCC.

In Fujimoto et al. (2017), the medial temporal lobe, which is usually damaged in AD dementia, was not associated with anosognosia. On the contrary, others found greater hypometabolism (Salmon et al., 2006) and atrophy in the medial temporal lobe (Tondelli et al., 2018) in anosognosic patients.

Clinical Correlates of Anosognosia in AD Dementia

Executive dysfunction is highly associated with anosognosia in patients with AD dementia (Lopez et al., 1994; Kashiwa et al., 2005; Amanzio et al., 2013). The ability to inhibit a response, "on-line" self-monitoring and set-shifting appeared to be important skills for awareness in a sample of patients with mild AD (Amanzio et al., 2013). Anosognosia was associated with both disinhibition as a psychiatric symptom (assessed using the Neuropsychiatric Inventory), and response inhibition

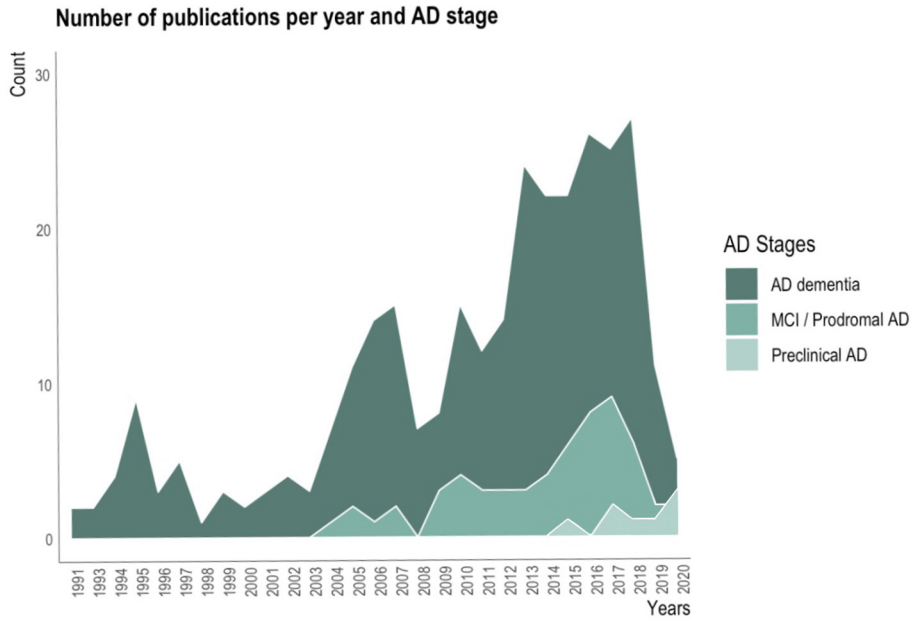


FIGURE 1 | Plot showing the number of revised publications about awareness of deficits in AD per year and stage of the disease.

impairment as a frontal cognitive dysfunction (Kashiwa et al., 2005).

Additionally, AD patients with the poorest memory functioning rated their performance highest (Gallo et al., 2007; Gilleen et al., 2014).

Moreover, there is compelling evidence that anosognosic AD patients report better-perceived quality of life, compared to those with normal insight (Comijs et al., 2002). It has importantly been found that depression and not awareness is the key driver of the quality of life: high ACD is only indirectly associated with lower quality of life *via* depressed mood (Risacher et al., 2016). Anosognosic patients generally show lower levels of depression and anxiety, compared to non-anosognosic patients (Horning et al., 2014).

Finally, several studies have shown that anosognosic patients, although less depressed and with better-perceived quality of life, have higher levels of apathy (Hurt et al., 2010; Trigg et al., 2011; Conde-Sala et al., 2013, 2014; Millenaar et al., 2017; Stites et al., 2017). It is known that apathy—as well as anosognosia—is related to frontal lobe dysfunction (Cines et al., 2015), thus apathy and anosognosia may be two consequences of frontal damage due to AD pathology. The reciprocal relationship between anosognosia and apathy still needs to be clarified.

Characteristics and Key Findings of Studies on Prodromal AD or MCI

Prevalence of Anosognosia in Prodromal AD (or MCI): Results of the Meta-Analysis

The mean number of MCI participants enrolled in the analyzed studies was on average 76.5 [Interquartile range (IQR) = 20.50–71.00]. Mean age was on average 74.1 (IQR = 72.78–76.10). Mean years of education were on average 11.5 (IQR = 9.32–13.61). Mean percentage of men was on average 47.45 (IQR = 42.80–54.60). Mean MMSE was on average 26.8 (IQR = 26.23–27.40).

Thirteen studies assessed the ACD as the discrepancy between subject's and informant's ratings of decline (Vogel et al., 2005; Onor et al., 2006; Ries et al., 2007; Orfei et al., 2010; Galeone et al., 2011; Spalletta et al., 2012; Maki et al., 2013; Zamboni et al., 2013; Ford et al., 2014; Jacus et al., 2015; Senturk et al., 2017; Tondelli et al., 2018; Oba et al., 2019). Four studies as the discrepancy between subjective and objective scores of cognitive functioning (O'Connell et al., 2014; Coutinho et al., 2016; Vannini et al., 2017a; Hanseeuw et al., 2020). In Stites et al. (2017), participants who responded affirmatively to any of the diagnosis-related questions were classified as "aware" of their diagnosis, whereas all others were coded "unaware."

Figure 2 and **Table 1** represent the between-group comparisons.

Forest plots are included as **Supplementary Figure 1**.

The degree of ACD was not significantly different between patients with amnestic and non-amnestic MCI [SMD (95% CI) = 0.09 (−0.21; 0.39), $p = 0.574$]. On average, the ACD was significantly lower in amnestic MCI [SMD (95% CI) = −0.56 (−0.88; −0.25), $p = 0.001$] and in mild AD [SMD (95% CI) = −1.39 (−1.92; −0.85), $p < 0.001$] than in controls. ACD was also significantly poorer in mild AD than in amnestic MCI [SMD (95% CI) = −0.75 (−1.02; −0.48), $p < 0.001$], as well as poorer than in non-amnestic MCI [SMD (95% CI) = −1.00 (−1.25; −0.76), $p < 0.001$].

The articles comparing subjects with non-amnestic vs. amnestic MCI had low heterogeneity ($I^2 = 20\%$; $Tau^2 = 0.01$, $p = 0.286$), as well as those comparing subjects with mild AD vs. non-amnestic MCI ($I^2 = 0\%$; $Tau^2 = 0.00$, $p = 0.887$).

On the contrary, heterogeneity of articles performing all other comparisons was substantial and significative (all $I^2 > 79\%$; all $Tau^2 = 0.36$; all $p \leq 0.001$).

Neural Correlates of Anosognosia in MCI

Few studies have investigated the neural correlates of ACD in MCI, indicating an involvement of a set of frontal and temporoparietal regions. This would be consistent with what has been identified in the studies including participants with AD dementia. In Ries et al. (2007), for instance, MCI participants showed subtly attenuated cortical midline structures activity during a fMRI self-appraisal task. They also found that poor ACD was significantly associated with attenuated activation in PFC and PCC during self-appraisal. In a study by Nobili et al. (2010), the PCC, the inferior parietal lobe, the angular gyrus and the precuneus seemed to be a key node of the network being involved in ACD. Similarly, Vannini et al. (2017b) found that the participants with amnestic MCI who showed greater anosognosia had a reduced glucose metabolism in the PCC and the hippocampus, and increased intrinsic connectivity disruption between the PCC and the orbitofrontal cortex as well as between the PCC and the inferior parietal lobe.

Tondelli et al. (2018) studied the neuroanatomical correlates of the three most commonly used methods to assess anosognosia (i.e., clinician rating, participant-informant discrepancy and subjective-objective discrepancy) in a sample of amnestic MCI patients and healthy controls. They found that all three scores positively correlated with atrophy in the medial temporal lobe, including the right hippocampus.

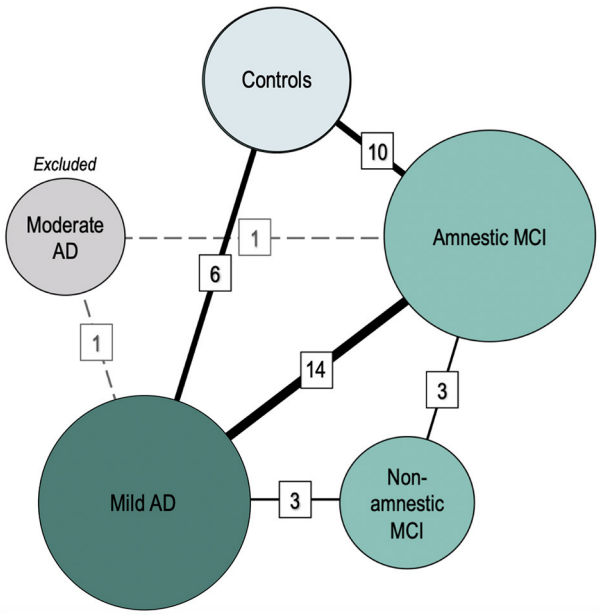


FIGURE 2 | Comparisons between clinical groups (meta-analysis). Nodes represent clinical groups. The size of the nodes is proportional to the number of studies including a certain clinical group. Solid lines connect the groups that have been studied in head-to-head comparisons in the meta-analyses. Dashed lines represent non-eligible connections (number of comparisons <3). Line thickness is proportional to the number of studies performing each comparison. The numbers in cells represent the number of comparisons available between two given groups.

Clinical Correlates of Anosognosia in MCI

In the study of Senturk et al. (2017), ACD positively correlated with MMSE and episodic memory, working memory, and executive functions scores. In Tremont and Alosco (2011), the anosognosic patients were comparable to non-anosognosic ones in all demographic characteristics, cognitive and behavioral domains, except that anosognosic patients obtained significantly lower scores in the learning domain.

In the study of Vogel et al. (2005), anosognosia positively correlated with cognitive impairment (MMSE score) and right inferior frontal gyrus blood flow, but not to tests of executive functions, both in MCI and AD dementia patients.

Furthermore, some authors have suggested that anosognosia in MCI is more related to non-cognitive (i.e., psychiatric) factors. In Oba et al. (2019), those who had no depressive symptoms were able to more accurately evaluate their memory impairment, suggesting that anosognosia should not be considered as a specific symptom of AD but as the result of an interaction between memory impairment and depression. Jacus et al. (2015) found a negative correlation between the degree of ACD and apathy.

Anosognosia in MCI and Risk of Progression to Dementia

The presence of anosognosia in a patient with MCI seems to increase the risk that he or she is affected by AD. A

TABLE 1 | Results of the meta-analyses comparing mean ACD between groups.

Group comparison	Number of studies	SMD [95% CI]	I^2	Tau^2	P	
					Comparison	Heterogeneity
Non-amnestic ($n = 113$) vs. amnestic MCI ($n = 109$)	3	0.09 [−0.21; 0.39]	20.12	0.01	0.575	0.286
Amnestic MCI ($n = 869$) vs. controls ($n = 815$)	10	−0.56 [−0.88; −0.25]	80.91	0.19	0.001*	<0.001*
Mild AD ($n = 781$) vs. amnestic MCI ($n = 1,050$)	14	−0.75 [−1.02; −0.48]	79.41	0.19	<0.001*	<0.001*
Mild AD ($n = 226$) vs. non-amnestic MCI ($n = 113$)	3	−1.00 [−1.25; −0.76]	0.00	0.00	<0.001*	0.887
Mild AD ($n = 320$) vs. controls ($n = 468$)	6	−1.39 [−1.92; −0.85]	84.10	0.36	<0.001*	<0.001*

*SMD, Standardized mean difference; CI, Confidence interval. n: Pooled group size. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance. Tau^2 indicates the extent of variation among the effects observed in different studies (between-study variance). *Statistically significant at the 0.01 level.*

recent 2-year longitudinal study (Therriault et al., 2018) found that anosognosic MCI participants showed greater amyloid burden and reduced brain metabolism in the posterior cingulate cortex at baseline than those without anosognosia, and had 3 times the risk of progression to dementia after 2 years. Furthermore, anosognosia at baseline predicted a reduced metabolism in the default mode network at the follow-up. Another 2-year long longitudinal study (Edmonds et al., 2018) also showed progressive anosognosia through the stages of MCI and dementia, driven by an increase in informant-reported ratings, despite stable self-reported complaints. In this study, anosognosic MCI participants had higher rates of cerebrospinal fluid AD biomarker positivity and progression to dementia.

Similar results have been reported in Munro et al. (2018) and Scherling et al. (2016).

In contrast with these studies, few others have found that the predictive value of reduced ACD was low. Cova et al. (2017), for example, found no relationship between ACD and progression to AD dementia after 28 months, but the authors commented on their result in light of a possible inadequacy of the method to measure anosognosia (a single question from the Geriatric Depression Scale being too simple a way to measure a complex symptom such as anosognosia).

It must be noted that in these studies MCI was seen as a possible transition phase between normal cognition and AD dementia, most of them did not include biomarker evidence to support AD pathology, thus questioning the appropriateness of the conclusions drawn regarding MCI due to AD (or prodromal AD). Indeed, MCI is a heterogeneous clinical entity, possibly resulting from different etiologies (e.g., neurodegenerative diseases, vascular lesions, psychiatric disorders, non-neurological diseases, among others) and with different clinical pictures and courses (declining, stable, or reversible).

Characteristics and Key Findings of Studies on Preclinical AD

Up until August 2020, 8 studies investigated ACD in asymptomatic individuals at risk for AD, and discussed the results within the scope of preclinical AD.

The first study that proposed the reduction of ACD as a more specific indicator of early-stage Alzheimer's than SCD is Cacciamani et al. (2017), investigating a cohort of memory-complainers at risk of preclinical AD due to their age and positive amyloid PET scan in 30% of subjects. Nineteen participants were found to have poor ACD, meaning that despite complaining about their memory, they reported less difficulty than their study-partner. This group was compared to 86 participants with heightened ACD, i.e., reporting more cognitive difficulties than their study-partner. The low ACD group had greater amyloid deposition than those with heightened ACD. Forty-seven percentage of subjects with low ACD were amyloid positive, vs. 24% of those with heightened ACD. The participants with low ACD also had a lower cortical glucose metabolism in frontal and temporoparietal regions known to be involved in both AD and anosognosia. On the contrary, the measures of SCD alone, i.e., without comparison with the informant report, did not correlate with any AD biomarker. Similarly, Sanchez-Benavides et al. (2018) compared the level of anxiety and depression, cognitive performance and brain atrophy of three groups of individuals from the ALFA cohort (Molinuevo et al., 2016): informant complaint only (therefore unaware subjects), subjects with SCD (with or without informant complaints) and controls (neither the subject nor the informant reported a decline). SCD subjects reported greater anxiety and depression than both unaware subjects and controls. Unaware subjects showed a poorer memory performance than controls (but no differences compared to SCD) which correlated with lower left posterior hippocampal volume. Unaware subjects presented brain volume increments in self-appraisal areas (medial frontal and insula). For this latter finding, they hypothesized non-linear volumetric changes, in which the volume of gray matter would increase and then decrease.

In two cross-sectional studies, ACD was non-linearly associated with amyloid load. In Vannini et al. (2017a), whereas cognitively-intact subjects harboring amyloid pathology at PET presented with *hypernosognosia* (self-report > informant-report), MCI patients with increased amyloid pathology showed anosognosia. In contrast, MCI patients with low amounts of amyloid were observed to have normal insight. Altered ACD tracked with amyloid pathology. A similar non-linear association was observed in Gagliardi et al. (2020) in 448 cognitively-normal individuals with SCD from the INSIGHT-PreAD and ADNI cohorts. ACD increased with increasing amyloid load up to a certain point, above which the increase in amyloid load was associated with a decline in ACD. Interestingly, the inflection point was around the amyloid positivity threshold, suggesting that complaints progress into decreasing ACD when the participants become amyloid-positive. In this study, the authors introduced and validated the Meta-Memory Ratio (MMR), a cohort independent measure of ACD based on the discrepancy between subjective and objective measures of cognitive decline.

Verfaillie et al. (2019) found different results by studying 106 SCD memory-clinic patients with amyloid PET scans from the Subjective Cognitive ImpairmENt Cohort (SCIENCe) study (Slot et al., 2018). They used two measures of ACD: (1) self-reported Cognitive Change Index (CCI) minus episodic memory; (2) a self-proxy index (self- minus informant-reported CCI). In this study as well as in the previous ones, amyloid burden was more associated with ACD than with self-report alone. However, amyloid burden was associated with heightened and not reduced ACD, and only when ACD was measured as a subjective-objective memory scores discrepancy. Significant interaction with education was found, implying a stronger effect in those with lower levels of education. These findings underline the fact that demographic features might be of importance when studying ACD.

To our knowledge, the first longitudinal study investigating ACD in cognitively-normal and MCI subjects at baseline was Wilson et al. (2015). A composite measure of memory performance was regressed on memory rating (i.e., two questions about their memory). In the subset of participants who progressed to dementia ($n = 239$), ACD was stable up to 2.6

years before dementia. During the prodromal phase, the ACD began to decline rapidly. This implies that the subjects had normal insight for the duration of the preclinical phase. However, in two more recent studies using more advanced statistical methods, ACD began to decline already in the preclinical phase, leading to anosognosia in the prodromal phase. Hanseeuw et al. (2020) studied the ADNI cohort and specifically amyloid-positive and amyloid-negative subjects with normal cognition, MCI and dementia. They computed the subject-informant discrepancy on the Everyday Cognition scale (ECog—memory subscale). ACD persistently declines across disease progression (controls > MCI > AD). The decline in ACD was driven by increasing study-partners' ratings over time and stable patients' ratings. It decreased faster in amyloid-positive participants. The interaction between amyloid load and clinical group had a significant effect on ACD changes in dementia and MCI groups, and had a small but significant effect also in CN subjects, suggesting that ACD starts to decrease in the preclinical AD stage. Cognitively-normal subjects reported significantly more cognitive complaints than their study-partners up to 1.6 years before progression to MCI indicating a state of heightened ACD (or hypernosognosia). Anosognosia was observed in individuals with MCI 3.2 years before progression to dementia. Low ACD predicted a greater risk of subsequent progression to dementia in participants with MCI as well as CN individuals with equal amyloid load and memory performance. Both the participants with low amyloid load and their study-partners reported more difficulties over time, resulting in stable ACD. A second longitudinal study (Vannini et al., 2020) selected 396 presenilin (PSEN1 E280A) variant carriers from the Colombia Alzheimer's Prevention Initiative Registry (Tariot et al., 2018), 59 of which were cognitively-impaired. ACD was measured as the subject-informant discrepancy on a memory complaint scale (Gatchel et al., 2020). The subjects presented with heightened ACD until on average 35 years of age and had anosognosia at ∼43 years of age (∼6 years before their estimated median age of dementia onset).

In summary, studies on ACD in preclinical AD are still few and heterogeneous. The main problem is the diversity in subjects inclusion criteria. However, these findings encourage a more in-depth study of how aware individuals who are developing AD are about their cognitive performance. This is particularly interesting considering that preclinical patients may show some decline from their previous cognitive efficiency, even though they do not by definition have frank cognitive impairment. The prevailing idea of the aforementioned articles is that the measure of ACD (hence the discrepancy between self-report and informant-report, or between self-report and objective scores) could be a more specific indicator of future cognitive decline than self-reported complaint alone as it is often studied in literature. However, it is not yet entirely certain whether hypernosognosia or reduced nosognosia is more characteristic of preclinical AD.

DISCUSSION

In this review, we summarized previously published studies about awareness of cognitive decline in AD over its full spectrum.

In **Figure 3A**, we graphed the longitudinal changes in the ACD based on the existing results.

Studies targeting preclinical AD identified an increased risk of AD (mainly abnormal biomarkers) both in subjects overestimating and underestimating their cognitive performance (when compared to their informant or to cognitive tests). Recent longitudinal studies (such as Vannini et al., 2017a; Hanseeuw et al., 2020) suggested that these two different states of altered ACD come in succession during preclinical AD in the same individual. This means that patients with very early-stage AD would begin to notice their first subtle cognitive changes when people around them do not yet, and neuropsychological tests do not yet detect objective cognitive deficits. They would therefore experience a *hypernosognosia* (in the terminology proposed by Vannini et al., 2017a) and might seek medical advice. Later, but still very early across the course of the disease, the patient's family or friends also begin to notice these changes as his or her cognitive efficiency gradually declines. The patient would soon begin to underestimate his or her impairment. The ACD is beginning to decline.

We would like to discuss a recent study on ACD in subjects at risk of preclinical AD, published after our bibliographic search (in October 2020) therefore not included in our review and meta-analysis. This study (Cacciamani et al., 2020) describes different trends of evolution of ACD over 3 years in the INSIGHT-PreAD cohort (memory-complainers, Dubois et al., 2018) and their association to amyloid burden and brain metabolism. 76.8% of the sample (235 out of 306 subjects) had an accurate ACD (i.e., self-report = informant-report), which remained unchanged over time. This class was chosen as the reference as it indicated normal insight. 18.95% (58 subjects) showed a steadily heightened ACD (i.e., self-report > informant-report). Interestingly, they were comparable to those with accurate ACD in terms of demographic characteristics and AD biomarkers, meaning that persistent cognitive complaints do not increase the risk of AD. On the contrary, 4.25% of the sample (13 subjects) constantly showed low ACD (i.e., self-report < informant-report) and had significantly higher amyloid burden than the reference class.

The transition from heightened ACD or hypernosognosia (patient report > informant report or test scores) to accurate ACD (patient report = informant report or test scores) and finally anosognosia (patient report < informant report or test scores) is gradual as does the accumulation of brain damage and disease progression. There are few studies to date that have attempted to establish at what moment of the course of the disease the patient no longer complains more than the informant and at what moment this begins to represent a real anosognosia. According to Hanseeuw et al. (2020), patients are no longer hypernosognosic about a year and a half before the diagnosis of MCI and that the onset of frank anosognosia begins during the prodromal phase (just over 3 years before the diagnosis of dementia). In our meta-analysis, MCI subjects had poorer ACD than healthy controls, but higher ACD than subjects with mild dementia. This suggests that in the prodromal phase of the disease, anosognosia is already present, although in a milder form than in the dementia stage. These results are very important when considering that subjective cognitive decline is a criterion for the

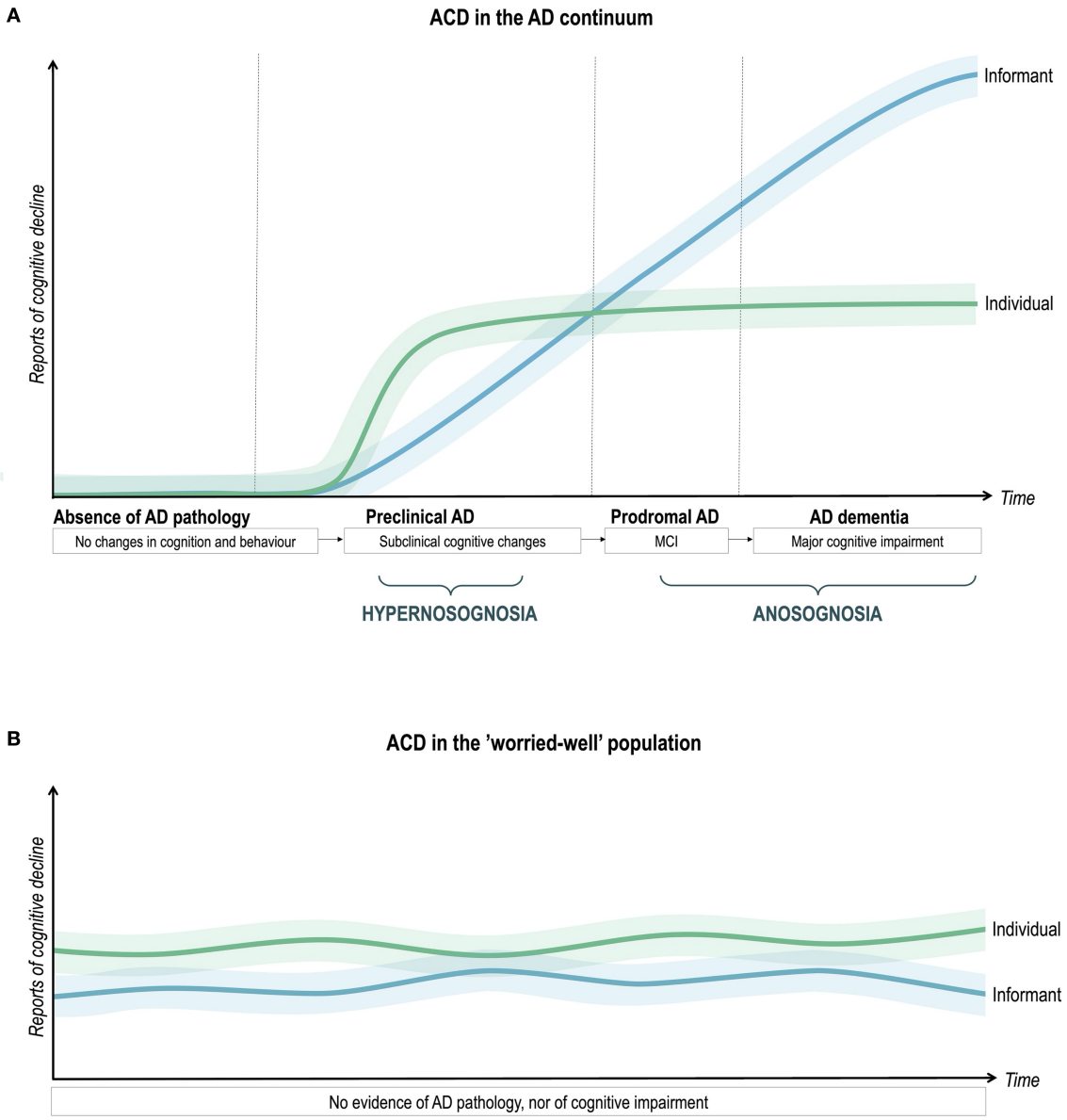


FIGURE 3 | Profiles of subjective reports of decline in individuals with and without AD pathology. **(A)** ACD in the AD continuum. **(B)** ACD in the "worried-well" population. Longitudinal trajectories of ACD in AD and "worried-well" individuals, conceptualized as the discrepancy between patient- and informant-reported cognitive decline. The green line displays how the individual's rating changes over time. The blue line represents the evolution of the informant's rating. The lighter areas represent potential individual deviations from the typical trajectories. In **(A)**, the duration of the disease stages has been established with reference to Vermunt et al. (2019).

diagnosis of MCI. This may actually contribute to misdiagnosis (Edmonds et al., 2014, 2018). On the one hand, this can lead to false-positives (individuals followed up for a suspected AD while their SCD is due to another cause). On the other hand, many individuals who underestimate their decline and are at greater risk of having a neurodegenerative disease may not have an adequate medical follow-up.

Finally, ACD would gradually lead to marked anosognosia in the advanced stage of dementia. Indeed, the widespread brain damage occurring in the advanced stages of AD compromises the information transfer and the anterograde memory, among other functions. Generally, this results in the patients having a very altered perception of their current experience, reduced awareness of what is happening in their surroundings, and to their state of health (O'Shaughnessy et al., 2021). At the late stage of the disease, the degradation is so massive that it affects not only the awareness of being ill but also the self-knowledge and sense of identity (Addis and Tippett, 2004).

Consistent with the reviewed neuroimaging studies, the patients who have anosognosia are those who show more

marked damage in prefrontal and temporoparietal regions, and they generally present an amnestic and dysexecutive clinical phenotype, which is the most common clinical presentation of AD. From the analysis of the literature, it appears that anosognosia is due to the dysfunction of a specific network, mainly in the right hemisphere, which includes: (i) prefrontal areas (dorsolateral, anterior cingulate, orbitofrontal), the lesion of which would compromise the online monitoring of performance, error detection and update of self-knowledge; (ii) dorsal and medial temporoparietal regions (e.g., posterior cingulate, angular gyrus, precuneus), which are the substrate of our capacity of judging our own performance assuming a third-person perspective; (iii) medial temporal regions, the dysfunction of which can lead to memory deficits, preventing proper comparison between current and past performance, and in particular causing the patient to judge current performance and abilities by anchoring to pre-morbid abilities.

To sum up, there would be a phase of heightened ACD or *hypernosognosia* at the very beginning of the disease in which the subject expresses cognitive complaints. Then the ACD would begin to progressively decrease leading to anosognosia during the prodromal phase and—especially—during the dementia phase. However, we do not preclude the existence of individual deviations from this model. A large variability may be ascribed to inter-individual differences in clinical phenotype of AD, premorbid personality traits, levels of anxiety, depression and nosophobia, comorbidity, cognitive reserve, and the localization of cerebral damage due to AD, among other factors (Alladi et al., 2006). Individual variability may range from severely decreased ACD since early pathological changes, to preserved ACD throughout the disease, as indicated by the lighter areas on each side of the colored lines of **Figure 3**.

We also propose a second scenario (**Figure 3B**), which represents the *worried-well* population, with persistent SCD without evidence of cognitive impairment, and without these subjective difficulties being confirmed by an informant. These individuals do not have an underlying AD pathology. We believe, consistently with Jessen et al. (2020), that confirmation of decline by an informant is one of the most important factors to consider when a patient with cognitive complaints seeks medical advice. This could allow distinguishing those who report cognitive changes due to an underlying neurodegenerative disease from worried-well individuals.

In practice, the clinician should always listen carefully to the patient's complaint. It might start by asking a general question about the reason of the visit. Subsequently, depending on the answer to the first question, the clinician may ask more specific questions, for example "do you happen to have memory difficulties?", "Are you having trouble finding words?", etc. This procedure helps to distinguish what the patient perceives as the main problem. It could happen that the patient reports some memory failures, but he or she could attribute them to age, and say that he or she is seeking medical advice because the family insisted. Since cognitive complaints are rather non-specific and present at every age (Dubois and Agid, 2002), the clinician should compare patient's complaints with a more objective source of information. An individual who is seeking medical advice for cognitive problems spontaneously or at the suggestion of his or her family, should perform a neuropsychological assessment to clarify if the perception of decline is confirmed by objective tests. The informant's assessment is also a very important time- and cost-saving source of information that the clinician should always consider. Although informant's assessment may be subject to bias, a tendency to underestimate cognitive decline is more likely to be the result of an ongoing neurodegenerative process (this is most commonly Alzheimer's disease, but not limited to). In research settings, ACD should be systematically measured by including a study-partner or by comparing subjective and objective decline. Another simple and quick method to evaluate the patient's degree of awareness is to ask him or her to evaluate his or her performance on a neuropsychological test just performed. This can be done simply by asking the patient "How do you think you performed this test?" moments after completing it. Or, for a more accurate and reliable measurement, one of the procedures proposed in the literature and described above can be adopted.

The framework and staging schemas described above have been drafted after considering the diversity of previous research findings, and developed to address the need for an integration of the existing evidence.

Further—and particularly longitudinal—studies are needed, to confirm the consecutive presence of hypernosognosia and poor ACD in the pre-dementia stages. Further studies should consider awareness of illness as a biopsychosocial construct, as many neuropathological, psychoaffective, relational and cognitive factors are known to affect the expression of this symptom. Therefore, the authors should take this into account when designing studies on anosognosia.

Limitations

The main limitation of this article is that we have carried out a meta-analysis of only a part of the articles (those conducted on subjects with MCI), as it could add evidence to current knowledge. Unfortunately, it was not possible to conduct a meta-analysis of the articles on preclinical AD.

Second, the articles included were heterogeneous. For example, the index of ACD was computed in many different ways, demonstrating that there is not yet a gold standard for the evaluation of ACD.

Third, the pre-dementia stages of AD were defined very differently in the studies, and only a minority of them involved the use of biomarkers to confirm the presence of AD pathology. Similarly, preclinical AD studies have focused on the presence of amyloid to define the condition of an individual at risk. No studies have based the definition of this condition on the simultaneous presence of amyloid and tau. According to certain criteria (for example in Dubois et al., 2016a), a cognitively-intact individual would be at risk of preclinical AD if he/she has a positive pathophysiological marker between amyloid and tau. However, the evidence suggests that the presence of both positive biomarkers increases the specificity of the diagnosis compared to only one of the two (Parnetti et al., 2019). The risk is that the subjects included in the studies discussed above may have cerebral amyloidosis not due to

AD, thus making the results found less specific for describing the ACD in AD. The same can also be extended to the studies on MCI.

Forth, although AD has a typical amnestic late-onset clinical manifestation, it is known that atypical forms exist, which are non-amnesic and often of early onset (Gorno-Tempini et al., 2004, 2008). This is the case, for example, of the dysexecutive variant, of the linguistic variant (logopenic primary progressive aphasia) and of posterior variants, for example the visuospatial one. It is also known that the degree of ACD differs in the different variants (Charles and Hillis, 2005). In our review and meta-analysis, we focus on the typical amnesic variant, but we do not exclude the possibility that individuals with different variants may have been included in the study samples.

Fifth, given the paucity of meta-analyzed articles, we decided not to use a certain *p*-value or effect size measure as an additional selection criterion. This may have led to the inclusion of studies reporting small effects.

Finally, we did not include unpublished or gray literature (e.g., dissertations, conference papers) in the review. Indeed, statistically non-significant results are less likely to be published (the so-called "file-drawer problem"), and this could represent a bias and an increased likelihood of Type I errors.

Conclusion and Implication

The study of ACD since the onset of AD pathology, its evolution and neural correlates is, notably, a piece of the larger understanding of the pre-dementia phase of AD. Therefore, it is a relevant research question in many respects.

First, the presence of poor ACD at the beginning of the disease may delay the search for medical help. Consequently, this limits the possibility of implementing treatment plans, of being included in clinical trials, and potentially delays the access to a disease-modifying treatment when one becomes available.

Furthermore, the lack of ACD is associated with poor decision-making skills (Oba et al., 2019): we might expect the patient with poor ACD to have troubles in making decisions related to his or her health, and in anticipating and preventing potential future work/administrative issues. The patient with reduced ACD may also assume to be able to achieve unrealistic therapeutic goals (for example, a regression of cognitive impairment or the regaining of lost daily-life abilities). The failure of such purposes may generate a sense of frustration, anger, low self-esteem and lack of motivation to continue the treatment.

In addition to this, caregivers' sense of responsibility and commitment may also be higher in the presence of reduced ACD or anosognosia, consequently having more chances to feel depressed and alienated (Starkstein et al., 2010; Spalletta et al., 2012; Jacus et al., 2015; Mak et al., 2015; Jacus, 2017).

Thus, if this symptom is recognized early-on during AD, it might benefit from therapeutic trials specifically targeting poor ACD.

Finally, concerning research, a greater understanding of this symptom could also allow to better describe preclinical and prodromal AD, and could guide researchers to include subjects with poor ACD together with a study-partner in clinical trials and cohort studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the present article. The data supporting the findings of this study and further inquiries are available from the corresponding author, Federica Cacciamani: federica.cacciamani@icm-institute.org.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design and provided expertise and insights into the interpretation of the results. Data were extracted from FC, GG, and MH. MH provided statistical expertise for the meta-analysis. The manuscript was drafted by FC and SE and critically reviewed and approved by all authors.

FUNDING

FC was funded by the Fondation pour la recherche sur Alzheimer, Fondation Thérèse et René Planiol, and Fondation des Treilles. SS received funding from Zon-MW Off Road (451001010). PV was funded by the NIH/National Institute on Aging 1R01 AG061083 and R21 AG064348.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.697234/full#supplementary-material

REFERENCES

Abdulrab, K., and Heun, R. (2008). Subjective memory impairment. A review of its definitions indicates the need for a comprehensive set of standardised and validated criteria. *Euro. Psychiatry* 23, 321–330. doi: 10.1016/j.eurpsy.2008.02.004

Addis, D. R., and Tippett, L. J. (2004). Memory of myself: autobiographical memory and identity in Alzheimer's disease. *Memory* 12, 56–74. doi: 10.1080/09658210244000423

Agnew, S. K., and Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: a review of the literature and a proposed model. *Aging Mental Health* 2, 9–15. doi: 10.1080/13607869856876

Akai, T., Hanyu, H., Sakurai, H., Sato, T., and Iwamoto, T. (2009). Longitudinal patterns of unawareness of memory deficits in mild Alzheimer's disease. *Geriatrics Gerontol. Int.* 9, 16–20. doi: 10.1111/j.1447-0594.2008.00512.x

Alladi, S., Arnold, R., Mitchell, J., Nestor, P. J., and Hodges, J. R. (2006). Mild cognitive impairment: applicability of research criteria in a memory clinic and characterization of cognitive profile. *Psychol. Med.* 36, 507–515. doi: 10.1017/S0033291705006744

Amanzio, M., Vase, L., Leotta, D., Miceli, R., Palermo, S., and Geminiani, G. (2013). Impaired awareness of deficits in Alzheimer's disease: the role of everyday executive dysfunction. *J. Int. Neuropsychol. Soc.* 19, 63–72. doi: 10.1017/S1355617712000896

Ansell, E. L., and Bucks, R. S. (2006). Mnemonic anosognosia in Alzheimer's disease: a test of agnew and morris (1998). *Neuropsychologia* 44, 1095–1102. doi: 10.1016/j.neuropsychologia.2005.10.019

Babinski, J. (1914). Contribution to the study of the mental disorders in hemiplegia of organic cerebral origin (anosognosia). Translated from the original ≪ Contribution à l'étude des troubles mentaux dans l'hémiplégie organique cérébrale (anosognosie) ≫. *Cortex* 61, 5–8.

Bertrand, J. M., Mazancieux, A., Moulin, C. J. A., Béjot, Y., Rouaud, O., and Souchay, C. (2019). In the here and now: short term memory predictions are preserved in Alzheimer's disease. *Cortex* 119, 158–164. doi: 10.1016/j.cortex.2019.03.027

Borenstein, M., Hedges, L. V., Higgins, J. P. T., and Rothstein, H. R. (2009). *Introduction to Meta-Analysis*. New York, NY: John Wiley and Sons.

Cacchione, P. Z., Powlishta, K. K., Grant, E. A., Buckles, V. D., and Morris, J. C. (2003). Accuracy of collateral source reports in very mild to mild dementia of the Alzheimer type. *J. Am. Geriatr. Soc.* 51, 819–823. doi: 10.1046/j.1365-2389.2003.51263.x

Cacciamani, F., Sambati, L., Houot, M., Habert, M. O., Dubois, B., Epelbaum, S., et al. (2020). Awareness of cognitive decline trajectories in asymptomatic individuals at risk for AD. *Alzheimer's Res. Ther.* 12:129. doi: 10.1186/s13195-020-00700-8

Cacciamani, F., Tandetnik, C., Gagliardi, G., Bertin, H., Habert, M. O., Hampel, H., et al. (2017). Low cognitive awareness, but not complaint, is a good marker of preclinical Alzheimer's disease. *J. Alzheimers Dis.* 59, 753–762. doi: 10.3233/JAD-170399

Cations, M., Radisic, G., Crotty, M., and Laver, K. E. (2018). What does the general public understand about prevention and treatment of dementia? A systematic review of population-based surveys. *PLoS ONE* 13:e0196085. doi: 10.1371/journal.pone.0196085

Charles, R. F., and Hillis, A. E. (2005). Posterior cortical atrophy: clinical presentation and cognitive deficits compared to Alzheimer's disease. *Behav. Neurol.* 16, 15–23. doi: 10.1155/2005/762569

Cines, S., Farrell, M., Steffener, J., Sullo, L., Huey, E., Karlawish, J., et al. (2015). Examining the pathways between self-awareness and well-being in mild to moderate Alzheimer disease. *Am. J. Geriatric Psychiatry* 23, 1297–1306. doi: 10.1016/j.jagp.2015.05.005

Comijs, H. C., Deeg, D. J., Dik, M. G., Twisk, J. W., and Jonker, C. (2002). Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics. A 6-year follow-up study. *J. Affective Disord.* 72, 157–165. doi: 10.1016/S0165-0327(01)00453-0

Conde-Sala, J. L., Reñé-Ramírez, R., Turró-Garriga, O., Gascón-Bayarri, J., Campdelacreu-Fumad,ó, J., Juncadella-Puig, M., et al. (2014). Severity of dementia, anosognosia, and depression in relation to the quality of life of patients with Alzheimer disease: discrepancies between patients and caregivers. *Am. J. Geriatric Psychiatry* 22, 138–147. doi: 10.1016/j.jagp.2012.07.001

Conde-Sala, J. L., Reñé-Ramírez, R., Turró-Garriga, O., Gascón-Bayarri, J., Juncadella-Puig, M., Moreno-Cordón, L., et al. (2013). Clinical differences in patients with Alzheimer's disease according to the presence or absence of anosognosia: implications for perceived quality of life. *J. Alzheimer Dis.* 33, 1105–1116. doi: 10.3233/JAD-2012-121360

Coutinho, G., Drummond, C., Teldeschi, A., and Mattos, P. (2016). Awareness of memory deficits is useful to distinguish between depression and mild cognitive impairment in the elderly. *Rev. Brasileira Psiquiatria.*38, 231–234. doi: 10.1590/1516-4446-2015-1772

Cova, I., Grande, G., Cucumo, V., Ghiretti, R., Maggiore, L., Galimberti, D., et al. (2017). Self-awareness for memory impairment in amnestic mild cognitive impairment: a longitudinal study. *Am. J. Alzheimer Dis Other Dement.* 32, 401–407. doi: 10.1177/1533317517725812

Dalla Barba, G., La Corte, V., and Dubois, B. (2015). For a cognitive model of subjective memory awareness. *J. Alzheimers Dis.* 48(Suppl. 1), S57–S61. doi: 10.3233/JAD-150141

Dourado, M., Marinho, V., Soares, C., Engelhardt, E., and Laks, J. (2007). Awareness of disease in dementia: development of a multidimensional rating scale. *Dementia Neuropsychol.* 1, 74–80. doi: 10.1590/S1980-57642008DN10100012

Dourado, M. C., Mograbi, D. C., Santos, R. L., Sousa, M. F., Nogueira, M. L., Belfort, T., et al. (2014). Awareness of disease in dementia: factor structure of the assessment scale of psychosocial impact of the diagnosis of dementia. *J. Alzheimer Dis.* 41, 947–956. doi: 10.3233/JAD-140183

Dubois, B., and Agid, Y. (2002). "Plainte mnésique, trouble cognitif léger et maladie d'Alzheimer au stade prédémentiel," in *Vulnérabilité et vieillissement: comment les prévenir, les retarder ou les métriser?*, ed Elsevier SAS (Paris: Editions Scientifiques et Médicales), 108–114.

Dubois, B., Epelbaum, S., Nyasse, F., Bakardjian, H., Gagliardi, G., Uspenskaya, O., et al. (2018). Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. *Lancet Neurol.* 17, 335–346. doi: 10.1016/S1474-4422(18)30029-2

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., et al. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* 9, 1118–1127. doi: 10.1016/S1474-4422(10)70223-4

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., et al. (2016a). Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement.* 12, 292–323. doi: 10.1016/j.jalz.2016.02.002

Dubois, B., Padovani, A., Scheltens, P., Rossi, A., and Dell'Agnello, G. (2016b). Timely diagnosis for Alzheimer's disease: a literature review on benefits and challenges. *J. Alzheimers Dis.* 49, 617–631. doi: 10.3233/JAD-150692

Duke, L. M., Seltzer, B., Seltzer, J. E., and Vasterling, J. J. (2002). Cognitive components of deficit awareness in Alzheimer's disease. *Neuropsychology* 16, 359–369. doi: 10.1037/0894-4105.16.3.359

Edmonds, E. C., Delano-Wood, L., Galasko, D. R., Salmon, D. P., Bondi, M. W., and Alzheimer's Disease Neuroimaging Initiative (2014). Subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. *J. Int. Neuropsychol. Soc.* 20, 836–847. doi: 10.1017/S135561771400068X

Edmonds, E. C., Weigand, A. J., Thomas, K. R., Eppig, J., Delano-Wood, L., Galasko, D. R., et al. (2018). Increasing inaccuracy of self-reported subjective cognitive complaints over 24 months in empirically-derived subtypes of mild cognitive impairment *J. Int. Neuropsychol. Soc.* 24, 842–853. doi: 10.1017/S1355617718000486

Farias, S. T., Mungas, D., Reed, B. R., Cahn-Weiner, D., Jagust, W., Baynes, K., et al. (2008). The measurement of everyday cognition (ECog): scale development and psychometric properties. *Neuropsychology* 22, 531–544. doi: 10.1037/0894-4105.22.4.531

Ford, A. H., Almeida, O. P., Flicker, L., Garrido, G. J., Greenop, K. R., Foster, J. K., et al. (2014). Grey matter changes associated with deficit awareness in mild cognitive impairment: a voxel-based morphometry study. *J. Alzheimer Dis.* 42, 1251–1259. doi: 10.3233/JAD-132678

Fujimoto, H., Matsuoka, T., Kato, Y., Shibata, K., Nakamura, K., Yamada, K., et al. (2017). Brain regions associated with anosognosia for memory disturbance in Alzheimer's disease: a magnetic resonance imaging study. *Neuropsychiatr. Dis. Treat.* 13, 1753–1759. doi: 10.2147/NDT.S139177

Gagliardi, G., Houot, M., Cacciamani, F., Habert, M. O., Dubois, B., and Epelbaum, S. (2020). The meta-memory ratio: a new cohort-independent way to measure cognitive awareness in asymptomatic individuals at risk for Alzheimer's disease. *Alzheimer Res. Therapy* 12:57. doi: 10.1186/s13195-020-00626-1

Galeone, F., Pappalardo, S., Chieffi, S., Iavarone, A., and Carlomagno, S. (2011). Anosognosia for memory deficit in amnestic mild cognitive impairment and Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 26, 695–701. doi: 10.1002/gps.2583

Gallo, D. A., Chen, J. M., Wiseman, A. L., Schacter, D. L., and Budson, A. E. (2007). Retrieval monitoring and anosognosia in Alzheimer's disease. *Neuropsychology* 21, 559–568. doi: 10.1037/0894-4105.21.5.559

Garcia-Ptacek, S., Cavallin, L., Kåreholt, I., Kramberger, M. G., Winblad, B., Jelic, V., et al. (2014). Subjective cognitive impairment subjects in our clinical practice. *Dement. Geriatr. Cogn. Dis. Extra* 4, 419–430. doi: 10.1159/000366270

Gatchel, J. R., Lopera, F., Norton, D. J., Baena, A., Guzman-Velez, E., Sanchez, J. S., et al. (2020). Association of subjective cognitive decline with markers of brain pathology in preclinical autosomal dominant Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatr.* 91, 330–332. doi: 10.1136/jnnp-2019-321205

Gil, N., and Josman, N. (2001). Memory and metamemory performance in Alzheimer's disease and healthy elderly: the contextual memory test (CMT). *Aging* 13, 309–315. doi: 10.1007/BF03353427

Gilleen, J., Greenwood, K., and David, A. S. (2014). The role of memory in awareness of memory deficits in Alzheimer's disease, schizophrenia, and brain injury. *J. Clin. Exp. Neuropsychol.* 36, 43–57. doi: 10.1080/13803395.2013.863835

Gorno-Tempini, M. L., Brambati, S. M., Ginex, V., Ogar, J., Dronkers, N. F., Marcone, A., et al. (2008). The logopenic/phonological variant of primary progressive aphasia. *Neurology* 71, 1227–1234. doi: 10.1212/01.wnl.0000320506.79811.da

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., et al. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Ann. Neurol.* 55, 335–346. doi: 10.1002/ana.10825

Graham, D. P., Kunik, M. E., Doody, R., and Snow, A. L. (2005). Self-reported awareness of performance in dementia. *Brain Res. Cogn. Brain Res.* 25, 144–152. doi: 10.1016/j.cogbrainres.2005.05.001

Hannesdottir, K., and Morris, R. G. (2007). Primary and secondary anosognosia for memory impairment in patients with Alzheimer's disease. *Cortex* 43, 1020–1030. doi: 10.1016/S0010-9452(08)70698-1

Hanseeuw, B. J., Scott, M. R., Sikkes, S., Properzi, M., Gatchel, J. R., Salmon, E., et al. (2020). Evolution of anosognosia in alzheimer's disease and its relationship to amyloid. *Ann. Neurol.* 87, 267–280. doi: 10.1002/ana.25649

Hanyu, H., Sato, T., Akai, T., Shimizu, S., Hirao, K., Kanetaka, H., et al. (2008). Neuroanatomical correlates of unawareness of memory deficits in early Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 25, 347–353. doi: 10.1159/000119594

Harwood, D. G., Sultzer, D. L., Feil, D., Monserratt, L., Freedman, E., and Mandelkern, M. A. (2005). Frontal lobe hypometabolism and impaired insight in Alzheimer disease. *Am. J. Geriatric Psychiatry* 13, 934–941. doi: 10.1097/00019442-200511000-00003

Horning, S. M., Melrose, R., and Sultzer, D. (2014). Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *Int. J. Geriatr. Psychiatry* 29, 77–84. doi: 10.1002/gps.3972

Hurt, C. S., Banerjee, S., Tunnard, C., Whitehead, D. L., Tsolaki, P., Mecocci, P., et al. (2010). Insight, cognition and quality of life in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatr.* 81, 331–336. doi: 10.1136/jnnp.2009.184598

Jack, C., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., et al. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease *Alzheimer's Dementia* 14, 535–562. doi: 10.1016/j.jalz.2018.02.018

Jacus, J. P. (2017). Awareness, apathy, and depression in Alzheimer's disease and mild cognitive impairment. *Brain Behav.* 7:e00661. doi: 10.1002/brb3.661

Jacus, J. P., Belorgey, N., Trivalle, C., and Gély-Nargeot, M. C. (2015). Factors associated with awareness in early stages of Alzheimer's disease and in mild cognitive impairment. *Encephale* 1, S44–S48. doi: 10.1016/j.encep.2014.08.011

Jedidi, H., Feyers, D., Collette, F., Bahri, M. A., Jaspar, M., d'Argembeau, A., et al. (2014). Dorsomedial prefrontal metabolism and unawareness of current characteristics of personality traits in Alzheimer's disease. *Soc. Cogn. Affect. Neurosci.* 9, 1458–1463. doi: 10.1093/scan/nst132

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Luis Molinuevo, J., et al. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol.* 19, 271–278. doi: 10.1016/S1474-4422(19)30368-0

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chetelat, G., et al. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's Dementia* 10, 844–852. doi: 10.1016/j.jalz.2014.01.001

Kalenzaga, S., and Clarys, D. (2013). Relationship between memory disorders and self-consciousness in Alzheimer's disease. *Gériatrie Et Psychologie Neuropsychiatrie Du Vieillissement* 11, 187–196. doi: 10.1684/pnv.2013.0403

Kashiwa, Y., Kitabayashi, Y., Narumoto, J., Nakamura, K., Ueda, H., and Fukui, K. (2005). Anosognosia in Alzheimer's disease: association with patient characteristics, psychiatric symptoms and cognitive deficits. *Psychiatry Clin. Neurosci.* 59, 697–704. doi: 10.1111/j.1440-1819.2005.01439.x

Lacerda, I. B., Santos, R. L., Belfort, T., Neto, J., and Dourado, M. (2020). Patterns of discrepancies in different objects of awareness in mild and moderate Alzheimer's disease. *Aging Ment. Health* 24, 789–796. doi: 10.1080/13607863.2018.1544219

Langer, K. G., and Levine, D. N. (2014). Babinski, J. (1914). Contribution to the study of the mental disorders in hemiplegia of organic cerebral origin (anosognosia). Translated by K.G. Langer and D.N. Levine: Translated from the original Contribution à l'Étude des Troubles Mentaux dans l'Hémiplégie Organique Cérébrale (Anosognosie). *Cortex* 61, 5–8. doi: 10.1016/j.cortex.2014.04.019

Lopez, O. L., Becker, J. T., Somsak, D., Dew, M. A., and DeKosky, S. T. (1994). Awareness of cognitive deficits and anosognosia in probable Alzheimer's disease. *Eur. Neurol.* 34, 277–282. doi: 10.1159/000117056

Mak, E., Chin, R., Ng, L. T., Yeo, D., and Hameed, S. (2015). Clinical associations of anosognosia in mild cognitive impairment and Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 30, 1207–1214. doi: 10.1002/gps.4275

Maki, Y., Yamaguchia, T., and Yamaguchia, H. (2013). Evaluation of anosognosia in Alzheimer's disease using the symptoms of early dementia-11 questionnaire (SED-11Q). *Dement. Geriatr. Cogn. Disord.* 3, 351–359. doi: 10.1159/000355367

McGlynn, S. M., and Kaszniak, A. W. (1991). When metacognition fails: impaired awareness of deficit in Alzheimer's disease. *J. Cogn. Neurosci.* 3, 183–187. doi: 10.1162/jocn.1991.3.2.183

McGlynn, S. M., and Schacter, D. L. (1989). Unawareness of deficits in neuropsychological syndromes. *J. Clin. Exp. Neuropsychol.* 11, 143–205. doi: 10.1080/01688638908400882

Migliorelli, R., Tesón, A., Sabe, L., Petracca, G., Petracchi, M., Leiguarda, R., et al. (1995). Anosognosia in Alzheimer's disease: a study of associated factors. *J. Neuropsychiatry Clin. Neurosci.* 7, 338–344.

Millenaar, J., Hvidsten, L., de Vugt, M. E., Engedal, K., Selbæk, G., Wyller, T. B., et al. (2017). Determinants of quality of life in young onset dementia - results from a European multicenter assessment. *Aging Ment. Health.* 21, 24–30. doi: 10.1080/13607863.2016.1232369

Mimura, M., and Yano, M. (2006). Memory impairment and awareness of memory deficits in early-stage Alzheimer's disease. *Rev. Neurosci.* 1, 253–266. doi: 10.1515/REVNEURO.2006.17.1-2.253

Mograbi, D. C., Brown, R. G., and Morris, R. G. (2009). Anosognosia in Alzheimer's disease-the petrified self. *Conscious. Cogn.* 18, 989–1003. doi: 10.1016/j.concog.2009.07.005

Mograbi, D. C., Brown, R. G., Salas, C., and Morris, R. G. (2012). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia* 50, 2075–2084. doi: 10.1016/j.neuropsychologia.2012.05.008

Molinuevo, J. L., Gramunt, N., Gispert, J. D., Fauria, K., Esteller, M., Minguillon, C., et al. (2016). The ALFA project: a research platform to identify early pathophysiological features of Alzheimer's disease. *Alzheimer's Dementia* 2, 82–92. doi: 10.1016/j.trci.2016.02.003

Monahan, P. O., Alder, C. A., Khan, B. A., Stump, T., and Boustani, M. A. (2014). The healthy aging brain care (HABC) monitor: validation of the patient self-report version of the clinical tool designed to measure and monitor cognitive, functional, and psychological health. *Clin. Interv. Aging* 9, 2123–2132. doi: 10.2147/CIA.S64140

Monahan, P. O., Boustani, M. A., Alder, C., Galvin, J. E., Perkins, A. J., Healey, P., et al. (2012). Practical clinical tool to monitor dementia symptoms: the HABC-monitor. *Clin. Interv. Aging* 7, 143–157. doi: 10.2147/CIA.S30663

Mosconi, L., Pupi, A., and De Leon, M. J. (2008). Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann. N. Y. Acad. Sci.* 1147, 180–195. doi: 10.1196/annals.1427.007

Munro, C. E., Donovan, N. J., Amariglio, R. E., Papp, K. V., Marshall, G. A., Rentz, D. M., et al. (2018). The impact of awareness of and concern about memory performance on the prediction of progression from mild cognitive impairment to Alzheimer disease dementia. *Am. J. Geriatric Psychiatry* 26, 896–904. doi: 10.1016/j.jagp.2018.04.008

Nobili, F., Mazzei, D., Dessi, B., Morbelli, S., Brugnolo, A., Barbieri, P., et al. (2010). Unawareness of memory deficit in amnestic MCI: FDG-PET findings. *J. Alzheimer Dis.* 22, 993–1003. doi: 10.3233/JAD-2010-100423

Oba, H., Matsuoka, T., Imai, A., Fujimoto, H., Kato, Y., Shibata, K., et al. (2019). Interaction between memory impairment and depressive symptoms can exacerbate anosognosia: a comparison of Alzheimer's disease with mild cognitive impairment. *Aging Mental Health* 23, 595–601. doi: 10.1080/13607863.2018.1442411

O'Connell, M. E., Dal Bello-Haas, V., Crossley, M., and Morgan, D. (2014). Clinical correlates of awareness for balance, function, and memory: evidence for the modality specificity of awareness. *J. Aging Res.* 1, 674–716. doi: 10.1155/2014/674716

Onor, M. L., Trevisiol, M., Negro, C., and Aguglia, E. (2006). Different perception of cognitive impairment, behavioral disturbances, and functional disabilities

between persons with mild cognitive impairment and mild Alzheimer's disease and their caregivers. *Am. J. Alzheimer Dis Other Demen.* 21, 333–338. doi: 10.1177/1533317506292454

Orfei, M. D., Varsi, A. E., Blundo, C., Celia, E., Casini, A. R., Caltagirone, C., et al. (2010). Anosognosia in mild cognitive impairment and mild Alzheimer's disease: frequency and neuropsychological correlates. *Am. J. Geriatric Psychiatry* 18, 1133–1140. doi: 10.1097/JGP.0b013e3181dd1c50

O'Shaughnessy, N. J., Chan, J. E., Bhome, R., Gallagher, P., Zhang, H., Clare, L., et al. (2021). Awareness in severe Alzheimer's disease: a systematic review. *Aging Mental Health* 25, 602–612. doi: 10.1080/13607863.2020.1711859

Oyebode, J. R., Telling, A. L., Hardy, R. M., and Austin, J. (2007). Awareness of memory functioning in early Alzheimer's disease: lessons from a comparison with healthy older people and young adults. *Aging Ment. Health* 11, 761–767. doi: 10.1080/13607860701366277

Parnetti, L., Chipi, E., Salvadori, N., D'Andrea, K., and Eusebi, P. (2019). Prevalence and risk of progression of preclinical Alzheimer's disease stages: a systematic review and meta-analysis. *Alzheimer Res. Ther.* 11:7. doi: 10.1186/s13195-018-0459-7

Prigatano, G. P. (1987). "Personality and psychosocial consequences after brain injury," in *Neuropsychological Rehabilitation*, eds M. Meir, L. Dillard, and A. Benton (London: Churchill Livingston).

Rabin, L. A., Smart, C. M., Crane, P. K., Amariglio, R. E., Berman, L. M., Boada, M., et al. (2015). Subjective cognitive decline in older adults: an overview of self-report measures used across 19 international research studies. *J. Alzheimer Dis.* 48(Suppl. 1), S63–S86. doi: 10.3233/JAD-150154

Rattanabannakit, C., Risacher, S. L., Gao, S., Lane, K. A., Brown, S. A., McDonald, B. C., et al. (2016). The cognitive change index as a measure of self and informant perception of cognitive decline: relation to neuropsychological tests. *J. Alzheimer Dis.* 51, 1145–1155. doi: 10.3233/JAD-150729

Ries, M. L., Jabbar, B. M., Schmitz, T., Trivedi, M. A., Gleason, C. E., Carlsson, C. M., et al. (2007). Anosognosia in mild cognitive impairment: relationship to activation of cortical midline structures involved in self-appraisal. *J. Int. Neuropsychol. Soc.* 13, 450–461. doi: 10.1017/S1355617707070488

Risacher, S. L., McDonald, B. C., Tallman, E. F., West, J. D., Farlow, M. R., Unverzagt, F. W., et al. (2016). Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol.* 73, 721–732. doi: 10.1001/jamaneurol.2016.0580

Robins, J., Breslow, N., and Greenland, S. (1986). Estimators of the mantel-haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* 42, 311–323. doi: 10.2307/2531052

Salmon, E., Perani, D., Herholz, K., Marique, P., Kalbe, E., Holthoff, V., et al. (2006). Neural correlates of anosognosia for cognitive impairment in Alzheimer's disease. *Hum. Brain Mapp.* 27, 588–597. doi: 10.1002/hbm.20203

Sanchez-Benavides, G., Grau-River, O., Cacciaglia, R., Suarez-Calvet, M., Falcon, C., Minguillon, C., et al. (2018). Distinct cognitive and brain morphological features in healthy subjects unaware of informant-reported cognitive decline. *J. Alzheimer Dis.* 65, 181–191. doi: 10.3233/JAD-180378

Schacter, D. L. (1989). "On the relation between memory and consciousness: dissociable interactions and conscious experience," in *Varieties of Memory and Consciousness: Essays in Honour of Endel Tulving*, eds H. L. Roediger III and F. Craik (New York, NY: Psychology Press), 355–389.

Scherling, C. S., Wilkins, S. E., Zakrezewski, J., Kramer, J. H., Miller, B. L., Weiner, M. W., et al. (2016). Decreased self-appraisal accuracy on cognitive tests of executive functioning is a predictor of decline in mild cognitive impairment. *Front. Aging Neurosci.* 8:120. doi: 10.3389/fnagi.2016.00120

Senturk, G., Bilgic, B., Arslan, A. B., Bayram, A., Hanagasi, H., Gurvit, H., et al. (2017). Cognitive and anatomical correlates of anosognosia in amnestic mild cognitive impairment and early-stage Alzheimer's disease. *Int. Psychogeriatr.* 29, 293–302. doi: 10.1017/S1041610216001812

Silva, A., Pinho, M. S., Macedo, L., Souchay, C., and Moulin, C. (2017). Mnemonic anosognosia in Alzheimer's disease is caused by a failure to transfer online evaluations of performance: evidence from memory training programs. *J. Clin. Exp. Neuropsychol.* 39, 419–433. doi: 10.1080/13803395.2016.1231799

Slot, R., Verfaillie, S., Overbeek, J. M., Timmers, T., Wesselman, L., Teunissen, C. E., et al. (2018). Subjective cognitive impairment cohort (SCIENCe): study design and first results. *Alzheimers Res. Ther.* 10, 1–13. doi: 10.1186/s13195-018-0390-y

Spalletta, G., Girardi, P., Caltagirone, C., and Orfei, M. D. (2012). Anosognosia and neuropsychiatric symptoms and disorders in mild Alzheimer disease and mild cognitive impairment. *J. Alzheimer Dis.* 29, 761–772. doi: 10.3233/JAD-2012-111886

Starkstein, S. E., Brockman, S., Bruce, D., and Petracca, G. (2010). Anosognosia is a significant predictor of apathy in Alzheimer's disease. *J. Neuropsychiatry Clin. Neurosci.* 22, 378–383. doi: 10.1176/jnp.2010.22.4.378

Stewart, G., McGeown, W. J., Shanks, M. F., and Venneri, A. (2010). Anosognosia for memory impairment in Alzheimer's disease. *Acta Neuropsychiatr.* 22, 180–187. doi: 10.1111/j.1601-5215.2010.00463.x

Stites, S. D., Karlawish, J., Harkins, K., Rubright, J. D., and Wolk, D. (2017). Awareness of mild cognitive impairment and mild Alzheimer's disease dementia diagnoses associated with lower self-ratings of quality of life in older adults. *J. Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 72, 974–985. doi: 10.1093/geronb/gbx100

Tariot, P. N., Lopera, F., Langbaum, J. B., Thomas, R. G., Hendrix, S., Schneider, L. S., et al. (2018). The Alzheimer's prevention initiative autosomal-dominant Alzheimer's disease trial: a study of crenezumab versus placebo in preclinical PSEN1 E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer's disease, including a placebo-treated noncarrier cohort. *Alzheimer's Dementia* 4, 150–160. doi: 10.1016/j.trci.2018.02.002

Therriault, J., Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Kang, M. S., Struyfs, H., et al. (2018). Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology* 90, e932–e939. doi: 10.1212/WNL.0000000000005120

Tondelli, M., Barbarulo, A. M., Vinceti, G., Vincenzi, C., Chiari, A., Nichelli, P. F., et al. (2018). Neural correlates of anosognosia in Alzheimer's disease and mild cognitive impairment: a multi-method assessment. *Front. Behav. Neurosci.* 17:100. doi: 10.3389/fnbeh.2018.00100

Tremont, G., and Alosco, M. L. (2011). Relationship between cognition and awareness of deficit in mild cognitive impairment. *Int. J. Geriatr. Psychiatry* 26, 299–306. doi: 10.1002/gps.2529

Trigg, R., Watts, S., Jones, R., and Tod, A. (2011). Predictors of quality of life ratings from persons with dementia: the role of insight. *Int. J. Geriatr. Psychiatry* 26, 83–91. doi: 10.1002/gps.2494

Turró-Garriga, O., Garre-Olmo, J., Reñé-Ramíre, R., Calvó-Perxas, L., Gascón-Bayarri, J., and Conde-Sala, J. L. (2016). Consequences of anosognosia on the cost of caregivers' care in Alzheimer's disease. *J. Alzheimer Dis.* 54, 1551–1560. doi: 10.3233/JAD-160419

Vannini, P., Amariglio, R., Hanseeuw, B., Johnson, K. A., McLaren, D. G., Chhatwal, J., et al. (2017a). Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease. *Neuropsychologia* 99, 343–349. doi: 10.1016/j.neuropsychologia.2017.04.002

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., et al. (2017b). Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *NeuroImage Clin.* 15, 408–414. doi: 10.1016/j.nicl.2017.05.020

Vannini, P., Hanseeuw, B. J., Gatchel, J. R., Sikkes, S., Alzate, D., Zuluaga, Y., et al. (2020). Trajectory of unawareness of memory decline in individuals with autosomal dominant Alzheimer disease. *JAMA Netw. Open* 3:e2027472. doi: 10.1001/jamanetworkopen.2020.27472

Verfaillie, S. C. J., Timmers, T., Slot, R. E. R., van der Weijden, C. W. J., Wesselman, L. M. P., Prins, N. D., et al. (2019). Amyloid-β Load is related to worries, but not to severity of cognitive complaints in individuals with subjective cognitive decline: the SCIENCe project. *Front. Aging Neurosci.* 11:7. doi: 10.3389/fnagi.2019.00007

Vermunt, L., Sikkes, S., van den Hout, A., Handels, R., Bos, I., van der Flier, W. M., et al. (2019). Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimer Dementia* 15, 888–898. doi: 10.1016/j.jalz.2019.04.001

Vogel, A., Hasselbalch, S. G., Gade, A., Ziebell, M., and Waldemar, G. (2005). Cognitive and functional neuroimaging correlates for anosognosia in mild cognitive impairment and Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 20, 238–246. doi: 10.1002/gps.1272

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Sytsma, J., Buchman, A. S., et al. (2015). Temporal course and pathological basis of unawareness of memory loss in dementia. *Neurology* 18, 984–991. doi: 10.1212/WNL.0000000000001935

Wolfsgruber, S., Jessen, F., Koppara, A., Kleineidam, L., Schmidtke, K., Frölich, L., et al. (2015). Subjective cognitive decline is related to CSF biomarkers of AD in patients with MCI. *Neurology* 84, 1261–1268. doi: 10.1212/WNL.0000000000001399

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, L., et al. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex* 49, 668–678. doi: 10.1016/j.cortex.2012.04.011

Conflict of Interest: BD has received consultancy fees from *Biogen, Boehringer Ingelheim, Eli Lilly*, and *MedAvante* and grants for his institution from *Merck, Pfizer,* and *Roche.* JM has received honoraria, as an educational speaker or consultant from *Roche diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector* and *Biocross.* SE has received honoraria as a speaker or consultant for *Eli Lilly, Biogen, Astellas Pharma, Roche* and *GE Healthcare.* SE reports personal fees from *Biogen, Roche*, and *GE Healthcare*, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Aging Neuroscience

BRIEF RESEARCH REPORT
published: 28 October 2021
doi: 10.3389/fnagi.2021.739422

Anosognosia in Amnestic Mild Cognitive Impairment Is Related to Diminished Hippocampal Volume Comparable to Alzheimer's Disease Dementia: Preliminary MRI Findings

*Juan Francisco Flores-Vázquez[1,2,3,4], Gabriel Ramírez-García[5], Oscar René Marrufo-Meléndez[6], Ruth Alcalá-Lozano[7], Morten Peter Lietz[3,4], Yaneth Rodríguez-Agudelo[8], Gilberto Isaac Acosta-Castillo[1,2], Remco J. Renken[4], Andre Aleman[3,4], Stefanie Enriquez-Geppert[3,4] and Ana Luisa Sosa-Ortiz[1,2]**

[1] Programa de Maestría y Doctorado en Ciencias Médicas, Odontológicas y de la Salud, Universidad Nacional Autónoma de México, Mexico City, Mexico, [2] Laboratorio de Demencias, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico, [3] Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, Netherlands, [4] Section of Cognitive Neuropsychiatry, Department of Biomedical Sciences of Cells and Systems, University of Groningen, Groningen, Netherlands, [5] Laboratorio de Neuropsicología, Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico, [6] Unidad de Neuroimagen, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico, [7] Subdirección de Investigaciones Clínicas, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, Mexico City, Mexico, [8] Departamento de Neuropsicología, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico

OPEN ACCESS

Edited by:
Bernard Jimmy Hanseeuw, Cliniques Universitaires Saint-Luc, Belgium

Reviewed by:
Tracy Fischer, Tulane University, United States
Elizabeth Kuhn, Institut National de la Santé et de la Recherche Médicale (INSERM), France

***Correspondence:**
Ana Luisa Sosa-Ortiz
drasosa@hotmail.com

Received: *10 July 2021*
Accepted: *05 October 2021*
Published: *28 October 2021*

Citation:
Flores-Vázquez JF, Ramírez-García G, Marrufo-Meléndez OR, Alcalá-Lozano R, Lietz MP, Rodríguez-Agudelo Y, Acosta-Castillo GI, Renken RJ, Aleman A, Enriquez-Geppert S and Sosa-Ortiz AL (2021) Anosognosia in Amnestic Mild Cognitive Impairment Is Related to Diminished Hippocampal Volume Comparable to Alzheimer's Disease Dementia: Preliminary MRI Findings. Front. Aging Neurosci. 13:739422. doi: 10.3389/fnagi.2021.739422

Although the presence of anosognosia in amnestic mild cognitive impairment (aMCI) may be predictive of conversion to Alzheimer's disease (AD), little is known about its neural correlates in AD and aMCI. Four different groups were compared using volumetric and diffusion magnetic resonance imaging metrics in regions of interest (hippocampus and cingulum cortex gray matter, cingulum bundle white matter): aMCI subjects with anosognosia (n = 6), aMCI subjects without anosognosia (n = 12), AD subjects with anosognosia (n = 6), and AD subjects without anosognosia (n = 9). aMCI subjects with anosognosia displayed a significantly lower gray matter density (GMD) in the bilateral hippocampus than aMCI subjects without anosognosia, which was accounted for by bilateral hippocampal differences. Furthermore, we identified that the mean hippocampal gray matter density of aMCI subjects with anosognosia was not statistically different than that of AD subjects. The groups of aMCI and AD subjects with anosognosia also displayed a lower GMD in the bilateral cingulum cortex compared to subjects without anosognosia, but these differences were not statistically significant. No statistically significant differences were found in the fractional anisotropy or mean diffusivity of the hippocampus or cingulum between subjects with and without anosognosia in aMCI or AD groups. While these findings are derived from a small population of subjects and are in need of replication, they suggest that anosognosia in aMCI might be a useful clinical marker to suspect brain changes associated with AD neuropathology.

Keywords: mild cognitive impairment, Alzheimer's disease, anosognosia, hippocampus, magnetic resonance imaging

INTRODUCTION

Anosognosia is defined as the loss or decline in a subject's awareness of problems in daily functioning, behavior, cognition, or mood (Starkstein, 2014). This condition is frequent throughout the trajectory of Alzheimer's disease (AD), with a prevalence ranging between 20 and 80%, and its presence is linked to increased dependence, reduced adherence to treatment and risk behaviors in patients, increased caregiver distress, and a greater economic burden for families and societies (Turró-Garriga et al., 2013; Starkstein, 2014).

Anosognosia can appear in amnestic mild cognitive impairment (aMCI), a diagnosis that implies a heightened risk for developing AD dementia, in which memory performance is diminished but autonomy in daily life is preserved (Mak et al., 2015). Interestingly, the presence of anosognosia in aMCI has been associated with underlying brain changes characteristic of AD, and may have a predictive value for further worsening of cognition and progression to AD dementia (Scherling et al., 2016; Gerretsen et al., 2017; Therriault et al., 2018; Hanseeuw et al., 2020). As only a fraction of aMCI-affected subjects will progress to dementia, the clinical characterization of subjects at a higher risk of developing AD is a major concern in current research. This, in turn, can support timely interventions before significant neural and functional impairment has taken place. The understanding of the neural changes associated with anosognosia is therefore necessary for the adequate characterization of aMCI and the early stages of AD (Mondragón et al., 2021).

According to a recent systematic review, anosognosia in AD is associated with a reduction in gray matter density, cerebral blood flow, and metabolism in several regions: the anterior and posterior cingulate cortex, the medial temporal lobe, the inferior, superior and medial frontal gyri, the orbitofrontal cortex, and the insula (Hallam et al., 2020). Most of these regions form part of the default mode network, a large-scale brain network that is altered from the early stages of the AD continuum (Grieder et al., 2018) and is associated with self-related cognition (e.g., introspection and autobiographic memory) (Zamboni et al., 2013). Said systematic review identified that measurement heterogeneity is one of the main limitations in integrating previous clinical studies on anosognosia in aMCI and AD dementia.

In clinical research, three methods have been mainly used to measure anosognosia in AD (Hallam et al., 2020). (1) *Clinical rating*, in which the clinician's judgment is used to rate the level of anosognosia on a scale after an interview with the patient and the caregiver. (2) *Patient-informant discrepancy*, in which after parallel interviewing of the patient and caregiver, a "discrepancy score" of the patient's symptoms is calculated, and finally. (3) *Performance discrepancy*, in which the performance of a patient on a neuropsychological test is compared to their own estimation of how well they think they performed on said test. Taking this into consideration, a multi-method magnetic resonance imaging (MRI) morphometric study showed that all three anosognosia measurement methods were independently associated with gray matter atrophy in the medial temporal lobe including the right hippocampus in AD participants (Tondelli et al., 2018). The consistent involvement of the medial temporal lobe and the hippocampus supports the view that anosognosia is principally caused by a decline in memory processes (such as the autobiographical episodic memory loss typically characterizing AD) that prevents the update of self-knowledge (Morris and Mograbi, 2013; Chavoix and Insausti, 2017). However, the neural substrate of anosognosia in AD is far from being fully elucidated, and there is a need for replication of previous findings along with the development of objective anosognosia measurements (Hallam et al., 2020).

A sound approach for the assessment of anosognosia has been developed under the more general construct of the behavioral dysexecutive syndrome (Godefroy et al., 2010). This syndrome groups twelve symptoms related to disturbances in the executive function brain network (e.g., anosognosia, apathy, irritability, and confabulations) that are frequently observed in several neurocognitive disorders. In mild AD dementia, 86% of patients have been found to exhibit a behavioral dysexecutive syndrome, with a large effect size when comparing the severity and of anosognosia between AD participants and healthy controls (Godefroy et al., 2014). Along with the definition of the syndrome, a straightforward structured questionnaire has been proposed, the Behavioral Dysexecutive Syndrome Inventory (BDSI), which is applied to an informant who knows the patient well, and aims to measure the frequency and severity of each symptom – including anosognosia (Godefroy et al., 2010).

In light of this evidence, we aimed to provide further evidence on the neural underpinnings of anosognosia in aMCI and AD using the BDSI in a clinical sample. To our knowledge, no previous studies have used this anosognosia measurement to study structural brain changes. We hypothesized that subjects with aMCI or AD dementia with anosognosia would exhibit volumetric and white-matter integrity changes in the bilateral hippocampus and cingulate cortex, relative to aMCI or AD subjects without anosognosia.

MATERIALS AND METHODS

Sample and Participants

Eighteen participants with aMCI and sixteen participants with AD were recruited from the outpatient consultation of the Dementia Laboratory of the National Institute of Neurology and Neurosurgery of Mexico in Mexico City. aMCI and AD dementia were diagnosed by certified specialists following current clinical criteria (Petersen, 2004; McKhann et al., 2011). Inclusion criteria further consisted of: being between 60 and 76 years of age, a Mini-Mental Score Examination (MMSE) score of 25 or higher in the aMCI group and 16 or higher in the AD dementia group, and having a knowledgeable informant living with the subject who could answer to the clinical questionnaires. Exclusion criteria consisted of a clinical history suggestive of non-AD dementia, current symptoms suggestive of delirium, major depression, substance-use disorders, or other major neuropsychiatric disorders (apart from aMCI or AD dementia), not being able to complete clinical or neuroimaging assessments, and MRI contraindications.

Clinical Measurements

General cognitive functioning was assessed using an adapted version of the MMSE widely used in Mexico (Ostrosky-Solís et al., 2000). For the assessment of anosognosia, a cross-culturally adapted Mexican version (Flores-Vazquez and Sosa-Ortiz, 2016) of the BDSI (Godefroy et al., 2010) was used. Subjects were divided into "anosognosia" or "no-anosognosia" groups if the answer given to the screening questions presented in **Table 1** was "yes" or "no." Additional analysis taking into consideration the severity and frequency of anosognosia can be consulted in the **Supplementary Material**.

Magnetic Resonance Imaging Acquisition and Processing

Magnetic resonance imagings were acquired using a 3 Tesla SIEMENS Skyra scanner (Erlangen, Germany) with a 20ch head coil.

T1-weighted images were obtained using a 3D MPRAGE sequence (TR/TE: 2,300/2.45 ms; FOV: 256 mm^2; matrix: 256 × 256; voxel size: 1 mm^3). Preprocessing included denoising and intensity inhomogeneity correction (Manjón et al., 2010; Avants et al., 2011). T1-weighted images were processed using the VBM-FSL toolbox (Douaud et al., 2007; Jenkinson et al., 2012). T1 image processing included brain extraction, tissue-type segmentation, the creation of a study-specific gray matter template, registration of all gray matter images into the template, Jacobian modulation, and smoothing. Of note, including the Jacobian modulation step in the processing pipeline handles the variability in the head size of the subjects at a local level, eliminating the need for controlling or correcting for by ICV (Douaud et al., 2007). The gray-matter regions of interest (ROIs) of the bilateral hippocampus and cingulate cortex were defined using the Harvard-Oxford Cortical and Subcortical atlases (Desikan et al., 2006), respectively (**Figure 1**). First, each ROI was eroded to reduce its size according to the anatomical region into the MNI standard space; then, all ROIs were binarized. These ROIs were used to extract the mean gray matter density (GMD).

Diffusion-weighted images (DWI) were obtained using an echo-planar spin-echo sequence with 64 directions (TR/TE: 5,000/102 ms; FOV: 220 mm^2; matrix: 100 × 100; voxel size: 2.2 mm^3). DWI image preprocessing included a first denoising step using a blockwise non-local means filter (Coupé et al., 2008), after which, eddy current and subject movement correction, binary mask creation, and diffusion tensor fitting to obtain the scalar anisotropy and diffusivity maps were completed using the TBSS-FSL toolbox (Smith et al., 2006; Jenkinson et al., 2012). Fractional anisotropy (FA) and mean diffusivity (MD) maps were non-linearly registered to the MNI standard space following the TBSS steps (Smith et al., 2006; Jenkinson et al., 2012). The white-matter ROIs of the bilateral cingulum bundle (**Figure 1**) were defined using the JHU-DTI-81 White-Matter Labels atlas (Wakana et al., 2007). First, each ROI was eroded to reduce its size according to the anatomical region into the MNI standard space; then, all ROIs were binarized. These ROIs were used to extract the mean FA or MD of the specific white matter tracts.

TABLE 1 | Anosognosia assessment in the behavioral dysexecutive syndrome inventory (Godefroy et al., 2010).

Screening questions: Does the subject minimize or fail to recognize the limitations or difficulties that they have and the consequences of those limitations in daily life? Does the subject make unrealistic plans? Does the subject think that they can do the same things they used to do even when this is no longer realistic?

Specific questions (used for clarification):

- Does the subject tend to minimize their own cognitive decline, for instance, their memory problems?
- Does the subject tend to minimize their behavioral problems?
- Does the subject tend to minimize their impairments when moving, seeing, or hearing?
- Is the subject indifferent to their impairments although these impairments impact their daily life?
- Does the subject blame their impairments on other people or the situation?
- Does the subject deny their impairments although other people can notice them?
- Does the subject act as if they had no illness and need no help from others?
- Does the subject make unrealistic plans and wrongly thinks they could retake previous activities?

Frequency scoring: 1 = Rarely: less than once a week. 2 = Sometimes = approximately once a week. 3 = Frequently: several times a week, but not every day. 4 = Very frequently = every day/most of the time.

Severity scoring: 1 = Mild: noticeable, few consequences in everyday life. 2 = Moderate: significant and disturbing, but manageable. 3 = Severe: very marked and disturbing, very difficult to manage

[a] If the answer to any of the screening questions is "yes," the anosognosia domain should be examined at depth using the specific questions, and the frequency and severity of the anosognosia domain should be scored

Statistical Analysis

Results are presented in means (M), medians (Mdn), interquartile ranges (IQR), and value ranges (Rng). For the description and comparison of demographic and clinical characteristics, Mann-Whitney *U* tests were used for analyzing continuous variables (years age, intracranial volume – ICV, and MMSE score), and Chi-square tests for dichotomous variables (sex).

For the group comparisons (aMCI-anosognosia vs. aMCI-no-anosognosia; AD-anosognosia vs. AD-no-anosognosia) of the averaged GMD or white matter FA in each ROI, Mann-Whitney *U* tests were used. An alpha of 0.05 was defined for statistically significant findings. In the case of statistically significant findings, we conducted a False Discovery Rate analysis, and present the Benjamini-Hochberg adjusted p value. The rank-biserial correlation (r_{rb}) is reported as a non-parametric effect size for the Mann-Whitney *U* test (Kerby, 2014). Statistical analyses were carried out in the JASP software version 0.14.1 (JASP Team, 2020) and IBM SPSS Statistics version 27 (IBM Corp, 2020).

Additional analysis assessing the correlation of the severity and frequency of anosognosia with the MRI metrics can be consulted in the **Supplementary Material**.

Ethical Considerations

This study was approved by the research and ethics committees of the National Institute of Neurology and Neurosurgery of Mexico after independent, blinded review (protocol number: 116/16)

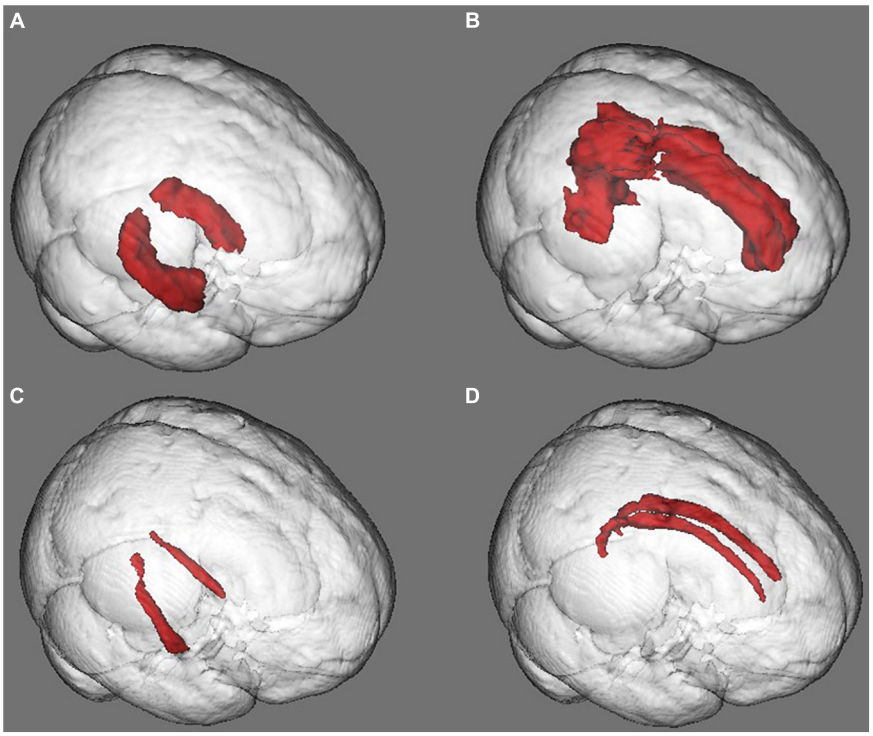


FIGURE 1 | Gray and white matter regions of interest (ROIs). **(A)** Hippocampal gray matter ROI. **(B)** Cingulum gray matter ROI. **(C)** Hippocampal white matter ROI. **(D)** Cingulum white matter ROI. The morphological or diffusion values were averaged in each ROI for between-group comparisons.

and carried out according to the Declaration of Helsinki. All participating subjects, as well as first-grade family members in the case of subjects with AD dementia, were informed about the study in detail and consented to it.

RESULTS

Demographic and Clinical Characteristics

In the aMCI group (n = 18), subjects displaying anosognosia (n = 6 and 2 female) had a Mdn of 72.0 years of age (IQR = 3.0) and a Mdn of 12.0 years of education (IQR = 5.3), obtained a Mdn MMSE score of 26.5 (IQR = 1.8), and had a Mdn ICV of 1358.4 (IQR = 147.0) cm^3. aMCI subjects not displaying anosognosia (n = 12 and 9 female) had a Mdn of 69.5 years of age (IQR = 7.0) and a Mdn of 12.0 years of education (IQR = 7.0), obtained a Mdn score of 28.0 in the MMSE (IQR = 1.3), and had a Mdn ICV of 1292.0 cm^3 (IQR = 64.5). Between-group differences were not statistically significant in any of these variables, median, ranges, test statistics, and p values are presented in **Table 2**.

In the AD group (n = 16), subjects displaying anosognosia (n = 7 and 5 female) had a Mdn of 72.0 years of age (IQR = 6.0), and a Mdn of 9.0 years of education (IQR = 3.5), obtained a Mdn score of 21.0 in the MMSE (IQR = 4.0), and had a Mdn ICV of 1358.1 cm^3 (IQR = 137.6). AD subjects not displaying anosognosia (n = 9 and 5 female) had a Mdn of 64.5 years of age (IQR = 6.0) and a Mdn of 12 years of education (IQR = 7.0), obtained a Mdn score of 22.0 in the MMSE (IQR = 4.0), and had a Mdn ICV of 1293.4 cm^3 (IQR = 117.3). Between-group differences were not statistically significant, and mean, ranges, test statistics with p values are presented in **Table 2**.

Gray Matter Volumetric Comparisons

In the aMCI group, subjects with anosognosia had a lower GMD in the bilateral hippocampus ROI (M = 0.55, Mdn = 0.54, IQR = 0.06, and Rng = 0.48–0.60) than subjects without anosognosia (M = 0.64, Mdn = 0.65, IQR = 0.08, and Rng = 0.51–0.73). This difference was statistically significant, showing a large effect size (W = 63.0, p = 0.01, *adjusted* p = 0.04, and r_{rb} = 0.75, see **Figure 2**), and was accounted for by bilateral hippocampal differences (right hippocampus: *anosognosia group* M = 0.55, Mdn = 0.54, IQR = 0.07, and Rng = 0.45–0.62; *non-anosognosia group* M = 0.67, Mdn = 0.67 IQR = 0.12, Rng = 0.55–0.77, W = 64.0, p = 0.01, and r_{rb} = 0.78; left hippocampus: *anosognosia group* M = 0.55, Mdn = 0.56, IQR = 0.05, and Rng = 0.51–0.57; *non-anosognosia group* M = 0.62, Mdn = 0.63, IQR = 0.06, Rng = 0.48–0.69 W = 62.0, p = 0.01, and r_{rb} = 0.72).

The group of aMCI subjects with anosognosia also displayed a lower GMD in the bilateral cingulum cortex ROI (M = 0.47, Mdn = 0.47, IQR = 0.02, and Rng = 0.44–0.51) than subjects without anosognosia (M = 0.51, Mdn = 0.51, IQR = 0.11, and Rng = 0.43–0.60), but this difference was not statistically significant (W = 49.0, p = 0.25, and r_{rb} = 0.36).

TABLE 2 | Demographic and clinical characteristics of patients with aMCI and AD displaying and not displaying anosognosia.

	aMCI (*n* = 18)			
	Anosognosia (*n* = 6)	**No anosognosia (*n* = 12)**	**Test statistic**	***p* value**
Age (Years)	*M* = 70.7 *Mdn* = 72.0 *IQR* = 3.0 *Rng* = 62.0 – 74.0	*M* = 68.8 *Mdn* = 69.5 *IQR* = 7.0 *Rng* = 60.0–75.0	27.5	0.45
Sex (Female, male)	2, 4	9, 3	2.9	0.09
Education (Years)	*M* = 12.8 *Mdn* = 12.0 *IQR* = 5.3 *Rng* = 6.0 – 17.0	*M* = 11.9 *Mdn* = 12.0 *IQR* = 7.0 *Rng* = 9.0 – 17.0	29.5	0.57
MMSE (Score)	*M* = 26.3 *Mdn* = 26.5 *IQR* = 1.8 *Rng* = 25.0 – 28.0	*M* = 27.6 *Mdn* = 28.0 *IQR* = 1.3 *Rng* = 25.0 – 30.0	53.5	0.10
ICV (cm^3)	*M* = 1312.1 *Mdn* = 1358.4 *IQR* = 147.0 *Rng* = 1058.9 – 1466.8	*M* = 1272.4 *Mdn* = 1292.0 *IQR* = 64.5 *Rng* = 1164.8.0 – 1397.2	25.0	0.34
	AD (*n* = 16)			
	Anosognosia (*n* = 7)	**No anosognosia (*n* = 9)**	**Test statistic**	***p* value**
Age (Years)	*M* = 71.6 *Mdn* = 72.0 *IQR* = 6.0 *Rng* = 65.0–76.0	*M* = 66.1 *Mdn* = 64.5 *IQR* = 6.0 *Rng* = 60.0–76.0	14.0	0.07
Sex (Female, male)	5, 2	5, 4	0.4	0.52
Education (Years)	*M* = 11.4 *Mdn* = 9.0 *IQR* = 3.5 *Rng* = 9.0–19.0	*M* = 12.6 *Mdn* = 12.0 *IQR* = 7.0 *Rng* = 6.0–20.0	38.5	0.47
MMSE (Score)	*M* = 21.3 *Mdn* = 21.0 *IQR* = 4.0 *Rng* = 17.0 - 26.0	*M* = 23.3 *Mdn* = 22.0 *IQR* = 4.0 *Rng* = 18.0 - 30.0	43.5	0.26
ICV (cm^3)	*M* = 1379.1 *Mdn* = 1358.1 *IQR* = 137.6 *Rng* = 1184.1–1414.8	*M* = 1284.5 *Mdn* = 1293.4 *IQR* = 117.3 *Rng* = 1262.6–1519.2	13.0	0.06

Values are presented as means (M), medians (Mdn), interquartile ranges (IQR) and ranges (Rng). Test statistics and p values for age, education, MMSE and ICV correspond to the Mann-Whitney U test. Test statistic and p value for sex corresponds to the Chi-square test. aMCI, Amnestic mild cognitive impairment; AD, Alzheimer's disease dementia; MMSE, Mini-Mental State Examination; ICV, Intracranial volume.

In the AD group, subjects with anosognosia had a lower GMD in the bilateral hippocampus ROI (M = 5.1, Mdn = 0.55, IQR = 0.25, and Rng = 0.33–0.71) than aMCI subjects without anosognosia (M = 0.56, Mdn = 0.57, IQR = 0.13, and Rng = 0.46–0.77), but this difference was not statistically significant (W = 39.0, p = 0.47, and r_{rb} = 0.24). In an exploratory analysis, we identified that the Mdn hippocampal GMD of aMCI subjects with anosognosia (M = 0.55, Mdn = 0.54, IQR = 0.06, and Rng = 0.48–0.60) was not statistically different than that the whole subset of AD subjects (M = 0.54, Mdn = 0.56 IQR = 0.14, Rng = 0.33–0.77, W = 48.0, p = 1.00, and $r_{rb} < 0.01$), this is illustrated in **Figure 2**.

Alzheimer's disease subjects with anosognosia also displayed a lower GMD in the bilateral cingulum cortex ROI (M = 0.41, Mdn = 0.43, IQR = 0.09, and Rng = 0.34–0.48) than subjects without anosognosia (M = 0.43, Mdn = 0.45 IQR = 0.10, and Rng = 0.29–0.53), but this difference was not statistically significant (W = 39.0, p = 0.47, and r_{rb} = 0.24).

White Matter Fractional Anisotropy Comparisons

No statistically significant differences in hippocampal FA were found between aMCI subjects with anosognosia (M = 0.29, Mdn = 0.31 IQR = 0.10, and Rng = 0.21–0.37) and without anosognosia (M = 0.29, Mdn = 0.27, IQR = 0.10, Rng = 0.20–0.37, W = 33.5, p = 0.85, and r_{rb} = −0.07). This was also the case in the cingulum FA, with no significant differences between aMCI with anosognosia (M = 0.44, Mdn = 0.47 IQR = 0.06, and Rng = 0.36–0.53) and without anosognosia (M = 0.44, Mdn = 0.42 IQR = 0.09, Rng = 0.36–0.53, W = 31.5, p = 0.71, and r_{rb} = −0.13).

Subjects with AD had similar results, with no significant differences in hippocampal FA between the anosognosia (M = 0.25, Mdn = 0.25, IQR = 0.11, and Rng = 0.15–0.39) and no anosognosia groups (M = 0.25, Mdn = 0.24 IQR = 0.04, Rng = 0.16–0.32 W = 28.0, p = 0.91, and r_{rb} = 0.01), and also no significant differences in cingulum FA between the groups (*anosognosia group* M = 0.38, Mdn = 0.36, IQR = 0.06, and Rng = 0.30–0.52; *non-anosognosia group* M = 0.41, Mdn = 0.40, IQR = 0.05, Rng = 0.34–0.49, W = 39.0, p = 0.23, and r_{rb} = 0.39).

White Matter Mean Diffusivity Comparisons

No statistically significant differences were found in hippocampal MD between aMCI subjects with anosognosia (M = 7.31e−4, Mdn = 5.07e−4, IQR = 4.71e−4, and Rng = 4.47e−4 – 8.07e−4) and without anosognosia (M = 7.25e−4, Mdn = 0.27, IQR = 0.10, Rng = 0.20–0.37, W = 30.0, p = 0.62, and r_{rb} = −0.17). This was also the case in the cingulum MD, with no significant differences between aMCI with anosognosia (M = 5.98e−4, Mdn = 4.97e−4 IQR = 2.43e−4, and Rng = 4.52e−4 – 8.39e−4) and without anosognosia (M = 6.28e−4, Mdn = 6.35e−4 IQR = 3.05e−4, Rng = 4.47e−4 – 8.07e−4, W = 32.5, p = 0.78, and r_{rb} = −0.10).

In the AD group, no significant differences were found in hippocampal MD between the anosognosia (M = 8.53e−4, Mdn = 6.32e−4, IQR = 7.00e−4, and Rng = 4.36e−4 - 1.00e−3) and no anosognosia groups (M = 9.67e−4, Mdn = 9.56e−4 IQR = 2.39e−4, Rng = 5.14e−4 - 2.00e−3 W = 29.0, p = 0.96, and r_{rb} = 0.04), and also no significant differences in cingulum MD between the groups (*anosognosia group* M = 6.81e−4, Mdn = 5.83e−4, IQR = 3.47e−4, and Rng = 4.63e−4 – 9.10e−4; *non-anosognosia group* M = 7.34e−4, Mdn = 7.91e−4, IQR = 1.28e−4, Rng = 4.78e−4 – 8.53e−4, W = 26.0, p = 0.86, and r_{rb} = −0.07).

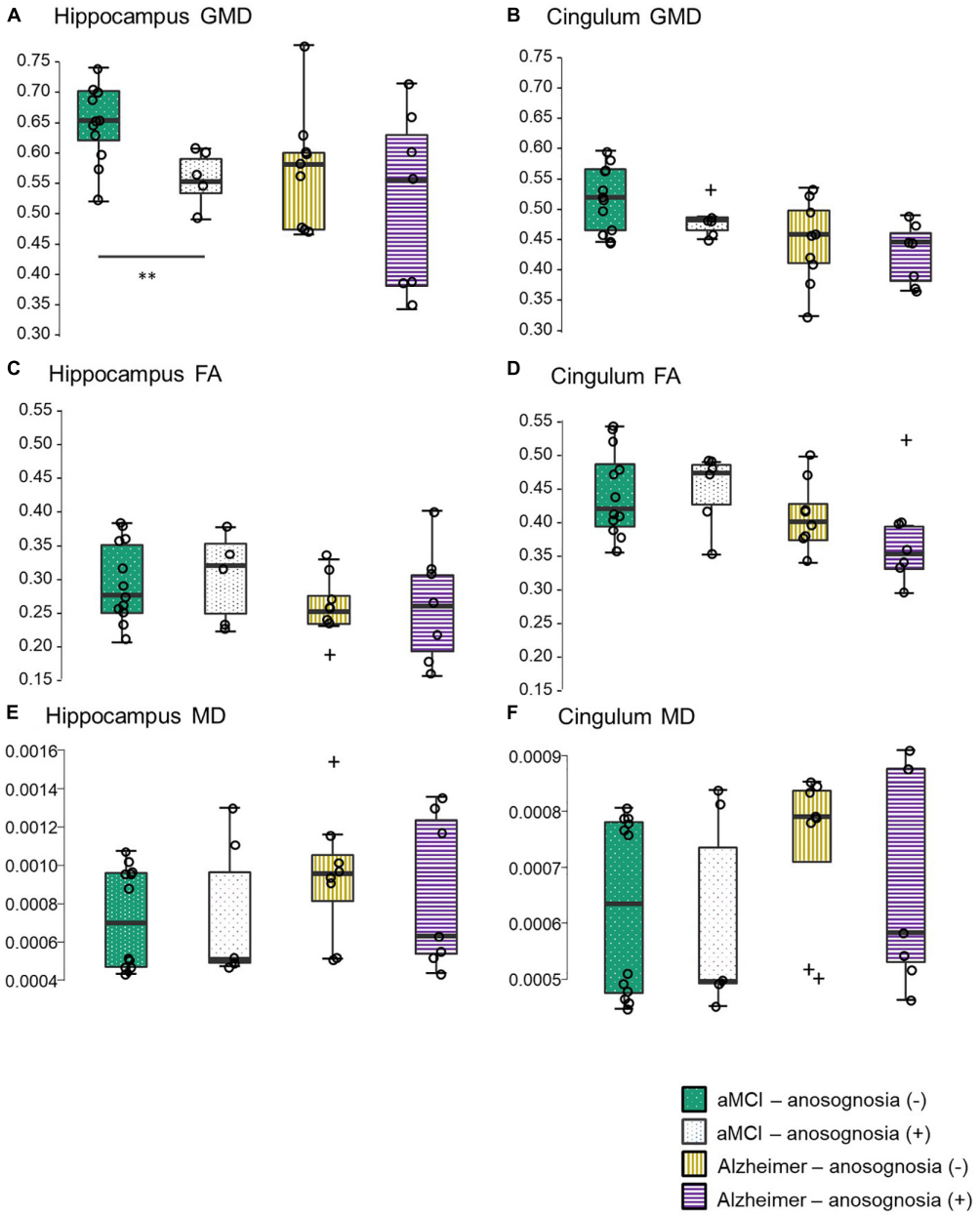


FIGURE 2 | Gray matter density in the hippocampal and cingulum regions of interest in aMCI subjects with and without anosognosia, and AD dementia participants. aMCI subjects with anosognosia displayed significantly less hippocampal gray matter density than aMCI subjects without anosognosia (**$p = 0.01$). The hippocampal gray matter density of aMCI subjects with anosognosia was not statistically different from participants with AD dementia. Boxplots represent mean group values and interquartile ranges, outliers (values outside the lower of upper limits of the quartile range) are represented with the symbol +. GMD, gray matter density; FA, fractional anisotropy; MD, mean diffusivity; aMCI, amnestic mild cognitive impairment; AD, Alzheimer's disease. Although most of these correlations were not significant, there are trends shown in **Supplementary Figure 1** that could inform future research, particularly the negative correlation between anosognosia scores and FA in both ROIs shown in AD participants. If replicated, this suggests that white-matter integrity disturbances could result in a more pronounced anosognosia presentation in AD.

DISCUSSION

One of the main findings in this study, where we assessed volumetric and white matter tract changes associated with anosognosia, is that a group of aMCI subjects displaying anosognosia had a lower hippocampal volume than a group of aMCI subjects without anosognosia. These groups did not differ significantly by age, sex distribution, MMSE score, or ICV, which suggests that these groups were comparable. However, even more interestingly, aMCI subjects with anosognosia had a similar hippocampal volume to subjects with AD in our study. In the following, we will discuss the implications in the clinical

characterization of aMCI and anosognosia assessment, neural and cognitive mechanisms underlying anosognosia, limitations of our study, and suggest future lines of research.

First, taking a clinical perspective, the association of reduced hippocampal volume with the presence of anosognosia in aMCI is in line with previous studies that place anosognosia as a risk factor for progression to AD dementia (Spalletta et al., 2014; Scherling et al., 2016). Hippocampal atrophy is independently and strongly correlated to AD progression from its early stages and to a heightened risk of progression from aMCI to AD dementia (Izzo et al., 2020; Zhuo et al., 2021). This implies that in clinical practice, an aMCI patient presenting to consultation with anosognosia might have a higher risk of progressing to dementia due to AD, and could benefit from a closer follow-up, a more comprehensive diagnostic workup, and potentially, disease-modifying strategies. Interestingly, our findings were obtained through a straight-forward classification of anosognosia. By using the screening questions of the BDSI (Godefroy et al., 2010), which are presented in **Table 1**, we dichotomized subjects as presenting and not presenting anosognosia, which is a simple approach that could be easily undertaken in everyday clinical assessments.

Regarding the neural and cognitive mechanisms underlying anosognosia, it has been hypothesized that because subjects affected by AD suffer from an inability to form new memories, they depend on remote personal semantics to evaluate their present performance, with inadequate self-appraisal (Morris and Mograbi, 2013; Vannini et al., 2017; Tondelli et al., 2018). This might explain why in our study anosognosia was significantly related to localized volumetric changes in the hippocampus, a fundamental structure for the formation of episodic memories (Eichenbaum, 2017). On the other hand, it is worth noting that AD subjects with anosognosia also displayed lower hippocampal and cingulum cortex volumes than AD subjects without anosognosia, but this difference was not statistically significant. This might imply that anosognosia in aMCI is an appropriate clinical marker of a brain phenotype that is within the AD continuum, but that anosognosia in AD arises from more subtle brain changes not limited to the hippocampus.

Some limitations of the current study are worth commenting on. The small sample size warrants caution in the interpretation of the results, which are thus in need of replication in larger samples. In addition, this implies that more subtle brain changes related to anosognosia might not have been detected. Another limitation that might explain the lack of differences in white matter tracts in our sample, is the concern that diffusion methods such as FA might be insufficient to study structures such as the cingulum bundle, where crossing-fiber anatomy might necessitate more specific measurements that track white matter-fibers more reliably (Douaud et al., 2011; Jeurissen et al., 2014).

Our findings are in contrast to recent studies that identify a link between poor awareness of memory performance and a loss of white-matter integrity in the corpus callosum, frontal-striatal fibers and anterior thalamocortical radiations, as well as in the full right hemisphere (Bertrand et al., 2021; Chang et al., 2021). Beyond the fact that the number of ROIs used in the current study is limited by a small sample size, it is worth noting that the definition of anosognosia used in each study (different assessments of awareness of memory performance vs. structured questionnaire of everyday behavior) limits the comparability of the findings.

In sum, our preliminary findings, if replicated, suggest that anosognosia might be a relevant clinical marker for the suspicion of structural brain changes within the AD continuum in subjects with aMCI. Future studies assessing larger populations are necessary in order to contribute both to the characterization of aMCI subtypes and the understanding of the neural changes underlying anosognosia.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Institute of Neurology and Neurosurgery Mexico City. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JF-V: study design, data collection, statistical design, data processing and analysis, and drafting of the manuscript. GR-G: data processing and analysis, and drafting of the manuscript. OM-M: study design, data collection, and the manuscript revision. RA-L: statistical design and the manuscript revision. ML: study design, statistical design, and the manuscript revision. YR-A: study design and data collection. GA-C: study design and data analysis. RR: study design and the manuscript revision. AA: study design, acquisition of funding, and the manuscript revision. SE-G: theoretical background, study design, and the manuscript revision. AS-O: theoretical background, study design, acquisition of funding, and drafting of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

JF-V is a doctoral student from Programa de Doctorado en Ciencias Médicas, Odontológicas y de la Salud at the Universidad Nacional Autoìnoma de México (UNAM) in a joint program with the University of Groningen, Netherlands (RUG), and received a fellowship (number 465686, CVU 670327) from CONACYT-México and the RUG. This study received funding from the University Medical Centre, Groningen, Netherlands.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.739422/full#supplementary-material

REFERENCES

Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., and Gee, J. C. (2011). An open source multivariate framework for n-tissue segmentation with evaluation on public data. *Neuroinformatics* 9, 381–400. doi: 10.1007/s12021-011-9109-y

Bertrand, E., van Duinkerken, E., Laks, J., Dourado, M. C. N., Bernardes, G., Landeira-Fernandez, J., et al. (2021). Structural Gray and White Matter Correlates of Awareness in Alzheimer's Disease. *J. Alzheimers Dis.* 81, 1321–1330. doi: 10.3233/jad-201246

Chang, Y.-L., Chao, R.-Y., Hsu, Y.-C., Chen, T.-F., and Tseng, W.-Y. I. (2021). White matter network disruption and cognitive correlates underlying impaired memory awareness in mild cognitive impairment. *NeuroImage Clin.* 30:102626. doi: 10.1016/j.nicl.2021.102626

Chavoix, C., and Insausti, R. (2017). Self-awareness and the medial temporal lobe in neurodegenerative diseases. *Neurosci. Biobehav. Rev.* 78, 1–12. doi: 10.1016/j.neubiorev.2017.04.015

Coupé, P., Yger, P., Prima, S., Hellier, P., Kervrann, C., and Barillot, C. (2008). An optimized blockwise nonlocal means denoising filter for 3-D magnetic resonance images. *IEEE Trans. Med. Imaging* 27, 425–441. doi: 10.1109/tmi.2007.906087

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31, 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Douaud, G., Jbabdi, S., Behrens, T. E. J., Menke, R. A., Gass, A., Monsch, A. U., et al. (2011). DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. *Neuroimage* 55, 880–890. doi: 10.1016/j.neuroimage.2010.12.008

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., et al. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain* 130, 2375–2386. doi: 10.1093/brain/awm184

Eichenbaum, H. (2017). Prefrontal–hippocampal interactions in episodic memory. *Nat. Rev. Neurosci.* 18, 547–558. doi: 10.1038/nrn.2017.74

Flores-Vazquez, J. F., and Sosa-Ortiz, A. L. (2016). Mexican cross-cultural adaptation/validation of the "behavioral dysexecutive syndrome inventory.". *Alzheimers Dement. J. Alzheimers Assoc.* 12:818. doi: 10.1016/j.jalz.2016.06.1660

Gerretsen, P., Chung, J. K., Shah, P., Plitman, E., Iwata, Y., Caravaggio, F., et al. (2017). Anosognosia is an independent predictor of conversion from mild cognitive impairment to Alzheimer's disease and is associated with reduced brain metabolism. *J. Clin. Psychiatry* 78, 1187–1196. doi: 10.4088/JCP.16m11367

Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., and Meulemans, T. (2010). Dysexecutive syndrome: diagnostic criteria and validation study. *Ann. Neurol.* 68, 855–864. doi: 10.1002/ana.22117

Godefroy, O., Martinaud, O., Verny, M., Mosca, C., Lenoir, H., Bretalut, E., et al. (2014). The dysexecutive syndrome of alzheimer's disease: the grefex study. *J. Alzheimers Dis.* 42, 1203–1208. doi: 10.3233/jad-140585

Grieder, M., Wang, D. J. J., Dierks, T., Wahlund, L.-O., and Jann, K. (2018). Default mode network complexity and cognitive decline in mild Alzheimer's disease. *Front. Neurosci.* 12:770. doi: 10.3389/fnins.2018.00770

Hallam, B., Chan, J., Costafreda, S. G., Bhome, R., and Huntley, J. (2020). What are the neural correlates of meta-cognition and anosognosia in Alzheimer's Disease? A systematic review. *Neurobiol. Aging* 94, 250–264. doi: 10.1016/j.neurobiolaging.2020.06.011

Hanseeuw, B. J., Scott, M. R., Sikkes, S. A. M., Properzi, M., Gatchel, J. R., Salmon, E., et al. (2020). Evolution of anosognosia in alzheimer's disease and its relationship to amyloid. *Ann. Neurol.* 87, 267–280. doi: 10.1002/ana.25649

IBM Corp (2020). *IBM SPSS Statistics for Windows, Version 27.0*. Armonk, NY: IBM Corp.

Izzo, J., Andreassen, O. A., Westlye, L. T., and van der Meer, D. (2020). The association between hippocampal subfield volumes in mild cognitive impairment and conversion to Alzheimer's disease. *Brain Res.* 1728:146591. doi: 10.1016/j.brainres.2019.146591

JASP Team (2020). *JASP (Version 0.14.1)[Computer software]*.

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., and Smith, S. M. (2012). Fsl. *Neuroimage* 62, 782–790. doi: 10.1016/j.neuroimage.2011.09.015

Jeurissen, B., Tournier, J.-D., Dhollander, T., Connelly, A., and Sijbers, J. (2014). Multi-tissue constrained spherical deconvolution for improved analysis of multi-shell diffusion MRI data. *Neuroimage* 103, 411–426. doi: 10.1016/j.neuroimage.2014.07.061

Kerby, D. S. (2014). The simple difference formula: an approach to teaching nonparametric correlation. *Compr. Psychol.* 3, 11–15.

Mak, E., Chin, R., Ng, L. T., Yeo, D., and Hameed, S. (2015). Clinical associations of anosognosia in mild cognitive impairment and Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 30, 1207–1214. doi: 10.1002/gps.4275

Manjón, J. V., Coupé, P., Martí-Bonmatí, L., Collins, D. L., and Robles, M. (2010). Adaptive non-local means denoising of MR images with spatially varying noise levels. *J. Magn. Reson. Imaging* 31, 192–203. doi: 10.1002/jmri.22003

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Mondragón, J. D., Maurits, N. M., Deyn, P. P., De Deyn, P. P., and Alzheimer's Disease Neuroimaging Initiative (2021). Functional connectivity differences in Alzheimer's disease and amnestic mild cognitive impairment associated with AT(N) classification and anosognosia. *Neurobiol. Aging* 101, 22–39. doi: 10.1016/j.neurobiolaging.2020.12.021

Morris, R. G., and Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex* 49, 1553–1565. doi: 10.1016/j.cortex.2012.09.006

Ostrosky-Solís, F., López-Arango, G., and Ardila, A. (2000). Sensitivity and specificity of the Mini-Mental State Examination in a Spanish-speaking population. *Appl. Neuropsychol.* 7, 25–31. doi: 10.1207/S15324826AN0701_4

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194. doi: 10.1111/j.1365-2796.2004.01388.x

Scherling, C. S., Wilkins, S. E., Zakrezewski, J., Kramer, J. H., Miller, B. L., Weiner, M. W., et al. (2016). Decreased self-appraisal accuracy on cognitive tests of executive functioning is a predictor of decline in mild cognitive impairment. *Front. Aging Neurosci.* 8:120. doi: 10.3389/fnagi.2016.00120

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31, 1487–1505. doi: 10.1016/j.neuroimage.2006.02.024

Spalletta, G., Piras, F., Piras, F., Sancesario, G., Iorio, M., Fratangeli, C., et al. (2014). Neuroanatomical correlates of awareness of illness in patients with amnestic mild cognitive impairment who will or will not convert to Alzheimer's disease. *Cortex* 61, 183–195. doi: 10.1016/j.cortex.2014.10.010

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: diagnosis, frequency, mechanism and clinical correlates. *Cortex* 61, 64–73. doi: 10.1016/j.cortex.2014.07.019

Therriault, J., Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Kang, M. S., Struyfs, H., et al. (2018). Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology* 90, e932–e939. doi: 10.1212/WNL.0000000000005120

Tondelli, M., Barbarulo, A. M., Vinceti, G., Vincenzi, C., Chiari, A., Nichelli, P. F., et al. (2018). Neural correlates of Anosognosia in Alzheimer's disease and mild cognitive impairment: a multi-method assessment. *Front. Behav. Neurosci.* 12:100. doi: 10.3389/fnbeh.2018.00100

Turró-Garriga, O., Garre-Olmo, J., Vilalta-Franch, J., Conde-Sala, J. L., de Gracia Blanco, M., and López-Pousa, S. (2013). Burden associated with the presence

of anosognosia in Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 28, 291–297. doi: 10.1002/gps.3824

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., et al. (2017). Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *NeuroImage Clin.* 15, 408–414. doi: 10.1016/j.nicl.2017.05.020

Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., et al. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage* 36, 630–644. doi: 10.1016/j.neuroimage.2007.02.049

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., et al. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex* 49, 668–678. doi: 10.1016/j.cortex.2012.04.011

Zhuo, J., Zhang, Y., Liu, Y., Liu, B., Zhou, X., Bartlett, P. F., et al. (2021). New trajectory of clinical and biomarker changes in sporadic Alzheimer's disease. *Cereb. Cortex* 31, 3363–3373. doi: 10.1093/cercor/bhab017

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 05 January 2022
doi: 10.3389/fnagi.2021.761932

Everyday Functioning in a Community-Based Volunteer Population: Differences Between Participant- and Study Partner-Report

*Merike Verrijp[1†], Mark A. Dubbelman[1†], Leonie N. C. Visser[1,2], Roos J. Jutten[1], Elke W. Nijhuis[1], Marissa D. Zwan[1], Hein P. J. van Hout[3], Philip Scheltens[1], Wiesje M. van der Flier[1,4] and Sietske A. M. Sikkes[1,5]**

[1] Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands, [2] Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden, [3] Department of General Practice and Medicine for Older Persons, Amsterdam Public Health Research Institute, Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [4] Department of Epidemiology and Biostatistics, Amsterdam UMC, Amsterdam, Netherlands, [5] Faculty of Behavioural and Movement Sciences, Clinical Developmental Psychology, Clinical Neuropsychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*

OPEN ACCESS

Edited by:
Stéphane Epelbaum, Hôpital Universitaire la Pitié-Salpêtrière, France

Reviewed by:
Nikki-Anne Wilson, Neuroscience Research Australia, Australia
Carol Persad, University of Michigan, United States
Arturo Pereiro, University of Santiago de Compostela, Spain

***Correspondence:**
Sietske A. M. Sikkes
s.sikkes@amsterdamumc.nl

† These authors have contributed equally to this work and share first authorship

Received: *20 August 2021*
Accepted: *16 November 2021*
Published: *05 January 2022*

Citation:
Verrijp M, Dubbelman MA, Visser LNC, Jutten RJ, Nijhuis EW, Zwan MD, van Hout HPJ, Scheltens P, van der Flier WM and Sikkes SAM (2022) Everyday Functioning in a Community-Based Volunteer Population: Differences Between Participant- and Study Partner-Report. Front. Aging Neurosci. 13:761932. doi: 10.3389/fnagi.2021.761932

Introduction: Impaired awareness in dementia caused by Alzheimer's disease and related disorders made study partner-report the preferred method of measuring interference in "instrumental activities of daily living" (IADL). However, with a shifting focus toward earlier disease stages and prevention, the question arises whether self-report might be equally or even more appropriate. The aim of this study was to investigate how participant- and study partner-report IADL perform in a community-based volunteer population without dementia and which factors relate to differences between participant- and study partner-report.

Methods: Participants (*N* = 3,288; 18–97 years, 70.4% females) and their study partners (*N* = 1,213; 18–88 years, 45.8% females) were recruited from the Dutch Brain Research Registry. IADL were measured using the Amsterdam IADL Questionnaire. The concordance between participant- and study partner-reported IADL difficulties was examined using intraclass correlation coefficient (ICC). Multinomial logistic regressions were used to investigate which demographic, cognitive, and psychosocial factors related to participant and study partner differences, by looking at the over- and underreport of IADL difficulties by the participant, relative to their study partner.

Results: Most A-IADL-Q scores represented no difficulties for both participants (87.9%) and study partners (89.4%). The concordance between participants and study partners was moderate (ICC = 0.55, 95% confidence interval [CI] = [0.51, 0.59]); 24.5% (*N* = 297) of participants overreported their IADL difficulties compared with study partners, and 17.8% (*N* = 216) underreported difficulties. The presence of depressive symptoms (odds ratio [OR] = 1.31, 95% CI = [1.12, 1.54]), as well as memory complaints (OR = 2.45, 95% CI = [1.80, 3.34]), increased the odds of participants overreporting their IADL difficulties.

Higher IADL ratings decreased the odds of participant underreport (OR = 0.71, 95% CI = [0.67, 0.74]).

Conclusion: In this sample of community-based volunteers, most participants and study partners reported no major IADL difficulties. Differences between participant and study partner were, however, quite prevalent, with subjective factors indicative of increased report of IADL difficulties by the participant in particular. These findings suggest that self- and study partner-report measures may not be interchangeable, and that the level of awareness needs to be considered, even in cognitively healthy individuals.

Keywords: instrumental activities of daily living, aging, preclinical, awareness, Alzheimer's disease, dementia, self report measures, study partner-reported outcomes

INTRODUCTION

As the research field of Alzheimer's disease (AD) shifts its attention to earlier stages of the disease, clinically meaningful outcome measures that show early changes are becoming increasingly important (Edgar et al., 2019). One such outcome measure is the concept of "instrumental activities of daily living" (IADL), which refers to cognitively complex everyday activities (Lawton and Brody, 1969). Previous studies have shown that study partners report a decline in IADL in preclinical AD, even before cognitive problems can be detected by the standard cognitive testing (Sperling et al., 2011; Marshall et al., 2012, 2017; Zoller et al., 2014). Due to impairments in awareness in persons with dementia (Hanseeuw et al., 2020), (I)ADL functioning has traditionally been assessed using study partner-report questionnaires (Loewenstein et al., 2001; Howorth and Saper, 2003; Wadley et al., 2003; Desai et al., 2004; Farias et al., 2005; Graham et al., 2005; Sikkes et al., 2009; Hackett et al., 2020).

However, it has been suggested that study partner-report may be biased, by factors such as depression, anxiety, and caregiver burden (Zanetti et al., 1999; Arguelles et al., 2001; Ready et al., 2004). With a shift toward studying cognitively normal or "at-risk" individuals, one might assume that participants are able to reliably reflect on their own level of functioning, as they are thought to have accurate or potentially heightened awareness of their functional and cognitive abilities, as reflected in the concept of subjective cognitive decline (SCD) (Steward et al., 2019; Hanseeuw et al., 2020). In such populations, participant-report may therefore be a more appropriate and direct assessment method (DeBettignies et al., 1990; Zanetti et al., 1999; Arguelles et al., 2001).

When investigating participant- and study partner-report, a few findings stand out. First, several studies have found that there is no perfect concordance between participants and study partners, even in cognitively normal populations (Farias et al., 2005; Okonkwo et al., 2008; Marshall et al., 2020). Factors such as participant education, depression, and anxiety, as well as the nature of the relationship and the frequency and intensity of contact between participants and study partners, may affect how either party reports impairments, leading to discordance where one may report more or fewer impairments than the other. Second, studies investigating the interplay of these factors in cognitively normal populations are scarce. Furthermore, findings are difficult to compare between studies, due to differences in IADL measurements and in the definition and operationalization of concordance and discordance.

The Amsterdam IADL Questionnaire (A-IADL-Q) was developed as a study partner-rated questionnaire and has been extensively validated in memory clinic and community-based international aging populations (Sikkes et al., 2012, 2013a,b; Koster et al., 2015; Jutten et al., 2017; Facal et al., 2018; Villeneuve et al., 2019; Bruderer-Hofstetter et al., 2020; Dubbelman et al., 2020a). It is not yet known how the participant-report version of the A-IADL-Q performs and how it relates to study partner-report. The aim of this study was to investigate how the participant- and study partner-reported versions of the A-IADL-Q perform in a community-based population, without dementia, and what factors relate to differences between participant- and study partner-reported IADL functioning.

MATERIALS AND METHODS

Participant Selection and Study Design

Participants were selected through the Dutch Brain Research Registry (Hersenonderzoek.nl), which is an online platform for people interested in cognition and brain-related research (Zwan et al., 2021). All eligible registrants were invited by email to participate in the study. The only inclusion criterion was participants being 18 years or older. Those who self-reported to have received a dementia-related diagnosis (i.e., dementia or mild cognitive impairment [MCI]) were excluded.

Data collection started in August 2018 and ended in December 2018. The study was approved by the medical ethical committee of the VU University Medical Center. The participants provided consent *via* Hersenonderzoek.nl. Since study partners were not recruited through Hersenonderzoek.nl, they provided consent prior to completing the online IADL questionnaire.

Measures

Amsterdam Instrumental Activities of Daily Living Questionnaire

The main outcome measure was the A-IADL-Q. The A-IADL-Q was developed as a study partner-report instrument aimed

at measuring problems in cognitively complex everyday functioning (Sikkes et al., 2012). For the current study, we adapted the study partner-report version to a participant-report version. Both versions consist of the same 30 items, covering a broad range of cognitive IADL. Each item assesses difficulty performing an activity due to cognitive problems, such as problems with memory, attention, or executive functioning. Item responses were rated on a five-point Likert scale, ranging from "no difficulty in performing this activity" (0) to "no longer able to perform this activity" (4). The total score is calculated using item response theory (IRT), assuming a single underlying construct (Reise and Waller, 2009), that is, IADL functioning, ranging from disability to ability. Total scores range from 20 to 70 and were reversed so that higher scores reflect better IADL functioning. A cutoff value for dementia was previously placed at 51.4 (Sikkes et al., 2013b), while scores above 60 were considered to indicate no IADL difficulties (Dubbelman et al., 2020b). The study partner-report version of the A-IADL-Q has undergone extensive validation, showing a good content and construct validity, high internal consistency, high test-retest reliability, good responsiveness to change and ablity to measure IADL across cultures and languages (Sikkes et al., 2013a,b; Koster et al., 2015; Jutten et al., 2017; Dubbelman et al., 2020a). The study partner version of the A-IADL-Q also includes questions about the type of relation to the participant and cohabitation. Study partners were classified as spouses, children, siblings, or "other." Study partners in the "other" category included friends, coworkers, or other family members.

Other Measures

Cognitive functioning was assessed using the Cognitive Online Self-Test Amsterdam (COST-A), an online cognitive self-test developed and validated by Van Mierlo et al. (2017). The COST-A included 10 tasks, namely, orientation, digit-sequence learning, immediate word recall, two trail-making tasks (i.e., connecting numbered dots and alternately connecting lettered and numbered dots), delayed word recall, delayed word recognition, immediate recall of word pairs, recognition of word pairs, and semantic comprehension. Performance on each of the tasks was standardized and averaged into a *Z*-score to represent overall cognitive functioning, where higher scores indicate better cognition. Visser et al. (2021) provided a more detailed description of the COST-A.

In addition, a single yes/no question ("Do you have memory complaints?") assessed subjective memory complaints. Depressive symptoms were assessed with the five-item short form of the Geriatric Depression Scale (GDS5) (Hoyl et al., 1999) with higher scores indicating more depressive symptoms. The education level was classified as low-medium (up to high school) and high education (college degree).

Defining Awareness of Instrumental Activities of Daily Living Functioning

In line with other studies, we defined concordance based on the discrepancy between participant- and study partner-report (Hanseeuw et al., 2020). Based on a previously determined clinically meaningful difference over time of 2.4 points, we categorized concordance into three groups, (Dubbelman et al., 2020) namely, (1) concordance between dyads, (2) discordance between dyads with the participant "overreporting" difficulties (i.e., scoring $\geq$ 2.4 points lower than their study partner), and (3) discordance between dyads with the participant "underreporting" difficulties (i.e., scoring $\geq$ 2.4 points higher than their study partner).

Statistical Analyses

Demographic differences between study partners and participants were tested using independent *t*-tests or chi-square tests. The frequency of IADL difficulties among cognitively normal participants and their study partners was determined. Then, in separate linear regression analyses, A-IADL-Q scores of both raters were associated with age, education, objective cognitive functioning, subjective cognitive functioning, and depressive symptoms.

The intraclass correlation coefficient (ICC) was computed to examine the absolute agreement between participant and study partner ratings. According to the criteria suggested by Koo et al., an ICC $<$ 0.5 shows poor agreement, an ICC of 0.5–0.75 shows moderate, and an ICC $>$ 0.75 shows good agreement (Koo and Li, 2016).

Using stepwise multinomial logistic regression models with backward selection, we investigated which factors related to concordance and discordance between dyads. The variables included the following parameters of participants: education level, sex, age, COST-A scores, memory complaints, GDS5 total score, study partner-reported IADL functioning, the type of relationship, cohabitation (yes/no), and the absolute age difference between dyads. For this analysis, COST-A scores were dichotomized into normal (more than -1.5 SD) and low (less than or equal to -1.5 SD) cognitive functioning. All analyses were performed using R version 4.0.3 software (R Core Team, 2020).

RESULTS

Of the 11,060 eligible registrants, 4,817 individuals (44%) were interested in participation and received study instructions. After receiving instructions, 3,288 (68%) individuals completed the participant-reported A-IADL-Q. On average, participants were 61.0 $\pm$ 12.1 years old and the majority of them were women (i.e., 2,315; 70.4%). Approximately, half the participants experienced memory complaints. **Table 1** displays all participant and study partner characteristics. Participant and study partner characteristics stratified by age groups are shown in **Supplementary Material**.

For 1,213 participants (36.9% of complete sample), the A-IADL-Q was also completed by a study partner (participant and study partner pairs will be referred to as "dyads"). Participants who were part of a dyad were 62.5 $\pm$ 11.1 years old, and the majority of them were women (i.e., 828; 68.3%). They were older ($p < 0.001$) and more often men ($p = 0.046$) than participants who were not part of a dyad. Within dyads, the participants were older ($p < 0.001$) and more likely to be women ($p < 0.001$) than study partners.

TABLE 1 | Participant and study partner characteristics.

	Participants (*N* = 3,288)	Dyads (*N* = 1,213)	
		Participants	Study partners
Age, mean (SD)	61.0 (12.1)	62.5 (11.1)	58.8 (14.2)
Range	18–97	18–93	18–88
Female, n (%)	2,315 (70.4)	828 (68.3)	556 (45.8)
High level of education, n (%)	2,323 (70.7)	854 (70.4)	—
A-IADL-Q score, mean (SD)	65.9 (4.8)	65.9 (4.7)	66.1 (4.6)
Range	40.9–70.0	40.7–70.0	42.7–70.0
Memory complaints present,[1] n (%)	1,429 (47.5)	586 (49.9)	—
COST-A,[2] abnormal performance (≤ -1.5SD), n (%)	225 (7.6)	86 (7.5)	—
GDS5,[1] median (IQR)	0 (0–1)	0 (0–1)	—
Type of relationship, n (%)			
Spouse		956 (78.8)	
Child		155 (12.8)	
Sibling		32 (2.6)	
Other		70 (5.8)	
Duration relationship, n (%)			
< 5 years		33 (2.7)	
5–10 years		58 (4.8)	
>10 years		1,119 (92.5)	
Living together, n (%)		960 (79.3)	

"—" denotes that the data were not available. [1]Data were available for 3,011 participants, of whom 1,175 were part of a dyad. [2]Data were available for 2,945 participants, of whom 1,149 were part of a dyad. A-IADL-Q, Amsterdam Instrumental Activities of Daily Living Questionnaire; COST-A, Cognitive Self-Test Amsterdam; GDS5, 5-item Geriatric Depression Scale; IQR, interquartile range; SD, standard deviation.

Instrumental Activities of Daily Living Difficulties in a Cognitively Normal Population

Figure 1 shows the distribution of participant- and study partner-reported A-IADL-Q scores. Among dyads, the participant-reported A-IADL-Q scores (65.9 ± 4.8) did not differ from the study partner-reported A-IADL-Q scores (66.1 ± 4.6; $p = 0.186$). Virtually all participants (3,232/3,288; 98.3%) and study partners (1,195/1,213; 98.5%) reported A-IADL-Q scores above a previously established cutoff for dementia (total score of 51.4). Moreover, the vast majority of both participant-reported (87.9%) and study partner-reported (89.4%) total scores were higher than 60, indicating no difficulties.

Then, we examined IADL difficulties at an item level. Half of all participants (i.e., 1,750/3,288, 53.2%) and study partners (i.e., 722/1,213, 59.5%) reported no difficulties in any activity. Those who reported difficulties mostly did so in only one activity (i.e., 35.2% of participants and 35.8% of study partners). **Figure 2** shows the percentage of participants and study partners who reported difficulties for each IADL activity. Most frequently reported IADL difficulties for both participants and study partners were working (i.e., 26.9 and 19.9%, respectively), household duties (i.e., 22.2 and 16.5%, respectively), and making minor repairs at home (i.e., 16.4 and 12.7%, respectively).

Table 2 shows the associations between age, education level, cognitive complaints, COST-A, GDS, and participant- and study partner-reported IADL performance. Higher age was associated with lower A-IADL-Q scores, and higher education was associated with better A-IADL-Q scores, but associations were weak. For example, with every 10 years increase in age, A-IADL-Q participant- and study partner-reported scores decreased with 1.2 and 1.8 points, respectively. Both participant- and study partner-reported A-IADL-Q scores were more highly associated with COST-A scores, memory complaints, and GDS. Higher COST-A scores, indicating better cognitive functioning, were associated with better IADL functioning, whereas a higher GDS, indicating more depressive symptoms, and presence of memory complaints were associated with worse IADL functioning. Associations with age, education, and COST-A scores were comparable for participant- and study partner-report, whereas associations with GDS and memory complaints were more strongly associated with participant-reported IADL scores.

Concordance and Discordance Between Dyads

There was a moderate agreement between participant- and study partner-reported IADL functioning (ICC = 0.55, 95% CI = [0.51, 0.59], $p < 0.001$; see **Supplementary Table 1**). Of all 1,213 dyads, 700 (57.7%) were in concordance. Two hundred sixteen participants (17.8%) underreported difficulties, compared with their study partners, and 297 participants (24.5%) overreported IADL difficulties, compared to their study partners. Compared with concordant dyads, participants with memory complaints (odds ratio [OR] = 2.44, 95% CI = [1.80, 3.32], $p < 0.001$) and with a higher GDS (OR = 1.31, 95% CI = [1.12, 1.53], $p = 0.001$) were more likely to overreport IADL difficulties (see **Table 3**). Participant underreport was less likely when there were fewer IADL difficulties (OR = 0.71, 95% CI = [0.67, 0.74], $p < 0.001$). Thus, concordance was more likely when the participant did not experience memory complaints, when they had lower GDS scores, and when IADL performance was higher. Education, age, gender, and COST-A scores of participants were not related to concordance between dyads.

DISCUSSION

In this study, we showed that the majority of IADL scores fell within the range of normal IADL functioning in this community-based population, but that discordance among dyads was quite prevalent. A small proportion reported subtle IADL difficulties, which was associated with older age, lower education, worse cognitive performance, presence of self-reported memory complaints, and more depressive symptoms of participants, for both participant- and study partner-report. A moderate agreement between participant- and study partner-reported IADL was found with discordance between dyads being more likely when the participant reported memory complaints, and had depressive symptoms and lower IADL performance.

While the large majority of participant- and study partner-reported IADL functioning fell within the range of normal IADL

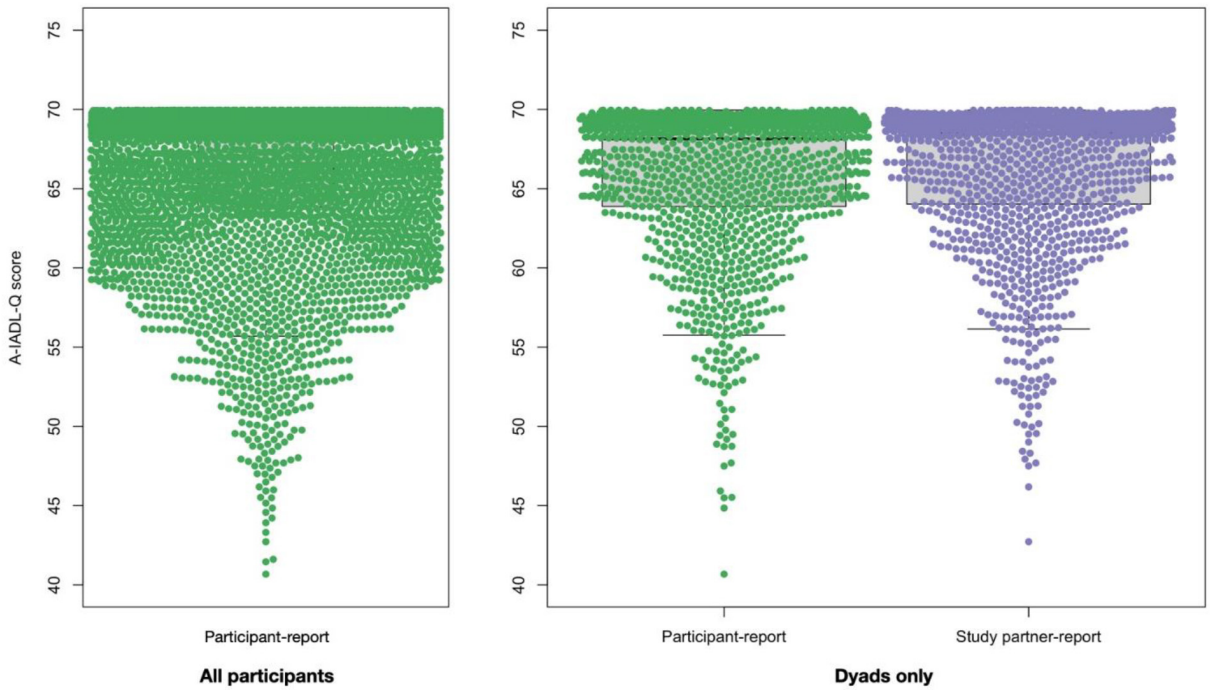


FIGURE 1 | A-IADL-Q total score distribution among all participants (left panel, *N* = 3,288) and among dyads (right panel, *N* = 1,213, participants are denoted in green and study partners are denoted in purple).

functioning, approximately a tenth of both participants and study partners scored below the previously established cutoff for normal IADL functioning (Dubbelman et al., 2020b). This prevalence of impaired IADL is comparable to other population-based studies (Ostbye et al., 1997; Pudaric et al., 2003; Crimmins et al., 2011; Scheel-Hincke et al., 2020). For example, Scheel-Hincke et al. (2020) reported a prevalence of impaired IADL of 12 to 20% in Western Europe, with impaired IADL defined as presence of any difficulties. Another population-based study by Pudaric et al. (2003) reported a prevalence of impaired IADL (inability to carry out shopping, cooking, or housework) of 6 to 11%. Despite this comparable prevalence of abnormal IADL functioning, it is important to note that approximately half of our population reported more subtle difficulties. If we applied the definition of Scheel-Hincke et al. (2020), the prevalence of impaired IADL in our study would be approximately 50%, which is substantially higher than the prevalence that they reported. There are two potential explanations for this difference: first, we included more activities, and second, and more importantly, we included more cognitively complex activities than other studies. This is illustrated by the fact that most problems were reported in working, household duties, and making repairs, which are especially cognitively complex (Jutten et al., 2017). These activities were not included in other IADL scales. For example, a population-based study that assessed five IADL items (Chan et al., 2012) reported most problems for shopping. In our population, problems with shopping were fourth most prevalent. We found a higher proportion of difficulties for more complex activities, supporting the notion that including more complex activities enabled detection of more fine-grained difficulties in IADL functioning.

With regard to potential sources of bias in the report of IADL functioning, we found low associations between both study partner- and participant-reported IADL functioning and age and education. This finding is supported by previous validation studies for the study partner version of the A-IADL-Q (Sikkes et al., 2013a; Jutten et al., 2017; Dubbelman et al., 2020a). Participant- and study partner-report were similarly associated with objective cognitive performance, but participant-reported IADL functioning was more strongly related to depressive symptoms, as well as subjective cognitive performance (i.e., presence of self-reported memory complaints). Consistent with recent literature suggesting that study partners are better able to assess the functioning of participants than the participant themselves (Howland et al., 2017), our findings might imply that study partner-report is less biased than participant-report by participant-related subjective factors.

Our findings demonstrated only a moderate concordance between dyads. While the distributions of study partner- and participant-reported IADL scores were largely similar, we found a moderate ICC and a high proportion of discordance (either over- or underreport). Other studies have also shown discordance in cognitively normal participants and, specifically, participant overreport (Ostbye et al., 1997; Farias et al., 2005; Okonkwo et al., 2008; Pol et al., 2011). For example, a study by Okonkwo et al. (2008) showed slight discordance between participant- and study partner-report of specific finance-related IADL. The proportion of discordance that we found

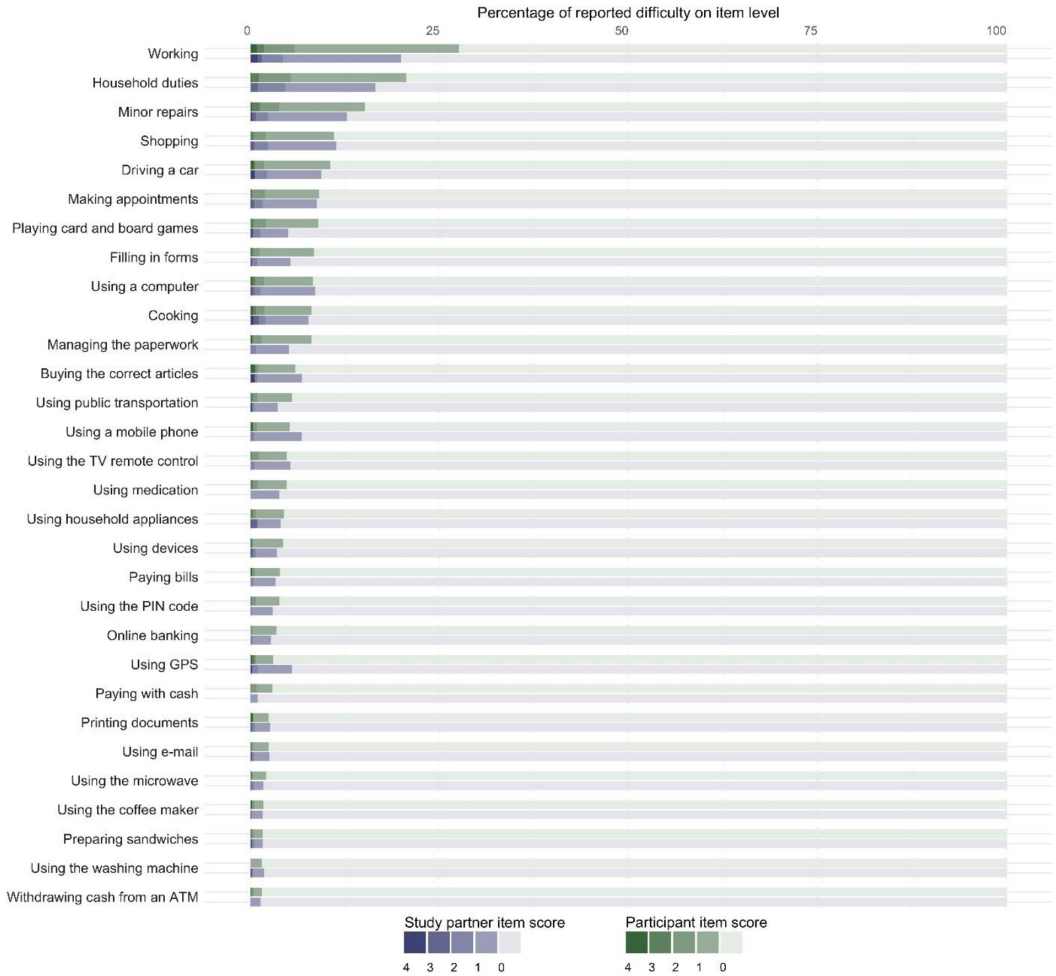


FIGURE 2 | Stacked bar chart showing the percentage of participants (denoted in shades of green) and study partners (denoted in shades of purple) who reported difficulties (N = 1,213). The dark shades represent difficulty with the activity: "no longer able to perform this activity" (4), "much more difficulty" (3), "more difficulty" (2), and "slightly more difficulty" (1). The lightest shade represents "no difficulty in performing this activity" (0). Displaying data from dyads only.

in our study is substantially higher, which is probably due to differences in IADL measures, definitions of concordance, and population differences. As opposed to Okonkwo et al. (2008), who calculated concordance based on an individual item, we determined concordance based on a more global measure of IADL with a wider range of activities. We calculated concordance based on a clinically meaningful difference in total scores. Another potential explanation may be that, even though we used a population-based sample, we did not screen for cognitive impairment. As such, it is possible that there were participants who had subtle cognitive impairment but did not meet criteria for MCI or dementia. Thus, while the proportion of discordance is difficult to compare with other studies, the fact that other studies also reported discordance suggests that participant- and study partner-report might not be interchangeable.

TABLE 2 | Linear regressions to investigate associations with participant- and study partner-reported IADL performance.

Measure	Participant-report	Study partner-report
Age	−0.12 [−0.16, −0.09]	−0.18 [−0.26, −0.14]
High education	0.09 [0.06, 0.13]	0.07 [0.02, 0.13]
Memory complaints present	−0.33 [−0.36, −0.29]	−0.24 [−0.30, −0.19]
COST-A	0.23 [0.19, 0.26]	0.25 [0.20, 0.31]
GDS5	−0.33 [−0.36, −0.29]	−0.21 [−0.30, −0.17]

Associations are shown as standardized beta [95% confidence interval]. Some measures were not available for the entire sample. Memory complaints were available for N = 3,011 participants and N = 1,175 participants who were part of a dyad. COST-A scores were available for N = 2,945 participants and N = 1,149 participants who were part of a dyad. GDS5 scores were available for N = 3,017 participants and N = 1,177 participants who were part of a dyad.

The potential limited interchangeability is further supported by our results, which indicate that concordance is influenced by self-reported memory complaints and depressive symptoms. Participants with memory complaints reported more difficulties, compared with their study partners. Participant overreport of memory complaints has previously been described as a

TABLE 3 | Multivariable multinomial logistic regression models comparing study partners reporting more IADL difficulties than participant (*N* = 216) and participant reporting more IADL difficulties than study partner (*N* = 297), compared with agreement between the participant and study partner (*N* = 700).

Predictor	Study partner > Participant (*N* = 216)		Participant > study partner (*N* = 297)	
	OR [95% CI]	*P*	OR [95% CI]	*P*
COST-A ≤ -1.5 SD	0.47 [0.21, 1.07]	0.070	1.36 [0.78, 2.39]	0.283
A-IADL-Q (study partner-report)	0.71 [0.67, 0.74]	<0.001	1.04 [0.99, 1.09]	0.148
Memory complaints present	0.76 [0.50, 1.15]	0.194	2.44 [1.80, 3.32]	<0.001
High education	0.92 [0.60, 1.40]	0.689	1.30 [0.93, 1.80]	0.121
Absolute age difference between dyads in years	1.00 [0.97, 1.04]	0.924	1.01 [0.98, 1.04]	0.924
Age in years (participant)	1.01 [0.99, 1.03]	0.467	1.01 [0.99, 1.02]	0.272
Female sex (participant)	0.74 [0.53, 1.02]	0.159	1.08 [0.78,1.49]	0.661
GDS5*	0.58 [0.50, 0.68]	<0.001	1.31 [1.12, 1.53]	<0.001
Type of relationship, study partner is a:†				
Child	2.19 [0.63, 7.60]	0.216	0.83 [0.30, 2.27]	0.716
Sibling	0.75 [0.13, 4.35]	0.744	0.57 [0.18, 1.85]	0.350
Other	0.81 [0.22, 2.98]	0.755	0.63 [0.24, 1.68]	0.355
Dyads live together	1.58 [0.70, 3.57]	0.277	1.04 [0.57, 1.90]	0.898

*OR, odds ratio; 95% CI, 95% confidence interval. Concordance was used as a reference group (N = 700). *More depressive symptoms; †Using spouse as a reference category.*

heightened awareness (Hanseeuw et al., 2020), which is thought to characterize early stages of AD and related disorders (Jessen et al., 2014; Slot et al., 2019; Hanseeuw et al., 2020). Following this theory, a subgroup of our study sample may have a heightened functional awareness. This idea is further supported by our finding that a large proportion of our sample had memory complaints, which may indicate a heightened memory awareness. While no other studies have investigated the effect of subjective cognitive functioning on the concordance of functional impairment, several studies (Weinberger et al., 1992; Ostbye et al., 1997; Albert et al., 1999; Tabert et al., 2002; Farias et al., 2005; Okonkwo et al., 2008; Pol et al., 2011) related objective cognitive functioning to concordance. These studies show that patients with poorer global cognition are more likely to underreport IADL difficulties. We did not find a significant association between concordance and objective cognition within our healthy volunteer population. This could be due to the fact that our population is presumably cognitively healthy, and lowered awareness may not occur until cognitive problems start to develop (Starkstein et al., 2006; Hanseeuw et al., 2020). Although not significant, in this population, lower cognitive performance seems to be related to reduced odds for participant underreport. This might suggest that the subtle cognitive problems of these individuals do not interfere with their disease insight, but rather, that they increase their awareness. Furthermore, participants with depressive symptoms were more likely to overreport, and less likely to underreport, IADL difficulties. This was also reported in studies in MCI and dementia that showed a greater chance of discordance when participants had depressive symptoms (Magaziner et al., 1996; Okonkwo et al., 2008). This is in line with the idea that negative self-perception in patients with depressive symptoms causes exaggeration of deficits (Lahr et al., 2007), as has also been shown by Okonkwo et al. (2008), who reported that underestimation of financial abilities was related to higher depressive symptoms. Thus, memory complaints and depressive symptoms both influence the report of IADL difficulties of participants and need to be taken into consideration when using participant-reported IADL measures.

The findings discussed earlier may have important implications for study design decisions and should be considered carefully when considering the use of a participant-reported IADL instrument. Although a concordance of 60% might seem low, the majority of both participant- and study partner-reported difficulties fell within the category of "no difficulties." This crude overlap indicates that participant-report IADL can be useful in cognitively normal populations in cross-sectional studies. However, when a deterioration of cognitive functioning and subsequently everyday functioning is to be expected, study partner-report might provide a more reliable indication of change in IADL functioning. The combination of participant- and study partner-report can be used to establish awareness, which is informative since it has been shown to predict future disease progression (Nosheny et al., 2019, 2020) and greater discordance seems to be related to a greater risk of Alzheimer pathology (Tabert et al., 2002; Hanseeuw et al., 2020). The combination of participant- and study partner-report might also be valuable as they seem to reflect different perspectives. This is reflected in the current study as participant-report seems to be more influenced by subjective factors than the study partner-report. The different perspectives were also implied in an article by Amariglio et al. (2021) who showed that distinct IADL items were related to amyloid pathology for participants and study partners. Thus, participant self-report can be used in cognitively normal populations but should ideally be supplemented by study partner-report, not only when considering the cognitive decline of participants in longitudinal studies but also to gain multiple perspectives and insight into the awareness of participants.

Some limitations should be considered when interpreting our findings. For the lack of an objective IADL measure, we cannot ascertain whether participants indeed overreport their difficulties or whether participants actually have IADL difficulties that the study partner does not yet notice. In contrast, a heightened participant awareness may also reflect lowered study partner awareness. This caveat notwithstanding, the absence of an association between participant overreport and objective cognitive functioning could indicate that participant overreport is more strongly influenced by subjective than objective factors. It should also be noted that objective cognition and IADL performance cannot be completely separated, as IADL performance is dependent on cognition. This may introduce

some level of circularity into the analyses. However, the association between our objective cognitive measure and the A-IADL-Q scores was only moderate. Furthermore, as the study partner-report is generally considered a gold standard in dementia research and clinical practice (Sikkes and De Rotrou, 2014), we used it as such in the current study. Another limitation is the selective nature of the volunteer registry, which consists mostly of highly educated and highly motivated individuals. This may limit generalizability to the general population. We did not include factors such as caregiver burden, personality traits, or more detailed information on the amount of contact between the participant and the study partner. Future studies should consider assessing these factors to obtain more detailed insight into the accuracy of assessments and possible biases. Furthermore, follow-up studies are needed to determine the pivot point until which the participant is still able to reliably evaluate their own level of daily functioning.

An important strength of this study is the large sample of cognitively healthy volunteers, representing a large range of ages, from early adulthood to late life. We included detailed information about the level of IADL difficulties from both self- and study partner-report in a cognitively healthy population, providing valuable new insights into the occurrence of more subtle IADL difficulties. While the clinically meaningful cutoff was determined for decline and not for differences between respondents, a strength of this clinically meaningful cutoff to distinguish concordance from discordance is that we believed that discordance actually represented an important, non-negligible difference in IADL report.

CONCLUSION

Our findings show a moderate concordance between participants and study partners in reporting IADL difficulties, with subjective factors influencing the level of concordance. These findings suggest caution in using self- and study partner-report measures interchangeably, even in cognitively healthy community-based samples. Our results suggest that participant report might be more related to subjective factors and that study partner-report is less associated with these factors, possibly reflecting differing perspectives.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the VU University Medical Center. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS, WF, HH, MV, and MZ: conception or design of the work. MZ, EN, LV, and MV: data collection. MV, MD, SS, WF, and HH: data analysis and interpretation. SS, MD, MV, and LV: drafting the manuscript. All authors provided critical revision of the article and final approval of the version to be published.

FUNDING

LV was supported by a fellowship grant received from Alzheimer Nederland (WE.15-2019-05) and recipient of ABOARD, which is a public-private partnership receiving funding from ZonMW (#73305095007) and Health Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). All funding is paid to the institution. WF has received funding from NWO, EU-FP7, EU-JPND, Alzheimer Nederland, CardioVascularOnderzoek Nederland, stichting Dioraphte, Gieskes-Strijbis fund, stichting Equilibrio, Pasman stichting, Biogen MA Inc., Boehringer Ingelheim, Life-MI, AVID, Roche BV, Fujifilm, and Combinostics. WF holds the Pasman chair, has performed contract research for Biogen MA Inc., and Boehringer Ingelheim, is a consultant to Oxford Health Policy Forum CIC, Roche, and Biogen MA Inc., and has been an invited speaker at Boehringer Ingelheim, Biogen MA Inc., Danone, Eisai, and WebMD Neurology (Medscape). All funding is paid to her institution. PS has acquired grant support (for the institution; Alzheimer Center Amsterdam) from GE Healthcare, Danone Research, Piramal, and MERCK. In the past 2 years, he has received consultancy/speaker fees (paid to the institution) from Lilly, GE Healthcare, Novartis, Sanofi, Nutricia, Probiodrug, Biogen, Roche, Avraham, and EIP Pharma. SS has received funding from Health Holland, Topsector Life Sciences & Health (Grant Nos. LSHM19051 and LSHM20084), and ZonMW (Grant Nos. #7330502051 and #73305095008) and has received consultancy fees from Biogen, Lundbeck, Boehringer, and Toyama and license fees for use of Amsterdam IADL Questionnaire from Green Valley, VtV Therapeutics, Alzheon, Vivoryon, Roche, Neuroscience, Janssen, Medavante, and Genentech. All funds are paid to her institution. The other authors have no relevant disclosures.

ACKNOWLEDGMENTS

The authors thank the participants and their study partners for their time and participation in this study. The participant recruitment was accomplished through Hersenonderzoek.nl, a Dutch online registry that facilitates participant recruitment for neuroscience studies (www.hersenonderzoek.nl).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.761932/full#supplementary-material

REFERENCES

Albert, S. M., Michaels, K., Padilla, M., Pelton, G., Bell, K., Marder, K., et al. (1999). Functional significance of mild cognitive impairment in elderly patients without a dementia diagnosis. *Am. J. Geriatr. Psychiatry* 7, 213–220. doi: 10.1097/00019442-199908000-00005

Amariglio, R. E., Sikkes, S. A. M., Marshall, G. A., Buckley, R. F., Gatchel, J. R., Johnson, K. A., et al. (2021). Item-level investigation of participant and study partner report on the cognitive function index from the A4 study screening data. *J. Prev. Alzheimers Dis.* 8, 257–262. doi: 10.14283/jpad.2021.8

Arguelles, S., Loewenstein, D. A., Eisdorfer, C., and Arguelles, T. (2001). Caregivers' judgments of the functional abilities of the Alzheimer's disease patient: impact of caregivers' depression and perceived burden. *J. Geriatr. Psychiatry Neurol.* 14, 91–98. doi: 10.1177/089198870101400209

Bruderer-Hofstetter, M., Dubbelman, M. A., Meichtry, A., Koehn, F., Munzer, T., Jutten, R. J., et al. (2020). Cross-cultural adaptation and validation of the Amsterdam Instrumental Activities of Daily Living questionnaire short version German for Switzerland. *Health Qual. Life Outcomes* 18:323. doi: 10.1186/s12955-020-01576-w

Chan, K. S., Kasper, J. D., Brandt, J., and Pezzin, L. E. (2012). Measurement equivalence in ADL and IADL difficulty across international surveys of aging: findings from the HRS, SHARE, and ELSA. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 67, 121–132. doi: 10.1093/geronb/gbr133

Crimmins, E. M., Kim, J. K., and Sole-Auro, A. (2011). Gender differences in health: results from SHARE, ELSA and HRS. *Eur. J. Public Health* 21, 81–91. doi: 10.1093/eurpub/ckq022

DeBettignies, B. H., Mahurin, R. K., and Pirozzolo, F. J. (1990). Insight for impairment in independent living skills in Alzheimer's disease and multi-infarct dementia. *J. Clin. Exp. Neuropsychol.* 12, 355–363. doi: 10.1080/01688639008400980

Desai, A. K., Grossberg, G. T., and Sheth, D. N. (2004). Activities of daily living in patients with dementia: clinical relevance, methods of assessment and effects of treatment. *CNS Drugs* 18, 853–875. doi: 10.2165/00023210-200418130-00003

Dubbelman, M. A., Verrijp, M., Facal, D., Sanchez-Benavides, G., Brown, L. J. E., van der Flier, W. M., et al. (2020a). The influence of diversity on the measurement of functional impairment: an international validation of the Amsterdam IADL Questionnaire in eight countries. *Alzheimers Dement. (Amst).* 12:e12021. doi: 10.1002/dad2.12021

Dubbelman, M. A., Verrijp, M., Jutten, R. J., Terwee, C. B., Visser, L. N. C., Van der Flier, W. M., et al. (2020) "OC39: detecting meaningful change in everyday functioning: a mixed-methods approach to establish clinical meaninguflnes of changes on the Amsterdam IADL Questionnaire," in *Symposia – Oral Communications – Late Breaking News. J. Prev. Alzheimers Dis.*, vol. 7, 2–54. doi: 10.14283/jpad.2020.54

Dubbelman, M. A., Verrijp, M., Visser, L. N. C., Terwee, C. B., van Der Flier, W., Scheltens, P., et al. (2020b). A mixed-methods approach to establish clinically meaningful categories of impairment in instrumental activities of daily living. *Alzheimers Dement.* 16:e045693.

Edgar, C. J., Vradenburg, G., and Hassenstab, J. (2019). The 2018 Revised FDA Guidance for early Alzheimer's disease: establishing the meaningfulness of treatment effects. *J. Prev. Alzheimers. Dis.* 6, 223–227. doi: 10.14283/jpad.2019.30

Facal, D., Carabias, M. A. R., Pereiro, A. X., Lojo-Seoane, C., Campos-Magdaleno, M., Jutten, R. J., et al. (2018). Assessing everyday activities across the dementia spectrum with the Amsterdam IADL Questionnaire. *Curr. Alzheimer Res.* 15, 1261–1266. doi: 10.2174/1567205015666180925113411

Farias, S. T., Mungas, D., and Jagust, W. (2005). Degree of discrepancy between self and other-reported everyday functioning by cognitive status: dementia, mild cognitive impairment, and healthy elders. *Int. J. Geriatr. Psychiatry* 20, 827–834. doi: 10.1002/gps.1367

Graham, D. P., Kunik, M. E., Doody, R., and Snow, A. L. (2005). Self-reported awareness of performance in dementia. *Brain Res. Cogn. Brain Res.* 25, 144–152. doi: 10.1016/j.cogbrainres.2005.05.001

Hackett, K., Mis, R., Drabick, D. A. G., and Giovannetti, T. (2020). Informant reporting in mild cognitive impairment: sources of discrepancy on the functional activities questionnaire. *J. Int. Neuropsychol. Soc.* 26, 503–514. doi: 10.1017/S1355617719001449

Hanseeuw, B. J., Scott, M. R., Sikkes, S. A. M., Properzi, M., Gatchel, J. R., Salmon, E., et al. (2020). Evolution of anosognosia in alzheimer's disease and its relationship to amyloid. *Ann. Neurol.* 87, 267–280. doi: 10.1002/ana.25649

Howland, M., Allan, K. C., Carlton, C. E., Tatsuoka, C., Smyth, K. A., and Sajatovic, M. (2017). Patient-rated versus proxy-rated cognitive and functional measures in older adults. *Patient Relat. Outcome Meas.* 8, 33–42. doi: 10.2147/PROM.S126919

Howorth, P., and Saper, J. (2003). The dimensions of insight in people with dementia. *Aging Ment. Health* 7, 113–122. doi: 10.1080/1360786031000072286

Hoyl, M. T., Alessi, C. A., Harker, J. O., Josephson, K. R., Pietruszka, F. M., Koelfgen, M., et al. (1999). Development and testing of a five-item version of the Geriatric Depression Scale. *J. Am. Geriatr. Soc.* 47, 873–878. doi: 10.1111/j.1532-5415.1999.tb03848.x

Jessen, F., Amariglio, R. E., Van Boxtel, M., Breteler, M. M. B., Ceccaldi, M., Chételat, G., et al. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement.* 10, 844–852. doi: 10.1016/j.jalz.2014.01.001

Jutten, R. J., Peeters, C. F. W., Leijdesdorff, S. M. J., Visser, P. J., Maier, A. B., Terwee, C. B., et al. (2017). Detecting functional decline from normal aging to dementia: development and validation of a short version of the Amsterdam IADL Questionnaire. *Alzheimers Dement. (Amst).* 8, 26–35. doi: 10.1016/j.dadm.2017.03.002

Koo, T. K., and Li, M. Y. (2016). A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J. Chiropr. Med.* 15, 155–163.

Koster, N., Knol, D. L., Uitdehaag, B. M., Scheltens, P., and Sikkes, S. A. M. (2015). The sensitivity to change over time of the Amsterdam IADL Questionnaire((c)). *Alzheimers Dement.* 11, 1231–1240. doi: 10.1016/j.jalz.2014.10.006

Lahr, D., Beblo, T., and Hartje, W. (2007). Cognitive performance and subjective complaints before and after remission of major depression. *Cogn. Neuropsychiatry* 12, 25–45. doi: 10.1080/13546800600714791

Lawton, M. P., and Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 9, 179–186. doi: 10.1093/geront/9.3_part_1.179

Loewenstein, D. A., Arguelles, S., Bravo, M., Freeman, R. Q., Arguelles, T., Acevedo, A., et al. (2001). Caregivers' judgments of the functional abilities of the Alzheimer's disease patient: a comparison of proxy reports and objective measures. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 56, 78–84. doi: 10.1093/geronb/56.2.p78

Magaziner, J., Bassett, S. S., Hebel, J. R., and Gruber-Baldini, A. (1996). Use of proxies to measure health and functional status in epidemiologic studies of community-dwelling women aged 65 years and older. *Am. J. Epidemiol.* 143, 283–292. doi: 10.1093/oxfordjournals.aje.a008740

Marshall, G. A., Aghjayan, S. L., Dekhtyar, M., Locascio, J. J., Jethwani, K., Amariglio, R. E., et al. (2017). Activities of daily living measured by the Harvard Automated Phone Task track with cognitive decline over time in non-demented elderly. *J. Prev. Alzheimers Dis.* 4, 81–86. doi: 10.14283/jpad.2017.10

Marshall, G. A., Amariglio, R. E., Sperling, R. A., and Rentz, D. M. (2012). Activities of daily living: where do they fit in the diagnosis of Alzheimer's disease? *Neurodegener. Dis. Manag.* 2, 483–491. doi: 10.2217/nmt.12.55

Marshall, G. A., Sikkes, S. A. M., Amariglio, R. E., Gatchel, J. R., Rentz, D. M., Johnson, K. A., et al. (2020). Instrumental activities of daily living, amyloid, and cognition in cognitively normal older adults screening for the A4 Study. *Alzheimers Dement. (Amst).* 12:e12118. doi: 10.1002/dad2.12118

Nosheny, R. L., Camacho, M. R., Jin, C., Neuhaus, J., Truran, D., Flenniken, D., et al. (2020). Validation of online functional measures in cognitively impaired older adults. *Alzheimers Dement.* 16, 1426–1437. doi: 10.1002/alz.12138

Nosheny, R. L., Jin, C., Neuhaus, J., Insel, P. S., Mackin, R. S., Weiner, M. W., et al. (2019). Study partner-reported decline identifies cognitive decline and dementia risk. *Ann. Clin. Transl. Neurol.* 6, 2448–2459. doi: 10.1002/acn3.50938

Okonkwo, O. C., Wadley, V. G., Griffith, H. R., Belue, K., Lanza, S., Zamrini, E. Y., et al. (2008). Awareness of deficits in financial abilities in patients with mild cognitive impairment: going beyond self-informant discrepancy. *Am. J. Geriatr. Psychiatry* 16, 650–659. doi: 10.1097/JGP.0b013e31817e8a9d

Ostbye, T., Tyas, S., McDowell, I., and Koval, J. (1997). Reported activities of daily living: agreement between elderly subjects with and without dementia and their caregivers. *Age Ageing* 26, 99–106. doi: 10.1093/ageing/26.2.99

Pol, M. C., Buurman, B. M., de Vos, R., and de Rooij, S. E. (2011). Patient and proxy rating agreements on activities of daily living and the instrumental activities of daily living of acutely hospitalized older adults. *J. Am. Geriatr. Soc.* 59, 1554–1556. doi: 10.1111/j.1532-5415.2011.03514.x

Pudaric, S., Sundquist, J., and Johansson, S.-E. (2003). Country of birth, instrumental activities of daily living, self-rated health and mortality: a Swedish population-based survey of people aged 55–74. *Soc. Sci. Med.* 56, 2493–2503. doi: 10.1016/s0277-9536(02)00284-8

R Core Team (2020). *R: A Language And Environment For Statistical Computing*. 2 Edn. Vienna: R Foundation for Statistical Computing.

Ready, R. E., Ott, B. R., and Grace, J. (2004). Validity of informant reports about AD and MCI patients' memory. *Alzheimer Dis. Assoc. Dis.* 18, 11–16. doi: 10.1097/00002093-200401000-00003

Reise, S. P., and Waller, N. G. (2009). Item response theory and clinical measurement. *Annu. Rev. Clin. Psychol.* 5, 27–48.

Scheel-Hincke, L. L., Moller, S., Lindahl-Jacobsen, R., Jeune, B., and Ahrenfeldt, L. J. (2020). Cross-national comparison of sex differences in ADL and IADL in Europe: findings from SHARE. *Eur. J. Ageing* 17, 69–79. doi: 10.1007/s10433-019-00524-y

Sikkes, S. A. M., de Lange-de Klerk, E. S., Pijnenburg, Y. A. L., Gillissen, F., Romkes, R., Knol, D. L., et al. (2012). A new informant-based questionnaire for instrumental activities of daily living in dementia. *Alzheimers Dement.* 8, 536–543. doi: 10.1016/j.jalz.2011.08.006

Sikkes, S. A. M., de Lange-de Klerk, E. S., Pijnenburg, Y. A. L., Scheltens, P., and Uitdehaag, B. M. (2009). A systematic review of Instrumental Activities of Daily Living scales in dementia: room for improvement. *J. Neurol. Neurosurg. Psychiatry* 80, 7–12. doi: 10.1136/jnnp.2008.155838

Sikkes, S. A. M., and De Rotrou, J. (2014). A qualitative review of instrumental activities of daily living in dementia: what's cooking? *Neurodegener. Dis. Manag.* 4, 393–400. doi: 10.2217/nmt.14.24

Sikkes, S. A. M., Knol, D. L., Pijnenburg, Y. A. L., de Lange-de Klerk, E. S., Uitdehaag, B. M., and Scheltens, P. (2013a). Validation of the Amsterdam IADL Questionnaire(c), a new tool to measure instrumental activities of daily living in dementia. *Neuroepidemiology* 41, 35–41. doi: 10.1159/000346277

Sikkes, S. A. M., Pijnenburg, Y. A. L., Knol, D. L., de Lange-de Klerk, E. S., Scheltens, P., and Uitdehaag, B. M. (2013b). Assessment of instrumental activities of daily living in dementia: diagnostic value of the Amsterdam Instrumental Activities of Daily Living Questionnaire. *J. Geriatr. Psychiatry Neurol.* 26, 244–250. doi: 10.1177/0891988713509139

Slot, R. E. R., Sikkes, S. A. M., Berkhof, J., Brodaty, H., Buckley, R., Cavedo, E., et al. (2019). Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. *Alzheimers Dement.* 15, 465–476. doi: 10.1016/j.jalz.2018.10.003

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 280–292. doi: 10.1016/j.jalz.2011.03.003

Starkstein, S. E., Jorge, R., Mizrahi, R., and Robinson, R. G. (2006). A diagnostic formulation for anosognosia in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 77, 719–725. doi: 10.1136/jnnp.2005.085373

Steward, K. A., Kennedy, R., Erus, G., Nasrallah, I. M., and Wadley, V. G. (2019). Poor awareness of IADL deficits is associated with reduced regional brain volume in older adults with cognitive impairment. *Neuropsychologia* 129, 372–378. doi: 10.1016/j.neuropsychologia.2019.04.023

Tabert, M. H., Albert, S. M., Borukhova-Milov, L., Camacho, Y., Pelton, G., Liu, X., et al. (2002). Functional deficits in patients with mild cognitive impairment: prediction of AD. *Neurology* 58, 758–764. doi: 10.1212/wnl.58.5.758

Van Mierlo, L. D., Wouters, H., Sikkes, S. A. M., Van der Flier, W. M., Prins, N. D., Bremer, J. A. E., et al. (2017). Screening for mild cognitive impairment and dementia with automated, anonymous online and telephone cognitive self-tests. *J. Alzheimers Dis.* 56, 249–259. doi: 10.3233/JAD-160566

Villeneuve, S. C., Houot, M., Cacciamani, F., Verrijp, M., Dubois, B., Sikkes, S., et al. (2019). Latent class analysis identifies functional decline with Amsterdam IADL in preclinical Alzheimer's disease. *Alzheimers Dement. (N Y).* 5, 553–562. doi: 10.1016/j.trci.2019.08.009

Visser, L. N. C., Dubbelman, M. A., Verrijp, M., Wanders, L., Pelt, S., Zwan, M. D., et al. (2021). The Cognitive Online Self-Test Amsterdam (COST-A): establishing norm scores in a community-dwelling population. *Alzheimers Dement. (Amst).* 13:e12234. doi: 10.1002/dad2.12234

Wadley, V. G., Harrell, L. E., and Marson, D. C. (2003). Self- and informant report of financial abilities in patients with Alzheimer's disease: reliable and valid? *J. Am. Geriatr. Soc.* 51, 1621–1626. doi: 10.1046/j.1532-5415.2003.51514.x

Weinberger, M., Samsa, G. P., Schmader, K., Greenberg, S. M., Carr, D. B., and Wildman, D. S. (1992). Comparing proxy and patients' perceptions of patients' functional status: results from an outpatient geriatric clinic. *J. Am. Geriatr. Soc.* 40, 585–588. doi: 10.1111/j.1532-5415.1992.tb02107.x

Zanetti, O., Geroldi, C., Frisoni, G. B., Bianchetti, A., and Trabucchi, M. (1999). Contrasting results between caregiver's report and direct assessment of activities of daily living in patients affected by mild and very mild dementia: the contribution of the caregiver's personal characteristics. *J. Am. Geriatr. Soc.* 47, 196–202. doi: 10.1111/j.1532-5415.1999.tb04578.x

Zoller, A. S., Gaal, I. M., Royer, C. A., Locascio, J. J., Amariglio, R. E., Blacker, D., et al. (2014). SIST-M-IR activities of daily living items that best discriminate clinically normal elderly from those with mild cognitive impairment. *Curr. Alzheimer Res.* 11, 785–791. doi: 10.2174/1567205011081409101222220

Zwan, M. D., van der Flier, W. M., Cleutjens, S., Schouten, T. C., Vermunt, L., Jutten, R. J., et al. (2021). Dutch Brain Research Registry for study participant recruitment: design and first results. *Alzheimers Dement. (N Y).* 7:e12132. doi: 10.1002/trc2.12132

Conflict of Interest: The authors declare that this study received funding from Stichting Stoffels-Hornstra. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

frontiers in Aging Neuroscience

BRIEF RESEARCH REPORT
published: 13 January 2022
doi: 10.3389/fnagi.2021.781426

Awareness for People With Alzheimer's Disease: Profiles and Weekly Trajectories

*Amandine Mayelle[1], Capucine Hazebrouck[2], Mohamad El Haj[3,4,5], Daniel C. Mograbi[6,7] and Pascal Antoine[1]**

[1] Univ. Lille, CNRS, UMR 9193—SCALab—Sciences Cognitives et Sciences Affectives, Lille, France, [2] Etablissements Pour Personnes Âgées Dépendantes La Colombe, Roncq and L'Orée du Monde, Halluin, France, [3] Nantes Université, Univ Angers, Laboratoire de Psychologie des Pays de la Loire (LPPL—EA 4638), Nantes, France, [4] Unité de Gériatrie, Centre Hospitalier de Tourcoing, Tourcoing, France, [5] Institut Universitaire de France, Paris, France, [6] Pontifical Catholic University, Rio de Janeiro, Brazil, [7] Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

Objective: To understand awareness and fluctuations of awareness in Alzheimer's disease (AD), it is fruitful to consider the objects of awareness, e.g., cognitive functioning or recognition of the disease, as well as the mechanisms and modes of expression underlying awareness. With a holistic and discourse-centered approach, we aimed to identify different awareness profiles and test whether these profiles were stable or whether transitions from one profile to another occurred over short time intervals.

Methods: Twenty-eight residents of nursing homes with a diagnosis of AD participated in four semistructured interviews at biweekly intervals. These interviews were cluster analyzed to determine profiles of awareness. A Markov chain was applied to model their fluctuation.

Results: Five awareness profiles were observed that differed in terms of objects and underlying processes. Awareness proved to be quite stable for four of the five profiles. Interindividual variability in awareness was also observed through numerous different trajectories that were identified.

Discussion: Self-awareness and disease awareness are characterized by profiles that vary subtly between individuals. Fluctuations in awareness underscore the need to employ assessment intervals that closely reflect daily life in institutions.

Keywords: Alzheimer's disease, anosognosia, awareness, temporal trajectory, profiles

OPEN ACCESS

Edited by:
Bernard Jimmy Hanseeuw, Cliniques Universitaires Saint-Luc, Belgium

Reviewed by:
Federica Cacciamani, INSERM U1127 Institut du Cerveau et de la Moelle Épinière (ICM), France
Geoffroy Gagliardi, Brigham and Women's Hospital and Harvard Medical School, United States

***Correspondence:**
Pascal Antoine
pascal.antoine@univ-lille.fr

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *22 September 2021*
Accepted: *20 December 2021*
Published: *13 January 2022*

Citation:
Mayelle A, Hazebrouck C, El Haj M, Mograbi DC and Antoine P (2022) Awareness for People With Alzheimer's Disease: Profiles and Weekly Trajectories. Front. Aging Neurosci. 13:781426. doi: 10.3389/fnagi.2021.781426

INTRODUCTION

Lack of awareness, also known as anosognosia, refers to the difficulties experienced by patients with certain neurological conditions, including Alzheimer's disease (AD), in acknowledging their condition, symptoms and changes (Mograbi and Morris, 2018). According to Clare (2010), awareness in people with severe dementia is the ability to hold a reasonable or realistic perception or appraisal of, and/or respond accordingly to, a given aspect of their environment, situation, functioning or performance. Studies have sought to assess the progression of awareness of disease through cross-sectional or longitudinal designs.

The main finding of cross-sectional studies has been that lack of awareness increases as AD progresses (Starkstein et al., 2006; Maki et al., 2012; Mograbi et al., 2012; Conde-Sala et al., 2014; Baptista et al., 2019). A decline in awareness has been observed independent of the type of evaluation used (e.g., comparison of a patient and a relative, Starkstein et al., 2006; Maki et al., 2012; Conde-Sala et al., 2014; Baptista et al., 2019; the prediction-performance paradigm, Mograbi et al., 2012) as well as the stage of disease studied. However, the examination of a narrow time frame under a cross-sectional design does not allow potential fluctuations to be discerned over a stage of life that extends over years and months. To examine a time frame that more closely reflects what is experienced in institutions, some studies have employed a longitudinal perspective.

Similar to the cross-sectional studies, longitudinal studies have mainly observed an increased lack of awareness over time (McDaniel et al., 1995; Aalten et al., 2006; Clare and Wilson, 2006; van Vliet et al., 2013; Turró-Garriga et al., 2016; Sousa et al., 2017; Hanseeuw et al., 2020). This progressive loss of awareness is not the only pattern that has been observed. Indeed, Clare and Wilson (2006) and Turró-Garriga et al. (2016) observed a progressive loss of awareness for some participants and stability in awareness, albeit to a lesser extent, for others. Recently, Dourado et al. (2016) observed that nearly a quarter of the sample exhibited a deficit at the 1-year point but found an improvement in awareness for 12.3% of the sample. Taken together, these longitudinal studies indicate different patterns of change in awareness of disease. When the amount of time between measurements is reduced, the observed variation in patterns tends to increase, thereby raising the question of whether the intervals of assessment should be further reduced (e.g., monthly, weekly, or even daily follow-up). Some studies have reported the daily experiences of relatives (Clare and Woods, 2005; Walmsley and McCormack, 2017) and reported "moments of lucidness," "flashes," or alternation between "moments of presence and moments of absence" (Rozotte, 2001). In their qualitative study, Wawrziczny et al. (2016) highlighted the changing nature of the symptoms and the discourse of spouses with dementia about their symptoms. If the discourse of people with the disease evolves on a small time scale, a caregiving spouse can be expected to see changes from 1 day to the next, or family members visiting a loved one in a nursing home can be expected to see changes in discourse from week to week or month to month. These discourses may reflect varying awareness levels of the patient. To our knowledge, no study has measured awareness of disease at such short intervals.

Previous cross-sectional and longitudinal studies have had limitations, such as the use of different samples, in the comparison of stages and long intervals between evaluations. The occurrence of daily fluctuations reported in some studies was based only on comparative assessments. Indeed, another limitation is the quasi-systematic use of comparative methods to evaluate awareness, such as with the use of clinical ratings (McDaniel et al., 1995; van Vliet et al., 2013), the prediction-performance paradigm (Mograbi et al., 2012; Avondino and Antoine, 2015), and/or comparison of a patient's assessment with that of a relative (Starkstein et al., 2006; Baptista et al., 2019; Hanseeuw et al., 2020). Although the information gained from such comparative methods is necessary and useful for understanding what the person with AD experiences, the perspective of the individual, what he or she understands about him- or herself and his or her evolution, and how this is expressed in his or her discourse deserve to be further explored. Finally, these evaluations tend to consider only one facet of awareness, namely, objects, the "what" that the evaluation is based on. In dementia research, several studies have even emphasized the need to distinguish between objects of awareness (Dourado et al., 2007; Markova et al., 2014), for example, by differentiating awareness of cognitive functioning and health condition, activities of daily living, emotional state, social functioning, and relationships (Lacerda et al., 2018). In the present study, objects refers to the basis of changes and new information (emotions, body, communication, autonomy, identity, cognitive abilities, memory, and AD) perceived by people with AD (Mayelle et al., 2019). Furthermore, O'Shaughnessy et al. (2021) stated that awareness is a multidimensional construct requiring a holistic approach. The phenomenon of awareness appears to be more than merely a "what" but rather a synergy associating the "what" (i.e., the objects of awareness) with the "how" in terms of the mechanisms and modes of expression underlying awareness (Mayelle et al., 2020).

Two key issues must be addressed. The first is the need to reduce the intervals of the observation of awareness to better approximate the patient's experiences, including the investigation of objects, mechanisms, and modes of expression. The second is the need to obtain a sense of awareness as experienced by people with AD through a person-centered approach, i.e., based on their discourse reflecting their own perceptions and the meaning they assign to those perceptions. We propose two hypotheses. The first concerns the observation of different "profiles" of awareness characterized by the awareness of objects and the presence of mechanisms and modes of expression. While we hypothesize that both fully "aware" and "unaware" profiles will be observed, we also expect to observe more nuanced profiles that exhibit differences in terms of awareness of objects, mechanisms and modes of expression. The second hypothesis concerns fluctuations in awareness. Based on the patterns of fluctuations observed in longitudinal studies, we hypothesize that the profiles of awareness identified will exhibit three different types of patterns: deficit, stability, or improvement.

MATERIALS AND METHODS

Design

This observational study was conducted at seven nursing homes in the Hauts-de-France region. Written consent was obtained for each participant. The ethics committee of the University of Lille approved the study (2018-267-S58).

Participants

To be included in the study, the participants had to have resided at the nursing home for at least the previous 3 months. This inclusion criterion allowed the influence of adaptation to a new environment on awareness to be avoided. All participants had a diagnosis of AD dementia by an experienced neurologist

or geriatrician based on the criteria of the National Institute on Aging–Alzheimer's Association (McKhann et al., 2011). The participants also had to speak French or at least be capable of communicating in French for several minutes with the investigator.

The sample contained 28 participants [mean (M) age: 85.21; standard deviation (SD): 6.71]. Of the participants, 23 were women (aged 70–96 years, *M*: 86.04 years; *SD*: 5.83) and five were men (aged from 66 to 90 years, *M*: 85.25 years, *SD*: 5.25). The mean Mini Mental State Exam (MMSE) score was 13.68 (*SD*: 4.29). The majority of participants were at a moderate stage of dementia ($n = 21$). A minority were at a mild ($n = 2$) or severe ($n = 5$) stage.

Procedure

Each participant was engaged in a series of four semistructured interviews based on systematic themes such as mood, emotions, well-being (physical and psychological), daily life, self-perception (body, personality), family, friends, relationship changes, cognitive functions, memory loss, elderly experience, disease and expectations for the future. The main questions were focused on personal experience, such as "How are you?" "What are you doing today?" and "Tell me about yourself." Moreover, the investigator used mainly reformulations or repetitions. The objective of the interview was to follow only the participants' experience and what they were able to say about it. For each participant, all four interviews were conducted, transcribed and rated by one of two trained psychologists.

Measure

Mini Mental State Exam

Cognitive functioning was assessed with the MMSE (Folstein et al., 1975), which is a test of spatiotemporal orientation, attention and calculation as well as memory, language and visual construction.

Awareness of Self and Disease Assessment

The Awareness of Self and Disease Assessment (ASDA) scale provides an evaluation of awareness of self and the disease that is centered on the person with AD (for a detailed description, see Mayelle et al., 2019). The ASDA is designed to be as close as possible to the subjective experience of having the disease. Each interview carried out with the ASDA was evaluated based on 22 items (see **Table 1**) in three categories: objects (9), mechanisms (5), and modes of expression (8). Objects refers to the basis of changes and new information (emotions, body, communication, autonomy, identity, cognitive abilities, memory, and AD) perceived by people with AD. Mechanisms refers to processes of awareness (e.g., observation of the environment, perception of the expressions of others, comparison between the past and the present, metacognition and confrontation with difficulties). Modes of expression are how people express their awareness (denial, expression of doubts, expression of changes with a causal attribution, a self-description, a self-assessment or a need).

Each item of the mechanisms and modes of expression categories was rated on a six-point Likert scale (1: "Minimally present," 2: "Slightly present," 3: "Mildly present," 4: "Moderately present," 5: "Strongly present," 6: "Extremely present"). Each item of the object category was also rated according to a six-point Likert scale (1: "Strong unawareness," 2: "Mild unawareness," 3: "Slight unawareness," 4: "Slight awareness, 5: "Mild awareness," 6: "Strong awareness"). A high rating was associated with a high level of awareness. For each category, the overall score, between 1 and 6, is the mean of its items. Cronbach's alpha was high (from0.77 to 0.86). The ASDA does not presently provide a cutoff

TABLE 1 | The 22 items of the Awareness of Self and Disease Assessment (ASDA).

Objects	1. Environment	Changes in the environment
	2. Emotions	All new emotions
	3. Body	Changes in sensations and physical abilities
	4. Communication	Difficulties with verbal treatment information and verbalization
	5. Autonomy	Difficulties during activities of daily living
	6. Identity changes	Personality/mental/social status changes
	7. Loss of cognitive abilities	Difficulties in concentration and location in space and time
	8. Memory	Difficulties in learning and remembering information
	9. Disease	Awareness of being a person with Alzheimer's disease
Mechanisms	1. Observation of the environment	Awareness of changes with environment observation
	2. Perception of the looks of others	Awareness of changes in the looks/discourses/actions of others
	3. Comparison between the past and the present	Awareness of differences in physical and psychological state and loss of independence and autonomy
	4. Metacognition	Discourse on changes during a metarepresentation/self-analysis
	5. Confrontation of difficulties	Awareness of changes by observation of decreased physical and psychological abilities
Modes of expression	1. Denial	Opposition, denial of changes and/or causes
	2. Bewilderment	Expression of doubts/hesitations about daily life and the future
	3. Attribution	Expression of changes with a causal attribution
	4. Description	Expression of changes with a self-description
	5. Judgment	Expression of changes with a self-assessment
	6. Recognition of the need for help	Expression of changes in recognizing the need for help during activities of daily living.
	7. Use of coping strategies	Expression of changes by using coping strategies
	8. Confirmation of the disease	Expression of changes by recognizing Alzheimer's disease

score; rather, the objective is to create a "profile of awareness" for each person with AD. The ASDA is a subjective measure based only on what the participant is able to say. Consequently, this method resulted in missing values, recorded as "Not evaluated." Overall, the rate of missing values was 14.85%, reflecting objects, mechanisms or modes of expression that could not be scored during an interview.

Data Analysis

The statistical analyses were carried out with R software (version 3.5.2). As a preliminary step, the "FactoMireR" and "MissMDA" packages allowed the description of the data and imputation for the missing values. A cluster analysis [i.e., a hierarchical ascendant classification (HAC)] was carried out to determine the different profiles of awareness. The aim was to ensure that the interviews within a profile were as similar as possible and that the profiles were as contrasting as possible. To do so, the HAC was used to measure the similarity (or, conversely, the distance) between the interviews in pairs based on the scores of the 22 items. All these measures together constitute a distance matrix. Two identical interviews will have a distance of zero. The more different the interviews are, the greater their distance. The HAC thus makes it possible to iteratively position the interviews in relation to each other to produce a dendrogram. The classification is hierarchical because it produces increasingly larger profiles, including subgroups within them. This dendrogram is then analyzed to produce the most easily interpretable organization of profiles.

The second analysis used a Markov chain method and was performed with the "Markovchain" package. This analysis allowed the probabilities of a transition from one profile to another to be quantified and modeled. Awareness is considered to be a dynamic system composed of states and transitions between these states. The states were defined by the profiles identified in the previous analysis, and we then attempted to measure the probability that each state (profile) would remain stable the next time or evolve toward any of the other possible states (profiles).

RESULTS

Profiles of Awareness

The analyses included all 112 interviews conducted with the 28 residents. We identified five clusters (**Table 2**).

Profile 1 was characterized by a high presence of mechanisms (M = 4.44, SD = 0.511), a moderate presence of modes of expression (M = 3.014, SD = 0.603) and a moderate awareness of objects (M = 3.728, SD = 0.469). Profile 2 was characterized by a low presence of mechanisms (M = 2.37, SD = 0.489), a moderate presence of modes of expression (M = 2.426, SD = 0.516), and a moderate awareness of objects (M = 3.148, SD = 0.465). Profile 3 was characterized by a moderate presence of mechanisms (M = 3.35, SD = 5.83), a low presence of modes of expression (M = 1.982, SD = 3.56), and a low awareness of objects (M = 2.77, SD = 0.367). Profile 4 was characterized by a high presence of mechanisms (M = 4.733, SD = 7.11) and modes of expression (M = 3.923, SD = 0.65) as well as a high level of awareness of objects. This profile represented a preserved awareness of self and disease. Profile 5 was characterized by a low presence of mechanisms (M = 1.944, SD = 1.17) and modes of expression (M = 1.59, SD = 0.625) and a low level of awareness of objects. Profile 5 represented a lack of awareness and thus was the opposite of profile 4.

TABLE 2 | Summary of the clusters derived from the hierarchical ascendant classification.

		HAC				
		Profile 1	**Profile 2**	**Profile 3**	**Profile 4**	**Profile 5**
Number of interviews		18	27	28	21	18
Mechanisms	*Mean*	4.44	2.37	3.35	4.73	1.94
	SD	0.511	0.49	0.58	0.711	1.17
Objects	*Mean*	3.73	3.15	2.77	4.56	1.98
	SD	0.47	0.47	0.37	0.45	0.58
Modes of expression	*Mean*	3.01	2.43	1.98	3.92	1.59
	SD	0.60	0.52	0.36	0.65	0.63

Fluctuations in Profiles as Modeled by a Markov Chain

The Markov chain used to model the biweekly fluctuations in the awareness of self and the disease is represented in **Figure 1**.

The modeling showed that over the 2-week period, awareness proved to be quite stable for four of the five profiles [probability (P) from 0.47 to 0.87], particularly for individuals who made abundant use of mechanisms, who made moderate use of modes of expression and who had a moderate level of awareness. In contrast, the profile corresponding to the lowest level of awareness appeared to be more transient and to have a low probability of stability (P = 0.20).

Furthermore, numerous intercluster transitions were observed. For example, profile 3 (moderate use of mechanisms, low use of modes of expression, and a low level of awareness of self and disease) appeared as a stable profile while connected with each of the other profiles (P = 0.06–0.20). The profiles tended to be connected with one another; that is, individuals passed from one profile to another, either in a bidirectional manner, such as between profile 4 and profile 3 (P = 0.12), or in a more unidirectional manner, such as between profile 4 and profile 1 (P = 0.07 and 0.24). Regarding the latter example, a person had a greater probability of changing from profile 4 to 1 than from profile 1–4. The highest probability of changing from one profile to another was between profile 5 and profile 2 (P = 0.60). Beyond the stability of their profiles, the participants in the study had a high probability of progressing from a low level of awareness of disease (with low use of both mechanisms and modes of expression) toward a low/moderate level of awareness (with moderate use of modes of expression and low use of mechanisms).

Finally, some profiles, such as profile 5 and profile 1, did not share a relationship,. That is, a person with a low level of awareness of disease (with low use of mechanisms and modes of expression) did not progress to a moderate level of awareness

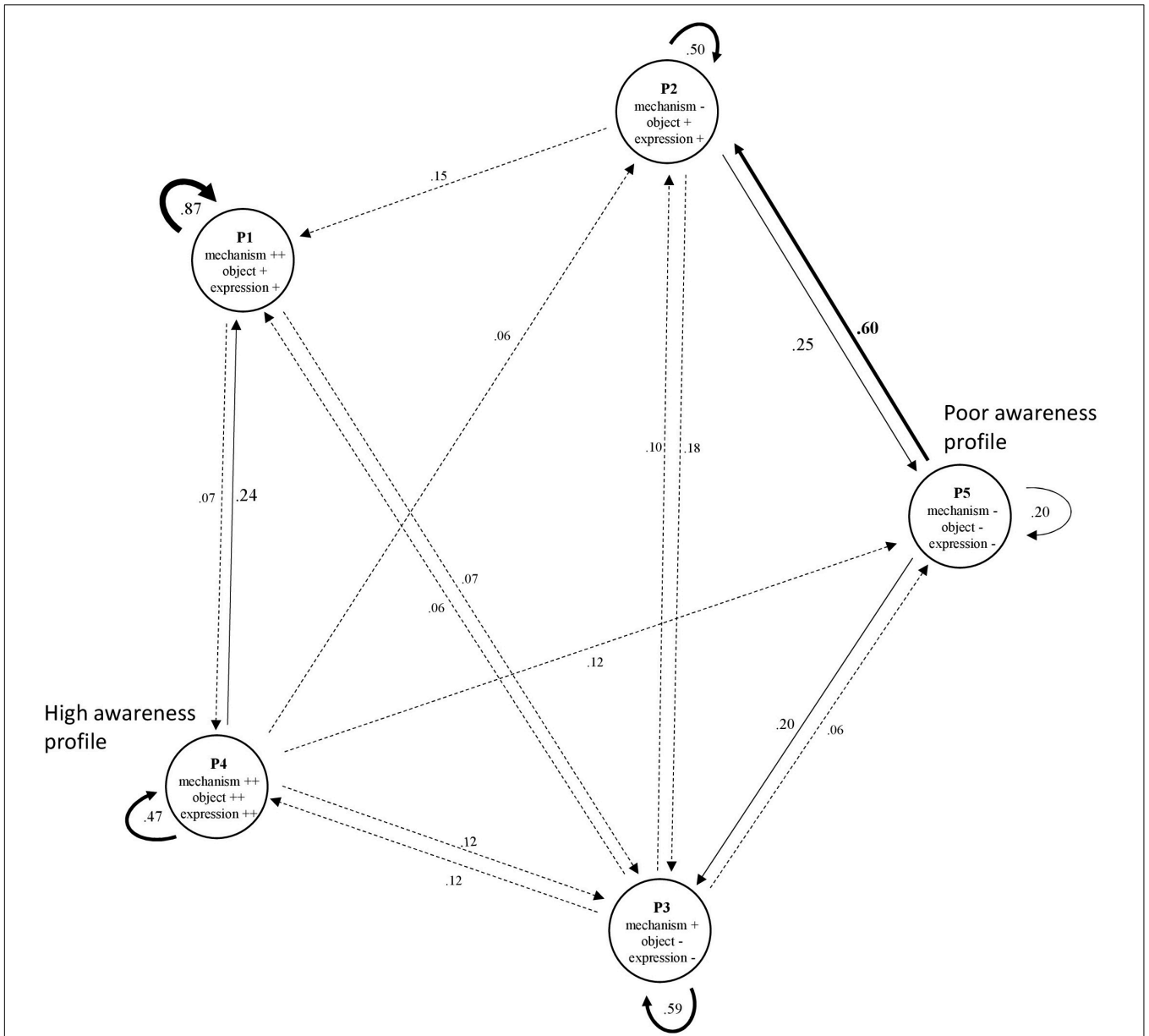


FIGURE 1 | Modeling of fluctuations in profiles of awareness by Markov chain. P, Profile; Mech, Mechanisms; Exp, Modes of expression. For ease of reading, the connections are coded according to the probability of the transition (dashed < 0.2; normal < 0.4 and bold > 0.4), as are the font sizes of the coefficients. The absence of a connection between two profiles is explained by the low occurrence or absence of a transition.

(with moderate use of modes of expression and a high level of use of mechanisms), and vice versa.

Focus on Individual Weekly Fluctuations in Awareness

It was possible to observe individual fluctuations for each of the 28 participants. **Table 3** shows the profile assessed at the four interview times for each resident and, in summary, their number of profiles and number of transitions.

The main finding is the interindividual variability in the evolution of awareness, with 24 distinct trajectories observed.

Complete stability (i.e., 0 transitions) was observed in six participants (approximately 21% of the sample) in profiles 2–5. In contrast, 6 participants switched at each interview among 2–4 profiles. The remaining 16 residents (57%) made one (n = 6) or two (n = 10) transitions.

DISCUSSION

Research on awareness in AD provides information regarding its heterogeneity and temporality. However, it does not allow

TABLE 3 | Individual fluctuations for each of the participants in the four stages.

Participants	Time 1	Time 2	Time 3	Time 4	Nb of profiles	Nb of changes
1	2	2	2	2	1	0
2	2	2	2	2	1	0
3	3	3	3	3	1	0
4	3	3	3	3	1	0
5	4	4	4	4	1	0
6	5	5	5	5	1	0
7	1	1	4	4	2	1
8	3	4	4	4	2	1
9	4	4	5	5	2	1
10	4	4	4	2	2	1
11	5	5	2	2	2	1
12	5	3	3	3	2	1
13	1	1	3	1	2	2
14	2	2	5	2	2	2
15	2	5	2	2	2	2
16	3	1	1	3	2	2
17	3	3	2	3	2	2
18	5	3	5	5	2	2
19	4	1	4	1	2	3
20	5	2	5	2	2	3
21	1	1	2	3	3	2
22	1	1	4	3	3	2
23	2	2	3	1	3	2
24	3	1	1	4	3	2
25	3	2	5	3	3	3
26	4	2	1	4	3	3
27	4	3	2	3	3	3
28	3	5	2	1	4	3

appreciation of the heterogeneity of the processes of awareness (Mayelle et al., 2019, 2020) and daily fluctuations in awareness. The first part of this work involved the observation of different profiles of awareness characterized by the awareness of objects and the presence of mechanisms and modes of expression. The second part of this work involved the observation of weekly fluctuations in these aspects.

We first hypothesized that profiles of awareness would range from extremes (i.e., aware vs. unaware) to more mixed profiles. We observed five different profiles, two of which indicated complete awareness and lack of awareness. The other three profiles differed mainly in terms of the use (i.e., frequency and adaptation) of mechanisms and modes of expression of awareness. Based on these results, we were able to confirm that awareness in AD is heterogeneous, highlighting distinct levels of awareness both in terms of objects (the "what") and processes (the "how") that characterize the disease (Mayelle et al., 2020).

In the second part of the study, our results were consistent with prior results, and they provide evidence of the non-linearity of awareness (Lacerda et al., 2020). While we were able to show that each participant exhibited a unique temporal trajectory of fluctuation(s) in awareness, the analysis of the transitions between the profiles revealed a number of trends. We observed that the profiles of awareness tended to remain stable between measurement times. However, the profiles could improve or worsen for certain components (i.e., objects, mechanisms, and/or modes of expression). Furthermore, while a high general level of awareness could become very low in the short period between measurements, a low level of awareness could not become very high.

Similarly, we noted that the highest probability of change was related to a slight improvement in the level of awareness of objects and the presence of modes of expression. For this particular fluctuation, we proposed three interpretations.

First, one perspective on this improvement is the concept of the petrified self (Mograbi et al., 2009). It is possible that when confronted with a mistake or criticism, a resident became temporarily aware of his or her condition or its evolution. However, the long-term integration of this new information would fail, resulting in a return to a lower level of awareness at the next interview.

Second, after returning to the interviews, we assumed that this fluctuation was specifically linked to events and/or changes in the environment and the participant's daily life (e.g., a room change). A person exhibits a specific profile of awareness that is influenced by an environmental change. Once this change becomes established, the person returns to the initial level, which translates into a deficit followed by an improvement. This interpretation particularly reflects changes in the integration and rejection of the disease as characteristic of the self (Pearce et al., 2002; Frazer et al., 2012). O'Shaughnessy et al. (2021) suggested that people with severe AD may not demonstrate awareness, not because they are unable to but rather because environmental factors are not conducive to expressing awareness.

Third, the relevant interviews tended to highlight the influence of the investigator and his or her attitude toward awareness. When a person has disorganized speech, the practices of reformulation, the verbalization of a thought, or the stimulation of verbal exchanges appear to help him or her express him- or herself in a more suitable and coherent manner, thereby restoring meaning (Ducato et al., 2013). According to the ASDA (e.g., **Table 1**), this process can be translated, for example, into the expression of changes with a self-description, the expression of doubts about daily life and the future, or the expression of a need for help. To best verify this effect, the ASDA could be made part of an interventional protocol employing dignity therapy (Martínez et al., 2017) or validation therapy (Neal and Barton Wright, 2003). These two approaches aim to support the person with AD with caring verbal expression to encourage him or her to integrate these events and give them meaning. A pre- and postintervention ASDA evaluation of awareness could quantify the effect of others' attitudes on awareness.

Our data allowed the modeling of fluctuations in awareness of disease that have often been studied from the perspective of patients' relatives (Rozotte, 2001; Clare and Woods, 2005; Walmsley and McCormack, 2017). The presentation of these profiles and their possible fluctuations to health professionals could allow these professionals to verbalize their daily experience in care and help them understand the relative instability of the patient's perspective and therefore the need to repeat the

interactions to understand the extent of that fluctuation. For example, the implementation of the methodology employed in the present study on a case-by-case basis in residential care facilities could allow caregivers to understand and then adjust to the reactions of people with AD while they provide support. Indeed, caregivers evolve in a reality that differs from that of the person with AD (Hertogh et al., 2004), and they can find themselves powerless when confronted with a refusal of care or only partial observance of treatment for which they do not understand all of the underlying processes (Fischer et al., 2019).

However, increasing the sample size appears to be necessary to reinforce the validation of the identified profiles of awareness. Such an increase in the sample size would also allow more clusters and hence more nuances in the profiles to be identified. Furthermore, an increase in the sample size would allow confirmation and increase the generalizability of the possible trajectories observed. Although the sample reflects the overrepresentation of women living in nursing homes, an increase in the number of male participants would allow verification of the impact of gender on awareness (Liu et al., 2017) and the distribution of the profiles. Indeed, the limitations of the study are linked mainly with the characterization of the sample and the impact of these parameters on the profiles of awareness and their possible fluctuations. As this was a pilot study, we essentially collected data centered on awareness without collecting information regarding education level, time since diagnosis or time living in a nursing home, the severity of the disease, neuropsychiatric symptoms (Yoon et al., 2017) or personality (Rankin et al., 2005). Now that this study has shown fluctuations in awareness, it is important to control, for example, the cognitive profile of the participants to understand the role played by these variables in the awareness profiles.

CONCLUSION

This study aimed to understand the awareness of self and disease in people with AD by adopting a perspective based on profiles rather than a single score. These profiles were studied on the basis of their fluctuations from a restricted temporal perspective. Multiple profiles and trajectories were identified, illustrating inter- and intraindividual variability in awareness. These results confirm the need to focus on the subjective experience of the person with assessment intervals that closely reflect his or her daily life.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the University of Lille (2018-267-S58). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM and PA were responsible for the conception and design of the study and responsible for the drafting of the manuscript. AM, CH, MEH, DM, and PA contributed to the collection and analysis of data. All authors critically revised the draft and approved the final version.

FUNDING

This work was supported by the LABEX (Excellence Laboratory, Program Investment for the Future), DISTALZ (Development of Innovative Strategies for a Transdisciplinary Approach to Alzheimer's disease), and the regional council of Hauts-de-France.

REFERENCES

Aalten, P., van Valen, E., de Vugt, M. E., Lousberg, R., Jolles, J., and Verhey, F. (2006). Awareness and behavioral problems in dementia patients: a prospective study. *Int. Psychogeriatr.* 18, 3–17. doi: 10.1017/S1041610205002772

Avondino, E., and Antoine, P. (2015). Heterogeneity of cognitive anosognosia and its variation with the severity of dementia in patients with Alzheimer's disease. *J. Alzheimer Dis.* 50, 89–99. doi: 10.3233/JAD-150496

Baptista, M. A. T., Santos, R. L., Kimura, N., Marinho, V., Simões, J. P., Laks, J., et al. (2019). Differences in awareness of disease between young-onset and late-onset dementia. *Alzheimer. Dis. Assoc. Disord.* 33, 129–135. doi: 10.1097/WAD.0000000000000299

Clare, L. (2010). Awareness in people with severe dementia: review and integration. *Aging Ment. Health* 14, 20–32. doi: 10.1080/13607860903421029

Clare, L., and Wilson, B. A. (2006). Longitudinal assessment of awareness in early-stage Alzheimer's disease using comparable questionnaire-based and performance-based measures: a prospective one-year follow-up study. *Aging. Ment. Health* 10, 156–165. doi: 10.1080/13607860500311888

Clare, L., and Woods, B. (2005). Awareness in dementia: a subject for scrutiny. *Aging Ment. Health* 9, 384–385. doi: 10.1080/13607860500142887

Conde-Sala, J. L., Reñé-Ramírez, R., Turró-Garriga, O., Gascón-Bayarri, J., Campdelacreu-Fumadó, J., Juncadella-Puig, M., et al. (2014). Severity of dementia, anosognosia, and depression in relation to the quality of life of patients with Alzheimer disease: discrepancies between patients and caregivers. *Am. J. Geriatr. Psychiatry* 22, 138–147. doi: 10.1016/j.jagp.2012.07.001

Dourado, M., Marinho, V., Soares, C., Engelhardt, E., and Laks, J. (2007). Awareness of disease in dementia development of a multidimensional rating scale. *Dement Neuropsychol.* 1, 74–80.

Dourado, M., Sousa, M. F. B., Santos, R. L., Neto, S., Nogueira, P. J., Belfort, M. L., et al. (2016). Quality of life in mild dementia: patterns of change in self and caregiver ratings over time. *Rev. Bras. Psiquiatr.* 38, 294–300. doi: 10.1590/1516-4446-2014-1642

Ducato, M.-G., Tabard, F., and Barbaroux, É (2013). Description du fonctionnement d'une unité Alzheimer en EHPAD. *NPG Neurol. Psychiatr. Gériatr.* 13, 210–216. doi: 10.1016/j.npg.2013.01.007

Fischer, A., Landeira-Fernandez, J., Sollero de Campos, F., and Mograbi, D. C. (2019). Empathy in Alzheimer's Disease: review of findings and proposed model. *J. Alzheimers. Dis.* 69, 921–933. doi: 10.3233/JAD-180730

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Frazer, S. M., Oyebode, J. R., and Cleary, A. (2012). How older women who live alone with dementia make sense of their experiences: an interpretative phenomenological analysis. *Dementia* 11, 677–693. doi: 10.1177/1471301211419018

Hanseeuw, B. J., Scott, M. R., Sikkes, S. A. M., Properzi, M., Gatchel, J. R., Salmon, E., et al. (2020). Evolution of anosognosia in alzheimer's disease and its relationship to amyloid. *Ann. Neurol.* 87, 267–280. doi: 10.1002/ana.25649

Hertogh, C. M. P. M., Anne Mei The, B., Miesen, B. M. L., and Eefsting, J. A. (2004). Truth telling and truthfulness in the care for patients with advanced dementia: an ethnographic study in Dutch nursing homes. *Soc. Sci. Med.* 59, 1685–1693. doi: 10.1016/j.socscimed.2004.02.015

Lacerda, I. B., Santos, R. L., Belfort, T., Neto, J. P. S., and Dourado, M. (2020). Patterns of discrepancies in different objects of awareness in mild and moderate Alzheimer's disease. *Aging Ment. Health* 24, 789–796. doi: 10.1080/13607863.2018.1544219

Lacerda, I. B., Santos, R. L., Belfort, T., Neto, J., and Dourado, M. (2018). Patterns of discrepancies in different objects of awareness in mild and moderate Alzheimer's disease. *Aging Ment. Health* 24, 789–796.

Liu, J., Abdin, E., Vaingankar, J. A., Shafie, S. B., Jeyagurunathan, A., Shahwan, S., et al. (2017). The relationship among unawareness of memory impairment, depression, and dementia in older adults with memory impairment in Singapore. *Psychogeriatrics* 17, 430–438. doi: 10.1111/psyg.12270

Maki, Y., Amari, M., Yamaguchi, T., Nakaaki, S., and Yamaguchi, H. (2012). Anosognosia: patients' distress and self-awareness of deficits in Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen.* 27, 339–345. doi: 10.1177/1533317512452039

Markova, I. S., Clare, L., Whitaker, C. J., Roth, I., Nelis, S. M., Martyr, A., et al. (2014). Phenomena of awareness in dementia: heterogeneity and its implications. *Conscious Cogn.* 25, 17–26. doi: 10.1016/j.concog.2014.01.008

Martínez, M., Arantzamendi, M., Belar, A., Carrasco, J. M., Carvajal, A., Rullán, M., et al. (2017). 'Dignity therapy', a promising intervention in palliative care: a comprehensive systematic literature review. *Palliat. Med.* 31, 492–509. doi: 10.1177/0269216316665562

Mayelle, A., El Haj, M., and Antoine, P. (2019). Awareness of Self and disease assessment: development and validation of a subjective measure in people with Alzheimer's disease. *J. Alzheimers Dis.* 71, 841–850. doi: 10.3233/JAD-190371

Mayelle, A., El Haj, M., and Antoine, P. (2020). "What" and "How": a new perspective for understanding unawareness in Alzheimer's disease through a combination of two perspectives. *Am. J. Alzheimers Dis. Other Dem.* 35:1533317520925333. doi: 10.1177/1533317520925333

McDaniel, K. D., Edland, S. D., and Heyman, A. (1995). Relationship between level of insight and severity of dementia in Alzheimer disease. CERAD clinical investigators. Consortium to establish a registry for Alzheimer's disease. *Alzheimer Dis. Assoc. Disord.* 9, 101–104. doi: 10.1097/00002093-199509020-00007

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., and Kawas, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Mograbi, D. C., and Morris, R. (2018). Anosognosia. *Cortex* 103, 385–386. doi: 10.1016/j.cortex.2018.04.001

Mograbi, D. C., Brown, R. G., and Morris, R. G. (2009). Anosognosia in Alzheimer's disease — the petrified self. *Conscious Cogn.* 18, 989–1003. doi: 10.1016/j.concog.2009.07.005

Mograbi, D. C., Brown, R. G., Salas, C., and Morris, R. G. (2012). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia* 50, 2075–2084. doi: 10.1016/j.neuropsychologia.2012.05.008

Neal, M., and Barton Wright, P. (2003). Validation therapy for dementia. *Cochr. Database Syst Rev.* 3:CD001394. doi: 10.1002/14651858.CD001394

O'Shaughnessy, N. J., Chan, J. E., Bhome, R., Gallagher, P., Zhang, H., Clare, L., et al. (2021). Awareness in severe Alzheimer's disease: a systematic review. *Aging Mental Health* 25, 602–612. doi: 10.1080/13607863.2020.1711859

Pearce, A., Clare, L., and Pistrang, N. (2002). Managing Sense of Self: Coping in the early stages of Alzheimer's disease. *Dementia* 1, 173–192. doi: 10.1177/147130120200100205

Rankin, K. P., Baldwin, E., Pace-Savitsky, C., Kramer, J. H., and Miller, B. L. (2005). Self awareness and personality change in dementia. *J. Neurol. Neurosurg. Psychiatry* 76, 632–639. doi: 10.1136/jnnp.2004.042879

Rozotte, C. (2001). Le concept de conscience au cśur des représentations sociales de la maladie d'Alzheimer étude des théories subjectives de l'intériorité psychique du patient. *Gérontol. Soc.* 24, 159–174. doi: 10.3917/gs.097.0159

Sousa, M. F. B., Santos, R. L., Simões, P., Conde-Sala, J. L., and Dourado, M. (2017). Discrepancies between Alzheimer's Disease patients' and caregivers' ratings about patients' quality of life: a 1-year observation study in Brazil. *Alzheimer Dis. Assoc. Disord.* 32, 240–246. doi: 10.1097/WAD.0000000000000232

Starkstein, S. E., Jorge, R., Mizrahi, R., and Robinson, R. G. (2006). A prospective longitudinal study of apathy in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 77, 8–11. doi: 10.1136/jnnp.2005.069575

Turró-Garriga, O., Garre-Olmo, J., Calvó-Perxas, L., Reñé-Ramírez, R., Gascón-Bayarri, J., and Conde-Sala, J. L. (2016). Course and determinants of anosognosia in Alzheimer's Disease: a 12-month follow-up. *J. Alzheimers Dis.* 51, 357–366. doi: 10.3233/JAD-150706

van Vliet, D., de Vugt, M. E., Köhler, S., Aalten, P., Bakker, C., Pijnenburg, Y. A. L., et al. (2013). Awareness and its association with affective symptoms in young-onset and late-onset Alzheimer disease: a prospective study. *Alzheimer Dis. Assoc. Disord.* 27, 265–271. doi: 10.1097/WAD.0b013e31826cffa5

Walmsley, B., and McCormack, L. (2017). Severe dementia: relational social engagement (RSE) during family visits. *Aging Mental Health* 21, 1262–1271. doi: 10.1080/13607863.2016.1220923

Wawrziczny, E., Antoine, P., Ducharme, F., Kergoat, M.-J., and Pasquier, F. (2016). Couples' experiences with early-onset dementia: an interpretative phenomenological analysis of dyadic dynamics. *Dementia* 15, 1082–1099. doi: 10.1177/1471301214554720

Yoon, B., Shim, Y. S., Hong, Y. J., Choi, S. H., Park, H. K., Park, S. A., et al. (2017). Anosognosia and its relation to psychiatric symptoms in early-onset Alzheimer disease. *J. Geriatr. Psychiatry Neurol.* 30, 170–177. doi: 10.1177/0891988717700508

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 21 January 2022
doi: 10.3389/fnagi.2021.802501

Episodic Memory Impairment Mediates the Loss of Awareness in Mild Cognitive Impairment

Geoffroy Gagliardi [1,2,3] and Patrizia Vannini [1,2,3] for the Alzheimer's Disease Neuroimaging Initiative*

[1] Neurology, Brigham and Women's Hospital, Boston, MA, United States, [2] Neurology, Massachusetts General Hospital, Boston, MA, United States, [3] Harvard Medical School, Cambridge, MA, United States

Introduction: Loss of awareness is a common symptom in Alzheimer's Disease (AD) and responsible for a significant loss of functional abilities. The mechanisms underlying loss of awareness in AD is unknown, although previous findings have implicated dysfunction of primary executive functioning (EF) or episodic memory (EM) to be the cause. Therefore, our main study objective was to explore the involvement of EF and EM dysfunction in amyloid-related loss of awareness across the clinical spectrum of AD.

Methods: A total of 895 participants (362 clinically normal [CN], 422 people with mild cognitive impairment [MCI] and 111 with dementia) from the Alzheimer's Disease Neuroimaging Initiative were used for the analyses. A sub-analysis was performed in 202 participants who progressed in their clinical diagnosis from CN to MCI or MCI to dementia as well as dementia patients. Mediation models were used in each clinical group with awareness (assessed with the Everyday Cognitive function questionnaire) as a dependent variable to determine whether EF and/or EM would mediate the effect of amyloid on awareness. We also ran these analyses with subjective and informant complaints as dependent variables. Direct correlations between all variables were also performed.

Results: We found evidence for a decline in awareness across the groups, with increased awareness observed in the CN group and decreased awareness observed in the MCI and dementia groups. Our results showed that EM, and not EF, partially mediated the relationship between amyloid and awareness such that greater amyloid and lower EM performance was associated with lower awareness. When analyzing each group separately, this finding was only observed in the MCI group and in the group containing progressors and dementia patients. When repeating the analyses for subjective and informant complaints separately, the results were replicated only for the informant's complaints.

Discussion: Our results demonstrate that decline in EM and, to a lesser degree, EF, mediate the effect of amyloid on awareness. In line with previous studies demonstrating the development of anosognosia in the prodromal stage, our findings suggest that decreased awareness is the result of an inability for the participant to update his/her insight into his/her cognitive performance (i.e., demonstrating a petrified self).

Keywords: awareness, episodic memory, executive functions, amyloid, Alzheimer's disease

OPEN ACCESS

Edited by:
Claudia Jacova, Pacific University, United States

Reviewed by:
Maria Donata Orfei, IMT School for Advanced Studies Lucca, Italy
Corinne Pettigrew, Johns Hopkins University, United States

****Correspondence:***
Geoffroy Gagliardi
ggagliardi@bwh.harvard.edu

Specialty section:
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

Received: *26 October 2021*
Accepted: *30 December 2021*
Published: *21 January 2022*

Citation:
Gagliardi G and Vannini P (2022) Episodic Memory Impairment Mediates the Loss of Awareness in Mild Cognitive Impairment. Front. Aging Neurosci. 13:802501. doi: 10.3389/fnagi.2021.802501

1. INTRODUCTION

Alzheimer's Disease (AD) is characterized by a specific pattern of brain pathology and cognitive impairment sufficient to interfere with functional activities of daily living (ADL) (Sperling et al., 2011; Dubois et al., 2016; Jack et al., 2018). Within the past decades, research made it possible to detect some biomarkers associated to AD (e.g., using brain imaging, blood sample, or genetic analyses). Two pathological hallmarks of AD, amyloid and tau (Braak and Braak, 1991; Braak et al., 2006), have been shown to accumulate, following a topographic sequence that can be related to the cognitive phenotype (Bejanin et al., 2017). Numerous neuroimaging studies have demonstrated that the accumulation of these pathologies begins decades before cognitive decline, and hence before a clinical diagnosis of AD can be made (Jansen et al., 2015; Ossenkoppele et al., 2015). It has been argued that pathology, occurring as early as the preclinical stage, is the cause of subtle cognitive impairments (Amieva et al., 2008, 2014; Baker et al., 2017; Zhao et al., 2018) primarily in executive functioning (EF) and episodic memory (EM) (Amieva et al., 2008, 2014; Hedden et al., 2013; Zhao et al., 2018). Of these, EF is defined as an assembly of cognitive processes that allows the person to perform an untrained goal-directed task that may involve both planning and inhibition of automatic behaviors (Lezak, 1982; Norman and Shallice, 1986; Miyake et al., 2000; Godefroy et al., 2010). Biologically, EF has primarily been associated with the integrity of frontal regions (Godefroy et al., 2010; Bettcher et al., 2016; Guarino et al., 2019). In contrast, EM is defined as a person's capacity to acquire and recall information associated with a temporo-spatial, and potentially affective (although this later is not always necessary), context (Tulving, 1972, 1985; Eustache and Desgranges, 2008). Being one of the core clinical symptoms at the AD dementia stage (Dubois et al., 2014), EM dysfunction has been demonstrated to show a strong relationship with pathology, especially in the medial temporal lobe (MTL) regions (Bejanin et al., 2017; Maass et al., 2018; Lowe et al., 2019). Although both EF (Elias et al., 2000; Baudic et al., 2006; Amieva et al., 2008, 2014; Marshall et al., 2011) and EM (Elias et al., 2000; Grober et al., 2000; Grober, 2008; Hedden et al., 2013) are impaired early in AD, some studies suggest that impairments in EM are a better and/or earlier predictor of prospective AD (Binetti et al., 1996; Derby et al., 2013; Burnham et al., 2016; Schindler et al., 2017). Moreover, declining EM and EF have been shown to significantly impair activities of daily living (ADL) by themselves (Marshall et al., 2011), but decline in these processes have also been associated with secondary impact in other cognitive domains. Importantly, it has been argued that a decline in these two processes could have an impact on an individual's self-referential processing, i.e., the awareness of our own cognitive abilities (Hannesdottir and Morris, 2007). However, the cause of changes in self-awareness, and especially the involvement of EF and EM dysfunction in loss of awareness across the AD spectrum, is unknown.

The prevalence of patients demonstrating loss of awareness (a.k.a., anosognosia) has been shown to increase along with the clinical progression of AD, with reported rates of 20 to 80% at the dementia stage (Starkstein, 2014). First used to describe two patients who, after a stroke, were unaware of their hemiplegia (Babinski, 1914), the concept of unawareness is now being applied more broadly. That is, although the circumstances may vary (Orfei et al., 2008), anosognosia is often used to describe a lack of awareness for a cognitive, behavioral or functional impairment (Weiler et al., 2016; Mograbi and Morris, 2018). Moreover, previous studies have proposed the existence of two types of anosognosia (Hannesdottir and Morris, 2007): primary anosognosia, which is described as an impairment of metacognitive processes and the inability for the individual to build a representation of oneself, and secondary anosognosia, which is the consequence of a decline in either EF or EM. In the first case, individuals would fail to either recognize or take into account their failures, while in the latter they would not be able to maintain the memory of such failures. Both incapacities prevent the individual from updating his/her own representations of cognitive functioning. In the case of EM impairment, this has led to the notion of a "petrified self," indicating that the individual is relying on outdated information to create this representation (Mograbi et al., 2009; Morris and Mograbi, 2013).

Although anosognosia is very common at the clinical stage of AD, recent studies have shown that awareness starts to change even before the AD dementia stage (Folstein et al., 1975; Cacciamani et al., 2017, 2020). Previous research has shown that some individuals may demonstrate heightened awareness of subtle cognitive changes at the preclinical stage, with a subsequent decline of awareness as the individual moves along the AD trajectory (Vannini et al., 2017a, 2020; Hanseeuw et al., 2020). Additionally, recent studies have suggested that loss of awareness may be present in the predementia stages of AD, e.g., in the prodromal (Perrotin et al., 2015; Vannini et al., 2017c; Edmonds et al., 2018; Munro et al., 2018; Therriault et al., 2018) and even preclinical stages (Folstein et al., 1975; Cacciamani et al., 2017; Vannini et al., 2017b). Longitudinal studies have further demonstrated that anosognosia starts to develop approximately 3-4 years before a clinical diagnosis of AD dementia can be made (Wilson et al., 2015; Hanseeuw et al., 2020). Furthermore, there is now evidence suggesting that loss of awareness is related to the accumulation of biomarkers of AD (Cacciamani et al., 2017; Gagliardi et al., 2020, 2021). Awareness has indeed been studied in relation to brain metabolism, functional connectivity, tau, and amyloid accumulation. Loss of awareness in AD has been shown to relate to brain hypometabolism (Starkstein, 2014), even at a preclinical stage (Cacciamani et al., 2017). Similarly, some authors have showed that anosognosia in AD could be associated with dysfunction of some brain regions (i.e., frontal and temporo-parietal), as well as the functional connectivity between these brain regions (Perrotin et al., 2015; Vannini et al., 2017b,c). In addition, a recent study showed that unawareness was related to tau burden—as measured with flortaucipir PET marker—in the medial temporal region (Gagliardi et al., 2021). Amyloid burden has significantly been found to be associated with changes in awareness over the course of AD, either through a phenomenon of heightened (Visser et al., 2009; Perrotin et al., 2012) or reduced (Cacciamani et al., 2017; Vannini et al., 2017a, 2020; Therriault et al., 2018; Gagliardi et al., 2020, 2021;

Hanseeuw et al., 2020) awareness. This relationship with amyloid could indicate that loss of awareness might be specific to AD. Additionally, some authors also found a relationship between anosognosia and brain connectivity in the Default Mode Network (DMN) (Mondragón et al., 2019, 2021). It is important to note that some authors showed that amyloid and tau accumulation patterns in the brain overlapped with the DMN (Wang et al., 2013). This allows us to hypothesize that an increasing brain pathology in these regions might affect their functioning and lead to loss of awareness and other cognitive functions, such as EF and EM (Greicius et al., 2004; Hedden et al., 2009; Sheline et al., 2010; Mormino et al., 2011; Brier et al., 2012).

However, it is still not clear if and how a deficit in EM or EF is related to changes in awareness in AD. Specifically, it is unknown whether a deficit in EF or EM mediates the AD pathology-related changes in awareness in a population comprised of cognitively normal (CN) individuals, those with a mild cognitive impairment (MCI), or those with a dementia diagnosis. Several methods have been validated to assess awareness in AD (Clare et al., 2011; Starkstein, 2014; Tondelli et al., 2018), such as clinical judgment by an examiner or the comparison between a subjective and an external measure. One of the most commonly used methods is to compare the subject's perception of his/her impairment with the informant's perception (Cacciamani et al., 2017, 2020; Hanseeuw et al., 2020; Vannini et al., 2020). Loss of awareness would then be defined as the informant complaining more than the subject. Using this approach, the current study attempts to determine the proportion of amyloid-related loss of awareness that can be explained by is EF and EM variations along the clinical AD spectrum (from the preclinical to dementia stage). Following the concept of secondary anosognosia and considering the early changes of awareness, EF, and EM, we hypothesize that loss of awareness is—at least partly—mediated by impairment of these cognitive domains, even in early stages of the disease. Additionally, given the previous observations of a decline in awareness as the disease progresses, we hypothesize that a decrease in awareness would be the result of the informant's complaint increasing as the participant's objective performance decline. To explore this hypothesis, the same models as for awareness were applied separately to the complaints of both participants and their informants.

2. MATERIALS AND METHODS

2.1. Population

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI is an ongoing, longitudinal, multicenter study conducted at 59 sites across North America, enrolling CN, amnestic MCI, and AD participants aged 55 to 94 years. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

In total, 902 participants were included in this study. Inclusion criteria included having a positron emission tomography (PET) scan data using a $^{18}F - AV45$ tracer for brain amyloidosis, subjective and objective cognitive measures (see *infra*), as well as an available clinical diagnosis. Using the clinical diagnosis, we further subdivided the sample into 362 CN participants, 429 with MCI and 111 with a dementia diagnosis. Demographic characteristics are summarized in **Table 1**.

We also defined a group of participants that could be considered to be in the Alzheimer spectrum, i.e., participants who progressed in their clinical diagnosis from CN to MCI ($N = 27$) or MCI to dementia ($N = 64$), as well as dementia patients ($N = 111$). This group will be referred to as the "progressors" group.

2.2. Cognitive Measures

All participants underwent a comprehensive neuropsychological assessment. Among the different tests available, we selected the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Trail Making Test (TMT) (Reitan, 1958), and Logical Memory (LM) (Wechsler, 1987). The MMSE was used to provide a measure of global cognitive functioning. The time difference of TMT parts A and B was used as a measure of EF, as done in previous research (Godefroy et al., 2010; Correia et al., 2015; Ritchie et al., 2017). This test is recommended for preclinical AD studies (Ritchie et al., 2017) and has been shown to distinguish between CN participants with and without significant levels of amyloid pathology (Doherty et al., 2015; Dubois et al., 2018). For EM, we used the delayed score of LM (LM-II), widely used in AD continuum research and proven to be sensitive, even at preclinical stages, to biomarker accumulation (Ritchie et al., 2017). Both tests are among the most-used measures in AD studies (Epelbaum et al., 2017) and have been used in previous studies examining awareness Starkstein (2014); Vannini et al. (2017a); Hanseeuw et al. (2020); Cacciamani et al. (2020); Gagliardi et al. (2020).

2.3. Awareness of memory

The Everyday cognition (ECog) scale (Farias et al., 2008) was used to assess awareness. The ECog scale is a 39-item questionnaire in which the participant and informant are asked identical questions to estimate the participant's current level of cognitive functioning as compared to 10 years ago. The responses are measured on a Likert scale from 1 ("Better or no change") to 4 ("Consistently much Worse,") where a higher ECog score indicates a perceived decline in cognition. The questionnaire consists of 6 domain-specific subscales, including Memory, Language, Visuospatial Abilities, Planning, Organization, and Divided Attention. A total score of cognitive complaint is also computed. In order to measure awareness, we computed an awareness index defined as the discrepancy score between the total scores of the participant and informant reports. Using this index, a negative score would indicate that the participant is overestimating his/her capacities as compared to the informant's appraisal (i.e., unawareness), whereas a positive score would indicate that the participant is underestimating his/her capacities

TABLE 1 | Demographic data and group comparisons.

Variables	All	CN	MCI	Dementia
N	902	362	429	111
Gender	0 (0 %)	0 (0 %)	0 (0 %) a**	0 (0 %) a**
Race	829 White (91.91 %)	328 White (90.61 %)	401 White (93.47 %)	100 White (90.09 %)
Ethnicity	859 Not Hisp/Latino (95.23 %)	341 Not Hisp/Latino (94.2 %)	413 Not Hisp/Latino (96.27 %)	105 Not Hisp/Latino (94.59 %)
Age	72.28 (7.08)	72.17 (6.32)	71.73 (7.34)	74.81 (7.84) a** b**
Education (Years)	16.4 (2.58)	16.75 (2.52)	16.22 (2.61) a**	15.98 (2.58) a**
MMSE (/30)	27.92 (2.39)	29.08 (1.17)	28.17 (1.67) a**	23.21 (2.04) a** b**
TMT B-A (Time in s.)	66.87 (54.23)	47.08 (35.13)	66.9 (48.28) a**	131.34 (74.04) a** b**
Logical Memory (Delayed Recall)	8.97 (5.06)	13.34 (3.21)	7.25 (3.18) a**	1.35 (1.85) a** b**
Amyloid (AV45 PET SUVr)	1.19 (0.22)	1.11 (0.17)	1.21 (0.23) a**	1.39 (0.22) a** b**
ECog - Self	1.64 (0.51)	1.38 (0.33)	1.81 (0.53) a**	1.85 (0.54) a**
ECog - Informant	1.62 (0.68)	1.19 (0.28)	1.7 (0.59) a**	2.71 (0.63) a** b**
Awareness (S vs I)	0.02 (0.68)	0.19 (0.34)	0.11 (0.7) a*	-0.86 (0.79) a** b**

*CN = Cognitively Normal, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, TMT = Trail Making Test, ECog = Everyday Cognition questionnaire, PET = positron emission tomography, SUVr = standard uptake value ratio, a = vs. CN, b = vs. MCI = $p < 0.07$, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.*

as compared to the informant's appraisal (i.e., heightened awareness) (Vannini et al., 2017a, 2020; Hanseeuw et al., 2020). A score of 0 would indicate a perfect match between participant and informant complaints.

2.4. Imaging

Florbetapir ($^{18}F - AV45$) PET tracer was used to measure brain amyloidosis. We used a global standard uptake value ratio (SUVr) computed using the whole cerebellum as a reference region. Amyloid was used as a continuous measure in all analyses. The details of the materials and methods related to florbetapir imaging have been described in Landau et colleagues (Landau et al., 2013).

2.5. Statistical Analyses

T-tests and chi-squared tests were used to compare continuous and categorical variables between the three clinical groups (i.e., CN, MCI, and Dementia). The relationship between our dependent and independent variables were explored using two main methods.

First, Pearson correlations were performed between awareness and TMT B-A, LM-II and amyloid within the whole sample and in the separate clinical groups. This analysis was performed to determine whether direct relationships between our dependent and independent variables existed in our whole sample and/or in our subgroups. This aimed to support the interpretation of potential relationships observed in the subsequent models. Second, linear regression models were also performed to explore the same relationships, taking into account demographic variables (see supplementary materials).

A model-based causal mediation analyses using a causal inference analysis approach (Imai et al., 2010) was used to investigate whether memory or executive function mediates the relationship between amyloid and awareness. Specifically, mediation analyses were performed on the whole sample, in the sub-group that contained progressors and dementia patients, and in each clinical group, using the awareness index as the dependent variable, amyloid as the independent variable, and cognition (either TMT B-A for EF, or LM-II for EM) as the mediator. Demographics (i.e., age, gender, and education) were included as covariates in all models. Both total, direct and mediated effects were calculated. Mediation models were computed using the `mediation` R package (Tingley et al., 2014). Standard errors were estimated using a quasi-Bayesian Monte-Carlo method based on normal approximation (Imai et al., 2010) with 1,000 iterations. All presented *p*-values were corrected for multiple comparisons using the Benjamin-Hochberg method. The models looking at the three clinical groups (CN, MCI, Dementia) were corrected for 9 comparisons (i.e., 3 groups and 3 conditions—awareness, informant, subject). The models looking at the Whole Sample and progressors group for 6 comparisons (2 groups and 3 conditions). All statistical analyses were performed using R 3.6.3 (https://www.R-project.org/).

3. RESULTS

3.1. Group Comparisons

The sample consisted of 362 clinically normal and 540 clinically impaired individuals (429 of which had MCI diagnosis and 111 diagnosed with dementia; see **Table 1**). As compared to CN participants, clinically impaired participants demonstrated a lower proportion of females as well as fewer years of education (mean years; both $p < 0.01$). Although no significant difference was observed between CN and MCI groups, participants diagnosed with dementia were significantly older those in both the CN and MCI groups (both $p < 0.01$). Group comparisons revealed that CN individuals showed better cognitive performance than MCI participants who, in turn, performed better than the dementia group (all $p < 0.01$). Group comparisons further revealed that dementia patients demonstrated significantly increased amyloid burden as

compared to MCI participants who, in turn, had significantly greater amyloid burden than CN participants (all $p < 0.01$). Regarding awareness, CN participants demonstrated greater levels of awareness as compared to the MCI group who, in turn, exhibited significantly higher scores than the dementia group (all $p < 0.01$). We observed that the informant complaints were at a lower level in the CN group as compared to MCI, and in the MCI group as compared to the dementia group (all $p < 0.01$). Finally, CN participants demonstrated lower subjective complaints than the MCI and the dementia groups (both $p < 0.01$). However, MCI participants and those diagnosed with dementia exhibited the same level of subjective complaints ($p > 0.05$).

3.2. Simple Correlations

All correlations are presented in **Figure 1**. When using the whole sample, the correlation analyses revealed weak negative significant associations between awareness and TMT B-A as well as between awareness and amyloid SUVr. A moderate positive significant association was found between awareness and LM-II (all $p<0.001$). When looking at the groups separately, the same pattern was observed in the MCI group for LM-II (r = 0.25, $p<0.001$) and amyloid SUVr (r=-0.23, $p<0.001$), but non-significant relationships were observed in the other groups. No significant correlations were observed for TMT B-A in any of the clinical groups. The linear regression models showed similar results for EM and amyloid (see **Supplementary Table** and **Supplementary Figures 2**, **3**). However, when adding demographics and diagnosis as covariates, TMT B-A was no longer significant in the whole sample (see **Supplementary Table** and **Figure 1**).

3.3. Mediation Models

Mediation models were performed to assess the influence of cognitive performance (episodic memory or executive function) on the relationship between amyloid and awareness, as well as the separate levels of complaint in informants and participants. In each model, the indirect effect was tested using bootstrapping procedures with 1,000 iterations.

3.3.1. Mediation Models Investigating Whether EM or EF Mediates the Association Between Amyloid and Awareness

For the whole sample, the effect of amyloid on awareness was partially mediated by cognition—both EM and EF (**Figure 2Ai**). A significant direct effect between amyloid and awareness was observed (β= -0.798; CI 95%= -1, -0.57; $p<0.001$) in that increased amyloid burden was related to a lower awareness score. Both EM and EF analyses demonstrated significant indirect effect (both $p<0.001$), with the unstandardized indirect effect equaling -0.657 (CI 95%= 0.083, 0.325; $p<0.001$) for TMT B-A and -0.421 (CI 95%= 0.338, 0.701; $p<0.001$) for LM-II. While no significant direct effect of amyloid was observed on awareness, in the "progressors" group (**Figure 2Bi**), we found a significant indirect effect of EM (β= −0.27; CI 95% = 0.049, 2.664; $p > 0.05$), but not of EF (unstandardized indirect effect β= −0.499; CI 95% = −0.175, 0.886; $p > 0.05$). When looking at each clinical group separately, this pattern was not observed for all groups (see **Figure 3i**). That is, no significant relationships, either direct or indirect, were found between amyloid and awareness in the CN or Dementia groups. However, in the MCI group, we found that LM-II partially mediated the effect between amyloid and awareness. That is, similarly to in the whole sample, this model displayed a significant direct effect between amyloid and awareness (β= −0.668; CI 95%= −0.998, −0.349; $p < 0.001$) as well as a significant indirect effect mediated by the LM-II delayed score (β= −0.199; CI 95%= −0.351, −0.083; $p < 0.001$). No significant indirect effect was observed for TMT B-A.

3.3.2. Mediation Models Investigating Whether EM or EF Mediates the Association Between Amyloid and Complaints

We also computed models using complaints from the participant (ii in **Figures 2**, **3**) as well as their informant (iii in **Figures 2**, **3**). Similar to the awareness index, results using the whole sample demonstrated partial mediation between amyloid and complaints (subjective and informant) with both executive and memory measures. Interestingly, when looking at these relationships in the groups separately, different patterns were observed. Models assessing participant complaints did not show any significant relationship, either direct or indirect, between amyloid and complaint after correction for multiple comparisons in any group (CN, MCI, Dementia, and "progressors"). Models predicting the informant's complaint in CN and Dementia participants did not show any significant associations. In the MCI group (**Figure 3iii**) a significant direct relationship was found such that a greater amyloid burden was related to increased informant complaints (β = 0.819; CI 95% = 0.572, 1.048; $p < 0.001$). No indirect effect was observed for executive functioning, although amyloid SUVr significantly predicted TMT B-A performance (β = 29.274, $p < 0.05$). However, a significant indirect effect was found for LM-II delayed score (β = 0.603; CI 95% = 0.341, 0.863; $p < 0.001$), indicating that it mediated the effect between amyloid and informant complaints in the MCI participants. The "progressors" group showed the same pattern as in the MCI model, with a significant direct effect of amyloid on the informant's complaint, as well as a significant indirect effect in EM (β = −0.27; CI 95% = 0.049, 2.664; $p < 0.05$) but not in EF ($p > 0.05$).

4. DISCUSSION

The current study investigated whether episodic memory and/or executive function mediates the relationship between amyloid and awareness in individuals across the AD spectrum, from preclinical to dementia stages. In the whole group, episodic memory and executive function partially mediated the associations between amyloid and awareness, such that greater amyloidosis was related to less cognitive efficiency, which in turn negatively impacted awareness. However, when looking at each group separately, we could only observe this mediation effect in the MCI group. When looking at the subjective and informant complaints separately, we found that episodic memory partially mediated the associations between amyloid and informants' complaints, with greater amyloidosis being related to less cognitive efficiency and increased complaints

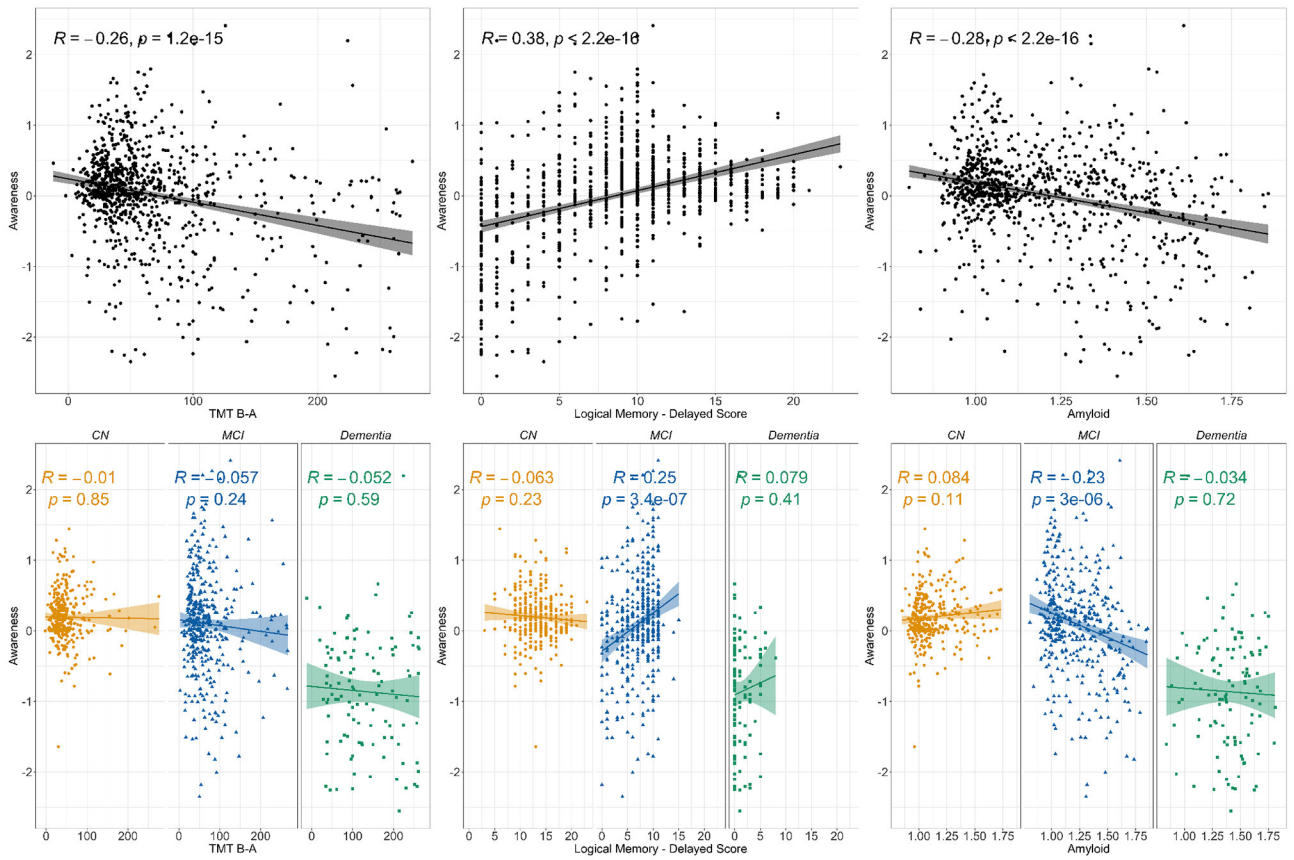


FIGURE 1 | Correlations between awareness and TMT B-A, Logical memory delayed score and amyloid. *Notes:* The figure presents the Pearson correlation coefficient for the relationship between awareness and cognition (Trail Making Test B-A for executive function and Logical Memory's delayed recall for episodic memory) as well as amyloid (SUVr). The top line presents the correlations for the whole sample while the bottom line displays clinical groups correlations. Three clinical groups are represented, i.e., Cognitively Normal (CN), Mild Cognitive Impairment (MCI), and participants diagnosed with Dementia.

by the informant. When analyzing the participants who either progressed or had a diagnosis of dementia, we also found that EM partially mediated the relationship between amyloid and awareness as well as informant complaints. All other mediation models were non-significant. These findings suggest that decreased awareness may be the result of an inability for the participant to update his/her insight of his/her cognitive performance (i.e., demonstrating a petrified self) and further suggests the impairment is happening in the prodromal stage. Furthermore, given the association with amyloid, these findings also suggest that this decline may be specific to AD.

The demographics varied across our three clinical groups. That is, the clinically normal group contained more females as compared to the impaired participants (i.e., MCI and Dementia groups). These results differ from the literature, as previous studies often report greater numbers of females in impaired samples (Dubois et al., 2016; Livingston et al., 2020). However, in line with previous studies, we found that our clinically impaired participants were less educated and older as compared to the clinically normal group. They also performed less well on cognitive tasks (with CN performing better than MCI and MCI performing better than the dementia group). Finally, dementia participants demonstrated higher amyloid burden as compared to MCI participants who, in turn, had higher amyloid burden as compared to the CN participants.

Looking at our awareness index, we found an increasing discordance between informant *vs.* participant complaint scores across the clinical stages. This suggests the progressive loss of awareness across the AD spectrum which has been shown in previous studies (Wilson et al., 2015; Hanseeuw et al., 2020). Looking more in detail, the awareness index was the highest in the CN group, suggesting heightened awareness, whereas it declined in the MCI group and further dropped in the Dementia group. These results could be interpreted in the sense that mean anosognosia appears progressively over the course of the disease and is preceded by a period of heightened awareness (or hyper-nosognosia) in the earlier stages (Folstein et al., 1975; Cacciamani et al., 2017; Vannini et al., 2017a, 2020; Hanseeuw et al., 2020). However, as the disease progresses, individuals progressively lose their ability to recognize their cognitive difficulties, ultimately resulting in low insight of their cognitive processing, often at

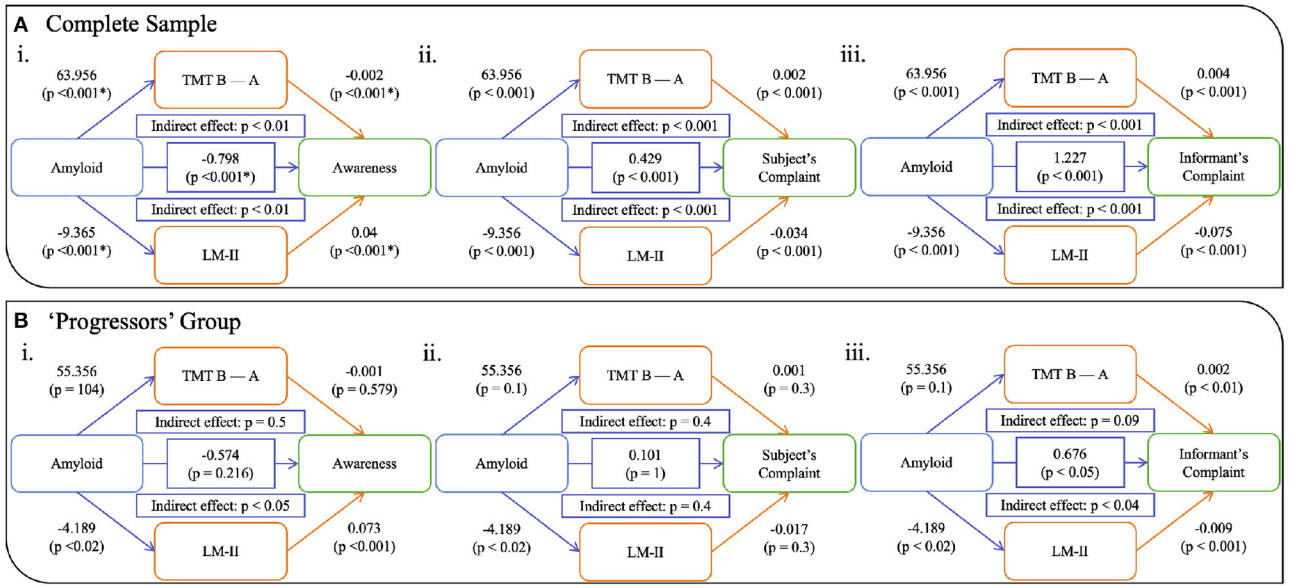


FIGURE 2 | Models showing the mediation of EM and EF on the relationship between amyloid and awareness (i), subjective complaints (ii), and informant's complaints (iii) in **(A)** the whole sample and **(B)** the progressor and dementia group. *Notes:* TMT B-A = Trail Making Test, Time B minus Time A; LM-II = Logical Memory Delayed Recall. All *p*-values are corrected for multiple comparison.

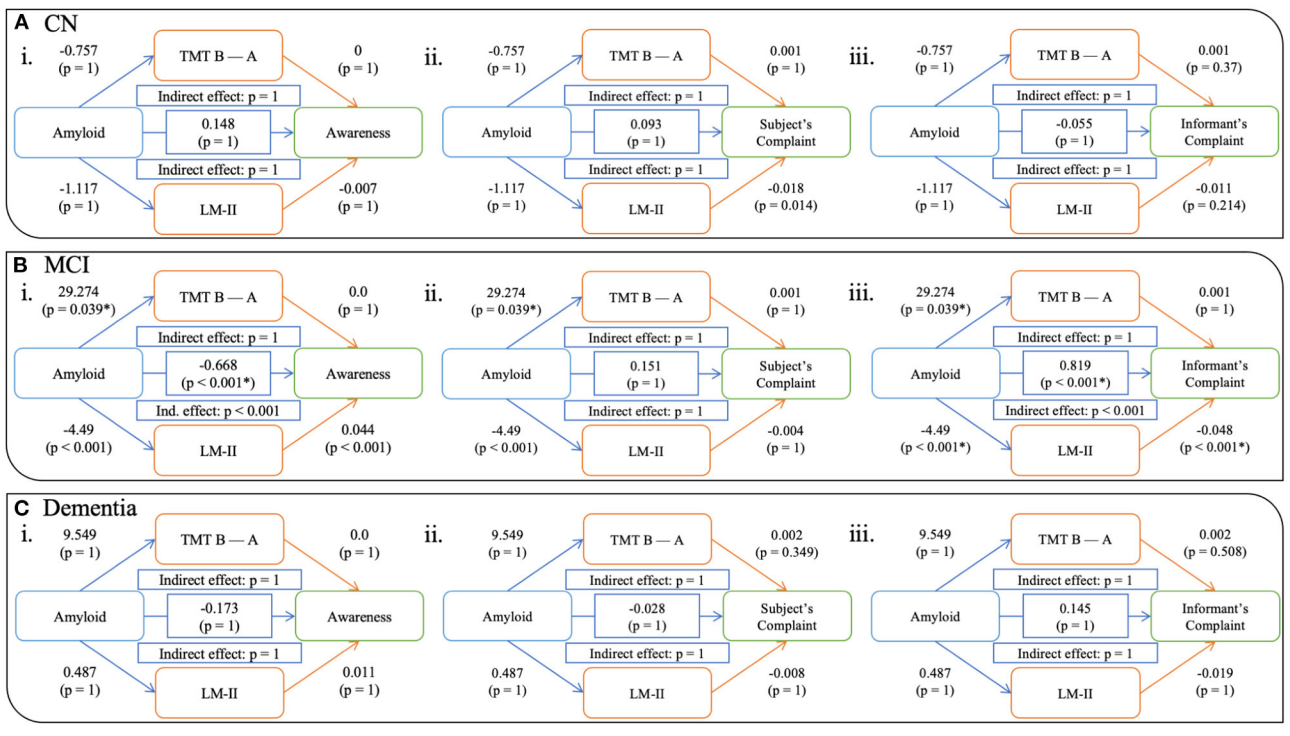


FIGURE 3 | Models showing the mediation of EM and EF on the relationship between amyloid and awareness (i), subjective complaints (ii), and informant's complaints (iii) in CN **(A)**, MCI **(B)**, and dementia **(C)** participants. *Notes:* All *p*-values are corrected for multiple comparison. CN = Cognitively Normal, MCI = Mild Cognitive Impairment.

the prodromal stage. Although the mechanism underlying the loss of awareness remains unknown, one hypothesis suggests that it is caused by the fact that the participant is relying on an outdated representation of their own abilities when judging their own cognitive performance, a phenomenon known as the "*petrified-self*" (Mograbi et al., 2009). In longitudinal studies this can be demonstrated by a non-significant increase in subjective complaints over time, even though their cognitive processes are declining, and their informant complaints are increasing.

Regarding the relationships between awareness and our variables of interest, we found that decreased awareness was related to increased amyloid burden, as well as lower EM and EF performances. These relationships should be interpreted with the disease progression in mind. That is, amyloid is thought of as one of the main and first biomarkers to accumulate in AD (Sperling et al., 2011; Dubois et al., 2016; Jack et al., 2018), even decades before a clinical diagnosis is made (Jansen et al., 2015; Ossenkoppele et al., 2015). Previous studies have shown that amyloid often accumulates in the ventromedial prefrontal cortex, medial parietal and posterior cingulate cortex, as well as the inferior parietal lobule. Interestingly, these brain regions overlap with the DMN (Wang et al., 2013), which has been implicated in self-referential processes (Mak et al., 2017) as well as EF and EM functioning (Greicius et al., 2004; Hedden et al., 2009; Sheline et al., 2010; Mormino et al., 2011; Brier et al., 2012). Within this framework, one possibility is that alterations in memory self-awareness represent an early indicator of progressive decline toward AD dementia due to increased dysfunction of the DMN. This hypothesis is consistent with previous studies relating loss of awareness in AD with DMN connectivity (Mondragón et al., 2019, 2021), but also with the relationship between anosognosia in AD with some neuropsychiatric disorders (Spalletta et al., 2012; Tondelli et al., 2021) which have also been associated with dysfunction of the DMN (Lee et al., 2020). When looking at the groups separately, we only observed a significant correlation between awareness and EM in the MCI individuals. The same pattern was found when looking at the mediation analyses, with partial mediation effects for the whole sample (for the awareness index as well as both complaints) for both EM and EF models. These results suggest that the significant effect that we observed of amyloidosis on awareness is mediated by an individual's objective performance of either EM or EF. In other words, amyloid accumulation in the brain would causes a decline in EM and EF that leads to a disturbance in awareness. However, when looking at each group separately, the results were not as clear. First, for all groups, the models using self-complaints did not show any significant relationship between amyloidosis and complaints, neither direct nor indirect. This result is not in line with previous studies which have found an association between increased amyloid pathology with increased complaints in clinically normal individuals (Jessen et al., 2010; Amariglio et al., 2012; Wang et al., 2013; Perrotin et al., 2015), a phenomenon called subjective cognitive decline (SCD). However, inconsistencies have been reported and might be due to the fact that SCD itself can be caused by multiple etiologies (Jessen et al., 2014, 2020; Rabin et al., 2017). In addition, some models using awareness and informant complaints remained significant for our groups. That is, although models in the CN and the Dementia groups did not show significant effects, neither direct nor indirect, significant partial mediations were observed in the MCI group with EM. To begin with, increased discordance between the informant's and participant's complaints have already been observed in the literature, using raw complaint scores (Amariglio et al., 2021) as well as awareness indices as in our study (Folstein et al., 1975; Cacciamani et al., 2017, 2020; Hanseeuw et al., 2020; Vannini et al., 2020). In our study, only the MCI group demonstrated a significant relationship between amyloidosis, cognition and awareness, with EM partially mediating the relationship between amyloid and awareness. Several reasons could explain this result. First, this might be a power issue, as the MCI group included more participants than the other groups. Another more plausible reason might be related to the dynamic of awareness changing across time. Previous research has proposed that awareness changes in the early stages of AD, with an initial increase in awareness before a subsequent decline, eventually leading to anosognosia in the prodromal and/or dementia stage (Vannini et al., 2017a). However, it is unclear when heightened awareness can be observed, with some studies suggesting it can be found in the preclinical (Folstein et al., 1975; Cacciamani et al., 2017; Hanseeuw et al., 2020) stage while other argue that it is observed in the prodromal (Vannini et al., 2017c; Edmonds et al., 2018; Munro et al., 2018; Therriault et al., 2018; Tondelli et al., 2018) stage of the disease. Accordingly, we could hypothesize different scenarios that might explain the non-significant effect found in the CN and Dementia groups. That is, in the preclinical stage, we might assume that the subtle cognitive decline that participants are experiencing is not sufficient for the effect to be detectable using objective neuropsychological tests, i.e., the EM and EF may be showing a ceiling effect. In contrast, in the dementia group, the lack of relationship between cognition and awareness might be since all measures might be too declined, i.e., having reached a floor effect. Another interpretation of the absence of a significant mediation of EM/EF on the relationship between amyloid and awareness in the dementia group could be that as unawareness progresses, anosognosia in the dementia stage might be the cause of primary anosognosia and not secondary anosognosia. Finally, the absence of an effect in the CN group can be explained by the fact that this group likely is heterogeneous, including both normal and preclinical participants. The absence of an effect could thus be explained by this mixture, and perhaps an early effect could be detected if future progressors and stable CN individuals were separated in a larger sample and follow-up (i.e., as our sample only included 27 CN progressors).

It is important to note that, in the MCI group, only the EM mediated effect survived. In the typical AD phenotype, EM has been demonstrated to be the cognitive domain that is most affected (Dubois et al., 2014). As previously mentioned, amyloidosis accumulates following a pattern that would disturb regions subserving EM. Previous studies have furthermore showed that EM starts to decline years before the clinical diagnosis of AD dementia (Elias et al., 2000; Grober, 2008; Derby et al., 2013), but would initially be too tenuous to be detectable in a regular neuropsychological assessment at the preclinical

stage. In the literature, unawareness has been proposed to be due to either a primary dysfunction of awareness processes, or a secondary effect due to impairment in either EM or EF processes (Hannesdottir and Morris, 2007). As compared to both CN participants, participants in the MCI roup demonstrated lower levels of awareness, as well as a lower cognitive efficiency (for both EM and EF). These results suggests that initial EM decline (i.e., at the preclinical stage / for CN participants) would not be sufficient to affect an individual's perception of growing difficulties. Participants would thus have correct insight into their initial memory decline. However, with the progression of this EM deficits, awareness would also start to show subsequent impairments. This scenario is also supported by our sub-analyses in the group containing progressors and dementia patients. Similar to the results observed in the MCI participants, we observed partial mediation of amyloid by EM on both awareness and informant complaints. These results suggest that the relationship between a decline in awareness and EM dysfunction is specific to AD. It also demonstrates the importance of the informant's reports as the disease progresses.

Additionally, the significant results in the group of participants that progressed can also be interpreted in another way. This "progressors" group consisted of both patients diagnosed with dementia or CN/MCI progressing to MCI/dementia. However, the mediation models showed significant results for the MCI group and not for the CN/dementia groups. Given the high proportion of MCI in this group, one possibility is that these individuals drove the results for this analysis.

The absence of a relationship (both in correlation and in the models) between awareness and the EF measure in the groups could be interpreted in several ways. In our study, we used the TMT B-A as a measure of EF functioning. However, EF is a generic term that refers to an ensemble of different high level cognitive processes (Lezak, 1982; Norman and Shallice, 1986; Miyake et al., 2000). The TMT, widely used as a measure of EF, has been suggested to involve working memory, switching and dividing attention (Strauss et al., 2006; Godefroy et al., 2010; Correia et al., 2015). Hannesdottir and Morris's definition suggested that this process involves a comparison executive mechanism (Hannesdottir and Morris, 2007) such that error detection, as well as correction, are part of EF (Luria, 1966). This, in turn, would rely partly on an attention orientation mechanism. Nevertheless, it is possible that the absence of a significant interaction involving the TMT could be because the task does not test specific executive processes that may be related to awareness. This could explain the discrepancy between our results and previous studies that found a relationship between EF and impaired awareness (Amanzio et al., 2013). For example, Amanzio and colleagues (Amanzio et al., 2013) did find such relationships using a dysexecutive battery including several tests, among which the TMT was included.

4.1. Limitations

This study has several limitations. To begin with, the TMT B-A was the only available measure to assess EF. In awareness conceptualization, executive dysfunctions that are postulated to be related to unawareness are comparison mechanisms (Hannesdottir and Morris, 2007). Thereby, it is possible that our models fail to show a relationship involving EF because the TMT could not involve the same type of EF processes as those suggested in the model. Future studies should investigate this further by using measures directly related to comparison and judgement. Another limitation is that we only used the global SUVr value when analyzing amyloid burden. Another approach could have been to focus on regional pathology, focusing specifically on brain regions known to be involved in awareness dysfunction. In particular, future studies should investigate whether increased amyloid in specific brain regions show an association with awareness and whether this differs between the groups. However, this approach might face the limit of multiple modelisation in order to be pursued. Further investigation also needs to be conducted using other pathological biomarkers, especially brain metabolism or tauopathy that are known to be more related to the cognitive phenotype (with the topography of the pathology matching the clinical expression) (Bejanin et al., 2017). Finally, a substantial number of studies have shown that AD can have a prevalence, expression and evolution that can vary depending on certain demographics. Our study suffers from an over-representation of Caucasian (91.91%), non-Hispanic (95.23%), and highly educated (16.41 mean years) participants. This limits the generalizability of our results and calls for future studies that replicate these findings in other, more diverse cohorts.

4.2. Conclusion

In summary, here, we studied the influence of both EF and EM on the relationship between amyloidosis and awareness across the AD spectrum. Our results suggest that EM, and not EF, mediates the effect between amyloid and awareness. In particular, a decrease of awareness was found in the MCI group and in participants that progressed to AD. This effect was not seen in the CN and Dementia stages, which might be explained by the fact that cognitive decline was either too subtle (in the CN group) or too advanced (in the dementia group) for the relationship to be detected.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: http://adni.loni.usc.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ADNI, obtained all IRB approvals and met all ethical standards in the collection of data. The following are the Ethics Committees and IRB boards that provided approval. The Ethics Committees/Institutional Review Boards that approved the ADNI study are: Albany

Medical Center Committee on Research Involving Human Subjects Institutional Review Board, Boston University Medical Campus and Boston Medical Center Institutional Review Board, Butler Hospital Institutional Review Board, Cleveland Clinic Institutional Review Board, Columbia University Medical Center Institutional Review Board, Duke University Health System Institutional Review Board, Emory Institutional Review Board, Georgetown University Institutional Review Board, Health Sciences Institutional Review Board, Houston Methodist Institutional Review Board, Howard University Office of Regulatory Research Compliance, Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects, Indiana University Institutional Review Board, Institutional Review Board of Baylor College of Medicine, Jewish General Hospital Research Ethics Board, Johns Hopkins Medicine Institutional Review Board, Lifespan - Rhode Island Hospital Institutional Review Board, Mayo Clinic Institutional Review Board, Mount Sinai Medical Center Institutional Review Board, Nathan Kline Institute for Psychiatric Research & Rockland Psychiatric Center Institutional Review Board, New York University Langone Medical Center School of Medicine Institutional Review Board, Northwestern University Institutional Review Board, Oregon Health and Science University Institutional Review Board, Partners Human Research Committee Research Ethics, Board Sunnybrook Health Sciences Centre, Roper St. Francis Healthcare Institutional Review Board, Rush University Medical Center Institutional Review Board, St. Joseph's Phoenix Institutional Review Board, Stanford Institutional Review Board, The Ohio State University Institutional Review Board, University Hospitals Cleveland Medical Center Institutional Review Board, University of Alabama Office of the IRB, University of British Columbia Research Ethics Board, University of California Davis Institutional Review Board Administration, University of California Los Angeles Office of the Human Research Protection Program, University of California San Diego Human Research Protections Program, University of California San Francisco Human Research Protection Program, University of Iowa Institutional Review Board, University of Kansas Medical Center Human Subjects Committee, University of Kentucky Medical Institutional Review Board, University of Michigan Medical School Institutional Review Board, University of Pennsylvania Institutional Review Board, University of Pittsburgh Institutional Review Board, University of Rochester Research Subjects Review Board, University of South Florida Institutional Review Board, University of Southern, California Institutional Review Board, UT Southwestern Institution Review Board, VA Long Beach Healthcare System Institutional Review Board, Vanderbilt University Medical Center Institutional Review Board, Wake Forest School of Medicine Institutional Review Board, Washington University School of Medicine Institutional Review Board, Western Institutional Review Board, Western University Health Sciences Research Ethics Board, and Yale University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the analyses, discussion of content, writing, reviewing and editing of the paper and approved the final version.

FUNDING

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. This work has been funded by NIH-NIA R01 AG061083 (PI: PV) and NIH/NIA R21 AG064348 (PI: PV).

ACKNOWLEDGMENTS

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf. The authors want to acknowledge Kayden Mimmack for his advices and help.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.802501/full#supplementary-material

Supplementary Table 1 | Relationship between executive function measure and awareness.

Supplementary Table 2 | Relationship between episodic memory measure and awareness.

Supplementary Table 3 | Relationship between amyloid measure and awareness.

Supplementary Table 4 | Number of participants extracted from ADNI cohorts.

Supplementary Figure 1 | Relationship between executive function measure and awareness.

Supplementary Figure 2 | Relationship between episodic memory measure and awareness.

Supplementary Figure 3 | Relationship between amyloid measure and awareness.

REFERENCES

Amanzio, M., Vase, L., Leotta, D., Miceu, R., and Palermo, S. (2013). Impaired Awareness of deficits in Alzheimer's disease : The Role of Everyday Executive Dysfunction. *J. Int. Neuropsychol. Soc.* 19, 63–72. doi: 10.1017/S13556l7712000896

Amariglio, R. E., Becker, J. A., Carmasin, J., Wadsworth, L. P., Lorius, N., Sullivan, C., et al. (2012). Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia* 50, 2880–2886. doi: 10.1016/j.neuropsychologia.2012.08.011

Amariglio, R. E., Sikkes, S. A. M., Marshall, G. A., Buckley, R. F., Gatchel, J. R., Johnson, K. A., et al. (2021). Item-level investigation of participant and study partner report on the cognitive function index from the A4 study screening data. *J. Prevent. Alzheimer's Disease* 3, 257–262. doi: 10.14283/jpad.2021.8

Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Prs, K., Barberger-Gateau, P., et al. (2008). Prodromal Alzheimer ' s disease : successive emergence of the clinical symptoms. *Ann. Neurol.* 64, 492–498. doi: 10.1002/ana.21509

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., et al. (2014). Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. *Brain* 137, 1167–1175. doi: 10.1093/brain/awu035

Babinski, J. F. F. (1914). Contribution l'tude des troubles mentaux dans l'hmiplgie organique crbrale (anosognosie). *Revue Neurologique* 27, 845–848. doi: 10.1016/j.cortex.2014.04.019

Baker, J. E., Lim, Y. Y., Pietrzak, R. H., Hassenstab, J., Snyder, P. J., Masters, C. L., et al. (2017). Cognitive impairment and decline in cognitively normal older adults with high amyloid?β: A meta?analysis. *Alzheimer's Dementia Diagnosis Assess. Disease Monitor.* 6, 108–121. doi: 10.1016/j.dadm.2016.09.002

Baudic, S., Dalla Barba, G., Thibaudet, M. C., Smagghe, A., Remy, P., and Traykov, L. (2006). Executive function deficits in early Alzheimer's disease and their relations with episodic memory. *Arch. Clin. Neuropsychol.* 21, 15–21. doi: 10.1016/j.acn.2005.07.002

Bejanin, A., Schonhaut, D. R., La Joie, R., Kramer, J. H., Baker, S. L., Sosa, N., et al. (2017). Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* 140, 3286–3300. doi: 10.1093/brain/awx243

Bettcher, B. M., Mungas, D., Patel, N., Elofson, J., Dutt, S., Wynn, M., et al. (2016). Neuroanatomical substrates of executive functions: Beyond prefrontal structures. *Neuropsychologia* 85, 100–109. doi: 10.1016/j.neuropsychologia.2016.03.001

Binetti, G., Magni, E., Padovani, A., Cappa, S. F., Bianchetti, A., and Trabucchi, M. (1996). Executive dysfunction in early Alzheimer's disease. *J. Neurol. Neurosurgery Psychiatry* 60, 91–93. 10.1136/jnnp.60.1.91

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., and Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathologica* 112, 389–404. doi: 10.1007/s00401-006-0127-z

Braak, H., and Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica* 82, 239–259.

Brier, M. R., Thomas, J. B., Snyder, A. Z., Benzinger, T. L., Zhang, D.,Raichle, M. E., et al. (2012). Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. *J. Neurosci.* 32, 8890–8899. doi: 10.1523/JNEUROSCI.5698-11.2012

Burnham, S. C., Bourgeat, P., Dor, V., Savage, G., Brown, B., Laws, S., et al. (2016). Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: a longitudinal study. *The Lancet Neurology* 15, 1044–1053. doi: 10.1016/S1474-4422(16)30125-9

Cacciamani, F., Sambati, L., Houot, M., Habert, M.-O., Dubois, B., and Epelbaum, S. (2020). Awareness of cognitive decline trajectories in asymptomatic individuals at risk for AD. *Alzheimer's Res. Therapy* 12, 129. doi: 10.1186/s13195-020-00700-8

Cacciamani, F., Tandetnik, C., Gagliardi, G., Bertin, H., Habert, M.-O., Hampel, H., et al. (2017). Low cognitive awareness, but not complaint, is a good marker of preclinical Alzheimer's disease. *J. Alzheimer's Disease JAD* 59, 753–762. doi: 10.3233/JAD-170399

Clare, L., Markov, I. S., Roth, I., and Morris, R. G. (2011). Awareness in Alzheimer's disease and associated dementias: theoretical framework and clinical implications. *Aging Mental Health* 15, 936–944. doi: 10.1080/13607863.2011.583630

Correia, S., Ahern, D. C., Rabinowitz, A. R., Farrer, T. J., Watts, A.K. S., Salloway, S., et al. (2015).Lowering the floor on trail making test Part B: Psychometric evidence for a new scoring metric. *Arch. Clin. Neuropsychol.* 30, 643–656. doi: 10.1093/arclin/acv040

Derby, C. A., Burns, L. C., Wang, C., Katz, M. J., Zimmerman, M. E., L'Italien, G., et al. (2013). Screening for predementia AD: time-dependent operating characteristics of episodic memory tests. *Neurology* 80, 1307–1314. doi: 10.1212/WNL.0b013e31828ab2c9

Doherty, B. M., Schultz, S. A., Oh, J. M., Koscik, R. L., Dowling, N. M., Barnhart, T. E., et al. (2015). Amyloid burden, cortical thickness, and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. *Alzheimer's Dementia Diagnosis Assess. Disease Monitor.* 1, 160–169. doi: 10.1016/j.dadm.2015.01.003

Dubois, B., Epelbaum, S., Nyasse, F., Bakardjian, H., Gagliardi, G., Uspenskaya, O., et al. (2018). Cognitive and neuroimaging features and brain β-amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. *Lancet Neurol.* 17, 335–346. doi: 10.1016/S1474-4422(18)30029-2

Dubois, B., Feldman, H. H., Jacova, C., Hampel, H., Molinuevo, J. L., Blennow, K., et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol.* 13, 614–629. doi: 10.1016/S1474-4422(14)70090-0

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., et al. (2016). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's Dementia* 12, 292–323. doi: 10.1016/j.jalz.2016.02.002

Edmonds, E. C., Weigand, A. J., Thomas, K. R., Eppig, J., Delano-Wood, L., Galasko D. R., et al. (2018). Increasing inaccuracy of self-reported subjective cognitive complaints over 24 months in empirically derived subtypes of mild cognitive impairment. *J. Int. Neuropsychol. Soc.* 24, 842–853. doi: 10.1017/S1355617718000486

Elias, M. F., Beiser, A., Wolf, P. A., Au, R., White, R. F., D'Agostino, R. B. (2000). The preclinical phase of Alzheimer disease. *Arch. Neurol.* 57, 808. doi: 10.1001/archneur.57.6.808

Epelbaum, S., Genthon, R., Cavedo, E., Habert, M. O., Lamari, F.,Gagliardi G., et al. (2017), Preclinical Alzheimer's disease: a systematic review of the cohorts underlying the concept. *Alzheimer's Dementia* 13, 454–467. doi: 10.1016/j.jalz.2016.12.003

Eustache, F., and Desgranges, B. (2008). MNESIS: towards the integration of current multisystem models of memory. *Neuropsychol. Rev.* 18, 53–69. doi: 10.1007/s11065-008-9052-3

Farias, S. T., Mungas, D., Reed, B. R., Cahn-Weiner, D., Jagust, W., Baynes, K., et al. (2008). The measurement of everyday cognition (ECog): scale

development and psychometric properties. *Neuropsychology* 22, 531–544. doi: 10.1037/0894-4105.22.4.531

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975).Mini-mental state. *J. Psychiatric Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Gagliardi, G., Houot, M., Cacciamani, F., Habert, M., Dubois, B., and Epelbaum, S. (2020). The meta-memory ratio: a new cohort-independent way to measure cognitive awareness in asymptomatic individuals at risk for Alzheimer's disease. *Alzheimer's Res. Therapy* 12, 57. doi: 10.1186/s13195-020-00626-1

Gagliardi, G., Kuppe, M., Lois, C., Hanseeuw, B., and Vannini, P. (2021). Pathological correlates of impaired self-awareness of memory function in Alzheimer's disease. *Alzheimer's Res. Therapy* 13, 118. doi: 10.1186/s13195-021-00856-x

Godefroy, O., Azouvi, P., Robert, P., Roussel, M., LeGall, D., and Meulemans, T. (2010). Dysexecutive syndrome: diagnostic criteria and validation study. *Ann. Neurol.* 68, 855–64. doi: 10.1002/ana.22117

Greicius, M. D., Srivastava, G., Reiss, A. L., and Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *PNAS* 101, 4637–4642. doi: 10.1073/pnas.0308627101

Grober, E., Hall, C. B., Lipton, R. B., Zonderman, A. B., Resnick, S. M., and Kawas, C. (2008). Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *J. Int. Neuropsychol. Soc. JINS* 14, 266–278. doi: 10.1017/S1355617708080302

Grober, E., Lipton, R. B., Hall, C., and Crystal, H. (2000). Memory impairment on free and cued selective reminding predicts dementia. *Neurology* 54, 827–832. doi: 10.1212/WNL.54.4.827

Guarino, A., Favieri, F., Boncompagni, I., Agostini, F., Cantone, M., and Casagrande, M. (2019). Executive functions in Alzheimer disease: a systematic review. *Front. Aging Neurosci.* 10:437. doi: 10.3389/fnagi.2018.00437

Hannesdottir, K., and Morris, R. G. (2007). Primary and secondary anosognosia for memory impairment in patients with Alzheimer's disease. *Cortex* 43, 1020–1030. doi: 10.1016/S0010-9452(08)70698-1

Hanseeuw, B. J., Scott, M. R., Sikkes, S. A. M., Properzi, M., Gatchel, J. R., Salmon, E., et al. (2020). Evolution of anosognosia in alzheimer's disease and its relationship to amyloid. *Annals of Neurology* 87, 267–280. doi: 10.1002/ana.25649

Hedden, T., Oh, H., Younger, A. P., and Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology* 80, 1341–1348. doi: 10.1212/WNL.0b013e31828ab35d

Hedden, T., Van Dijk, K. R. A., Becker, J. A., Mehta, A., Sperling, R. A., Johnson, K. A., et al. (2009). Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *J. Neurosci.* 29, 12686–12694. doi: 10.1523/JNEUROSCI.3189-09.2009

Imai, K., Keele, L., and Tingley, D. (2010). A general approach to causal mediation analysis. *Psychol. Methods* 15, 309–334. doi: 10.1037/a0020761

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., et al. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimer's Dementia* 14, 535–562. doi: 10.1016/j.jalz.2018.02.018

Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R. J., et al. (2015). Prevalence of cerebral amyloid pathology in persons without dementia. *JAMA* 313, 1924. doi: 10.1001/jama.2015.4668

Jessen, F., Amariglio, R. E., Boxtel, M. van, Breteler, M., Ceccaldi, M., Chtelat, G., et al. (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's Dementia* 10, 844–852. doi: 10.1016/j.jalz.2014.01.001

Jessen, F., Amariglio, R. E., Buckley, R. F., Flier, W. M. van der, Han, Y., Molinuevo, J. L., et al. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol.* 19, 271–278. doi: 10.1016/S1474-4422(19)30368-0

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Klsch, H., et al. (2010). Prediction of dementia by subjective memory impairment. *Arch. Gen. Psychiatry* 67, 414–422. doi: 10.1001/archgenpsychiatry.2010.30

Landau, S. M., Breault, C., Joshi, A. D., Pontecorvo, M., Mathis, C. A., Jagust, W. J., et al. (2013). Amyloid- imaging with pittsburgh compound B and florbetapir: comparing radiotracers and quantification methods. *J. Nucl. Med.* 54, 70–77. doi: 10.2967/jnumed.112.109009

Lee, J. S., Kim, J. H., and Lee, S. K. (2020). The relationship between neuropsychiatric symptoms and default-mode network connectivity in alzheimer's disease. *Psychiatry Investigat.* 17, 662–666. doi: 10.30773/pi.2020.0009

Lezak, M. D. (1982). The problem of assessing executive functions. *Int. J. Psychol.* 17, 281–297.

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* 396, 413–446. doi: 10.1016/S0140-6736(20)30367-6

Lowe, V. J., Bruinsma, T. J., Wiste, H. J., Min, H. K., Weigand, S. D., Fang, P., et al. (2019). Cross-sectional associations of tau-PET signal with cognition in cognitively unimpaired adults. *Neurology* 93, E29–E39. doi: 10.1212/WNL.0000000000007728

Luria, A. R. (1966). *Higher Cortical Functions in MAN*. New York, NY: Basic Books.

Maass, A., Lockhart, S. N., Harrison, T. M., Bell, R. K., Mellinger, T., Swinnerton, K., et al. (2018). Entorhinal tau pathology, episodic memory decline, and neurodegeneration in aging. *J. Neurosci.* 38, 530–543. doi: 10.1523/JNEUROSCI.2028-17.2017

Mak, L. E., Minuzzi, L., MacQueen, G., Hall, G., Kennedy, S. H., and Milev, R. (2017). The Default mode network in healthy individuals: a systematic review and meta-analysis. *Brain Connect.* 7, 25–33. doi: 10.1089/brain.2016.0438

Marshall, G. A., Rentz, D. M., Frey, M. T., Locascio, J. J., Johnson, K. A., and Sperling, R. A. (2011). Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimer's Dementia* 7, 300–308. doi: 10.1016/j.jalz.2010.04.005

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter,A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi: 10.1006/cogp.1999.0734

Mograbi, D. C., Brown, R. G., and Morris, R. G. (2009). Anosognosia in Alzheimer's disease - the petrified self. *Consciousness Cogn.* 18, 989–1003. doi: 10.1016/j.concog.2009.07.005

Mograbi, D. C., and Morris, R. G. (2018). Anosognosia. *Cortex* 103, 385–386. doi: 10.1016/j.cortex.2018.04.001

Mondragón, J. D., Maurits, N. M., and De Deyn, P. P. (2019). Functional neural correlates of anosognosia in mild cognitive impairment and alzheimer's disease: a systematic review. *Neuropsychol. Rev.* 29, 139–165. doi: 10.1007/s11065-019-09410-x

Mondragón, J. D., Maurits, N. M., and De Deyn, P. P. (2021). Functional connectivity differences in Alzheimer's disease and aMCI associated with AT(N) classification and anosognosia. *Neurobiol. Aging* 101, 22–39. doi: 10.1016/j.neurobiolaging.2020.12.021

Mormino, E. C., Smiljic, A., Hayenga, A. O., H. Onami, S., Greicius, M. D., Rabinovici, et al. (2011). Relationships between beta-amyloid and functional connectivity in different components of the default mode network in aging. *Cerebral Cortex* 21, 2399–2407. doi: 10.1093/cercor/bhr025

Morris, R. G., and Mograbi, D. C. (2013). Anosognosia, autobiographical memory and self knowledge in Alzheimer's disease. *Cortex* 49, 1553–1565. doi: 10.1016/j.cortex.2012.09.006

Munro, C. E., Donovan, N. J., Amariglio, R. E., Papp, K. V., Marshall, G. A., Rentz, D. M., et al. (2018). The impact of awareness of and concern about memory performance on the prediction of progression from mild cognitive impairment to Alzheimer disease dementia. *Amer. J. Geriatric Psychiatry* 26, 896–904. doi: 10.1016/j.jagp.2018.04.008

Norman, D. A., and Shallice, T. (1986). "Attention to action," in *Consciousness and Self-Regulation*, eds R. Davidson, R. Schwartz, and D. Shapiro (Boston, MA: Springer US), 1–18. doi: 10.1007/978-1-4757-0629-1_1

Orfei, M. D., Robinson, R. G., Bria, P., Caltagirone, C., and Spalletta, G. (2008). Unawareness of illness in neuropsychiatric disorders: phenomenological certainty versus etiopathogenic vagueness. *Neuroscientist* 14, 203–222. doi: 10.1177/1073858407309995

Ossenkoppele, R., Jansen, W. J., Rabinovici, G. D., Knol, D. L., Flier, W. M. van der, Berckel, B. N. M. van, et al. (2015). Prevalence of amyloid PET positivity in dementia syndromes. *JAMA* 313, 1939. doi: 10.1001/jama.2015.4669

Perrotin, A., Desgranges, B., Landeau, B., Mzenge, F., La Joie, R., Egret, S., et al. (2015). Anosognosia in Alzheimer disease: disconnection between memory and self-related brain networks. *Ann. Neurol.* 78, 477–486. doi: 10.1002/ana.24462

Perrotin, A., Mormino, E. C., Madison, C. M., Hayenga, A. O., and Jagust, W. J. (2012). Subjective cognition and amyloid deposition imaging: a

pittsburgh compound B positron emission tomography study in normal elderly individuals. *Arch. Neurol.* 69, 223–9. doi: 10.1001/archneurol.2011.666

Rabin, L. A., Smart, C. M., and Amariglio, R. E. (2017). Subjective cognitive decline in preclinical Alzheimer's disease. *Ann. Rev. Clin. Psychol.* 13, 369–396. doi: 10.1146/annurev-clinpsy-032816-045136

Reitan, R. M. (1958). Validity o f the Ttrail making test as an indicator. *Perceptu. Motor Skills* 8, 271–276. doi: 10.2466/pms.1958.8.3.271

Ritchie, K., Ropacki, M., Albala, B., Harrison, J., Kaye, J., Kramer, J., et al. (2017). Recommended cognitive outcomes in preclinical Alzheimer's disease : consensus statement from the European prevention of Alzheimer's dementia project. *Alzheimer's Dementia* 13, 186–195. doi: 10.1016/j.jalz.2016.07.154

Schindler, S. E., Jasielec, M. S., Weng, H., Hassenstab, J. J., Grober, E., McCue, L. M., et al. (2017). Neuropsychological measures that detect early impairment and decline in preclinical Alzheimer disease. *Neurobiol. Aging* 56, 25–32. doi: 10.1016/j.neurobiolaging.2017.04.004

Sheline, Y. I., Raichle, M. E., Snyder, A. Z., Morris, J. C., Head, D., Wang, S., et al. (2010). Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biol. Psychiatry* 67, 584–587. doi: 10.1016/j.biopsych.2009.08.024

Spalletta, G., Girardi, P., Caltagirone, C., and Orfei, M. D. (2012). Anosognosia and neuropsychiatric symptoms and disorders in mild alzheimer disease and mild cognitive impairment. *J. Alzheimer's Disease* 29, 761–772. doi: 10.3233/JAD-2012-111886

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dementia* 7, 280–292. doi: 10.1016/j.jalz.2011.03.003

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: Diagnosis, frequency, mechanism and clinical correlates. *Cortex* 61, 64–73. doi: 10.1016/j.cortex.2014.07.019

Strauss, E., Sherman, E. M. S., and Spreen, O. (2006). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 3rd Ed. New York, NY: Oxford University Press.

Therriault, J., Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Kang, M. S., Struyfs, H., et al. (2018). Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology* 90, e932–e939. doi: 10.1212/WNL.0000000000005120

Tingley, D., Yamamoto, T., Hirose, K., Keele, L., and Imai, K. (2014). mediation : R package for causal mediation analysis. *J. Stat. Softw.* 59, 1–38. doi: 10.18637/jss.v059.i05

Tondelli, M., Barbarulo, A. M., Vinceti, G., Vincenzi, C., Chiari, A., Nichelli, P. F., et al. (2018). Neural correlates of anosognosia in Alzheimer's disease and mild cognitive impairment: a multi-method assessment. *Front. Behav. Neurosci.* 12, 1–11. doi: 10.3389/fnbeh.2018.00100

Tondelli, M., Galli, C., Vinceti, G., Fiondella, L., Salemme, S., Carbone, C., et al. (2021). Anosognosia in early- and late-onset dementia and its association with neuropsychiatric symptoms. *Front. Psychiatry* 12, 1–8. doi: 10.3389/fpsyt.2021.658934

Tulving, E. (1972). "Episodic and semantic memory," in *Organization of Memory*, eds E. Tulving and W. Donaldson (New York, NY: Academic Press), 381–402.

Tulving, E. (1985). Memory and consciousness. *Can. Psychol.* 26, 1–12.

Vannini, P., Amariglio, R., Hanseeuw, B., Johnson, K. A., McLaren, D. G., Chhatwal, J., et al. (2017a). Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease. *Neuropsychologia* 99, 343–349. doi: 10.1016/j.neuropsychologia.2017.04.002

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., et al. (2017c). Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *NeuroImage. Clinical* 15, 408–414. doi: 10.1016/j.nicl.2017.05.020

Vannini, P., Hanseeuw, B. J., Gatchel, J. R., Sikkes, S. A. M., Alzate, D., Zuluaga, Y., et al. (2020). Trajectory of unawareness of memory decline in individuals with autosomal dominant Alzheimer disease. *JAMA Netw. Open* 3:e2027472. doi: 10.1001/jamanetworkopen.2020.27472

Vannini, P., Hanseeuw, B. J., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., et al. (2017b). Hippocampal hypometabolism in older adults with memory complaints and increased amyloid burden. *Neurology* 88, 1759–1767. doi: 10.1212/WNL.0000000000003889

Visser, P. J., Verhey, F., Knol, D. L., Scheltens, P., Wahlund, L.-O., Freund-Levi, Y., et al. (2009). Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol.* 8, 619–627. doi: 10.1016/S1474-4422(09)70139-5

Wang, Y., Risacher, S. L., West, J. D., McDonald, B. C., MaGee, T. R., Farlow, M. R., et al. (2013). Altered default mode network connectivity in older adults with cognitive complaints and amnestic mild cognitive impairment. *J. Alzheimer's Disease* 35, 751–760. doi: 10.3233/JAD-130080

Wechsler, D. (1987). *Manual for the Wechsler Memory Scale—Revised*. San Antonio: TX: The Psychological Corporation.

Weiler, M., Northoff, G., Damasceno, B. P., and Balthazar, M. L. F. (2016). Self, cortical midline structures and the resting state: implications for Alzheimer's disease. *Neurosci. Biobehav. Rev.* 68, 245–255. doi: 10.1016/j.neubiorev.2016.05.028

Wilson, R. S., Boyle, P. A., Yu, L., Barnes, L. L., Sytsma, J., Buchman, A. S., et al. (2015). Temporal course and pathologic basis of unawareness of memory loss in dementia. *Neurology* 85, 984–991. doi: 10.1212/WNL.0000000000001935

Zhao, Y., Tudorascu, D. L., Lopez, O. L., Cohen, A. D., Mathis, C. A., Aizenstein, H. J., et al. (2018). Amyloid β deposition and suspected non-Alzheimer pathophysiology and cognitive decline patterns for 12 years in oldest old participants without dementia. *JAMA Neurol.* 75, 88. doi: 10.1001/jamaneurol.2017.3029

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 31 January 2022
doi: 10.3389/fnagi.2021.806432

Longitudinal Trajectories of Participant- and Study Partner-Rated Cognitive Decline, in Relation to Alzheimer's Disease Biomarkers and Mood Symptoms

Catherine E. Munro[1], Rachel Buckley[2,3,4], Patrizia Vannini[1,5], Carla DeMuro[6], Reisa Sperling[3,5], Dorene M. Rentz[2,3], Keith Johnson[3,7], Jennifer R. Gatchel[2,8†] and Rebecca Amariglio[1*†]*

[1] Center for Brain/Mind Medicine, Brigham and Women's Hospital, Boston, MA, United States, [2] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [3] Center for Alzheimer's Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, MA, United States, [4] Melbourne School of Psychological Sciences, Florey Institute, The University of Melbourne, Melbourne, VIC, Australia, [5] Massachusetts General Hospital, Boston, MA, United States, [6] Department of Patient-Centered Outcomes Assessment, RTI Health Solutions, Research Triangle Park, NC, United States, [7] Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [8] McLean Hospital, Belmont, MA, United States

OPEN ACCESS

Edited by:
Kristy A. Nielson,
Marquette University, United States

Reviewed by:
Brad Christian,
University of Wisconsin–Madison, United States
Ganesh M. Babulal,
Washington University School of Medicine, United States

***Correspondence:**
Jennifer R. Gatchel
jgatchel@partners.org
Rebecca Amariglio
ramariglio@mgh.harvard.edu

[†] These authors share senior authorship

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: 31 October 2021
Accepted: 29 December 2021
Published: 31 January 2022

Citation:
Munro CE, Buckley R, Vannini P, DeMuro C, Sperling R, Rentz DM, Johnson K, Gatchel JR and Amariglio R (2022) Longitudinal Trajectories of Participant- and Study Partner-Rated Cognitive Decline, in Relation to Alzheimer's Disease Biomarkers and Mood Symptoms. Front. Aging Neurosci. 13:806432. doi: 10.3389/fnagi.2021.806432

Whereas discrepancies between participant- and study partner-reported cognitive concerns on the Alzheimer's disease (AD) continuum have been observed, more needs to be known regarding the longitudinal trajectories of participant- vs. study partner-reported concerns, particularly their relationship to AD biomarkers and mood symptomology. Additionally, it is unclear whether years of in-clinic data collection are needed to observe relationships with AD biomarkers, or whether more frequent, remote assessments over shorter periods of time would suffice. This study primarily sought to examine the relationships between longitudinal trajectories of participant- and study partner-rated cognitive decline and baseline biomarker levels [i.e., amyloid and tau positron emission tomography (PET)], in addition to how mood symptomatology may alter these trajectories of concerns over a 2-year period. Baseline mood was associated with longitudinal participant-rated concerns, such that participants with elevated depression and anxiety scores at baseline had decreasing concerns about cognitive decline over time (fixed estimate = −0.17, 95% CI [−0.29 to −0.05], $t = -2.75$, df = 457, adj. $p = 0.012$). A significant interaction between baseline amyloid (fixed estimate = 4.07, 95% CI [1.13–7.01], $t = 2.72$, df = 353, adj. $p = 0.026$) and tau (fixed estimate = 3.50, 95% CI [0.95–6.06], $t = 2.70$, df = 331, adj. $p = 0.030$) levels was associated with increasing study partner concerns, but not participant concerns, over time. The interaction between amyloid and study partner concerns remained significant when utilizing only the first year of concern-related data collection. Overall, these results suggest that frequent, remote assessment of study partner-reported concerns may offer additional insight into the AD clinical spectrum, as study partners appear to more accurately update their concerns over time with regard to pathology, with these concerns less influenced by participants' mood symptomatology.

Keywords: cognitive concerns, Alzheimer's disease, amyloid, tau, depression, anxiety, mood, longitudinal

INTRODUCTION

Discrepancies between participant- and study partner-reported cognitive decline exist on the preclinical and clinical Alzheimer's disease (AD) continuum (Amariglio et al., 2015; Vannini et al., 2017; Nuño et al., 2019; Ryan et al., 2019). However, the longitudinal course of these concerns about cognitive decline remains unclear, particularly with regard to their relationships with brain-based AD biomarkers (i.e., cerebral amyloid and tau protein burden) in the preclinical or prodromal stages of disease. By linking the longitudinal trajectories of these concerns with cross-sectional *in vivo* brain pathology, we may be able to detect and identify cognitive changes earlier in the course of the disease in clinical practice to provide more time for the intervention and treatment. Additionally, whereas most dementia clinical trials require study partners for reasons of consent, compliance, and collection data that the participant is unable to provide, the rationale for the requirement of study partners in preclinical AD trials and ongoing involvement of study partners throughout the study is less clear (Nuño et al., 2019). If longitudinal discrepancies exist between participant and study partner concerns and are linked to biomarker data, this could represent an additional, sensitive outcome measure that is more cost-effective and less burdensome to both participants and study staff. One recent longitudinal study found that participant-reported cognitive concerns were significantly associated with progression from cognitively unimpaired to a diagnosis of mild cognitive impairment in amyloid-beta-positive (Aβ+) individuals, whereas study partner-rated cognitive decline was more associated with progression from mild cognitive impairment to dementia in Aβ+ participants (Nosheny et al., 2019). Prior work has linked participant-rated cognitive decline to cerebrospinal fluid (CSF) biomarkers, showing subtle relationships between increased participant-reported cognitive concerns and higher CSF tau levels or lower CSF Aβ levels (Wolfsgruber et al., 2015; Miebach et al., 2019; Espenes et al., 2020). In contrast, other work has found that study-partner report of cognitive decline was more consistently and/or more strongly associated with objective cognition and CSF biomarker burden than participant report (Rueda et al., 2015; Valech et al., 2015; Wolfsgruber et al., 2020). More work needs to be done to fully understand the relationship between longitudinal trajectories of participant- and study partner-rated cognitive decline and *in vivo* cerebral tau burden, as data collection for many longitudinal tau positron emission tomography (PET) studies is ongoing.

In many longitudinal observational studies examining cognitive concerns, assessments occur annually during in-clinic visits over the span of many years. However, recent research has suggested that remote (i.e., delivered *via* online or *via* mail) assessments are both acceptable and feasible for many participants and study partners (Geddes et al., 2020). Remote assessment has not only been shown to be feasible in young, cognitively unimpaired individuals, but also in older individuals with and without neurological and/or psychiatric disorders (D'Arcy et al., 2013; George et al., 2016; Wadsworth et al., 2016; Jacobs et al., 2021; Lavigne et al., 2021). For impaired participants, remote assessment might be preferred to reduce participant and study-partner burden as traveling into clinic becomes more physically challenging. The feasibility of remote assessment raises the question as to whether years of annual, in-clinic assessment are needed to provide valuable data predictive of AD biomarker status, or whether more frequent, remote assessments over shorter time periods are sufficient to observe any relationships present.

Finally, there is a well-documented cross-sectional relationship between cognitive concerns and mood symptomatology, in that individuals with greater mood symptomatology often have more cognitive concerns (Lehrner et al., 2014; Yates et al., 2017). Additional work has shown a consistent relationship between participant-reported depressive symptoms and cognitive concerns, though these participant-rated cognitive concerns are not linked to objective cognitive performance (Zlatar et al., 2018). However, some data suggest that mood symptoms alongside cognitive concerns may impact longitudinal outcomes regarding risk of dementia and/or AD biomarker levels; for example, one group demonstrated that higher Aβ+ burden in cognitively unimpaired older adults was associated with increasing mood symptomatology over time, suggesting that emerging neuropsychiatric symptoms may indicate manifestations of preclinical AD (Donovan et al., 2018). A recent longitudinal study also found that individuals with both depression and subjective cognitive decline were at higher risk for dementia than those with either depression or subjective cognitive decline alone (Wang et al., 2021). Additionally, another group showed that in older individuals unlike younger individuals, depressive symptoms were correlated with cognitive concerns and associated with an increased likelihood of self-rated memory decline the following year (Hill et al., 2020). Given known discrepancies between self- and study partner-reported cognitive concerns, obtaining collateral information may represent valuable data to help accurately identify participants with elevated mood symptoms and cognitive concerns which represent preclinical manifestations of AD pathology, compared to those whose cognitive concerns are more related to preexisting mood conditions. Additionally, it is unclear whether participant depressive symptoms modify the longitudinal trajectories of both participant- and study partner-rated cognitive concerns over time.

This study had several aims to address these gaps in the literature. First, we sought to assess the impact of baseline mood symptomatology (i.e., depression and anxiety) on longitudinal trajectories of both participant- and study partner-rated cognitive decline. We hypothesized that participants with elevated mood symptoms would report greater cognitive decline, whereas study partner ratings would be less impacted by mood symptomatology. For our second aim, we sought to compare longitudinal trajectories of both participant- and study partner-rated cognitive decline to cross-sectional biomarker pathology on PET imaging (i.e., amyloid and tau levels). We hypothesized that study partner report will be more associated with biomarkers longitudinally than participant report. Finally, we wanted to determine whether more frequent assessment over shorter time frames (i.e., 1 year of data collection, or the first four

remote sessions completed) would be sufficient to observe any longitudinal relationships present in the full, 2-year dataset.

MATERIALS AND METHODS

Participants

All participants were from the Harvard Aging Brain Study (HABS), a longitudinal observational cohort of cognitively unimpaired individuals aged 65 or older at baseline (Dagley et al., 2017). Inclusion criteria at HABS baseline included a score of 0 on the Clinical Dementia Rating Scale, a score of greater than 25 on the Mini-Mental State Examination, scores above age and education-adjusted cutoffs on the 30-Min Delayed Recall of the Logical Memory Story (Wechsler, 1987; ADNI based cutoffs)[1], and a score of less than 11 on the Geriatric Depression Scale (GDS; Yesavage et al., 1982) at study entry (no score cutoff criteria were set for subsequent annual GDS scores in the study). Exclusion criteria included history of drug or alcohol abuse, head trauma, or current serious medical/psychiatric illness at the time of recruitment. All HABS participants undergo extensive cognitive testing and multimodal neuroimaging, including PET imaging, every 3 years. Each HABS participant is also required to have a study partner who interacts regularly with the participant and can comment on their cognitive abilities and daily activities. Consistent with other observational studies of cognitively normal individuals, imaging biomarker status is not disclosed to participants or study partners.

The analyses presented here utilize data from the Cognitive Function and Mood Study of HABS. The Cognitive Function and Mood Study is a subset of 70 participants (mean age = 76.8, 55.7% women), who are selected from among those HABS participants who were entering a neuroimaging year of the HABS study (**Table 1**). This subset was demographically generally representative of the overall HABS sample with a slightly smaller percentage of impaired individuals (about 6% impaired in the overall HABS sample with about 4% impaired in this sample), though the Cognitive Function and Mood subset had slightly higher levels of education (overall HABS mean = 15.8 years of education; Cognitive Function and Mood Study mean = 16.7 years of education; $p = 0.0248$). The Cognitive Function and Mood Study was initiated 7 years after the HABS began, and three participants in this sample had progressed to mild cognitive impairment as determined by clinical consensus. Regarding the study timeline, the remote Cognitive Function and Mood Study began with an in-clinic PET imaging visit, after which participants and their study partners were sent questionnaires online *via* REDCap within 1–6 months after their in-clinic visit. Participants and study partners completed additional remote assessments every 3 months thereafter, with a mean of eight sessions completed or about 2 years of assessment in total (**Figure 1**). Participants had 1 month to complete questionnaires with automatic daily reminders sent out *via* e-mail the first week after they were sent out. Follow-up phone calls were performed by a research assistant as needed if questionnaires were not completed within a week. These REDCap surveys could be completed on any device with access to the Internet and were not restricted to computers. Massachusetts General Hospital Institutional Review Board approval was obtained for both the HABS and the Cognitive Function and Mood substudy prior to study initiation, and informed consent was obtained for both studies from all participants prior to study procedures being performed.

TABLE 1 | Participant demographics at baseline.

N **= 70**	**Mean (SD) [range]**
Age	76.8 (6.3) [58–89]
Sex (% F)	55.7
Race (% W)	83
Ethnicity (% NH)	97
Years of education	16.7 (2.6) [12–20]
AMNART VIQ	123.9 (8.2) [90–132]
CDR	0.04 (0.1) [0–0.5]
MCI (n)	3
No. Remote visits completed	7.9 (1.6) [5–10]
Fully completed visits	90%
E4+	27.1%
PIB+ (cutoff of 1.185)	28.1%
FLR PIB DVR	1.2 (0.2) [1.0–1.9]
Entorhinal Tau SUVR	1.1 (0.1) [0.8–1.7]
Geriatric Depression Scale	3.7 (4.3) [0–24]
Geriatric Anxiety Inventory	1.4 (2.7) [0–16]

F, female; W, White; NH, non-Hispanic; AMNART, American National Adult Reading Test; VIQ, verbal intelligence quotient; CDR, clinical dementia rating; MCI, mild cognitive impairment; E4+, ApoE4-positive; PIB+, Pittsburgh compound B-positive; FLR PIB DVR, frontal, lateral, and retrosplenial Pittsburgh compound B distribution volume ratio; SUVR, standardized uptake ratio.

Questionnaires

Questionnaire data were collected and managed using REDCap electronic data capture tools hosted at Massachusetts General Hospital (Harris et al., 2009, 2019). Research electronic data capture (REDCap) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

The primary measure of interest was a modified version of the cognitive function instrument (aka *Current CFI*; **Table 2**), comprised of 20 questions regarding current, high-level cognitive functioning using a 5-point Likert scale (i.e., "Never," "Rarely," "Sometimes," "Often," and "Always") where a higher score is indicative of greater perceived cognitive decline. This represents an adaptation of the original CFI, which measures participant- and study partner-rated cognitive concerns about change in cognition over the past year over 14 questions and uses a 3-point response scale (i.e., "Yes," "No," and "Maybe"; Li et al., 2017). These modifications were made to increase sensitivity and interpretability of data collection and to better capture change in

[1]http://www.adni-info.org

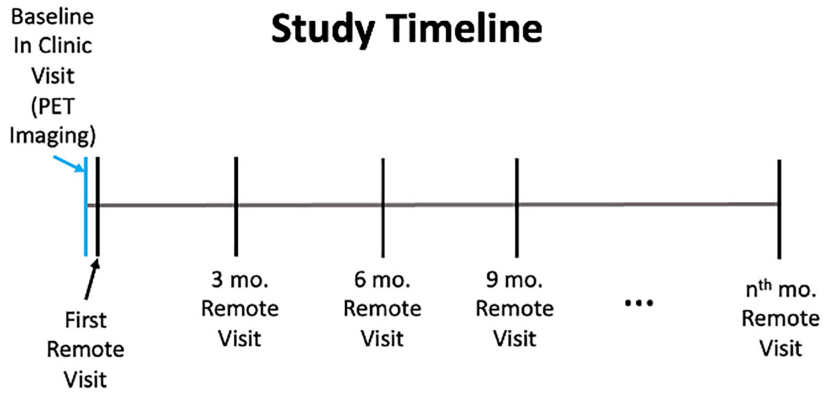


FIGURE 1 | Study timeline.

concerns over shorter time periods, as participants were asked about their perceived cognitive decline more frequently than the original CFI. *Current CFI* was administered remotely to both participants and their study partners independently *via* online REDCap surveys every 3 months. A current CFI total score was created for each time point by summing all responses on the 5-point response scale. In terms of compliance, 90% of participants and their study partners fully completed all remote assessments, with the remaining 10% only missing 1–2 remote assessments in total.

Mood was assessed using two scales, the Geriatric Depression Scale (GDS) long form and the Geriatric Anxiety Inventory (GAI; Yesavage et al., 1982; Pachana et al., 2007). The GDS includes 30 yes/no questions designed to measure depressive symptomatology in elderly individuals, with higher scores indicating greater depressive symptoms. On the GDS, scores of 0–9 represent no to mild depressive symptomatology; scores of 11–19 represent mild to moderate depressive symptomatology, and scores of 20–30 represent moderate to severe depressive symptomatology. The GAI is comprised of 20 yes/no questions designed to measure levels of anxiety in elderly individuals, with higher scores indicating greater levels of anxiety. Whereas initial analyses have suggested that a score of 10–11 points indicates significantly elevated levels of anxiety, other studies have found that a score of 8–9 points can adequately detect individuals with an anxiety disorder. The GDS and the GAI were administered in their unmodified forms to participants online *via* REDCap every 3 months.

Neuroimaging

Magnetic resonance imaging (MRI) was performed on a 3T Tim Trio (Siemens, Washington, DC, United States) and included a magnetization-prepared rapid gradient-echo (MPRAGE) processed with FreeSurfer (FS) as described previously to identify gray-white and pial surfaces to permit ROI parcelation (Braak and Braak, 1997; Delacourte et al., 2002; Fischl et al., 2004; Braak et al., 2006; Becker et al., 2011).

General PET acquisition parameters for HABS have been published previously (Johnson et al., 2016; Dagley et al., 2017).

TABLE 2 | Current cognitive function instrument (CFI), participant version.

Please complete these questions thinking about your current ability (most recent experience). "Never," "Rarely," "Sometimes," "Often," "Always"	
1.	How often do you have memory difficulties?
2.	How often do others tell you that you tend to repeat questions over and over?
3.	How often do you misplace things?
4.	How often must you rely on written or electronic reminders (e.g., shopping lists, calendars)?
5.	How often do you forget appointments or family occasions?
6.	How often do you have difficulty remembering important conversations?
7.	How often do you have difficulty recalling names?
8.	How often do you have problems finding the right word when speaking?
9.	How often do you have difficulty with your driving (such as driving more slowly, getting lost, having accidents)?
10.	How often do you have difficulty managing money (such as paying bills, calculating change, doing taxes)?
11.	How often do you turn down invitations for social activities?
12.	How often do you have difficulty with your work performance (paid or volunteer)?
13.	How often do you have difficulty following the news or plots of books, movies, or TV shows?
14.	How often do you have difficulty with your activities (such as hobbies, card games, crafts)?
15.	How often do you become disoriented or lost in familiar places?
16.	How often do you have difficulty using household appliances (such as the washing machine, microwave)?
17.	How often do you have difficulty using electronic devices (such as the cell phone, computer)?
18.	How often do you have difficulty planning an event (such as a dinner party, trip)?
19.	How often do you have difficulty keeping living and work spaces organized?
20.	How often do you have difficulty participating in conversations with a group of friends or family?

The study partner version of the current CFI is identical to the participant version, with the exception of substituting "your partner" for "your" in the directions.

All PET images were acquired on a Siemens ECAT EXACT HR+ scanner. At each time point, PET data were rigidly coregistered to the individual's closest MPRAGE using SPM12

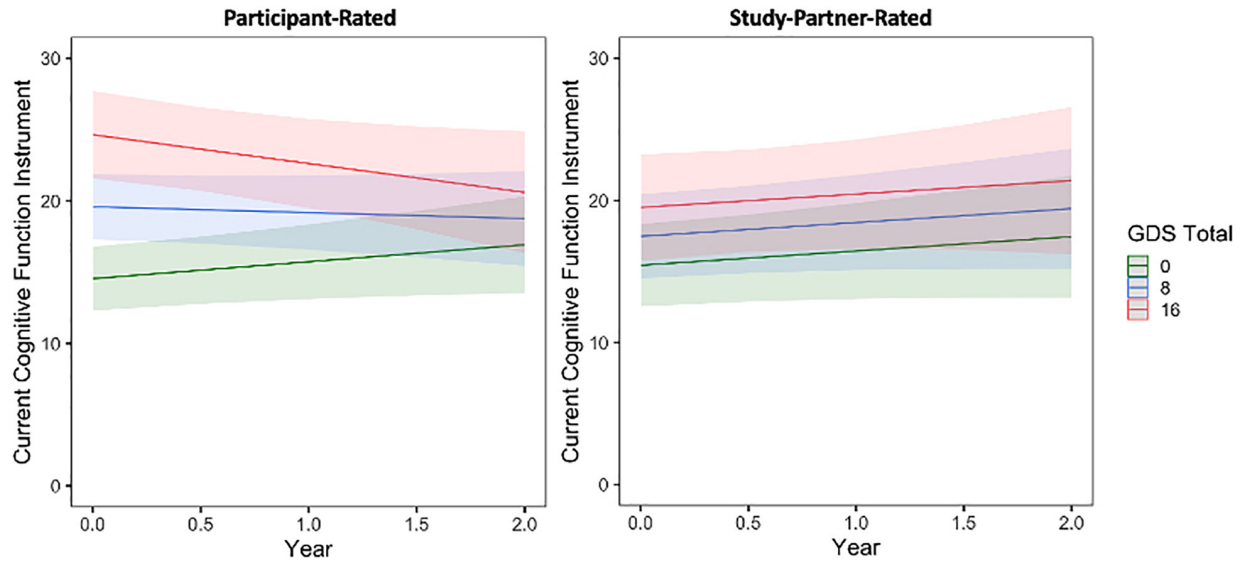


FIGURE 2 | The interaction between baseline participant GDS score and time to predict participant-rated (left) and study partner-rated (right) cognitive concerns using the current CFI. A significant interaction was seen between GDS and time when predicting participant-rated cognitive concerns (fixed estimate = –0.17, adj. $p = 0.0012$), in that participant concerns decreased over time in participants with higher GDS score at baseline (indicative of greater depressive symptomatology). The interaction between GDS score and time predicting study partner-rated cognitive concerns was not significant (fixed estimate = –0.003, adj. $p = 0.964$).

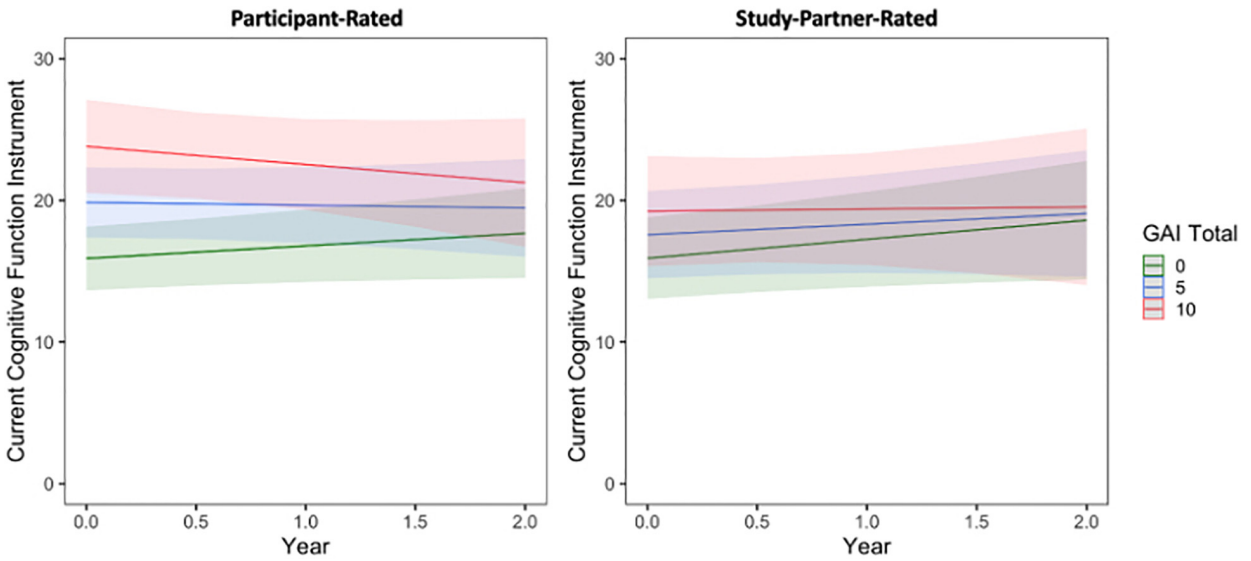


FIGURE 3 | The interaction between baseline participant GAI score and time to predict participant-rated (left) and study partner-rated (right) cognitive concerns using the current CFI. A significant interaction was seen between GAI score and time when predicting participant-rated cognitive concerns (fixed estimate = –0.19, adj. $p = 0.0450$), in that participant concerns decreased over time in participants with higher GAI score at baseline (indicative of greater anxiety symptoms). The interaction between GAI score and time predicting study partner-rated cognitive concerns was not significant (fixed estimate = –0.12, adj. $p = 0.380$).

(Wellcome Department of Cognitive Neurology, Functional Imaging Laboratory, London, United Kingdom). All PET data presented were partial volume corrected using the Müller-Gärtner method, though results were similar when utilizing data that were not partial volume corrected (see **Supplementary Material** for non-partial volume corrected analyses; Müller-Gärtner et al., 1992).

Cerebral amyloid burden was measured using the Pittsburgh compound B (PIB) radiotracer. PIB-PET images were acquired with a 60-min dynamic acquisition starting directly postinjection. For PIB-PET, distribution volume ratios (DVRs) were calculated *via* Logan plotting with a cerebellar gray reference tissue. Cortical regions of interest were defined from the Desikan–Killiany atlas *via* FreeSurfer v6.0 (Desikan et al., 2006). Frontal, lateral, and

retrosplenial (FLR) regions were averaged into a widely accepted global aggregate, as previously reported (Mormino et al., 2014; Johnson et al., 2016; Buckley et al., 2018).

Cerebral tau burden was measured using the Flortaucipir (FTP, formerly known as AV1451) radiotracer, using previously described methods (Johnson et al., 2016). FTP-PET images were acquired approximately 80–100 min after injection. FTP-PET data were examined regionally for these analyses, specifically focusing on bilateral entorhinal cortices (EC) using a FS-defined ROI given the higher likelihood of tau deposition in this region based on a largely cognitively unimpaired sample. FTP binding was expressed in FS ROIs as the SUVR, using the FS cerebellar gray ROI as reference.

Statistical Analyses

All analyses were conducted in *R* and RStudio, version 4.0.3 (R Core Team, 2019). Linear mixed-effects models were first used to examine potential change in mood (i.e., depression or anxiety measures) and cognitive concerns (both participant- and study partner-reported) over time:

Longitudinal participant or study partner concerns or longitudinal mood ∼ time.

Linear mixed ∼ effects models were also used to assess the interaction between either baseline participant mood (i.e., depression or anxiety measures) or biomarker burden (i.e., amyloid and tau) and time to separately predict longitudinal participant ∼ and study partner ∼ rated cognitive decline:

Longitudinal participant or study partner concerns ∼ baseline amyloid, tau, or mood × time.

In secondary sensitivity analyses, separate linear mixed-effects models were run using a truncated dataset using only the first year of data collection (first four time points for all participants), to examine relationships with biomarkers over a shorter time frame. These models also looked at the interaction between baseline biomarker levels with time to predict longitudinal participant- and study partner-rated cognitive decline, but used only data collected from the first four remote sessions completed. Linear regression models were utilized to observe main effects of the aforementioned models. All models included age, sex, and education as covariates. All *p*-values provided are adjusted using an FDR correction (Benjamini and Hochburg, 1995; Jafari and Ansari-Pour, 2019). Sensitivity analyses were also run, removing subjects with MCI and, for analyses with GDS, removing items related to cognition from the total GDS score.

RESULTS

Baseline Mood Symptomatology Predicting Longitudinal Trajectories of Cognitive Concerns

First, regarding longitudinal trajectories of participant-reported mood symptoms over the course of the study, GAI scores were generally stable (slope = 0.01, t = 0.04, p = 0.9642) whereas GDS scores increased over time, albeit very minimally by about half of a point over each time point (slope = 0.65, t = 3.08, p = 0.0022). Next, when examining the effects of baseline mood on longitudinal trajectories of cognitive concerns, a significant association was observed between participant-rated cognitive concerns over time and baseline participant GDS score (**Figure 2**). This interaction was such that individuals with a higher GDS score, indicating greater depressive symptomatology, at baseline had decreasing self-reported cognitive concerns over time (fixed estimate = −0.17, 95% CI [−0.29 to −0.05], t = −2.75, df = 457, adj. p = 0.012). Results were similar in a sensitivity analyses, using a modified GDS score when items related to cognition or thinking were removed from the GDS total score (fixed estimate = −0.21, 95% CI [−0.36 to −0.07], t = −2.84, df = 457, p = 0.005) and when individuals with MCI were removed from the sample (fixed estimate = −0.17, 95% CI [−0.29 to −0.04], t = −2.54, df = 447, p = 0.012). A significant main effect of GDS score was also observed, such that individuals with higher GDS scores tended to have more cognitive concerns at baseline (t = 7.83, adj. p = 0.004; **Figure 2**). The interaction between participant GDS score and time was not significant when predicting study partner-rated concerns (fixed estimate = −0.003, 95% CI [1.67–30.38], t = −0.05, df = 362, adj. p = 0.964), indicating that study partner concerns did not change over time in relation to the level of participant depressive symptomatology reported. These results were similar when using a modified GDS score (removing cognitive items) and when removing individuals with MCI from the sample. Interaction results for predicting study partner-rated concerns were also similar when items related to cognition or thinking were removed from the GDS total score (fixed estimate = 0.04, 95% CI [−0.17 to 0.24], t = 0.35, df = 58, p = 0.726) and when individuals with MCI were removed (fixed estimate = 0.01, 95% CI [−0.40 to 0.62], t = 0.09, df = 352, p = 0.927). A significant main effect was seen such that higher participant-rated baseline GDS score, indicating greater depressive symptomatology, was associated with more study partner-rated cognitive decline at baseline (t = 2.42, adj. p = 0.025). However, this the effect size was smaller compared to that observed in the model predicting participant-rated concerns.

Similar results were obtained when comparing participant- and study partner-rated concerns to baseline participant GAI score (**Figure 3** and see **Supplementary Material**).

Baseline Biomarker Levels Predicting Longitudinal Trajectories of Cognitive Concerns

A significant interaction was seen between baseline amyloid level and time when predicting longitudinal study partner-rated cognitive decline (**Figure 4**), such that a higher participant baseline amyloid burden was associated with increasing study partner concerns over time (fixed estimate = 4.07, 95% CI [1.13–7.01], t = 2.72, df = 353, adj. p = 0.026). Results were similar when data from participants with MCI were removed from analyses (fixed estimate = 2.95, 95% CI [0.16–5.74], t = 2.08, df = 343, adj. p = 0.038). A main effect of amyloid was also significant (t = 2.40, adj. p = 0.026), indicating greater study partner-reported concerns for participants with higher levels of amyloid at baseline. A main effect of amyloid (i.e., higher

baseline amyloid levels were related to higher concerns) was also significant in participant ratings (t = 2.61, adj. p = 0.023; **Figure 4**), indicating that individuals with higher levels of amyloid had more cognitive concerns at baseline. However, the interaction between amyloid burden and time was not significant when predicting the trajectory of participant-rated cognitive concerns (fixed estimate = 0.44, 95% CI [−1.41 to 2.30], t = 0.47, df = 440, adj. p = 0.635), suggesting that there was no significant change in participant cognitive concerns over time in relation to baseline amyloid levels.

A significant interaction was also seen between baseline entorhinal cortex tau burden and time when predicting longitudinal study partner-rated cognitive decline (**Figure 5**), such that a higher participant baseline tau burden was associated with increasing study partner concerns over time (fixed estimate = 3.50, 95% CI [0.95–6.06], t = 2.70, df = 331, adj. p = 0.03). This interaction was no longer significant when individuals with MCI were removed from analyses (fixed estimate = 2.09, 95% CI [−0.39 to 4.57], t = 1.66, df = 321, adj. p = 0.099). A main effect between study partner concerns and baseline participant entorhinal tau burden was marginally significant (t = 2.14, adj. p = 0.075), trending toward greater study partner-reported concerns for participants who had greater entorhinal tau burden at baseline. When examining participant-rated cognitive concerns, the interaction between entorhinal tau and time (fixed estimate = −1.47, 95% CI [−3.54 to 0.60], t = −1.40, df = 409, adj. p = 0.162) was not significant (**Figure 5**). A model examining the association between participant-reported cognitive concerns and entorhinal tau levels at baseline was also non-significant (t = 1.73, adj. p = 0.120).

Results examining the interaction between baseline tau levels in other temporal lobe regions (i.e., bilateral amygdala and inferior temporal cortex) and time were similar to main analyses and are presented in **Supplementary Material**, section "Supplementary Biomarker Analyses."

Secondary Analyses: Baseline Biomarker Burden Predicting Longitudinal Trajectories of Cognitive Concerns Over Shorter Time Frames

In separate models using participant baseline amyloid and tau burden to predict longitudinal trajectories of participant- and study partner-rated cognitive decline over only the first year of data collection (the first four remote sessions), the interaction between amyloid burden and time in study partner-rated cognitive decline remained significant (fixed estimate = 7.13, 95% CI [1.33–12.92], t = 2.43, df = 170, adj. p = 0.033; **Figure 6**). The interaction between entorhinal tau level and time in study partner-rated cognitive decline was not significant when truncating the dataset to only the first four sessions (fixed estimate = 3.38, 95% CI [−1.79 to 8.56], t = 1.29, df = 353, adj. p = 0.397). Similar to the full dataset, neither the interaction between amyloid and time (fixed estimate = 0.20, 95% CI [−4.92 to 5.31], t = −0.08, df = 187, adj. p = 0.940) nor the interaction between entorhinal tau and time (fixed estimate = −1.24, 95% CI [−6.81 to 4.32], t = −0.44, df = 184, adj. p = 0.661) significantly predicted participant-rated concerns.

DISCUSSION

We observed a significant association between baseline mood symptomatology and participant-rated concerns over time, such that participants with higher depression and anxiety scores at baseline had decreasing cognitive concerns over time. Additionally, there was a strong main effect of mood symptomatology on participant-rated concerns, with higher mood symptoms at baseline associated with more cognitive concerns overall. These results persisted when adjusting models for amyloid and EC tau (see **Supplementary Material**), suggesting that this finding was not solely driven by greater pathology. Moreover, in a further exploratory analysis, the interaction between baseline mood symptoms and AD biomarkers was not significant in predicting trajectory of participant concerns over time, suggesting that the phenomena observed were not solely driven by participants with greater burden of both mood symptoms and pathology (data not shown). The interaction between participant mood symptoms and time was not seen for study partner-reported concerns, and the main effect of participant mood symptoms on concerns was smaller in study partners. These data indicate that participant-rated cognitive concerns are influenced by their mood symptomatology at baseline, and moreover, that this influence may change over time. Whereas it is still somewhat unclear why participant-rated cognitive concerns decreased over time in those with higher mood symptoms at baseline, this could possibly be explained by enhanced accuracy of participant assessment over time after repeated prompting to reflect on current concerns; results from our sensitivity and exploratory analyses above suggest this is less likely due to participants with greater mood symptomatology at baseline having decreasing awareness of cognitive changes over time. However, future work in larger samples and with longer-term follow-up of the trajectory of mood symptoms and concerns in both participants and study partners is needed to fully differentiate between these alternatives.

Main effects of baseline biomarker burden (i.e., amyloid and tau) predicting both participant- and study partner-reported cognitive concerns were observed, such that higher levels of biomarker burden at baseline were generally associated with greater concerns in both groups. However, we found that higher participant biomarker (i.e., amyloid and tau) levels at baseline were associated only with increasing study partner-rated, but not participant-rated, cognitive concerns over time. These findings are in line with prior research suggesting that, whereas subtle relationships may be seen between participant-reported concerns and biomarkers, there are discrepancies between study partner and participant report that suggest study partner data becomes increasingly valuable as participants progress along the preclinical and clinical AD continuum.

In secondary analyses, the interaction with amyloid remained significant even when utilizing a truncated dataset which

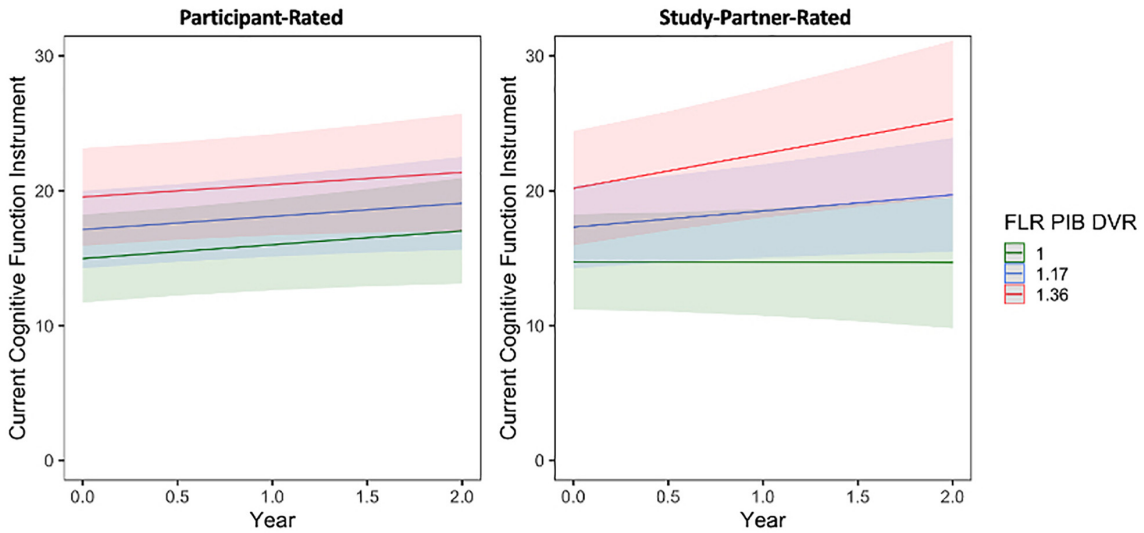


FIGURE 4 | The interaction between baseline participant cerebral amyloid burden (FLR DVR) and time to predict participant-rated (left) and study partner-rated (right) cognitive concerns using the current CFI. A significant interaction was seen between amyloid and time when predicting study partner-rated cognitive concerns (fixed estimate = 4.07, adj. p = 0.0260), in that study partner concerns increased over time in participants with higher amyloid burden at baseline. The interaction between amyloid and time predicting participant-rated cognitive concerns was not significant (fixed estimate = 0.44, adj. p = 0.6350).

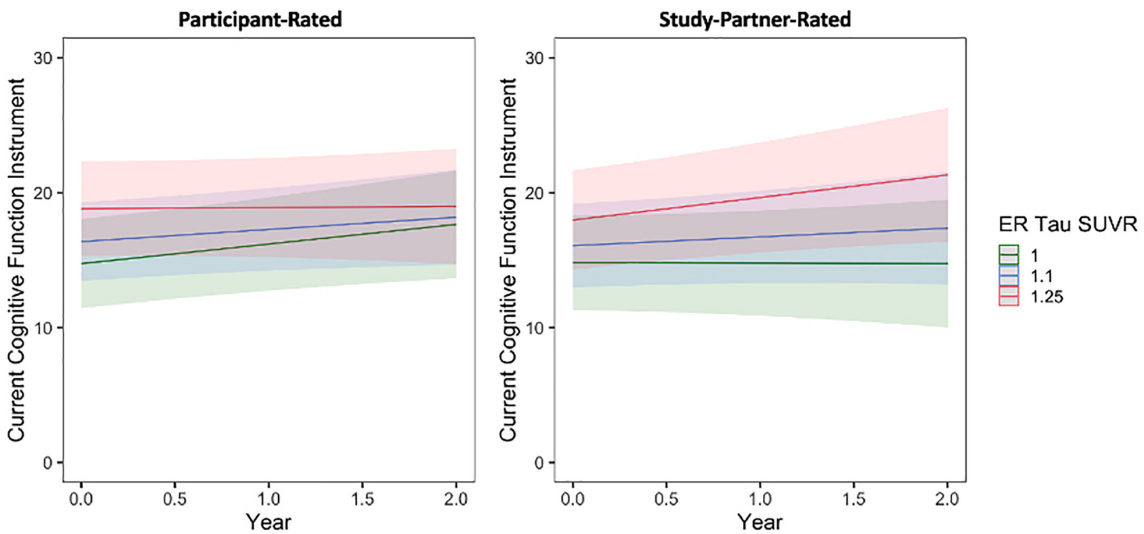


FIGURE 5 | The interaction between baseline participant cerebral entorhinal tau burden (ER SUVR) and time to predict participant-rated (left) and study partner-rated (right) cognitive concerns using the current CFI. A significant interaction was seen between tau and time when predicting study partner-rated cognitive concerns (fixed estimate = 3.50, adj. p = 0.030), in that study partner concerns increased over time in participants with higher tau burden at baseline. The interaction between tau and time predicting participant-rated cognitive concerns was not significant (fixed estimate = −1.47, adj. p = 0.1620).

included only the first year of data collection (first four remote sessions), suggesting that more frequent remote assessment of study partner concerns may offer additional insight into clinical trajectories over shorter time periods. Additionally, the interaction with amyloid remained significant when individuals with MCI were removed, highlighting that this analysis is sensitive to detect relationships between study partner concerns and amyloid in preclinical individuals. The interaction with tau was not significant using a truncated dataset, indicating a potential power issue (stemming from a small sample size combined with relatively low cerebral tau burden across most participants), or perhaps that more time is needed to observe the relationship between study partner concerns and cerebral tau burden. The fact that the interaction between tau and time predicting study partner-rated cognitive decline lost significance when individuals with MCI were removed seems to provide support for the former explanation, that study partner ratings may be more linked to tau burden in individuals further along

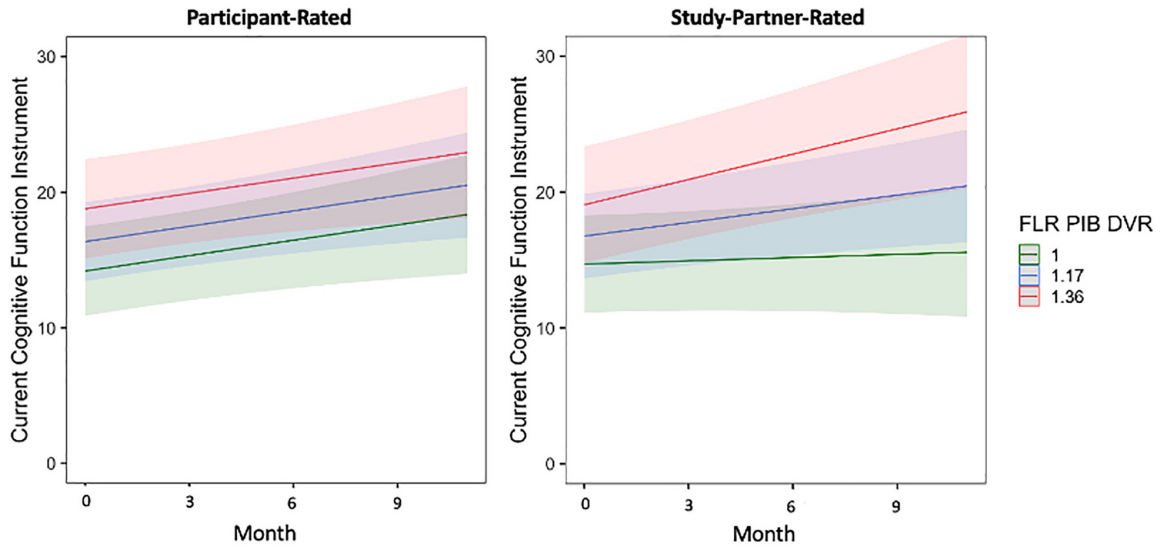


FIGURE 6 | The interaction between baseline participant cerebral amyloid burden (FLR DVR) and time to predict participant-rated (left) and study partner-rated (right) cognitive concerns using the current CFI over only the first year of data collection (first four remote sessions). A significant interaction was seen between amyloid and time when predicting study partner-rated cognitive concerns (fixed estimate = 7.13, adj. p = 0.0330), in that study partner concerns increased over time in participants with higher amyloid burden at baseline. The interaction between amyloid and time predicting participant-rated cognitive concerns over the first year of data collection was not significant (fixed estimate = 0.20, adj. p = 0.940).

the clinical spectrum and may be a good indicator of certain brain pathologies even over shorter time frames.

With regard to the limitations of this study, whereas each participant completed an average of eight remote assessments and compliance with these assessments was strong (90% of participants and study partners fully completed all remote visits), the sample size was relatively small (n = 70) and this may have affected our overall ability to observe relationships (i.e., the interaction between tau and time to predict longitudinal study partner-rated cognitive decline) in the truncated dataset of the first four remote sessions. We are also hoping to explore item-level analyses using the current CFI in a larger sample to determine whether there are specific items or factors that may be more predictive of cerebral pathophysiology. Additionally, our sample was largely comprised of cognitively unimpaired adults with relatively low amyloid and/or tau levels and largely subclinical mood symptomatology. Stronger relationships may be observed in samples with more cognitively impaired individuals or individuals with current clinical mood disorders. Additional studies are also needed to explore relationships with tau pathology in other brain regions and consider the impact of mood symptom variability on longitudinal trajectories of cognitive concerns in both participants and study partners. Finally, the lack of racial and ethnic diversity in our highly educated and non-Hispanic or White sample that was slightly more homogenous than the main Harvard Aging Brain Study represents a significant limitation that is seen across many ongoing longitudinal aging studies. Future research studies are needed with participant groups that are more representative of our overall population in terms of racial, ethnic, and socioeconomic diversity to be able to adequately generalize these results.

CONCLUSION

Our findings indicated that, over time, study partner rather than participant-reported complaints are more closely associated with participant AD biomarkers and were overall less vulnerable to participant-reported mood symptoms when compared to participants' ratings of their own cognitive functioning. Moreover, whereas mood symptoms may influence participant-reported concerns, our data suggest that this influence may wane with repeated participant assessment of concerns. This may be in part due to the influence of impaired insight as participants progress along the AD continuum, though more work needs to be done to further investigate this phenomenon using objective cognitive measures and to additionally parse out the specific impact of mood symptomatology over time. Regarding remote data collection, it was demonstrated that frequent, remote assessment of cognitive concerns, particularly with study partners, may offer additional insight into clinical trajectories over shorter periods of time. These findings have implications for both clinical practice and future clinical and observational research studies, highlighting the importance of obtaining longitudinal data from not only participants but also study partners when seeking to identify preclinical or clinical AD.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://habs.mgh.harvard.edu/researchers/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Mass General Brigham. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM performed the statistical analysis, interpreted the data, prepared figures, and drafted the manuscript. RB performed the statistical analysis, provided assistance or guidance with the interpretation of the data and preparation of figures, and performed critical review of the manuscript. PV and CD performed critical review of the manuscript. RS designed the study and performed critical review of the manuscript. DR performed cognitive assessments and critical review of the manuscript. KJ designed the study and the neuroimaging protocols and performed review of the manuscript. JG performed cognitive assessments, assisted with interpretation of the data, and performed critical review of the manuscript. RA designed the study, performed cognitive assessments, assisted with the interpretation of the data, and performed critical review of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Institute on Aging (P01AG036694, R01 AG046396, R01 AG027435, K24 AG035007, and P50 AG005134), NCRR P41 RR14075, K01 AG040197, the Harvard NeuroDiscovery Center, and Alzheimer's Association and other philanthropic organizations. This research was carried out in whole or in part at the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital, using resources provided by the Center for Functional Neuroimaging Technologies, P41EB015896, a P41 Biotechnology Resource Grant supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health. This work also involved the use of instrumentation supported by the NIH Shared Instrumentation Grant Program and/or High-End Instrumentation Grant Program; specifically, grant number(s) S10RR021110, S10RR023043, and S10RR023401. PV was funded by the NIH-NIA R01 AG061083. JG received support from AACF-16-440965 and K23 AG058805. RB received support from R00AG061238 and AARF-20-675646. RA received support from AARG-17-529011 and NIH R01AG058825. Research reported in this publication was supported by the National Institute on Aging of the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ACKNOWLEDGMENTS

We thank all the collaborators and contributors to the Harvard Aging Brain Study (https://www.nmr.mgh.harvard.edu/lab/harvardagingbrain/aboutus). Finally, we are grateful to our research participants for their altruism and willingness to take part in our study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2021.806432/full#supplementary-material

REFERENCES

Amariglio, R. E., Mormino, E. C., Pietras, A. C., Marshall, G. A., Vannini, P., Johnson, K. A., et al. (2015). Subjective cognitive concerns, amyloid-β, and neurodegeneration in clinically normal elderly. *Neurology* 85, 56–62. doi: 10.1212/WNL.0000000000001712

Becker, J. A., Hedden, T., Carmasin, J., Maye, J., Rentz, D. M., Putcha, D., et al. (2011). Amyloid-β associated cortical thinning in clinically normal elderly. *Ann. Neurol.* 69, 1032–1042. doi: 10.1002/ana.22333

Benjamini, Y., and Hochburg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* 57, 289–300. doi: 10.1111/j.2517-6161.1995.tb02031.x

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., and Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol.* 112, 389–404. doi: 10.1007/s00401-006-0127-z

Braak, H., and Braak, E. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol. Aging* 18, 351–357. doi: 10.1016/S0197-4580(97)00056-0

Buckley, R. F., Mormino, E. C., Amariglio, R. E., Properzi, M. J., Rabin, J. S., Ying, Y., et al. (2018). Sex, amyloid, and APOE ε 4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimers Dement.* 14, 1193–1203. doi: 10.1016/j.jalz.2018.04.010

D'Arcy, S., Rapcan, V., Gali, A., Burke, N., O'Connell, G. C., Robertson, I. H., et al. (2013). A study into the automation of cognitive assessment tasks for delivery via the telephone: lessons for developing remote monitoring applications for the elderly. *Technol. Health Care* 21, 387–396. doi: 10.3233/THC-130740

Dagley, A., Lapoint, M., Huijbers, W., Hedden, T., Donald, G., Chatwal, J. P., et al. (2017). Harvard aging brain study: dataset and accessibility. *NeuroImage* 144(Pt B), 255–258. doi: 10.1016/j.neuroimage.2015.03.069.Harvard

Delacourte, A., Sergeant, N., Wattez, A., Maurage, C.-A., Lebert, F., Pasquier, F., et al. (2002). Tau aggregation in the hippocampal formation: an ageing or a pathological process? *Exp. Gerontol.* 37, 1291–1296. doi: 10.1016/S0531-5565(02)00141-9

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., et al. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* 31, 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Donovan, N. J., Locascio, J. J., Marshall, G. A., Gatchel, J. R., Hanseeuw, B. J., Rentz, D. M., et al. (2018). Longitudinal association of amyloid-β and anxious-depressive symptoms in cognitively normal older adults. *Am. J. Psychiatry* 175, 530–537. doi: 10.1176/appi.ajp.2017.17040442

Espenes, R., Kirsebom, B. E., Eriksson, C., Waterloo, K., Hessen, E., Johnsen, S. H., et al. (2020). Amyloid plaques and symptoms of depression links to medical help-seeking due to subjective cognitive decline. *J. Alzheimers Dis.* 75, 879–890. doi: 10.3233/JAD-190712

Fischl, B., Salat, D. H., van der Kouwe, A. J. W., Makris, N., Ségonne, F., Quinn, B. T., et al. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage* 23(Suppl. 1), S69–S84. doi: 10.1016/j.neuroimage.2004.07.016

Geddes, M. R., O'Connell, M. E., Fisk, J. D., Gauthier, S., Camicioli, R., and Ismail, Z. (2020). Remote cognitive and behavioral assessment: report of the Alzheimer society of Canada task force on dementia care best practices for COVID-19. *Alzheimers Dement. (Amst.)* 12:e12111. doi: 10.1002/dad2.12111

George, M. F., Holingue, C. B., Briggs, F. B. S., Shao, X., Bellesis, K. H., Whitmer, R. A., et al. (2016). Feasibility study for remote assessment of cognitive function in multiple sclerosis. *J. Neurol. Neuromed.* 1, 10–18.

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., et al. (2019). The REDCap consortium: building an international community of software platform partners. *J. Biomed. Inform.* 95:103208. doi: 10.1016/j.jbi.2019.103208

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., and Conde, J. G. (2009). Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 42, 377–381. doi: 10.1016/j.jbi.2008.08.010

Hill, N. L., Mogle, J., Bhargava, S., Bell, T. R., Bhang, I., Katz, M., et al. (2020). Longitudinal relationships among depressive symptoms and three types of memory self-report in cognitively intact older adults. *Int. Psychogeriatr.* 32, 719–732. doi: 10.1017/S104161021900084X

Jacobs, D. M., Peavy, G. M., Banks, S. J., Gigliotti, C., Little, E. A., and Salmon, D. P. (2021). A survey of smartphone and interactive video technology use by participants in alzheimer's disease research: implications for remote cognitive assessment. *Alzheimers Dement. (Amst.)* 13:e12188. doi: 10.1002/dad2.12188

Jafari, M., and Ansari-Pour, N. (2019). Why, when, and how to adjust your P values? *Cell J.* 20, 604–607. doi: 10.22074/cellj.2019.5992

Johnson, K. A., Schultz, A., Betensky, R. A., Becker, J. A., Sepulcre, J., Rentz, D., et al. (2016). Tau positron emission tomographic imaging in aging and early Alzheimer disease. *Ann. Neurol.* 79, 110–119. doi: 10.1002/ana.24546

Lavigne, K., Sauve, G., Raucher-Chéné, D., Guimond, S., Lecomte, T., Bowie, C. R., et al. (2021). Remote cognitive assessment in severe mental illness: a scoping review. *PsyArXiv* [Pre-print]. doi: 10.31234/osf.io/r7ymj

Lehrner, J., Moser, D., Klug, S., Gleiß, A., Auff, E., Dal-Bianco, P., et al. (2014). Subjective memory complaints, depressive symptoms and cognition in patients attending a memory outpatient clinic. *Int. Psychogeriatr.* 26, 463–473. doi: 10.1017/S1041610213002263

Li, C., Neugroschl, J., Luo, X., Zhu, C., Aisen, P., Ferris, S., et al. (2017). The utility of the cognitive function instrument (CFI) to detect cognitive decline in non-demented older adults. *J. Alzheimers Dis.* 60, 427–437. doi: 10.3233/JAD-161294

Miebach, L., Wolfsgruber, S., Polcher, A., Peters, O., Menne, F., Luther, K., et al. (2019). Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. *Alzheimers Res. Ther.* 11:66. doi: 10.1186/s13195-019-0515-y

Mormino, E. C., Betensky, R. A., Hedden, T., Schultz, A. P., Ward, A., Huijbers, W., et al. (2014). Amyloid and APOE e4 interact to influence short-term decline in preclinical Alzheimer disease. *Neurology* 82, 1760–1767. doi: 10.1212/WNL.0000000000000431

Müller-Gärtner, H. W., Links, J. M., Prince, J. L., Bryan, R. N., McVeigh, E., Leal, J. P., et al. (1992). Measurement of radiotracer concentration in brain gray matter using positron emission tomography: MRI-based correction for partial volume effects. *J. Cereb. Blood Flow Metab.* 12, 571–583. doi: 10.1038/jcbfm.1992.81

Nosheny, R. L., Jin, C., Neuhaus, J., Insel, P. S., Mackin, R. S., and Weiner, M. W. (2019). Study partner-reported decline identifies cognitive decline and dementia risk. *Ann. Clin. Transl. Neurol.* 6, 2448–2459. doi: 10.1002/acn3.50938

Nuño, M. M., Gillen, D. L., and Grill, J. D. (2019). Study partner types and prediction of cognitive performance: implications to preclinical Alzheimer's trials. *Alzheimers Res. Ther.* 11:92. doi: 10.1186/s13195-019-0544-6

Pachana, N. A., Byrne, G. J., Siddle, H., Koloski, N., Harley, E., and Arnold, E. (2007). Development and validation of the geriatric anxiety inventory. *Int. Psychogeriatr.* 19, 103–114. doi: 10.1017/S1041610206003504

R Core Team. (2019). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Rueda, A., Lau, K., Saito, N., Harvey, D., Risacher, S., Aisen, P., et al. (2015). Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease. *Alzheimers Dement.* 11, 1080–1089. doi: 10.1016/j.jalz.2014.09.002.Self-rated

Ryan, M. M., Grill, J. D., Gillen, D. L., and Alzheimer's Disease Neuroimaging Initiative (2019). Participant and study partner prediction and identification of cognitive impairment in preclinical Alzheimer's disease: study partner vs. participant accuracy. *Alzheimers Res. Ther.* 11:85. doi: 10.1186/s13195-019-0539-3

Valech, N., Mollica, M. A., Olives, J., Tort, A., Fortea, J., Lleo, A., et al. (2015). Informants' perception of subjective cognitive decline helps to discriminate preclinical Alzheimer's disease from normal aging. *J. Alzheimers Dis.* 48, S87–S98. doi: 10.3233/JAD-150117

Vannini, P., Amariglio, R., Hanseeuw, B., Johnson, K. A., McLaren, D. G., Chhatwal, J., et al. (2017). Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease. *Neuropsychologia* 99, 343–349. doi: 10.1016/j.neuropsychologia.2017.04.002

Wadsworth, H. E., Galusha-Glasscock, J. M., Womack, K. B., Quiceno, M., Weiner, M. F., Hynan, L. S., et al. (2016). Remote neuropsychological assessment in rural American Indians with and without cognitive impairment. *Arch. Clin. Neuropsychol.* 31, 420–425. doi: 10.1093/arclin/acw030

Wang, S. M., Han, K. D., Kim, N. Y., Um, Y. H., Kang, D. W., Na, H. R., et al. (2021). Late-life depression, subjective cognitive decline, and their additive risk in incidence of dementia: a nationwide longitudinal study. *PLoS One* 16:e0254639. doi: 10.1371/journal.pone.0254639

Wechsler, D. (1987). *WMS-R Wechsler Memory Scale-Revised Manual*, The Psychological Corporation Edn. San Antonio, TX: Harcourt Brace Jovanovich, Inc.

Wolfsgruber, S., Jessen, F., Koppara, A., Kleineidam, L., Schmidtke, K., Frölich, L., et al. (2015). Subjective cognitive decline is related to CSF biomarkers of AD in patients with MCI. *Neurology* 84, 1261–1268. doi: 10.1212/WNL.0000000000001399

Wolfsgruber, S., Kleineidam, L., Guski, J., Polcher, A., Frommann, I., Roeske, S., et al. (2020). Minor neuropsychological deficits in patients with subjective cognitive decline. *Neurology* 95:e1134. doi: 10.1212/WNL.0000000000010142

Yates, J. A., Clare, L., and Woods, R. T. (2017). Subjective memory complaints, mood and MCI: a follow-up study. *Aging Ment. Health* 21, 313–321. doi: 10.1080/13607863.2015.1081150

Yesavage, J., Brink, T., Rose, T., Lum, O., Huang, V., Adey, M., et al. (1982). Development and validation of a geriatric depression screening scale: a preliminary report. *J. Psychiatr Res.* 17, 37–49.

Zlatar, Z. Z., Muniz, M., Galasko, D., and Salmon, D. P. (2018). Subjective cognitive decline correlates with depression symptoms and not with concurrent objective cognition in a clinic-based sample of older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 73, 1198–1202. doi: 10.1093/geronb/gbw207

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 03 February 2022
doi: 10.3389/fnagi.2021.781465

Altered Interplay Among Large-Scale Brain Functional Networks Modulates Multi-Domain Anosognosia in Early Alzheimer's Disease

*Jose Manuel Valera-Bermejo[1], Matteo De Marco[2] and Annalena Venneri[1,2]**

[1] Department of Neuroscience, University of Sheffield, Sheffield, United Kingdom, [2] Department of Life Sciences, Brunel University London, Uxbridge, United Kingdom

Decline in self-awareness is a prevalent symptom in Alzheimer's disease (AD). Current data suggest that an early breakdown in the brain's default mode network (DMN) is closely associated with the main symptomatic features in AD patients. In parallel, the integrity of the DMN has been shown to be heavily implicated in retained self-awareness abilities in healthy individuals and AD patients. However, the global contribution to awareness skills of other large-scale networks is still poorly understood. Resting-state functional magnetic resonance imaging (rs-fMRI) scans were acquired and pre-processed from 53 early-stage AD individuals. A group-level independent component analysis was run to isolate and reconstruct four intrinsic connectivity large-scale brain functional networks, namely left and right central executive fronto-parietal networks (FPN), salience network, and anterior and posterior DMN. Hypothesis-driven seed-based connectivity analyses were run to clarify the region-specific underpinnings of multi-domain anosognosia. Multiple regression models were run on large-scale network- and seed-based connectivity maps, including scores of memory, non-memory and total anosognosia obtained via the Measurement of Anosognosia Questionnaire. Memory anosognosia scores were associated with selective lower fronto-temporal connectivity and higher parieto-temporal connectivity. Non-memory anosognosia scores were associated with higher connectivity between the anterior DMN and the cerebellum, between the left medial prefrontal seeds and the contralateral prefrontal cortex, and between the left hippocampal seed and the left insula; lower connectivity was observed between the right prefrontal cortex and the right lingual seed. Lastly, total anosognosia scores were associated with large-scale network alterations, namely reduced left-FPN expression in the left posterior cingulate, reduced right-FPN expression in the left inferior lingual gyrus and adjacent inferior occipital cortex, and increased right-FPN expression in the right anterior cingulate. Seed-based analyses yielded significant connectivity differences only in the connectivity pattern associated with the left hippocampal seed by displaying lower intercommunication with the right prefrontal cortex, but higher

OPEN ACCESS

Edited by:
Howard Rosen,
University of California,
San Francisco, United States

Reviewed by:
Oriol Turró-Garriga,
Institute of Biomedical Research of Girona, Spain
Christine Bastin,
University of Liège, Belgium

***Correspondence:**
Annalena Venneri
annalena.venneri@brunel.ac.uk

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *22 September 2021*
Accepted: *29 December 2021*
Published: *03 February 2022*

Citation:
Valera-Bermejo JM, De Marco M and Venneri A (2022) Altered Interplay Among Large-Scale Brain Functional Networks Modulates Multi-Domain Anosognosia in Early Alzheimer's Disease. Front. Aging Neurosci. 13:781465. doi: 10.3389/fnagi.2021.781465

connectivity with the left caudate nucleus. These findings support the hypothesis that alterations in functional connectivity of frontal lobe regions involved in executive-related mechanisms represent the neural correlates of domain-specific anosognosia in early AD. Up-regulated connectivity with subcortical structures appears to contribute to changes in the network dynamics interplay and fosters the appearance of anosognosia.

Keywords: anosognosia, large-scale networks, mild cognitive impairment, functional MRI, unawareness, resting-state

INTRODUCTION

Anosognosia in Alzheimer's disease (AD) is a prevalent symptom that can be defined as the inability of a patient to recognize decline in their own cognitive functioning (Hanseeuw et al., 2020). The clinical manifestations of anosognosia at an individual level affect efficiency in the various cognitive domains in a highly heterogeneous way (Starkstein, 2014). The onset of this symptom, however, tends to occur quite early on throughout the clinical timeline, either at the stage of mild cognitive impairment (MCI), or even before that, during the preclinical period when individuals who are still psychometrically normal but report subjective cognitive complaints might show poorer awareness of the extent of their decline than their informant would report (Cacciamani et al., 2017; Hanseeuw et al., 2020). Anosognosia might not manifest only as lack of awareness of a memory impairment but can also apply to other cognitive domains, such as unawareness of executive dysfunction, of socio-emotional deficits or of difficulties with daily life activities (Lacerda et al., 2021). This heterogeneity highlights the multidimensionality of this phenomenon and warrants the necessity for a multi-domain clinical assessment (Leicht et al., 2010; de Ruijter et al., 2020).

The use of resting-state fMRI (rs-fMRI) in AD holds great potential as an early diagnostic biomarker, as evidenced by studies that found disruptions of intrinsic large-scale network connectivity in the prodromal and mild AD stages (Sorg et al., 2007; Vemuri et al., 2012; Antoine et al., 2019). It is now well recognized that three of the brain main large-scale functional networks play a crucial role in efficient human cognition, namely the *default mode network* (DMN), the nodes of which are centered in the medial prefrontal cortex, posterior cingulate cortex/precuneus and medial temporal cortices, including the hippocampus (Raichle, 2015; Alves et al., 2019), the *salience networ*k, of which the anterior cingulate cortex and insula are the most representative hubs, and the *central executive fronto-parietal network,* with its computational regions found predominantly in the dorsolateral prefrontal and posterior parietal cortices (Bressler and Menon, 2010). Published evidence suggests that DMN down-regulation is significantly associated with cognitive decline during the early clinical stages of AD (Greicius et al., 2004; Badhwar et al., 2017; Grieder et al., 2018). At the same time, however, functional integrity of DMN hubs is implicated in self-awareness abilities, as evidenced in healthy individuals (Northoff et al., 2006; Davey et al., 2016). Consequently, AD patients with alterations affecting the DMN might have difficulties with self-awareness or may manifest anosognosia very early in the course of the disease.

To clarify the role of dysfunction in regions of the DMN when anosognosia is present in AD, partial insight is provided by fMRI studies that investigated hemodynamic activation in patients with AD during tasks tapping self-awareness abilities. These studies reported 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) regions during tasks of self-reflection and perspective-changing, with an additional, yet limited, activation of posteromedial parietal regions (Amanzio et al., 2011). When resting-state activity within the DMN was studied in relation to anosognosia in this patient population, Berlingeri et al. (2015) found that anosognosia for memory impairment was associated with reduced connectivity of the DMN network, the left lateral temporal cortex, the hippocampus and the insula. Perrotin et al. (2015) found reduced connectivity between the medial temporal lobe and both orbitofrontal cortex and posterior cingulate. Vannini et al. (2017) showed reduced connectivity between the precuneus and the bilateral inferior parietal lobe, the left posterior cingulate and orbitofrontal cortex, and between the right hippocampus and the fusiform gyrus. Lastly, Mondragón et al. (2021) showed that stronger connectivity of the bilateral anterior cingulate cortex was associated with anosognosia in prodromal AD. Notably, regardless of the applied methodology, all task-based and rs-fMRI studies reported an involvement of the frontal lobe cortex and/or anterior cingulate cortex as the essential neural substrates modulating 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., 2017; Antoine et al., 2019; Mondragón et al., 2021).

At the cognitive level, the most influential theoretical framework at the basis of disorders of awareness is the Cognitive Awareness Model (Agnew and Morris, 1998). This model posits that a "Mnemonic Comparator" based on executive resources plays a major role in sustaining awareness. It has, thus, been proposed that loss of functional integrity within fronto-temporo-parietal networks (including the DMN) may result in dysfunctional changes to the comparator system, and this, in turn, may lead to deficits in self-awareness abilities (Tagai et al., 2020). In this respect, an association between anosognosia and the integrity of the DMN has been reported by multiple studies (Zamboni and Wilcock, 2011; Antoine et al., 2019; Mondragon et al., 2019). Furthermore, the presence of anosognosia at the MCI stage has been found to predict hypometabolism in regions

of the DMN and progression to dementia at a 2-year follow up (Therriault et al., 2018). The role that other, non-DMN large-scale networks play in the genesis and persistence of this symptom, however, is still poorly understood. Clarifying in more detail the changes to the overall neurofunctional circuitry (i.e., which networks are involved and in what direction the association is observed) that are associated with domain-specific anosognosia would provide valuable insights into the mechanisms fostering the presence of this symptom in AD.

Although the reviewed literature provides some evidence of the involvement of resting-state functional connectivity in the mechanisms of anosognosia in early AD, no study has yet investigated seed-based and data-driven (i.e., as informed by latent-variable models) pathways in a systematic way, including non-DMN networks, and by differentiating anosognosia for memory and non-memory impairments. Relying on the "Mnemonic Comparator" notion introduced as part of the Cognitive Awareness Model (Agnew and Morris, 1998), we hypothesized that connectivity alterations ascribable to fronto-limbic dysfunction would be associated with single-domain (i.e., "memory"/"non-memory") and multi-domain (i.e., memory plus non-memory, or "total") anosognosia in the early stage of AD. In addition, we also hypothesized that alterations to the DMN of adaptive and compensatory nature, such as increased abnormal network-to-network interplay, would be deployed (and, thus, would emerge as statistically significant) in the presence of anosognosia.

MATERIALS AND METHODS

Experimental Design

This study followed a correlational design in which measures of domain-specific (memory and non-memory) and total anosognosia and statistical maps of brain activity extracted from fMRI images acquired in resting state were entered into linear regression models to explore the relationship between different brain network activities and patients' levels of cognitive awareness.

Participants

Fifty-three patients with cognitive impairment were included in this study. Recruitment of patients and administration of study procedures were carried out as an ancillary study of the EU-funded Virtual Physiological Human—DementiA Research Enabled by IT initiative[1], a multicenter project coordinated by the Department of Neuroscience, University of Sheffield, United Kingdom. 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 if they also met the eligibility criterion for this additional study, i.e., having a reliable informant. Our intention was to cover the entire continuum of early AD clinical severity (i.e., from MCI to mild dementia) in order to maximize numerical variability of outcome variables (i.e., voxel-by-voxel indices of connectivity) as well as of the main predictors (i.e., the anosognosia scores). Of the total sample, $n = 24$ had a clinical diagnosis of mild AD, as per the National Institute of Aging diagnostic criteria typically implemented in clinical settings (McKhann et al., 2011) and $n = 29$ had a diagnosis of MCI due to AD (Albert et al., 2011) based on clinical, neuropsychological and structural neuroimaging biomarkers of neuronal injury (Albert et al., 2011, p. 8). Patient diagnoses were corroborated by regular clinical longitudinal follow ups that were carried out for at least 4 years after recruitment. In all cases included in this report the clinical course and structural imaging findings were supportive of an AD etiology. A series of exclusion criteria (applied at recruitment and, retrospectively, at each clinical follow up examination) was defined to rule out signs and symptoms suggestive of a condition incompatible with the objective of this study. This included: significant neurological conditions (e.g., history of acute or chronic cerebrovascular disease or transient ischemic attacks), history of epilepsy or presence of uncontrolled brain seizures, peripheral neuropathy, significant neuropsychiatric symptoms or evidence of radiological abnormalities (other than those seen as part of the typical AD profile); 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 interventions displaying important organic adverse effects or medications used in other research protocols) and presence of major disabilities significantly affecting daily life activities. Since the indices of anosognosia were obtained from patient-caregiver dyads, patients from the primary study without a reliable informant were not offered participation. A brief screening of caregivers' neurological status was completed by a senior clinician to rule out neurological or psychological factors that could have prevented them from providing reliable information. This study received ethical approval by the Regional Ethics Committee of Yorkshire and Humber (Ref No: 12/YH/0474). In accordance with data-collection procedures approved by the European Union, ethical approval was reiterated by the relevant local ethics committees at recruitment sites. Written informed consent was obtained from all participants.

Anosognosia Assessment

The *Measurement of Anosognosia Instrument* (Stewart et al., 2010) was used to quantify the patients' level of (or lack of) awareness of difficulties in a set of daily life scenarios. This questionnaire consists of 15 dichotomical "yes/no" questions on cognitive deficits that may manifest during daily life routines and the responses are split into two functional domains: "memory" (9 items) and "non-memory" (including anosognosia for executive dysfunction and anosognosia for deficits in daily life activities; 6 items). All 15 questions must be answered independently by the patient and by the informant. As a result, two set of scores are obtained: that provided by the informant (construed as the "standard-of-truth" of the patient's abilities) and that provided by the patient as a self-evaluative measure. Individual informant-based and patient-based responses were compared

[1]https://cordis.europa.eu/project/id/601055

to quantify the number of discrepant answers (i.e., higher discrepancy scores indicate a higher degree of anosognosia). Discrepancy scores were used to quantify the presence of domain-specific anosognosia ("memory," max score: 9; "non-memory," max score: 6) and a "total" score that was also obtained by the sum of the memory and non-memory scores (max score: 15) (Migliorelli et al., 1995; Stewart et al., 2010).

Functional Magnetic Resonance Imaging Acquisition and Pre-Processing

Brain MRI data were acquired following the protocol for multicenter harmonization for Philips MRI scanners defined by the VPH-DARE@IT consortium. Images were acquired on two Philips scanners. The following parameters were used for acquisition of resting state functional MRI (rs-fMRI) images on the 3 T Philips Ingenia scanner: 35 axial slices, reconstructed in-plane voxel dimensions = 1.8 × 1.8 mm^2, slice thickness = 4.0 mm, 128 × 128 matrix size, 230 mm field of view, repetition time = 2.6 s, echo time = 35 ms, flip angle = 90°, number of temporal dynamics = 125. Acquisitions of rs-fMRI images on the Philips Achieva 1.5 T scanner had the following specifications: voxel size: 3.28 × 3.28 mm^2, slice thickness = 6.00 mm, 64 × 64 matrix size, 230 mm field of view, repetition time = 2 s, echo time = 50 ms and flip angle = 90°, number of temporal dynamics = 240. As per protocol, 20 s of dummy acquisitions were set at the beginning of each sequence to enable the scanner to reach electromagnetic equilibrium. A T1-weighted image was also obtained for each participant as part of the MRI protocol.

Functional brain images were processed with Statistical Parametric Mapping (SPM) 12 software running in MATLAB R2014a (V.8.3) through a standardized fMRI data pre-processing pipeline that included slice-timing, realignment, normalization, temporal band-pass filtering (0.01–0.1 Hz) and a 6-mm full-width at half-maximum Gaussian kernel smoothing (Postema et al., 2019). In addition, total intracranial volumes were computed from the T1-weighted scans using the *get_totals* MATLAB script[2] and summing the maps of gray matter, white matter and cerebrospinal fluid volumes.

Independent Component Analysis

Pre-processed rs-fMRI images were analyzed with a group independent component analysis (ICA), to extract functional large-scale network connectivity maps. The GIFT toolbox (v1.3i)[3] was used to this end. The Infomax optimization principle was applied and the number of components to be extracted set at 20, as a reliable number that typically separates human resting-state connectivity into its fundamental networks (Wang and Li, 2015). Individual independent component maps were reconstructed for each of the five main brain functional networks of interest and these were selected via visual inspection that was carried out independently by the three co-authors with 100% agreement. These five pathways were the anterior DMN (aDMN), the posterior DMN (pDMN), the left frontoparietal network (l-FPN), the right frontoparietal network (r-FPN), and the salience network. Large-scale network connectivity *beta*-score maps were then extracted for each participant for group-level inferential modeling.

Seed-Signal Extraction and Seed-Based First Level Analyses

Region of interest (ROI) analyses were carried out on each individual patient's rs-fMRI acquisition to define the association between the hemodynamic signal extracted from a series of seed regions and the signal throughout the entire brain. The resulting maps are typically interpreted as the functional connectivity of those seed regions. Cytoarchitectonically-defined seed regions were created using the WFU PickAtlas toolbox and AAL human brain atlas (Tzourio-Mazoyer et al., 2002; Maldjian et al., 2003). Informed by the Cognitive Awareness Model and based on previous neuroimaging research (Mondragon et al., 2019), the following 9 ROIs were chosen: anterior cingulate cortex, medial prefrontal cortex, medial orbitofrontal cortex, precuneus, and posterior cingulate cortex were selected for their established role in self-awareness (Northoff et al., 2006), while precentral gyrus, lingual gyrus, fusiform gyrus, and hippocampus were selected based on published evidence suggesting that these are part of the neural substrate associated with levels of anosognosia in the early stages of AD (Valera-Bermejo et al., 2020). Seed time-courses were extracted independently for the left and right hemispheres (18 seeds in total) with the SPM-based MarsBaR toolbox[4] (Brett et al., 2002).

First-level analyses were devised in the form of general linear models with the seed time-course as predictor. The physiological signal from the global maps of white matter and cerebrospinal fluid was regressed out to minimize the impact of non-neural sources of variability. Twenty-four parameters related to head-motion i.e., the six rigid-body transformation regressors generated during realignment, their temporal derivatives, and all squared values were also regressed out (max. translational motion 3 mm and max. rotational motion 3°). This methodology also allowed for functional scans to address and minimize the impact of the differences in magnetic field strength as there is evidence that signal extent and intensity are not affected by this effect, but signal-to-noise ratio may variate depending on magnetic field-strength (Voss et al., 2006).

Group-Level Data Modeling

Multiple regression analyses were carried out at group level to test the functional associations of domain-specific (i.e., memory and non-memory) and total anosognosia scores with large-scale network connectivity maps extracted through ICA and individual ROI maps obtained through seed-based first-level analysis. The cluster-forming threshold of significance was set at $p = 0.005$ uncorrected. Clusters were considered significant only if they survived a family-wise error (FWE)-corrected threshold of $p < 0.05$ (Whitwell, 2009). All statistical models were controlled for age, years of education, total intracranial volume, and normalized hippocampal volumes (Cardoso et al., 2013). The

[2] http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m

[3] mialab.mrn.org/software/gift

[4] http://marsbar.sourceforge.net/

latter served to control for an index of neurodegeneration-informed disease severity. Peak regions were transposed from Montreal Neurological Institute coordinates to the Talairach space, to permit identification through the Talairach Daemon Client, version 2.4.3 (Lancaster et al., 2000).

RESULTS

Demographics

Demographic and sample characteristics are reported in **Table 1**.

Large-Scale Network Results

Significant associations emerged in some of the networks of interest (the extent of the clusters in voxels is indicated with *k*). Negative associations were found between expression of the l-FPN and both memory ($k = 298$, $p = 0.02$) and total anosognosia scores ($k = 375$, $p = 0.006$). These were in limbic-occipital regions, namely the left lingual gyrus and left posterior cingulate (**Table 2** and **Figure 1**). Conversely, a significant positive association was found between expression of the r-FPN and total anosognosia ($k = 264$, $p = 0.036$). This was located in the left lingual gyrus and left inferior occipital gyrus (**Table 2** and **Figure 2**). Along the same directional lines, positive associations were found between non-memory anosognosia scores and aDMN expression in the cerebellar culmen, bilaterally ($k = 263$, $p = 0.038$), and between total anosognosia and aDMN expression in the right anterior cingulate ($k = 261$, $p = 0.039$; **Table 2** and **Figure 3**). No significant associations were found in the pDMN or salience network.

Seed-Based Analyses Results

Memory anosognosia scores were negatively associated with: right anterior cingulate connectivity in a cluster extending from the right fusiform gyrus (BA 20) to the caudate ($k = 383$, $p = 0.025$); right hippocampal connectivity in the territory of the bilateral caudate and right thalamus ($k = 394$, $p = 0.016$); and left hippocampal connectivity in the right dorsolateral prefrontal cortex ($k = 333$, $p = 0.040$). Memory anosognosia scores were also positively associated with: right precuneal connectivity in the left fusiform and lingual gyri ($k = 358$, $p = 0.028$); right posterior cingulate connectivity in the right inferior occipital gyrus and cuneus ($k = 407$, $p = 0.025$); and left anterior cingulate connectivity in the precentral and postcentral gyri ($k = 346$, $p = 0.029$). All these results are summarized in **Table 3** and **Figure 4**.

TABLE 1 | Demographic characteristics of the sample.

Variable	Mean (*SD*)/*n* = 53	Median/*n* = 53	Range (min–max)
Age	71.68 (10.20)	77	48–89
Gender (%) (Male/Female)	27 (51%)/26 (49%)	–	–
Years of education	10.62 (4.05)	11	5–20
Mini-Mental State Examination	23.38 (3.77)	24	15–30
Total intracranial volume (mm^3)	1422.63 (161.48)	1389.37	1131–1793
Memory anosognosia scores	1.34 (2.38)	2	−4–6
Non-memory anosognosia scores	1.04 (1.86)	1	−3–5
Total anosognosia scores	2.38 (3.75)	2	−6–10

TABLE 2 | Results emerging from large-scale brain functional networks obtained via independent component analysis.

Peak-based localization	HS	Cluster extent	T Score	MNI coordinates			FWE *P*-value
				x	*y*	*z*	
l-FPN							
Memory anosognosia (−)							
Posterior cingulate cortex (BA 30)	L	298	4.70	−20	−62	8	0.020
Lingual gyrus (BA 19)	L		4.59	−22	−68	−4	
Lingual gyrus (BA 18)	L		3.05	−16	−70	−12	
Total anosognosia (−)							
Lingual gyrus (BA 19)	L	375	5.22	−22	−68	−4	0.006
Posterior cingulate cortex (BA 30)	L		4.49	−24	−62	4	
Posterior cingulate cortex (BA 30)	L		3.75	−14	−66	4	
r-FPN							
Total anosognosia (+)							
Inferior occipital cortex (BA19)	L	264	4.89	−40	−74	−14	0.036
Inferior occipital cortex (BA19)	L		4.50	−36	−80	−10	
Lingual gyrus (BA 18)	L		3.36	−16	−84	−12	
aDMN							
Non-memory anosognosia (+)							
Cerebellum—culmen	L	263	5.21	−12	−48	−14	0.038
Cerebellum—culmen	R		4.94	4	−52	−14	
Cerebellum—culmen	L		3.49	−6	−36	−8	
Total anosognosia (+)							
Anterior cingulate cortex (BA 24)	R	261	4.35	10	18	20	0.039
Anterior cingulate cortex (BA 24)	R		3.70	16	28	16	

(−), negative correlation; (+), positive correlation; aDMN, anterior Default Mode Network; BA, Brodmann Area; FWE, Family-Wise Error; HS, Hemispheric Side; l-FPN, left Frontoparietal Network; MNI, Montreal Neurological Institute; r-FPN, right Frontoparietal Network.

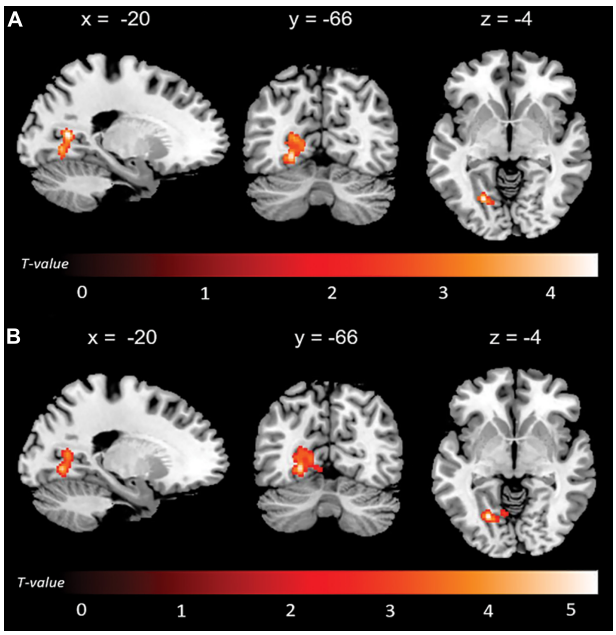


FIGURE 1 | Negative correlations between functional connectivity of the left fronto-parietal network (l-FPN) and **(A)** memory and **(B)** total anosognosia.

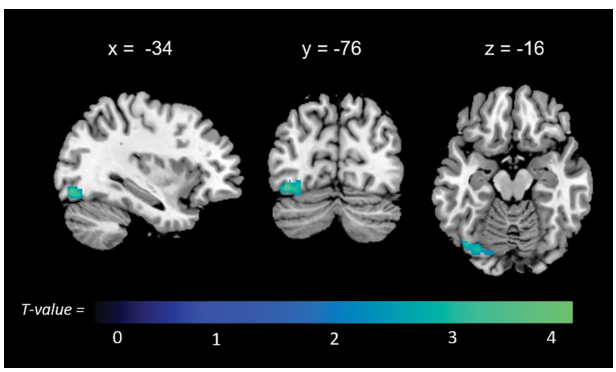


FIGURE 2 | Positive correlations between functional connectivity of the right frontoparietal network (r-FPN) and total anosognosia.

Non-memory anosognosia scores were negatively associated with: right lingual connectivity in the right dorsolateral prefrontal cortex (k = 590, p = 0.002); right precuneal connectivity in the right transverse temporal gyrus (BA 41) and in a caudate-thalamic area (k = 802, p = 0.001). Non-memory anosognosia scores were positively associated with: left anterior-cingulate connectivity in the right dorsolateral prefrontal cortex (k = 434, p = 0.012); left medioprefrontal connectivity in the right dorsolateral prefrontal cortex (k = 318, p = 0.048); and left hippocampal connectivity in a left caudate-insular cluster (k = 354, p = 0.031). All these findings are shown in **Table 4** and **Figure 5**.

Total anosognosia scores, finally, were negatively associated with left hippocampal connectivity in the right dorsolateral

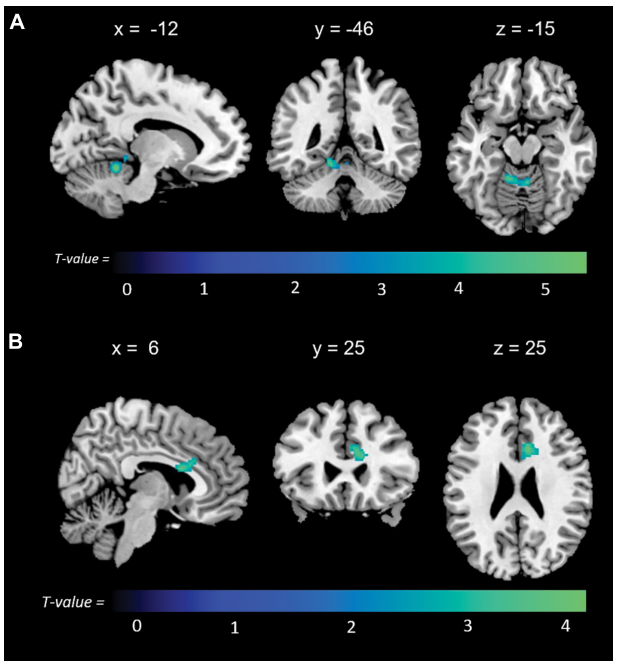


FIGURE 3 | Positive correlations between functional connectivity of the anterior default mode network (aDMN) and **(A)** non-memory and **(B)** total anosognosia.

prefrontal cortex (k = 457, p = 0.009), and positively associated with the left caudate nucleus (k = 330, p = 0.042). These findings are reported in **Table 5** and **Figure 6**.

DISCUSSION

The present study provides evidence of a specific combination of functional brain network dynamic changes associated with multi-domain anosognosia in the early stages of AD. A better understanding of the functional substrates of domain-specific anosognosia provides insight into how disconnection of structures at the basis of the Cognitive Awareness Model translates into different mechanisms, leading to impairment of self-awareness.

Functional Connectivity Associated With Memory Anosognosia

Unawareness of memory deficits was linked to specific patterns of functional connectivity of large-scale neural networks and region-to-region pathways. Memory anosognosia scores were linked negatively to l-FPN functional connectivity within the left lingual gyrus and posterior cingulate (a DMN node). In addition, seed-based models showed a negative link with structures in the frontotemporal territory, i.e., the right fusiform gyrus (right anterior cingulate seed, aDMN associated structure), and the right dorsolateral prefrontal cortex (left hippocampal seed, DMN associated structure). It appears, therefore, that within the main human large-scale neural functional networks, there

TABLE 3 | Neural correlates of memory anosognosia emerging from functional-connectivity patterns obtained via seed-based analysis.

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

BA, Brodmann Area; FWE, Family-Wise Error; HS, Hemispheric Side; L, Left; MNI, Montreal Neurological Institute; R, Right.

might be a possible inter-network down-regulation of FPN-DMN connectivity leading to memory anosognosia. A negative association was then found in the pathway between the right caudate and both right anterior cingulate and right hippocampal seeds. The involvement of temporal cortical structures in early AD patients presenting with higher memory anosognosia scores and functional connectivity alterations follows a pattern aligned with the pathophysiological progression of clinical AD. In this context, degeneration of the medial temporal lobe induces disruption of memory performance, but at the same time neuronal loss in these regions hampers functional interactions between crucial areas leading to reduced awareness of memory difficulties (Chavoix and Insausti, 2017). A histopathological study showed that AD patients with anosognosia had increased amyloid plaque density in the hippocampal pre-subiculum at *post-mortem* (Marshall et al., 2004). This finding, however, could have been partly driven by the severe pathological changes that typically affect the medial temporal lobe regions in the final stages of the disease. Pioneering studies that explored the neurofunctional substrates of memory anosognosia in AD through single-photon emission computerized tomography (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 highlighted right frontal cortical structures as the most consistent neural correlate. In a functional MRI study by Zamboni et al. (2013), AD patients showed decreased frontotemporal brain activation in relation to self-awareness. This evidence is aligned with our findings detecting an association with frontotemporal connectivity.

Additionally, memory anosognosia scores were also positively associated with connectivity between the right precuneus seed and the left lingual and fusiform gyrus and between the left anterior cingulate seed and left postcentral gyrus. Two recurring regions from our pattern of findings were the fusiform and lingual gyri. These structures have also been associated with anosognosia and reduced brain gray matter volumes in early AD (Guerrier et al., 2018; Valera-Bermejo et al., 2020). Functional alterations of the fusiform (Vannini et al., 2017) and lingual gyrus (Mitelpunkt et al., 2020) have been found to be associated with anosognosia in AD and might have strong links with regions within a broader network in charge of sustaining cognitive awareness. Increased frontal and parietal activity was found by Ruby et al. (2009) in a functional task-based fMRI 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 had higher activation of parietal cortices when engaging in tasks based on self-monitoring activities.

Functional Connectivity Associated With Non-memory Anosognosia

Anosognosia for executive and everyday-life deficits was positively associated with aDMN connectivity in the cerebellum. Increased connectivity in the cerebellar cortex within the aDMN could contribute to improving the cross-talk with functional networks that are involved in higher cognitive functions, as it has been shown that structures in the cerebellum provide substantial contributions to cognition, e.g., executive functions (Nowrangi et al., 2014; Xu et al., 2020). Our findings also stress the relevance

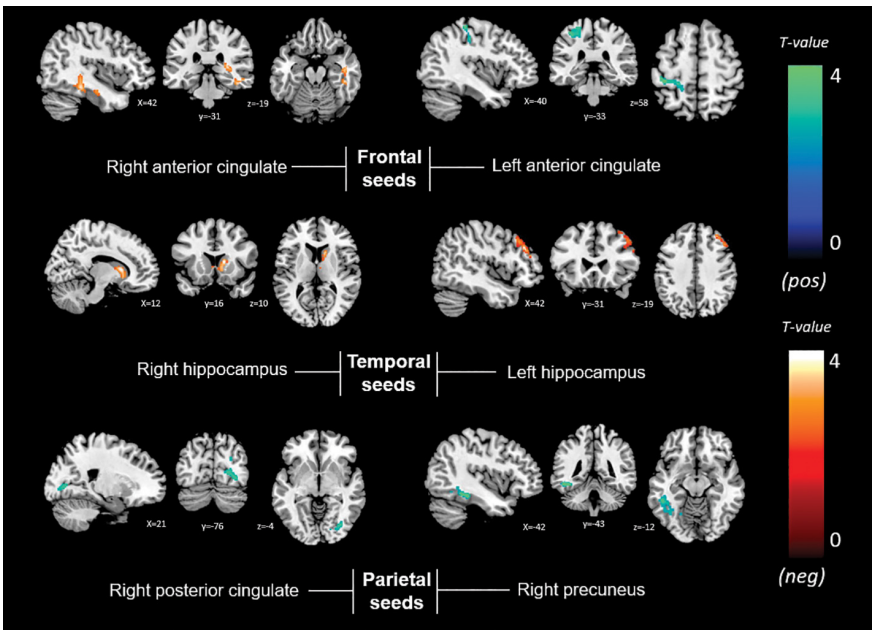


FIGURE 4 | Positive (blue) and negative (red) correlations between brain functional connectivity of selected unilateral seed regions and memory anosognosia scores.

of subcortical structures in contributing to the DMN in the presence of self-awareness impairment, as evidenced by the role played by the cerebellum (Buckner et al., 2011; Alves et al., 2019).

Similarly, the more anosognosic, the stronger the functional connectivity pattern between left anterior brain seeds (anterior cingulate, a salience network node, and medioprefrontal cortex, a DMN node) and the right dorsolateral prefrontal cortex (a FPN node). A positive association was also found in the pattern of left hippocampal connectivity (DMN associated) with the left insular cortex (a salience network node) and left caudate. Findings in the insula show consistency with those in the literature centered on the neuroscience of self-awareness (Lou et al., 2017). One study that highlighted gray matter volumetric changes in left insular-hippocampal regions was carried out by Sánchez-Benavides et al. (2018) who found that individuals self-assessed as unaware of cognitive decline had larger gray matter insular volumes compared with individuals displaying subjective cognitive decline. Additionally, informant-related reports of cognitive changes (unrelated to self-awareness status) were associated with smaller gray matter volume in the left hippocampus. The latter study provides valuable insights about a link between insular-hippocampal alterations in psychometrically-normal older adults and abnormalities in cognitive awareness. While we found higher connectivity between the left hippocampus and insula in relation to non-memory anosognosia, Berlingeri et al. (2015) reported reduced connectivity between these same structures in dementia patients, but for memory anosognosia. These results indicate that insulo-mediotemporal regions disconnection might be pivotal for the onset of anosognosia, with the insula serving as a vicarious salience system in the presence of unawareness for executive and daily life functions, and a "mnemonic" hub relating instead to memory unawareness. Moreover, the insula has been found to be concomitantly active alongside the prefrontal cortex and anterior cingulate in tasks requiring self-referential processing, such as interoception, self-recognition, or socio-emotional awareness (Craig, 2009; Modinos et al., 2009). Higher connectivity with the executive fronto-parietal network in this structure has been found in association with higher scores on tasks involving awareness of others (tasks of social cognition/theory of mind) in patients with early stage AD (Valera-Bermejo et al., 2021). The insula, a core region of the salience network, might up-regulate its functional connectivity toward regions typically targeted by the AD etiopathological cascade to support network function, as a way to allocate additional neural resources in support of dysfunctional DMN pathways, in an attempt to minimize the loss of connectivity and, thus, sustain the circuits that are responsible for acknowledging the presence of illness. In summary, it seems that non-memory anosognosia might be modulated by the up-regulation of the executive frontoparietal and salience network in the presence of a weakened DMN, although any attempted compensatory effect is ultimately unsuccessful.

Additionally, significant negative associations were found within the map of right lingual connectivity in the right dorsolateral prefrontal cortex and within the map of right precuneal connectivity in right subcortical regions (caudate and thalamus). The findings of this study bring compelling evidence of an involvement of the right dorsolateral prefrontal cortex in modulating awareness of cognitive difficulties, with both higher connectivity observed in the left frontal lobe and lower connectivity observed in the right lingual cortex. The main nodes of the central-executive FPN are centered in the dorsolateral prefrontal cortex and posterior parietal cortex (Bressler and Menon, 2010). The dorsolateral prefrontal cortex has been associated with executive functions and working

TABLE 4 | Neural correlates of non-memory anosognosia emerging from functional-connectivity patterns obtained via seed-based analysis.

Peak-based localization	HS	Cluster extent	T score	MNI coordinates			FWE *P*-value
				x	*y*	*z*	
Non-memory anosognosia							
Reduced connectivity							
Right lingual seed							
Middle frontal gyrus (BA 9)	R	590	5.26	32	44	30	0.002
Middle frontal gyrus (BA 9)	R		4.50	24	54	22	
Superior frontal gyrus (BA 10)	R		3.38	12	54	32	
Right precuneus seed							
Transverse temporal gyrus (BA 41)	R	802	4.98	40	−32	10	0.001
Thalamus	R		3.99	24	−24	16	
Caudate	R		3.99	22	−36	10	
Increased connectivity							
Left anterior cingulate cortex seed							
Superior frontal gyrus (BA 10)	R	434	4.35	20	58	18	0.012
Middle frontal gyrus (BA 9)	R		3.88	40	46	20	
Middle frontal gyrus (BA 9)	R		3.63	28	40	32	
Left medial prefrontal cortex seed							
Middle frontal gyrus (BA 9)	R	318	4.59	26	36	22	0.048
Middle frontal gyrus (BA 9)	R		3.71	30	44	30	
Superior frontal gyrus (BA 9)	R		3.26	20	50	20	
Left hippocampus seed							
Caudate	L	354	3.88	−16	−38	20	0.031
Insula (BA 13)	L		3.25	−26	−36	24	

BA, Brodmann Area; FWE, Family-Wise Error; HS, Hemispheric Side; L, Left; MNI, Montreal Neurological Institute; R, Right.

memory and a selective age-related vulnerability has been observed in the older population (MacPherson et al., 2002). Moreover, the right dorsolateral prefrontal cortex involvement in AD patients presenting with anosognosia has been evidenced in the current literature across multiple neuroimaging approaches (Reed et al., 1993; Starkstein et al., 1995; Ries et al., 2012). There is evidence that this region is part of an executive-control network that, in conjunction with the anterior cingulate cortex, coordinates behavior aimed at accomplishing life-related objectives (Cohen et al., 2000; Amanzio et al., 2011; Xu et al., 2020). In addition, the contribution of the dorsolateral prefrontal cortex to declarative memory has been established in AD (Kumar et al., 2017; Turriziani et al., 2019), as this structure is involved in working memory for manipulation and updating of conscious information that operates in close relation with a central executive system (Funahashi, 2017). Furthermore, the executive control network appears to rely on cerebro-cerebellar support in the presence of executive decline (Xu et al., 2020). Bi-directional dorsolateral prefrontal connectivity (i.e., a positive association found in contralateral frontal structures and a negative association found in ipsilateral temporal regions) might be at the basis of a role played by this region in sustaining adaptive cognitive control required by abilities such as attention (Gbadeyan et al., 2016).

Functional Connectivity Associated With Total Anosognosia

Total anosognosia scores in this early AD sample were negatively associated with l-FPN expression in the left posterior cingulate, and seed-based analyses yielded significant negative connectivity associations between the left hippocampal seed and the right dorsolateral prefrontal cortex. These findings translate into changes in inter-network communication; indeed, the posterior cingulate and hippocampal regions are intrinsically associated with the DMN while the dorsolateral prefrontal cortex supports the executive fronto-parietal network (Bressler and Menon, 2010; Alves et al., 2019). Therefore, these findings provide evidence of reduced inter-communication between the DMN and the executive fronto-parietal networks.

Positive associations were found with r-FPN expression in the left inferior lingual gyrus and adjacent inferior occipital cortex, and between the aDMN expression in the right anterior cingulate (a salience network node). Therefore, total anosognosia might be the symptomatic expression of abnormally increased up-regulation of DMN-Salience inter-network connectivity in support of cognitive shifting of reduced self-related internal abilities to external salient stimuli. In addition, seed-based analyses revealed positive significant connectivity associations between the left hippocampal seed and the left caudate nucleus. The interplay between the fronto-parietal network and the lingual gyrus is in line with a hypothesis of frontally-mediated control of disorders of awareness. The lingual gyrus is a region essential for visual perception (Yang et al., 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).

A comprehensive overview of the results in the present study indicates that the anterior cingulate cortex has a strong involvement in the overall clinical manifestation of multi-domain anosognosia. Structural changes are commonly seen later than functional changes in the course of AD (Ewers et al., 2011), but there is, however, evidence that variability in gray matter of the anterior cingulate cortex is related to non-memory and total anosognosia in early AD (Valera-Bermejo et al., 2020). The present rs-fMRI findings extend the involvement of this structure to anosognosia for multiple cognitive domains. Regardless of

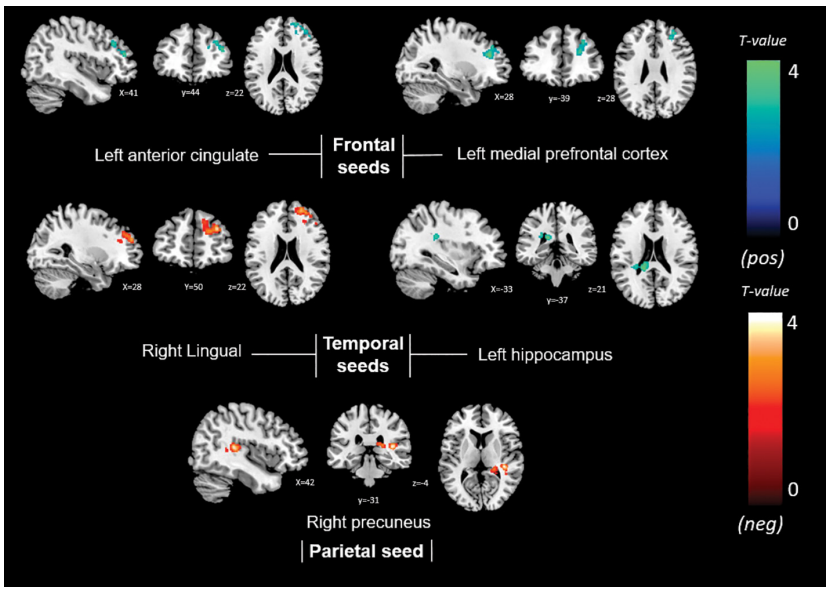


FIGURE 5 | Positive (blue) and negative (red) correlations between brain functional connectivity of selected unilateral seed regions and non-memory anosognosia scores.

the methodological approach, the anterior cingulate has been significantly implicated in modulating levels of awareness of symptoms in early AD (Hanyu et al., 2008; Amanzio et al., 2011; Zamboni et al., 2013; Guerrier et al., 2018; Mondragón et al., 2021). These results show consistency with the premise that midline anterior brain structures are essential for self-awareness and self-referential processing (Northoff et al., 2006; Lou et al., 2017). Structure and function of the anterior cingulate cortex could play a significant role alongside the resources deployed as part of the executive supporting system. This region could serve a major role in the executive comparator system described within the Cognitive Awareness Model (Agnew and Morris, 1998), in which the presence of synaptic dysfunction in anterior midline structures could generate a mismatch in the perceived reality and lead, therefore, to an event of cognitive unawareness. On this note, executive impairment, measured through a composite neuropsychological score, was shown to be associated with hypometabolism in the anterior cingulate in patients with a PET-informed diagnosis of prodromal AD, regardless of the extent of their amyloid burden (Yoon et al., 2019). Notably, the anterior cingulate has been found to be centrally involved in the manifestation of neuropsychiatric symptoms in AD (Boublay et al., 2016), where anosognosic symptoms are also listed as part of a spectrum of behavioral disorders that affects this clinical population (Tagai et al., 2020). In this context, the anterior cingulate cortex can be considered a core region that modulates behavior through reward, motivation, and initiation, i.e., the ability to commence a task (Devinsky et al., 1995). This could result in patients presenting with self-awareness deficits and displaying higher behavioral alterations when losing aspects of their sense of self.

TABLE 5 | Neural correlates of total anosognosia emerging from functional-connectivity patterns obtained via seed-based analysis.

Peak-based localization	HS	Cluster extent	T score	MNI coordinates			FWE *P*-value
				x	*y*	*z*	
Total anosognosia							
Reduced connectivity							
Left hippocampus seed							
Middle frontal gyrus (BA 46)	R	457	4.91	48	32	28	0.009
Middle frontal gyrus (BA 9)	R		4.70	36	36	40	
Middle frontal gyrus (BA 6)	R		4.35	28	60	60	
Increased connectivity							
Left hippocampus seed							
Caudate	L	330	3.71	−16	−38	18	0.042
Caudate	L		3.57	−22	−30	26	

BA, Brodmann Area; FWE, Family-Wise Error; HS, Hemispheric Side; L, Left; MNI, Montreal Neurological Institute; R, Right.

Subcortical Contributions to Anosognosia

Anosognosia scores were also associated with subcortical connectivity. Memory anosognosia scores were negatively associated with connectivity between the frontal and temporal

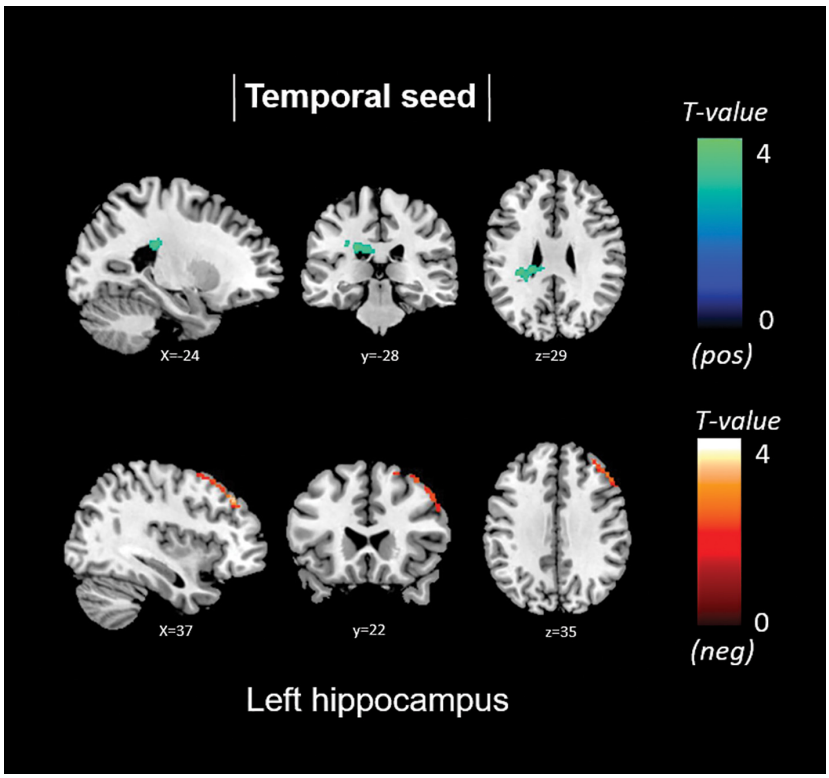


FIGURE 6 | Positive (blue) and negative (red) correlations between brain functional connectivity of selected unilateral seed regions and total anosognosia scores.

cortex and the bilateral caudate and right thalamus. Non-memory anosognosia scores were also negatively associated with connectivity between the right precuneus and both right thalamus and caudate. Reduced functional connectivity between the medioprefrontal cortex and the caudate was also reported to be associated with the presence of memory anosognosia in early AD (Ries et al., 2012).

Increased connectivity was evidenced between the left hippocampus and left caudate. The latter pattern of results was also replicated when total anosognosia scores were analyzed. Subcortical contributions have been reported in dementia patients who overestimate their overall cognitive functions or during emotional control (Shany-Ur et al., 2014). This finding has been interpreted in the context of some subcortical regions being associated with the dopaminergic system that is involved in reward actions based on self-centered attention, resulting from life accomplishments (Shany-Ur et al., 2014). Dopaminergic activity has been proposed to enhance function in paralimbic structures involved in self-referential processing. Through their projections, these regions provide subcortical support to medial frontal cortical regions during conscious self-monitoring (Lou et al., 2017). Therefore, structural and functional alterations might result from adaptive, although ineffective, up-regulation of dopaminergic inputs in a systemic attempt to cope with symptoms related to unawareness.

In summary, taken together, the pattern of findings suggests that in the early stage of neurodegeneration there might be a rearrangement of activity within the main functional network dynamic interactions that normally support full awareness of cognitive function. Increases in activity can be interpreted as a surge in system effort that increases demands on neural resources without, however, succeeding in sustaining cognitive function. Increases in neural activity that do not result in successful performance have been reported before in MCI and early stage AD (e.g., Gardini et al., 2015) and interpreted as a progressive maladaptive reorganization of how neural resources are allocated and an early coping mechanism in response to progressive neural depletion. An alternative reading of the pattern of findings of this study would be to interpret them as a reflection of alterations in the equilibrium of activity between anticorrelated networks, in this instance the DMN and FPN, expression of their inherent functions in internal and external mediation, respectively (Fox et al., 2005). This pattern of alteration among these networks' dynamic interactions was observed in association with all aspects of anosognosia in this study. Changes in inter-network activity expressed as increased connectivity between the DMN and the salience network, also found in this study in association with anosognosia, have been previously reported in mild probable AD dementia (Sarli et al., 2021). It might be suggested, therefore, that changes in activity in anticorrelated networks would alter the level of mutual inhibition exerted among their regions leading to a progressive loss of network integration and, in turn, to detectable cognitive and functional impairments, including alterations of awareness.

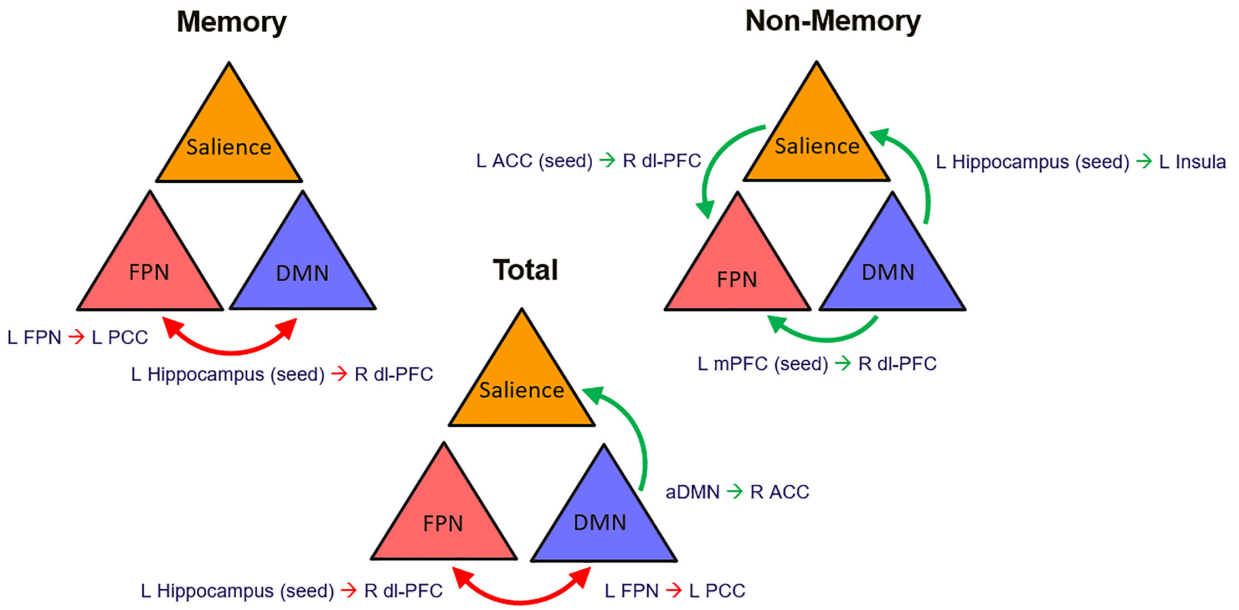


FIGURE 7 | Graphical representation of the proposed network dynamic changes that define multi-domain anosognosia in the early stages of AD. ACC, anterior cingulate cortex; aDMN, anterior Default Mode Network; dl-PFC, dorsolateral prefrontal cortex; FPN, Fronto-Parietal Network; mPFC, medial prefrontal cortex; red arrows, decreased connectivity; green arrows, increased connectivity.

Limitations

One of the main limitations of this study, and in general of the field of anosognosia research, is the choice of instrument to measure this symptom. Although, no method to detect anosognosia is recognized as the "gold-standard", the analysis of discrepancy scores is currently the most accepted methodological approach (de Ruijter et al., 2020). Discrepancy scoring relies on the response given by both patient and informant. Caregiver burden may inadvertently shift the perception of the patient's abilities into an over/under-estimation. To rule out this possibility, we chose to rely on a robust instrument that has undergone methodological validation. We acknowledge, however, that there are other ways to assess anosognosia, such as the discrepancy between subjective estimate of skills and actual objective performance on a task. Lastly, 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. The lack of large-scale findings within the salience network and pDMN connectivity might be due to insufficient sample size affecting statistical power to delineate the functional neural correlates of multi-domain anosognosia. This was a major reason why we chose to rely on the supportive evidence provided by seed-based models.

CONCLUSION

Large-scale brain functional networks and seed-based findings showed negative fronto-temporal associations, while positive associations of parieto-temporal connectivity related with level of awareness of memory dysfunction in early AD. Conversely, awareness of symptoms within the non-memory (executive and daily-life) domain was positively linked to connectivity between the aDMN and cerebellum, between left hippocampus and left insula and between left medioprefrontal and right dorsolateral prefrontal cortex. Lastly, the total score reflective of the combined level of awareness of dysfunction in multiple cognitive and everyday-life domains showed a positive correlation with fronto-temporal pathways and with connectivity between the aDMN and the right anterior cingulate. The prefrontal cortex seems to be a critical mediator of single and multi-domain anosognosia in the early stages of AD.

Contextualizing our findings based on the organization into nodes of the central large-scale brain functional networks, an overall pattern emerged of reduced interplay between the central executive FPN and the DMN influencing awareness for memory dysfunction as well as more globally when the memory and non-memory domain scores were summed together. On the other hand, increased intercommunication of the nodes within an executive system with both the DMN and salience network was found for non-memory anosognosia (**Figure 7**). This could translate into a reorganization of network dynamics in an attempt of the functional system to support its awareness abilities hampered by DMN dysfunction mechanisms. The dysfunction of a central executive comparator that influences levels of awareness could promote adaptive neural changes of increased network traffic to broader brain regions such as subcortical and supporting temporo-occipital territories (fusiform-lingual gyri) to sustain awareness in the early stages of AD degeneration. This neural coping attempts, however, do not appear to exert any behavioral benefit. These early changes in network dynamics provide insights on the evolution of deficits in awareness in AD

where subtle alterations can be detected even at a preclinical stage (Cacciamani et al., 2017). Multi-domain assessment of awareness, therefore, could potentially provide early signs of worse disease outcome. In the presence of anosognosia, clinicians should suspect early brain functional network breakdowns that could potentially modulate negatively the phenotypical presentation of the disease and act as a potential trigger of comorbid neuropsychiatric manifestations. Awareness of the potential implications of this symptom should lead to better cognitive and therapeutic interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Ethics Committee of Yorkshire and Humber (Ref No: 12/YH/0474). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JMV-B contributed to data processing and data modeling, result interpretation, and writing of the initial draft of the manuscript. MDM contributed to data collection, result interpretation, and critical revision of the manuscript. AV contributed to study conception and funding, clinical assessment and diagnosis, and revising and finalizing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The MRI costs for the scans included in this study were covered by funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 601055, VPH-DARE@IT to AV. JMV-B was funded by a scholarship by the Consejo Nacional de Ciencia y Tecnología (CONACYT), Mexico.

REFERENCES

Agnew, S. K., and Morris, R. G. (1998). The heterogeneity of anosognosia for memory impairment in Alzheimer's disease: a review of the literature and a proposed model. *Aging Ment. Health* 2, 7–19. doi: 10.1080/13607869856876

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Alves, P. N., Foulon, C., Karolis, V., Bzdok, D., Margulies, D. S., Volle, E., et al. (2019). An improved neuroanatomical model of the default-mode network reconciles previous neuroimaging and neuropathological findings. *Commun. Biol.* 2:370. doi: 10.1038/s42003-019-0611-3

Amanzio, M., Torta, D. M. E., Sacco, K., Cauda, F., D'Agata, F., Duca, S., et al. (2011). Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex. *Brain* 134, 1061–1076. doi: 10.1093/brain/awr020

Antoine, N., Bahri, M. A., Bastin, C., Collette, F., Phillips, C., Balteau, E., et al. (2019). Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Hum. Brain Mapp.* 40, 5330–5340. doi: 10.1002/hbm.24775

Badhwar, A., Tam, A., Dansereau, C., Orban, P., Hoffstaedter, F., and Bellec, P. (2017). Resting-state network dysfunction in Alzheimer's disease: a systematic review and meta-analysis. *Alzheimers Dement.* 8, 73–85. doi: 10.1016/j.dadm.2017.03.007

Berlingeri, M., Ravasio, A., Cranna, S., Basilico, S., Sberna, M., Bottini, G., et al. (2015). Unrealistic representations of "the self": a cognitive neuroscience assessment of anosognosia for memory deficit. *Conscious. Cogn.* 37, 160–177. doi: 10.1016/j.concog.2015.08.010

Boublay, N., Schott, A. M., and Krolak-Salmon, P. (2016). Neuroimaging correlates of neuropsychiatric symptoms in Alzheimer's disease: a review of 20 years of research. *Eur. J. Neurol.* 23, 1500–1509. doi: 10.1111/ene.13076

Bressler, S. L., and Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends Cogn. Sci.* 14, 277–290. doi: 10.1016/j.tics.2010.04.004

Brett, M., Anton, J. L., Valabrgue, R., and Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002, Sendai, Japan. *Neuroimage* 13, 210–217.

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., and Yeo, B. T. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *J. Neurophysiol.* 106, 2322–2345. doi: 10.1152/jn.00339.2011

Cacciamani, F., Tandetnik, C., Gagliardi, G., Bertin, H., Habert, M. O., Hampel, H., et al. (2017). Low Cognitive Awareness, but Not Complaint, is a Good Marker of Preclinical Alzheimer's Disease. *J. Alzheimers Dis.* 59, 753–762. doi: 10.3233/jad-170399

Chavoix, C., and Insausti, R. (2017). Self-awareness and the medial temporal lobe in neurodegenerative diseases. *Neurosci. Biobehav. Rev.* 78, 1–12. doi: 10.1016/j.neubiorev.2017.04.015

Cohen, J. D., Botvinick, M., and Carter, C. S. (2000). Anterior cingulate and prefrontal cortex: who's in control? *Nat. Neurosci.* 3, 421–423. doi: 10.1038/74783

Craig, A. D. (2009). How do you feel — now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. doi: 10.1038/nrn2555

Davey, C. G., Pujol, J., and Harrison, B. J. (2016). Mapping the self in the brain's default mode network. *Neuroimage* 132, 390–397. doi: 10.1016/j.neuroimage.2016.02.022

de Ruijter, N. S., Schoonbrood, A. M. G., van Twillert, B., and Hoff, E. I. (2020). Anosognosia in dementia: a review of current assessment instruments. *Alzheimers Dement.* 12:e12079. doi: 10.1002/dad2.12079

Derouesne, C., Thibault, S., Lagha-Pierucci, S., Baudouin-Madec, V., Ancri, D., and Lacomblez, L. (1999). Decreased awareness of cognitive deficits in patients with mild dementia of the Alzheimer type. *Int. J. Geriatr. Psychiatry* 14, 1019–1030. doi: 10.1002/(sici)1099-1166(199912)14:12<1019::Aid-gps61>3.0.Co;2-f

Devinsky, O., Morrell, M. J., and Vogt, B. A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain* 118, 279–306. doi: 10.1093/brain/118.1.279

Ewers, M., Sperling, R. A., Klunk, W. E., Weiner, M. W., and Hampel, H. (2011). Neuroimaging markers for the prediction and early diagnosis of Alzheimer's disease dementia. *Trends Neurosci.* 34, 430–442. doi: 10.1016/j.tins.2011.05.005

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., and Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. U. S. A.* 102, 9673–9678. doi: 10.1073/pnas.0504136102

Funahashi, S. (2017). Working Memory in the Prefrontal Cortex. *Brain Sci.* 7:49. doi: 10.3390/brainsci7050049

Gardini, S., Venneri, A., Sambataro, F., Cuetos, F., Fasano, F., Marchi, M., et al. (2015). Increased functional connectivity in the default mode network in mild cognitive impairment: a maladaptive compensatory mechanism associated with

poor semantic memory performance. *J. Alzheimers Dis.* 45, 457–470. doi: 10.3233/JAD-142547

Gbadeyan, O., McMahon, K., Steinhauser, M., and Meinzer, M. (2016). Stimulation of Dorsolateral Prefrontal Cortex Enhances Adaptive Cognitive Control: a High-Definition Transcranial Direct Current Stimulation Study. *J. Neurosci.* 36, 12530–12536. doi: 10.1523/jneurosci.2450-16.2016

Greicius, M. D., Srivastava, G., Reiss, A. L., and Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc. Natl. Acad. Sci. U. S. A.* 101, 4637–4642. doi: 10.1073/pnas.0308627101

Grieder, M., Wang, D. J. J., Dierks, T., Wahlund, L. O., and Jann, K. (2018). Default Mode Network Complexity and Cognitive Decline in Mild Alzheimer's Disease. *Front. Neurosci.* 12:770. doi: 10.3389/fnins.2018.00770

Guerrier, L., Le Men, J., Gane, A., Planton, M., Salabert, A. S., Payoux, P., et al. (2018). Involvement of the Cingulate Cortex in Anosognosia: a Multimodal Neuroimaging Study in Alzheimer's Disease Patients. *J. Alzheimers Dis.* 65, 443–453. doi: 10.3233/jad-180324

Hanseeuw, B. J., Scott, M. R., Sikkes, S. A. M., Properzi, M., Gatchel, J. R., Salmon, E., et al. (2020). Evolution of anosognosia in alzheimer's disease and its relationship to amyloid. *Ann. Neurol.* 87, 267–280. doi: 10.1002/ana.25649

Hanyu, H., Sato, T., Akai, T., Shimizu, S., Hirao, K., Kanetaka, H., et al. (2008). Neuroanatomical correlates of unawareness of memory deficits in early Alzheimer's disease. *Dement. Geriatric Cogn. Disord.* 25, 347–353. doi: 10.1159/000119594

Harwood, D. G., Sultzer, D. L., Feil, D., Monserratt, L., Freedman, E., and Mandelkern, M. A. (2005). Frontal Lobe Hypometabolism and Impaired Insight in Alzheimer Disease. *Am. J. Geriatric Psychiatry* 13, 934–941. doi: 10.1097/00019442-200511000-00003

Jedidi, H., Feyers, D., Collette, F., Bahri, M. A., Jaspar, M., d'Argembeau, A., et al. (2014). Dorsomedial prefrontal metabolism and unawareness of current characteristics of personality traits in Alzheimer's disease. *Soc. Cogn. Affect. Neurosci.* 9, 1458–1463. doi: 10.1093/scan/nst132

Cardoso, M. J., Leung, K., Modat, M., Keihaninejad, S., Cash, D., Barnes, J., et al. (2013). STEPS: similarity and Truth Estimation for Propagated Segmentations and its application to hippocampal segmentation and brain parcelation. *Med. Image Anal.* 17, 671–684. doi: 10.1016/j.media.2013.02.006

Kumar, S., Zomorrodi, R., Ghazala, Z., Goodman, M. S., Blumberger, D. M., Cheam, A., et al. (2017). Extent of Dorsolateral Prefrontal Cortex Plasticity and Its Association With Working Memory in Patients With Alzheimer Disease. *JAMA Psychiatry* 74, 1266–1274. doi: 10.1001/jamapsychiatry.2017.3292

Lacerda, I. B., Santos, R. L., Belfort, T., Neto, J. P. S., and Dourado, M. C. N. (2021). Domains of awareness in Alzheimer's disease: the influence of executive function. *Int. J. Geriatric Psychiatry* 36, 926–934. doi: 10.1002/gps.5495

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Hum. Brain Mapp.* 10, 120–131.

Leicht, H., Berwig, M., and Gertz, H. J. (2010). Anosognosia in Alzheimer's disease: the role of impairment levels in assessment of insight across domains. *J. Int. Neuropsychol. Soc.* 16, 463–473. doi: 10.1017/s1355617710000056

Lou, H. C., Changeux, J. P., and Rosenstand, A. (2017). Towards a cognitive neuroscience of self-awareness. *Neurosci. Biobehav. Rev.* 83, 765–773. doi: 10.1016/j.neubiorev.2016.04.004

MacPherson, S. E., Phillips, L. H., and Della Sala, S. (2002). Age, executive function, and social decision making: a dorsolateral prefrontal theory of cognitive aging. *Psychol. Aging* 17, 598–609.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., and Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 19, 1233–1239.

Marshall, G. A., Kaufer, D. I., Lopez, O. L., Rao, G. R., Hamilton, R. L., and DeKosky, S. T. (2004). Right prosubiculum amyloid plaque density correlates with anosognosia in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 75, 1396–1400. doi: 10.1136/jnnp.2003.030007

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Migliorelli, R. T. A., Sabe, L., Petracca, G., Petracchi, M., Leiguarda, R., and Starkstein, S. E. (1995). Anosognosia in Alzheimer's disease: a study of associated factors. *J. Neuropsychiatry Clin. Neurosci.* 7, 338–344. doi: 10.1176/jnp.7.3.338

Mitelpunkt, A., Galili, T., Kozlovski, T., Bregman, N., Shachar, N., Markus-Kalish, M., et al. (2020). Novel Alzheimer's disease subtypes identified using a data and knowledge driven strategy. *Sci. Rep.* 10, 1327–1327. doi: 10.1038/s41598-020-57785-2

Modinos, G., Ormel, J., and Aleman, A. (2009). Activation of anterior insula during self-reflection. *PLoS One* 4:e4618. doi: 10.1371/journal.pone.0004618

Mondragon, J. D., Maurits, N. M., and De Deyn, P. P. (2019). Functional Neural Correlates of Anosognosia in Mild Cognitive Impairment and Alzheimer's Disease: a Systematic Review. *Neuropsychol. Rev.* 29, 139–165. doi: 10.1007/s11065-019-09410-x

Mondragón, J. D., Maurits, N. M., and De Deyn, P. P. (2021). Functional connectivity differences in Alzheimer's disease and amnestic mild cognitive impairment associated with AT(N) classification and anosognosia. *Neurobiol. Aging* 101, 22–39. doi: 10.1016/j.neurobiolaging.2020.12.021

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., and Panksepp, J. (2006). Self-referential processing in our brain–a meta-analysis of imaging studies on the self. *Neuroimage* 31, 440–457. doi: 10.1016/j.neuroimage.2005.12.002

Nowrangi, M. A., Lyketsos, C., Rao, V., and Munro, C. A. (2014). Systematic review of neuroimaging correlates of executive functioning: converging evidence from different clinical populations. *J. Neuropsychiatry Clin. Neurosci.* 26, 114–125. doi: 10.1176/appi.neuropsych.12070176

Perrotin, A., Desgranges, B., Landeau, B., Mezenge, F., La Joie, R., Egret, S., et al. (2015). Anosognosia in Alzheimer disease: disconnection between memory and self-related brain networks. *Ann. Neurol.* 78, 477–486. doi: 10.1002/ana.24462

Postema, M. C., De Marco, M., Colato, E., and Venneri, A. (2019). A study of within-subject reliability of the brain's default-mode network. *Magnet. Reson. Mater. Phys. Biol. Med.* 32, 391–405. doi: 10.1007/s10334-018-00732-0

Raichle, M. E. (2015). The Brain's Default Mode Network. *Annu. Rev. Neurosci.* 38, 433–447. doi: 10.1146/annurev-neuro-071013-014030

Reed, B. R., Jagust, W. J., and Coulter, L. (1993). Anosognosia in Alzheimer's disease: relationships to depression, cognitive function, and cerebral perfusion. *J. Clin. Exp. Neuropsychol.* 15, 231–244. doi: 10.1080/01688639308402560

Ries, M. L., Jabbar, B. M., Schmitz, T. W., Trivedi, M. A., Gleason, C. E., Carlsson, C. M., et al. (2007). Anosognosia in mild cognitive impairment: relationship to activation of cortical midline structures involved in self-appraisal. *J. Int. Neuropsychol. Soc.* 13, 450–461. doi: 10.1017/s1355617707070488

Ries, M. L., McLaren, D. G., Bendlin, B. B., Guofanxu, Rowley, H. A., Birn, R., et al. (2012). Medial prefrontal functional connectivity–relation to memory self-appraisal accuracy in older adults with and without memory disorders. *Neuropsychologia* 50, 603–611. doi: 10.1016/j.neuropsychologia.2011.12.014

Ruby, P., Collette, F., D'Argembeau, A., Péters, F., Degueldre, C., Balteau, E., et al. (2009). Perspective taking to assess self-personality: what's modified in Alzheimer's disease? *Neurobiol. Aging* 30, 1637–1651. doi: 10.1016/j.neurobiolaging.2007.12.014

Sánchez-Benavides, G., Grau-Rivera, O., Suárez-Calvet, M., Minguillon, C., Cacciaglia, R., Gramunt, N., et al. (2018). Brain and cognitive correlates of subjective cognitive decline-plus features in a population-based cohort. *Alzheimers Res. Ther.* 10, 123–123. doi: 10.1186/s13195-018-0449-9

Sarli, G., De Marco, M., Hallikainen, M., Soininen, H., Bruno, G., and Venneri, A. (2021). Regional Strength of Large-Scale Functional Brain Networks is Associated with Regional Volumes in Older Adults and in Alzheimer's Disease. *Brain Connect.* 11, 201–212. doi: 10.1089/brain.2020.0899

Shany-Ur, T., Lin, N., Rosen, H. J., Sollberger, M., Miller, B. L., and Rankin, K. P. (2014). Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention. *Brain* 137, 2368–2381. doi: 10.1093/brain/awu161

Sorg, C., Riedl, V., Mühlau, M., Calhoun, V. D., Eichele, T., Läer, L., et al. (2007). Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A* 104, 18760–18765. doi: 10.1073/pnas.0708803104

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: diagnosis, frequency, mechanism and clinical correlates. *Cortex* 61, 64–73. doi: 10.1016/j.cortex.2014.07.019

Starkstein, S. E., Vázquez, S., Migliorelli, R., Tesón, A., Sabe, L., and Leiguarda, R. (1995). A single-photon emission computed tomographic study of anosognosia in alzheimerand#39;s disease. *Arch. Neurol.* 52, 415–420. doi: 10.1001/archneur.1995.00540280105024

Stewart, G., McGeown, W. J., Shanks, M. F., and Venneri, A. (2010). Anosognosia for memory impairment in Alzheimer's disease. *Acta Neuropsychiatr.* 22, 180–187. doi: 10.1111/j.1601-5215.2010.00463.x

Tagai, K., Nagata, T., Shinagawa, S., and Shigeta, M. (2020). Anosognosia in patients with Alzheimer's disease: current perspectives. *Psychogeriatrics* 20, 345–352. doi: 10.1111/psyg.12507

Therriault, J., Ng, K. P., Pascoal, T. A., Mathotaarachchi, S., Kang, M. S., Struyfs, H., et al. (2018). Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology* 90, e932–e939. doi: 10.1212/wnl.0000000000005120

Turriziani, P., Smirni, D., Mangano, G. R., Zappalà, G., Giustiniani, A., Cipolotti, L., et al. (2019). Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex Enhances Recognition Memory in Alzheimer's Disease. *J. Alzheimers Dis.* 72, 613–622. doi: 10.3233/jad-190888

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289. doi: 10.1006/nimg.2001.0978

Valera-Bermejo, J. M., De Marco, M., Mitolo, M., Cerami, C., Dodich, A., and Venneri, A. (2021). Large-Scale Functional Networks, Cognition and Brain Structures Supporting Social Cognition and Theory of Mind Performance in Prodromal to Mild Alzheimer's Disease. *Front. Aging Neurosci.* 13:766703. doi: 10.3389/fnagi.2021.766703

Valera-Bermejo, J. M., De Marco, M., Mitolo, M., McGeown, W. J., and Venneri, A. (2020). Neuroanatomical and cognitive correlates of domain-specific anosognosia in early Alzheimer's disease. *Cortex* 129, 236–246. doi: 10.1016/j.cortex.2020.04.026

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., et al. (2017). Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *Neuroimage Clin.* 15, 408–414. doi: 10.1016/j.nicl.2017.05.020

Vemuri, P., Jones, D. T., and Jack, C. R. Jr. (2012). Resting state functional MRI in Alzheimer's Disease. *Alzheimers Res. Ther.* 4:2. doi: 10.1186/alzrt100

Voss, H. U., Zevin, J. D., and McCandliss, B. D. (2006). Functional MR Imaging at 3.0 T versus 1.5 T: a Practical Review. *Neuroimag. Clin. North Am.* 16, 285–297. doi: 10.1016/j.nic.2006.02.008

Wang, Y., and Li, T.-Q. (2015). Dimensionality of ICA in resting-state fMRI investigated by feature optimized classification of independent components with SVM. *Front. Hum. Neurosci.* 9:259–259. doi: 10.3389/fnhum.2015.00259

Whitwell, J. L. (2009). Voxel-Based Morphometry: an Automated Technique for Assessing Structural Changes in the Brain. *J. Neurosci.* 29:9661.

Xu, W., Chen, S., Xue, C., Hu, G., Ma, W., Qi, W., et al. (2020). Functional MRI-Specific Alterations in Executive Control Network in Mild Cognitive Impairment: an ALE Meta-Analysis. *Front. Aging Neurosci.* 12:578863. doi: 10.3389/fnagi.2020.578863

Yang, Y.-L., Deng, H.-X., Xing, G.-Y., Xia, X.-L., and Li, H.-F. (2015). Brain functional network connectivity based on a visual task: visual information processing-related brain regions are significantly activated in the task state. *Neural Regener. Res.* 10, 298–307. doi: 10.4103/1673-5374.152386

Yoon, H. J., Kim, S. G., Kim, S. H., Choo, I. L. H., Park, S. H., and Seo, E. H. (2019). Distinct Neural Correlates of Executive Function by Amyloid Positivity and Associations with Clinical Progression in Mild Cognitive Impairment. *Yonsei Med. J.* 60, 935–943. doi: 10.3349/ymj.2019.60.10.935

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., et al. (2013). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex* 49, 668–678. doi: 10.1016/j.cortex.2012.04.011

Zamboni, G., and Wilcock, G. (2011). Lack of awareness of symptoms in people with dementia: the structural and functional basis. *Int. J. Geriatric Psychiatry* 26, 783–792. doi: 10.1002/gps.2620

Zhang, L., Qiao, L., Chen, Q., Yang, W., Xu, M., Yao, X., et al. (2016). Gray Matter Volume of the Lingual Gyrus Mediates the Relationship between Inhibition Function and Divergent Thinking. *Front. Psychol.* 7:1532. doi: 10.3389/fpsyg.2016.01532

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 09 March 2022
doi: 10.3389/fnagi.2022.787552

Subjective Cognitive Decline Is More Accurate When Metamemory Is Better

Silvia Chapman[1,2†], Jillian L. Joyce[1,3†], Megan S. Barker[1,2], Preeti Sunderaraman[1,2,3,4,5,6], Sandra Rizer[1,2], Edward D. Huey[1,2,3,4,7], Jordan Dworkin[1,7], Yian Gu[1,2,4] and Stephanie Cosentino[1,2,3,4]*

[1] Cognitive Neuroscience Division, Columbia University Irving Medical Center, New York, NY, United States, [2] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Irving Medical Center, New York, NY, United States, [3] Gertrude H. Sergievsky Center, Columbia University Irving Medical Center, New York, NY, United States, [4] Department of Neurology, Columbia University Irving Medical Center, New York, NY, United States, [5] Department of Neurology, Boston University School of Medicine, Boston, MA, United States, [6] Brain Aging Program, Framingham Heart Study, Framingham, MA, United States, [7] Department of Psychiatry, Columbia University Irving Medical Center, New York, NY, United States

OPEN ACCESS

Edited by:
Bernard Jimmy Hanseeuw, Cliniques Universitaires Saint-Luc, Belgium

Reviewed by:
Christopher Hertzog, Georgia Institute of Technology, United States
Serena Sabatini, University of Exeter, United Kingdom
Catherine Munro, Center for Brain/Mind Medicine, Brigham and Women's Hospital, United States

***Correspondence:**
Stephanie Cosentino
sc2460@cumc.columbia.edu

[†] These authors have contributed equally to this work

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: 30 September 2021
Accepted: 24 January 2022
Published: 09 March 2022

Citation:
Chapman S, Joyce JL, Barker MS, Sunderaraman P, Rizer S, Huey ED, Dworkin J, Gu Y and Cosentino S (2022) Subjective Cognitive Decline Is More Accurate When Metamemory Is Better. Front. Aging Neurosci. 14:787552. doi: 10.3389/fnagi.2022.787552

Objective: Subjective cognitive decline (SCD) has emerged as one of the first manifestations of Alzheimer's disease (AD). However, discrepancies in its relationship with tests of memory and other cognitive abilities have hindered SCD's diagnostic utility. Inter-individual heterogeneity in metamemory, or memory awareness, and the use of clinical measures of cognition lacking sensitivity to early cognitive dysfunction, may contribute to these discrepancies. We aimed to assess if the relationship between SCD and markers of early cognitive dysfunction is moderated by metamemory abilities.

Methods: The sample included 79 cognitively healthy older adults (77% female, 68% White, and 32% Black participants) with a mean age of 74.4 (*SD* = 6.1) and 15.9 (*SD* = 2.7) years of education. Metamemory was assessed using an episodic Feeling of Knowing test with four 5-item trials. Outcome measures included a resolution metric defined as a gamma correlation reflecting the accuracy of item-level predictions ("Will you know the correct answer?"). Early cognitive dysfunction was measured through the Loewenstein-Acevedo Scale for Semantic Interference and Learning (LASSI-L) and the Short-Term Memory Binding Test (STMB), measures sensitive to preclinical AD. SCD was assessed with a 20-item questionnaire that asked participants to compare themselves to others their age on a 7-point Likert scale. Regression analyses examined whether a potential relation between SCD and early cognitive dysfunction was moderated by metamemory.

Results: Subjective cognitive decline was associated with susceptibility to semantic proactive interference such that greater complaints were associated with increased susceptibility to semantic proactive interference ($b = -0.30$, $p = 0.003$) only. Metamemory moderated the association between SCD and susceptibility to and recovery of semantic proactive interference such that those with more accurate metamemory showed a stronger association between increased complaints and susceptibility to semantic proactive interference ($b = -0.71$, $p = 0.005$; $b = -0.62$,

p = 0.034). Metamemory, however, did not moderate the association of SCD with retroactive semantic interference nor short term memory binding.

Discussion: The accuracy of an individual's metamemory, specifically their ability to adjust moment to moment predictions in line with their performance, can influence the extent to which SCD maps onto objective cognition. Such self-referential assessment should be considered when interpreting SCD.

Keywords: subjective cognitive decline, metamemory, preclinical Alzheimer's disease, self awareness, early cognitive dysfunction

INTRODUCTION

Researchers are mapping the earliest end of the Alzheimer's disease (AD) continuum to identify patients in a critical window for therapeutic intervention (Dubois et al., 2016). While *in vivo* detection of AD pathologies using biomarkers is central to this process (Sperling et al., 2011), it is not sufficient given the imperfect association between neuropathology and clinical manifestation of disease (Negash et al., 2013). Indeed, at least a third of cognitively normal older adults have evidence of pathological AD on autopsy (Negash et al., 2013) or amyloid imaging (Chételat et al., 2013), and the pathological definition of AD continues to be debated (de la Torre, 2004; Castellani and Smith, 2011; Castellani and Perry, 2014). The ongoing questions and controversies surrounding clinical-pathological correlations in AD (Castellani and Smith, 2011; Castellani and Perry, 2014) emphasize the importance of identifying the earliest *clinical* manifestations of disease. Subjective cognitive decline (SCD), defined as the perception of cognitive decline despite normal performance on traditional neuropsychological testing, is likely to be one such early manifestation of illness with studies increasingly pointing to the potential relevance of SCD as an inexpensive and easily obtainable "pre-clinical" marker of AD (Geerlings et al., 1999; Reisberg et al., 2008; Sperling et al., 2011; Rabin et al., 2017; Jessen et al., 2020).

Research in AD as well as in aging generally supports an association between SCD and objective memory both cross-sectionally and longitudinally, and there is emerging evidence of the association between SCD and AD biomarkers (Gilewski et al., 1990; Hertzog et al., 1990; Pearman and Storandt, 2004; Beaudoin and Desrichard, 2011; Amariglio et al., 2012; Perrotin et al., 2012; Hülür et al., 2014; Snitz et al., 2015; Chen et al., 2019, 2021). However, the utility of SCD as a marker of cognitive functioning and biomarker status appears to vary as a function of multiple factors including task factors (e.g., measurement and operationalization issues) and person factors (e.g., individual characteristics) which together obscure its association with objective markers of disease (Schmidt et al., 2001; Jessen et al., 2010; Tandetnik et al., 2015; Ossenkoppele and Jagust, 2017). For example, the perceptions that memory is worse than others of the same age (i.e., age-anchored SCD) maps on more closely to AD biomarkers than perceptions of memory being bad in general, or worse than before, for example (Perrotin et al., 2012; Tandetnik et al., 2015; Chapman et al., 2021). With regard to person factors, there is recognition that personality and mood are likely important in the conceptualization of SCD; however, other factors remained to be explored (Pearman and Storandt, 2004; Slavin et al., 2010; Merema et al., 2013; Steinberg et al., 2013).

From a self-awareness perspective, SCD may be considered a hyperaware state (hypernosognosia) indicative of early dysfunction not yet detectable, or which does not reach a formal threshold for impairment, on clinical neuropsychological measures. As disease progresses, disordered awareness in the form or lack of awareness of deficits (anosognosia) likely follows SCD in a subset of individuals with mild cognitive impairment; this disordered awareness can be a prognostic indicator of disease progression as well as important clinical outcomes (Starkstein, 2014; Vannini et al., 2017; Munro et al., 2018). Knowledge of one's own cognitive abilities (e.g., metacognition) has been examined extensively in healthy young and older adults (Nelson, 1990; Price et al., 2010; Hertzog and Dunlosky, 2011; Souchay and Isingrini, 2012; Cauvin et al., 2019; Siegel and Castel, 2019; Gagliardi et al., 2020) and has proven useful in understanding the clinical phenomenon of anosognosia, particularly disordered awareness of memory loss (Cosentino et al., 2007; Galeone et al., 2011; Rosen et al., 2014; DeLozier and Davalos, 2016).

Indeed, several groups have used metamemory testing to measure memory awareness in AD, and this type of assessment may offer a unique vantage point into the accuracy of SCD. As a direct measure of one's memory awareness, metamemory is a critical person factor that should be considered in the interpretation of SCD. Specifically, individuals who demonstrate good metamemory (i.e., who have good awareness of their actual memory function), may be expected to have a more accurate subjective report of cognitive decline than those who have poor metamemory. Despite its clear relevance for understanding the prognostic relevance of SCD, metamemory has rarely been examined in relation to SCD (Buckley et al., 2016; Vannini et al., 2019; Chi et al., 2020; Gagliardi et al., 2020), perhaps because metamemory as a construct evolved primarily in the field of cognitive psychology and is not a formal component of clinical neuropsychological evaluations (Sunderaraman and Cosentino, 2017; Chapman et al., 2020).

The aim of this paper is to examine the extent to which metamemory moderates the relation between SCD and objective memory. As performance on traditional neuropsychological assessments of memory is by definition "normal" in individuals with SCD, we must utilize more challenging and sensitive neuropsychological tests to more rigorously examine the accuracy of SCD. The current study includes two memory

measures shown to be sensitive to SCD as well as to AD biomarkers among clinically normal older adults. As stated above, our hypothesis postulates that those with better metamemory will have more accurate SCD; defined as a stronger association between SCD and objective memory testing on sensitive tasks.

MATERIALS AND METHODS

Participants

Participants included in this study were selected from a larger cohort that comprises 157 participants recruited from the Columbia University Medical Center Aging and Dementia Neurology Clinic (n = 12) and ongoing aging studies at Taub Institute at Columbia University (n = 145). Two clinical cases were referred to the neurology clinic through a memory-concern screener administered in the Columbia University Department of Obstetrics and Gynecology. Referral studies included the Alzheimer's Disease Research Center (n = 73), Washington Heights Inwood Columbia Aging Project (n = 35), Testing Olfaction in Primary care to detect Alzheimer's disease and other Dementias (n = 11), and Cognitive Reserve and Reference Ability Neural Network studies (n = 22), Imaging inflammation in elders with different clinical and biomarker profiles of Alzheimer's disease (n = 2) Concerns About Memory Problems (n = 2). To be included in the current study, participants were required to have performed within normal limits on standard neuropsychological testing (demographically adjusted z-scores above −1.5) within the last 12 months (see **Supplementary Table 1** for neuropsychological screening measures). Exclusion criteria included past or current history of neurological conditions such as aneurysm, stroke, traumatic brain injury, epilepsy, etc. This study was reviewed and approved by Columbia University's Institutional Review Board (Protocol AAAR5197). Participants provided written informed consent.

Subjective Cognitive Decline

Subjective cognitive decline was measured using a 20-item, age-anchored scale previously shown to detect a range of self-reported cognitive problems among cognitively normal older adults (see Chapman et al., 2021 for full description). In brief, the scale comprises 10 items assessing aspects of episodic memory, and 10 non-memory items covering aspects of attention, language, spatial function, and executive abilities. Participants are asked to judge the extent to which they have difficulty with each item as compared to others their age. Responses are given ordinally (0 = no problem – 6 = major problem) with a total score ranging from 0 to 120. Higher scores represent more subjective cognitive problems.

Cognitive Markers of Subtle Cognitive Dysfunction

Short-Term Memory Binding

The short-term memory binding task (STMB) assesses the integration of multi-modal information in short-term memory (Parra et al., 2010, 2011). Specifically, this task assesses the ability to integrate two features of a stimulus (shape and color) and hold this representation in short-term memory (Parra et al., 2010). The STMB has been shown to be robust against age effects (Parra et al., 2009) and is specific to AD dementia (Della Sala et al., 2012) showing high sensitivity and specificity for pre-clinical AD (Parra et al., 2010). The main outcome of the STMB task represents total stimuli correctly recognized, ranging from 0 to 16 with higher scores indicating better performance (see Parra et al., 2009 for full description). To ensure the validity of the STMB outcome measure, participants are required to pass a practice trial in which they need to integrate shape and color with no demands on short-term memory. The ability to integrate these two features has been associated primarily with posterior parietal-occipital regions implicated in the ventral visual stream, regions hypothesized to be affected during the sub-hippocampal stages of AD, which suggests the task can detect the earliest stages of AD development (Parra et al., 2014).

The Loewenstein-Acevedo Scales of Semantic Interference and Learning

The Loewenstein-Acevedo Scales of Semantic Interference and Learning (LASSI-L) (Crocco et al., 2014) is a newly developed list-learning test that measures proactive semantic interference, retroactive interference, and the ability to recover from proactive semantic interference. Participants first read aloud a list of 15 words, List A, from three semantic categories: fruits, musical instruments, and articles of clothing. This is followed by a cued recall, with the three semantic categories as cues ("Can you tell me all the words on the list that were fruits?"). List A is then read again, followed by another cued recall. Then participants are presented with a new set of 15 words, List B, from the same semantic categories (fruits, musical instruments, and articles of clothing), followed by recall (*B1, susceptibility to proactive semantic interference*). The participants are presented with List B again, and recall (*B2, recovery from semantic interference*). Immediately following B2, participants are asked to recall all of the words from List A (*A3, susceptibility to retroactive semantic interference*). These three primary outcome measures (B1, B2, and A3) were included because they associate with biomarkers of AD such as amyloid load and volumetric loss. Specifically, this task has been shown to associate with amyloid accumulation in AD vulnerable regions such as the cingulate, precuneus, and frontal lobe in addition to volumetric and cortical reduction in the medial temporal lobe regions including the hippocampus (Loewenstein et al., 2016; Crocco et al., 2018).

Metamemory

Metamemory was assessed with a modified feeling of knowing (FOK) (Cosentino et al., 2007). This task is comprised of four trials with five fictional trivia items per trial (e.g., Cole Porter attended law school in Chicago). Participants are instructed as follows: "During this task, I am going to tell you about five people. I will tell you their name and something about their background. Your task is to try to remember this information as best you can. Please listen carefully"). Following the first learning trial of the five fictional trivia, participants are queried regarding each

of the five items, one at a time in a random order (e.g., Who attended law school in Chicago?). For each item, the examiner asks participants to estimate the likelihood of knowing the right answer (FOK judgment; "There are eight possible answers on the next page). Will you know which one is right ("Yes, Maybe, or No?"). After each individual FOK judgment, participants are asked to identify the correct answer (e.g., Porter) from eight possible choices including the correct answer as well as seven distractors. Item level judgments are given ordinal values of 0 (No), 0.5 (Maybe), and 1 (Yes). Memory for each item is scored as 0 (incorrect) and 1 (correct). There are four learning trials yielding a total of 20 FOK judgments. This task has been utilized in both patients with AD and healthy older adults (Cosentino et al., 2007, 2011a,b).

The primary metamemory outcome derived from this task is a resolution score representing a person's ability to adjust judgments of performance in line with actual memory performance from one item to the next. This score is calculated *via* the Goodman Kruskal gamma statistic; a rank order correlation assessing the total number of concordances (C) across the test (instances in which judgments and performance both increase from one item to another) versus the total number of discordances (*D*; judgments for performance decrease when performance increases and vice versa). Gamma is calculated as $(C - D)/(C + D)$. Following this formula, tests characterized by relatively more concordances than discordances will result in a gamma value closer to 1 (perfect resolution), while the opposite will result in a gamma value closer to −1. This calculation does not take into account the number of "ties" across items, that is, any two items in which either the judgment or memory values are equal. Therefore, if someone "ties" across all items (e.g., always judges that they will know the answer), gamma is not calculated (Cosentino et al., 2007).

Statistical Analyses

All analyses were conducted with IBM SPSS v.26. Descriptive statistics were conducted for demographic, SCD, metamemory, and memory measures. Spearman one-tailed correlations were conducted to examine the bivariate associations between SCD, gamma and memory. To examine the moderating effect of metamemory on the association between SCD and memory outcomes, linear regression models were conducted in complete case data. Influential univariate outliers (standardized residuals >3 or <−3) and multivariate outliers (determined through Mahalanobis distance) were examined for each model. To test for a specification error in the moderation models, namely that there is curvilinearity in the relation of each predictor to the dependent variable, quadratic effects of both SCD and gamma were included in separate models (Lubinski and Humphreys, 1990). Next, models were rerun without cases of gamma = 1 to examine if the frequency of these cases biased results. Finally, sensitivity analyses were conducted with imputed case data. A regression based multiple imputation approach was utilized for imputation. The pooled data from 25 imputations were utilized to obtain the estimates of variables in the model. All models were adjusted for demographic factors including age, self-reported gender, race, and education. In addition, a False Discovery Rate correction was implemented to complete cases that adjusted for the main comparisons of interest in the study which included demographical associations with main variables of interest, main effects of SCD and gamma on cognitive outcomes as well as their interactive effects.

RESULTS

Descriptives

Table 1 summarizes descriptives of demographics, cognitive, and metacognitive measures in the sample. All participants completed the SCD questionnaire (n = 157). A total of 156 participants completed the metamemory test, and 1 refused. Of the 156, 29 participants had ties across their pairs in the metamemory test and therefore gamma could not be calculated. The LASSI-L was available for 98 participants, as it was added to the study battery later. Finally, 9 participants failed to pass the validity trial for the STMB and one refused to complete due to color blindness leaving a total sample of 79 participants with all available measures. Descriptives are thus provided for these 79 participants with available data across all measures in **Table 1**. Demographics were found to be associated with gamma and cognitive outcomes. Specifically, age was negatively associated with gamma, susceptibility and ability to recover from proactive interference and retroactive interference (r range = −0.20, −0.29, p range = 0.004, 0.042). Greater levels of educational attainment were significantly associated with better performance in trials assessing susceptibility and ability to recover from proactive interference as well as retroactive interference (r range = 0.21, 0.36, p range = <0.001, 0.035). With regards to race, significant differences were observed with regards to performance in the STMB task only wherein White participants had higher performance (M = 10.61, SD = 9.56) than Black participants (M = 9.56, SD = 2.27) [$t(77)$ = 2.24, p = 0.028], however, this difference did not withstand adjustment for educational attainment. No differences were observed in SCD, gamma nor cognitive outcomes regarding gender.

Bivariate Analyses

Table 2 summarizes bivariate association between SCD, metamemory and cognitive outcomes. Increased SCD was associated with worse recall on B1 and A3 indicating that individuals endorsing more complaints had increased susceptibility to semantic proactive and retroactive interference. For sensitivity analyses with imputed data please see **Supplementary Table 2**.

Regression Models

Table 3 summarizes main effect models without interaction terms and **Table 4** summarizes results of the interactive effect of metamemory (gamma) with SCD on cognitive outcomes. Increased age, SCD, being male and having lower educational attainment was associated with increased susceptibility to

TABLE 1 | Demographics, subjective cognitive decline (SCD), memory and metamemory (n = 79).

	M (*SD*) or *n* (%)	Sample range
Age (years)	74.4 (6.1)	62 – 88
Education (years)	15.9 (2.5)	10 – 20
Gender – female participants	61 (77%)	
Race		
Black participants	25 (32%)	–
White participants	54 (68%)	–
SCD (0 – 120)	22.2 (16.9)	0 – 60
Metamemory – gamma (−1 – 1)	0.6 (0.5)	−1 – 1
LASSI-L outcomes		
LASSI-L B1 (0 – 15)	8.3 (3.0)	1 – 15
LASSI-L B2 (0 – 15)	11.9 (2.6)	6 – 15
LASSI-L A3 (0 – 15)	9.7 (2.5)	4 – 15
STMB	10.2 (2.0)	5 – 14

TABLE 3 | Main effect models of SCD, gamma and demographic associations with LASSI-L and STMB outcomes.

	B (*SE*)	Std. *B*	*p*-value
SCD = >B1			
SCD	−0.41 (0.14)	−0.30	0.003
Gamma	−0.28 (0.54)	−0.05	0.613
Age	−0.14 (0.05)	−0.29	0.004
Gender (0 = men, 1 = women)	1.60 (0.68)	0.23	0.020
Education	0.35 (0.13)	0.29	0.008
Race (0 = white, 1 = black)	−0.52 (0.68)	−0.08	0.450
SCD = >B2			
SCD	−0.09 (0.13)	−0.07	0.514
Gamma	−0.14 (0.53)	−0.03	0.798
Age	−0.12 (0.05)	−0.30	0.009
Gender (0 = men, 1 = women)	1.08 (0.65)	0.18	0.101
Education	0.17 (0.13)	0.17	0.174
Race (0 = white, 1 = black)	−0.29 (0.66)	−0.05	0.660
SCD = > A3			
SCD	−0.22 (0.12)	−0.19	0.080
Gamma	−0.25 (0.49)	−0.06	0.606
Age	−0.11 (0.04)	−0.27	0.015
Gender (0 = men, 1 = women)	0.85 (0.61)	0.15	0.163
Education	0.18 (0.12)	0.19	0.125
Race (0 = white, 1 = black)	−0.36 (0.61)	−0.07	0.555
SCD = > STMB			
SCD	−0.14 (0.10)	−0.15	0.172
Gamma	−0.20 (0.41)	−0.05	0.636
Age	−0.59 (0.04)	−0.18	0.111
Gender (0 = men, 1 = women)	0.39 (0.51)	0.08	0.451
Education	0.14 (0.10)	0.18	0.148
Race (0 = white, 1 = black)	−0.74 (0.52)	−0.18	0.155

proactive semantic interference reflected by lower recall on B1. In the second main effect model with B2 as the outcome, increased age was associated with reduced ability to recover from proactive interference. In the third main effect model examining A3 as an outcome, increased age was associated with increased susceptibility to retroactive semantic interference. Finally, in the main effect model of STMB, there were no variables that individually predicted STMB. With regard to moderation models, a significant interaction effect of metamemory and SCD was observed for B1 (*susceptibility to proactive semantic interference*) such that individuals with higher levels of metamemory had a stronger negative association between SCD and proactive interference. Metamemory's also moderated the association SCD and B2 (*ability to recover from proactive semantic interference*).

One multivariate outlier was found in the moderation models with B1 and B2 as outcomes; exclusion of this outlier did not change results. In order to examine the influence of gamma = 1, moderation regression models were rerun without these cases (n = 60); the significant moderation effect remained. Specifically, the moderating effect of gamma was significant in models with B1 and B2 as outcomes (p = 0.006; p = 0.020). Third, in order to examine specification error, moderation models were rerun with quadratic terms of SCD and gamma. The moderation effect of gamma remained significant (p = 0.009) for the model with B1 as an outcome but not B2 where the effect lost significance at the margin (p = 0.055). Further, given that various measures had missing data, sensitivity analyses were conducted with all imputed data. Please see **Supplementary Tables 3**, **4**. Whilst most results remained consistent, the moderating effect of gamma for models with B2 as an outcome lost significance (p = 0.085) consistent with our FDR correction.

TABLE 2 | Bivariate associations between SCD, cognition and metamemory (n = 79).

	SCD			Metamemory – gamma		
	r	*p*	CI	*r*	*p*	CI
Metamemory – gamma	−0.05	0.32	−0.26, 0.18	–	–	–
LASSI-L outcomes						
LASSI-L B1	**−0.30**	**0.003**	**−0.51,−0.08**	−0.01	0.470	−0.25, 0.26
LASSI-L B2	−0.07	0.270	−0.31, 0.15	0.012	0.457	−0.19, 0.24
LASSI-L A3	**−0.19**	**0.047**	**−0.42, 0.03**	−0.01	0.457	−0.26, 0.21
STMB	−0.15	0.099	−0.36, 0.10	−0.015	0.446	−0.19, 0.20

Confidence intervals (CI) calculated from 1,000 bootstrapping samples. Significant associations bolded.

TABLE 4 | Moderation models of gamma on SCD's associations with cognitive outcomes.

	B (*SE*)	Std. *B*	*p*-value
SCD = >B1			
SCD	0.07 (0.21)	0.05	0.745
Gamma	2.90 (1.22)	0.53	0.020
SCD* gamma	**−0.72 (0.25)**	**−0.71**	**0.005**
Age	−0.13 (0.05)	−0.26	0.006
Gender (0 = men, 1 = women)	1.50 (0.65)	0.21	0.023
Education	0.33 (0.12)	0.28	0.009
Race (0 = white, 1 = black)	−0.64 (0.65)	−0.10	0.328
SCD = >B2			
SCD	0.27 (0.21)	0.228	0.197
Gamma	2.23 (1.21)	0.474	0.069
SCD* gamma^	**−0.54 (0.25)**	**−0.62**	**0.034**
Age	−0.12 (0.05)	−0.28	0.013
Gender (0 = men, 1 = women)	1.01(0.637)	0.17	0.117
Education	0.16 (0.122)	0.16	0.197
Race (0 = white, 1 = black)	−0.3 (0.642)	−0.07	0.555
SCD = >A3			
SCD	0.02 (0.20)	0.02	0.924
Gamma	1.30 (1.14)	0.29	0.259
SCD* gamma	−0.35 (0.24)	−0.43	0.138
Age	−0.10 (0.04)	−0.26	0.020
Gender (0 = men, 1 = women)	0.81 (0.60)	0.14	0.185
Education	0.17 (0.12)	0.18	0.140
Race (0 = white, 1 = black)	−0.42 (0.61)	−0.08	0.489
SCD = >STMB			
SCD	−0.07 (0.17)	−0.08	0.682
Gamma	0.28 (0.98)	0.08	0.776
SCD* gamma	−0.11 (0.20)	−0.16	0.593
Age	−0.06 (0.04)	−0.17	0.126
Gender (0 = men, 1 = women)	0.37 (0.52)	0.08	0.471
Education	0.14 (0.10)	0.18	0.157
Race (0 = white, 1 = black)	−0.76 (0.52)	−0.18	0.148

*Significant interaction terms bolded. ^Did not survive FDR correction. *Represents the interaction terms where SCD is multiplied by metamemory.*

DISCUSSION

This study examined the extent to which metamemory moderated the association between SCD and memory abilities in older adults. Consistent with previous work showing an association between SCD and rigorous measures of subtle cognitive dysfunction (Chapman et al., 2021), bivariate associations revealed that individuals with higher SCD had weaker performance on select list learning measures including greater susceptibility to both proactive interference and retroactive interference. With regard to the moderating role of metamemory, results from this study support the idea that in general, SCD is more strongly linked to memory abilities among individuals with better metamemory. Indeed, metamemory moderated the association between SCD and susceptibility to proactive interference Metamemory did not, however, moderate the association between SCD and retroactive interference or short-term memory binding. Below we offer potential interpretations for these findings and discuss current issues in the measurement and conceptualization of SCD more broadly, beginning with the variable associations between SCD and the memory outcomes selected for the current study.

The selective associations between SCD and only two of four memory outcomes, all previously shown to be sensitive to preclinical AD (Parra et al., 2010; Loewenstein et al., 2016; Crocco et al., 2018), was somewhat unexpected. For example, both proactive and retroactive interference on the LASSI-L have been linked to total cortical loading of amyloid and the precuneus specifically, among cognitively normal older adults (Loewenstein et al., 2016). In fact, the ability to *recover* from proactive interference has repeatedly been shown to be more sensitive to pre-clinical AD than other LASSI markers (Loewenstein et al., 2016, 2017). It is thus not immediately clear why SCD relates differently to each of these metrics. Susceptibility to proactive interference, associated with SCD in the current study, is assessed by measuring recall of List B after two study trials of List A. Recovery from proactive interference, not currently associated with SCD, is defined as recall of List B after its second presentation. It may be that in the current cognitively normal sample, there is little variability in performance after studying this list twice, limiting the degree to which it maps onto SCD. Indeed, average scores were higher (11.9) and the minimum score higher (6) than on the susceptibility metric (8.3 and 1, respectively). Nevertheless, the selective associations between SCD and increased susceptibility to proactive and retroactive interference may reflect specific early dysfunctions in cognitive control mechanisms. Previous research has shown that individuals with reduced working memory capacity (Rosen and Engle, 1998; Brewin and Smart, 2005) or inhibitory control (Anderson et al., 2000; Anderson, 2003; Anderson and Levy, 2007) tend to be more susceptible to interference effects and intrusive thoughts. Subtle changes in these cognitive control mechanisms could impact the use of specific and more effective retrieval mechanisms (Anderson and Levy, 2007; Unsworth, 2016, 2019).

Unexpectedly, SCD was also unrelated to short-term memory binding, the latter measure having previously been associated with SCD in a subset of this same cohort (Chapman et al., 2021). It is important to keep in mind, however, that while both the LASSI-L and STMB are sensitive to preclinical AD, their neural underpinnings are not synonymous. As highlighted earlier, LASSI-L measures have been associated with amyloid load in key AD regions such as cingulate, precuneus, frontal lobe as well as volumetric and cortical integrity of medial temporal lobe regions including the hippocampus. In contrast, the STMB has been associated primarily with posterior parietal-occipital regions implicated in the ventral visual stream, regions hypothesized to be affected during the sub-hippocampal stages of AD (Parra et al., 2014). As such, depending on the regional distribution of potential brain changes among individuals in a given sample, the extent to

which SCD maps onto one or another cognitive measure will likely differ.

The inconsistency of metamemory as a moderator was also unexpected. While the size and direction of the moderation effect were generally comparable across different outcome measures, the moderating effect was only significant for SCD and measures of proactive interference (susceptibility to and recovery from), but not retroactive interference or short-term memory binding. There are several factors that could have led to this discrepancy. First, the link between SCD and memory itself is variable as discussed above. It may not be feasible to detect a significant moderation effect in situations where SCD is not even weakly associated with a specific memory outcome, as was the case for STMB in the current study. A second potential issue is that metamemory itself is heterogeneous, consisting of two broad categories: monitoring (i.e., what you know about your memory) and control (i.e., how you manage your memory). Monitoring, the focus of the current study, is itself multi-dimensional and can be operationalized in a number of ways that capture individuals' confidence level (i.e., calibration) as well as their ability to adjust their expectations for performance as it varies over the course of a test (i.e., resolution). Furthermore, metamemory can be measured at different levels including an item-by-item basis (e.g., *will you know the answer to this question?*), or a summary level (e.g., *how many answers will you know overall?*) as well as at different points in time, including prior to or following memory performance (Nelson, 1984, 1990). Different studies have revealed nuances in the correlates of individual metamemory measures depending on a variety of factors including the score that is used (calibration versus resolution), the level at which it is measured (item versus summary), and the population in which it is measured (cognitively normal older adults versus AD) (Kikyo et al., 2002; Maril et al., 2003; Kikyo and Miyashita, 2004; Chua et al., 2006, 2009; Cosentino et al., 2007; Bertrand et al., 2018). From a cognitive perspective, aging studies have shown that confidence in retrieval judgments may be susceptible to variations in memory functioning (Hertzog et al., 2010, 2021). In line with this, reduced memory abilities in older adults may limit their access to diagnostic cues necessary to make accurate metacognitive judgments (Dunlosky and Metcalfe, 2008). Alternatively, older adults might have access to adequate cues but be unable to make valid inferences to reach accurate metacognitive judgments, possibly due to age-related changes in pre-frontal networks (Perrotin et al., 2008; Thomas et al., 2011; Fleming and Dolan, 2012). Given the seeming susceptibility in the current cohort to interference effects, and the moderating effects in this domain, we could also speculate that early vulnerability in frontal medial regions results in compromise to inferential judgments and resultingly to less accurate metacognitive judgments. Additional work is needed to tease apart the underlying cognitive as well as neuroanatomical substrates of both the susceptibility to interference and the moderating effects of metamemory ability.

In conclusion, results partially support our hypothesis that metamemory would moderate the association between SCD and memory performance, and provide rationale for consideration of metamemory when evaluating the accuracy of SCD. However, this study was not without limitations. First, the current sample included only participants with all available measures which reduced the sample significantly. However, in order to address this limitation, a multiple imputation approach was conducted in sensitivity analyses which revealed no significant differences between the initial model and the imputed model with the exception of the interactive effect of gamma and SCD on B2, also indicated in the False Discovery Rate adjusted *p*-values applied to complete-case analyses. A second limitation was that in 24 participants, gamma was not computed due to ties (i.e., no variability in either their FOK judgments or performance accuracy, with the majority of these cases always indicating "yes" for the FOK judgment with accuracy scores = 1). These cases *could* be considered as having perfect metamemory, highlighting a possible limitation of our task which for some participants may have a ceiling effect. A greater number of items within each learning trial would increase the likelihood of calculable gamma scores and provide a more comprehensive measure of metamemory in older adults. Another possible limitation was the relatively low level of SCD reported within this sample, along with possible ceiling effects on some cognitive measures which also may have reduced the strength of associations between SCD and cognition, as well as the moderating role of metamemory. Finally, the cohort included in this sample primarily included individuals drawn from other ongoing research studies rather than individuals presenting to a memory disorders clinic, which could skew not only the distribution of SCD but the level of concern regarding SCD, a factor known to increase SCD's utility as a maker of preclinical AD (Jessen et al., 2010). Ideally, this study would have included sensitivity analyses to explore the effects of community/research recruited versus clinically recruited. This analysis, however, was not possible given that only 13/157 individuals were clinic recruited. There are numerous ways in which we are currently tailoring our ongoing study of SCD, including increasing SCD screenings and referrals from the community and local clinical practices to enroll individuals with higher levels of SCD. Moreover, we are tracking participants longitudinally to examine the extent to which SCD predicts decline over time, as well as the extent to which change in SCD is more predictive than a single SCD assessment. The current literature is mixed; For example, while Drouin et al. (2021) found that subjective memory change predicted longitudinal memory change, Hertzog et al. (2018) found that subjective memory change was more related to current memory complaint rather than an indicator of actual memory change.

This study also had a number of considerable strengths including the prospective, rigorous assessment of SCD using an age-anchored framework shown to relate more closely than other measurement frameworks (e.g., comparing one's memory to 5 years ago) to objective measures of cognition (Perrotin et al., 2012; Tandetnik et al., 2015; Chapman et al., 2021). Another notable strength was the inclusion of objective metamemory testing, as well as two novel memory tests sensitive to pre-clinical AD, all of which have rarely if ever been combined in a single cohort. Finally, all participants completed comprehensive neuropsychological testing to ensure that they did not meet

criteria for Mild Cognitive Impairment. Ongoing work, in addition to enriching our sample with individuals who present to the clinic with complaints, is examining not only the relative contribution of metamemory as a moderator, but of other person factors such as mood, personality, and attitudes about aging (Chapman et al., in preperation). Together, these analyses will continue to inform the way in which SCD can be optimized as a marker of pre-clinical AD.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because due to IRB restrictions we cannot share the data. Requests to access the datasets should be directed to StC, sc2460@cumc.columbia.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB COLUMBIA UNIVERSITY. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

FUNDING

This study was funded by the National Institute on Aging (NIA) R01 award AG054525-01A1, P30 award AG066462 and the National Center for Advancing Translational Sciences, National Institutes of Health, through award UL1TR001873.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.787552/full#supplementary-material

REFERENCES

Amariglio, R. E., Becker, J. A., Carmasin, J., Wadsworth, L. P., Lorius, N., Sullivan, C., et al. (2012). Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia* 50, 2880–2886. doi: 10.1016/j.neuropsychologia.2012.08.011

Anderson, M. C. (2003). Rethinking interference theory: executive control and the mechanisms of forgetting. *J. Mem. Lang.* 49, 415–445. doi: 10.1016/j.jml.2003.08.006

Anderson, M. C., Bjork, E. L., and Bjork, R. A. (2000). Retrieval-induced forgetting: evidence for a recall-specific mechanism. *Psychon. Bull. Rev.* 7, 522–530. doi: 10.3758/BF03214366

Anderson, M. C., and Levy, B. J. (2007). "Theoretical issues in inhibition: insights from research on human memory," in *Inhibition in Cognition*, eds D. S. Gorfein and C. M. MacLeod (Washington: DC: American Psychological Association), 81–102.

Beaudoin, M., and Desrichard, O. (2011). Are memory self-efficacy and memory performance related? A meta-analysis. *Psychol. Bull.* 137, 211–241. doi: 10.1037/a0022106

Bertrand, E., Azar, M., Rizvi, B., Brickman, A. M., Huey, E. D., Habeck, C., et al. (2018). Cortical thickness and metacognition in cognitively diverse older adults. *Neuropsychology* 32, 700–710. doi: 10.1037/neu0000458

Brandt, J. (1991). The hopkins verbal learning test: development of a new memory test with six equivalent forms. *Clin. Neuropsychol.* 5, 125–142. doi: 10.1080/13854049108403297

Brewin, C. R., and Smart, L. (2005). Working memory capacity and suppression of intrusive thoughts. *J. Behav. Ther. Exp. Psychiatry* 36, 61–68. doi: 10.1016/j.jbtep.2004.11.006

Buckley, R. F., Laming, G., Chen, L. P. E., Crole, A., and Hester, R. (2016). Assessing Error Awareness as a Mediator of the Relationship between Subjective Concerns and Cognitive Performance in Older Adults. *PLoS One* 11:e0166315. doi: 10.1371/journal.pone.0166315

Buschke, H. (1984). Cued recall in Amnesia. *J. Clin. Neuropsychol.* 6, 433–440. doi: 10.1080/01688638408401233

Castellani, R. J., and Perry, G. (2014). The complexities of the pathology-pathogenesis relationship in Alzheimer disease. *Biochem. Pharmacol.* 88, 671–676. doi: 10.1016/j.bcp.2014.01.009

Castellani, R. J., and Smith, M. A. (2011). Compounding artefacts with uncertainty, and an amyloid cascade hypothesis that is 'too big to fail'. *J. Pathol.* 224, 147–152. doi: 10.1002/path.2885

Cauvin, S., Moulin, C. J. A., Souchay, C., Kliegel, M., and Schnitzspahn, K. M. (2019). Prospective Memory Predictions in Aging: increased Overconfidence in Older Adults. *Exp. Aging Res.* 45, 436–459. doi: 10.1080/0361073x.2019.1664471

Chapman, S., Colvin, L. E., and Cosentino, S. (2020). Translational Aspects of the Multidisciplinary Study of Metacognition. *Transl. Issues Psychol. Sci.* 6, 26–31. doi: 10.1037/tps0000224

Chapman, S., Sunderaraman, P., Joyce, J. L., Azar, M., Colvin, L. E., Barker, M. S., et al. (2021). Optimizing Subjective Cognitive Decline to Detect Early Cognitive Dysfunction. *J. Alzheimers Dis.* 80, 1185–1196. doi: 10.3233/jad-201322

Chen, X., Farrell, M. E., Moore, W., and Park, D. C. (2019). Actual memory as a mediator of the amyloid-subjective cognitive decline relationship. *Alzheimers Dement.* 11, 151–160. doi: 10.1016/j.dadm.2018.12.007

Chen, X., Farrell, M. E., Rundle, M. M., Chan, M. Y., Moore, W., Wig, G. S., et al. (2021). The relationship of functional hippocampal activity, amyloid deposition, and longitudinal memory decline to memory complaints in cognitively healthy older adults. *Neurobiol. Aging* 105, 318–326. doi: 10.1016/j.neurobiolaging.2021.04.020

Chételat, G., La Joie, R., Villain, N., Perrotin, A., de La Sayette, V., Eustache, F., et al. (2013). Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *NeuroImage Clin.* 2, 356–365. doi: 10.1016/j.nicl.2013.02.006

Chi, S. Y., Chua, E. F., Kieschnick, D. W., and Rabin, L. A. (2020). Retrospective metamemory monitoring of semantic memory in community-dwelling older adults with subjective cognitive decline and mild cognitive impairment. *Neuropsychol. Rehabil.* [Epub Online ahead of print], doi: 10.1080/09602011.2020.1831552

Chua, E. F., Schacter, D. L., Rand-Giovannetti, E., and Sperling, R. A. (2006). Understanding metamemory: neural correlates of the cognitive process and subjective level of confidence in recognition memory. *Neuroimage* 29, 1150–1160. doi: 10.1016/j.neuroimage.2005.09.058

Chua, E. F., Schacter, D. L., and Sperling, R. A. (2009). Neural correlates of metamemory: a comparison of feeling-of-knowing and retrospective confidence judgments. *J. Cogn. Neurosci.* 21, 1751–1765. doi: 10.1162/jocn.2009.21123

Cosentino, S., Metcalfe, J., Butterfield, B., and Stern, Y. (2007). Objective metamemory testing captures awareness of deficit in Alzheimer's disease. *Cortex* 43, 1004–1019.

Cosentino, S., Metcalfe, J., Cary, M. S., De Leon, J., and Karlawish, J. (2011a). Memory Awareness Influences Everyday Decision Making Capacity about

Medication Management in Alzheimer's Disease. *Int. J. Alzheimers Dis.* 2011:9. doi: 10.4061/2011/483897

Cosentino, S., Metcalfe, J., Holmes, B., Steffener, J., and Stern, Y. (2011b). Finding the self in metacognitive evaluations: metamemory and agency in nondemented elders. *Neuropsychology* 25, 602–612. doi: 10.1037/a0023972

Crocco, E., Curiel, R. E., Acevedo, A., Czaja, S. J., and Loewenstein, D. A. (2014). An Evaluation of Deficits in Semantic Cueing and Proactive and Retroactive Interference as Early Features of Alzheimer's Disease. *Am. J. Geriatr. Psychiatry* 22, 889–897. doi: 10.1016/j.jagp.2013.01.066

Crocco, E. A., Loewenstein, D. A., Curiel, R. E., Alperin, N., Czaja, S. J., Harvey, P. D., et al. (2018). A novel cognitive assessment paradigm to detect Pre-mild cognitive impairment (PreMCI) and the relationship to biological markers of Alzheimer's disease. *J. Psychiatr. Res.* 96, 33–38. doi: 10.1016/j.jpsychires.2017.08.015

de la Torre, J. C. (2004). Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol.* 3, 184–190. doi: 10.1016/s1474-4422(04)00683-0

D'Elia, L., Satz, P., Uchiyama, C. L., and White, T. (1996). *Color Trails Test*. Odessa, FL: PAR.

Della Sala, S., Parra, M. A., Fabi, K., Luzzi, S., and Abrahams, S. (2012). Short-term memory binding is impaired in AD but not in non-AD dementias. *Neuropsychologia* 50, 833–840. doi: 10.1016/j.neuropsychologia.2012.01.018

DeLozier, S. J., and Davalos, D. (2016). A Systematic Review of Metacognitive Differences Between Alzheimer's Disease and Frontotemporal Dementia. *Am. J. Alzheimers Dis. Other Demen.* 31, 381–388. doi: 10.1177/1533317515618899

Drouin, S. M., McFall, G. P., and Dixon, R. A. (2021). Subjective memory concerns, poor vascular health, and male sex predict exacerbated memory decline trajectories: an integrative data-driven class and prediction analysis. *Neuropsychology*. doi: 10.1037/neu0000784

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., et al. (2016). Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement.* 12, 292–323. doi: 10.1016/j.jalz.2016.02.002

Dunlosky, J., and Metcalfe, J. (2008). *Metacognition*. Thousand Oaks: Sage Publications.

Fleming, S. M., and Dolan, R. J. (2012). The neural basis of metacognitive ability. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 367, 1338–1349. doi: 10.1098/rstb.2011.0417

Gagliardi, G., Houot, M., Cacciamani, F., Habert, M. O., Dubois, B., and Epelbaum, S. (2020). The meta-memory ratio: a new cohort-independent way to measure cognitive awareness in asymptomatic individuals at risk for Alzheimer's disease. *Alzheimers Res. Ther.* 12:57. doi: 10.1186/s13195-020-00626-1

Galeone, F., Pappalardo, S., Chieffi, S., Iavarone, A., and Carlomagno, S. (2011). Anosognosia for memory deficit in amnestic mild cognitive impairment and Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 26, 695–701. doi: 10.1002/gps.2583

Geerlings, M. I., Jonker, C., Bouter, L. M., Ader, H. J., and Schmand, B. (1999). Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. *Am. J. Psychiatry* 156, 531–537. doi: 10.1176/ajp.156.4.531

Gilewski, M. J., Zelinski, E. M., and Schaie, K. W. (1990). The Memory Functioning Questionnaire for assessment of memory complaints in adulthood and old age. *Psychol. Aging* 5, 482–490. doi: 10.1037/0882-7974.5.4.482

Hertzog, C., Curley, T., and Dunlosky, J. (2021). Are age differences in recognition-based retrieval monitoring an epiphenomenon of age differences in memory? *Psychol. Aging* 36, 186–199. doi: 10.1037/pag0000595

Hertzog, C., Dixon, R. A., and Hultsch, D. F. (1990). Relationships between metamemory, memory predictions, and memory task performance in adults. *Psychol. Aging* 5, 215–227. doi: 10.1037/0882-7974.5.2.215

Hertzog, C., and Dunlosky, J. (2011). Metacognition in Later Adulthood: spared Monitoring Can Benefit Older Adults' Self-regulation. *Curr. Dir. Psychol. Sci.* 20, 167–173. doi: 10.1177/0963721411409026

Hertzog, C., Dunlosky, J., and Sinclair, S. M. (2010). Episodic Feeling-of-Knowing Resolution Derives from the Quality of Original Encoding. *Mem. Cogn.* 38, 771–784. doi: 10.3758/MC.38.6.771

Hertzog, C., Hülür, G., Gerstorf, D., and Pearman, A. M. (2018). Is subjective memory change in old age based on accurate monitoring of age-related memory change? Evidence from two longitudinal studies. *Psychol. Aging* 33, 273–287. doi: 10.1037/pag0000232

Hülür, G., Hertzog, C., Pearman, A., Ram, N., and Gerstorf, D. (2014). Longitudinal associations of subjective memory with memory performance and depressive symptoms: between-person and within-person perspectives. *Psychol. Aging* 29, 814–827. doi: 10.1037/a0037619

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Molinuevo, J. L., et al. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol.* 19, 271–278. doi: 10.1016/s1474-4422(19)30368-0

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kölsch, H., et al. (2010). Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch. Gen. Psychiatry* 67, 414–422. doi: 10.1001/archgenpsychiatry.2010.30

Kikyo, H., and Miyashita, Y. (2004). Temporal lobe activations of "feeling-of-knowing" induced by face-name associations. *Neuroimage* 23, 1348–1357. doi: 10.1016/j.neuroimage.2004.08.013

Kikyo, H., Ohki, K., and Miyashita, Y. (2002). Neural Correlates for Feeling-of-Knowing: an fMRI Parametric Analysis. *Neuron* 36, 177–186. doi: 10.1016/S0896-6273(02)00939-X

Lezak, M. D. (1995). *Neuropsychological Assessment*, 3rd Edn. New York, NY: Oxford University Press.

Loewenstein, D. A., Curiel, R. E., Greig, M. T., Bauer, R. M., Rosado, M., Bowers, D., et al. (2016). A Novel Cognitive Stress Test for the Detection of Preclinical Alzheimer Disease: discriminative Properties and Relation to Amyloid Load. *Am. J. Geriatr. Psychiatry* 24, 804–813. doi: 10.1016/j.jagp.2016.02.056

Loewenstein, D. A., Curiel, R. E., Wright, C., Sun, X., Alperin, N., Crocco, E., et al. (2017). Recovery from Proactive Semantic Interference in Mild Cognitive Impairment and Normal Aging: relationship to Atrophy in Brain Regions Vulnerable to Alzheimer's Disease. *J. Alzheimers Dis.* 56, 1119–1126. doi: 10.3233/JAD-160881

Lubinski, D., and Humphreys, L. G. (1990). Assessing spurious "moderator effects": illustrated substantively with the hypothesized ("synergistic") relation between spatial and mathematical ability. *Psychol. Bull.* 107, 385–393. doi: 10.1037/0033-2909.107.3.385

Maril, A., Simons, J. S., Mitchell, J. P., Schwartz, B. L., and Schacter, D. L. (2003). Feeling-of-knowing in episodic memory: an event-related fMRI study. *Neuroimage* 18, 827–836. doi: 10.1016/s1053-8119(03)00014-4

Merema, M. R., Speelman, C. P., Foster, J. K., and Kaczmarek, E. A. (2013). Neuroticism (not depressive symptoms) predicts memory complaints in some community-dwelling older adults. *Am. J. Geriatr. Psychiatry* 21, 729–736. doi: 10.1016/j.jagp.2013.01.059

Munro, C. E., Donovan, N. J., Amariglio, R. E., Papp, K. V., Marshall, G. A., Rentz, D. M., et al. (2018). The Impact of Awareness of and Concern About Memory Performance on the Prediction of Progression From Mild Cognitive Impairment to Alzheimer Disease Dementia. *Am. J. Geriatr. Psychiatry* 26, 896–904. doi: 10.1016/j.jagp.2018.04.008

Negash, S., Wilson, R. S., Leurgans, S. E., Wolk, D. A., Schneider, J. A., Buchman, A. S., et al. (2013). Resilient brain aging: characterization of discordance between Alzheimer's disease pathology and cognition. *Curr. Alzheimer Res.* 10, 844–851. doi: 10.2174/15672050113109990157

Nelson, T. O. (1984). A comparison of current measures of the accuracy of feeling-of-knowing predictions. *Psychol. Bull.* 95, 109–133.

Nelson, T. O. (1990). "Metamemory: a Theoretical Framework and New Findings," in *Psychology of Learning and Motivation*, ed. G. H. Bower (Cambridge, MA: Academic Press), 125–173. doi: 10.1080/13546805.2016.1167031

Ossenkoppele, R., and Jagust, W. J. (2017). The Complexity of Subjective Cognitive Decline. *JAMA Neurol.* 74, 1400–1402. doi: 10.1001/jamaneurol.2017.2224

Parra, M. A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S., and Sala, S. D. (2009). Short-term memory binding deficits in Alzheimer's disease. *Brain* 132, 1057–1066. doi: 10.1093/brain/awp036

Parra, M. A., Abrahams, S., Logie, R. H., Méndez, L. G., Lopera, F., and Della Sala, S. (2010). Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain* 133, 2702–2713. doi: 10.1093/brain/awq148

Parra, M. A., Della Sala, S., Logie, R. H., and Morcom, A. M. (2014). Neural correlates of shape–color binding in visual working memory. *Neuropsychologia* 52, 27–36. doi: 10.1016/j.neuropsychologia.2013.09.036

Parra, M. A., Sala, S. D., Abrahams, S., Logie, R. H., Méndez, L. G., and Lopera, F. (2011). Specific deficit of colour–colour short-term memory binding in sporadic and familial Alzheimer's disease. *Neuropsychologia* 49, 1943–1952. doi: 10.1016/j.neuropsychologia.2011.03.022

Pearman, A., and Storandt, M. (2004). Predictors of subjective memory in older adults. *J. Gerontol. Ser. B Psychol. Sci. Soc. Sci.* 59, 4–6. doi: 10.1093/geronb/59.1.p4

Perrotin, A., Mormino, E. C., Madison, C. M., Hayenga, A. O., and Jagust, W. J. (2012). Subjective Cognition and Amyloid Deposition Imaging: a Pittsburgh Compound B Positron Emission Tomography Study in Normal Elderly Individuals. *Arch. Neurol.* 69, 223–229. doi: 10.1001/archneurol.2011.666

Perrotin, A., Tournelle, L., and Isingrini, M. (2008). Executive functioning and memory as potential mediators of the episodic feeling-of-knowing accuracy. *Brain Cogn.* 67, 76–87. doi: 10.1016/j.bandc.2007.11.006

Price, J., Hertzog, C., and Dunlosky, J. (2010). Self-regulated learning in younger and older adults: does aging affect metacognitive control? *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn.* 17, 329–359. doi: 10.1080/13825580903287941

Rabin, L. A., Smart, C. M., and Amariglio, R. E. (2017). Subjective Cognitive Decline in Preclinical Alzheimer's Disease. *Annu. Rev. Clin. Psychol.* 13, 369–396. doi: 10.1146/annurev-clinpsy-032816-045136

Reisberg, B., Prichep, L., Mosconi, L., John, E. R., Glodzik-Sobanska, L., Boksay, I., et al. (2008). The pre-mild cognitive impairment, subjective cognitive impairment stage of Alzheimer's disease. *Alzheimers Dement.* 4, S98–S108. doi: 10.1016/j.jalz.2007.11.017

Reitan, R. M., and Wolfson, D. (1985). *The Halstead–Reitan Neuropsycholgical Test Battery: Therapy and Clinical Interpretation*. Tucson, AZ: Neuropsychological Press.

Rosen, H. J., Alcantar, O., Zakrzewski, J., Shimamura, A. P., Neuhaus, J., and Miller, B. L. (2014). Metacognition in the behavioral variant of frontotemporal dementia and Alzheimer's disease. *Neuropsychology* 28, 436–447. doi: 10.1037/neu0000012

Rosen, V. M., and Engle, R. W. (1998). Working Memory Capacity and Suppression. *J. Mem. Lang.* 39, 418–436. doi: 10.1006/jmla.1998.2590

Schmidt, I. W., Berg, I. J., and Deelman, B. G. (2001). Relations between subjective evaluations of memory and objective memory performance. *Percept. Mot. Skills* 93, 761–776. doi: 10.2466/pms.2001.93.3.761

Siegel, A. L. M., and Castel, A. D. (2019). Age-related differences in metacognition for memory capacity and selectivity. *Memory* 27, 1236–1249. doi: 10.1080/09658211.2019.1645859

Slavin, M. J., Brodaty, H., Kochan, N. A., Crawford, J. D., Trollor, J. N., Draper, B., et al. (2010). Prevalence and Predictors of "Subjective Cognitive Complaints" in the Sydney Memory and Ageing Study. *Am. J. Geriatr. Psychiatry* 18, 701–710. doi: 10.1097/JGP.0b013e3181df49fb

Snitz, B. E., Small, B. J., Wang, T., Chang, C.-C. H., Hughes, T. F., and Ganguli, M. (2015). Do Subjective Memory Complaints Lead or Follow Objective Cognitive Change? A Five-Year Population Study of Temporal Influence. *J. Int. Neuropsychol. Soc. JINS* 21, 732–742. doi: 10.1017/S1355617715000922

Souchay, C., and Isingrini, M. (2012). Are feeling-of-knowing and judgment-of-learning different? Evidence from older adults. *Acta Psychol.* 139, 458–464. doi: 10.1016/j.actpsy.2012.01.007

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 280–292. doi: 10.1016/j.jalz.2011.03.003

Starkstein, S. E. (2014). Anosognosia in Alzheimer's disease: diagnosis, frequency, mechanism and clinical correlates. *Cortex* 61, 64–73. doi: 10.1016/j.cortex.2014.07.019

Steinberg, S. I., Negash, S., Sammel, M. D., Bogner, H., Harel, B. T., Livney, M. G., et al. (2013). Subjective memory complaints, cognitive performance, and psychological factors in healthy older adults. *Am. J. Alzheimers Dis. Other Demen.* 28, 776–783. doi: 10.1177/1533317513504817

Sunderaraman, P., and Cosentino, S. (2017). Integrating the Constructs of Anosognosia and Metacognition: a Review of Recent Findings in Dementia. *Curr. Neurol. Neurosci. Rep.* 17:27. doi: 10.1007/s11910-017-0734-1

Tandetnik, C., Farrell, M. T., Cary, M. S., Cines, S., Emrani, S., Karlawish, J., et al. (2015). Ascertaining Subjective Cognitive Decline: a Comparison of Approaches and Evidence for Using an Age-Anchored Reference Group. *J. Alzheimers Dis.* 48, S43–S55. doi: 10.3233/jad-150251

Thomas, A. K., Bulevich, J. B., and Dubois, S. J. (2011). Context affects feeling-of-knowing accuracy in younger and older adults. *J. Exp. Psychol. Learn. Mem. Cogn.* 37, 96–108. doi: 10.1037/a0021612

Unsworth, N. (2016). Working memory capacity and recall from long-term memory: examining the influences of encoding strategies, study time allocation, search efficiency, and monitoring abilities. *J. Exp. Psychol. Learn. Mem. Cogn.* 42, 50–61. doi: 10.1037/xlm0000148

Unsworth, N. (2019). Individual differences in long-term memory. *Psychol. Bull.* 145, 79–139. doi: 10.1037/bul0000176

Vannini, P., Amariglio, R., Hanseeuw, B., Johnson, K. A., McLaren, D. G., Chhatwal, J., et al. (2017). Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease. *Neuropsychologia* 99, 343–349. doi: 10.1016/j.neuropsychologia.2017.04.002

Vannini, P., d'Oleire Uquillas, F., Jacobs, H. I. L., Sepulcre, J., Gatchel, J., Amariglio, R. E., et al. (2019). Decreased meta-memory is associated with early tauopathy in cognitively unimpaired older adults. *Neuroimage Clin.* 24:102097. doi: 10.1016/j.nicl.2019.102097

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Aging Neuroscience

BRIEF RESEARCH REPORT
published: 12 April 2022
doi: 10.3389/fnagi.2022.816648

Eliciting Implicit Awareness in Alzheimer's Disease and Mild Cognitive Impairment: A Task-Based Functional MRI Study

*Manuela Tondelli[1,2,3], Francesca Benuzzi[1], Daniela Ballotta[1], Maria Angela Molinari[2], Annalisa Chiari[2] and Giovanna Zamboni[1,2]**

[1] Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università di Modena e Reggio Emilia, Modena, Italy, [2] U.O. Neurologia, Azienda Ospedaliera Universitaria di Modena, Modena, Italy, [3] Dipartimento di Cure Primarie, Azienda Unitá Sanitaria Locale (AUSL) Modena, Modena, Italy

Background: Recent models of anosognosia in dementia have suggested the existence of an implicit component of self-awareness about one's cognitive impairment that may remain preserved and continue to regulate behavioral, affective, and cognitive responses even in people who do not show an explicit awareness of their difficulties. Behavioral studies have used different strategies to demonstrate implicit awareness in patients with anosognosia, but no neuroimaging studies have yet investigated its neural bases.

Methods: Patients with amnestic mild cognitive impairment and dementia due to Alzheimer's disease underwent functional magnetic resonance imaging (fMRI) during the execution of a color-naming task in which they were presented with neutral, negative, and dementia-related words (Dementia-Related Emotional Stroop).

Results: Twenty-one patients were recruited: 12 were classified as aware and 9 as unaware according to anosognosia scales (based on clinical judgment and patient-caregiver discrepancy). Behavioral results showed that aware patients took the longest time to process dementia-related words, although differences between word types were not significant, limiting interpretation of behavioral results. Imaging results showed that patients with preserved explicit awareness had a small positive differential activation of the posterior cingulate cortex (PCC) for the dementia-related words condition compared to the negative words, suggesting attribution of emotional valence to both conditions. PCC differential activation was instead negative in unaware patients, i.e., lower for dementia-related words relative to negative-words. In addition, the more negative the differential activation, the lower was the Stroop effect measuring implicit awareness.

Conclusion: Posterior cingulate cortex preserved response to dementia-related stimuli may be a marker of preserved implicit self-awareness.

Keywords: anosognosia, unawareness, implicit awareness, Alzheimer's disease, dementia

OPEN ACCESS

Edited by:
Howard Rosen, University of California, San Francisco, United States

Reviewed by:
Christine Bastin, University of Liège, Belgium
Eric Salmon, University of Liège, Belgium

***Correspondence:**
Giovanna Zamboni
giovanna.zamboni@unimore.it

Specialty section:
This article was submitted to Neurocognitive Aging and Behavior, a section of the journal Frontiers in Aging Neuroscience

Received: *16 November 2021*
Accepted: *25 February 2022*
Published: *12 April 2022*

Citation:
Tondelli M, Benuzzi F, Ballotta D, Molinari MA, Chiari A and Zamboni G (2022) Eliciting Implicit Awareness in Alzheimer's Disease and Mild Cognitive Impairment: A Task-Based Functional MRI Study. Front. Aging Neurosci. 14:816648. doi: 10.3389/fnagi.2022.816648

INTRODUCTION

Patients with mild cognitive impairment (MCI) and dementia due to Alzheimer's Disease (AD) may be unaware of their cognitive and behavioral symptoms. The inability to recognize or adequately appreciate the severity of deficit in cognitive or affective functioning is termed "anosognosia" or "impaired self-awareness" (Prigatano, 2010).

Early imaging studies on anosognosia have mainly looked at correlations between clinical measurements of anosognosia and imaging variables capturing brain metabolism (such as 18-F fluorodeoxyglucose positron emission tomography, FDG-PET) and brain morphology (such as volumetric MRI) (Zamboni and Wilcock, 2011; Tondelli et al., 2018). More recent studies have related measurements of anosognosia to brain functional connectivity using resting state functional magnetic resonance imaging (fMRI) (Perrotin et al., 2015; Vannini et al., 2017; Mondragon et al., 2019). In all these studies, anosognosia was assessed at an explicit level by measuring the discrepancy between the patient's self-report on their performance on cognitive tests with their actual performance, or between the patient's opinion and the opinion of a caregiver or clinician (Tondelli et al., 2018). The few studies that have used task-based functional magnetic resonance imaging (fMRI) to explore mechanisms underlying anosognosia in patients with cognitive impairment have also adopted functional tasks explicitly eliciting self-reflection (Ries et al., 2007; Ruby et al., 2009; Zamboni et al., 2013b).

Nevertheless, increasing evidence has shown that some patients with cognitive impairment are able to adjust their behavior to their decreased abilities despite the presence of anosognosia at an explicit level, suggesting the persistence of mechanisms of awareness on their cognitive difficulties at an implicit level in dementia, in parallel to models of implicit awareness in anosognosia for hemiplegia (Cocchini et al., 2010; Fotopoulou et al., 2010; Geurten et al., 2021). Using an emotional Stroop paradigm, Martyr et al. found that patients with dementia as well as their caregivers showed increased response times to salient words related to dementia and forgetfulness in comparison to neutral words. Importantly, this effect in dementia patients was unrelated to the degree of awareness that they demonstrated in explicit tasks (Martyr et al., 2011). Similarly, Mograbi et al. (2012b) showed that patients with AD had preserved emotional reactivity to failure, both in terms of self-report and facial expression, despite reduced explicit awareness of performance. Based on this evidence, the notion of a possible double pathway involving implicit and explicit self-awareness has been incorporated in theoretical models of anosognosia in dementia suggesting that an implicit component, that bypasses explicit awareness, may be responsible for behavioral and affective regulation even in the absence of explicit awareness (Mograbi and Morris, 2013, 2014; Saj et al., 2013).

To our knowledge, no neuroimaging study has yet explored the neural substrates of implicit anosognosia in cognitively impaired patients. The purpose of this study was to investigate the correlates of implicit awareness with an implicit fMRI task based on a modified emotional Stroop paradigm.

METHODS

Subjects

Patients were recruited from the Cognitive Neurology Clinic of the Azienda Ospedaliero Universitaria di Modena, Italy. Clinical diagnoses of MCI due to AD and dementia due to AD were made according to published criteria (Albert et al., 2011; McKhann et al., 2011). The degree of cognitive impairment was assessed by the Mini-Mental State Examination (MMSE, Folstein et al., 1975) and only patients with MMSE $\geq$ 22 were recruited. Handedness was assessed by means of the Edinburgh Inventory (Oldfield, 1971). Exclusion criteria also included the Hachinski score $\geq$ 4, prior, current, or past history of other neurological diseases, neurosurgery, or major psychiatric disorders (including depression), and the presence of behavioral disturbances other than anosognosia. The study was approved by the local ethics committee, and written informed consent was obtained from participants prior to the experiment, according to the Declaration of Helsinki.

Measurement of Anosognosia

The presence of anosognosia or lack of overt awareness was assessed by means of two methods: (I) clinical judgment evaluated by Clinical Insight Rating Scale (CIRS, Ott et al., 1996), which defines 4 domains of a patient's awareness (reason for the visit, cognitive deficits, functional deficits, and perception of the progression of deficits) rated by the examiner based on a separate interview with the patient and the caregiver on a scale from 0 (full insight) to 2 (no insight), and summed to obtain a total score between 0 and 8; (II) discrepancy score evaluated by Anosognosia Questionnaire Dementia (AQ-D, Migliorelli et al., 1995). This consists of 30 questions divided in the cognitive and behavioral section; the same questions are administered to patients (form A) and to their caregivers (form B) who are blind to the patient's answers and the total AQ-D score is given by the difference between form B—form A. According to previous reports (Leicht et al., 2010; Tondelli et al., 2018), we classified patients with score $\geq$ 2 at CIRS and score $\geq$ 14 at AQ-D as having anosognosia, i.e., with no overt awareness of their cognitive deficits.

Measurement of Implicit Awareness and fMRI Paradigm

The task used during the fMRI experiment consisted of a modified version of the Dementia-Related Emotional Stroop used by Martyr et al. (2011), which we adapted for use as fMRI paradigm in the scanner. This is a type of Emotional Stroop test in which dementia-related words are used to test if they have greater interference (therefore greater reaction time, RT) than neutral words, thus providing a measurement of implicit awareness (Martyr et al., 2011). The task that we developed consisted of 3 experimental conditions using neutral (e.g., apple, paper, car), negative (e.g., dramatic, war, hate), and dementia-related (e.g., dementia, forgetful, disabled) words, respectively. Words were selected during a preliminary study for stimuli validation that involved 40 healthy elderly subjects (20 men, 20 women, aged between 35 and 75 years) who were asked to

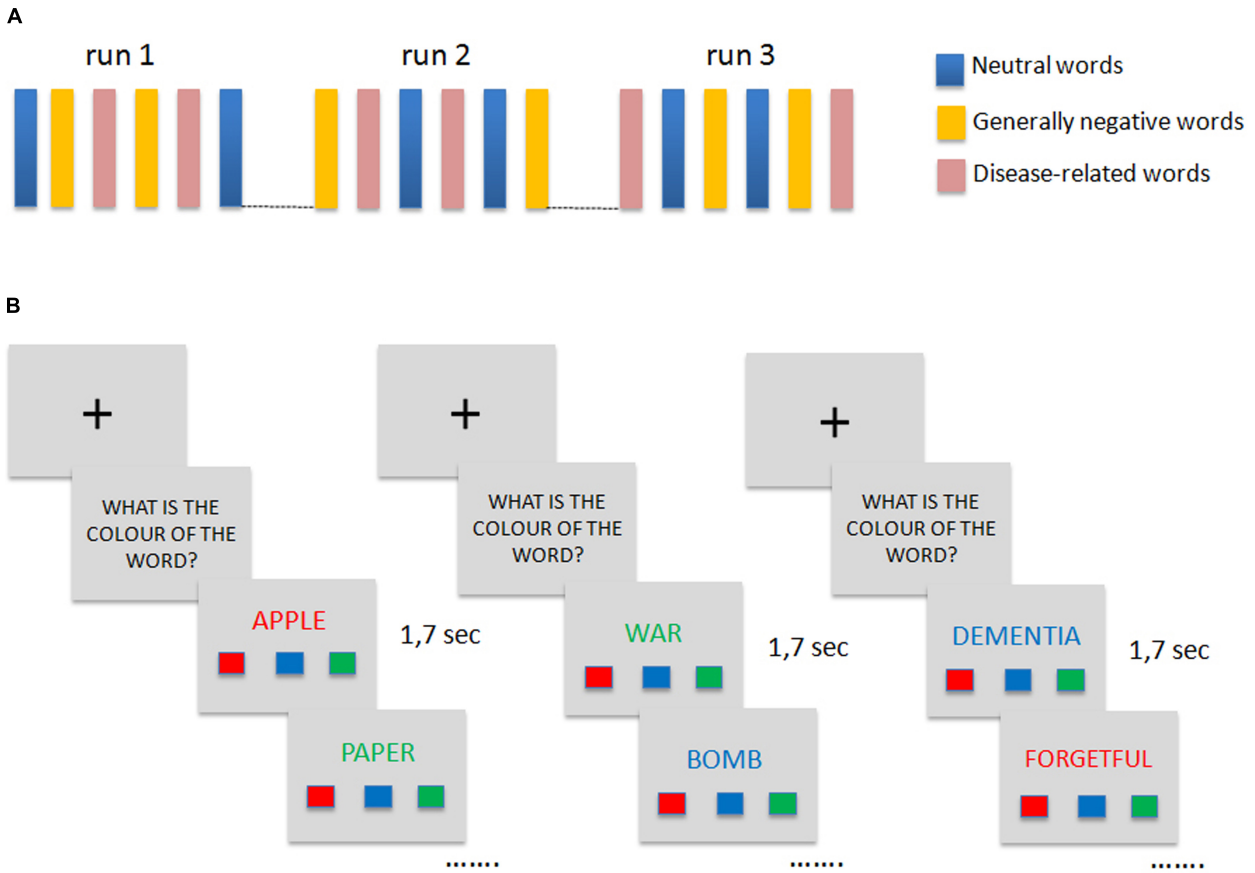


FIGURE 1 | Emotional Stroop fMRI paradigm. **(A)** Graphical representation of the block-design protocol paradigm. **(B)** Examples of stimuli used in the experiment for each group of words (from left to right: neutral words, negative words, dementia-related words) and order of presentation within the block.

rate 216 words on the dimension of emotional valence (positive or negative) and relation to Alzheimer's Disease (dementia-related or not related) using a 7 point scale (from-3 to + 3). Seventy-two words were included in the final modified version of the Dementia-Related Emotional Stroop: 24 neutral words were selected from words rating between-0.5 and 0.5 in the emotional valence questionnaire, 24 negative words were selected from those rated between-2.5 and -1 in the emotional valence questionnaire, 24 dementia-related words were selected from those words rating $\geq$ 1.5 in the dementia-related questionnaire, and between-2.5 and -1 in the emotional valence questionnaire to match emotional negative valence across the two groups of "emotional" words. Word types were matched on the frequency of occurrence, length, and concreteness. The fMRI paradigm was based on a block design: a total of 18 blocks of 12 neutral, negative, or dementia-related words were presented across three sessions or runs (**Figure 1**). The order of blocks was randomized between the sessions. Each word was presented for 1.7 s and at the beginning and at the end of each session a fixation cross was presented for 10 s. Stimuli words were arranged in a 512 × 384 pixel image using Adobe Photoshop (Adobe Systems Inc.) and were presented centrally on the screen in three different colors (red, blue, and green) on a gray background. Under each word, three colored rectangles arranged horizontally and representing red, blue, and green buttons from left to right were visible. **Figure 1** graphically summarizes the experimental paradigm. Patients were instructed to press the button corresponding to the color of the word by means of an MRI-compatible button-box (Current Design Inc.); they were also instructed to press the button as fast as possible but also as correctly as possible. Accuracy and reaction time data were collected during the scanning sessions by means of a custom-made software developed in Visual Basic 6[1]. The same software was used to present stimuli. Demographical, clinical, and behavioral data were analyzed using the Stata11 software[2] and parametric or non-parametric statistic was applied as appropriate.

Image Acquisition and Analysis

Data were acquired with a 3T Philips Intera System scanner. Gradient echo-planar imaging T2* -weighted images were acquired (TR 2,000 ms; FOV 230 mm; 128 × 128 matrix, voxel size = 3 mm^3). A total of 137 volumes were acquired

[1]http://web.tiscali.it/MarcoSerafini/stimoli_video/

[2]http://www.stata.com

for each session. In addition, a high resolution T1-weighted anatomical image of each subject was acquired to allow anatomical localization. The volume consisted of 170 sagittal slices (TR = 9.9 ms; TE = 4.6 ms; in plane matrix = 256 × 256; voxel size = 1 mm × 1 mm × 1 mm).

Voxel-based morphometry (VBM) was performed using T1-weighted anatomical images to determine if there were gray matter (GM) volume differences between aware and unaware patients that might account for any observed fMRI differences. VBM was performed using VBM8[3] a toolbox of SPM8[4]. Briefly, the individual structural images were segmented into gray matter, white matter, and cerebrospinal fluid, spatially normalized to the MNI space using the DARTEL approach (Ashburner, 2007), with intensity modulation by the amount of contraction to obtain the local GM corrected for individual brain size, and spatially smoothed using a 12-mm FWHM Gaussian kernel. An independent t-test comparison was performed between aware and unaware patients and statistical significance was evaluated at $p < 0.05$ corrected for multiple comparisons using family-wise error correction.

A functional MRI analysis was performed using Matlab and SPM8 software (Wellcome Department of Imaging Neuroscience, London, United Kingdom). The following preprocessing steps were used: realignment to the first volume acquired, normalization to the standard SPM template, and smoothing with a 6 mm full width maximum isotropic Gaussian kernel to improve the signal-to-noise ratio. Data analysis was performed modeling three different conditions: neutral words, generally negative words, and dementia-related words. Condition effects were estimated according to the general linear model and region-specific effects were compared using several linear contrasts. Contrast images for each condition were entered into a second-level random effect analysis model and group effect (aware and unaware) was assessed by means of different two-sample t-test. Age, MMSE score, and disease duration were entered in the second level model as a covariance of no effect to prevent possible bias in results analyses due to disease severity or duration. A double statistical threshold (voxel-wise $p < 0.001$ and spatial extent = 47) was adopted to achieve a combined significance, corrected for multiple comparisons, of $\alpha < 0.05$, as computed by 3dClustSim AFNI routine, using the "-acf" option (see details of procedure at[5] and in Forman et al., 1995). Mean beta values were extracted from the region of interest revealed by the main analysis (disease-related vs. negative words in aware vs. unaware patients) and were plotted based on awareness classification. Mean beta values were also used to perform a correlation analysis with differential reaction time scores between disease-related vs. negative words; in this analysis, MMSE and age were entered as non-interest variable. In addition, a separate correlation analysis in all patients (irrespective of their clinical diagnosis and awareness classification) was performed between anosognosia scores measured with CIRS and functional brain response for dementia-related words (relative to negative and neutral words); age, MMSE score, and disease duration were entered in the model as covariates of no effect and a statistical threshold of uncorrected $p < 0.001$ was accepted for this follow-up analysis.

[3]http://dbm.neuro.uni-jena.de/vbm/

[4]http://www.fil.ion.ucl.ac.uk/spm/

[5]https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html

RESULTS

Twenty-one elderly participants took part in the fMRI study. Among them, 12 (3 AD and 9 MCI) were overtly aware of their cognitive deficits whereas 9 patients (5 AD and 4 MCI) presented anosognosia. The two groups of aware and unaware patients only differed on AQ-D and CIRS scores; no statistically significant difference was detected in the global measure of cognitive impairment and demographical features (**Table 1**).

Reaction times (RTs) were collected for 16 subjects (9 aware and 7 with anosognosia), as the recording system failed in five subjects, limiting the possibility of subsequent classification of the subjects in implicitly aware vs. implicitly not aware on the basis of task performance. Subjects took the longest to respond to dementia-related words (mean 913 ± 205 ms), which was longer than the time they took to respond to negative (mean 900 ± 191 ms) and neutral (mean 894 ± 163 ms) words, although differences were not statistically significant ($p = 0.466$). A 2*3 mixed between-within subjects analysis of variance conducted to assess the impact of the type of words (neutral, negative, dementia-related) on subjects' RT with and without anosognosia neither showed significant main effects of word type ($p = 0.53$) or group ($p = 0.56$), nor a significant interaction between them ($p = 0.502$). No differences in the mean number of errors for the three types of words and across the two groups of subjects were detected either.

Comparisons of structural MRI data between aware and unaware patients performed with VBM did not show any GM volume difference in the two groups, indicating the absence of

TABLE 1 | Demographic and clinical characteristics of participant.

	Aware (n = 12)	Unaware (n = 9)	Groups comparison
Demographical and clinical characteristics			
Gender F:M	6:6	7:2	$p = 0.7$
Age (years)	72.4 (± 6.3)	72.3 (± 7.4)	$p = 0.9$
Years of education	6.5 (3–15)	5 (4–8)	$p = 0.1$
Disease duration (years)	4.5 (3–10)	4 (2–7)	$p = 0.5$
MMSE	26.4 (± 1.2)	25 (± 3.7)	$p = 0.08$
AQ-D	7.2 (± 5.7)	23.7 (± 3.6)	**$p < 0.0001$**
CIRS	0.9 (± 0.9)	6 (± 1.06)	**$p < 0.0001$**

Reported values are means with standard deviation values in parenthesis for age, MMSE, AQ-D, CIRS; reported values are median with range in parenthesis for years of education and disease duration. Comparisons between aware and unaware groups were performed with Mann–Whitney or independent t-test, as appropriate, for continuous variables and chi-square tests for dichotomous variables; a p-value < 0.008 was considered statistically significant after Bonferroni correction for multiple comparison (shown in bold).

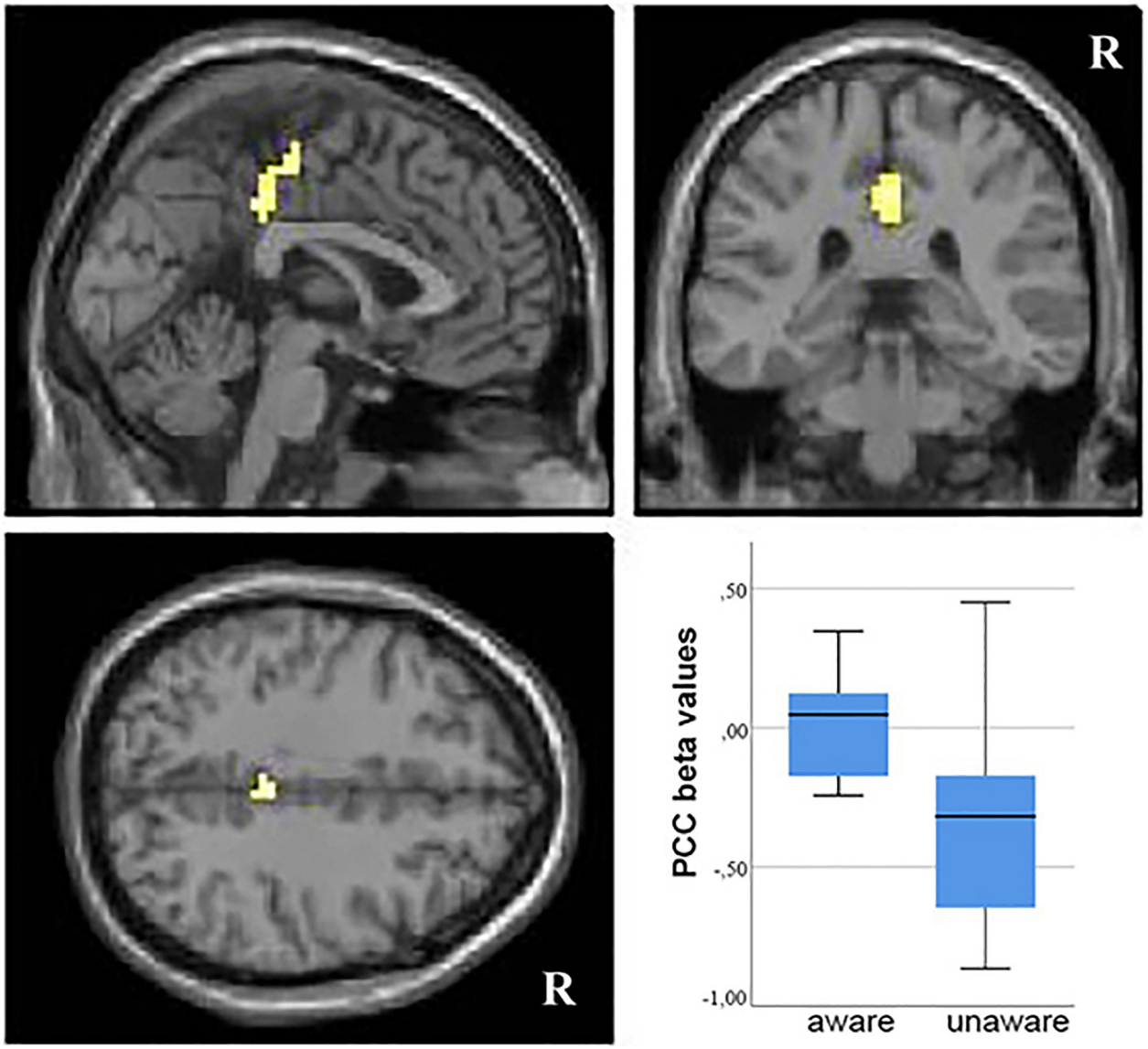


FIGURE 2 | Group analysis fMRI results. Areas of increased differential signal in response to dementia-related vs. negative words in the comparison between aware vs. unaware patients (voxel-wise $p < 0.001$ and cluster size ≥ 47 voxels, as determined by 3dClustSim AFNI routine). R, right. Resulting clusters are superimposed on the MNI template implemented in SPM8. On the right, box plot of mean beta values extracted from the posterior cingulate cortex (PCC) region of interest in aware and unaware patients.

potential effects that groups-specific structural differences may have had on the fMRI results.

In functional MRI analyses, significant results only emerged from the comparison between groups classified on explicit awareness. Analysis of functional MRI data showed that aware patients had greater differential activation for dementia-related vs. negative words in the posterior cingulate cortex (PCC) relative to unaware patients (BA 23 and 31, MNI coordinates of peak voxel: 0, –30, 44, *Z* value = 3.82, cluster size = 55, **Figure 2**). Patients with preserved explicit awareness had a small positive differential activation for dementia-related vs. negative words in the resulting PCC region (mean Beta value = 0.02, *SD* = 0.19, range –0.24 to 0.35), whereas unaware patients had negative differential activation in the same region (mean beta = –0.32, *SD* = 0.38, range –0.87 to 0.45).

The same region also emerged when contrasting dementia-related words vs. neutral words in the comparison of aware relative to unaware patients. No difference in functional activity was detected in the reverse condition. When comparing negative to neutral words, no difference in neural activity was demonstrated between the two groups of patients.

The correlation analysis between mean beta values extracted from the PCC and differential reaction times between disease-related vs. negative words showed a positive correlation

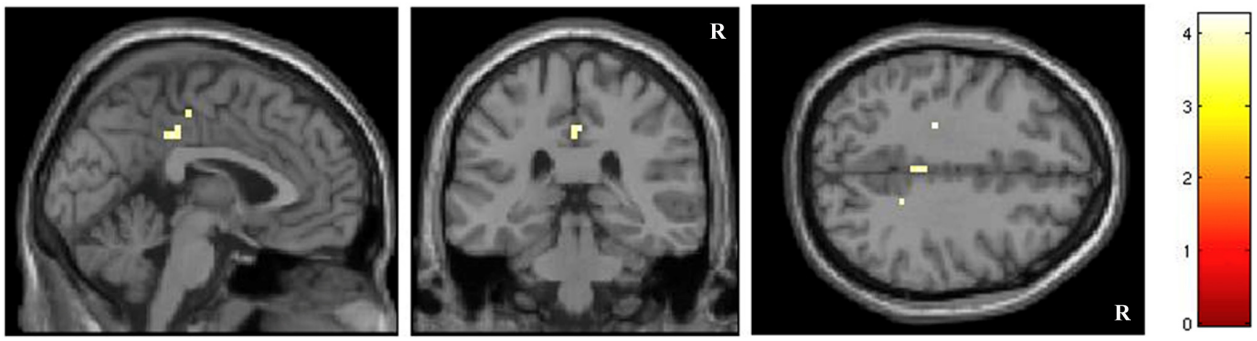


FIGURE 3 | Correlation voxel-wise analysis between anosognosia scores measured with CIRS and functional brain response for dementia-related words ($p < 0.001$ uncorrected).

(r = 0,516; p = 0.054), suggesting that higher differential RT (meaning longer disease-related RT) were correlated to higher PCC activation.

A correlational voxel-wise analysis across the whole brain showed that CIRS scores (high scores indicate greater severity of anosognosia) were significantly negatively correlated with brain response for dementia-related words (relative to negative words) in the PCC (MNI coordinates peak voxel: 0,–33, 37, **Figure 3**). This confirmed that the highest the differential activation of this region for dementia-related words, the highest the level of awareness of patients. No significant correlations emerged from the correlational analysis on disease-related relative to neutral words.

DISCUSSION

In this study, we investigated the neural responses involved in implicit awareness of cognitive impairment in patients with Alzheimer's Disease by using dementia-related words in a color-naming task (Dementia-Related Emotional Stroop). We assumed that in subjects with preserved implicit awareness dementia-related words would be more emotionally salient therefore would have greater interference in the task than neutral words. We found that the difference in the activity of the posterior cingulate between experimental conditions (dementia-related words vs. neutral or negative words) was greater in patients with preserved awareness than in patients with anosognosia.

The emotional Stroop task is a variant of the Stroop test that measures the interfering properties of emotionally salient words in a color-naming task (Williams et al., 1996). The interference effect arises if the words themselves are of particular relevance to the responder or induce a feeling of threat, or if the word has a high emotional valence. The effect is thought to occur because the emotional salience of the words leads to a processing bias operating at an automatic pre-attentive processing level, with emotionally salient words subject to greater interference than neutral words (Mogg et al., 1989). Emotional Stroop tasks have been largely used to study attentional biases in people with borderline personality (Wingenfeld et al., 2009), and panic disorders (Dresler et al., 2012), but only one previous behavioral study used the emotional Stroop paradigm with dementia-related words in dementia patients (Martyr et al., 2011). The authors suggested that dementia-related words would be emotionally salient and therefore would give greater interference effect in patients with preserved implicit awareness. They demonstrated that dementia-related words elicited a processing bias in patients with dementia, since they were slower to respond to dementia-related that to neutral words.

The main result of our study was that implicit processing of dementia-related stimuli was associated with greater differential activation (relative to negative stimuli) of the PCC in the aware patients than those with anosognosia. More precisely, in patients with preserved explicit awareness, there was a small positive difference in the PCC activity between dementia-related stimuli and negative stimuli, whereas in patients with anosognosia this difference was negative, i.e., the activation for dementia-related stimuli was lower than activation for negative stimuli. Across all patients, such PCC differential activation correlated with the Stroop effect: the lower the PCC activation for dementia-related words, the smaller the difference in reaction time for disease-related relative to negative words. In other words, patients whose PCC activation for dementia-related words was comparable to their PCC activation for negative words showed a Stroop effect, a measure of implicit awareness.

A separate further imaging analysis still showed that in the PCC there was a significant voxel-wise correlation between differential activation for dementia-related relative to negative words and severity of anosognosia (measured by CIRS): the highest was CIRS, the more negative was the difference in the response of the PCC between dementia-related and negative words.

The role of PCC in the processing of emotional words is well known. Several task-based fMRI studies conducted in healthy subjects have consistently shown that the PCC is activated by stimuli with an emotional or threatening valence (Maddock et al., 2003a,b). We found that patients who activated

the PCC also for dementia-related words (and not only for negative words) were those who were either explicitly aware or had a longer reaction time in response to dementia-related words (Stroop effect). Our results suggest that these patients were able to attribute an emotional or threatening valence to dementia-related words, i.e., they had preserved implicit awareness. The PCC is also a key structure of the so-called default mode network (DMN) (Raichle et al., 2001), one of the most relevant large-scale resting-state networks that can be identified with functional MRI acquired at rest, which are considered blueprints of the functional organization of the healthy (Fox and Raichle, 2007) and diseased (Zamboni et al., 2013a; Rolinski et al., 2015) brain. The DMN has been associated with self-referential processing and introspection (D'Argembeau et al., 2005; Buckner et al., 2008), as opposed to externally oriented cognitive tasks. Several studies have shown that DMN activity is also reduced in patients with AD relative to healthy controls (Greicius et al., 2004; Zamboni et al., 2013c). The hypothesis that the DMN may be the RSN whose dysfunction is associated with anosognosia in AD has been supported by recent resting-state fMRI studies (Perrotin et al., 2015; Vannini et al., 2017; Antoine et al., 2019). In particular, these studies showed an association between anosognosia and decreased functional connectivity between the PCC and the hippocampus (Perrotin et al., 2015; Vannini et al., 2017), which are both vulnerable to early AD neuropathological process (Tondelli et al., 2012). Older task-based fMRI studies conducted in healthy subjects have constantly demonstrated the activation of PCC in relation to self-appraisal (Johnson et al., 2002) and autobiographical memory (Fink et al., 1996; D'Argembeau et al., 2008). Interestingly, in the present study, we did not find significant involvement of the medial prefrontal regions during the execution of our implicit awareness task, whereas these more anterior regions have been frequently found in association with the PCC in these previous task-based fMRI studies using self-appraisal tasks (Ries et al., 2007). In particular, another task-based fMRI study among the few conducted in patients with MCI and AD showed an association between appraisal of one's own physical, behavioral, and cognitive traits (self-appraisal) and functional activation of the medial prefrontal cortex, which was inversely correlated with measures of explicit anosognosia (Zamboni et al., 2013b). Compared to these previous task-based fMRI studies which purposefully investigated explicit domains of self-awareness by asking patients to give overt judgments on their traits, our paradigm was aimed at measuring awareness at an implicit level (Clare et al., 2011; Mograbi et al., 2012a). Thus, the PPC might represent a key structure for self-referential processing even in the absence of an explicit act of reflection about oneself. No previous study has investigated the functional correlates of implicit awareness in cognitively impaired patients, but it is plausible that in the absence of an explicit reflection about the self, the involvement of more posterior regions of the cortical midline system may emerge, whereas higher-order explicit processing may rely on more anterior regions such as the medial prefrontal cortex. Thus, in line with models of anosognosia, the PCC may possibly be a core structure for the implicit awareness pathway and serve as the sentinel node within a network involving lower/implicit and higher/explicit level mechanisms (Mograbi and Morris, 2013).

The major limitation of our study is that we did not find significant differences between experimental conditions and patient groups at the behavioral level, possibly because of the small sample size, thus limiting the interpretability of the task-based fMRI results. Nevertheless, it is not uncommon to see fMRI data in which conditions of interest elicit significant activations when contrasts are applied, even if in absence of behavioral differences between conditions. The positive correlation between PCC activation and reaction times for disease-related words (a measure of the Stroop effect), as well as the overlap of the imaging results obtained from comparisons of groups with those obtained from the correlational analysis with measures of anosognosia reconciliate the correspondence between imaging and behavior. They add confidence that our task effectively captured implicit awareness. Future studies conducted in larger numbers of patients are, nonetheless, needed to better investigate mechanisms of implicit awareness in patients with anosognosia, stratified on the basis of measures of implicit awareness. Another limitation is the heterogeneity of patients included, both AD and MCI; however, aware and anosognosic patients did not show significant differences in cognitive measures and, more importantly, VBM analysis did not show any difference in gray matter volume between the two groups, confirming that our results were not driven by structural brain difference or disease severity.

In conclusion, by using task-based fMRI with an implicit awareness paradigm in cognitively impaired patients for the first time, the present study confirmed the involvement of the PCC in mechanisms of self-awareness. Our results suggest that PCC-preserved response to dementia-related stimuli may be a marker of preserved implicit self-awareness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Comitato Etico Provinciale di Modena, code 252.09. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT and GZ were responsible for the conceptualization, data collection, formal analysis, investigation, methodology, and writing the original draft along with FB, DB, MM, and AC who were also responsible for editing the draft. All authors contributed to the article and approved the submitted version.

FUNDING

The study was supported by a grant "Fondo di Ateneo per la Ricerca 2015" to GZ and "Dipartimenti di eccellenza 2018–2022", MIUR, Italy, to the Department of Biomedical, Metabolic and Neural Sciences, University of Modena.

ACKNOWLEDGMENTS

We are grateful to all the patients and their families, and to the general practices that referred patients to our service and collaborated with the study. We are grateful to Prof. Paolo Nichelli who provided insightful comments on the study design.

REFERENCES

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers. Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Antoine, N., Bahri, M. A., Bastin, C., Collette, F., Phillips, C., Balteau, E., et al. (2019). Anosognosia and default mode subnetwork dysfunction in Alzheimer's disease. *Hum. Brain Mapp.* 40, 5330–5340. doi: 10.1002/hbm.24775

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage* 38, 95–113. doi: 10.1016/j.neuroimage.2007.07.007

Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124, 1–38. doi: 10.1196/annals.1440.011

Clare, L., Whitaker, C. J., Nelis, S. M., Martyr, A., Markova, I. S., Roth, I., et al. (2011).). Multidimensional assessment of awareness in early-stage dementia: a cluster analytic approach. *Dement. Geriatr. Cogn. Disord.* 31, 317–327. doi: 10.1159/000327356000327356

Cocchini, G., Beschin, N., Fotopoulou, A., and Della Sala, S. (2010). Explicit and implicit anosognosia or upper limb motor impairment. *Neuropsychologia* 48, 1489–1494. doi: 10.1016/j.neuropsychologia.2010.01.019

D'Argembeau, A., Collette, F., Van der Linden, M., Laureys, S., Del Fiore, G., Degueldre, C., et al. (2005). Self-referential reflective activity and its relationship with rest: a PET study. *Neuroimage* 25, 616–624. doi: 10.1016/j.neuroimage.2004.11.048

D'Argembeau, A., Feyers, D., Majerus, S., Collette, F., Van der Linden, M., Maquet, P., et al. (2008). Self-reflection across time: cortical midline structures differentiate between present and past selves. *Soc. Cogn. Affect. Neurosci.* 3, 244–252. doi: 10.1093/scan/nsn020

Dresler, T., Hindi Attar, C., Spitzer, C., Lowe, B., Deckert, J., Buchel, C., et al. (2012). Neural correlates of the emotional Stroop task in panic disorder patients: an event-related fMRI study. *J. Psychiatr. Res.* 46, 1627–1634. doi: 10.1016/j.jpsychires.2012.09.004

Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., and Heiss, W. D. (1996). Cerebral representation of one's own past: neural networks involved in autobiographical memory. *J. Neurosci.* 16, 4275–4282. doi: 10.1523/JNEUROSCI.16-13-04275.1996

Folstein, M. F., Folstein, S. E., and McHugh, P. R. (1975).). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. doi: 10.1016/0022-3956(75)90026-6

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., and Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn. Reson. Med.* 33, 636–647. doi: 10.1002/mrm.1910330508

Fotopoulou, A., Pernigo, S., Maeda, R., Rudd, A., and Kopelman, M. A. (2010). Implicit awareness in anosognosia for hemiplegia: unconscious interference without conscious re-representation. *Brain* 133(Pt 12), 3564–3577. doi: 10.1093/brain/awq233

Fox, M. D., and Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8, 700–711. doi: 10.1038/nrn2201

Geurten, M., Salmon, E., and Bastin, C. (2021). Impaired explicit self-awareness but preserved behavioral regulation in patients with Alzheimer disease. *Aging Ment. Health* 25, 142–148. doi: 10.1080/13607863.2019.1675142

Greicius, M. D., Srivastava, G., Reiss, A. L., and Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc. Natl. Acad. Sci. U S A* 101, 4637–4642. doi: 10.1073/pnas.0308627101

Johnson, S. C., Baxter, L. C., Wilder, L. S., Pipe, J. G., Heiserman, J. E., and Prigatano, G. P. (2002). Neural correlates of self-reflection. *Brain* 125(Pt 8), 1808–1814. doi: 10.1093/brain/awf181

Leicht, H., Berwig, M., and Gertz, H. J. (2010). Anosognosia in Alzheimer's disease: the role of impairment levels in assessment of insight across domains. *J. Int. Neuropsychol. Soc.* 16, 463–473. doi: 10.1017/S1355617710000056

Maddock, R. J., Buonocore, M. H., Kile, S. J., and Garrett, A. S. (2003a). Brain regions showing increased activation by threat-related words in panic disorder. *Neuroreport* 14, 325–328. doi: 10.1097/00001756-200303030-00006

Maddock, R. J., Garrett, A. S., and Buonocore, M. H. (2003b). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Hum. Brain Mapp.* 18, 30–41. doi: 10.1002/hbm.10075

Martyr, A., Clare, L., Nelis, S. M., Roberts, J. L., Robinson, J. U., Roth, I., et al. (2011). Dissociation between implicit and explicit manifestations of awareness in early stage dementia: evidence from the emotional Stroop effect for dementia-related words. *Int. J. Geriatr. Psychiatr.* 26, 92–99. doi: 10.1002/gps.2495

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R. Jr., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers. Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

Migliorelli, R., Teson, A., Sabe, L., Petracca, G., Petracchi, M., Leiguarda, R., et al. (1995). Anosognosia in Alzheimer's disease: a study of associated factors. *J. Neuropsychiatr. Clin. Neurosci.* 7, 338–344. doi: 10.1176/jnp.7.3.338

Mogg, K., Mathews, A., and Weinman, J. (1989). Selective processing of threat cues in anxiety states: a replication. *Behav. Res. Ther.* 27, 317–323. doi: 10.1016/0005-7967(89)90001-6

Mograbi, D. C., Brown, R. G., Salas, C., and Morris, R. G. (2012b). Emotional reactivity and awareness of task performance in Alzheimer's disease. *Neuropsychologia* 50, 2075–2084. doi: 10.1016/j.neuropsychologia.2012.05.008

Mograbi, D. C., Brown, R. G., and Morris, R. G. (2012a). Emotional reactivity to film material in Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 34, 351–359. doi: 10.1159/000343930000343930

Mograbi, D. C., and Morris, R. G. (2013). Implicit awareness in anosognosia: clinical observations, experimental evidence, and theoretical implications. *Cogn. Neurosci.* 4, 181–197. doi: 10.1080/17588928.2013.833899

Mograbi, D. C., and Morris, R. G. (2014). The developing concept of implicit awareness: a rejoinder and reply to commentaries on Mograbi and Morris (2013). *Cogn. Neurosci.* 5, 138–142. doi: 10.1080/17588928.2014.905522

Mondragon, J. D., Maurits, N. M., and De Deyn, P. P. (2019). Functional Neural Correlates of Anosognosia in Mild Cognitive Impairment and Alzheimer's Disease: a Systematic Review. *Neuropsychol. Rev.* 29, 139–165. doi: 10.1007/s11065-019-09410-x

Oldfield, R. C. (1971). The assesment and the analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Ott, B. R., Lafleche, G., Whelihan, W. M., Buongiorno, G. W., Albert, M. S., and Fogel, B. S. (1996). Impaired awareness of deficits in Alzheimer disease. *Alzheimer. Dis. Assoc. Disord.* 10, 68–76. doi: 10.1097/00002093-199601020-00003

Perrotin, A., Desgranges, B., Landeau, B., Mezenge, F., La Joie, R., Egret, S., et al. (2015). Anosognosia in Alzheimer disease: disconnection between memory and self-related brain networks. *Ann. Neurol.* 78, 477–486. doi: 10.1002/ana.24462

Prigatano, G. P. (2010). *The study of anosognosia*. Oxford: Oxford University Press.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., and Shulman, G. L. (2001). A default mode of brain function. *Proc. Natl. Acad. Sci. U S A* 98, 676–682. doi: 10.1073/pnas.98.2.67698/2/676

Ries, M. L., Jabbar, B. M., Schmitz, T. W., Trivedi, M. A., Gleason, C. E., Carlsson, C. M., et al. (2007). Anosognosia in mild cognitive impairment: relationship to activation of cortical midline structures involved in self-appraisal. *J. Int. Neuropsychol. Soc.* 13, 450–461. doi: 10.1017/S1355617707070488

Rolinski, M., Griffanti, L., Szewczyk-Krolikowski, K., Menke, R. A., Wilcock, G. K., Filippini, N., et al. (2015). Aberrant functional connectivity within the basal ganglia of patients with Parkinson's disease. *Neuroimage Clin.* 8, 126–132. doi: 10.1016/j.nicl.2015.04.003

Ruby, P., Collette, F., D'Argembeau, A., Peters, F., Degueldre, C., Balteau, E., et al. (2009). Perspective taking to assess self-personality: what's modified in Alzheimer's disease? *Neurobiol. Aging* 30, 1637–1651. doi: 10.1016/j.neurobiolaging.2007.12.014

Saj, A., Vocat, R., and Vuilleumier, P. (2013). On the contribution of unconscious processes to implicit anosognosia. *Cogn. Neurosci.* 4, 198–199. doi: 10.1080/17588928.2013.854760

Tondelli, M., Barbarulo, A. M., Vincenzi, C., Chiari, A., Nichelli, P. F., and Zamboni, G. (2018). Neural correlates of anosognosia in alzheimer's disease and mild cognitive impairment: a multidimensional assessment. *Front. Behav. Neurosci.* 12:100. doi: 10.3389/fnbeh.2018.00100

Tondelli, M., Wilcock, G. K., Nichelli, P., De Jager, C. A., Jenkinson, M., and Zamboni, G. (2012). Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. *Neurobiol. Aging* 33(4), 825e825–e836. doi: 10.1016/j.neurobiolaging.2011.05.018

Vannini, P., Hanseeuw, B., Munro, C. E., Amariglio, R. E., Marshall, G. A., Rentz, D. M., et al. (2017). Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *Neuroimage Clin.* 15, 408–414. doi: 10.1016/j.nicl.2017.05.020

Williams, J. M., Mathews, A., and MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychol. Bull.* 120, 3–24. doi: 10.1037/0033-2909.120.1.3

Wingenfeld, K., Rullkoetter, N., Mensebach, C., Beblo, T., Mertens, M., Kreisel, S., et al. (2009). Neural correlates of the individual emotional Stroop in borderline personality disorder. *Psychoneuroendocrinology* 34, 571–586. doi: 10.1016/j.psyneuen.2008.10.024

Zamboni, G., Drazich, E., McCulloch, E., Filippini, N., Mackay, C. E., Jenkinson, M., et al. (2013b). Neuroanatomy of impaired self-awareness in Alzheimer's disease and mild cognitive impairment. *Cortex* 49, 668–678. doi: 10.1016/j.cortex.2012.04.011

Zamboni, G., de Jager, C. A., Drazich, E., Douaud, G., Jenkinson, M., Smith, A. D., et al. (2013a). Structural and functional bases of visuospatial associative memory in older adults. *Neurobiol. Aging* 34, 961–972. doi: 10.1016/j.neurobiolaging.2012.07.011

Zamboni, G., Wilcock, G. K., Douaud, G., Drazich, E., McCulloch, E., Filippini, N., et al. (2013c). Resting functional connectivity reveals residual functional activity in Alzheimer's disease. *Biol. Psychiatr.* 74, 375–383. doi: 10.1016/j.biopsych.2013.04.015

Zamboni, G., and Wilcock, G. (2011). Lack of awareness of symptoms in people with dementia: the structural and functional basis. *Int. J. Geriatr. Psychiatr.* 26, 783–792. doi: 10.1002/gps.2620

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Aging Neuroscience

ORIGINAL RESEARCH
published: 16 June 2022
doi: 10.3389/fnagi.2022.811739

Differential Patterns of Domain-Specific Cognitive Complaints and Awareness Across the Alzheimer's Disease Spectrum

Federica Cacciamani[1,2], Valérie Godefroy[3], Simona M. Brambati[4,5], Raffaella Migliaccio[3,6], Stéphane Epelbaum[1,6] and Maxime Montembeault[7,8,9] for the Alzheimer's Disease Neuroimaging Initiative†*

[1]*ARAMISLab, Inserm, CNRS, Sorbonne Université, Inria, Paris Brain Institute (ICM), Pitié-Salpêtrière Hospital, Paris, France,* [2]*PHARes Team, Bordeaux Population Health, University of Bordeaux, Inserm, Bordeaux, France,* [3]*FrontLab, Paris Brain Institute (ICM), Pitié-Salpêtrière Hospital, Paris, France,* [4]*Department of Psychology, University of Montreal, Montreal, QC, Canada,* [5]*Centre de recherche de l'Institut Universitaire de Gériatrie de Montréal, Montréal, QC, Canada,* [6]*Institute of Memory and Alzheimer's disease (IM2A), Pitié-Salpêtrière Hospital, Paris, France,* [7]*Douglas Mental Health University Institute, Montreal, QC, Canada,* [8]*Department of Psychiatry, McGill University, Montreal, QC, Canada,* [9]*Memory & Aging Center, Department of Neurology, University of California, San Francisco, San Francisco, CA, United States*

Background: Characterizing self- and informant-reported cognitive complaints, as well as awareness of cognitive decline (ACD), is useful for an early diagnosis of Alzheimer's disease (AD). However, complaints and ACD related to cognitive functions other than memory are poorly studied. Furthermore, it remains unclear which source of information is the most useful to distinguish various groups on the AD spectrum.

Methods: Self- and informant-reported complaints were measured with the Everyday Cognition questionnaire (ECog-Subject and ECog-StudyPartner) in four domains (memory, language, visuospatial, and executive). ACD was measured as the subject-informant discrepancy in the four ECog scores. We compared the ECog and ACD scores across cognitive domains between four groups: 71 amyloid-positive individuals with amnestic AD, 191 amnestic mild cognitive impairment (MCI), or 118 cognitively normal (CN), and 211 amyloid-negative CN controls, selected from the ADNI database. Receiver operating characteristic curves analysis was performed to evaluate the accuracy of the ECog and ACD scores in discriminating clinical groups.

Results: Self- and informant-reported complaints were generally distributed as follows: memory, language, executive, and visuospatial (from the most severe to the least severe). Both groups of CN participants presented on average more memory and language complaints than their informant. MCI participants showed good agreement with their informants. AD participants presented anosognosia in all domains, but especially for the executive domain. The four ECog-StudyPartner sub-scores allowed excellent discrimination between groups in almost all classifications and performed significantly better than the other two classifiers considered. The ACD was excellent in distinguishing the participants with AD from the two groups of CN participants. The ECog-Subject was the least accurate in discriminating groups in four of the six classifications performed.

OPEN ACCESS

Edited by:
Allison B. Reiss,
New York University, United States

Reviewed by:
Christine Bastin,
University of Liège, Belgium
Elodie Bertrand,
Université de Paris, France

****Correspondence:***
Federica Cacciamani
federica.cacciamani@inserm.fr

†Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Specialty section:
This article was submitted to Alzheimer's Disease and Related Dementias, a section of the journal Frontiers in Aging Neuroscience

Received: *09 November 2021*
Accepted: *29 April 2022*
Published: *16 June 2022*

Citation:
Cacciamani F, Godefroy V, Brambati SM, Migliaccio R, Epelbaum S and Montembeault M (2022) Differential Patterns of Domain-Specific Cognitive Complaints and Awareness Across the Alzheimer's Disease Spectrum. Front. Aging Neurosci. 14:811739. doi: 10.3389/fnagi.2022.811739

Conclusion: In research, the study of complaint and anosognosia should not be reduced solely to the memory domain. In clinical practice, non-amnestic complaints could also be linked to Alzheimer's disease. The presence of an informant also seems necessary given its accuracy as a source of information.

Keywords: awareness, metacognition, anosognosia, Alzheimer's disease, language, executive function, memory, visuospatial abilities

INTRODUCTION

In the past, Alzheimer's disease (AD) was clinically defined as a dementia syndrome (McKhann et al., 1984). The arrival of biomarkers has allowed a more accurate description of its pre-dementia stages. Technical and scientific progress has made it possible to develop increasingly precise diagnostic techniques. They allow to visualize the patient's brain *in vivo* and to measure pathological hallmarks of AD, such as amyloid and tau pathology, and its neurodegenerative processes. We now know that years pass before neuropathology causes cognitive changes (i.e., *preclinical AD*, Dubois et al., 2010). The disease begins to manifest with a *transitional* or *subtle* cognitive decline (Sperling et al., 2011; Jack et al., 2018), meaning that performance is below the individual's baseline cognitive level, although neuropsychological scores are not yet considered pathological. This condition precedes *mild cognitive impairment* (MCI, Albert et al., 2011), also known as *prodromal AD* (Dubois et al., 2010), which is instead detectable by neuropsychological testing, and which in turn precedes dementia.

One of the central pieces of information used to establish a diagnosis on the AD spectrum is the report of cognitive complaints from both the patient and the informant, which are usually collected during the initial clinical interview. History-taking from the patient and a knowledgeable informant is necessary, as stated in the current diagnostic criteria for dementia due to AD (McKhann, 2011), mild cognitive impairment (Albert et al., 2011), and subjective cognitive decline (Jessen et al., 2020). Therefore, the characterization of the cognitive complaints typical of patients with early-stage AD is one of the most studied topics to better understand the pre-dementia stages and for better early detection of AD (Jessen et al., 2020). In fact, the report of a cognitive complaint is one of the few ways that individuals with early neurodegeneration come to medical attention (Stewart et al., 2010). Cognitive-complainers are more likely to have abnormal biomarkers consistent with AD pathology, e.g., increased amyloid deposition (Perrotin et al., 2012), decreased metabolism (Mosconi et al., 2008), and cortical atrophy (Saykin et al., 2006). However, it is also a condition known to be nonspecific, with a high prevalence in the general population (Condret-Santi, 2013). Therefore, investigating the cognitive difficulties reported by a family member or close friend has also been studied for this purpose, and appears to be a particularly useful indicator of AD pathology (Gavett, 2011; Brunet et al., 2019), as well as for diagnostic accuracy (Gifford, 2015). The combination of self- and informant-reported cognitive complaints can also inform about the awareness of cognitive decline (ACD), which is another crucial information for individuals on the AD spectrum. Recent studies have shown that patients with early-stage AD may already present with reduced ACD (Hanseeuw et al., 2020), leading, in most cases (Turró-Garriga et al., 2016), to overt anosognosia in late-stage AD. The index of ACD, calculated for example as the difference between self- and informant-reports (Cacciamani et al., 2017, 2020), could provide added value for assessing the risk of AD in an individual, and function as a good predictor of future decline.

Due to the high frequency of amnestic AD dementia, research in the field of cognitive complaints and awareness is highly focused on episodic memory (Gagliardi et al., 2020; Jessen et al., 2020). In this context, non-amnestic cognitive complaints are less studied, but still of interest. First, patients or their families also report difficulties other than memory problems, such as language complaints or difficulty retrieving words (Rohrer, 2008; Montembeault et al., 2022), executive functioning (Valech et al., 2018), and visuospatial complaints (Mendez, 1990). Secondly, recent studies have highlighted the relevance of non-amnestic cognitive complaints in patients on the AD spectrum.

For example, in cognitively unimpaired individuals, word-finding complaints are as frequent and severe as memory complaints, and these complaints are more frequent and severe than executive and visuospatial complaints (Montembeault et al., 2022). Furthermore, self-reported cognitive complaints in language and executive function domains have been shown to help in distinguishing cognitively-normal amyloid-negative and amyloid-positive controls (La Joie et al., 2016; Valech et al., 2018; Montembeault et al., 2022). Shokouhi et al. (2019) investigated whether domain-specific complaints were equally or differently associated with amyloid and tau pathology in a group of cognitively-normal elderly individuals. They found that planning and visuospatial complaints were primarily associated with tau pathology, while memory and organizational complaints were primarily associated with amyloid deposits. This suggests that domain-specific complaints can be subtended by different processes (Shokouhi et al., 2019). Nonetheless, additional evidence across the full AD spectrum is needed to fully establish if complaints and awareness of non-amnestic domains (language, visuospatial, executive) are clinically useful. Anosognosia is also a multidimensional construct (Bertrand et al., 2019; Mayelle et al., 2022). In Bertrand and collaborators, patients with AD presented anosognosia regarding their overall medical condition and executive disorders, but they were well aware of their levels of disinhibition and apathy (Bertrand et al., 2019). Another study has shown more severe anosognosia for memory and activities of daily living alterations in patients with dementia, but

an under-estimation of function in the socio-emotional domain (Marková et al., 2014).

While the clinical relevance of self- and informant-reported cognitive complaints and ACD have been shown, only a very few studies have investigated which piece of information is the most useful in distinguishing individuals at different stages on the AD spectrum. A study by Rueda (2015) compared the utility of informant- and self-report of cognitively-relevant functional abilities to discriminate diagnostic groups across the AD spectrum. They found that informants' complaints were systematically more accurate than self-reports in distinguishing different stages of the disease, and that informant-report was consistently more associated with objective markers of the disease than self-reports, although self-reported functional status may still have some utility in early disease. However, they did not compare the respective utilities of informant- and self-report with the utility of ACD to predict the stage of the disease. Besides, they only used a global score of cognitive abilities (ECog total score), without considering the predictive values for each cognitive domain. Answering these questions could guide researchers and clinicians on the most optimal measures to use to distinguish these populations, both in terms of sources of information and specific cognitive domains.

In this study, we measured self-reported cognitive complaints, informant-reported complaints, and ACD across four cognitive domains (memory, language, visuospatial, executive) and between 71 amyloid-positive individuals with amnestic AD, 191 amnestic mild cognitive impairment (MCI) or 118 cognitively normal (CN), and 211 amyloid-negative CN controls from the ADNI database. Our first objective was to compare the intensity of self-reported complaints, informant-reported complaints, and ACD, by cognitive domain across the AD spectrum. We hypothesize that while episodic memory complaints will be the most elevated in all groups, non-amnestic cognitive complaints, especially language and executive complaints, will also distinguish the different groups on the AD spectrum and therefore be useful clinically. Furthermore, we expect AD patients to present anosognosia in all cognitive domains, but especially in memory and executive functioning. Our second objective was to measure how accurately self- and informant-reported complaints and ACD (i.e., subject-informant discrepancy) in the four investigated cognitive domains can discriminate the four clinical groups. We hypothesize that informant-reported cognitive complaints and ACD will be better than self-reported complaints in distinguishing clinical groups. Furthermore, demonstrating that informant-reported complaints and ACD in all cognitive domains allow for a good prediction of clinical groups will underline the clinical significance of investigating non-amnestic domains even in amnestic MCI and AD.

MATERIALS AND METHODS

Participants

Data used in the preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

We selected four groups of participants: amyloid-positive (Aβ+) individuals diagnosed with AD, MCI, or cognitively-normal (CN) at baseline, and amyloid-negative (Aβ−) healthy controls. Participants were considered Aβ+ when they had at least one positive amyloid marker. Amyloid markers considered were ^{8}F-AV-45 PET [positive if retention ratio >1.1 (Landau, 2013)], PiB-PET [positive if retention ratio >1.5 (Donohue et al., 2014)], and CSF [positive if β− amyloid level <192 pg/ml (Donohue et al., 2014)] No restrictions were imposed based on their cognitive status. We included Aβ+ subjects with normal cognition (i.e., subjects at risk of preclinical AD), with a diagnosis of MCI (or *prodromal AD*), or with a diagnosis of AD. The group of healthy controls consisted of cognitively unimpaired individuals who presented a negative status to all three amyloid markers considered, using the same reference values indicated above.

The CN status was reserved for participants with normal memory on the Wechsler Memory Scaled - Revised (WMS-R) Logical Memory II (LM II) test, Mini-Mental State Examination (MMSE) score between 24 and 30 (inclusive), Clinical Dementia Rating (CDR) = 0, and without significant impairment in activities of daily living. There was no criterion regarding memory complaints. Participants were classified as MCI if they presented subjective memory concerns as reported by the subject, their study-partner or clinician, had abnormal memory function on the WMS-R LM II test, an MMSE score between 24 and 30 (inclusive) and a CDR score = 0.5. Their general cognition and functional performance were sufficiently preserved so that a diagnosis of AD could not be made. Diagnosis of AD was made in participants with a memory complaint confirmed by a study-partner (or reported only by the study-partner), with abnormal memory on the WMS-R LM II test, with an MMSE score between 20 and 26 (inclusive), with a CDR score = 0.5 or 1, and who met the NINCDS/ADRDA criteria for probable AD.

All participants were aged between 55 and 90 years (inclusive), had completed a minimum of six degrees of education and did not have vascular dementia, depression, sensory disturbances, or other medical conditions that could interfere with the study. A study-partner who had frequent contact with the participant (for example, an average of 10 h per week or more) also accompanied him/her to visits and filled out questionnaires. We selected only participants with a maximum of one missing observation per cognitive domain for self- and informant-reported complaints (i.e., only subjects with a maximum of 10% missing data).

Subjective Measures of Cognitive Decline

Subjects and study-partners independently completed two parallel versions of the Everyday Cognition questionnaire (ECog-Subject and ECog-StudyPartner; Farias, 2008), which asks to compare the subject's current cognitive efficiency with that of

10 years ago. Four areas are assessed: Memory (eight items, for example, "Remembering a few shopping items without a list"), Language (nine items, for example, "Forget the name of objects"), Visuospatial ability (seven items, for example, "Follow a map to find a new location") and Executive functions (15 items from the planning, organization, and divided attention subscales, for example, "Plan a sequence of stops on a shopping trip"). Answers are on a 4-point scale from 1 ("No change or performs better than 10 years ago") to 4 ("Performs task much worse than 10 years ago"). The ECog-Subject and ECog-StudyPartner scores were calculated by averaging the responses on the items related to each cognitive domain, with a possible range between 1 and 4. We also calculated a global score for the Ecog-Subject and Ecog-StudyPartner by averaging the four domains.

Awareness of Cognitive Decline (ACD)

As a measure of ACD, we used the subject-informant discrepancy (ECog Subject *minus* ECog-StudyPartner), which we calculated separately for each of the four ECog sub-scales. This resulted in four measures of awareness of changes in memory, language, visuospatial, and executive functions, respectively. We also calculated a global score for the ACD by averaging the four domains. The awareness scores ranged from −3 to 3. A score of zero indicates perfect agreement between the subject and the study-partner. A score of −3 indicates complete anosognosia (i.e., ECog-Subject >Ecog - StudyPartner). A score of 3 indicates an intense cognitive complaint not confirmed by the study-partner (i.e., ECog-Subject <Ecog-StudyPartner).

Cognitive Scores

We used the MMSE as a global measure of cognitive functioning. As objective measures of memory, language, executive function and visuospatial abilities, we used four cognitive composites developed from the ADNI neuropsychological battery using item response theory. The memory composite included the Rey Auditory Verbal Learning Test, AD Assessment Schedule - Cognition (ADAS-Cog) memory items, MMSE memory items, and Logical Memory (Crane et al., 2012). The language composite included the Boston Naming Test, Category Fluency—animals, Category Fluency—vegetables, ADAS-Cog language items, MMSE language items, and MoCA language items (Choi et al., 2020). The visuospatial composite included the Clock drawing test, ADAS-Cog language items, and MMSE language items (Choi et al., 2020). The executive function composite included Category Fluency—animals, Category Fluency—vegetables, Trails A and B, Digit span backward, WAIS-R Digit Symbol Substitution, and five Clock Drawing items (circle, symbol, numbers, hands, time; Gibbons et al., 2012).

Statistical Analysis

Statistical analyses were performed using RStudio (version 1.2.5033, RStudio, Inc) and IBM SPSS Statistics, Armonk, NY (version 26.0.0.1). Missing observations in ECog items were systematically imputed when a maximum of one response was missing per subscale (i.e., per cognitive domain), which represents a maximum of 10% of items per subject. Missing observations were imputed by the mean score of all other items of the subscale.

Study Population

We used χ^2 test for categorical variables and one-way ANOVA (with Tukey correction) for continuous variables to compare demographical and clinical data between clinical groups.

Objective 1: Comparison of ECog-Subject, ECog-StudyPartner, and ACD Between Cognitive Domains and Clinical Groups

We used a mixed ANOVA design to test the main and interaction effects of the clinical group (between-subjects factor) and cognitive domain (within-subjects factor) on the eight ECog scores (four ECog-Subject, four ECog-StudyPartner) and the four anosognosia scores, controlling for age, sex, and education. To explore significant effects, we performed *post-hoc* comparisons using one-way ANOVA followed by pairwise *t*-tests with Bonferroni correction for multiple comparisons.

Objective 2: Accuracy of Domain-Specific ECog-Subject, ECog-StudyPartner, and ACD in Discriminating the Four Groups

Receiver operating characteristic curves (ROC) and the nonparametric estimate of the area under the ROC (AUC) based on the trapezoidal rule were used to evaluate the accuracy of predicting clinical groups using the ECog-Subject, ECog-StudyPartner, and ACD measures by domain (Hosmer and Lemeshow, 2000). We, therefore, ran 72 models (four domains * three sources of information * six discriminations). Discriminations of interest were structured in a hierarchical manner, comparing clinical groups with more impairment to groups with no or less impairment. Specifically, we tested the discrimination between Aβ− healthy controls and each of the other clinical groups among Aβ+ subjects (CN, MCI, AD), between Aβ+/CN, and each of the more impaired clinical groups (MCI, AD), and between MCI and AD. AUCs were adjusted for age, sex, and education level. The higher the AUC, the better the predictor is at distinguishing between two clinical groups. For each analysis, the specificity corresponding to a sensitivity of 80% was reported as the optimal cut-off score for that same sensitivity.

Finally, we tested whether there were significant differences in the accuracy of the three information sources in each of the six discrimination tasks mentioned above. We used the DeLong et al. (1988) method to perform pairwise comparisons between the accuracy (i.e., the AUCs) of the self-reported complaint, informant-reported complaint, and ACD. We used global ECog and ACD scores (and not by cognitive domain) to make the results more interpretable.

RESULTS

Study Population

We included 380 Aβ+ subjects, distributed as follows: 31% had normal cognition (Aβ+/CN, n = 118), 50.3% had MCI (Aβ+/MCI, n = 191), and 18.7% had received a diagnosis of AD

(Aβ+/AD, $n = 71$). We also included 211 Aβ−/CN subjects with normal cognition as healthy controls (**Table 1**).

Aβ−/CN controls were younger than the other groups ($F_{(3,587)} = 7.376$, $\eta^2 = 0.036$, $p < 0.001$) and had higher levels of education than Aβ+/AD subjects ($F_{(3,587)} = 5.392$, $\eta^2 = 0.027$, $p = 0.001$). Women were overrepresented in the Aβ+/CN group (about 71%, $\chi^2 = 23.632$, $p < 0.001$ compared to men). The number of APOE ε4 carriers differed between groups, $F_{(3,568)} = 42.790$, $\eta^2 = 0.189$, $p < 0.001$ (Aβ−/CN < Aβ+/CN < Aβ+/MCI < Aβ+/AD, the latter difference not being statistically significant). All further analyses were controlled for age, sex and education.

The Memory and Executive composites were significantly different between groups (Aβ−/CN = Aβ+/CN > Aβ+/MCI > Aβ+/AD; Memory: $\eta^2 = 0.51$, $p < 0.01$; Executive: $\eta^2 = 0.28$, $p < 0.01$). The Language and Visuospatial composite scores were on average significantly lower (indicating greater impairment) in the AD group than in the other groups (Language: $\eta^2 = 0.29$, $p < 0.01$; Visuospatial: $\eta^2 = 0.08$, $p < 0.01$).

Objective 1: Comparisons of ECog-Subject, ECog-StudyPartner, and ACD by Cognitive Domain and Clinical Group

Figure 1 and **Table 2** show the patterns of cognitive complaints (ECog-Subject, ECog-StudyPartner) and ACD across the four investigated domains (Memory, Language, Visuospatial abilities, and Executive functions) in the four groups (CN/Aβ+, MCI/Aβ+, AD/Aβ+, and CN/Aβ−). The analyses for Objective 1 were controlled for age, sex, and education. Detailed statistical indices for Objective 1 are available in **Supplementary Materials**.

ECog-Subject Scores

The effect of the Group*Domain interaction was significant ($F_{(91,761)} = 16.761$, partial $\eta^2 = 0.016$, $p < 0.001$; **Table 2**).

In all groups combined, the ECog-Subject scores were significantly different in each cognitive domain($F_{(31,761)} = 422.787$, partial $\eta^2 = 0.131$, $p < 0.001$). *Post-hoc* pairwise comparison showed that memory was globally the domain in which the participants reported the greatest complaints, followed by language, executive functions, and finally, visuospatial abilities. The only exception was in Aβ+/AD participants, in which language and executive function complaints were not significantly different.

The ECog-Subject scores also differed significantly between the groups ($F_{(3,587)} = 55.175$, partial $\eta^2 = 0.220$, $p < 0.001$). Aβ+/CN participants and Aβ-/CN controls reported complaints of similar intensity, while Aβ+/MCI and Aβ+/AD participants reported significantly greater difficulties than the two groups of CN participants. No significant difference was observed between Aβ+/MCI and Aβ+/AD participants.

ECog-StudyPartner Scores

The effect of the Group*Domain interaction was significant ($F_{(91,761)} = 28.476$, partial $\eta^2 = 0.018$, $p < 0.001$).

In all groups combined, the ECog-StudyPartner scores were significantly different in each cognitive domain ($F_{(31,761)} = 270.578$, partial $\eta^2 = 0.057$, $p < 0.001$). More specifically, the study-partners reported that memory was the most impaired cognitive domain in the subjects, followed by language and executive functions, with no differences between these two. Complaints regarding visuospatial abilities were significantly less intense than in the other domains in Aβ-/CN and Aβ+/MCI, but not in Aβ+/CN and Aβ+/AD.

The ECog-StudyPartner score also differed significantly between the groups ($F_{(3,587)} = 262.240$, partial $\eta^2 = 0.573$, $p < 0.001$). *Post-hoc* pairwise comparisons showed that study-partners of Aβ+/CN subjects and Aβ-/CN controls globally reported complaints of similar intensity, followed by—in increasing order—Aβ+/MCI and Aβ+/AD.

Awareness of Cognitive Decline

The effect of the Group*Domain interaction was significant ($F_{(91,761)} = 28.476$, partial $\eta^2 = 0.018$, $p < 0.001$).

In all groups combined, the ACD scores were significantly different in each cognitive domain($F_{(31,761)} = 42.301$, partial $\eta^2 = 0.013$, $p < 0.001$). In both Aβ-/CN and Aβ+/CN, awareness of memory and language performance was higher than awareness of visuospatial and executive performance. In Aβ+/MCI, awareness of memory and language performance was significantly higher than awareness of executive function, and awareness of language performance was higher than awareness of visuospatial performance. Finally, in Aβ+/AD, awareness of executive performance was significantly poorer than awareness for visuospatial and language performance.

The ACD also differed significantly between the groups ($F_{(3,587)} = 75.646$, partial $\eta^2 = 0.279$, $p < 0.001$). *Post-hoc* pairwise comparisons showed that Aβ+/AD participants had significantly lower ACD than all other groups, regardless of the cognitive domain.

Objective 2: Discriminant Value of Ecog-Subject, Ecog-StudyPartner, and Awareness of Cognitive Decline Per Cognitive Domain

Table 3 summarizes the ROC curve analysis with specificity (at 80% of sensitivity) for each diagnostic comparison. It shows how accurately the ECog and ACD scores in each cognitive domain can discriminate clinical groups (six pairwise discriminations between Aβ-/CN, Aβ+/CN, Aβ+/MCI, and Aβ+/AD groups).

Discriminant Value of ECog-Subject by Domain

ECog-Subject scores performed globally better than chance in distinguishing between groups, although they did not have excellent accuracy: the highest AUC was 0.85, AUC above 0.80 was not frequent and specificities were inferior to 69%.

The best performance of the ECog-Subject was in the discrimination between MCI and Aβ-/CN (AUC memory = 0.83), between AD and Aβ-/CN (AUC memory = 0.85, AUC executive function = 0.81, AUC visuospatial = 0.81) and between AD and Aβ+/CN (AUC memory = 0.80, AUC visuospatial = 0.80).

TABLE 1 | Baseline characteristics of the participants.

	Aβ-/CN (controls)[a] (*n* = 211)	Aβ+ (*n* = 380)			*p*
		CN[b] (*n* = 118)	MCI[c] (*n* = 191)	AD[d] (*n* = 71)	
Age [years]	70.92 ± 5.89 (55.8–89)[b,c,d]	73.34 ± 6.46 (56.5–90.1)[a]	72.91 ± 6.92 (55-87.8)[a]	74.61 ± 7.83 (55.6–90.3)[a]	<0.01*
Education [years]	16.85 ± 2.41 (12–20)[d]	16.48 ± 2.64 (8-20)	16.22 ± 2.79 (9-20)	15.49 ± 2.46 (10-20)[a]	0.01*
Sex [female]	106 (50.24%)[b]	84 (71.19%) [a,c,d]	86 (45.03%)[b]	31 (43.66%)[b]	<0.01*
APOE-ε4 carriers	45 (21.84%)[b,c,d]	57 (51.90%)[a,c,d]	125 (67.02%)[a,b]	53 (77.94%)[a,b]	<0.01*
MMSE	29.16 ± 1.16 (24–30)[c,d]	28.97 ± 1.07 (26-30)[c,d]	27.89 ± 1.84 (19-30)[a,b,d]	22.73 ± 2.31 (18-26)[a,b,c]	<0.01*
Memory Score	1.1 ± 0.6 (−1.1 to 3.1)[c,d]	0.98 ± 0.56 (−0.7 to 2.7)[c,d]	0.25 ± 0.64 (−1.5 to 2.2)[a,b,d]	−0.92 ± 0.56 (−2.8-0.6)[a,b,c]	<0.01*
Language Score	0.24 ± 0.61 (−1.7 to 0.7)[d]	0.19 ± 0.57 (−1.5-0.7)[d]	−0.04 ± 0.73 (−2.5 to 0.7)[d]	−0.51 ± 0.95 (−3.2 to 0.7)[a,b,c]	<0.01*
Visuospatial Score	0.97 ± 0.71 (<0.9–3.1) [d]	0.76 ± 0.69 (−1.2 to 2.8) [d]	0.29 ± 0.79 (−1.9 to 2.6) [d]	−0.78 ± 0.92 (−3.7 to 1.6)[a,b,c]	<0.01*
Executive Score	1.05 ± 0.80 (−1.2 to 3)[c,d]	0.78 ± 0.71 (<0.7 to 3)[c,d]	0.32 ± 0.92 (−1.9 to 3)[a,b,d]	−0.89 ± 0.93 (−3 to 1)[a,b,c]	<0.01*

*Note. Results are given as mean ± standard deviation (Min-Max) or as n (%). APOE, Apolipoprotein; MMSE, Mini Mental State Examination; ECog, Everyday Cognition questionnaire. For the APOE genotype, the n and % represent the number and percentage of subjects presenting at least one ε4 allele. *Indicates statistical significance. Superscripted a, b, c, and d indicate significant pairwise between-group comparisons.*

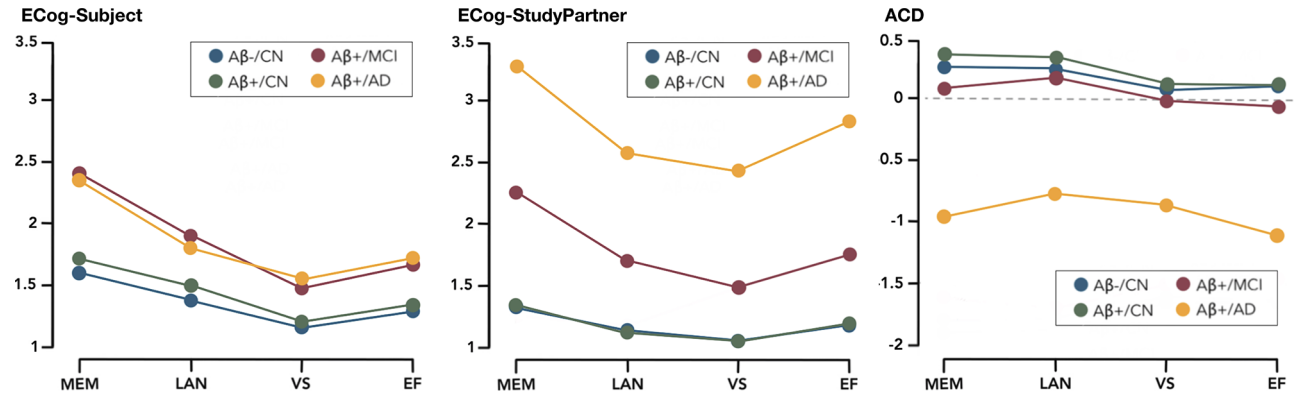


FIGURE 1 | ECog-Subject, ECog-StudyPartner, and ACD by domain between groups.

The worst performances were in the discrimination between the two CN groups (all AUCs = 0.70), and between MCI and AD (all AUCs between 0.60 and 0.61).

Discriminant Value of ECog-StudyPartner by Domain

ECog-StudyPartner scores showed good to excellent accuracy in almost all discriminations. The best performance of the Ecog-StudyPartner scores was in the discrimination between AD and Aβ-/CN (AUCs between 0.96 and 0.98) and between AD and Aβ+/CN (AUCs between 0.96 and 0.99). Specificities could reach very high levels (99% as a maximum).

No ECog-StudyPartner score (i.e., in any cognitive domain) seems useful to distinguish Aβ+/CN and Aβ-/CN subjects (all AUCs between 0.69 and 0.70).

Discriminant Value of Awareness of Cognitive Decline by Domain

ACD scores showed good to excellent accuracy in the discrimination between AD and Aβ+/CN (AUCs between 0.88 and 0.93), between AD and Aβ-/CN (AUCs between 0.84 and 0.91), and between AD and MCI (AUC_{ef} = 0.82, AUC_{vs} = 0.85). In these discriminations, specificities could reach very high levels (99% as a maximum), especially in the visuospatial and executive domains. Accuracies were low to moderate in the other discriminations (AUCs between 0.61 and 0.79).

Comparison of the Three Sources of Information

Globally, the ECog-StudyPartner performed significantly better than the other two sources of information in all discriminations, except Aβ−/CN vs. Aβ+/CN, where the three sources of information did not differ significantly (all AUCs between 0.69 and 0.70); ECog-Subject vs. ECog-StudyPartner: $Z = -1.65$, $p = 0.09$; ECog-StudyPartner vs. ACD: $Z = -1.89$, $p = 0.06$; ECog-Subject vs. ACD: $Z = -0.54$, $p = 0.59$.

ACD was significantly less accurate than ECog-Subject in two out of six discriminations, namely Aβ−/CN vs. MCI (ECog-Subject vs. ACD: $Z = 5.47$, $p < 0.01$) and Aβ+/CN vs. MCI (ECog-Subject vs. ACD: $Z = 3.01$, $p < 0.01$). The ACD score was significantly more accurate than the ECog-Subject in the other discriminations. More details are in **Figure 2**.

Post-hoc Analysis: Correlation Between Subjective and Objective Cognitive Measures

The results from the analysis comparing the various sources of information suggest that the ECog-StudyPartner performs better at discriminating the groups than the ECog-Subject.

TABLE 2 | Comparison of ECog-Subject, ECog-StudyPartner, and ACD by Domain between Groups.

SELF-REPORTED COMPLAINT (ECog-Subject)						
	Memory	**Language**	**Visuospatial abilities**	**Executive functions**	***p***	**Intragroup effects**
Aβ-/CN	1.60 ± 0.52	1.38 ± 0.40	1.15 ± 0.27	1.28 ± 0.34	<0.01	M > L > E > V
Aβ+/CN	1.71 ± 0.47	1.49 ± 0.43	1.18 ± 0.26	1.32 ± 0.32	<0.01	M > L > E > V
Aβ+/MCI	2.38 ± 0.70	1.90 ± 0.68	1.48 ± 0.59	1.67 ± 0.61	<0.01	M > L > E > V
Aβ+/AD	2.34 ± 0.78	1.80 ± 0.67	1.56 ± 0.58	1.71 ± 0.61	<0.01	M > L = E > V
p	<0.01	<0.01	<0.01	<0.01		
Intergroup effects	Aβ-/CN = Aβ+/CN < MCI = AD	Aβ-/CN = Aβ+/CN < MCI = AD	Aβ-/CN = Aβ+/CN < MCI = AD	Aβ-/CN = Aβ+/CN < MCI = AD		
INFORMANT-REPORTED COMPLAINT (ECog-StudyPartner)						
	Memory	**Language**	**Visuospatial abilities**	**Executive functions**	***p***	**Intragroup effects**
Aβ-/CN	1.32 ± 0.43	1.13 ± 0.24	1.06 ± 0.16	1.17 ± 0.34	<0.01	M > E = L > V
Aβ+/CN	1.33 ± 0.43	1.12 ± 0.22	1.06 ± 0.15	1.18 ± 0.33	<0.01	M > E = L = V
Aβ+/MCI	2.27 ± 0.83	1.70 ± 0.69	1.48 ± 0.61	1.73 ± 0.70	<0.01	M > E = L > V
Aβ+/AD	3.28 ± 0.63	2.57 ± 0.76	2.41 ± 0.84	2.81 ± 0.76	<0.01	M > E = L = V
p	<0.01	<0.01	<0.01	<0.01		
Intergroup effects	Aβ-/CN = Aβ+/CN < MCI < AD	Aβ-/CN = Aβ+/CN < MCI < AD	Aβ-/CN = Aβ+/CN < MCI < AD	Aβ-/CN = Aβ+/CN < MCI < AD		
AWARENESS OF COGNITIVE DECLINE, ACD (ECog-Subject *minus* ECog-StudyPartner)						
	Memory	**Language**	**Visuospatial abilities**	**Executive functions**	***p***	**Intragroup effects**
Aβ-/CN	0.28 ± 0.55	0.25 ± 0.42	0.09 ± 0.27	0.11 ± 0.36	<0.01	M = L > E = V
Aβ+/CN	0.38 ± 0.47	0.36 ± 0.41	0.12 ± 0.26	0.13 ± 0.37	<0.01	M = L > E = V
Aβ+/MCI	0.10 ± 0.89	0.20 ± 0.88	0.00 ± 0.78	<0.06 ± 0.83	<0.01	L > E = V; M > E; L = M; M =V
Aβ+/AD	<0.94 ± 1.00	<0.77 ± 0.88	<0.85 ± 0.95	−1.10 ± 0.90	0.01	M = L, E, V; L > E; V > E
p	<0.01	<0.01	<0.01	<0.01		
Intergroup effects	Aβ-/CN = Aβ+/CN = MCI > AD	Aβ-/CN = Aβ+/CN = MCI > AD	Aβ-/CN = Aβ+/CN = MCI > AD	Aβ-/CN = Aβ+/CN = MCI > AD		

Note. Results are given as mean ± standard deviation. In the intragroup effects, M, Memory; L, Language; V, Visuospatial abilities; E, Executive functions. In the intergroup and intragroup effects, > indicates "significantly higher than"; <indicates "significantly lower than", = indicates "not significantly different".

TABLE 3 | Results of ROC/AUC analysis.

	ECog-Subject		ECog-Study Partner		ACD	
	AUC	**Specificity at sensitivity = 0.8**	**AUC**	**Specificity at sensitivity = 0.8**	**AUC**	**Specificity at sensitivity = 0.8**
Memory						
Aβ+/CN vs. Aβ</CN	0.70	0.31	0.69	0.22	0.70	0.20
Aβ+/MCI vs. Aβ-/CN	**0.83**	0.69	**0.86**	0.74	0.63	0.15
Aβ+/AD vs. Aβ-/CN	**0.85**	0.59	**0.98**	0.99	**0.88**	0.73
Aβ+/MCI vs. Aβ+/CN	0.78	0.57	**0.87**	0.79	0.71	0.15
Aβ+/AD vs. Aβ+/MCI	0.60	0.14	**0.83**	0.73	0.77	0.52
Aβ+/AD vs. Aβ+/CN	**0.80**	0.46	**0.99**	0.99	**0.93**	0.76
Language						
Aβ+/CN vs. Aβ-/CN	0.70	0.30	0.70	0.21	0.70	0.27
Aβ+/MCI vs. Aβ-/CN	0.75	0.54	**0.81**	0.63	0.61	0.03
Aβ+/AD vs. Aβ-/CN	0.78	0.42	**0.97**	0.98	**0.86**	0.61
Aβ+/MCI vs. Aβ+/CN	0.75	0.41	**0.83**	0.63	0.69	0.14
Aβ+/AD vs. Aβ+/MCI	0.61	0.17	**0.80**	0.67	0.78	0.57
Aβ+/AD vs. Aβ+/CN	0.75	0.30	**0.98**	0.98	**0.91**	0.72
Visuospatial Ability						
Aβ+/CN vs. Aβ-/CN	0.70	0.25	0.70	0.22	0.70	0.22
Aβ+/MCI vs. Aβ-/CN	0.73	0.30	0.79	0.36	0.62	0.08
Aβ+/AD vs. Aβ-/CN	**0.81**	0.58	**0.96**	0.97	**0.84**	0.92
Aβ+/MCI vs. Aβ+/CN	0.75	0.24	**0.82**	0.32	0.79	0.09
Aβ+/AD vs. Aβ+/MCI	0.61	0.29	**0.82**	0.66	**0.85**	0.64
Aβ+/AD vs. Aβ+/CN	**0.80**	0.52	**0.96**	0.98	**0.88**	0.93
Executive Functions						
Aβ+/CN vs. Aβ-/CN	0.70	0.30	0.70	0.20	0.70	0.28
Aβ+/MCI vs. Aβ-/CN	0.73	0.52	**0.80**	0.64	0.64	0.11
Aβ+/AD vs. Aβ-/CN	**0.81**	0.52	**0.97**	0.98	**0.91**	0.92
Aβ+/MCI vs. Aβ+/CN	0.74	0.44	**0.81**	0.66	0.69	0.14
Aβ+/AD vs. Aβ+/MCI	0.61	0.20	**0.85**	0.74	**0.82**	0.68
Aβ+/AD vs. Aβ+/CN	0.79	0.44	**0.97**	0.95	**0.91**	0.90

Note. AUC, Area Under the ROC; ACD, Awareness of Cognitive Decline. To facilitate understanding of the table, all AUCs between 0.80 and 0.90 are in bold, and all AUCs > 0.90 are in bold and underlined.

One possible interpretation is that informants are more accurate at assessing the cognitive levels of the subjects than the subjects themselves. To explore this interpretation, we carried Pearson's correlations between objective measures of cognition (four composite scores) and subjective measures (four ECog-Subject, four ECog-StudyPartner). To compare the correlation coefficients obtained between the objective measures of cognition and the ECog-Subject, versus the correlation coefficients obtained between the objective measures and the ECog-StudyPartner, we performed tests of significance using the "cocor" R package for the comparison of two overlapping correlations based on dependent groups.

In both subjects and informants, the cognitive composite scores correlated significantly and negatively with the cognitive complaints in all four cognitive domains (**Table 4**). The negative correlations indicate that elevated cognitive complaints are associated with lower objective cognitive performance. When comparing the correlation coefficients between subjects and informants, we found that the objective composite scores were significantly more strongly correlated with the ECog-StudyPartner (all r between −0.29 and −0.64) than with the ECog-Subject (all r between −0.16 and −0.38), for all cognitive domains. A more extensive correlation matrix is also included in the **Supplementary Materials**.

DISCUSSION

In this study, we investigated domain-specific cognitive complaints across the amnestic AD spectrum (more precisely, in amyloid-positive individuals ranging from normal cognition to dementia) and controls, using three sources of information: self-reported complaints, informant-reported complaints, and the discrepancy between these two reports as a measure of awareness of cognitive decline (ACD). To briefly recap the main findings of this study, the intensity of cognitive complaints, both self- and informant-reported, was generally distributed according to the following trend: memory, language, executive, and visuospatial (from most to least impaired). The two groups with normal cognition (i.e., amyloid negative and positive) reported experiencing a more marked decline in memory and language than noticed by their informants. The Aβ+/MCI participants had good agreement with their informants, while AD participants presented poor ACD (anosognosia), especially for the executive domain. In terms of the ability of these sources of information to discriminate between groups, we found that informant-reported cognitive complaints in all domains performed the best. ACD scores, in all domains, accurately distinguish AD from CN participants. Self-reported complaints were not as accurate in discriminating the groups. Finally, while both self-reported and informant-reported complaints were

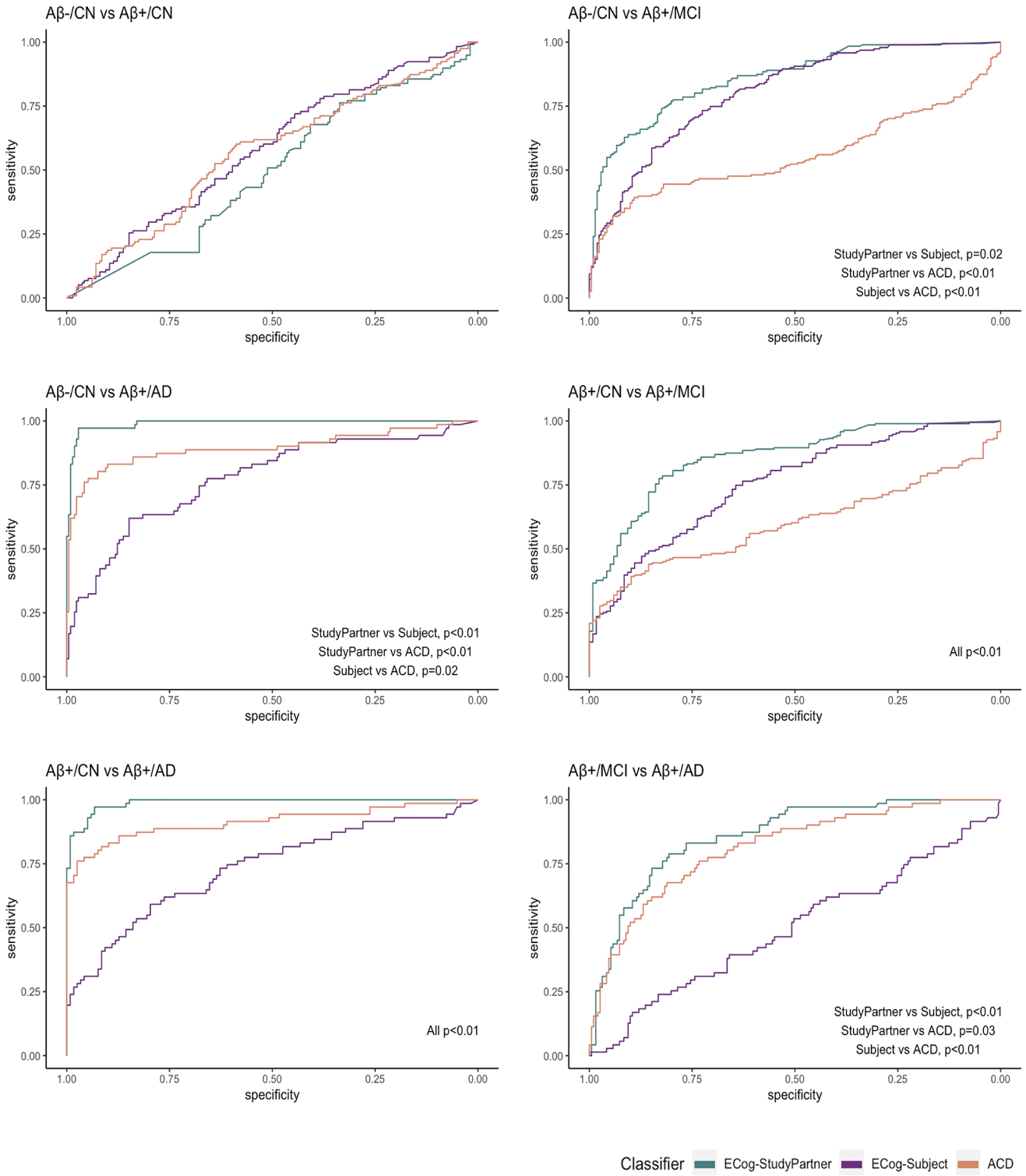


FIGURE 2 | ROC comparisons between the three sources of information.

correlated with objective cognitive scores in each cognitive domain, informant-reported complaints were significantly more correlated with objective cognitive scores than self-reported complaints.

Amnestic and Non-amnestic Cognitive Complaints Across the Amnestic AD Spectrum

Subjects and study-partners from all groups reported the most complaints in the memory domain. This was expected given the inclusion criteria of ADNI, which requires significant memory complaints in the MCI and AD participants. Episodic memory is also the most frequently impaired cognitive domain in AD (Sarazin et al., 2007). Language and executive functions were the domains reported to be most impaired after memory. Language and executive disorders appear quite early in the course of the disease and become more and more marked in the patient's clinical picture (Ahmed et al., 2013; Harrington et al., 2013). For instance, a recent study including healthy controls, cognitive-complainers without objective deficit (hence with *subjective cognitive decline* or SCD, Jessen et al., 2020), and patients with AD found that the majority of subjects reported memory complaints (including 26% of healthy controls) but also language complaints (including 37% of controls; Miebach et al., 2019). Finally, subjects and study-partners from all groups reported visuospatial disorders to be the least intense compared to the other domains. Indeed, visuospatial disorders, such as difficulty in the spatial localization of objects, generation of mental pathways, and spatial navigation, might occur later in the course of the disease (Cherrier et al., 2001). In our study, Aβ+/CN and MCI subjects performed similarly to healthy controls on the visuospatial composite score, while only AD patients performed significantly worse. Recent studies show that mild visuospatial disorders may also be present in early-stage AD (Joray et al., 2004), but it must be noted that these are difficulties that the patient and those around them may not recognize in daily life until that they become more severe.

The Clinical Utility of Domain-Specific Informant-Reported Cognitive Complaints

Informant-reported cognitive complaints were globally the best measures to distinguish groups, in comparison to self-reported complaints and ACD, consistent with what has already been identified from previous studies (Gifford, 2015; Rueda, 2015). Therefore, this source of information should be prioritized by clinicians during clinical interviews. All ECog-StudyPartner scores were good to excellent predictors for discriminating groups of individuals at different stages of AD and controls. The only discrimination in which the informant report was not sufficiently sensitive was between Aβ+/CN from Aβ-/CN participants. This suggests that the informant report, as measured by the ECog, is not sensitive enough to detect the disease when the patient is asymptomatic.

Furthermore, informant reports strongly correlated with the same-domain composite cognitive scores, suggesting that they may be taken as a gold standard to collect information about the patient's cognitive functioning in daily life. Nonetheless, we acknowledge that informant-reported complaints may be potentially biased by factors such as anxiety, depression, caregiver burden, or personality traits. However, study-partners were accurate in previous studies despite these potential biases: in a study by Cacchione and colleagues, the accuracy of the study-partner in predicting patient's cognitive decline was above chance even for informants who were not spouses, who did not live with the patient, or who spoke with the patient less than daily, and for older or less educated patients (Cacchione et al., 2003).

TABLE 4 | Comparison of correlation coefficients between subjective and objective measures of cognitive decline.

	Same-domain ECog-Subject	Same-domain ECog StudyPartner	*p*-values
Memory composite	−0.38*	−0.64*	<0.01
Language composite	−0.34*	−0.51*	<0.01
Visuospatial composite	−0.32*	−0.49*	<0.01
Executive composite	−0.16*	−0.29*	<0.01

*Note. The table reports correlation coefficients between each of the four composite scores and the same-domain ECog-Subject and ECog-StudyPartner, separately. *Indicates significant correlations. p-values refer to the pairwise comparisons between correlation coefficients.*

Self-Reported Cognitive Complaints and Subject's Self-Awareness

In the present study, the self-reported complaints were the less accurate measures to distinguish groups along the AD spectrum. Although our *post-hoc* analysis showed that self-reported complaints correlated significantly with objective cognitive scores, the strength of associations was significantly weaker than between informant-reported complaints and objective cognitive scores. Also, in our sample, some individuals tended to underestimate their cognitive abilities (especially CN subjects), while others overestimated them (especially AD subjects). On the other hand, the ACD measure was slightly more accurate than self-report complaints but less accurate than the informant-report. It would be interesting to understand if the subject-informant discrepancy can better discriminate patients with different pathologies than the informant-report alone. Although progressive anosognosia is a common symptom of several neurological or psychiatric diseases—e.g., frontotemporal dementia (Zamboni et al., 2010) or Huntington's disease (Hoth, 2007), identifying a certain degree of anosognosia could be useful in the differential diagnosis.

Aβ+/CN subjects (at risk for preclinical AD) and Aβ−/CN controls reported complaints of similar intensity, and this measure discriminated the two CN groups slightly better than chance. When relating the self-reported complaint to the informant-reported complaint (ACD score) we found that both CN groups exhibited more marked memory and language complaints than their informants, and this was not the case with executive and visuospatial complaints. This is consistent with a previous study highlighting the importance of word-finding complaints in CN, on top of memory complaints (Montembeault et al., 2022). The difference between self- and informant-reported complaints in CN may be consistent with the concept of *hypernosognosia* (Vannini et al., 2017), a term used when cognitively unimpaired individuals with high levels of amyloid deposition perceive

a subtle decline in memory and language that their informant does not notice yet. On the other hand, since this pattern (memory and language ECog-Subject >StudyPartner) was also observed in control subjects, it may suggest that cognitive complaints are nonspecific and common even among healthy individuals. Previous studies also found that most healthy elderly express some degree of cognitive complaints (Jessen, 2010; van Harten, 2018). This may be partially related to anxiety, depression, medication intake, and age-related cognitive changes (Buckley, 2013). Nonetheless, many studies have demonstrated a relationship between cognitive complaints and amyloid status (La Joie et al., 2016; Valech et al., 2018; Miebach et al., 2019; Montembeault et al., 2022). Another noteworthy aspect to discuss is that our control subjects were not from the general population but were part of a cohort selected to study AD, presenting with memory complaints at inclusion, which could have affected the results.

MCI participants and their study-partner reported similar levels of cognitive decline across all domains, meaning they did not show anosognosia. In some previous studies, MCI patients exhibited marked cognitive complaints (more marked than informant-reported complaints; Kalbe et al., 2005; Piras et al., 2016), while others found mild anosognosia (e.g., Hanseeuw et al., 2020; Cacciamani et al., 2021). These conflicting findings on self-awareness in MCI are likely due to the heterogeneity of the concept of MCI itself, in addition to a known inter-individual variability in the rate of disease progression and in the ordering of symptom onset (Goyal et al., 2018).

Concerning AD participants, they did not perceive more cognitive impairment than those with MCI despite the fact that they had more marked disorders at testing, which were also noticed by their study-partner. Indeed, AD participants presented with anosognosia. These results are consistent with the *petrified self theory*, suggesting that anosognosia in AD may be due to patients' self-assessment being petrified or anchored to their pre-morbid abilities (Mograbi et al., 2009). They may recognize their cognitive errors soon after they are made, but the knowledge about these failures is only partially and temporarily incorporated into their self-knowledge (Mograbi et al., 2009; Kalenzaga and Clarys, 2013). Thus, the subjective perception of decline would not coincide with the actual progression of cognitive impairment. The ACD measure that performed best on the AUC analysis was the Executive.

Function subscale. This means that anosognosia for executive function disorders is the most sensitive measure to distinguish individuals with dementia from other groups, among the four domains considered. Another study has shown that the level of ACD differs depending on the object studied in AD patients, with awareness of the overall condition and executive functions and for the overall condition being the most impaired, while the awareness of disinhibition and apathy was more preserved (Bertrand et al., 2019). This reiterates that the investigation of domains other than episodic memory could provide added value of clinical utility.

LIMITATIONS

This study has some limitations. The main limitation of this study is that the diagnosis of MCI and AD in the ADNI cohort is partly made on the basis of memory complaints. Although the main variables of interest in the present study are also cognitive complaints which could lead to circularity, it is important to note that the complaints used for diagnosis were strictly amnestic (did not concern other cognitive domains) and were reported during the clinical interview (not measured using the ECog). Nonetheless, this had an impact on our results. First, because cognitive complaints were required for inclusion in the MCI and AD group, but not for the two CN groups, it was expected that complaints would be more elevated in MCI and AD versus CNs. However, this limitation does not affect the comparison of cognitive complaints in MCI vs. AD and in Aβ−/CN vs. Aβ+/CN. Secondly, because our MCI and AD population were amnestic, it was expected that cognitive complaints would be more elevated in the memory domain than in other cognitive domains. Nonetheless, the current study provides novel knowledge on non-memory cognitive complaints in this population. To verify the generalisability of our results, a population-based cohort with no criteria for memory complaints could be studied. A second limitation is that we have no information about the study-partner, for example, the degree of kinship with the subject, how long they have known the subject, and how much time they spend with them. However, the strong correlation with cognitive score suggests that informant-related complaints are representative of objective cognitive measures. Finally, it was not possible to use the level of tau protein as it was not available in many subjects. This may have led to a bias in the selection of subjects. Indeed, it would have been more precise if it were based on the two biomarkers, amyloid, and tau (Jack et al., 2018).

CONCLUDING REMARKS

Our results can have interesting applications for both research and clinical practice. They highlight the limitations and benefits of three sources of information that are valuable to the clinician and the researcher, namely self-reported complaint, informant-reported complaint, and concordance or discrepancy between the two (as a measure of ACD), all relating to different cognitive domains. The inclusion of an informant or study-partner seems to be an important added value for an accurate, early diagnosis, and for effective selection of individuals in clinical trials. Given the predictive power of study-partner complaint in disease staging, further studies could identify thresholds of abnormality of the ECog-StudyPartner score for use in clinical practice. The patients themselves, on the contrary, are less accurate in their reports and may tend to both overestimate their abnormal performance (as a form of anosognosia) or underestimate their normal performance (as in worried-well individuals). These results also suggest that patients and study-partners complain not only about memory but also about other cognitive domains, and non-amnesic complaints and ACD also provided important

clinical information. This is important to emphasize, as the current research criteria defining complaints typical of AD patients are memory-related (Jessen et al., 2020), and we believe they should be revised to also include non-amnesic complaints. To facilitate the application of these results in clinical practice, an interesting perspective for future studies is to understand whether there are specific questions, relating to the different cognitive domains, to ask the subject and the informant in order to detect the disease earlier. Much attention has been paid to memory complaints (e.g., Jessen et al., 2020) and awareness of memory disorders (e.g., Gagliardi et al., 2020), but the clinical presentation of AD is more diverse (Goyal et al., 2018). Focusing solely on memory could, for example, exclude all patients with a non-amnestic phenotype.

DATA AVAILABILITY STATEMENT

The dataset is owned by the Alzheimer's Disease Neuroimaging Initiative (ADNI). Data are publicly and freely available from http://adni.loni.usc.edu upon sending a request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Good Clinical Practice guidelines, US 21CFR Part 50—Protection of Human Subjects, and Part 56—Institutional Review Boards (IRBs)/Research Ethics Boards (REBs), and state and federal HIPAA regulations. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design and provided expertise and insights into the interpretation of the results. FC, VG, and MM provided statistical expertise. The manuscript was drafted by FC, VG, and MM, and critically reviewed and approved by all authors. All authors contributed to the article and approved the submitted version.

FUNDING

FC is funded by the Fondation pour la recherche sur Alzheimer. VG is supported by Malakoff Médéric Humanis company. SB is supported by research funding from Fonds de Recherche en Santédu Québec (FRQS), Heart and Stroke Foundation of Canada, Canadian Institutes for Health Research (CIHR), and Alzheimer Society of Canada. RM is supported by Fondation Recherche Alzheimer, France Alzheimer, Philippe Chartrier Foundations, and by Rosita Gomez association. MM is funded by Fonds de Recherche du Québec en Santé (FRQS) and Canadian Institutes of Health Research (CIHR).

ACKNOWLEDGMENTS

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI; National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health www.fnih.org. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.811739/full#supplementary-material.

REFERENCES

Ahmed, S., Haigh, A. M., de Jager, C. A., and Garrard, P. (2013). Connected speech as a marker of disease progression in autopsy-proven Alzheimer's disease. *Brain* 136, 3727–3737. doi: 10.1093/brain/awt269

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement.* 7, 270–279. doi: 10.1016/j.jalz.2011.03.008

Bertrand, E., Mograbi, D. C., Brown, R. G., Landeira-Fernandez, J., and Morris, R. G. (2019). Heterogeneity of anosognosia in Alzheimer's disease according to the object of awareness. *Psychol. Neurosci.* 12, 282–290. doi: 10.1037/pne0000164

Brunet, H. E., Miller, J. B., Shi, J., Chung, B., Munter, B. T., and Sabbagh, M. N. (2019). Does informant-based reporting of cognitive symptoms predict amyloid positivity on positron emission tomography?

Alzheimer's Dement. (Amst) 11, 424–429. doi: 10.1016/j.dadm.2019.04.004

Buckley, R. (2013). Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect and age. *Int. Psychogeriatr.* 25, 1307–1315. doi: 10.1017/S1041610213000665

Cacchione, P. Z., Powlishta, K. K., Grant, E. A., Buckles, V. D., and Morris, J. C. (2003). Accuracy of collateral source reports in very mild to mild dementia of the Alzheimer type. *J. Am. Geriatr. Soc.* 51, 819–823. doi: 10.1046/j.1365-2389.2003.51263.x

Cacciamani, F., Sambati, L., Houot, M., Habert, M. O-., Dubois, B., and Epelbaum, S. (2020). Awareness of cognitive decline trajectories in asymptomatic individuals at risk for AD. *Alzheimers Res. Ther.* 12:129. doi: 10.1186/s13195-020-00700-8

Cacciamani, F., Tandetnik, C., Gagliardi, J., Bertin, H., Habert, M.-O., Hampel, H., et al. (2017). Low cognitive awareness, but not complaint, is a good marker of preclinical Alzheimer's disease. *J. Alzheimers Dis.* 59, 753–762. doi: 10.3233/JAD-170399

Cacciamani, F., Valladier, A., Maheux, E., Koval, I., Durrleman, S., and Epelbaum, S. (2021). Changes in the awareness of cognitive decline across the course of Alzheimer's disease: comparison of two assessment methods. *Alzheimer's Dement.* 17:e053074. doi: 10.1002/alz.053074

Cherrier, M., Mendez, M., and Perryman, K. (2001). Route learning performance in Alzheimer disease patients. *Neuropsychiatry Neuropsychol. Behav. Neurol.* 14, 159–168.

Choi, S. E., Mukherjee, S., Gibbons, L. E., Sanders, R. E., Jones, R. N., Tommet, D., et al. (2020). Development and validation of language and visuospatial composite scores in ADNI. *Alzheimers Dement. (N Y)* 6:e12072. doi: 10.1002/trc2.12072

Condret-Santi, V. (2013). Prevalence of word retrieval complaint and prediction of dementia in a population-based study of elderly subjects. *Dement. Geriatr. Cogn. Disord.* 35, 313–324. doi: 10.1159/000342594

Crane, P. K., Carle, A., Gibbons, L. E., Insel, P., Mackin, R. S., Gross, A., et al. (2012). Development and assessment of a composite score for memory in the Alzheimer's disease neuroimaging initiative (ADNI). *Brain Imaging Behav.* 6, 502–516. doi: 10.1007/s11682-012-9186-z

DeLong, E. R., DeLong, D. M., and Clarke-Pearson, D. L. (1988). Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44, 837–845.

Donohue, M. C., Sperling, R. A., Salmon, D. P., Rentz, D. M., Raman, R., Thomas, R. G., et al. (2014). The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol.* 71, 961–970. doi: 10.1001/jamaneurol.2014.803

Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., et al. (2010). Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol.* 9, 1118–1127. doi: 10.1016/S1474-4422(10)70223-4

Farias, S. T. (2008). The measurement of everyday cognition (ECog): scale development and psychometric properties. *Neuropsychology* 22, 531–544. doi: 10.1037/0894-4105.22.4.531

Gagliardi, G., Houot, M., Cacciamani, F., Habert, M., Dubois, B., and Epelbaum, S. (2020). The meta-memory ratio: a new cohort-independent way to measure cognitive awareness in asymptomatic individuals at risk for Alzheimer's disease. *Alzheimers Res. Ther.* 12:57. doi: 10.1186/s13195-020-00626-1

Gavett, R. (2011). The cognitive change in women study (CCW): Informant ratings of cognitive change but not self-ratings are associated with neuropsychological performance over 3 years. *Alzheimer Dis. Assoc. Disord.* 25, 305–311. doi: 10.1097/WAD.0b013e31820d8652

Gibbons, L. E., Carle, A. C., Mackin, R. S., Harvey, D., Mukherjee, S., Insel, P., et al. (2012). A composite score for executive functioning, validated in Alzheimer's disease neuroimaging initiative (ADNI) participants with baseline mild cognitive impairment. *Brain Imaging Behav.* 6, 517–527. doi: 10.1007/s11682-012-9176-1

Gifford, K. A. (2015). Inclusion of an informant yields strong associations between cognitive complaint and longitudinal cognitive outcomes in non-demented elders. *J. Alzheimers Dis.* 43, 121–132. doi: 10.3233/JAD-131925

Goyal, D., Tjandra, D., Migrino, R. Q., Giordani, B., Syed, Z., and Wiens, J. (2018). Characterizing heterogeneity in the progression of Alzheimer's disease using longitudinal clinical and neuroimaging biomarkers. *Alzheimers Dement. (Amst)* 10, 629–637. doi: 10.1016/j.dadm.2018.06.007

Hanseeuw, B. J., Scott, M. R., Sikkes, S., Properzi, M., Gatchel, J., Salmon, E., et al. (2020). Evolution of anosognosia in Alzheimer's disease and its relationship to amyloid. *Ann. Neurol.* 87, 267–280. doi: 10.1002/ana.25649

Harrington, K. D., Lim, Y. Y., Ellis, K. A., Copolov, C., Darby, D., Weinborn, M., et al. (2013). The association of abeta amyloid and composite cognitive measures in healthy older adults and MCI. *Int. Psychogeriatr.* 25, 1667–1677. doi: 10.1017/S1041610213001087

Hosmer, D. W., and Lemeshow, S. (2000). *Applied Logistic Regression*. New York, NY: John Wiley & Sons. doi: 10.1002/0471722146

Hoth, K. F. (2007). Patients with Huntington's disease have impaired awareness of cognitive, emotional and functional abilities. *J. Clin. Exp. Neuropsychol.* 29, 365–376. doi: 10.1080/13803390600718958

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., et al. (2018). NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 14, 535–562. doi: 10.1016/j.jalz.2018.02.018

Jessen, F. (2010). Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Arch. Gen. Psychiatry* 67, 414–422. doi: 10.1001/archgenpsychiatry.2010.30

Jessen, F., Amariglio, R. E., Buckley, R. F., van der Flier, W. M., Han, Y., Molinuevo, J. L., et al. (2020). The characterisation of subjective cognitive decline. *Lancet Neurol.* 19, 271–278. doi: 10.1016/S1474-4422(19)30368-0

Joray, S., Herrmann, F., Mulligan, R., and Schnider, A. (2004). Mechanism of disorientation in Alzheimer's disease. *Eur. Neurol.* 52, 193–197. doi: 10.1159/000082034

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., et al. (2005). Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. *Dement. Geriatr. Cogn. Disord.* 19, 349–356. doi: 10.1159/000084704

Kalenzaga, S., and Clarys, D. (2013). [Relationship between memory disorders and self-consciousness in Alzheimer's disease]. *Gériatrie et Psychologie Neuropsychiatrie du Vieillissement* 11, 187–196. doi: 10.1684/pnv.2013.0403

La Joie, R., Perrotin, A., Egret, S., Pasquier, F., Tomadesso, C., Mézenge, F., et al. (2016). Qualitative and quantitative assessment of self-reported cognitive difficulties in nondemented elders: association with medical help seeking, cognitive deficits and β-amyloid imaging. *Alzheimers Dement. (Amst)* 5, 23–34. doi: 10.1016/j.dadm.2016.12.005

Landau, S. M. (2013). Amyloid-β imaging with Pittsburgh compound B and Florbetapir: comparing radiotracers and quantification methods. *J. Nucl. Med.* 54, 70–77. doi: 10.2967/jnumed.112.109009

Mayelle, A., Hazebrouck, C., El Haj, M., Mograbi, D. C., and Antoine, P. (2022). Awareness for people with Alzheimer's disease: profiles and weekly trajectories. *Front. Aging Neurosci.* 13:781426. doi: 10.3389/fnagi.2021.781426

Marková, I.S., Clare, L., Whitaker, C.J., Roth, I., Nelis, S.M., Martyr, A., et al. (2014). Phenomena of awareness in dementia: heterogeneity and its implications. *Conscious. Cogn.* 25, 17–26. doi: 10.1016/j.concog.2014.01.008

McKhann, G. M. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 34, 939–944. doi: 10.1212/wnl.34.7.939

Mendez, M. F. (1990). Complex visual disturbances in Alzheimer's disease. *Neurology* 40, 439–443. doi: 10.1212/wnl.40.3_part_1.439

Miebach, L., Wolfsgruber, S., Polcher, A., Peters, O., Menne, F., Luther, K., et al. (2019). Which features of subjective cognitive decline are related to amyloid pathology? Findings from the DELCODE study. *Alzheimers Res. Ther.* 11:66. doi: 10.1186/s13195-019-0515-y

Mograbi, D. C., Brown, R. G., and Morris, R. G. (2009). Anosognosia in Alzheimer's disease – the petrified self. *Conscious. Cogn.* 18, 989–1003. doi: 10.1016/j.concog.2009.07.005

Montembeault, M., Stijelja, S., and Brambati, S. M. (2022). Self-reported word-finding complaints are associated with cerebrospinal fluid beta-amyloid

and atrophy in cognitively normal older adults. *Alzheimers Dement. (Amst)* 14:e12274. doi: 10.1002/dad2.12274

Mosconi, L., Pupi, A., and De Leon, M. J. (2008). Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease. *Ann. N Y Acad. Sci.* 1147, 180–195. doi: 10.1196/annals.1427.007

Perrotin, A., Mormino, E. C., Madison, C. M., Hayenga, A. O., and Jagust, W. J. (2012). Subjective cognition and amyloid deposition imaging: a pittsburgh compound B positron emission tomography study in normal elderly individuals. *Arch. Neurol.* 69, 223–229. doi: 10.1001/archneurol.2011.666

Piras, F., Piras, F., Orfei, M., Caltagirone, C., and Spalletta, G. (2016). Self-awareness in mild cognitive impairment: quantitative evidence from systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 61, 90–107. doi: 10.1016/j.neubiorev.2015.10.002

Rohrer, J. D. (2008). Word-finding difficulty: a clinical analysis of the progressive aphasias. *Brain* 131, 8–38. doi: 10.1093/brain/awm251

Rueda, A. D. (2015). Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease. *Alzheimers Dement.* 11, 1080–1089. doi: 10.1016/j.jalz.2014.09.002

Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S., et al. (2007). Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. *Neurology* 69, 1859–1867. doi: 10.1212/01.wnl.0000279336.36610.f7

Saykin, A. J., Wishart, H. A., Rabin, L. A., Santulli, R. B., Flashman, L. A., West, J. D., et al. (2006). Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. *Neurology* 67, 834–842. doi: 10.1212/01.wnl.0000234032.77541.a2

Shokouhi, S., Conley, A. C., Baker, S. L., Albert, K., Kang, H., Gwirtsman, H. E., et al. (2019). The relationship between domain-specific subjective cognitive decline and Alzheimer's pathology in normal elderly adults. *Neurobiol. Aging* 81, 22–29. doi: 10.1016/j.neurobiolaging.2019.05.011

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the national institute on aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 280–292. doi: 10.1016/j.jalz.2011.03.003

Stewart, G., McGeown, W. J., Shanks, M. F., and Venneri, A. (2010). Anosognosia for memory impairment in Alzheimer's disease. *Acta Neuropsychiatr.* 22, 180–187. doi: 10.1111/j.1601-5215.2010.00463.x

Turró-Garriga, O., Garre-Olmo, J., Reñé-Ramíre, R., Calvó-Perxas, L., Gascón-Bayarri, J., and Conde-Sala, J. L. (2016). Consequences of anosognosia on the cost of caregivers' care in Alzheimer's disease. *J. Alzheimers Dis.* 54, 1551–1560. doi: 10.1016/j.wasman.2020.07.048

Valech, N., Tort-Merino, A., Coll-Padrós, N., Olives, J., León, M., Rami, L., et al. (2018). Executive and language subjective cognitive decline complaints discriminate preclinical Alzheimer's disease from normal aging. *J. Alzheimers Dis.* 61, 689–703. doi: 10.3233/JAD-170627

van Harten, A. C. (2018). Subjective cognitive decline and risk of MCI: the mayo clinic study of aging. *Neurology* 91, e300–e312. doi: 10.1212/WNL.0000000000005863

Vannini, P., Amariglio, R., Hanseeuw, B., Johnson, K. A., McLaren, D. G., Chhatwal, J., et al. (2017). Memory self-awareness in the preclinical and prodromal stages of Alzheimer's disease. *Neuropsychologia* 99, 343–349. doi: 10.1016/j.neuropsychologia.2017.04.002

Zamboni, G., Grafman, J., Krueger, F., Knutson, K. M., and Huey, E. D. (2010). Anosognosia for behavioral disturbances in frontotemporal dementia and corticobasal syndrome: a voxel-based morphometry study. *Dement. Geriatr. Cogn. Disord.* 29, 88–96. doi: 10.1159/000255141

Conflict of Interest: SE has received honoraria as a speaker or consultant for Eli Lilly, Biogen, Astellas Pharma, Roche, and GE Healthcare.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership