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Federica Cacciamani

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AWARENESS OF COGNITIVE DECLINE IN EARLY-STAGE ALZHEIMER'S DISEASE: IMPLICATIONS FOR DIAGNOSIS, PATIENT MANAGEMENT AND RESEARCH

Prise de conscience du déclin cognitif dans la maladie d'Alzheimer
au stade débutant : implications pour le diagnostic, la prise en charge
du patient et la recherche

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A dissertation submitted in fulfilment of the requirements
for the degree of doctor of philosophy

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ABSTRACT

In this thesis, we describe 6 original studies that address different aspects of the association between patients' level of awareness of cognitive decline (ACD) and their risk of Alzheimer's disease (AD). The studies were conducted on INSIGHT-PreAD and ADNI cohorts. We used both classical statistical methods and machine learning. This thesis shows that a subtle cognitive and functional decline is already present in "preclinical" AD. Patients may begin to notice these early changes when neither the informant nor objective cognitive tests do. However, family members or cognitive tests very quickly become more reliable sources of information than the patient him/herself: during the progression from the preclinical to the prodromal stage, ACD begins to decline. In the prodromal phase, the patient is more and more unaware of his/her disease until he/she usually reaches clear anosognosia in the dementia phase. The clinician should carefully consider patients' cognitive complaint, but also compare it to other sources of information, such as cognitive scores or family members. In research, these findings may help in better inclusion criteria for studies targeting pre-dementia AD.

Keywords: Alzheimer's disease, Awareness, Anosognosia, Early Diagnosis

RÉSUMÉ

Contexte : Grâce aux progrès de la recherche sur la maladie d'Alzheimer (MA) au cours des 20 dernières années, nous avons appris qu'il faut des années pour que les lésions cérébrales entraînent des troubles cognitifs. Cela a changé l'attitude des gens à l'égard de la maladie. Les patients demandent de plus en plus un avis médical pour une plainte mnésique, craignant de commencer à manifester la maladie. Étant donné que la plainte mnésique est courante chez les personnes âgées et a une étiologie hétérogène, nous n'avons pas encore identifié le profil de plainte exact caractérisant les patients atteints de MA. Nous avons récemment découvert que les sujets qui sous-estiment leur déclin ont un risque plus élevé de marqueurs positifs de la MA, par rapport à ceux qui le surestiment. Il y a encore peu de preuves à ce sujet. Dans cette thèse, nous testons l'hypothèse selon laquelle une réduction progressive de la conscience du déclin cognitif (*Awareness of Cognitive Decline*, ACD), et non une plainte cognitive persistante, pourrait être un indicateur précoce de la MA.

Méthodes : Nous décrivons 6 études originales abordant différents aspects de l'association entre l'ACD des patients et leur risque de MA. Les études ont été menées sur les cohortes INSIGHT-PreAD et ADNI. INSIGHT-PreAD comprend 318 individus âgés présentant une plainte mnésique, dont 30% ont également des biomarqueurs positifs pour la MA. De la cohorte ADNI, nous avons sélectionné des sujets avec une MA définie par les biomarqueurs et couvrant l'ensemble de son spectre clinique. Nous avons utilisé à la fois des méthodes statistiques « classiques » et le *machine learning*. Parmi les méthodes statistiques « classiques », nous avons réalisé (i) une analyse en classes latentes, pour suivre les trajectoires longitudinales latentes de l'ACD dans la MA préclinique, et étudier leur association avec les biomarqueurs de la MA et le risque de progression vers la MA clinique; (ii) Courbes ROC/AUC, pour identifier la sensibilité et la spécificité de la plainte du sujet et de l'informant, ainsi que de l'ACD, dans 4 domaines cognitifs (mémoire, langage, fonctions exécutives et visuospatiales) pour discriminer les témoins sains des patients à différents stades de la MA; (iii) une méta-analyse, pour mesurer l'ACD moyenne chez des sujets présentant un trouble cognitif mineur (MCI); (iv) et nous avons développé et validé une nouvelle méthode pour mesurer l'ACD, le Meta-Memory Ratio (MMR). Concernant le *machine learning*, nous avons utilisé deux logiciels développés par notre équipe. Avec Leaspy, nous avons créé une cartographie du décours de la MA (*AD Course Map*) en

mettant l'accent sur l'évolution de l'ACD à travers le continuum de la MA. Nous avons également utilisé Clinica pour l'analyse multimodale des images cérébrales, afin d'étudier les corrélats neuronaux de la réduction de l'ACD dans la MA.

Résultats : Les concepts de plainte mnésique et ACD réduite ne sont qu'apparemment opposés puisqu'ils peuvent coexister chez un même individu. C'est le cas des individus qui se plaignent d'un certain degré de difficultés cognitives, sous-estimant encore leur gravité ou leur impact dans la vie quotidienne (par rapport à l'évaluation faite par leur entourage ou à l'aide de tests neuropsychologiques). Cette thèse montre qu'un déclin cognitif et fonctionnel subtil est déjà présent dans la MA préclinique. Les patients commencent à remarquer ces premiers changements lorsque ni leur entourage ni les tests ne le font. Cependant, l'entourage et les tests cognitifs deviennent très rapidement une source d'information plus fiable que le patient lui-même : pendant la progression du stade préclinique au stade prodromal, l'ACD commence à diminuer. Dans la phase prodromale et, en particulier, dans celle de démence, les patients sont généralement anosognosiques.

Conclusion : La recherche porte actuellement une attention particulière à la plainte mnésique comme indicateur précoce de la MA. Bien que la plainte puisse guider le clinicien vers un diagnostic précoce, elle peut également contribuer à un diagnostic erroné. Des individus pourraient être suivis pour une suspicion de MA, provoquant de la peur, de l'anxiété et des coûts considérables pour des examens spécialisés, tandis que leur plainte est due à une autre cause. D'autres individus qui sous-estiment leur déclin et qui présentent un risque plus élevé de développer une démence peuvent ne pas recevoir de soins médicaux adéquats. Le clinicien doit examiner attentivement la plainte du patient, mais aussi la comparer à une autre source d'information, comme la plainte de l'entourage ou les scores cognitifs. Nous discutons également s'il est possible et souhaitable de traiter la diminution de l'ACD et l'anosognosie. En recherche, ces résultats peuvent aider à une meilleure sélection des sujets à inclure dans les essais ciblant la MA pré-démence.

Introduction

Overarching aim of the thesis 1

At a time when research strives to identify methods to diagnose (and treat) Alzheimer's disease as early as possible, we conducted 6 original studies with the general aim of investigating the usefulness of a new potential early indicator of the disease, that is reduced patient's awareness of his/her cognitive decline.

This is part of a currently very active research area, which aims to characterize the typical cognitive complaint profile of patients harboring Alzheimer's disease, and to understand how reliable patients' cognitive complaint is in guiding the diagnosis and tracking disease progression. We tried to go further, not only examining the patient's complaint and associated risk of Alzheimer's, but also comparing it to more objective measures of decline, such as the informant's complaint or scores on standardized cognitive tests. From the discrepancy between subjective complaint and objective impairment (on tests or as reported by the informant), we obtained measures of patient's awareness of cognitive decline, and studied its evolution over time, its association with AD biomarkers and the risk of progression to dementia.

Our general hypothesis was that reduced awareness of cognitive decline may serve as a more specific early indicator of Alzheimer's disease than subjective cognitive complaint itself.

Biology and clinical manifestations of Alzheimer's disease 2

Modified from: Migliaccio, R. and Cacciamani, F. (Invited) The temporal lobe in typical and atypical Alzheimer's disease. In Miceli, Bartolomeo, and Navarro (Eds.), *The temporal lobe* (Elsevier). Paragraphs 2.2, 2.3 and 2.4 have been published in: Cacciamani, F., Houot, M., Gagliardi, G., Dubois, B., Sikkas, S., Sánchez-Benavides, G., Denicolò, E., Molinuevo, J. L., Vannini, P., & Epelbaum, S. (2021). Awareness of Cognitive Decline in Patients With Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Frontiers in aging neuroscience*, 13.

Alzheimer's disease (AD) is a neurodegenerative disease occurring most commonly in later life, and particularly after the age of 65 (Mayeux, 2012). The disease is named after Alois Alzheimer, a German psychiatrist interested in the link between microscopic brain changes and psychic alterations, at a time when this link was mostly unknown. The first patient described by Alzheimer, Auguste D., was a woman of just 50 years, hospitalized for progressive memory loss, delusions and agitation in Frankfurt between 1901 and 1906 (Lage, 2006). Alzheimer called this condition the *disease of forgetfulness*.

2.1 Pathological hallmarks and neurodegenerative process in AD

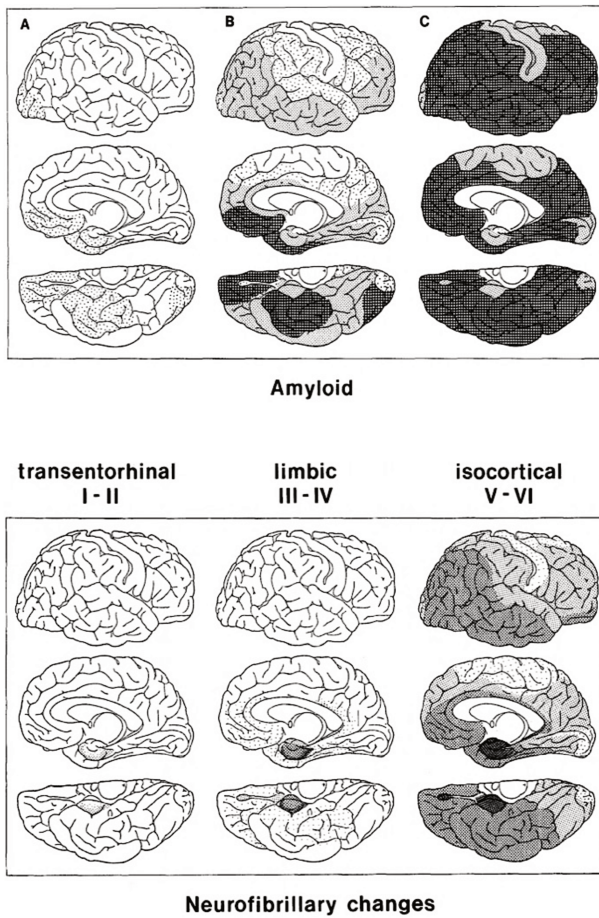
After Auguste D.'s death, caused by sepsis, Alzheimer examined her brain both morphologically and histologically using silver staining. The brain appeared very atrophied on macroscopic examination. He described characteristic changes in the neurofibrils (tau pathology) and he also found that an abnormal substance was deposited in abundant dispersion outside the neurons throughout the entire cortex, particularly in the upper layers (amyloid deposits).

Decades of research have allowed a more detailed definition of AD pathologic hallmarks. Pathogenic amyloid is formed when the amyloid precursor protein, a transmembrane glycoprotein, is cleaved by two enzymes: beta and gamma-secretase. The resulting fragment is a 42-amino acid peptide called beta-amyloid ($A\beta_{42}$), which is hydrophobic and has a tendency to aggregate in oligomers, fibrils and then plaques. This aggregation triggers a series of biological reactions that lead to neurodegeneration - the so-called amyloid cascade (Hardy & Higgins, 1992).

Amyloid plaques are currently believed to activate tau pathology. The function of tau protein is to stabilize the microtubules within neurons. Microtubules are part of the cytoskeleton, provide structural support to the neuron and ensure the intracellular transport of organelles and vesicles. In AD, tau protein is hyperphosphorylated and loses its chemical properties and therefore its function in binding microtubules. Hyperphosphorylated tau aggregates within neurons to form neurofibrillary tangles. The microtubules disassemble and no longer guarantee the maintenance of the neuronal structure and the transport of substances (for example acetylcholine), leading to neuronal death. Tau pathology propagates from one neuron to another, spreading across different brain areas, along neuroanatomical connections (Clavaguera et al., 2013).

The clinical manifestations of AD depend on which brain region is most affected by tau pathology. According to the current perspective, indeed, it would be tau and not amyloid to cause the cognitive symptoms. The propagation pattern of amyloid and tau pathology has been described by Braak and Braak in their disease progression staging system (Braak & Braak, 1991). $A\beta_{42}$ begins to accumulate progressively in the neocortex, generally proceeding from associative to primary cortical areas. In the advanced stage of the disease, $A\beta_{42}$ can also be deposited outside the neocortex, in subcortical structures. Deposits of $A\beta_{42}$ in the hippocampus are absent or rare even in the advanced stage (Figure 1). Conversely, neurofibrillary tangles are first observed in the transentorhinal region, then in limbic regions such as the hippocampus, and finally spread extensively towards the neocortex (Figure 1). The profiles of cognitive impairment in AD, addressed in greater detail below (see paragraphs 2.2.1 and 2.3.2), correlate to tau pathology than to amyloid plaques. However,

Figure 1. Braak & Braak disease progression staging



the pathological substrate most directly related to the cognitive syndrome is neurodegeneration, and more specifically the loss of synapses.

Amyloid and tau pathology are pathophysiological markers that can be detected at all stages of the disease through cerebrospinal fluid (CSF) analysis or by PET scan using specific ligands. In clinical practice, topographic markers of neurodegeneration are usually visualized by structural magnetic resonance imaging (MRI) or functional positron emission tomography (Fluorodeoxyglucose-PET). Net brain metabolism at FDG-PET is a valid indicator of the synaptic dysfunction accompanying neurodegeneration in AD.

In AD, hypometabolism follows a specific pattern in a lateral temporal-parietal and posterior cingulate, precuneus distribution (Jagust, Reed, Mungas, Ellis, & Decarli, 2007). Structural MRI instead provides a measure of brain atrophy, which is caused by dendritic pruning and loss of synapses and neurons. Brain damage begins in the medial temporal limbic areas (including the hippocampus) and spreads from there to the adjacent limbic and paralimbic areas, and subsequently to the associative areas. The severity of cognitive impairment is strongly correlated with the severity of brain damage. The increase in atrophy is non-linear, which means that it progresses faster as symptoms appear (Jack Jr et al., 2009).

2.2 Alzheimer's dementia

For a long time, AD was considered solely as a form of dementia. The first diagnostic criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS–ADRDA) have been used for many years (McKhann et al., 1984). According to these criteria, AD referred to a progressive alteration of at least two cognitive functions that compromised autonomy in elderly individuals.

2.2.1 Typical cognitive profile of Alzheimer’s dementia

Dementia is by definition the condition in which cognitive disorders are sufficiently severe and diffuse among the cognitive domains to limit the patient's social functioning and autonomy, who therefore becomes dependent on others. The typical profile of dementia due to AD involves a decline in episodic memory (see 2.3.2 for more details about the amnesic syndrome due to AD) and those cognitive functions associated with the neocortex, resulting in a progressive aphaso-apracto-agnosic syndrome (Giannakopoulos et al., 1999; Lesourd et al., 2013; Van der Stigchel et al., 2018; Verma & Howard, 2012). This means that patients with AD dementia usually have language disorders, difficulty performing gestures (such as holding a glass), difficulty with treatment of visuospatial information, and difficulty in visually recognizing objects or people around them. Subcortico-frontal impairment, such as slowness of thought or executive dysfunction (i.e., difficulty in problem solving, reduced mental flexibility, impaired logic and strategic thinking), is also present but less characteristic of dementia due to AD.

2.2.2 Anosognosia in AD dementia

Anosognosia is a well-known symptom of AD dementia. The term *anosognosia* derives from the Greek α (*without*), $\nu\omicron\sigma\sigma\omicron\zeta$ (*disease* or *illness*), $\gamma\nu\omega\sigma\iota\zeta$ (*knowledge*). It was originally coined by Joseph Babinski in 1914 (Langer & Levine, 2014) to describe the reports of unawareness of left hemiparesis in patients with damage to the right hemisphere of the brain. “[Babinski’s] first patient was a woman who had been paralyzed down the left side for years, but who never mentioned the fact. If asked to move the affected limb she remained immobile and silent, behaving as though the question had been put to someone else.

Babinski's second patient was also a victim of left hemiplegia. Whenever she was asked what was the matter with her, she talked about her backache, or her phlebitis, but never once did she refer to her powerless left arm. When told to move that limb, she did nothing and said nothing, or else a mere, "Voilà, c'est fait!" (i.e., "There it's done!")" (Critchley, 1953).

To date, the term has a much broader meaning, and encompasses an array of failures in acknowledging a particular pathological state. Anosognosia may be limited to some aspects of the disease – e.g., a patient may ignore some of the deficits he/she suffers from and/or underestimate their impact on activities of daily living – or it may extend to the overall unawareness of being affected by an illness.

Anosognosia represents a neurological dysfunction, that is an organically-based lack of awareness of deficits due to a mainly frontal brain damage (Michon, Deweer, Pillon, Agid, & Dubois, 1994). *Loss or lack of insight, awareness or consciousness of the disease* have been used interchangeably in literature as synonyms of anosognosia. Other terms that are often discussed in relation to anosognosia but are in fact different phenomenon are *anosodiaphoria* and *denial*. *Anosodiaphoria*, from **αδιαφορά**, *unconcern* (Langer & Levine, 2014) or *belle indifference*, meaning *good indifference* in French (Breuer & Freud, 1895) refer to patients who seem not to attach any importance to their disability, despite being aware of it. *Denial* (Clare, 2003; Flashman, 2002; Sevush & Leve, 1993) has been described as an ego-protective mechanism against the anxiety and depression that often derive from awareness of the illness (Weinstein, 1991). Phenomenologically, anosognosia and denial of illness share many expressions and can be hard to differentiate. In fact, neurological studies of anosognosia and denial go back a century to the original studies by Anton and Babinski (Anton, 1896; Langer & Levine, 2014). Based on their seminal findings, anosognosia was attributed to brain damage, whereas denial was defined as a psychological defence mechanism not caused by brain damage. From a research perspective, it has proven challenging to differentiate the two phenomena.

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, Hanyu, Sakurai, Sato, & Iwamoto, 2009; Maki, Yamaguchia, & Yamaguchia, 2013; Turró-Garriga, López-Pousa, Vilalta-Franch, & Garre-Olmo, 2012).

Prevalence estimations may also vary according to how the anosognosia was operationalized and measured. In fact, 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 failures, difficulties in everyday tasks, and changes in interests and mood. In contrast, a higher prevalence of anosognosia in dementia was found using the Assessment Scale of Psychosocial Impact of the Diagnosis of Dementia (Akai et al., 2009; Dourado, M., Marinho, Soares, Engelhardt, & Laks, 2007; Dourado, M. C. N., Laks, & Mograbi, 2016; Lacerda, Santos, Belfort, Neto, & Dourado, 2018; Maki et al., 2013; Turró-Garriga et al., 2012). 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.

In previous studies, anosognostic patients with mild to severe AD dementia showed reduced perfusion, glucose metabolism and grey matter volume in the prefrontal cortex (PFC), both dorsolateral and in the anterior cingulate gyrus (Fujimoto et al., 2017; Hanyu et al., 2008; Harwood et al., 2005; Jedidi et al., 2014).

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. Anosognostic 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

(Kashiwa et al., 2005). One study (Lacerda et al., 2018) found that anosognosia correlated with a greater amount of amyloid in the PCC.

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

Clinical correlates of anosognosia in AD dementia

Executive dysfunction is highly associated with anosognosia in patients with AD dementia (Amanzio et al., 2013; Kashiwa et al., 2005; Lopez, Becker, Somsak, Dew, & DeKosky, 1994). 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 and response inhibition impairment as a frontal cognitive dysfunction (Kashiwa et al., 2005).

Additionally, AD patients with the poorest memory functioning rated their performance highest. Indeed, the patient may be unaware of his/her cognitive impairment because he/she does not remember having had such cognitive failure. He/she would forget to forget. However, given that the involvement of the medial temporal lobe in anosognosia is not yet clearly established, it can reasonably be assumed that memory deficit can be associated with anosognosia without being neither necessary nor sufficient.

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

Finally, several studies have shown that anosognostic patients, although less depressed and with better-perceived quality of life, have higher levels of apathy (Conde-Sala et al., 2013; Conde-Sala et al., 2014; Hurt et al., 2010; Millenaar et al., 2017; Stites, Karlawish,

Harkins, Rubright, & Wolk, 2017; Trigg, Watts, Jones, & Tod, 2011). 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.

Methods for assessing ACD

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/she perceives cognitive difficulties (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, La Corte, & Dubois, 2015); and (ii) the accuracy of pre-test predictions or post-test estimates of performance (Graham, Kunik, Doody, & Snow, 2005; Hannesdottir & Morris, 2007; Mograbi, Brown, Salas, & Morris, 2012). Hannesdottir and Morris for example propose the 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: $[(\text{estimated score} - \text{actual score}) / \text{maximum possible score on measure}] \times 100$ (Hannesdottir & Morris, 2007). 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). The subject-informant discrepancy is one of the most used methods in literature to measure ACD. 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 (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 participant. We describe here the main questionnaires allowing to compute the subject-informant discrepancy. The Cognitive Change Index or 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, 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 behavioural 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-behavioural spheres (Monahan et al., 2012; Monahan, Alder, Khan, Stump, & Boustani, 2014). Finally, the Patient Competency Rating Scale was developed to evaluate anosognosia following brain trauma. It includes 30 questions covering cognitive, but also behavioural 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. Few studies explored the psychometric properties of these questionnaires (Monahan et al., 2012; Monahan et al., 2014). The subject-informant discrepancy method assumes that the informant's report is an accurate source of information. The possibility that the informant's report could be distorted by factors such as anxiety, depression, burden, personality traits, should also be taken into consideration. The informant's rating, for instance, significantly predicted his/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 (Cacchione, Powlishta, Grant, Buckles, & Morris, 2003).

Finally, qualitative methods, such as the detailed analysis of interview contents or videotaped sessions (Mayhew, Acton, Yauk, & Hopkins, 2001), remain difficult to implement in research settings, since they are time-consuming, require specific preparation and have low generalizability.

See Clare et al. (2005) and Rabin et al. (2015) for a review.

Theoretical models of anosognosia in AD

According to the Dissociable Interactions and Conscious Experience (DICE) theory (McGlynn & Schacter, 1989; McGlynn & Kaszniak, 1991; Schacter, 1989) the activation distinctive cognitive modules representing specific cognitive functions would trigger the Conscious Awareness System, resulting in good 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. Morris and collaborators (Agnew & Morris, 1998; Mograbi, Brown, & Morris, 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. 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 (Mograbi et al., 2009). This amnesic pattern, together with

executive dysfunction, would result in a petrified self-evaluation based on premorbid abilities (Kalenzaga & 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 (Ansell & Bucks, 2006; Bertrand, J. M. et al., 2019; Duke, Seltzer, Seltzer, & Vasterling, 2002; Gil & Josman, 2001; Hannesdottir & Morris, 2007; Mimura & Yano, 2006; Oyeboode, Telling, Hardy, & Austin, 2007; Stewart, McGeown, Shanks, & Venneri, 2010).

Another interesting theoretical model of awareness is the biopsychosocial framework (Ownsworth, T., 2006a). It attributes the reduction in self-awareness to a complex and varying interplay of biological, psychological and social factors. (i) Among the biological factors is certainly brain damage due to the disease and subsequent cognitive impairment. Neurocognitive deficits, such as executive function deficits and the amnesic syndrome, are thought to contribute to the emergence of anosognosia. Indeed, the patient would no longer be able to control his/her own performance, he/she will have poor judgment skills and will forget that he/she has failed a test, or has had a cognitive failure in everyday life. (ii) Anosognosia also has a psychological component. If it is now recognized that anosognosia is a neurological symptom directly attributable to AD pathology, it is possible that the patient also use denial as a coping strategy to adapt to the disease. In addition, the person will react to the disease based on their pre-morbid personality and behaviour patterns. Finally, (iii) the social context also influences how the patient perceives the disease and reports his/her symptoms. AD is prone to stigma and negative stereotypes (Prince, 2011) and the tendency to minimize the impact of the disorders, or not to talk about the disease, may be partly a reflection of the desire not to appear ill in the eyes of others.

2.3 Prodromal AD

Over the past two decades, advances in basic and clinical research have provided a better understanding of the natural history of AD. While previously AD was mostly regarded as a

disease causing dementia, it is now known that years pass before the pathophysiological changes due to AD lead to cognitive impairment. AD has therefore been reconceptualized as a continuum from normal cognition to dementia, through an intermediate stage of mild disorders.

2.3.1 Evolution of the concept

Since the 1990s, this pre-dementia phase has been designated by the term *Mild Cognitive Impairment* or MCI (Petersen et al., 1999; Petersen, 2004; Winblad et al., 2004). The introduction of the concept of MCI emphasized that cognitive decline in AD is progressive: mild deficits are present before the onset of dementia syndrome, opening up the possibility of more timely diagnosis and secondary prevention if new treatments prove effective. The definition of MCI has since evolved. The first classification defined amnesic MCI as a possible transition phase from normal cognition to AD dementia (Petersen et al., 1999). It gradually became a broader concept that included different cognitive profiles due to various aetiologies (Winblad et al., 2004). Despite these refinements, the main criticism of the concept of MCI is that it describes a nonspecific clinical syndrome that can result from many different aetiologies, potentially limiting its usefulness in clinical practice. The diagnostic label of MCI not always allows to predict whether the patient will progress towards a more marked cognitive decline, remain stable or revert to normal cognition. MCI may indeed result from a neurodegenerative disease, but also from cerebrovascular disease, head trauma, brain tumours, etc.

The discovery of pathophysiological and topographical biomarkers represented a critical moment for the definition of the predementia stages of AD. A working group from the National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed criteria for the definition of MCI due to AD (Albert et al., 2011): (i) presence of a cognitive complaint, objective cognitive deficit, preserved autonomy, and absence of dementia syndrome, and (ii) the presence of a positive pathophysiological and/or neurodegeneration biomarker.

The International Working Group on diagnostic criteria for AD (IWG) (Dubois et al., 2010) proposed the expression *prodromal AD*. Prodromal AD is defined as follows: (i) presence

of a hippocampal amnesic syndrome, (ii) preserved autonomy, and (iii) CSF or imaging provide evidence supportive of AD pathology. This framework has also proposed reserving the MCI label for cases where there is no disease to which MCI can be attributed. For example, an individual with cognitive impairment and negative biomarkers.

2.3.2 Typical memory profile of prodromal AD

During the prodromal phase of AD, the medial temporal lobes already appear reduced in volume. In a study by Whitwell and collaborators (Whitwell et al., 2007), atrophy particularly affected the amygdala, anterior hippocampus, and entorhinal cortex in subjects with MCI three years before the diagnosis of AD. One year before the diagnosis of AD, atrophy was more widespread, involving the remaining parts of the hippocampus, more lateral and posterior regions of the temporal lobe and part of the parietal lobe. This pattern of progression is consistent with the Braak and Braak stages of tau pathology mentioned above.

The medial temporal structures have a well-known role in episodic memory, and the most common clinical phenotype of AD is characterized by an early and progressive hippocampal memory disorder (Sarazin et al., 2007). More specifically, the hippocampus has a critical role in creating memory traces, that is, storing episodic memories in the brain using the mechanisms of neuronal plasticity. Recent memories are more vulnerable in the case of hippocampal lesions and this concept is known as Ribot's law. The hippocampal amnesic disorder typical of AD is therefore a disorder of storage and consolidation of information in long-term memory.

Other episodic memory processes rely on different brain regions and can be compromised in the case of pathologies other than AD or injuries. This results in amnesic syndromes different from those found in patients with AD. A patient may have a memory impairment mainly due to poor attention span during the information encoding phase. The encoding is therefore not efficient and the information cannot be stored and then retrieved. This may be the result of anxiety, depression, of taking certain medications, among others. Otherwise, a patient may have difficulty retrieving information that had been well consolidated and stored.

This type of memory impairment reflects a dysfunction of the prefrontal cortex, as found in Parkinson's disease, for example. In clinical practice, it is possible to differentiate these amnesic syndromes through the use of specially developed tests. The best known is probably the Free and Cued Selective Reminding Test (Grober, Sanders, Hall, & Lipton, 2010). It asks to memorize words or images, depending on the version. After reading the words or naming the images, the examiner asks the participant to name the semantic category of each item, to check that the participant is paying attention to the coding of the information. The participant is subsequently asked to recall the elements without any cues (free recall), and then with the help of semantic cues provided by the examiner. Deficient free recall that does not improve with semantic cues indicates a storage disorder (hippocampal amnesic syndrome). Poor free recall which benefits from semantic cueing, on the contrary, suggests a retrieval disorder (frontal amnesic syndrome).

2.3.3 Anosognosia in prodromal AD

The degree of awareness of this amnesic syndrome in MCI patients remains debated. Some argue that patients with MCI are well aware of having a cognitive impairment. They found spared ACD in MCI (Lindau & Bjorkb, 2012) or an overestimation of cognitive problems (Kalbe et al., 2005). In a longitudinal study with a two-year follow-up (Silva et al., 2016), 34 MCI patients seeking medical advice at a memory clinic showed high ACD at baseline, which remained relatively stable during the 2-year follow-up, with a slight but not significant decline. The degree of ACD was not significantly different between individuals with stable MCI and those progressing to mild AD. The predictive value of ACD was low. However, these results should be considered with caution given the small sample size. Cova et al. found no relationship between ACD and progression to AD dementia at follow-up, i.e., after 28 months (Cova et al., 2017). In this study, anosognosia was measured using a single item from the Geriatric Depression Scale ("Do you feel you have more problems with memory than most people?"). The authors commented on this result in light of a possible inadequacy of this method to measure anosognosia, a single question being too simple a way to measure a complex symptom such as anosognosia. Furthermore, in both these studies the two-year follow-up was probably too short to observe the progression to dementia of all participants affected by the disease.

2.4.1 Definitions of the concept

Preclinical AD is the first stage in AD continuum, between the earliest pathogenic events and the first appearance of cognitive symptoms. Until about twenty years ago, post-mortem examination was the only way of detecting individuals at this stage, i.e., individuals who were cognitively normal at the time of death but had AD lesions at autopsy. We can now detect these individuals in vivo. IWG criteria have defined two different preclinical states (Dubois et al., 2010): (i) *Pre-symptomatic AD* refers to cognitively-intact individuals (i.e., with normal age- and education-adjusted scores on cognitive tests) carrying rare autosomal dominant monogenic AD mutations and who will inevitably progress to clinical AD over time; (ii) *Asymptomatic at-risk* state refers to cognitively-intact individuals with in vivo evidence of at least one biomarker of Alzheimer pathology. Neural compensatory mechanisms such as hyperactivity of (mainly) frontal regions are present in this phase to maintain normal brain functioning (Dubois et al., 2018; Gaubert et al., 2019).

According to the definition given by the National Institute on Aging–Alzheimer’s Association, NIA-AA (Jack Jr et al., 2018), an asymptomatic at-risk individual may show a subclinical decrease in cognitive efficiency compared to his/her own baseline level, but still achieving normal cognitive scores (i.e., a *transitional* cognitive decline). Our recent study (Villeneuve et al., 2019) also showed that subtle changes in activities of daily living may be already present in very early - mostly preclinical – AD, which might be useful to inform about potential future onset of AD dementia. This means that while patients at this very early stage do not present objective cognitive impairment at testing and maintain their independence in daily life, they may still show gradual changes in both cognition and function from the past.

2.4.2 The concept of subjective cognitive decline

The description of the natural history of AD and the conceptual shift that followed has increasingly oriented research towards the exploration of this first stage of the disease. Indeed, a timely diagnosis opens up a wide spectrum of possibilities for the patients and

their family, but also at the community and societal level (Dubois, Padovani, Scheltens, Rossi, & Dell’Agnello, 2016). 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, to 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). People are increasingly seeking medical advice for a self-perceived decline in cognition, especially in memory. A growing number of studies are currently investigating whether Subjective Cognitive Decline (SCD) could represent an early indicator of AD. The Subjective Cognitive Decline Initiative (SCD-I) working group has been instituted in 2012, including international researchers who work in the field of subjective cognitive impairment as a potential indicator of very early AD. According to the framework on subjective impairment in preclinical AD produced by SCD-I group (Jessen et al., 2014), it may represent a very early condition during which neuropathology is present but does not produce impairment on neuropsychological testing. It would result however in mild or occasional memory failures causing a personal sense of decline (i.e., transitional cognitive decline). The construct has been initially described in 1982 (Reisberg, Ferris, de Leon, & Crook, 1982), and then the subjective experience of cognitive decline has been defined as *subjective cognitive impairment*, *subjective memory decline*, *subjective memory impairment*, and *memory complaints*, among other terminologies. The SCD-I working group proposed to use the terminology *Subjective Cognitive Decline*. SCD is therefore 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 self-reported experience of cognitive decline is important to consider in current research on neurodegenerative pathologies, because it is one of a few ways in which individuals with early neurodegeneration request for medical care (Stewart et al., 2011). Particularly, it is uncertain how seriously should a complaint of cognitive impairment be taken in clinical practice.

Association between SCD and AD

SCD is neither a disease nor a feature of a specific disease. It is rather a condition that can be present in various contexts. Although etiologically diversified, subjective reports of cognitive decline in everyday life, in absence of any other condition known to cause cognitive disorders, is primarily associated with an increased risk of developing dementia and it is thought to be a sensitive symptomatic indicator of preclinical AD (Abdulrab & Heun, 2008; Amariglio et al., 2012; Jessen et al., 2014). In the very initial stage, in which identifying the disease is difficult, cognitive complaints may be useful, since they could represent a first consequence of AD pathology between full compensation and first objective decline.

The onset of SCD within the last few years seems to be more predictive of following development of dementia (Treves, Verchovsky, Klimovitzky, & Korczyn, 2005). The subjects with SCD most at risk of cognitive decline were those over the age of 61 years (Fonseca et al., 2015). Most at risk was also who reported SCD together with a decline-related worry (Koppara et al., 2015). A meta-analysis by Mitchell and collaborators (Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014) found that in longitudinal studies, 24% of individuals with SCD developed MCI within 4 years and 11% progressed to dementia, compared to 5% of those without SCD. Otherwise, healthy older adults with SCD, followed for 7 years, had 4.5 times the risk of progressing to MCI or dementia than people without SCD (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). Similarly, they were 4 times more likely to progress to MCI over a mean follow-up period of 2.4 years in a study by Donovan and collaborators. (Donovan et al., 2014). Buckley et al. found that individuals with SCD and high amyloid load had a fivefold increased risk of progression to MCI or AD dementia (Buckley et al., 2016).

Many studies have found an increased likelihood of biomarker abnormalities consistent with AD pathology in individuals with SCD.

Several studies used PET ligands binding to amyloid plaques and CSF levels of $A\beta_{42}$. In Perrotin et al., for instance, the intensity of SCD correlated with amyloid deposition at scan (Perrotin et al., 2012).

The synaptic dysfunction observed in AD can be detected by decreased FDG uptake with in parieto-temporal-precuneus areas (Jagust et al., 2004) and it correlates with disease

progression (Herholtz et al., 2011). Mosconi et al. found a parietotemporal and parahippocampal hypometabolism in subjects with SCD (Mosconi, Pupi, & De Leon, 2008). Individuals with SCD showed significant gray matter loss compared to controls without SCD, particularly in the medial temporal lobe, frontotemporal cortex, and other neocortical regions. The degree of grey matter loss was associated with the intensity of memory impairment (Saykin et al., 2006).

Genetic studies have found SCD to be associated with ApoE ϵ 4 allele overrepresentation, a well-documented risk factor for AD dementia (Abdulrab & Heun, 2008). In another study, 31% subjects with SCD had ApoE ϵ 4 genotype, compared to 19% of cognitively normal subjects (Snitz et al., 2018).

SCD due to other conditions

Although numerous studies have shown an association between the presence of SCD and an increased risk of AD, it should be noted that SCD is a common condition and not all complainers progress to dementia. Population-based studies show that at least half of older adults (over 70 years of age) with normal cognition express some degree of cognitive complaint (Jessen, 2010; van Harten et al., 2018). Indeed, conditions other than neurodegeneration may cause SCD. Elderly individuals may take their normal aging-related decline too seriously, assuming it is a clinically relevant cognitive problem. Anxiety and fear of potentially having dementia may play a central role in determining the emergence of cognitive complaints. Depression may lead the individual to overestimate the decline due to normal aging. The use of certain medications, physical health problems and chronic diseases may also lead to SCD. In Hollands et al., for instance, SCD assessed with different questionnaires did not differ significantly between amyloid-positive and amyloid-negative individuals. ApoE ϵ 4 carriage was also unrelated to SCD (Hollands et al., 2015). In another study, SCD was only linked to more severe symptoms of anxiety and depression (though subclinical) in cognitively-intact individuals. It was not related to cognitive scores or AD biomarkers (amyloid deposition and atrophy) (Buckley, 2013).

One of the main reasons for these conflicting results is the lack of a gold standard definition of SCD. Although the importance of SCD is recognized, there is a debate on the exact profile of SCD typical of AD that may encourage the clinician to carry out more in-depth investigations. Recent criteria have defined the concept of *SCD-Plus*, that is the SCD profile more related to AD. It would occur in individuals 60 years of age and older who would be persistently (for at least 5 years) concerned about a memory decline confirmed by an observer, and for which they sought medical advice (Jessen et al., 2020). These criteria for SCD are still subject to ongoing validation and refinement, as also stated by the authors.

2.4.3 Previous results on awareness of cognitive performance in preclinical AD

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). Poor ACD would be more specific than SCD, and should encourage more in-depth patient monitoring.

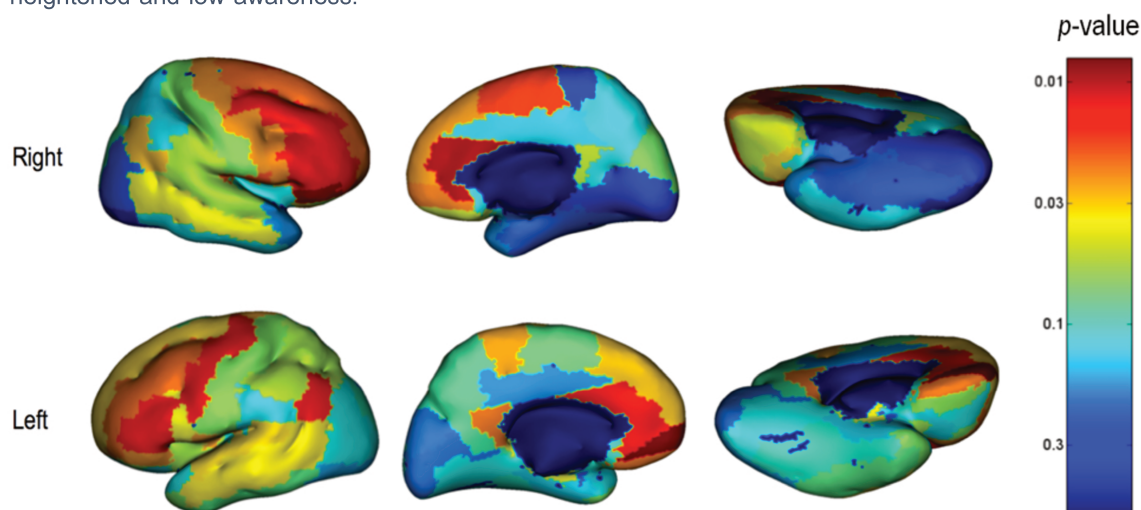
In a recent theoretical model (Dalla Barba et al., 2015), anosognosia and SCD are considered as counterparts. Individuals with SCD view their normal cognition as abnormal, while individuals with anosognosia view their abnormal cognition as normal. However, we believe that the relationship between SCD and anosognosia may be more multifaceted than proposed by Dalla Barba et al. The possibility that poor ACD could serve as an early indicator of AD may thus seem to run counter to research results on SCD. But the concepts of SCD and poor awareness are only apparently opposed since they can coexist in the same individual, as we found in a cohort of memory-complainers at risk for AD (Cacciamani et al., 2017; Cacciamani et al., 2020). This is the case of individuals who complain of a certain degree of cognitive impairment, still underestimating how much this impairment affects his/her daily life, relationships and autonomy, when compared to the assessment made by an informant or using cognitive tests ("I have memory problems, but it's not very serious, it's normal for my age, it has no real impact on my life") (Frederiks, 1996).

To date, few studies investigated ACD in asymptomatic individuals at risk for AD, and discussed the results within the scope of preclinical AD.

In a previous study conducted at the Institute of Memory and Alzheimer's Disease (IM2A), Pitié-Salpêtrière Hospital, Paris, we were the first to propose the reduction of ACD as a more specific indicator of early-stage Alzheimer's than SCD (Cacciamani et al, 2017). We investigated 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. 47% of subjects with low ACD were amyloid positive, versus 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 (Figure 2).

On the contrary, the measures of SCD alone, i.e., without comparison with the informant report, did not correlate with any AD biomarker.

Figure 2. Difference in brain glucose metabolism assessed by FDG-PET between subjects with heightened and low awareness.



Note. Warmer colors (yellow to red) indicate significantly lower metabolism in the “low awareness” group, compared to the “heightened awareness” group. Figure from Cacciamani et al., 2017.

Similarly, Sanchez-Benavides et al. 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 (Sanchez-Benavides et al., 2018).

Verfaillie et al. 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, 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 (Verfaillie et al., 2019).

To our knowledge, the first longitudinal study investigating ACD in subjects who were cognitively-normal and MCI 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, two more recent studies using more advanced statistical methods allowed to describe a more gradual progression of ACD. ACD began to slightly

decline already in the preclinical phase, leading to anosognosia in the prodromal phase. Hanseeuw et al. 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 declined 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 *hypermognosia*). 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 (Hanseeuw et al., 2020). A second longitudinal study (Vannini, Patrizia et al., Invalid date) selected 396 presenilin (PSEN1 E280A) variant carriers from the Columbia 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 approximately 43 years of age (approximately 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 subject 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 *hypermnesia* or reduced nosognosia is more characteristic of preclinical AD.

Objectives of this thesis 3

To achieve the general aim of understanding whether changes in ACD can be useful as an early indicator of disease, we have formulated the following objectives:

1. To identify groups of individuals at risk for preclinical AD that are similar in terms of ACD longitudinal trajectory, and find the one or those most associated with AD neuroimaging markers and risk of progression to dementia (Chapter 4).

We hypothesized that participants who showed an increase in ACD followed by its gradual reduction, and not those with steadily heightened ACD, would be at greater risk of preclinical AD.

2. To compare the intensity of the subject's and informant's complaints, and of ACD (i.e., subject-informant discrepancy), by cognitive domain between groups of individuals at different stages of the disease, and to determine how accurately these measures can discriminate clinical groups (Chapter 5).

We hypothesize that while episodic memory complaints will be the most marked, non-amnesic measures (especially informant's complaint and ACD) would also distinguish the different groups.

3. To design a new cohort-independent procedure to assess ACD and validate it in subjects at risk for preclinical AD (Chapter 6).

We hypothesized that, using the discrepancy between the subjects' assessment of their cognitive performance and their objective scores, we could demonstrate reduced ACD in those with biomarkers indicative of AD.

4. To understand whether ACD is already reduced in prodromal AD, and discuss its potential neuronal and clinical correlates and the associated risk of progression from mild impairment to dementia (Chapter 7).

We hypothesized that ACD would be already reduced in the prodromal phase of the disease, although with greater inter-individual variability and in a milder form than in dementia.

5. To use machine learning to outline how ACD changes along the disease continuum (from normal cognition to dementia), by describing the longitudinal trajectory of the average subjects' and informants' complaints (Chapter 9).

We hypothesized that the ACD changes would be driven by a subject's complaint that remained stable in intensity over time, or "petrified", while the informant's complaint would increase with increasing disease severity.

6. To use machine learning to create an AD Course Map that shows when some of the major symptoms and biomarker abnormalities occur in the course of the disease, including subject's and study-partner's complaints. We aim to know when they become abnormal (more marked than in healthy individuals), in terms of average age but also of order compared to the other symptoms and biomarker abnormalities (Chapter 9).

We hypothesized that the informant's complaint would be one of the first measures to identify abnormalities among the different tests and biomarkers considered, while the subject's complaint would be one of the least sensitive.

7. To define the neural correlates of changes in ACD in early-stage AD, and more specifically to understand which pathological processes and brain regions are most involved (Chapter 10).

We hypothesized that in pre-dementia AD, changes in ACD would be already linked to amyloid accumulation at a predominantly fronto-parietal level, in addition to neurodegeneration, with also a medial temporal involvement.

Poor awareness of cognitive decline (ACD)
as an early indicator of Alzheimer's disease:
Classical statistical methods

Evolution of ACD and risk of preclinical AD

4

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The reference frameworks for the definition of SCD (Jessen et al., 2014; Jessen et al., 2020) have been developed to characterize the SCD profile typical of early-stage AD, in order to learn to recognize among the cognitive-complainers those who have an increased risk of AD. In fact, as already mentioned (see 2.4.2), SCD is a common condition, not always due to incipient Alzheimer's. These frameworks report, among other criteria, that cognitive complaint would represent an increased risk of early-stage AD when it is persistent (not sporadic) and expressed for at least 5 years.

There is evidence that the duration of SCD is shorter in individuals who will progress to dementia (approximately 2.5 years in Treves et al.), compared to those who will not progress and exhibited SCD for all 4 years of follow-up (Treves et al., 2005). However, the duration of SCD in AD is not yet clear. SCD is a condition that emerges gradually and patients often fail to report exactly when it started. Furthermore, it generally fades into anosognosia as the disease progresses and more marked cognitive symptoms appear, and this compromises an accurate measurement of the duration of SCD both in research and in clinical practice. Finally, patients with AD differ from each other in terms of the rate of disease progression, and therefore it is difficult to give a cut-off to identify a typical duration of SCD in AD. However, this is very important in order to characterize the SCD due to AD and offer the patient a more in-depth follow-up. On the one hand, we should not consider sporadic

cognitive complaints as suggestive of an underlying AD. On the other hand, a purely subjective complaint lasting many years is most often typical of the "worried-well" population (Sutherland, 2021), not affected by AD but complaining of cognitive difficulties due to normal aging, or who tend to underestimate their cognitive performance due to their anxiety or depressive syndromes, or due to certain personality traits.

Another criterion proposed by the SCD-I is the confirmation of cognitive decline by a person who knows the patient well, since many studies have demonstrated its reliability (Valech et al., 2015). A longitudinal study of the subject-informant discrepancy (i.e., a measure of ACD) could inform us about the patient's risk of progressing towards clinical AD. In our study, we described the different evolution trajectories of ACD in a population at risk of AD (Cacciamani et al., 2020).

4.1 Aims

1. To track the temporality of the changes in the ACD during preclinical AD. More specifically, we aimed at identifying groups of participants who shared a similar longitudinal trajectory of the ACD and to characterize each group/trajectory according to their demographical data and AD neuroimaging markers at baseline (amyloid burden and brain metabolism);
2. To test the hypothesis that an early reduction in ACD is associated with progressive cognitive decline, by studying the impact of baseline ACD on changes in cognitive scores across the 3-year study period;
3. To study the association between longitudinal changes in ACDI and longitudinal changes in cognitive scores, to clarify whether a certain pattern of ACD evolution is associated with a more marked cognitive decline.

4.2 Methods

4.2.1 Participants

This study was conducted on data from the INSIGHT-PreAD cohort, described above. In short, this is a cohort of cognitively-intact individuals (MMSE > 27 and CDR = 0 and FCSRT TR > 40) who answered "YES" to the questions "Are you complaining about your memory?" and "Is it a regular complaint that has lasted now more than 6 months?".

INSIGHT-PreAD is a prospective ongoing cohort study. When we performed the statistical analyses (Sep 2019), the participants were undergoing their M54 or M60 visit. Only data up to M36 were analysed in this study (7 timepoints), because the data of subsequent visits had not yet been fully collected and/or checked. At the time of the analyses, 14 participants had been labelled as "decliners" (that is, exhibit at least two of the following changes over two consecutive evaluations 6 months apart: CDR increasing from 0 to 0.5 and/or an MMSE below 26 and/or a FCSRT total score below 40). The INSIGHT-PreAD protocol stipulated that participants would stop the follow-up as soon as they were classified as "decliners." Three subjects were classified as "decliners" at the 24-month visit, three subjects at 36 months, one at 42 months, one at 54 months, and eight subjects at 60 months.

4.2.2 Cognitive measures

We investigated the impact of baseline ACD on the evolution of the cognitive scores that are supposed to be most relevant to the study of ACD in early-stage AD. All INSIGHT-PreAD participants performed cognitive screening tests every 6 months and underwent a comprehensive neuropsychological evaluation every 12 months. On the one hand, impaired awareness is associated with a suboptimal online self-monitoring, error detection and disinhibition (Amanzio et al., 2013; Kashiwa et al., 2005; Lopez et al., 1994). On the other hand, memory disorders prevent correct comparisons between current and past performance (Michon et al., 1994).

Therefore, we included:

(1) the Trail Making Test (TMT) B-A score, the Lexical and Semantic Fluency and the Frontal Assessment Battery (FAB), as measures of executive functioning;

- (2) the free recall and total recall scores from the FCSRT, an episodic memory test sensitive to hippocampal damage;
- (3) the Mini-Mental State Examination (MMSE) as a measure of global cognitive functioning.

4.2.3 Determination of the Awareness of Cognitive Decline Index (ACDI)

The procedure for identifying ACDI is reported in our previous publication (Cacciamani et al., 2017). In summary, the subjects and their study-partners filled out two similar versions of the Healthy Aging Brain Care Monitor (HABC-M) (Monahan et al., 2012; Monahan et al., 2014). This is a questionnaire asking how often, during the last 2 weeks, the participant has encountered certain difficulties in his/her everyday life. The questions are the same in the participant version and the study-partner version and only asked slightly differently. For example, the first question in the participant version is “Over the past two weeks, how often did you have problems with judgment or decision making?”. In the informant version it is “Over the past two weeks, how often did your loved one have problems with judgment or decision making?”. Answers range from 0 (never) to 3 (very often).

Since we aimed at studying awareness of cognitive decline, we only considered the HABC-M cognitive score, which is the sum of 6 items, and ranges from 0 to 18. The ACDI was determined by subtracting the HABC-M cognitive score obtained by the informant from that obtained by the subject. The ACDI ranged from -18 to 18, where higher scores indicated heightened ACD (patient’s report > informant’s report), and lower scores, low ACD. The ACDI was computed at each visit (every 6 months) and treated as a continuous variable.

4.2.4 Brain imaging

In the present study, we included baseline neuroimaging markers of AD.

All participants performed amyloid-PET imaging using ^{18}F -AV-45 (^{18}F -florbetapir; AmyvidTM, Avid Radiopharmaceuticals) as a tracer. The standardized uptake value (^{18}F -AV-45-SUV) was calculated in target regions (i.e., left and right precuneus, anterior cingulum, posterior

cingulum, parietal, temporal, and orbitofrontal cortex) with the CATI pipeline (Centre d'Acquisition et de Traitement d'Images, <https://cati-neuroimaging.com>), and normalized to the cerebellum and pons, resulting in a SUV ratio (SUVr). In the present study, we considered the amyloid load as a continuous variable (mean ^{18}F -AV-45 SUVr of the aforementioned regions) and as a dichotomic variable. To this end, the SUVr positivity threshold was 0.79, which was analogous to the threshold found using a method validated within the IMAP study.

We also examined cortical glucose metabolism using fluorodeoxyglucose (FDG) PET. A metabolism index was calculated by averaging the FDG-SUVr of four bilateral regions of interest, whose metabolic changes are considered to be a "signature" of AD (Jack & Holtzman, 2018): posterior cingulate cortex, inferior parietal lobule, precuneus, and inferior temporal gyrus. The pons was used as a reference region. The FDG-SUVr has been included as a continuous variable.

More details about imaging data acquisition are available in previous works (Dubois et al., 2018).

4.2.5 Statistical analysis

For the first objective, we performed a Latent Class Linear Mixed Model (LCLMM) (Proust & Jacqmin-Gadda, 2005) to investigate heterogeneous trajectories of ACD, since they are expected in a cohort of memory-complainers. The LCLMM first identifies G classes of subjects who share a similar trend of evolution of the ACDI and then compares the classes. In order to find the adequate and clinically relevant number of classes G , we computed the model from one to three classes and selected the one which minimized the Bayesian Information Criterion (BIC). The mean of posterior probabilities and the percentage of posterior probabilities higher than 0.7 were computed. The evolution of the ACDI was modeled by the interaction between classes and visits. Using a multinomial logistic model, the baseline characteristics of each class (i.e., amyloid load, glucose metabolism, age, gender, and educational level) were compared to the class with the largest number of subjects. Normality of residuals and random effects as well as heteroskedasticity were

checked visually. For this analysis, subjects with at least two timepoints of ACDI and with no missing baseline data (amyloid load, metabolism, age, gender, and education) were included.

We also performed generalized linear mixed effects models (GLMM) to evaluate the effect of the ACDI at baseline on changes in cognitive scores (objective 2) and the effect of longitudinal changes in ACDI on the evolution of cognitive scores (objective 3). Link function was chosen for the underlying data generation mechanism with logit for binomial data and identity for continuous data. One GLMM was performed for each score, and then the Benjamini-Hochberg method was used to correct for multiple comparisons. For the second objective, we entered the following baseline variables as fixed effects: ACDI, age, gender, and educational level, visit, and the interaction between visit and ACDI, to test the impact of ACDI at baseline on changes in cognitive scores. All two-way interactions between these effects were tested independently and were added in the final model if significant. The participant was added as a random effect. For the third objective, we entered the following baseline variables as fixed effects: class, age, gender, and educational level and visit. All two-way interactions between these effects were tested independently and were added in the final model if significant. The participant was added as a random effect. Type II likelihood ratio tests were used to test each fixed effect and interaction. Cohen's f^2 were calculated, using the marginal R^2 , for each effect to estimate their size.

For this analysis, we only included subjects with at least two timepoints for each cognitive score, and with no missing data for ACDI at baseline, age at baseline, gender, and education. Baseline characteristics were compared between subjects included and excluded in the analysis using the χ^2 test for categorical variables and Student's t -test for continuous variables. A p value < 0.05 was considered significant. Statistical analyses were performed using R3.6.1. The packages lme4 (1.1-21) and LCMM (1.8.1) were used to perform LMM and LCLMM, respectively.

4.3.1 Objective 1: study of trends of ACIDI evolution and their association to AD biomarkers

The longitudinal evolution of ACIDI was studied in 306 out of 318 subjects. Indeed, we excluded 12 subjects who had only one ACIDI available ($n = 6$) or none ($n = 6$) (Figure 1). The baseline characteristics of the included subjects are presented in Table 1.

Figure 1. Sample selection for the three objectives

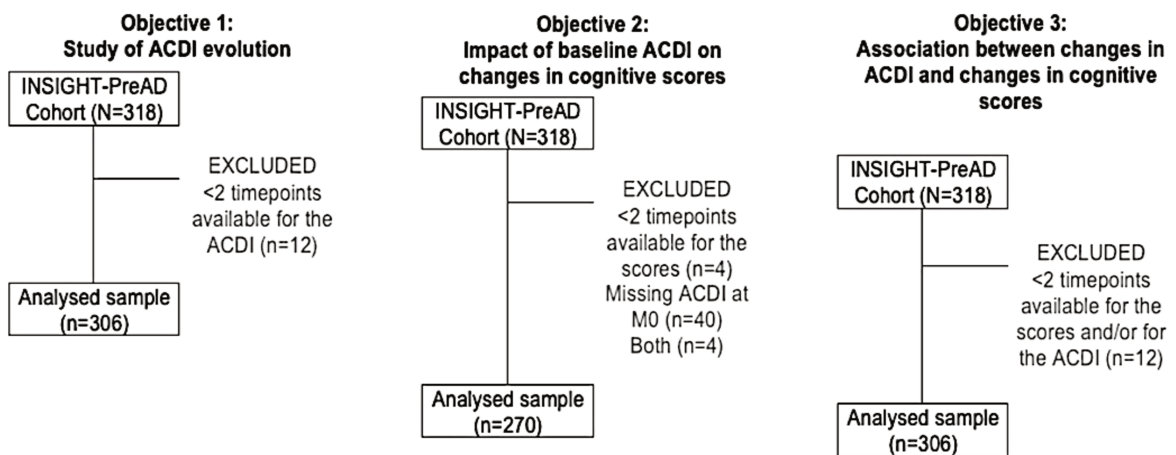


Table 1. Baseline characteristics of the participants included in the analysis for the Objective 1

	Subjects included N=306 (96.23%)
Age [years; $M \pm SD$]	75.95 \pm 3.43
Gender [female; n (%)]	192 (62.75%)
Education [high [§] ; n (%)]	211 (68.95%)
Awareness of Cognitive Decline Index, ACIDI [$M \pm SD$]	1.44 \pm 2.92
HABC-M Cognitive score (subject) [$M \pm SD$]	3.32 \pm 2.79
HABC-M Cognitive score (informant) [$M \pm SD$]	1.84 \pm 2.21
MMSE [$M \pm SD$]	28.67 \pm 0.95
FSCRT Total Recall [$M \pm SD$]	46.10 \pm 1.97
FAB [$M \pm SD$]	16.44 \pm 1.66
TMT B-A [seconds; $M \pm SD$]	47.81 \pm 35.40
Lexical fluency [$M \pm SD$]	22.46 \pm 5.91
Semantic fluency [$M \pm SD$]	31.44 \pm 7.16
APOE [presence of $\epsilon 4$; n (%)]	60 (19.61%)
Amyloid load [¹⁸ F-AV-45 SUVr; $M \pm SD$]	0.78 \pm 0.19
Brain glucose metabolism [¹⁸ F-FDG SUV; $M \pm SD$]	2.45 \pm 0.25

Note. [§]Equal to or higher than high-school diploma (≥ 12 years).

The three-class LCLMM provided the best fit with a BIC = 8287.2, compared to 8384.0 for the two-class LCLMM and 8626.7 for the one-class LCLMM. In each class, at least 70% of the subjects had at least 6 timepoints. The three classes were distinct, with Class 1 mean posterior probabilities of 0.91 belonging to Class 1, Class 2 mean posterior probabilities of 0.96 belonging to Class 2, and Class 3 mean posterior probabilities of 0.94 belonging to Class 3. Moreover, more than 90% of the subjects in each class had a posterior probability higher than 0.7.

The three trajectories identified by the LCLMM are presented in Figure 2.

Class 1 included 58 subjects (18.95% of the sample) having a positive ACDI, meaning that these participants persistently reported more cognitive difficulties than their study-partner. We refer to these participants as belonging to the *Steadily heightened ACD* class.

Class 2 included 235 subjects (76.8% of the sample) with an ACDI of around 0, indicating a good match between the subject's and the informant's assessments (*Accurate ACD* class). The ACDI of this class remained unchanged over time.

Class 3 included 13 subjects (4.25% of the sample) with a relatively low ACDI (below zero), which means that these participants expressed less difficulties compared to their informant. In this class, ACDI slightly increased at 6 months and then tended to decline. We refer to this group as the *Low ACD* class.

We compared the characteristics of Classes 1 and 3 with those of Class 2, which was chosen as the reference (Table 2). Indeed, this was the numerically largest class, and the average ACDI was constantly around 0 in this class, indicating that the subject and his/her study-partner had similarly assessed the subject's cognitive functioning.

Compared to Class 2, individuals in Class 3 (low ACDI) had higher amyloid burden (OR \pm SE 57.2 \pm 69.9; $p = 0.0009$), were mostly amyloid-positive (OR \pm SE 3.70 \pm 2.31; $p = 0.0357$), and were mostly men (OR \pm SE 4.7 \pm 3.3; $p = 0.0307$). No statistical difference was found in terms of age, educational level, and brain metabolism between these two classes. Class 3 includes 3 subjects (23.1% of this class) whose cognition became abnormal after 24, 42, and 54 months of follow-up, respectively.

Figure 2. Evolution of the ACDI across the 36 months of study in the three classes of subjects identified by the LCLMM (Objective 1).

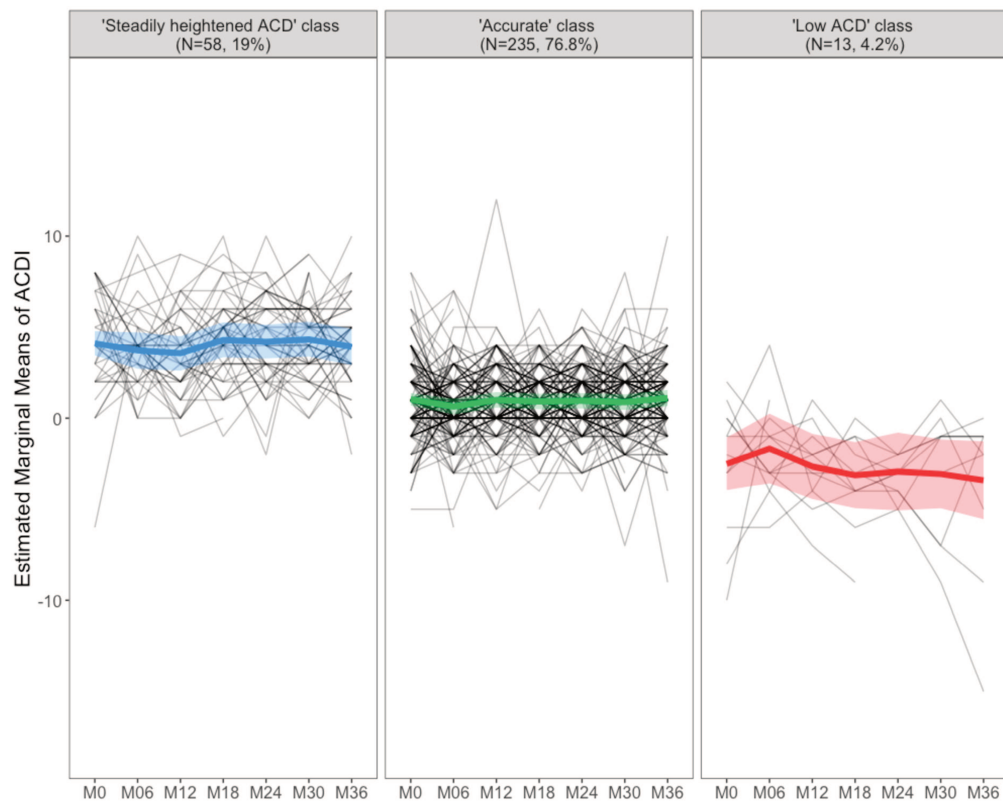
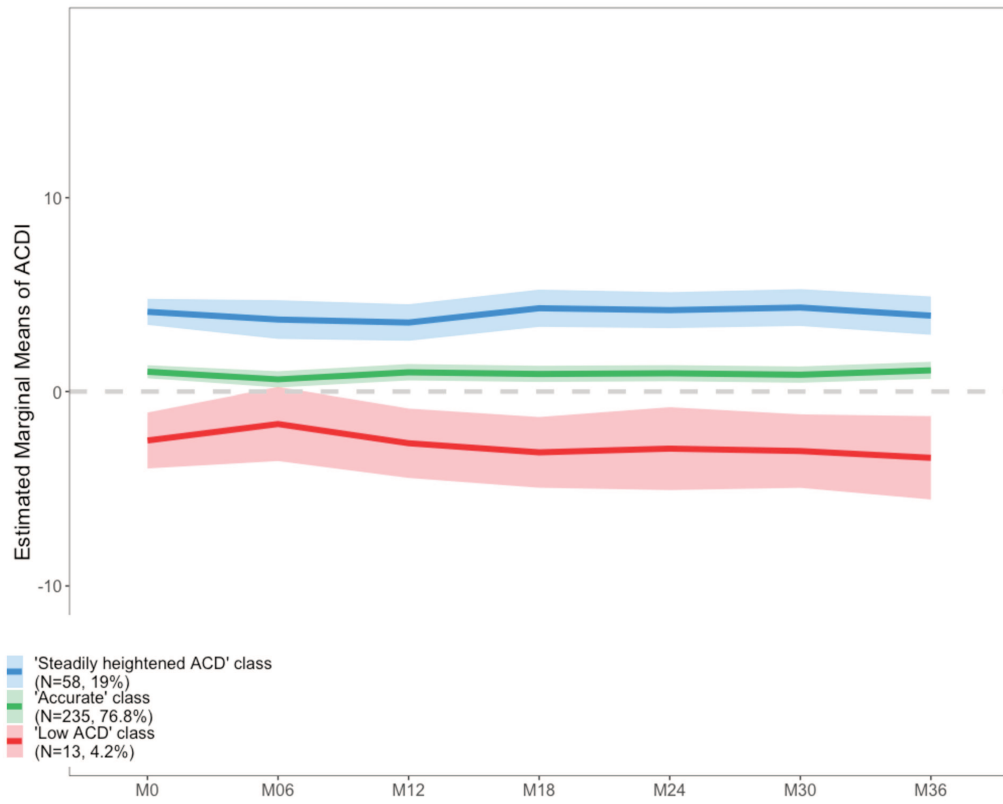


Table 2. Comparison between Class 2 (reference) and both Class 1 and 3.

	Class 1 ("Heightened ACD", n=58) vs Class 2 (reference, n=235)		Class 3 ("Low ACD", n=13) vs Class 2 (reference, n=235)	
	OR ± se	p	OR ± se	p
Intercept	0.03 ± 0.12	0.3566	1867.11 ± 14807.31	0.3422
Age at baseline	1.02 ± 0.04	0.6175	0.87 ± 0.08	0.1325
Gender [female]	1.47 ± 0.46	0.2123	4.66 ± 3.32	0.0307*
Education [high§]	1.73 ± 0.53	0.0783	0.28 ± 0.30	0.2389
Amyloid load [¹⁸ F-AV-45 SUVr]	0.99 ± 0.85	0.9950	57.18 ± 69.93	0.0009*
Amyloid status [Aβ- subjects]	0.84 ± 0.30	0.6262	3.70 ± 2.31	0.0357*
Brain metabolism [¹⁸ F-FDG SUV]	1.03 ± 0.62	0.9560	0.18 ± 0.26	0.2289

Note. Class 2, with stable evolution and matching subject's and informant's ratings of decline, was the reference class. For categorical variables, category in brackets was the reference. ¹⁸F-AV-45 SUVr: Florbetapir standardized uptake value ratio (index of amyloid deposition). Effect adjusted for age, gender, education and FDG load. ¹⁸F-FDG SUV: Fluorodeoxyglucose standardized uptake value (metabolic index). § Equal to or higher than high-school diploma (≥ 12 years). OR: odd ratio; se: standard errors

No statistically significant difference was found when comparing Classes 1 and 2 in terms of age, gender, educational level, amyloid burden, and brain metabolism. Class 1 included 1 subject labeled as a "decliner" at the 36-month visit, representing 1.72% of this class. Class 2 included 10 decliners (n = 2 after 24 months of follow-up; n = 8 after 60 months), which represents 4.25% of this class.

4.3.2 Objective 2: impact of ACDI at baseline on changes in cognitive scores

The second objective of this study was to investigate if the ACDI at baseline had an impact on changes in cognitive scores of interest across the 3-year study period. To do so, we only analysed the participants who had ACDI available at baseline and at least two timepoints for one or more cognitive score(s) (n = 270) (Figure 1). No significant difference was found when comparing subjects included and excluded from this analysis, in terms of demographic variables, cognitive scores, and biomarkers (all p > 0.156). The mean age

was 75.9 (SD = 3.4) and subjects included were mostly women (61.9%) and had high educational level (68.5%).

Concerning the GLMM, the final models also included interactions between gender and visit, educational level and age, and ACDI and age, in addition to the effects stated in the statistical analysis paragraph. Marginal R^2 , based on the GLMM fixed part, were very low from 0.05 (MMSE model) to 0.12 (Lexical fluency model). There was a significant overall change to all cognitive scores, except for the TMT B-A ($p = 0.1449$). However, this effect was very small (Cohen's f^2 ranging from 0.004 to 0.034 for the different scores).

The main effect of the ACDI at baseline on the evolution of the scores was not significant for any test (all $p > 0.6236$). The interaction between age and ACDI had a significant effect on the average evolution of Semantic Fluency score ($p_{\text{non-corrected}} = 0.0443$) and TMT B-A score ($p_{\text{non-corrected}} = 0.0166$), but the effect size was small (Cohen's $f^2 = 0.009$ for Semantic Fluency score; Cohen's $f^2 = 0.015$ for TMT B-A score), and the two effects did not survive the correction for multiple comparisons ($p = 0.1160$ for TMT B-A score; $p = 0.1550$ for Semantic Fluency score).

The effect of the interaction between timepoint and ACDI on the scores was not significant (all $p > 0.1649$).

4.3.3 Objective 3: association between trends of changes in the ACD and changes in cognitive scores

We found no significant effect of the variable "class" (i.e., the trend of evolution of the ACDI: "steadily heightened ACD," "accurate," "low ACD") on the MMSE, FCSRT free and total recall, TMT B-A, and Semantic and Lexical fluency (all $p_{\text{non-corrected}} > 0.0554$; all $p_{\text{corrected}} > 0.1523$; all Cohen's $f^2 < 0.015$). Only the "low ACD" class had a significantly higher FAB score than the "accurate" class ($p = 0.0260$), but this effect did not survive the correction for multiple comparisons using the Benjamini-Hochberg method ($p_{\text{corrected}} = 0.0911$), and the effect size was small (Cohen's $f^2 = 0.004$).

This is one of the first studies to appreciate the longitudinal evolution of ACD in a population of asymptomatic individuals at risk for AD, due to their age, cognitive complaints, and amyloid burden (where appropriate).

In our sample, we identified three patterns of evolution of the ACD across the 3 years of study. Most subjects (around 77%) consistently expressed an accurate assessment of their own cognitive functioning, that is, the cognitive difficulties reported by the subject were comparable to those reported by his/her study-partner (ACDI consistently around 0). This represents an accurate ACD. The other two classes represented two forms of altered ACD (in agreement with the model proposed by Dalla Barba and colleagues).

On the one hand, around 19% of participants belonged to the *Steadily heightened ACD* class, since they persistently reported more cognitive difficulties than their study-partner did. These individuals were comparable to those with accurate ACD in terms of demographic characteristics and AD neuroimaging markers, which means that subjects with persistent cognitive complaints do not have a greater risk of having positive AD markers. Moreover, only one of these participants (1.72%) was classified as decliner during the follow-up. This is consistent with previous studies (Cacciamani et al., 2017; Sanchez-Benavides et al., 2018). Indeed, these individuals may subjectively experience a cognitive decline that is actually normal for their age (Harada et al., 2013), or due to conditions other than AD, such as sleep disturbances (Wolkove N, 2007), or medications that impact cognition (Risacher et al., 2016). Anxiety and fear of potentially having dementia may play a central role in determining the emergence of cognitive complaints (Alladi, Arnold, Mitchell, Nestor, & Hodges, 2006). The condition of heightened ACD cannot therefore be considered as specific to AD.

On the other hand, approximately 4% of subjects had a low ACD, as they persistently reported fewer cognitive difficulties than estimated by their study-partner. This means that the ACD could already be reduced in asymptomatic elderly individuals at risk for AD and is

particularly interesting if we consider that we studied a population of memory complainers. Thus, it seems that these two phenomena (low ACD and cognitive complaints) can coexist in the same individual, despite being apparently opposed. Indeed, individuals from the “low ACD” group were all complaining of a certain degree of cognitive difficulties, still underestimating them when compared to an informant.

These subjects showed higher amyloid burden than those with normal ACD and, as a consequence, a higher risk of developing AD (Hardy and Higgins, 1992). Around 1/4 of them ($n = 3$) were tagged as decliners during follow-up, a fraction which is qualitatively larger than in the other classes (although no statistics were performed due to the low number of decliners).

Interestingly, we found no difference between individuals with low and normal ACD in terms of brain metabolism. This suggests that the reduction of ACD would be associated with amyloid accumulation prior to neurodegeneration, of which brain hypometabolism is a marker (Benvenuto et al., 2018). This would be consistent with previous evidence concerning how the temporal sequence of imaging markers reflecting the pathological cascade of AD (Jack, Barrio and Kepe, 2013) and underlines how this symptom could occur very early in the course of the disease. It should be noted, however, that we examined the mean glucose metabolism in AD “signature” regions (Jack & Holtzman, 2013) and that this could mask regional differences. Indeed, we believe that ACD reduction could be associated with reduced local brain metabolism (in particular, in the frontal lobe) and not in other brain areas. Additional studies should be conducted to explore these regional differences, both in the glucose metabolism and in amyloid accumulation.

Another key result of this study is that individuals with low ACD were mostly men, consistent with previous evidence. For instance, a study conducted in the context of brain injuries found that men were less aware of their brain injury-related deficits compared to women (Niemeier et al., 2014). A socio-cultural process could be responsible for the observed gender-related differences. It is well-known that men and women learn different gendered attitudes and behaviors from cultural values and norms, which result in different expectations regarding their social role. These experiences also include health-related behaviors. Research findings have been strikingly consistent in showing that men, as a group, are more likely to avoid seeking help for physical and mental health problems.

Indeed, seeking help is associated with behaviors such as admitting vulnerability and showing weakness, leading men to experience a gender-role conflict (Addis & Mahalik, 2003). For the same reasons, when men do seek medical help, their behaviors may be different compared to women. For instance, they may ask fewer questions than women do (Courtney, 2000). We believe that these socio-cultural factors could explain why the group of subjects who underestimated their cognitive difficulties were mostly men. However, further studies should investigate an alternative explanation, namely that low ACD in the preclinical phase could be a better indicator for future progression to AD in men than women, due, for instance, to biological differences.

The longitudinal trajectory of the ACDI showed an increase at 6 months and then a tendency to decline, in those with consistently low ACD. We believe that the ACD is likely to be amplified in the presence of the earliest subtle cognitive difficulties (i.e., SCD), and later, in the preclinical phase, it would begin to decrease and becomes a clear anosognosia in AD dementia.

In the present study, we also explored (objective 2) whether an early reduction in ACD could anticipate a progressive cognitive impairment. We found that the changes in cognitive scores over 3 years did not depend on baseline ACD, meaning that the subjects who had lower ACD showed no more marked cognitive decline than the other subjects.

We also found (objective 3) that the three patterns of evolution of the ACDI identified were not associated with different trends of changes in cognitive function. Indeed, this is a cohort of cognitively intact individuals, with a fraction of them likely being in an early (preclinical) stage of AD. On average, their cognitive scores remained stable during follow-up. Therefore, a lack of association between baseline or longitudinal ACD and the evolution of cognitive scores was somewhat expected, consistently with what we found in our previous study in the same cohort (Cacciamani et al., 2017). We believe that if the follow-up had been longer, we would have identified an association between ACD and cognitive scores' evolution (i.e., those with an early low ACD would experience a more marked cognitive decline).

Taken together, our findings suggest that the caregiver/study-partner report should be systematically collected, both in clinical settings for diagnostic purposes and in research settings to better select the subjects for inclusion in studies targeting early-stage AD. The informant's report should be collected in order to compare it with the participant's (or patient's) report.

Limitations

While this study was conducted on a single-center cohort, with highly standardized clinical assessment, neuropsychological testing, and imaging acquisition procedures, it should be noticed that our results may possibly be biased by the high average education level of participants and the over-representation of women, both of which could limit the generalization of our findings.

Conclusion

To conclude, ACD may start to decrease in the very early stages of AD, especially in a certain group of individuals who need to be further characterized through additional studies. This group is of great interest because it is more at risk of being affected by AD than other individuals. Indeed, the subjects who expressed less cognitive difficulties than their study-partner for 3 years had a higher risk of AD than the worried-well population (i.e., patient complaint > study-partner). The presence of an informant is therefore strongly recommended both in clinical practice and in research trials. Indeed, this can be useful to orient the clinician towards making a timely diagnosis of AD. Inclusion criteria of studies investigating preclinical AD should also take into consideration this evidence.

Domain-specific SCD and ACD 5

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Due to the high frequency of amnesic 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-amnesic cognitive complaints are less studied, but still of interest. First, patients or their families often report difficulties other than memory problems, such as language complaints or difficulty retrieving words (Rohrer et al., 2008), executive functioning (Valech, 2018) and visuospatial complaints (Mendez et al., 1990). Secondly, recent studies have highlighted the relevance of non-amnesic cognitive complaints in patients on the AD spectrum. Valech and colleagues found that self-reported cognitive complaints in language and executive function domains, but not in the episodic memory domain, helped in distinguishing cognitively-normal amyloid-negative and amyloid-positive controls (Valech et al., 2017). Another study showed that attention and language complaints, but not episodic memory complaints, were higher in amyloid-positive controls (La Joie et al, 2016). Nonetheless, additional evidence across the full AD spectrum is needed to fully establish that complaints and awareness of non-amnesic domains (language, visuospatial, executive) are clinically useful.

While the clinical relevance of patient-reported cognitive complaints, informant-reported cognitive difficulties and awareness 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 et al. compared the utility of

informant- and self-report of cognitively-relevant functional abilities to discriminate diagnostic groups across the AD spectrum (Rueda et al., 2014). They found that informants' complaints were systematically more accurate than self-report in distinguishing different stages of the disease, and that informant-report was consistently more associated with objective markers of disease than self-report, 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 disease. Besides, they only used a global score of cognitive abilities (total ECog), without considering the predictive values for each cognitive domain. Indeed, complaints and awareness might be useful in different ways according to the specific cognitive domain.

5.1 Aims

1. To compare the intensity of the subject's and informant's complaints, and of ACD by cognitive domain (i.e., memory, language, visuospatial ability, and executive functions) across the AD spectrum (in 4 clinical groups: cognitively-normal amyloid-negative controls, cognitively-normal amyloid-positive individuals, MCI amyloid-positive individuals, and AD amyloid-positive individuals). We hypothesize that while episodic memory complaints will be the most elevated, non-amnestic cognitive complaints will also distinguish the different groups on the AD spectrum and therefore be useful clinically.
2. To measure how accurately subject's and study-partner's complaints and ACD (i.e., subject-informant discrepancy) can discriminate the 4 clinical groups in the 4 investigated cognitive domains. We hypothesize that informant-reported cognitive complaints and ACD, in all cognitive domains, will be able to distinguish clinical groups.

5.2 Methods

5.2.1 Participants

We analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI, <http://adni.loni.usc.edu>) cohort. This is a multicentric study designed to develop biomarkers for the early detection and tracking of AD. 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. In this study, we used baseline data only.

We selected four groups of participants: amyloid-positive ($A\beta+$) individuals diagnosed with AD, MCI or cognitively-normal (CN) at baseline, and amyloid-negative ($A\beta-$) healthy controls.

Subjects were considered $A\beta+$ when they had at least one positive amyloid marker. Amyloid markers considered were 8F -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 $A\beta+$ 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-normal 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 concern as reported by the subject, his/her 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 6 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 hours 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 the subject's complaints and for the study-partner's complaints (i.e., only subjects with a maximum of 10% missing data).

5.2.2 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 et al., 2008), which asks to compare the subject's current cognitive efficiency with that of 10 years ago. Four areas are assessed: Memory (8 items, for example "Remembering a few shopping items without a list"), Language (9 items, for example "Forget the name of objects"), Visuospatial ability (7 items, for example "Follow a map to find a new location") and Executive functions (15 items, 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").

5.2.3 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 4 ECog subscales. This resulted in four measures of awareness of changes in memory, language, visuospatial and executive functions, respectively. The score ranges from -8 to 8. Higher scores indicate heightened awareness (i.e., ECog-StudyPartner > ECog-Subject), lower scores indicate greater anosognosia (i.e., ECog-Subject > ECog-StudyPartner), and 0 indicates perfect agreement between the subject and the study-partner.

5.2.4 Cognitive scores

For the purposes of the sample description, we used the MMSE and the Montréal Cognitive Assessment (MoCA), both scores between 0 and 30, as overall measures of cognitive impairment. We have also included the Rey Auditory Verbal Learning Test (RAVLT) immediate recall score, which evaluates episodic memory; the copy of the clock, which evaluates visuospatial abilities and executive functions (such as planning) and which ranges from 0 to 5; and the Boston Naming Test (BNT), which mainly evaluates language. In each of these tests, a higher score indicates better cognitive abilities.

5.2.5 Statistical analysis

Statistical analyses were performed using RStudio (version 1.2.5033, RStudio, Inc) and SPSS (version 26.0.0.1). Missing observations (maximum 10% per subject) in the answers to ECog items were systematically imputed with the mean score for the item.

Study population description

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

We used a mixed ANOVA design to test the main and interaction effects of clinical group (between-subjects factor) and cognitive domain (within-subjects factor) on the 8 ECog scores (4 ECog-Subject, 4 ECog-StudyPartner) and the 4 anosognosia scores, controlling for age, sex and education. To explore significant effects, we did post-hoc comparisons using one-way ANOVA followed by pairwise t-tests with Bonferroni correction for multiple comparisons.

Objective 2

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. The higher the AUC, the better the predictor is at distinguishing between two clinical groups. 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 A β - healthy controls and each of the other clinical groups among A β + subjects (CN, MCI, AD), between CN and each of the more impaired clinical groups (MCI, AD), and between MCI and AD. For each analysis, the specificity corresponding to a sensitivity of 80% was reported as the optimal cut-off score for that same sensitivity.

5.3 Results

5.3.1 Study population description

We included 380 A β + subjects, distributed as follows: 31% had normal cognition (A β + /CN, n = 118), 50.3% had MCI (A β + /MCI, n = 191), and 18.7% had received a diagnosis of AD (A β + /AD, n = 71). We also included 211 A β - /CN subjects as healthy controls.

A β -/CN controls were younger than the other groups ($F(3,587) = 7.376, \eta^2 = 0.036, p < .001$) and had higher levels of education than A β +/AD subjects ($F(3,587) = 5.392, \eta^2 = 0.027, p = .001$). Women were overrepresented in the A β +/CN group (about 71%, $\chi^2 = 23.632, p < .001$). The number of APOE $\epsilon 4$ carriers differed between groups (A β -/CN < A β +/CN < A β +/MCI < A β +/AD, the latter difference not being statistically significant, $F(3,568) = 42.790, \eta^2 = 0.189, p < .001$). The MMSE, the MoCA and the RAVLT scores were significantly different between groups (A β -/CN > A β +/CN > A β +/MCI > A β +/AD, all $\eta^2 > 0.40$, all $p < .001$).

BNT and clock copy were also different between groups (BNT: $\eta^2 = 0.21, p < 0.001$; Clock: $\eta^2 = 0.21, p < 0.001$) but with no significant difference between CN and A β +/MCI subjects (A β -/CN = A β +/CN = A β +/MCI > A β +/AD). More details on the characteristics of the included subjects are presented in Table 1.

Table 1. Baseline characteristics of the participants

	A β -/CN (controls) ^a	A β + (n=380)			p
	(n=211)	A β +/CN ^b (n=118)	A β +/MCI ^c (n=191)	A β +/AD ^d (n=71)	
Age [years]	70.9 \pm 5.8 (55-89) ^{b,c,d}	73.3 \pm 6.4 (56-90) ^a	72.9 \pm 6.9 (55-87.8) ^a	74.6 \pm 7.8 (55-90) ^a	<.001*
Education [y]	16.8 \pm 2.4 (12-20) ^d	16.4 \pm 2.6 (8-20)	16.2 \pm 2.7 (9-20)	15.4 \pm 2.4 (10-20) ^a	.001*
Gender [fem]	106 (50.2%) ^b	84 (71.1%) ^{a,c,d}	86 (45.0%) ^b	31 (43.6%) ^b	<.001*
APOE [$\epsilon 4$]	45 (21.8%) ^{b,c,d}	57 (51.9%) ^{a,c,d}	125 (67.0%) ^{a,b}	53 (77.9%) ^{a,b}	<.001*
MMSE	29.1 \pm 1.1 (24-30) ^{c,d}	28.9 \pm 1.0 (26-30) ^{c,d}	27.8 \pm 1.8 (19-30) ^{a,b,d}	22.7 \pm 2.3 (18-26) ^{a,b,c}	<.001*
MoCA	26.2 \pm 2.4 (19-30) ^{c,d}	25.4 \pm 2.4 (20-30) ^{c,d}	23.3 \pm 3.3 (12-30) ^{a,b,d}	16.8 \pm 4.9 (4-25) ^{a,b,c}	<.001*
RAVLT imm	47.0 \pm 10.6 (18-71) ^{c,d}	44.7 \pm 10.0 (23-66) ^{c,d}	35.7 \pm 10.0 (14-65) ^{a,b,d}	22.1 \pm 7.3 (3-40) ^{a,b,c}	<.001*
BNT	28.4 \pm 1.9 (17-30) ^d	27.9 \pm 2.09 (20-30) ^d	26.4 \pm 3.4 (13-30) ^d	22.1 \pm 5.6 (4-30) ^{a,b,c}	<.001*
Clock copy	4.7 \pm 0.5 (2-5) ^d	4.6 \pm 0.5 (3-5) ^d	4.4 \pm 0.8 (1-5) ^d	3.3 \pm 4.14 (1-5) ^{a,b,c}	<.001*

Note. Results are given as mean \pm standard deviation (Min-Max) or as n (%). APOE: Apolipoprotein; CSF: cerebrospinal fluid; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test; BNT: Boston Naming Test; ECog: Everyday Cognition questionnaire. For the APOE genotype, the n and % represent the number and percentage of subjects presenting at least one $\epsilon 4$ allele.

5.3.2 Objective 1: Comparisons of ECog-Subject, ECog-StudyPartner and ACD by cognitive domain and clinical group

Figure 1 shows 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 clinical groups (CN/A β +, MCI/A β +, AD/A β +, and CN/A β -). The analyses for objective 1 were controlled for age, gender and education.

ECog-Subject scores

The ECog-Subject differed significantly according to the cognitive domain, regardless of the clinical group ($F(3, 1761) = 422.787$, partial $\eta^2 = .131$, $p < .001$). Post-hoc pairwise comparison showed that memory was globally the domain in which the participants reported the greatest impairment, followed by language, executive functions and finally visuospatial abilities.

The ECog-Subject score also differed significantly between the groups ($F(3, 587) = 55.175$, partial $\eta^2 = .220$, $p < .001$). A β +/CN subjects and A β -/CN controls reported complaints of similar intensity, while A β +/MCI and A β +/AD subjects reported significantly greater difficulties than the two groups of CN subjects. No difference was observed between A β +/MCI and A β +/AD subjects.

The effect of the Group*Domain interaction was significant ($F(9, 1761) = 16.761$, partial $\eta^2 = .016$, $p < .001$). More details on post-hoc analysis are presented in Table 2. Indeed, we found that the A β +/AD subjects were slightly different from the other clinical groups as they did not report a significantly higher complaint in the domain of language compared to the executive function domain.

ECog-StudyPartner scores

The ECog-StudyPartner differed significantly according to the cognitive domain, regardless of the clinical group ($F(3, 1761) = 270.578$, partial $\eta^2 = .057$, $p < .001$). 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.

The ECog-StudyPartner score also differed significantly between the groups ($F(3, 587) = 262.240$, partial $\eta^2 = .573$, $p < .001$). Post-hoc pairwise comparisons showed that study-

partners of A β + /CN subjects and A β - /CN controls globally reported complaints of similar intensity, followed by - in increasing order - A β + /MCI and A β + /AD.

The effect of the Group*Domain interaction was significant ($F(9, 1761) = 28.476$, partial $\eta^2 = .018$, $p < .001$). We observed that, among the A β + groups, only the study-partners of MCI subjects reported significantly lower complaint regarding visuospatial abilities compared to the language and executive function domains (whereas no difference was found between the three domains for the A β + /CN and A β + /AD groups).

Awareness of cognitive decline

The ACD differed significantly according to the cognitive domain, regardless of clinical group ($F(3, 1761) = 42.301$, partial $\eta^2 = .013$, $p < .001$). In the whole sample, awareness of memory and language performance was higher than awareness of visuospatial abilities and executive functions.

The ACD also differed significantly between the groups ($F(3, 587) = 75.646$, partial $\eta^2 = .279$, $p < .001$). Post-hoc pairwise comparison showed that A β + /AD subjects were significantly more anosognostic than all other groups, regardless of the cognitive domain.

The effect of the Group*Domain interaction was significant ($F(9, 1761) = 28.476$, partial $\eta^2 = .018$, $p < .001$). We observed that in A β + /AD, awareness of memory was not significantly higher than awareness of visuospatial abilities and executive functions, as it was the case in other groups.

Figure 2. ECog-Subject, ECog-StudyPartner and anosognosia by domain between clinical groups

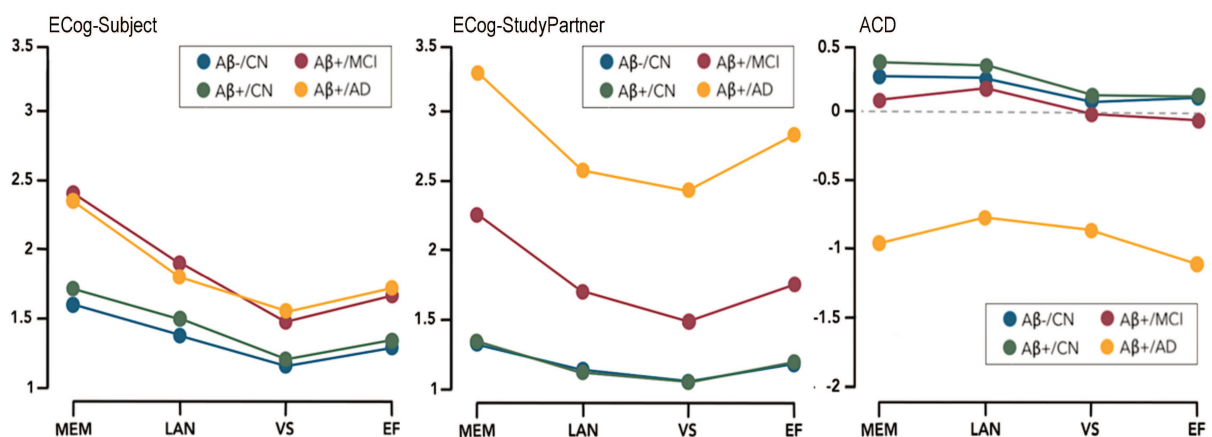


Table 2. Comparison of ECog-Subject, ECog-StudyPartner and self-awareness by domain between clinical groups

ECog-Subject						
	Memory	Language	Visuospatial Abilities	Executive Functions	<i>p</i>	Intragroup effects
Aβ-/CN	1.60 ± 0.52	1.38 ± 0.40	1.15 ± 0.27	1.28 ± 0.34	<.001	M > L > E > V
Aβ+/CN	1.71 ± 0.47	1.49 ± 0.43	1.18 ± 0.26	1.32 ± 0.32	<.001	M > L > E > V
Aβ+/MCI	2.38 ± 0.70	1.90 ± 0.68	1.48 ± 0.59	1.67 ± 0.61	<.001	M > L > E > V
Aβ+/AD	2.34 ± 0.78	1.80 ± 0.67	1.56 ± 0.58	1.71 ± 0.61	<.001	M > L = E > V
<i>p</i>	< .001	< .001	< .001	< .001		
Intergroup effects	Aβ-/CN = Aβ+/CN < MCI = AD		Aβ-/CN = Aβ+/CN < MCI = AD		Aβ-/CN = Aβ+/CN < MCI = AD	
ECog-StudyPartner						
	Memory	Language	Visuospatial Abilities	Executive Functions	<i>p</i>	Intragroup effects
Aβ-/CN	1.32 ± 0.43	1.13 ± 0.24	1.06 ± 0.16	1.17 ± 0.34	<.001	M > E = L > V
Aβ+/CN	1.33 ± 0.43	1.12 ± 0.22	1.06 ± 0.15	1.18 ± 0.33	<.001	M > E = L = V
Aβ+/MCI	2.27 ± 0.83	1.70 ± 0.69	1.48 ± 0.61	1.73 ± 0.70	<.001	M > E = L > V
Aβ+/AD	3.28 ± 0.63	2.57 ± 0.76	2.41 ± 0.84	2.81 ± 0.76	<.001	M > E = L = V
<i>p</i>	< .001	< .001	< .001	< .001		
Intergroup effects	Aβ-/CN = Aβ+/CN < MCI < AD		Aβ-/CN = Aβ+/CN < MCI < AD		Aβ-/CN = Aβ+/CN < MCI < AD	
Awareness of cognitive decline (ACD)						
	Memory	Language	Visuospatial Abilities	Executive Functions	<i>p</i>	Intragroup effects
Aβ-/CN	0.28 ± 0.55	0.25 ± 0.42	0.09 ± 0.27	0.11 ± 0.36	<.001	M = L > E = V
Aβ+/CN	0.38 ± 0.47	0.36 ± 0.41	0.12 ± 0.26	0.13 ± 0.37	<.001	M = L > E = V
Aβ+/MCI	0.10 ± 0.89	0.20 ± 0.88	0.00 ± 0.78	-0.06 ± 0.83	<.001	L > E; L > V
Aβ+/AD	-0.94 ± 1.00	-0.77 ± 0.88	-0.85 ± 0.95	-1.10 ± 0.90	.001	L > E
<i>p</i>	< .001	< .001	< .001	< .001		
Intergroup effects	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 intergroup and intragroup effects, > indicates 'significantly higher than'; < indicates 'significantly lower than', = indicates 'not significantly different'.

5.3.3 Objective 2: Discriminant value of ECog-Subject, ECog-StudyPartner and ACD 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 (pairwise discrimination between $A\beta^-/CN$, $A\beta^+/CN$, $A\beta^+/MCI$ and $A\beta^+/AD$ groups).

ECog-Subject scores

ECog-Subject scores performed globally better than chance in distinguishing between clinical groups, yet being rather poorly accurate: the highest AUC was 0.82, AUC above 0.70 were not frequent and specificities were always inferior to 70%.

Results besides show that ECog-Subject scores are rather accurate to discriminate CN groups (mostly $A\beta^-/CN$) from $A\beta^+/MCI$ and $A\beta^+/AD$ groups but can neither be used to distinguish $A\beta^-/CN$ and $A\beta^+/CN$, nor $A\beta^+/MCI$ and $A\beta^+/AD$. We can notice that ECog-Subject scores are better at discriminating CN groups from others in the memory domain than in all other domains.

ECog-StudyPartner scores

The ECog-StudyPartner was globally a better discriminator than the ECog-Subject: the highest AUC was 0.98, most of the AUC were above 0.70 and specificities could reach very high levels (99% as a maximum).

No ECog-StudyPartner score (in any cognitive domain) seems useful to distinguish $A\beta^+/CN$ and $A\beta^-/CN$ subjects (all AUC < 0.55, all specificity indices < 0.22), but all of them can discriminate MCI and AD from CN, as well as AD from MCI with a good accuracy (all AUC > 0.72). Moreover, ECog-StudyPartner scores show high specificity (> 95%) in the discrimination of AD and CN subjects in all domains.

Awareness of cognitive decline

Overall, the ACD score was a better discriminator compared to the ECog-Subject, but not compared to the ECog-StudyPartner: the highest AUC was 0.90, AUC above 0.70 were moderately frequent (half of them) and the maximum specificity was 93%.

In all cognitive domains, the ACD score allows to distinguish A β + /AD subjects from the CN and MCI subjects (all AUC > 0.76). High levels of specificity (>90%) are observed for the discrimination of AD from CN groups (both A β + and A β -) but only for ACD in the visuospatial and executive domains.

Table 3. Results of the analysis of the ROC curves.

	ECog-Subject		ECog-StudyPartner		ACD	
	AUC [95% CI]	Specificity	AUC [95% CI]	Specificity	AUC [95% CI]	Specificity
Memory						
A β + /CN vs A β - /CN	0.58 [0.51-0.64]	0.31	0.50 [0.43-0.56]	0.22	0.56 [0.49-0.62]	0.20
A β + /MCI vs A β - /CN	0.82 [0.78-0.86]	0.69	0.85 [0.82-0.89]	0.74	0.59 [0.52-0.64]	0.15
A β + /AD vs A β - /CN	0.78 [0.71-0.84]	0.59	0.98 [0.97-0.99]	0.99	0.85 [0.79-0.91]	0.73
A β + /MCI vs A β + /CN	0.78 [0.73-0.83]	0.57	0.85 [0.81-0.89]	0.79	0.62 [0.56-0.68]	0.15
A β + /AD vs A β + /MCI	0.49 [0.40-0.57]	0.14	0.82 [0.77-0.88]	0.73	0.77 [0.70-0.83]	0.52
A β + /AD vs A β + /CN	0.74 [0.66-0.81]	0.46	0.98 [0.97-0.99]	0.99	0.88 [0.82-0.93]	0.76
Language						
A β + /CN vs A β - /CN	0.57 [0.51-0.64]	0.30	0.49 [0.44-0.55]	0.21	0.58 [0.51-0.64]	0.27
A β + /MCI vs A β - /CN	0.75 [0.69-0.79]	0.54	0.79 [0.76-0.84]	0.63	0.49 [0.43-0.55]	0.03
A β + /AD vs A β - /CN	0.69 [0.61-0.76]	0.42	0.97 [0.95-0.99]	0.98	0.84 [0.77-0.90]	0.61
A β + /MCI vs A β + /CN	0.69 [0.63-0.75]	0.41	0.81 [0.75-0.85]	0.63	0.56 [0.49-0.62]	0.14
A β + /AD vs A β + /MCI	0.55 [0.47-0.62]	0.17	0.80 [0.75-0.86]	0.67	0.78 [0.72-0.84]	0.57
A β + /AD vs A β + /CN	0.63 [0.54-0.71]	0.30	0.97 [0.95-0.99]	0.98	0.88 [0.81-0.93]	0.72
Visuospatial Ability						
A β + /CN vs A β - /CN	0.57 [0.50-0.63]	0.25	0.55 [0.49-0.62]	0.22	0.56 [0.49-0.62]	0.22
A β + /MCI vs A β - /CN	0.67 [0.62-0.73]	0.30	0.73 [0.68-0.77]	0.36	0.54 [0.48-0.60]	0.08
A β + /AD vs A β - /CN	0.73 [0.66-0.80]	0.58	0.95 [0.91-0.98]	0.97	0.84 [0.77-0.91]	0.92
A β + /MCI vs A β + /CN	0.64 [0.58-0.69]	0.24	0.72 [0.66-0.77]	0.32	0.57 [0.50-0.63]	0.09
A β + /AD vs A β + /MCI	0.55 [0.47-0.63]	0.29	0.81 [0.76-0.87]	0.66	0.76 [0.69-0.83]	0.64
A β + /AD vs A β + /CN	0.69 [0.61-0.77]	0.52	0.95 [0.91-0.98]	0.98	0.85 [0.78-0.92]	0.93
Executive Functions						
A β + /CN vs A β - /CN	0.55 [0.49-0.61]	0.30	0.49 [0.43-0.55]	0.20	0.55 [0.48-0.61]	0.28
A β + /MCI vs A β - /CN	0.72 [0.67-0.77]	0.52	0.81 [0.76-0.85]	0.64	0.59 [0.52-0.64]	0.11
A β + /AD vs A β - /CN	0.72 [0.65-0.79]	0.52	0.97 [0.94-0.99]	0.98	0.90 [0.84-0.95]	0.92
A β + /MCI vs A β + /CN	0.68 [0.62-0.74]	0.44	0.80 [0.75-0.85]	0.66	0.61 [0.54-0.66]	0.14
A β + /AD vs A β + /MCI	0.52 [0.44-0.60]	0.20	0.85 [0.80-0.90]	0.74	0.80 [0.74-0.86]	0.68
A β + /AD vs A β + /CN	0.69 [0.61-0.77]	0.44	0.96 [0.94-0.99]	0.95	0.90 [0.84-0.95]	0.90

Note. AUC: Area Under the ROC. CI: Confidence Interval. Specificity: Specificity at sensitivity = 0.80; ACD: Awareness of Cognitive Decline. To facilitate understanding of the table, all AUC > 0.70 are in bold following Hosmer & Lemeshow guidelines for interpreting AUC (2000), according to which AUC < 0.70 indicates inaccurate discrimination.

In this study we investigated the degree of domain-specific cognitive decline across the AD spectrum (more precisely, amyloid-positive individuals ranging from normal cognition to dementia) using three sources of information: self-reported complaint, informant-reported complaint, and the discrepancy between these two reports as a measure of awareness of cognitive decline (ACD). We aimed at describing differences between cognitive domains and clinical groups, depending on the source measure of cognitive decline. We also investigated the capacity of each source of information across the different domains to discriminate the different clinical groups.

5.4.1 Subject's and study-partner's complaints and ACD by group and cognitive domain

Subjects and study-partners from all groups reported that memory was the domain in which participants had the most difficulty, followed by language, executive functions, and finally visuospatial abilities. In fact, memory is the most impaired cognitive domain in typical AD (Sarazin et al., 2010), and it is not surprising that complaints mostly related to memory. Language and executive disorders also 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). Subjects and study-partners from all groups reported visuospatial disorders to be the least intense. Indeed, visuospatial disorders, such as difficulty in the spatial localization of objects, generation of mental pathways, and spatial navigation, occur later in the course of the disease (e.g., Millet et al., 2009; Cushman & Duffy, 2007; Cherrier et al., 2001). In our study, A β + /CN and A β + /MCI subjects performed similarly to healthy controls on the clock copy test, while only subjects with dementia performed significantly worse. Recent studies show that mild visuospatial disorders can 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 him/her may not recognize in daily life until that they become more severe.

Another interesting result that we obtained is that cognitively-normal amyloid-positive individuals expressed more marked memory and language complaints than their informants. This could mean that individuals with high levels of cerebral amyloid perceive a subtle decline in memory and language that their informant does not notice. This heightened ACD is known as *hypermnesia* (Vannini et al., 2017) and could represent an indicator of the disease before the onset of objective symptoms. However, it should be noted that even healthy controls tended to underestimate their memory and language performance. This seems to suggest that this behavior is not specific to preclinical AD, but is also present in healthy controls.

Finally, MCI and AD subjects expressed similar levels of cognitive complaints, while, as expected, objective cognitive impairment was significantly different between the groups in every neuropsychological test considered (AD > MCI > CN). Similarly, study-partners of CN and MCI subjects reported complaints of similar intensity, while study-partners of AD subjects reported greater difficulties. This is in agreement with the concept of *petrified self* (Mograbi, Brown and Morris, 2009), according to which AD patients' self-assessment is petrified or anchored to their pre-morbid abilities. They may recognize their cognitive errors soon after they are made, but the knowledge about these failures only partially and temporarily incorporates their self-knowledge (Mograbi et al., 2009; Kalenzaga & Clarys, 2013). Thus, the subjective perception of decline would not coincide with the actual progression of cognitive impairment. This suggests different discriminative utilities of the three investigated sources measuring cognitive decline.

5.4.2 Discriminant value of different assessments of cognitive decline across domains

Self-report of decline, regardless of the cognitive domain considered, was the least accurate measure in distinguishing clinical groups. The self-report could not discriminate amyloid-positive CN participants (at risk for preclinical AD) from controls. This means that cognitive complaint is nonspecific and common even among healthy subjects, consistent with previous studies that have found that most healthy elderly express some degree of cognitive impairment (Jessen et al., 2010; van Harten et al., 2018). This may be related for example to anxiety, depression, medication intake, age-related cognitive changes (Buckley et al.,

2013). Among the four domains, the self-reported memory complaint was relatively more accurate than the other domains in distinguishing individuals at different stages of the disease, but still not sufficiently to allow for good discrimination.

The informant-report was the best measure in discriminating clinical groups, although it could not distinguish A β + /CN from A β - /CN participants. The informant's report therefore appears not to be sufficiently accurate to detect the disease when cognitive decline is still subtle, that is, when cognitive functioning, although declining, continues to be within a normal range for age and level of education (as found in preclinical AD, Sperling et al., 2011; Jack et al., 2018). However, informant's report becomes a reliable source of information when it comes to detecting the disease in individuals with objective but mild disorders, which do not yet have an impact on autonomy (i.e., MCI). This supports the importance of including study-partners in studies targeting predementia AD, as well as in clinical practice for both diagnosis and patient follow-up. Previous studies found that informant-report would be accurate although it may be biased by factors such as anxiety, depression, caregiver burden, or personality traits. In a study by Cacchione et al. (2003) the accuracy of the informant-report 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. 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 level of ACD discriminated only dementia from CN and MCI participants, confirming the presence of frank anosognosia in AD dementia. In our study, participants with MCI and their study-partner reported similar levels of cognitive decline across all domains, meaning they did not show anosognosia. The degree of ACD of patients with MCI is heterogeneous across studies. Some authors found that MCI subjects show marked cognitive complaints (more marked than informants' complaints) (e.g., Piras et al., 2016; Kalbe et al., 2015), while others found mild anosognosia (e.g., Cacciamani et al., 2021; Hanseeuw et al., 2020; see Chapter 7). These conflicting findings on anosognosia in MCI are likely due to the heterogeneity of the concept of MCI itself (see 2.3.1), in addition to a known inter-individual variability in the

rate of disease progression and in the ordering of symptom onset (Goyal et al., 2008). In our study, the ACD measure discriminated worse A β + /CN participants from A β - /CN, and the two CN groups from MCI participants, than the informant-report alone. It would be interesting to understand if ACD can better discriminate patients with different pathologies than informant-report. 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 et al., 2007), identifying a certain degree of anosognosia could be useful in the differential diagnosis.

Limitations and concluding remarks

This study has some limitations. First, it was not possible to use the level of tau protein as very few subjects had the dosage of tau in CSF available. 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). Second, we have no information about the study-partner, for example the degree of kinship with the subject, how long he/she has known the subject and how much time he/she spends with him/her. Finally, the diagnosis of MCI and AD in the ADNI cohort is made on the basis of memory complaints and memory scores. This may have had an impact on the results of the study of complaints and ACD by cognitive domain.

Despite these limits, our results can have interesting applications for clinical practice. They highlight the limitations and benefits of 3 sources of information that are valuable to the clinician, namely subject's complaint, informant's complaint, and concordance or discrepancy between the two (as a measure of ACD), all relating to different cognitive domains. The inclusion of an informant seems to be an important added value for an accurate, early diagnosis. It is also useful in monitoring patients' disease staging. The patients him/herself, on the contrary, is less accurate in his/her report and may tend to both overestimate his/her abnormal performance (as a form of anosognosia) or underestimate his/her 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 information to the clinician. 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 questions, relating to the different cognitive domains, to ask the subject and the informant in order to early detect the disease. In fact, previous studies have shown that the most informative questions are not only related to episodic memory but also to other cognitive domains (Snitz et al., 2012).

The MMR: a new cohort-independent measure of ACD 6

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The diversity of methodologies for calculating and analyzing ACD in early-stage AD can contribute to clouding understanding of awareness disorders (see 2.2.2 for a summary of the ACD assessing methods). The subject-informant discrepancy is one of the most widely used methods as it has obvious advantages in terms of ease, speed and cost. However, an informant is not always available or reliable, both in research protocols and in clinical practice. A valid alternative is the subjective-objective score discrepancy. This is the comparison between (i) the score on a questionnaire that asks the participant to assess his/her current cognitive functioning and (ii) the actual cognitive functioning as measured by objective tests.

It is common practice to calculate the subject-informant discrepancy by subtraction. In fact, the subject and the informant fill in two identical questionnaires, and therefore the two scores are comparable. In the case of the subjective-objective score discrepancy, on the contrary, the two scores (subjective and objective) will not be on the same scale. It is therefore necessary to transform them to make them comparable. In a study by Vannini and collaborators (2017), for example, the two raw scores were converted to z-scores for each subject, using the mean and SD from the control group. The authors then subtracted one score from the other. In another study (O'Connell, Crossley, & Morgan, 2014), the two scores were transformed into a linear scale ranging from 1 to 5, with 1 indicating the lowest

memory self-assessment and poorest memory performance. The measure of awareness was created on the basis of the congruence between the two, with 5 indicating perfect congruence. The procedure used in the various studies to calculate this score is therefore inhomogeneous.

6.1 Aims

1. To create a cohort-independent procedure to assess ACD using any subjective and objective score of cognitive functioning
2. To validate this procedure by using it to study ACD in preclinical AD

6.2 Methods

6.2.1 Participants

We analyzed data from two cohorts, INSIGHT-PreAD and ADNI.

In short, the INSIGHT-PreAD cohort (Dubois et al., 2018) includes cognitively-intact elderly memory-complainers. For the present study, some participants were excluded from the original sample (i.e., 1 participant due to missing metabolic imaging, 1 due to missing memory scores, 24 due to missing questionnaires). In addition, two outliers (i.e., 1 on a memory score, 1 on brain metabolism) were also removed from the sample. Our final sample included 290 participants from the INSIGHT-PreAD cohort.

From the ADNI cohort, we included only participants with SCD (i.e., tagged as Significant Memory Concern), in order to be fully comparable to INSIGHT-PreAD participants. These are subjects with normal cognition ($MMSE \geq 24/30$; normal Logical Memory Delayed Recall, $CDR = 0$) and memory concerns (Cognitive Change Index, sum of the first 12 items $> 12/16$) (Dubois et al., 2018). We identified 277 participants meeting these criteria. We excluded the

participants with missing data, and a total of 158 participants from ADNI cohort were retained in the final sample.

Our final sample consisted of 448 CN participants with SCD. We used only baseline data.

6.2.2 Development of the MMR

Objective memory assessment

In this study, we have chosen to focus on memory. Indeed, recent research shows that the subtle memory decline occurring in preclinical AD would be among the earliest to evidence of a transition to a subsequent prodromal AD (Bateman, 2012; Elias, 2000; Grober, 2008). Therefore, we selected three episodic memory scores: the Free and Cued Selective Reminding Test (FCSRT), the Delayed Matched to Sample test 48 items (DMS48), and the Rey-Osterrieth Complex Figure (ROCF). For the FCSRT, we selected both immediate and delayed total free recalls (FR) and total recalls (i.e., FR + cued recalls; TR), the number of intrusions and perseverations. For both visual tests (i.e., DMS48 and ROCF), we used immediate and delayed memory measures.

For the ADNI cohort, we selected three memory tests, namely the Rey Auditory Verbal Learning Test (RAVLT, “immediate,” “forgetting,” and “learning” scores), the Logical Memory II (LMII) test from the Wechsler Memory Scale, and the Q4 (memory) score from the Alzheimer Disease Assessment Scale (ADAS-Cog).

Subjective cognitive assessment

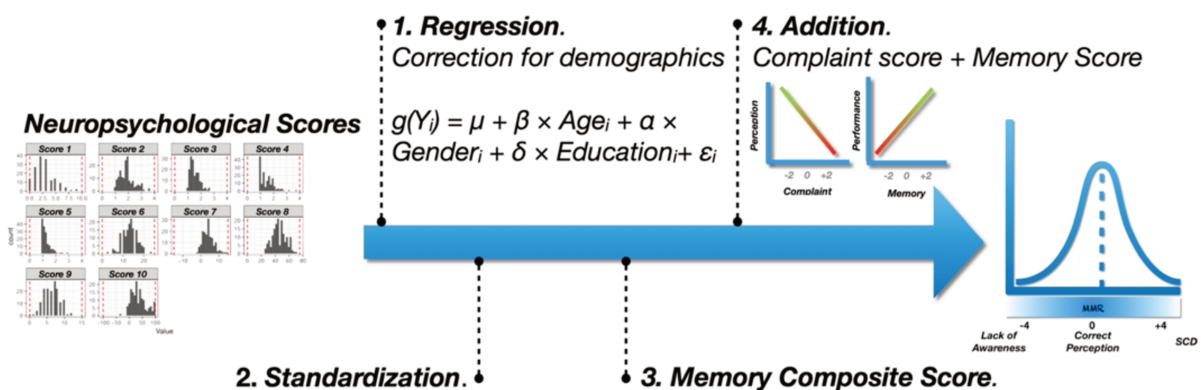
For the INSIGHT-PreAD cohort, we used the cognitive subscale of the Healthy Aging Brain Care – Monitor questionnaire (Monahan et al., 2012; Monahan et al., 2014). This questionnaire asks subjects to rate the frequency of occurrence of certain cognitive disturbances during the last two weeks, i.e., from 0 “not at all (0–1 day)” to 3 “almost daily (12–14 days)”. The HABC-M cognitive scale consists of 6 items, the majority of which are related to the memory domain. The total score ranges from 0 to 18.

For the ADNI cohort, we used the memory subscale of the Everyday Cognition questionnaire (E-Cog) score (Farias et al., 2008). These questions ask the participant to compare his/her current memory ability in everyday tasks to that of 10 years ago. The estimate is based on a 4-point scale from 1 (“Better or no change”) to 4 (“Consistently much worse”). A “Do not know” answer is also possible. The total score then ranges from 8 to 32. Higher scores indicate that the participant perceives a more marked cognitive decline.

The meta-memory ratio

To compute the awareness score, the same procedure was implemented independently in each cohort (Figure 1).

Figure 1. Development of the MMR



Note. Figure from Gagliardi et al. 2020

First, since the two samples had different demographic distributions and these variables can be associated with the scores of interest, we started by removing their impact on the scores. Each score of interest (i.e., memory performances and SCD questionnaires) was integrated into a generalized linear model (GLM), as a dependent variable. Demographic variables (i.e., age, gender and socio-cultural level) were included as covariates, to correct for their potential effects. For each measure, the type of model used was selected according to the distribution of each score (i.e., linear regressions for ROCF, E-Cog, immediate RAVLT, and ADAS-Q4; logistics for FCSRT intrusions and perseverations; and binomial for the other

measures mentioned). Subsequently, we extracted the model residuals to obtain objective and subjective measures of decline net of these effects.

Secondly, we computed a composite score of memory functioning by averaging all memory scores collected for each subject. These scores had previously been centered and reduced in order to make them comparable (i.e., z-score transformation). The choice of relying on a composite score rather than choosing a single memory score addressed two needs. It allowed us not to select a certain score *a priori*. In addition, the use of a composite score also allowed to gather variables that are thought to measure the same cognitive construct (Hendrix, 2012). We would have used this procedure also for complaint measures, if the cohorts had included more than one questionnaire.

Thirdly, we transformed the memory composite and the E-Cog score to get two scores ranging from -2 (worst memory performance or lowest subjective rating) to 2 (excellent memory performance or best subjective rating).

Finally, we added these two scores. The MMR therefore ranges from -4 to 4. An MMR close to -4 indicates very poor awareness (or anosognosia). An MMR close to 0 indicates normal awareness, i.e., a good match between subjective rating and objective performance. And an MMR close to 4 indicates a marked memory complaint while the actual memory performance is not affected as much.

6.2.3 Brain imaging acquisition and processing

Amyloid PET imaging

In the INSIGHT-PreAD cohort, participants underwent PET with a florbetapir tracer [¹⁸F-Florbetapir, AmyvidTM, Avid Radiopharmaceuticals]. A standardized uptake value ratio (SUVr) was calculated with the CATI pipeline (Centre d'Acquisition et de Traitement d'Images, <https://cati-neuroimaging.com>), with a focus on selected target regions (i.e., bilateral precuneus, anterior and posterior cingulum, temporal cortex and orbitofrontal). Details of the imaging procedure and threshold calculations have previously been presented (Dubois et al., 2018, Habert et al., 2018). For ADNI participants, we selected those with SUVr values calculated using the same radiotracer (i.e., florbetapir). The details of both imaging procedures are presented in supplementary materials.

To make the two cohorts neuroimaging features comparable, we normalized the SUVR using the respective amyloid positivity threshold of each cohort. To do so, we divided the SUVR of each participant by the positivity threshold, i.e., 0.79 for the INSIGHT-PreAD cohort and 1.11 for ADNI. Thus, any normalized SUVR above 1 could be considered significantly pathological (i.e., amyloid-positive patients).

FDG-PET imaging

For both cohorts, we calculated a mean metabolism index using fluorodeoxyglucose positron emission tomography (FDG-PET) by averaging the regions of interest (ROIs) of AD, namely the posterior cingulate cortex, inferior parietal lobule, precuneus, and inferior temporal gyrus (Landau et al., 2011). Then, since the FDG-PET did not have an established cutoff, we normalized this meta-ROI using a centered-reduced method (i.e., intra-cohort z-score transformation). As for amyloid PET imaging, details are available in supplementary materials.

Statistical analysis

The different scores of interest (MMR, complaint and memory) and demographic variables were compared between the two cohorts using Welch's t tests for the numerical variables and a χ^2 test for the gender variable.

MMR scores were normally distributed. In order to evaluate the influence of AD biomarkers on awareness, we computed a linear regression model with the MMR as dependent variable. To account for the specific effect of each biomarker, amyloidosis (AV45-PET) and metabolism (FDG-PET) were both included in the model. We also included interactions between the "cohort" effect and biomarkers to determine whether the effect of biomarkers varied across cohorts. Finally, we adjusted the results including demographic (i.e., age, gender and education) and the cohort variables as covariates.

Looking at the scatterplot between MMR and AV45-SUVr, we identified a non-linear effect of amyloid on the MMR. Therefore, we added a quadratic effect of amyloid to the models. The main effects and interactions (both with linear and quadratic effect) were tested via the

likelihood ratio test type II. Normality of residuals and heteroskedasticity were checked visually. Cook's distances and hat values were computed to investigate potential influencers and outliers. We also performed these computations with an additional group of cognitively normal (CN, that is normal cognition without cognitive complaint) from ADNI without anosognosia (data not shown). Finally, the same analysis was performed with an MMR calculated from a single rather than a composite memory score. These results can be found in supplementary material.

Statistical analyses were performed using R 3.5.2 (<https://www.R-project.org/>). An R package was developed (<https://github.com/GagGeo/MMAD>).

6.3 Results

6.3.1 Inter-cohort comparisons

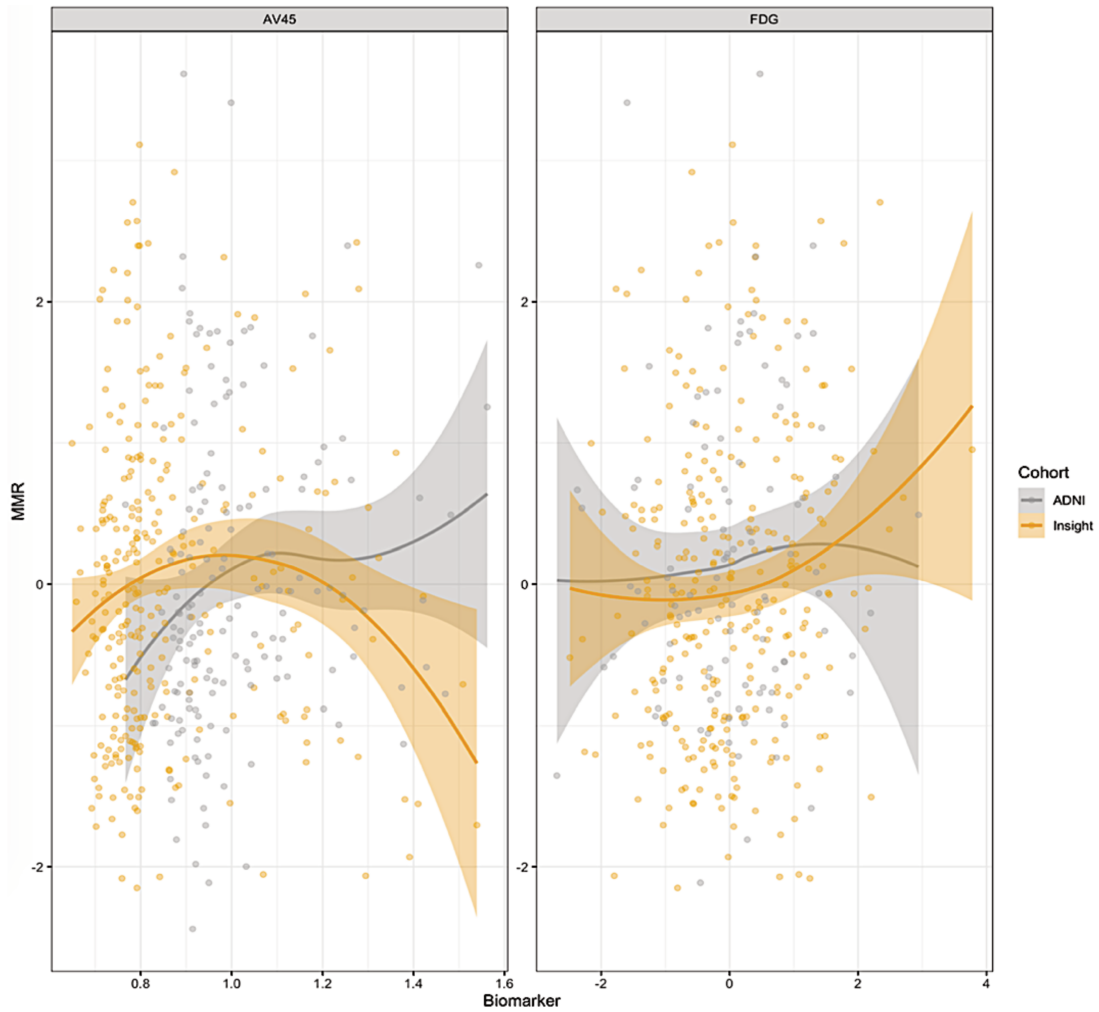
ADNI participants were younger (72.0 ± 5.8 vs 76.0 ± 3.5), had higher education (99% vs 67%) and higher amyloid load (1 ± 0.2 vs 0.9 ± 0.2) than INSIGHT-PreAD subjects (Table 1). Overall, imaging variables appeared to be normally distributed across the two cohorts (Figure 2).

Table 1. Comparison of the two cohorts

	ADNI (N = 158)	INSIGHT-PreAD (N = 290)	T/ChiSq	Pval
Age	71.97 ± 5.79	76.02 ± 3.5	-8,03	<0.001*
Gender (F)	95 (60.1%)	183 (63.1%)	0,27	0.604
Education (H)	157 (99.4%)	196 (67.6%)	59,94	<0.001*
AV45	1.01 ± 0.16 [0.77;1.56]	0.86 ± 0.17 [0.65;1.54]	9,42	<0.001*
FDG	0 ± 1 [-2.69;2.94]	0 ± 1 [-2.49;3.78]	0	1.000
Memory	0 ± 0.38 [-0.93;1.41]	0 ± 0.54 [-1.97;1.23]	0,04	0.970
Complain	0 ± 1 [-1.86;3.21]	0 ± 1 [-1.26;3.41]	0	1.000
Informant	0 ± 1 [-1.31;4.41]	0 ± 1 [-0.97;4.59]	0	1.000
MMR	0 ± 1.07 [-2.44;3.61]	0 ± 1.08 [-2.15;3.11]	0,02	0.988

Note. Mean ± standard deviation [minimum, maximum] or N (%)

Figure 2. Comparison of the relative effect of biomarkers on MMR by cohort.



6.3.2 MMR models

The model (Figure 3) showed a slight association between metabolism and awareness measures. In particular, the MMR decreased with decreasing brain metabolism. This trend, however, was not statistically significant ($p = 0.063$). Regarding amyloid load, we found a significant combined (linear and squared; $p = 0.035$) effect on the MMR score. In the curve of this quadratic effect, an inflection point is observed at a normalized SUVr value of 1.09.

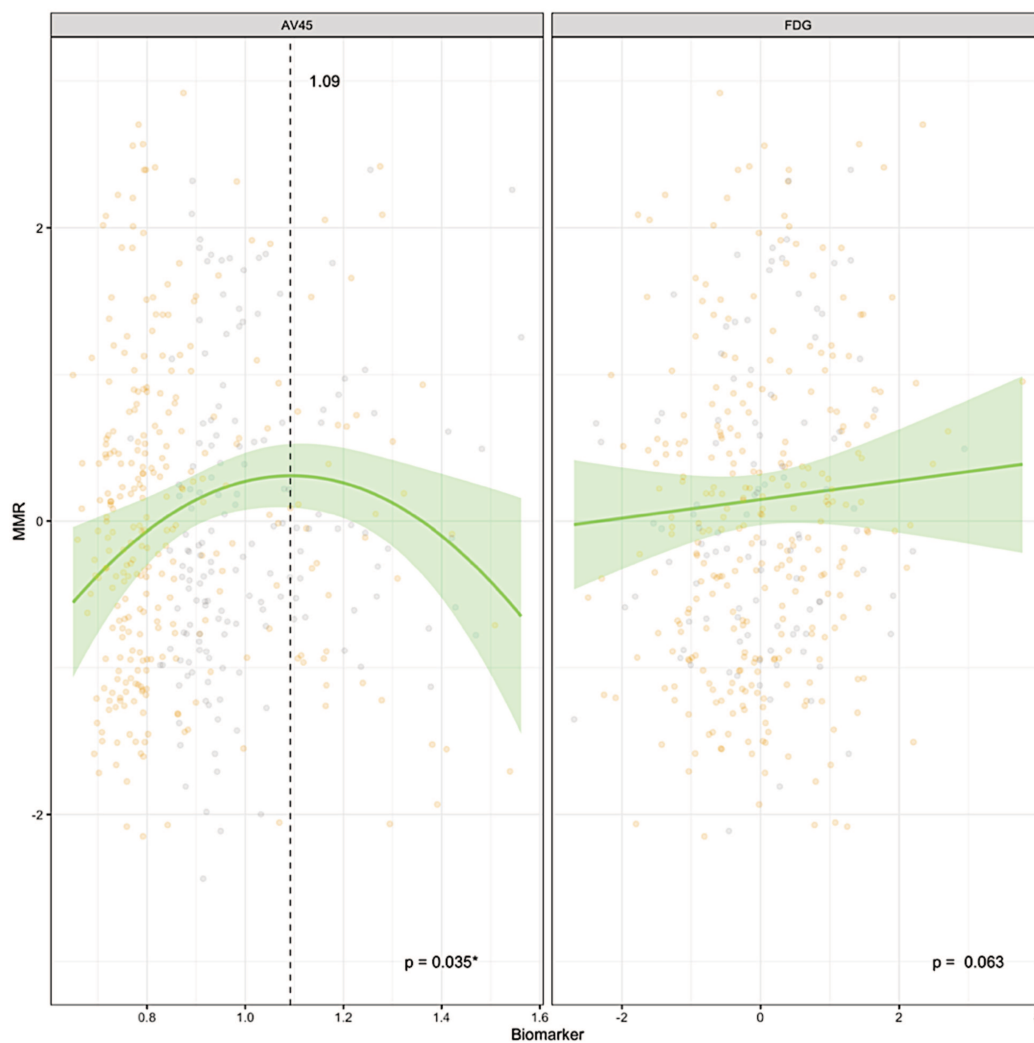
We did not find any significant differences of the cohort variable nor for the interactions (all $p > 0.05$), indicating that the effect of the biomarkers was not statistically different on MMR in the two cohorts (Table 2).

Table 2. Results of linear models

Measures	Coefficients \pm SE	ESs	Pvalue
Intercept	-4.67 \pm 2.3	<0.001	
Age	-0.01 \pm 0.01	<0.001	0.267
Gender (M)	0.03 \pm 0.12	<0.001	0.714
Education (Lower)	0.13 \pm 0.14	<0.001	0.334
Cohort (ADNI)	1.51 \pm 0.92	<0.001	0.385
FDG	0.96 \pm 1.38	<0.001	0.063
AV45		-0.007	0.035*
Linear	10.31 \pm 3.69		
Squared	-4.37 \pm 1.6		
AV45:FDG	0.87 \pm 1.26	<0.001	0.787
AV45:Cohort (ADNI)	-1.52 \pm 0.91	<0.001	0.578
FDG:Cohort (ADNI)	0.01 \pm 0.15	<0.001	0.450

Note. Coefficients and standard errors were extracted from complete LMs with all interactions. For each categorical effect, the reference category is given in bracket. SE: standard errors; ESs: effect sizes (Cohen's f^2)

Figure 3. Effect of amyloid burden on MMR in the whole sample.



When a CN group without cognitive complaint was added, the results were also not showing any variable effect between the different groups. However, this significant effect (amyloid) and trend (metabolism) was no longer present, as the addition of the no-complaint group masked the effects observed in the previous samples (all $p > 0.05$; data not shown).

6.4 Discussion

We have developed the meta-memory ratio (MMR), which provides a continuous measure of the awareness of memory performance. We implemented it in two samples, the INSIGHT-PreAD cohort and SCD participants from ADNI, in order to assess its trans-cohort applicability. The MMR has the advantage of being easy to compute (with an R package available) and is potentially applicable in any cohort that has at least a cognitive score and a self-rating measure of cognitive functioning.

The regression between MMR and AD biomarkers (i.e., amyloid load and brain metabolism) showed a significant quadratic effect of amyloid load: the MMR scores increased, indicating a complaint without objective decline, with increasing amyloid load, up to a certain threshold, above which the increase in amyloid load was associated with a lower MMR score, indicating a decline in the ACD. This is consistent with previous studies indicating that both SCD and low ACD could be associated with a greater risk of AD pathology (Cacciamani et al., 2017; Glodzik-Sobanska et al., 2007; Reisberg et al., 2010). These findings may appear contradictory. However, they can be understood as two successive chronological phases. Indeed, our results are in line with the aforementioned study by Vannini and colleagues (2017) proposing that, at the preclinical stage, a hyper-vigilance towards otherwise undetected cognitive difficulties (i.e., *hypernosognosia*) would precede subsequent low ACD. Individuals with hypernosognosia would be at an early stage of the disease, before the decrease in ACD. Interestingly, with the inflection point at 1.09, the disorder appears to progress to low ACD as participants become amyloid-positive. Previous studies had already shown a link between amyloidosis and anosognosia in MCI populations

(Therriault et al., 2018, Vannini et al., 2017). The present study demonstrated this relationship in CN individuals.

These results have strong implications in both research and clinical practice. Indeed, some consider that the appearance and aggravation of a complaint could be used as a marker of risk of having AD lesions (Glodzik-Sobanska et al., 2007). However, our study showed that the accumulation of amyloidosis initially leads to increasing complaints, eventually turning into poor awareness. Thus, the presence of persistent cognitive complaints should not be considered as indicative of AD, but due to other etiologies (Jessen et al., 2014; Rabin et al., 2015). Even in the presence of amyloid accumulation, cognitive complaints should be considered as a minor risk for AD. Indeed, some studies showed an increase in amyloid burden with advancing age (Jack, 2014), regardless of whether or not there is a subsequent conversion to AD. Demonstrating that the decrease in awareness takes place beyond the amyloid-positivity threshold, it seems that low awareness, rather than complaints, should be taken as marker of AD. Taken together, our results seem to validate the chronological models mentioned above, which assumes an increase and then a decrease in the ACD during the evolution towards the diagnosis of AD (Vannini et al., 2017).

In the present study, we also identified a slight (not significant) effect of metabolism on ACD (i.e., higher metabolism resulting in a higher MMR score). There are several possible reasons. To begin with, since amyloid is the first biomarker to accumulate (Jack et al., 2010), hypometabolism only occurs later. Demonstrating a relationship between amyloidosis but not neurodegeneration (represented here by hypometabolism), these data could mean that awareness disorders may be earlier than variations in brain metabolism. In addition, we analyzed mean metabolic indices in AD ROIs, selected from previous research for their sensitivity and specificity in clinical AD (Landau, 2011). Awareness has often been associated with cortical midline structures (Perrotin et al., 2015), as well as right prefrontal regions (Antoine et al., 2004). For instance, a recent study conducted as part of the INSIGHT-PreAD study found that low awareness was related to lower brain metabolism in a fronto-temporo-parietal network (Cacciamani et al., 2017). This network does not overlap with the ROIs considered in this study. Traditionally, AD symptoms have been attributed to tauopathy (Giannakopoulos et al., 2009). However, at this preclinical stage, tauopathy is

mainly localized in the mesial temporal regions (Braak et al., 2011), and it is probably subtle, given the absence of significant memory deficits. Amyloidosis, on the other hand, begins to accumulate upstream (Jack et al., 2010; Jansen, 2018) notably in prefrontal regions which seems to be related to awareness (Stuss et al., 2001, Antoine et al., 2004). This may explain the stronger relationship of MMR with amyloid load than with metabolism.

In this study, we compared objective performance with the subjective perception of participants. As explained above, other methods exist to evaluate ACD. It would be interesting to directly compare the MMR methodology to existing assessment methods.

We selected participants with subjective cognitive complaint and normalized their scores (subjective and objective) on the basis of the sample they belonged to. As a result, some participants could obtain a low relative complaint score. Similarly, we interpret lower scores on the MMR as signs of low ACD. It could be suggested that low ACD is inconsistent with the presence of SCD. However, ACD is defined in relation to the reference sample.

Limitations

There are some limitations to our study. First, despite our efforts to make the measures comparable with each other, the scores used to compute the MMR are not exactly the same in the two cohorts, and they might involve slightly different cognitive processes. Second, the cohorts varied on two of the three demographic variables considered, with INSIGHT-PreAD participants being older and proportionally less educated. Among the participants in the ADNI cohort, only one individual had a level of education of less than 12 years. This overrepresentation of graduates does not seem to be in line with the general population proportions, which raises the question of the generalization of the results. Indeed, the research on the concept of cognitive reserve has shown a significant effect of education on the clinical expression of brain damage (Prince et al., 2013, Jansen et al., 2018). Third, a higher proportion of positive amyloid participants (i.e., normalized AV45-SUVr ≥ 1) is found in ADNI than in INSIGHT-PreAD. Fourth, the construction of the MMR involved a pre-processing of the data whereby participants were ranked according to their relative

performance in their sample. In doing so, it was assumed that individuals with low levels of functioning might show a decline from prior normal function. However, despite the normalization of scores, it is possible that these are simply life-long low performers. This limitation could be controlled by a longitudinal study of the MMR and its evolution. Fifth, amyloid load was normalized using cohort positivity thresholds. This method is less accurate than the Centiloid scale (Klunk, 2015). However, Habert and colleagues showed a strong correlation between the Avid (used in ADNI) and CATI (used in INSIGHT-PreAD) methods ($r = 0.9$). We thus considered our SUVR normalization as an acceptable approximation, with improved processing time and simplicity (Habert et al., 2018).

Conclusion

The MMR has demonstrated its trans-cohort applicability. Using this methodology, we observed a quadratic relationship between ACD and cerebral amyloidosis. The more cerebral amyloidosis our participants had, the more they expressed cognitive complaints up to a certain threshold beyond which this tendency reversed. Future studies should include the MMR in longitudinal analyses to focus on the ACD evolution and to validate this chronological model. Similarly, further studies are needed to determine the sensitivity and specificity for AD of decreased ACD versus SCD. This question can be examined both through the use of research cohorts (e.g., ADNI, INSIGHT-PreAD), clinical cohorts (e.g., Subjective Cognitive Impairment Cohort – SCIENCE), or in general population studies (e.g., Wisconsin Registry for Alzheimer’s Prevention – WRAP–, Mayo Clinic Study of Aging – MCSA).

Overall, our results promoted the value of assessing ACD in elderly CN individuals as a measure of the risk of conversion to later clinical AD. Therefore, the inclusion of a measure of ACD would be valuable in cohorts targeting preclinical AD as an enrichment variable.

The ACD in prodromal AD: 7 a meta-analysis

Published as: Cacciamani, F., Houot, M., Gagliardi, G., Dubois, B., Sikkes, S., Sánchez-Benavides, G., Denicolò, E., Molinuevo, J. L., Vannini, P., & Epelbaum, S. (2021). Awareness of Cognitive Decline in Patients With Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Frontiers in aging neuroscience*, 13.

The changes in ACD are gradual, as is the accumulation of brain damage and the progression of the disease. There are few studies to date that have attempted to establish at what point in the course of the disease patients begin to underestimate his/her decline, and at what moment that begin to be frankly anosognostic. According to a recent study (Hanseeuw et al., 2020), the hyperanosognosia phase would end about a year and a half before the diagnosis of MCI and the onset of anosognosia would begin during the prodromal phase (3 years before dementia). However, as already mentioned in the Introduction (see 2.3.3), the degree of awareness in individuals with MCI is still debated (Piras et al., 2016).

7.1 Aims

1. To understand whether there is evidence of poor ACD in prodromal AD, and therefore whether it can be used as an early indicator of AD;
2. To qualitatively summarize the main results obtained for a better understanding of the neural and clinical correlates of ACD in prodromal AD, and of the association between degree of ACD and risk of progression to AD dementia.

7.2.1 Search strategy and study eligibility criteria

The 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 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 expressed as mean and standard deviation (SD) or as percentage of subjects with intact and impaired ACD. 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. Therefore, we have established that subjects must be (at least one): (i) diagnosed with prodromal AD, (ii) diagnosed with 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., amnesic or non-amnesic).

We imposed no demographical restrictions. Articles must be in English or French.

7.2.2 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.

7.2.3 Data collection process and data items

We used an information extraction 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 study, we recorded:

- (a) aim
- (b) sample size
- (c) diagnostic classification of the participants
- (d) mean age
- (e) mean MMSE
- (f) range of the MMSE (min-max) when available
- (g) mean years of education
- (h) percentage of men
- (i) measure used to assess ACD
- (j) statistical model performed
- (k) key findings relevant for this review

For studies treating the measure of ACD as a continuous variable, we also extracted:

- (l) mean ACD of each clinical group
- (m) standard deviation (SD) for each clinical group
- (n) size of the whole sample
- (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.

For studies treating the measure of ACD as a categorical variable, we extracted:

- (p) percentage of subjects with impaired ACD of each clinical group
- (q) size of the whole sample
- (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.

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

7.2.4 Summary measures

We decided a priori to conduct a meta-analysis when at least three articles compared the same pair of clinical groups. 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, Breslow and Greenland, 1986) and converted it to Hedges' *g* estimate (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.

7.2.5 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; (iii) absence of evidence of abnormal AD biomarkers in case of MCI diagnosis; (iv) heterogeneity in the definition of prodromal AD.

7.3 Results

7.3.1 Study selection

The bibliographical search yielded 662 citations (Figures 1 and 2), published between 1991 and August 2020. Of these, 644 did not meet the eligibility criteria and were excluded. 18 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. These studies compared ACD between clinical groups: controls, amnesic MCI, non-amnesic MCI, mild AD.

Figure 2. Flow diagram for study selection and analysis.

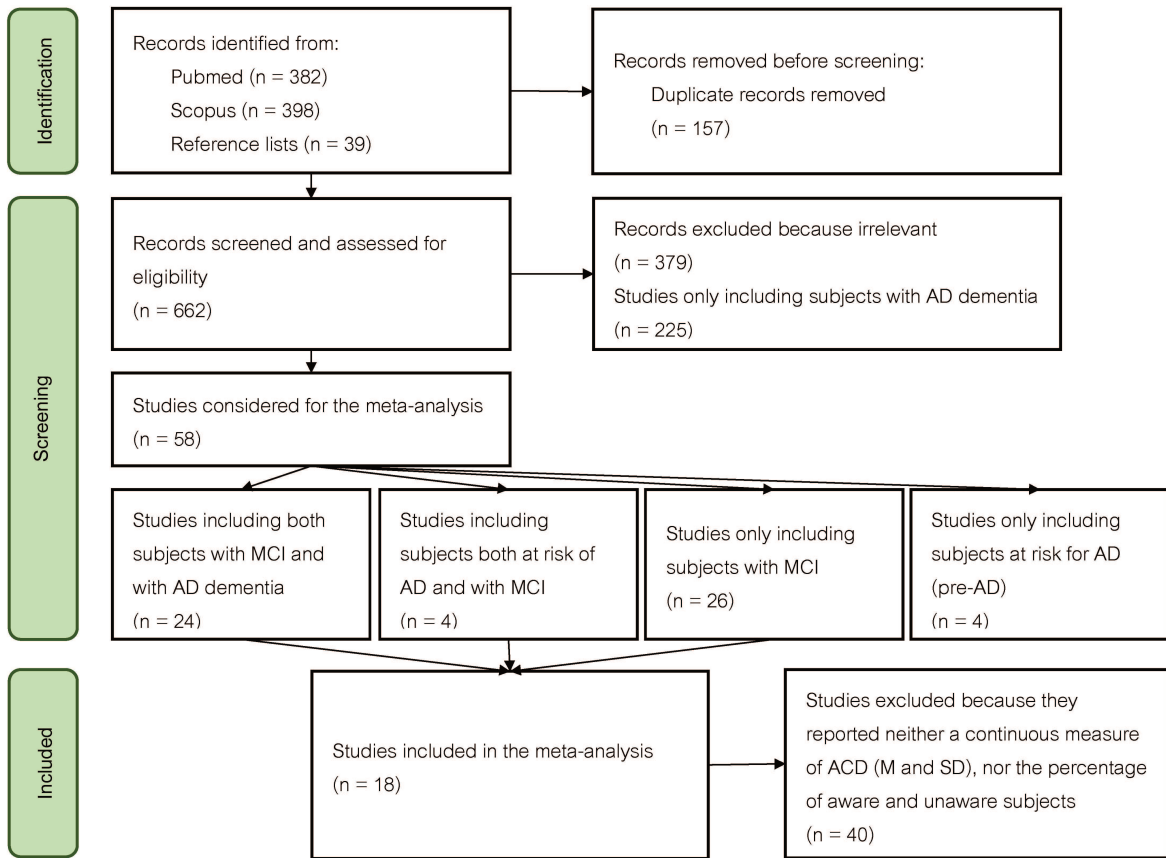
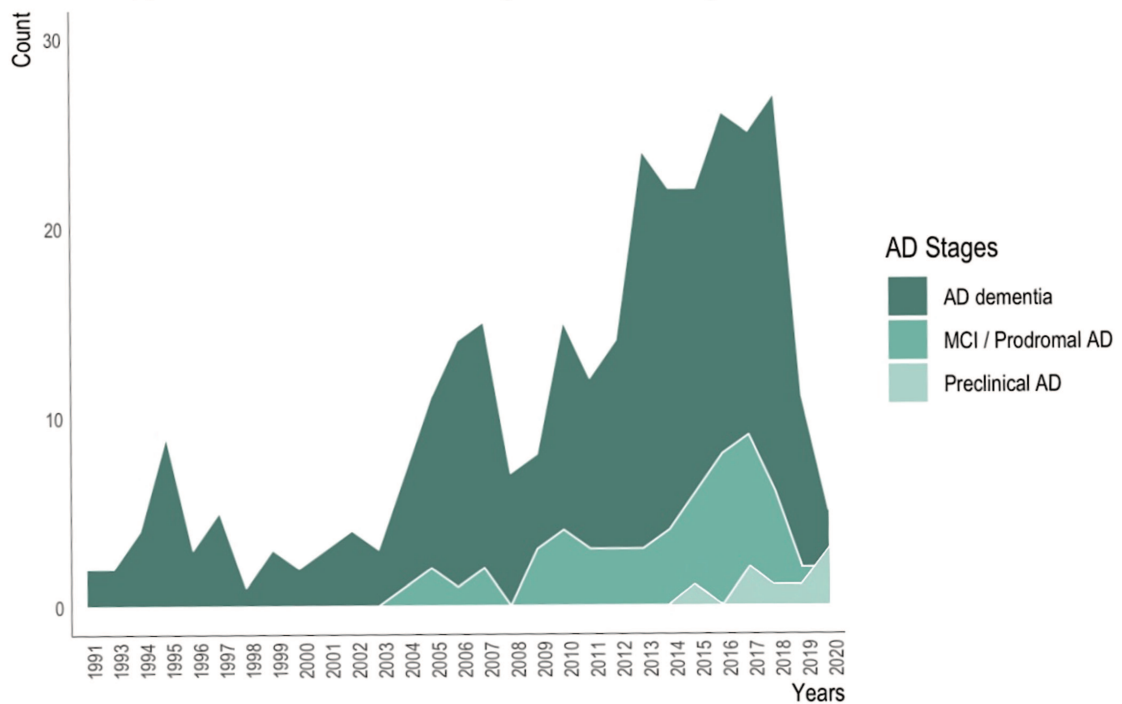


Figure 1. Number of publications found about awareness of deficits in AD per year and stage of the disease, prior to the selection of those eligible for meta-analysis.



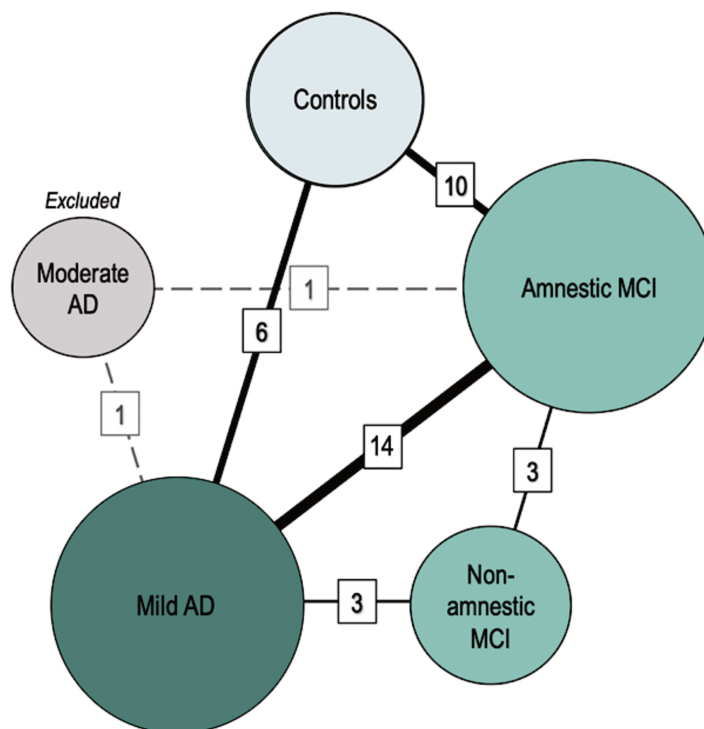
7.3.2 Prevalence of anosognosia in prodromal AD (or MCI)

The mean number of MCI participants enrolled in the analyzed studies was on average 76.50 (Interquartile range (IQR) = 20.50 – 71.00). Mean age was on average 74.10 (IQR = 72.78 – 76.10). Mean years of education were on average 11.50 (IQR = 9.32 – 13.61). Mean percentage of men was on average 47.45 (IQR = 42.80 – 54.60). Mean MMSE was on average 26.80 (IQR = 26.23 – 27.40). Fourteen studies assessed the ACD as the discrepancy between subject's and informant's ratings of decline (subject-informant discrepancy) (Ford, 2014; Galeone, Pappalardo, Chieffi, Iavarone, & Carlomagno, 2011; Jacus, Belorgey, Trivalle, & Gély-Nargeot, 2015; Maki et al., 2013; Oba et al., 2019; Onor, 2006; Orfei et al., 2010; Ries et al., 2007; Senturk et al., 2017; Spalletta, Girardi, Caltagirone, & Orfei, 2012; Tondelli et al., 2018; Zamboni et al., 2013). Three studies as the discrepancy between subjective and objective scores of cognitive functioning (subjective-objective scores discrepancy) (Coutinho, 2016; O'Connell et al., 2014; Vannini, P. et al., 2017). In one study (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 3 and Table 1 represent the between-group comparisons. Forest plots are in Figure 4. The degree of ACD was not significantly different between patients with amnesic and non-amnesic MCI (SMD [95%CI] = 0.09 [-0.21; 0.39], $p = 0.574$). On average, the ACD was significantly lower in amnesic 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 amnesic MCI (SMD [95%CI] = -0.75 [-1.02; -0.48], $p < 0.001$), as well as poorer than in non-amnesic MCI (SMD [95%CI] = -1.00 [-1.25; -0.76], $p < 0.001$).

The articles comparing subjects with non-amnesic vs amnesic MCI had low heterogeneity ($I^2 = 20\%$; $\text{Tau}^2 = 0.01$, $p = 0.286$), as well as those comparing subjects with mild AD vs non-amnesic MCI ($I^2 = 0\%$; $\text{Tau}^2 = 0.00$, $p = 0.887$). On the contrary, heterogeneity of articles performing all other comparisons was substantial and significant (all $I^2 > 79\%$; all $\text{Tau}^2 = 0.36$; all $p \leq 0.001$).

Figure 3. Comparisons between clinical groups



Note. Nodes represent clinical groups. The size of the nodes is proportional to the number of studies including the 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.

Table 1. Results of the meta-analysis 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*

Note. 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. Tau² indicates the extent of variation among the effects observed in different studies (between-study variance).

Figure 4. Meta-analysis forest plots

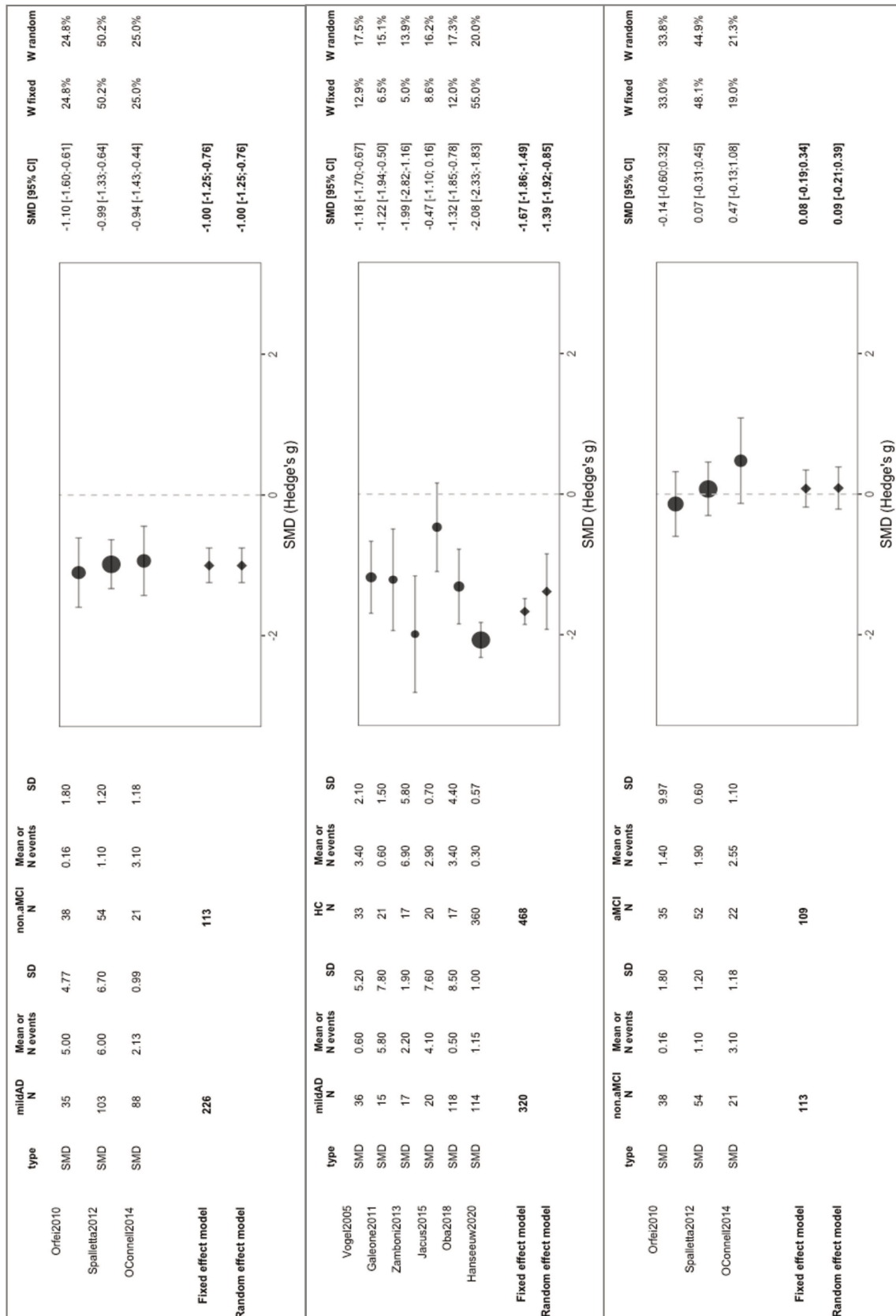
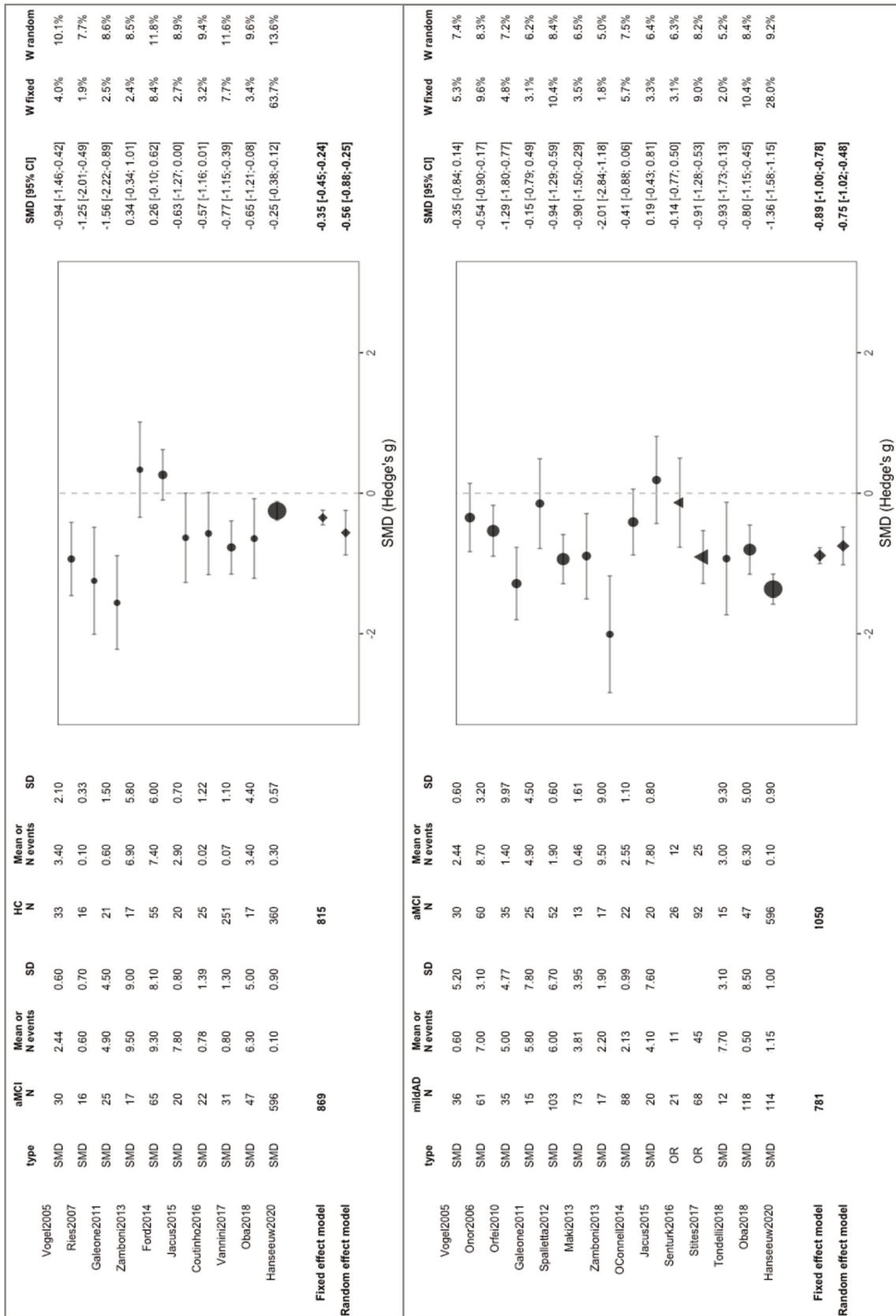


Figure 4. Meta-analysis forest plots (Continued)



In our meta-analysis, MCI subjects had poorer ACD than healthy controls, but higher ACD than subjects with mild dementia. This suggests that anosognosia is already present in the prodromal phase of the disease, although in a milder form than in the dementia stage. These results are important when considering that cognitive complaint is a criterion for the diagnosis of MCI (Albert et al., 2011). This may actually contribute to misdiagnosis (Edmonds, Delano-Wood, Galasko, Salmon, & Bondi, 2014; Edmonds et al., 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.

7.4.1 Neural correlates of anosognosia in prodromal AD (or MCI)

These studies showed that ACD reduction in MCI correlates with alterations in a set of frontal and temporoparietal regions, consistently with what has been identified in the studies including participants with AD dementia. In Ries et al., 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 (Ries et al., 2007). In a study by Nobili et al., 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 (Nobili et al., 2010). Similarly, Vannini et al. found that the participants with amnesic 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 (Vannini et al., 2017). Tondelli et al. studied the neuroanatomical correlates of the three most commonly used methods to assess anosognosia (i.e., clinician rating, participant-informant discrepancy and subjective-objective scores discrepancy) in a sample of amnesic MCI patients and healthy controls. They found that all three scores positively correlated with atrophy in the medial temporal lobe, including the right hippocampus (Tondelli et al., 2018).

7.4.2 Clinical correlates of anosognosia in prodromal AD (or MCI)

In the study by Senturk et al., ACD positively correlated with MMSE and episodic memory, working memory, and executive functions scores (Senturk et al., 2017), while in Vogel et al., anosognosia in MCI and AD dementia patients positively correlated with MMSE and right inferior frontal gyrus blood flow but not with executive function tests (Vogel et al., 2005). In Tremont & Alosco (2011), the patients with anosognosia were comparable to non-anosognostic ones in all demographic characteristics, cognitive and behavioural domains, except that anosognostic patients obtained significantly lower scores in the learning domain.

Furthermore, some authors have suggested that anosognosia in MCI is more related to non-cognitive (i.e., psychiatric) factors. In Oba et al., 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 (Oba et al., 2019). Jacus et al. found a negative correlation between the degree of ACD and apathy (Jacus et al., 2015).

7.4.3 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/she is affected by AD. A recent 2-year longitudinal study (Therriault et al., 2018) found that anosognostic 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 two 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, anosognostic MCI participants had higher rates of cerebrospinal fluid AD biomarker positivity and progression to dementia. Similar results have been reported in two other studies (Munro et al., 2018, Scherling et al., 2006).

7.4.4 Limitations

The present study has some limitations. First, the index of ACD was computed in many different ways, demonstrating that there is not yet a gold standard for the evaluation of ACD. Second, prodromal AD was defined differently in the studies. MCI was seen as a possible transition phase between normal cognition and AD dementia, but most of them did not include biomarker evidence to support AD pathology, 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). Third, although AD has a typical amnesic 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; Gorno-Tempini et al., 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 & 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. Fourth, 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.

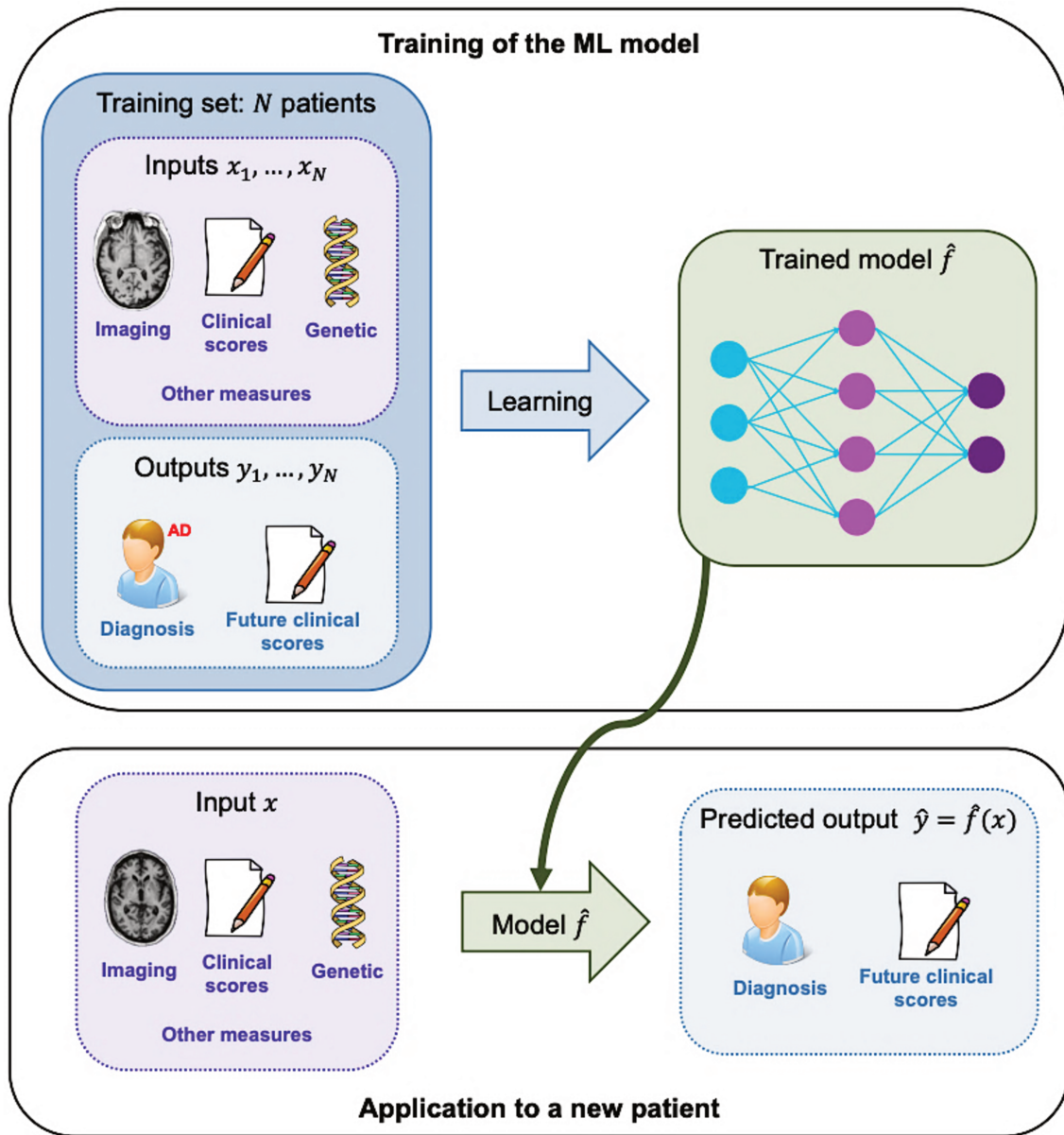
III

Poor awareness of cognitive decline (ACD)
as an early indicator of Alzheimer's disease:
Machine Learning methods

Use of machine learning in neurology 8

Machine learning (ML) is a subfield of artificial intelligence that started being used for brain disorders about 15 years ago (Gerardin, Chételat, Chupin, & et al, 2009; Klöppel, Stonnington, Chu, & et al, 2008), and has since made great progress. ML is a family of techniques in which the computer learns statistical patterns from a dataset, the training set, which includes both inputs (e.g., brain images, clinical data, etc.) and outputs (e.g., diagnosis) for N subjects. These are essentially multivariate analysis techniques. The estimated model (mathematical function) will then be applied to new data (the test set) in order to predict the output for new subjects, e.g., the diagnosis. The goal is to find the best model to predict the output, minimizing the error between the estimated result and the actual result (Figure 1). In order to test the discriminating power of the estimated model, ROC curves and AUC analysis are often used to test the accuracy of the classifier (method already described in Chapter 5), and tests of significance are also used to verify that the classifier performs better than chance.

Figure 1. Basic concepts of machine learning



Note. Figure from Burgos and Colliot, 2020

8.1 Examples of application of ML in neurology

ML techniques can be used in clinical practice for the screening of new patients and potential referral to specialist physicians, to diagnose difficult cases, to optimize the

treatment plan, and to predict the course of disease in a certain individual (Burgos & Colliot, 2020).

8.1.1 Computer-aided diagnosis

ML is mainly used to optimize diagnosis, for example to distinguish ill from healthy individuals or for differential diagnosis (Morin, 2020; Péran, 2018; Tong, 2017). It has been applied in AD, frontotemporal dementia (FTD) (Meyer, 2017), multiple sclerosis (Zurita, 2018), schizophrenia (Fan, 2005), epilepsy (Chen, 2020). For example, Peran et al. distinguished patients with PD from patients with multisystem atrophy with an accuracy of 95% using a model estimated from MRI. In Tong et al. the classification of subjects with AD, FTD, vascular dementia, dementia with Lewy bodies and patients with SCD had good accuracy (70%). It was based on MRI and CSF biomarkers. Most research has been carried out using neuroimaging data as inputs because it is digital and easy to access, but more recently multimodal approaches are more and more used, for example integrating clinical and genomic data (Ansart, 2019; Samper-González, 2018). Learning from cognitive data significantly improves model performance compared to when it is not included (Ansart et al., 2019), as opposed to structural magnetic resonance.

8.1.2 Prediction of disease evolution

Another common application of ML in neurology is the prediction of the disease evolution. There are at least two ways to apply ML to predict the evolution of the disease.

The first way is to predict a future condition, for example whether a patient who was initially cognitively-normal will develop cognitive deficits, or will receive a certain diagnosis, after a predetermined period of time. A review revealed that 172 papers exist that attempted to predict progression from MCI to AD (Ansart et al., 2019), this number steadily increasing since 2010. The accuracy of these predictions was between acceptable (70%) and excellent (85%), and increased over time.

The second application consists in estimating when a certain event of interest will occur (diagnosis, death, etc.). For instance, van der Burgh et al. predicted survival time after onset of symptoms in patients with amyotrophic lateral sclerosis using deep learning, and more precisely a model learnt from clinical and MRI data (structural connectivity and brain morphology), with an accuracy of 84,4% (van der Burgh, 2016).

8.2 Potential problems for the application of ML in clinical practice

Despite extensive research on these topics, ML still faces limitations for its application in clinical practice. For example, the reproducibility and replicability of the results are often low because the estimates are not explained in sufficient detail. There are also data access and code sharing issues, which do not make it possible to verify that the results are sufficiently robust (Samper-González et al., 2018). Second, these methods may not find application in clinical practice also because they may be perceived as complex for daily practice by health personnel. Radiology is the medical specialty that has advanced the most in terms of the development of AI tools and, in a recent study, radiologists were the least reluctant to use such tools among the various medical specialties (Lai, 2020). Third, the doctor may also be reluctant to use AI tools due to the “black box” problem. Especially in ML, the computer obtains a classification (e.g., healthy versus sick) by independently looking for patterns in the data. The doctor would therefore not be able to provide the patient with sufficient information on how this response was found and its reliability (problem of *interpretability*) (Lai, 2020).

However, AI should not replace humans in clinical practice, but rather provide additional information.

For a comprehensive review of studies focusing on ML in neurology, see Burgos and Colliot (2020).

AD Course Map: 9

focus on the trajectory of ACD

This chapter presents some preliminary results obtained in collaboration with Dr Stanley Durrleman, Dr Igor Koval, Arnaud Valladier and Etienne Maheux, which are still subject to further analysis.

AD is a complex disease, in which alterations occur in various aspects of brain functioning and structure (e.g., accumulation of amyloid, reduced metabolism, loss of neurons, etc.). This is further complicated by the fact that there is no exact and consistent correspondence between the severity of the neuropathologic changes and the severity of clinical manifestation. There are in fact patients with extensive brain lesions and mild cognitive disorders, or conversely with less extensive lesions with severe cognitive impairment (Snowdon, 2003). Moreover, patients differ according to their age at the onset of symptoms, the rate of disease progression, and the order of occurrence of symptoms (for example, an individual may develop language disorders before memory disorders) (Goyal, 2018).

The alteration of ACD is also a rather complex aspect of AD manifestation. When conducting longitudinal studies, therefore, we must take these aspects into consideration. Longitudinal studies on ACD along the continuum of AD (including very early stages) are very few. To give two examples (see 2.4.3 for more details), Hanseeuw et al. showed a gradual decrease in ACD driven by an increase in study-partner complaint, while patient complaint remained stable. ACD began to decline in preclinical AD, after a phase of heightened ACD (or hyperanosognosia). Gradual anosognosia began within the MCI phase about 3 years before

dementia diagnosis (Hanseeuw et al., 2020). Another longitudinal study (Vannini et al., 2020) was conducted on a sample of presymptomatic and cognitively-impaired participants carrying the PSEN1 E280A mutation. Participants had an initial phase of hypernosognosia, followed by a gradual decrease in ACD, which began about 6 years before dementia.

There is therefore a need to carry out further longitudinal studies on the participant integrating other aspects of the disease, including biomarker changes. To address this need, we have chosen to study the evolution of ACD along AD progression (i.e., participants with biomarker-defined AD covering the entire continuum of AD clinical manifestation) with a statistical method which allowed us to take its complexity into account.

9.1 Aims

1. To identify how ACD changes in individuals with pathophysiological markers suggestive of AD and spanning the entire continuum of the disease (from normal cognition to dementia), by describing the longitudinal trajectory of participant and study-partner complaints.
2. To place the evolution of participant and study-partner complaints among some of the other pathological events that occur in AD, in order to appreciate their timing and order throughout the progression of the disease.

9.2 Methods

9.2.1 Participants

We referred to the A/T/N conceptual framework (Jack et al., 2016) to identify participants with biomarker-defined AD from the Alzheimer's Disease Neuroimaging Initiative cohort (ADNI, <http://adni.loni.usc.edu>).

Enrolled participants were positive for both amyloid and tau (A+T+). More specifically, we used the following inclusion criteria:

(i) at least one amyloid marker must be positive on any one visit, with no known change from positive to negative status on the subsequent visits. Amyloid markers considered were the same as in Chapter 5 (see 5.2.1)

(ii) AND the participant must have positive CSF pTau [positive if > 23 pg/ml (Shaw et al., 2009)] on any one visit, with no known change from positive to negative on the subsequent visits

Visits prior to amyloid or tau positive status were excluded.

We had no restrictions in terms of cognitive status or diagnosis. Indeed, we aimed to include:

- cognitively-normal (CN) participants with positive biomarkers (A+T+), or at risk for preclinical AD
- A+T+ MCI participants,
- and A+T+ participants diagnosed with AD.

Criteria for CN, MCI and AD status are described in Chapter 5 (see 5.2.1).

We also enrolled A-T- control participants, using the following inclusion criteria:

- (i) all three amyloid markers must be negative at all visits where they were available
- (ii) and CSF ptau must be negative at all visits where CSF ptau was available
- (iii) and must be classified as CN at all visits

One study-partner for each participant also participated in the research. This was a person who knew the participant well and who had frequent contact with him/her (e.g., >10 hours per week).

9.2.2 Measures

Self- and informant-reported decline

Subjects and study-partners assessed the subject's cognition by comparing it to that of 10 years earlier, using the Everyday Cognition questionnaire or ECog (Farias et al., 2008). The two parallel forms are composed of 39 questions each, for example "Recalling conversations a few days later". The subject and the study-partner indicate whether the subject is able to perform this activity as 10 years ago or worse, with answers ranging from 1 to 4. The total score is the average of all questions. Higher scores indicate more deteriorated cognition.

Cognition

We used the MMSE, ranging from 0 to 30, as a measure of global cognitive functioning. As a measure of memory function, we calculated a composite score as the sum of the first item (Word Recall Task) of the AD Assessment Scale-Cognition (ADAS-Cog), the learning score from the Rey Auditory Verbal Learning Test (RAVLT) and the differed recall score from the Logical Memory II test.

Autonomy in daily life

The Functional Activities Questionnaire (FAQ) measures instrumental activities of daily living. It consists of 10 questions, for example "Writing checks, paying bills, balancing checkbook". Answers range from 0 to 3.

Metabolism

As an index of pathological metabolic change, we used the FDG uptake at PET scan in a set of pre-defined regions of interest (Landau et al, 2011): Left Angular Gyrus, Right Angular Gyrus, Bilateral Posterior Cingular, Left Inferior Temporal Gyrus, Right Inferior Temporal Gyrus.

In particular, we considered the mean glucose metabolism normalized to pons. Details of the PET images acquisition protocol are publicly available here: http://www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml.

Hippocampal volume ratio

ADNI structural magnetic resonance images (MRI) were collected using 1.5 Tesla scanners at different centers, and specific protocols for each were used. Quality control was performed according to previously published criteria (Simmons et al., 2009). To summarize, a FreeSurfer pipeline was used to perform volumetric segmentation of the hippocampus in mm³ and to calculate intracranial volume (ICV), which was the sum of white matter, gray matter, and ventricles. In this way, we were able to use the ratio of hippocampal volume to ICV as a measure of hippocampal atrophy, one of the most characteristic features of AD. The smaller the ratio, the more marked the atrophy.

9.2.3 Statistical analysis

Study population

We used χ^2 test (with Phi-coefficient for effect size) for categorical variables, and t-test (with Cohen's d for effect size) for continuous variables, to compare demographic and clinical data between A+T+ participants and A-T- controls (α was set at 0.05).

Objective 1

We used Leaspy (LEARNING Spatiotemporal Patterns in Python), a python library developed by Dr Stanley Durrleman and his team (ARAMISLab, Paris Brain Institute) for statistical analysis of repeated measures, available here: <https://gitlab.com/icm-institute/aramislab/leaspy/>. The main function of Leaspy is the reconstruction of longitudinal changes in a set of variables in a given group of individuals, from a series of repeated observations (e.g., cognitive scores obtained on different visits). The particularity of Leaspy is that it makes it possible to reconstruct these longitudinal variations by taking into account both temporal and spatial information, including age at onset (time shift), rate of progression (acceleration factor) and sequence of events (Koval, 2017).

Figure 1 illustrates the steps of the analysis of a memory score carried out by Leaspy.

First, all 7 variables of interest (e.g., both ECog scores, memory score, etc.) have been rescaled between 0 and 1 to make them more comparable to each other, so that 0 corresponded to a normal value, and 1 corresponded to an abnormal/pathological value. Figure 1A shows the normalized scores obtained by a group of individuals (varying in age, disease stage, etc.) on a hypothetical memory test administered over multiple visits.

Second, the model realigned these normalized raw observations based on the severity of the different symptoms or imaging evidence considered. This is done using the Markov Chain Monte Carlo (MCMC) stochastic approximation expectation minimization (SAEM) algorithm (Allasonnière, 2010). This time reparametrization led to a new "Time" axis ("Reparametrized age" in Figure 1B): a lower reparametrized age indicates an earlier stage of the disease, and a higher reparametrized age indicates a more advanced stage of the disease. Only one model is run for all variables at a time, so that the different scores are aligned on a common timeline.

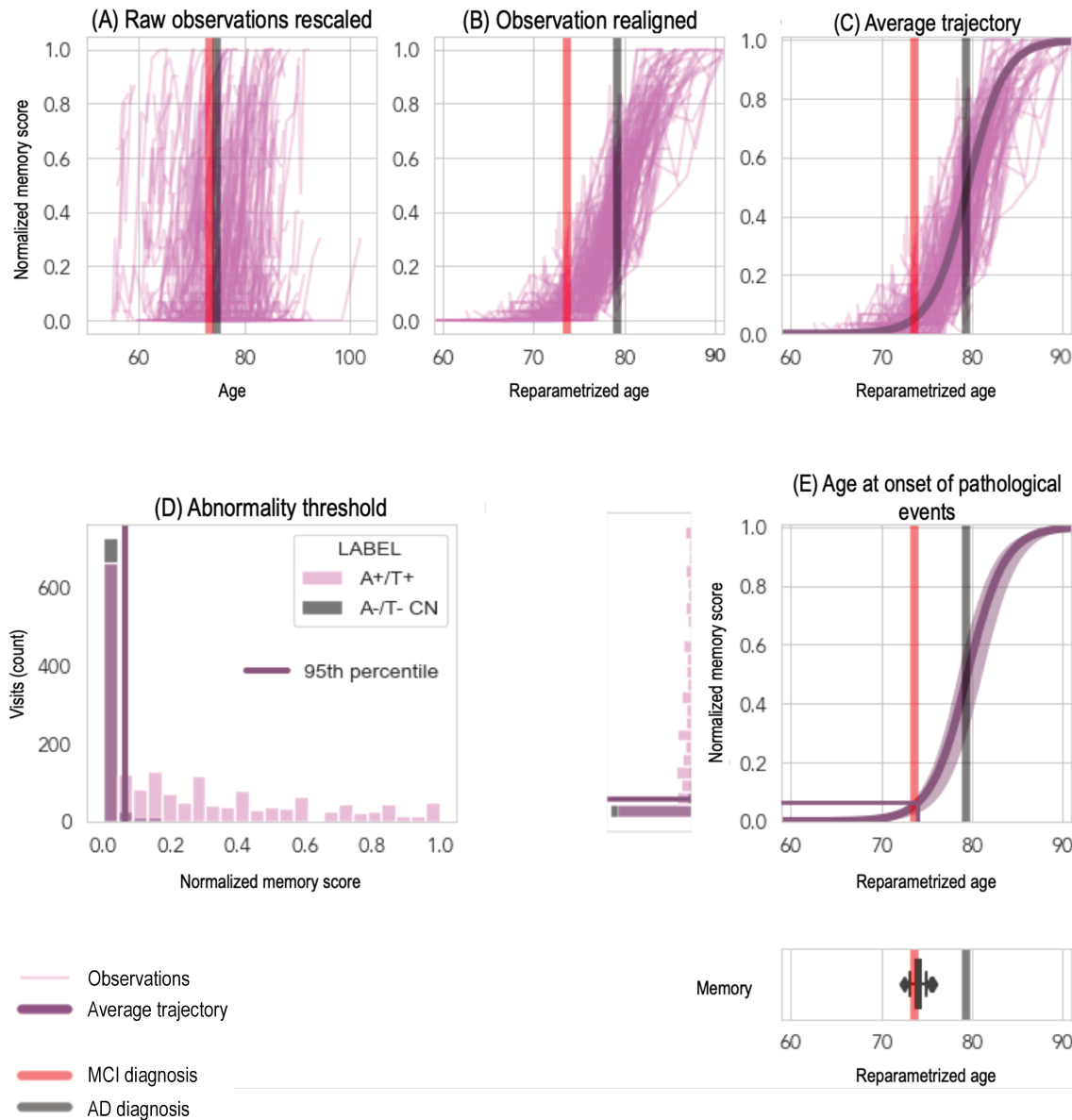
Third, we estimated the long-term average evolution of the variables from realigned data (Figure 1C).

Objective 2

We identified an abnormality threshold for each variable (Figure 1D). We chose the 95th percentile of the distribution of controls (i.e., CN A-T-).

Once the threshold for each variable was identified, Leaspy calculated at what reparametrized age the participants reached on average the threshold, and therefore at what moment of the disease our variable of interest became abnormal, i.e., more impaired than 5% of controls who had the worst performance (as represented in Figure 1E by a curve and by a boxplot).

Figure 3. From raw observations to an average long-term scenario using Leaspy.



Note. The figure shows the example of the evolution of one variable, a memory score, modeled using Leaspy. In the present study, however, we modeled 7 variables. A single model was performed including all the variables, which all contributed to create the AD Course Map. This means that the test scores and biomarker values have been realigned on a common disease timeline (i.e., reparametrized age) that takes into account the evolution of all variables. On the contrary, the reparametrized age is based only on the memory score in the example figure above. In the Figure, the red vertical line indicates the age at progression from CN to MCI. The grey vertical line, the age at AD diagnosis.

9.3.1 Study population

We included a total of 334 A+T+ participants and 137 A-T- CN controls. Among the A+T+ participants, 17% (n = 57) were CN at baseline, 58% had MCI at baseline (n = 195), and 24% (n = 82) were diagnosed with AD at baseline. A+T+ participants had an average age of just over 73 years, while controls were about 72 years on average, but this difference was not significant, $p = 0.08$, Cohen's $d = -0.178$. A+T+ participants were followed for a shorter

Table 1. Demographic and clinical characteristics of A+T+ and CN A-T- controls.

	A+T+ participants (n=334)	A-T- CN controls (n=137)	Effect size	p-value
CN at baseline [N (%)]	57 (17.06%)	137 (100%)		
MCI at baseline [N (%)]	195 (58.39%)	0 (0%)		
AD at baseline [N (%)]	82 (24.55%)	0 (0%)		
Age [years; M \pm SD]	73.3 \pm 7.0	71.7 \pm 5.7	-0.178	0.080
Follow-up duration [years; M \pm SD]	4.1 \pm 2.7	6.0 \pm 2.5	0.624	< .001*
Visits' number [mean \pm SD]	7.4 \pm 3.0	7.6 \pm 2.7	-0.058	0.568
Gender [female; n (%)]	151 (45%)	76 (55%)	0.093	0.043*
Education [years; M \pm SD]	16.0 \pm 2.7	16.7 \pm 2.6	0.357	< .001*
APOE genotype [ϵ 4 (1 or 2 copies); n (%)]	240 (72%)	25 (18%)	0.491	< .001*
ECog-Subject at baseline [M \pm SD]	1.80 \pm 0.56	1.38 \pm 0.33	-0.776	< .001*
ECog-StudyPartner at baseline [M \pm SD]	2.08 \pm 0.80	1.16 \pm 0.20	-1.271	< .001*
Memory composite at baseline [M \pm SD]	9.04 \pm 2.43	13.36 \pm 1.70	2.044	< .001*
MMSE at baseline [M \pm SD]	26.74 \pm 2.81	29.12 \pm 1.19	0.993	< .001*
FAQ at baseline [M \pm SD]	5.84 \pm 6.62	1.80 \pm 0.56	-2.475	< .001*
Hippocampal volume at baseline [M \pm SD]	1.20 \pm 0.15	1.33 \pm 0.10	0.894	< .001*
Metabolism at baseline [18 F-FDG SUV; M \pm SD]	0.09 \pm 0.12	1.30 \pm 0.06	0.623	< .001*

Note. Results are given as mean \pm standard deviation or as count and percentage. CN: cognitively-normal; MCI: mild cognitive impairment; AD: diagnosed with AD; APOE: Apolipoprotein; ECog: Everyday Cognition questionnaire; MMSE: Mini Mental State Examination; FAQ: Functional Assessment Questionnaire. Effect size has been calculated as Cohen's d for continuous variables, and phi-coefficient for categorical variables. * Indicates statistically significant effects ($\alpha = 0.05$).

period of time (for an average of 4 years) than controls (6 years on average), $p < 0.001$, Cohen's $d = 0.624$. The A+T+ group was composed of 45% of women, while the control group was composed of 55% of women, $p = 0.043$, Cohen's $d = 0.093$. The prevalence of APOE- $\epsilon 4$ alleles was higher in the A+T+ group (72%) than in the control group (18%), $p < 0.001$, Cohen's $d = 0.491$.

The two ECog scores were significantly higher at baseline in the A+T+ group than in the control group (ECog-Subject: $p < 0.001$, Cohen's $d = -0.776$; ECog-StudyPartner: $p < 0.001$, Cohen's $d = -1.271$). A+T+ participants were significantly more impaired on average on the memory composite, the MMSE, and the FAQ, than the control group (Memory: $p < 0.001$, Cohen's $d = 2.044$; MMSE: $p < 0.001$, Cohen's $d = 0.993$; FAQ: $p < 0.001$, Cohen's $d = -2.475$).

A+T+ participants also had a smaller hippocampal volume ratio than the control group ($p < 0.001$, Cohen's $d = 0.894$) and lower brain glucose metabolism ($p < 0.001$, Cohen's $d = 0.623$).

More details are shown in Table 1.

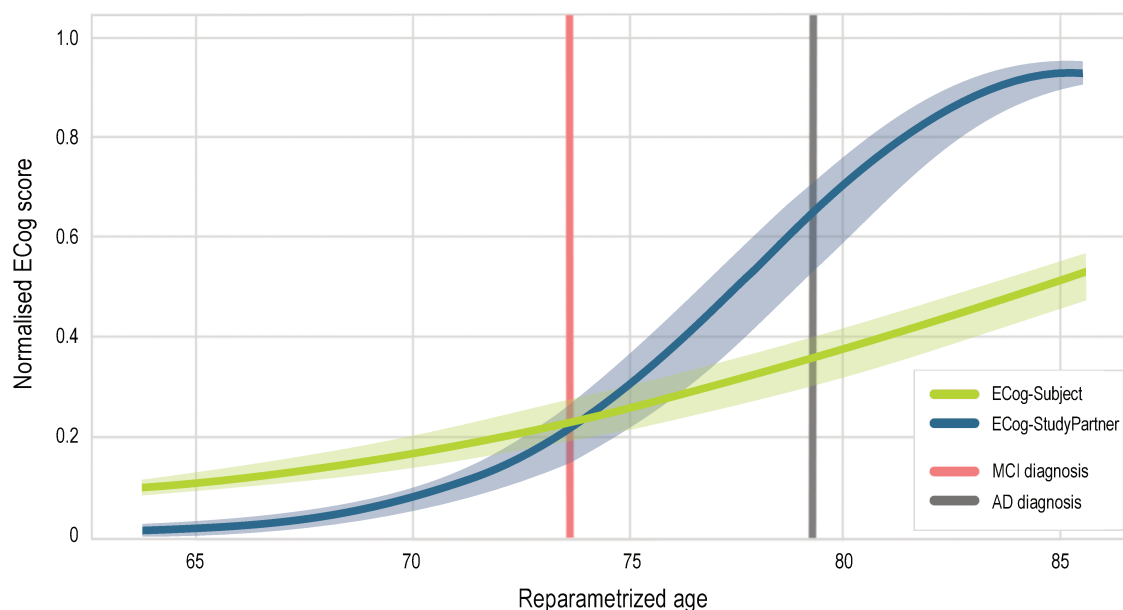
9.3.2 Objective 1: Longitudinal changes in subject and study-partner complaint during AD progression

In Figure 2, the y-axis represents the normalized ECog scores. The x-axis represents the reparametrized age, which means that we were able to reconstruct the evolution of the disease over two decades, from data collected over an average period of 4 years. We also entered the mean age of progression from normal cognition to MCI (red vertical line, 73.7 years), and from MCI to AD (grey vertical line, 79.3 years).

The graph shows that A+T+ participants perceived some degree of cognitive decline at disease onset (they had on average a normalized ECog-Subject score of 0.1 out of 1). The average subjective complaint increased over time to reach a maximum score of 0.55 out of 1 at the most advanced stage of the disease. Study-partners, on the other hand, reported no difficulty at disease onset (normalized ECog-StudyPartner score = 0), but their complaint increased on average over the course of the disease to a maximum score of 0.95 out of 1.

The average study-partners' complaint was therefore lower than that of the participants at the onset of the disease, and exceeded it in intensity about 3 and a half months after the diagnosis of MCI.

Figure 2. Longitudinal trajectories of subject and study-partner complaints in A+T+ participants

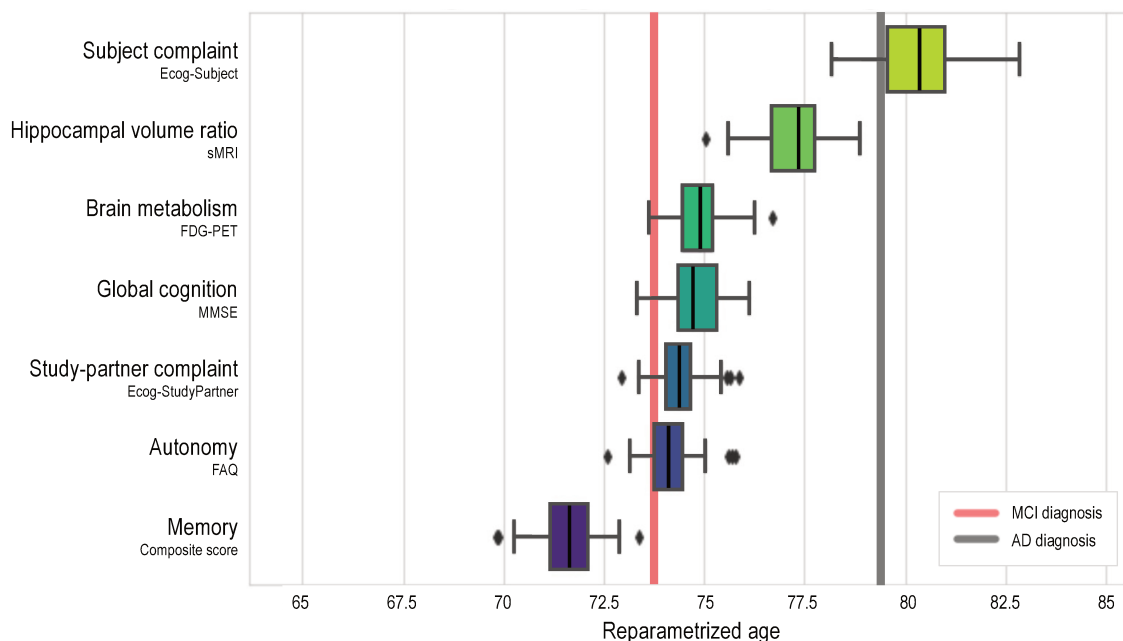


9.3.3 Objective 2: Timing and order of pathological events in AD

Figure 3 represents the average reparametrized age at the onset (i) of the main symptoms of AD – i.e., memory disorders, global cognitive impairment (MMSE), decreased autonomy (FAQ); (ii) of two of the main biomarker alterations – i.e., hippocampal atrophy and hypometabolism; and (iii) of abnormalities in the ECog scores (Subject and Study-Partner).

The first variable that became abnormal in our A+T+ group was memory. The abnormality threshold identified for the memory composite as 95% of the distribution of controls was a score of 10 (normalized score = 0.31 out of 1). Participants reached this threshold on average at 71.6 years, that is 2.1 years before diagnosis of MCI and 7.7 years before diagnosis of dementia.

Figure 3. Mean age at onset of the main symptoms or anomalies in biomarkers in A+T+ individuals



Autonomy was the second variable to become abnormal, i.e., FAQ score ≥ 2 out of 30 (normalized score ≥ 0.08 out of 1). Participants reached this threshold on average at 74.1 years, that is 6 months after diagnosis of MCI and 5.2 years before diagnosis of dementia. The study-partner complaint (ECog-StudyPartner) was abnormal when ≥ 1.76 out of 4 (normalized score ≥ 2.5 out of 1). Participants reached this threshold at 74.4 years on average, that is 8.4 months after diagnosis of MCI and 4.9 years before diagnosis of dementia.

The MMSE score was the fourth variable to become abnormal. The abnormality threshold identified was a score of 27 out of 30 (normalized score = 0.1 out of 1). Participants reached this threshold on average at 74.7 years, that is 1.1 years after diagnosis of MCI and 4.6 years before diagnosis of dementia.

Brain metabolism (FDG uptake at PET scan) was considered to be abnormal when ≤ 1.18 (normalized score ≥ 0.52 out of 1). Participants reached this threshold on average at 74.9 years, that is 1.2 years after diagnosis of MCI and 4.4 years before diagnosis of dementia.

The hippocampal volume ratio was the sixth and penultimate variable to become abnormal. The abnormality threshold identified was 0.004 (normalized score = 0.50 out of 1). Participants reached this threshold on average at 77.4 years, that is 3.7 years after diagnosis of MCI and 2 years before diagnosis of dementia.

Finally, the subject's complaint (ECog-Subject) was the last variable to become abnormal (i.e., ≥ 2.15 out of 4; normalized score ≥ 0.39 out of 1). Participants reached this threshold on average at 80.4 years, that is 6.7 years after diagnosis of MCI and 1.1 years after diagnosis of dementia.

9.4 Discussion

In the present study, we analyzed AD progression using machine learning methods (i.e., Leaspy library). This allowed us to take into account inter-individual differences in terms of the number of visits available, age at disease onset, severity of cognitive impairment, and rate of disease progression, as well as the order in which different symptoms or abnormalities occur. From multimodal longitudinal data collected over an average period of 4 years, we were therefore able to build an AD Course Map, that is a broad and overall view or perspective of the evolution of the disease over two decades.

A first result that we obtained concerns the longitudinal evolution of patient complaints. On the onset of the disease, our individuals who were accumulating brain damage due to AD complained of some degree of cognitive decline. At the same time, they still performed cognitive tests normally (since they were in the preclinical phase of the disease) and their study-partner did not report any difficulties. This means that in an initial period of about 6 years, the patient is the only one to notice changes in his/her cognitive efficiency. This is a longer period than in Hanseeuw et al. (where hyperosognosia was visible from 4 years to 1.6 years before progression to MCI), but this is likely due to a number of methodological differences, especially in subjects' selection, in the definition of abnormality thresholds or in the procedure used.

Further analysis to better understand the nature of this initial cognitive complaint is needed. Our results seem to confirm the diagnostic utility of subjective cognitive decline or SCD (Jessen et al., 2014; Jessen et al., 2020) in the very first stage of the disease. SCD is defined as a persistent cognitive decline experienced by the patient, compared to a previous normal state and not related to an acute event, while performance on standardized tests is normal.

Older people with SCD have been reported to be at increased risk for abnormal AD biomarkers and progression to dementia (see 2.4.2). This concept is linked to that of hyperanosognosia (Vannini et al., 2017), i.e., the initial state of the disease in which the individual complains of a more severe decline than that reported by the study-partner, which then gradually transforms into progressive anosognosia. A large proportion of patients with preclinical AD experience SCD, so much so that they consult their doctor or a specialist. SCD is therefore one of the most frequent ways in which an individual who develops the disease comes to the doctor's attention. However, we wonder about the specificity of this behavior for diagnostic purposes. From a preliminary analysis of our data not reported here, it seems to us that such a subjective complaint is also typical behavior of our healthy control subjects. This would be consistent with other studies that have found a high prevalence of complaints in the general population, resulting in low specificity and therefore low diagnostic utility. To clarify this point, we will continue these analyzes by testing the difference between the ECog-Subject score of A+T+ participants at the beginning of the disease and that of healthy controls.

A second interesting result of our study is the relatively small increase in subjects' average complaint over the course of the disease. They continued to report difficulties similar in severity to those reported at the onset of the disease, although they progressed to cognitive impairment and then loss of autonomy. This result is a further confirmation of the concept of "petrified self" (Mograbi, Brown and Morris, 2009) already illustrated above (see 2.2.2). At the same time, complaints from study-partners increased on average, almost reaching a ceiling effect in the latest stage of the disease. The study-partner therefore seems to be a more reliable source of information than the patient him/herself to track the evolution of the disease. Starting around 4 months after the diagnosis of MCI, the subjects began to be unaware of the severity of their decline that was noticed by the study-partner. This therefore confirms our previous studies which had identified a partial anosognosia in the prodromal phase (as in Chapters 7 and 10). The patient begins to be more and more anosognostic as the disease progresses.

In this study, we also tried to understand when and in what order symptoms and biomarker abnormalities appear, including subject and study-partner complaints. We identified that the memory composite was the most sensitive measure among those considered, as it was the first to become abnormal at around 71.5 years old, or 2 years before the diagnosis of MCI. It should be noted that in our study we did not use the abnormality thresholds already known for the different tests or biomarker values, as they were not always available (for example, for the ECog). We therefore calculated the thresholds as the 95th percentile of the distribution of healthy controls. A score (or biomarker value) was therefore considered abnormal when it was higher (i.e., more altered) than in 5% of healthy controls who had the highest scores (i.e., the worst-performing). Thus, our A+T+ participants were diagnosed with MCI at approximately 73 and a half years of age, during the visit at which their WMS-R LM II score was pathological. However, their memory began to decline as early as 2 years before the diagnosis of MCI, because they began to score worse than the worst-performing healthy controls. This seems to coincide with the concept of subtle (Sperling et al., 2011) or transitional (Jack et al., 2018) cognitive decline. Likewise, autonomy was also abnormal very early in the course of the disease (6 months after the diagnosis of MCI). This is particularly interesting because MCI is by definition the condition in which the patient is still independent despite the onset of cognitive disorders. Indeed, the FAQ questionnaire indicates a loss of autonomy when the score is greater than 9 out of 30. In our study we had identified an abnormal threshold of 2 out of 30. This shows that although the patient is overall sufficiently intact to maintain his/her autonomy in daily life, there are already some subtle difficulties in carrying out the activities. In a previous study, we have already demonstrated consistent results (Villeneuve et al., 2019).

In this context of mild disorders, both cognitive and functional, the study-partner begins to notice differences compared to 10 years earlier. In fact, study-partners of A+T+ participants started to report more cognitive changes than those of healthy controls about 8 months after diagnosis of MCI. The study-partner would therefore be a more sensitive measure than MMSE, brain metabolism and hippocampal atrophy. The MMSE and metabolism indeed became abnormal in A+T+ participants at about the same time, 1 year after the diagnosis of MCI. This is not surprising as FDG-PET is an indicator of the synaptic dysfunction

accompanying neurodegeneration in AD, which occurs in a regional pattern related to cognitive impairment (see 2.1). Three and a half years after the diagnosis of MCI, the hippocampal volume was also abnormal. The sequence of biomarkers we have identified is similar to that proposed by the conceptual model of Jack et al., supported by numerous neuroimaging studies (Jack et al., 2010; Jack et al., 2013). In Jack et al., amyloid and structural changes at MRI were the first and last neuroimaging markers to become abnormal, respectively. In between was the metabolism curve (in certain brain regions), which showed abnormalities before the MRI curve (in the same regions). Both in Jack et al.'s model and in ours, the results are always interpreted considering that all biomarkers once become abnormal continue to progress towards increasingly pathological values, although they become abnormal sequentially (Perrin, Fagan and Holtzman, 2009; Jack, Lowe and Weigand, 2009). Another point in common with Jack et al.'s model is that the trajectories were not linear but sigmoidal, indicating an acceleration, followed by a deceleration, in the rate of brain damage, as also identified by several previous studies (Ridha et al., 2006; Jack, Weigand and Shiung, 2008). What differs between our results and Jack et al.'s model is the evolution of cognitive impairment. In Jack et al., cognition became abnormal last, after neuroimaging markers, due to cognitive reserve processes (Stern, 2012). On the contrary, memory was the first variable, among those considered, to become abnormal in our A+T+ participants, before hypometabolism and hippocampal atrophy. The MMSE score (global cognition) became abnormal after metabolism but before hippocampal atrophy. It therefore appears that the mere presence of amyloid and tau in doses sufficient to exceed the abnormality thresholds may lead to a decrease in memory efficiency (and in global cognition when hypometabolism is also present). More specifically, this decline was not defined by pathological scores on standardized tests, but as a poorer performance than in 5% of the worst performing healthy controls. This definition of anomaly could therefore allow the detection of *subtle* or *transitional* cognitive decline better than by considering the test thresholds validated in the literature.

The participant's complaint was the last measure to become abnormal more than one year after the diagnosis of AD. This means that up to the mild dementia stage, subjects reported cognitive difficulties similar to controls. In other words, they judged their cognitive

performance the same way healthy controls judged theirs. This is linked to the non-specificity of the subject's complaint already mentioned above.

Future perspectives

This chapter describes preliminary results which are still the subject of further analysis. First, we would like to address a third objective, namely to understand the impact of gender, education and APOE genotype on changes in awareness. Indeed, gender differences were highlighted in the level of awareness (for example, in Cacciamani et al., 2020, men tended to be more unaware than women, possibly due to socio-cultural factors). Education may also have an impact, as previous evidence identified that subjects with a lower level of education tended to be less aware of their decline (Verfaillie et al., 2019). Finally, from an exploratory investigation on data which has not been reported here and which would require a more in-depth analysis, it seems that the presence of APOE $\epsilon 4$ alleles accelerates the entry into anosognosia. In addition, as already mentioned, we wish to deepen the comparison between the subjective complaint of the A+T+ group and that of the controls, in order to study the specificity of hyperanosognosia (subject complaint > study-partner complaint). We also want to include a measure of executive dysfunction which is known both as a symptom of AD and as a cognitive correlate of anosognosia. The executive score would be a further variable taken into account for modeling the AD Course Map, and we would like to study when it becomes abnormal to better understand the dynamics of the disease and of the reduction in awareness.

Neural correlates of ACD in pre-dementia AD 10

This chapter presents some unpublished results. The article Cacciamani, F., Houot, H., Thibeau-Sutre, E., Migliaccio, R., Epelbaum, E., Neural Correlates of Awareness of Cognitive Decline in Pre-Dementia Alzheimer's Disease: a Multimodal Study, is in preparation.

The neuroanatomical substrate of changes in ACD and the pathological mechanisms underlying them are a matter of debate. It is indeed a symptom common to many neurological diseases and might take different forms depending on the underlying pathology and the location of brain damage.

In the first seminal studies on the subject, anosognosia for hemiplegia was described as the consequence of damage to the right parietal lobe mostly due to stroke (Poltz, 1925; Barkman, 1925). But a more recent meta-analysis that gathers decades of research on this topic (Pia, 2004) found that anosognosia for hemiplegia is linked to damage to the frontal, parietal, or temporal cortex (separately or in combination, only right-sided or bilateral). Subcortical lesions may also be involved. Indeed, more than 40% of subjects presenting anosognosia due to hemiplegia presented extensive subcortical lesions, especially in the basal ganglia. In this meta-analysis, the likelihood of anosognosia was highest when the lesions were in both the parietal and the frontal lobes.

The brain damage observed in patients with AD is not the same as that observed in the classical cases of anosognosia for hemiplegia described in the literature. AD is a complex disease underlined by many pathological processes, which do not occur suddenly but

gradually and sequentially (Jack et al., 2010). For example, the accumulation of beta-amyloid is considered an upstream process, followed by the accumulation of phosphorylated Tau, decreased brain glucose metabolism and cortical atrophy, to name just the main ones (Jack et al., 2010). The identification of these processes in a given patient allows us to trace the evolution of the disease, or at least of its neuropathology. In fact, the correspondence between neuropathology and clinical manifestation is complicated by interindividual differences in the brain and cognitive reserve, as well as by comorbidities (Stern, 2012).

As in the hemiplegia studies, anosognosia was also associated with frontal, parietal and temporal brain damage in AD. Specifically, anosognosia in AD dementia and MCI has been associated with both functional (such as decreased glucose metabolism) and structural (such as decreased grey matter volume) alterations in the lateral and medial prefrontal cortex (Harwood et al., 2005; Hanyu et al., 2008; Jedidi et al., 2014; Fujimoto et al., 2017; Derouesne et al., 1999), the lateral and medial parietal cortex (Ries et al., 2007; Nobili et al., 2010; Ott, 1996; Salmon et al., 2006), and in the medial temporal lobe, including the hippocampus, but the latter's involvement is more conflictual. For example, medial temporal atrophy was not associated with anosognosia in Fujimoto et al. (2017), while other authors have found greater medial temporal hypometabolism and atrophy in anosognostic patients with dementia or MCI (Salmon et al., 2006; Tondelli et al., 2018; Vannini et al., 2017). In these studies, the brain damage was not clearly lateralized in the right hemisphere.

As interest in the study of ACD has recently shifted to the pre-dementia stages, including the preclinical stage, we wanted to address the paucity of neuroimaging studies on the subject.

10.1 Aim

In this multimodal study we investigated which pathological processes (including amyloid accumulation, hypometabolism and atrophy) at regional level (in the prefrontal, inferior parietal and medial temporal lobes) could drive changes in ACD in pre-dementia AD.

10.2.1 Participants

This cohort study analyzed data from the Alzheimer's Disease Neuroimaging Initiative (ADNI, <http://adni.loni.usc.edu>) cohort. The ADNI is a multicenter longitudinal study launched in 2003 with the aim of identifying biomarkers capable of detecting AD as early as possible and monitoring its evolution. ADNI investigators contributed to its design and implementation and 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.

We have selected three groups of subjects.

The first group consisted of cognitively-normal subjects with positive amyloid status at baseline (CN/A+), that is subjects at risk of AD or with "preclinical AD" according to the IWG criteria. In the ADNI, subjects were classified as CN if they had normal memory on the Wechsler Memory Scaled - Revised Logical Memory II test, a Mini-Mental State Examination (MMSE) score between 24 and 30 inclusive, Clinical Dementia Rating (CDR) = 0, and they could perform daily activities as usual. Subjects were considered as amyloid positive based on the same criteria as in Chapters 5 (see 5.2.1) and 9 (see 9.2.1). Subjects were considered A+ if at least one of the three markers was positive at baseline.

The second group consisted of MCI subjects with positive amyloid status at baseline (MCI/A+), that is subjects with "prodromal AD" according to the IWG criteria. In the ADNI, subjects were classified as MCI if they had memory complaints as reported by the subject, his/her study-partner or clinician, abnormal performance on the Logical Memory II test, MMSE between 24 and 30 inclusive, CDR = 0.5, and global cognition and functional performance preserved enough that a diagnosis of AD cannot be made.

The third group consisted of control subjects who had normal cognition and negative amyloid status (i.e., all three amyloid markers listed above were negative) at each available visit.

A study-partner who had frequent contact with the subject also took part in the research.

10.2.2 Awareness of cognitive decline index (ACDI)

The examiners administered two parallel forms of the Everyday Cognition questionnaire, ECog (Farias et al., 2008), one to the subject and one to his/her study-partner (ECog-Subject and ECog-StudyPartner). This questionnaire asks to evaluate if the subject's cognitive functioning is unchanged, better or worse than that of 10 years earlier. For example, the first item is: "Remember some shopping items without a list". The participant answers on a 4-point scale from 1 ("No change or performs better than 10 years ago") to 4 ("Performs this task much worse than 10 years ago"). Both parallel forms of the questionnaire are composed of 39 items, and the two scores are the average of the participant's responses (thus ranging from 1 to 4). The total ECog score was calculated when at least 50% of the questions were answered.

As an index of awareness of cognitive decline (ACDI), we used the subject-informant discrepancy (ECog-Subject *minus* ECog-StudyPartner). The ACDI is therefore a continuous measure ranging from -3 to 3. An ACDI of 0 indicates perfect agreement between the subject and the study-partner. High ACDIs indicate that the subject reports more cognitive difficulties than the study-partner. Lower ACDIs indicates that the subject reports less cognitive difficulties than the study-partner (anosognosia).

10.2.3 Biomarkers

We used regional measures of amyloid load (^{18}F -AV-45 PET), brain glucose metabolism (^{18}F -FDG PET), and cortical thickness as index of atrophy (T1 MRI). Technical procedures manuals can be found in <https://adni.loni.usc.edu/>.

First, we extracted the amyloid load, metabolism, thickness and surface of each region of the AICHA (for Atlas of Intrinsic Connectivity of Homotopic Areas) atlas (Joliot et al., 2015). It includes the whole brain, and the parcellation is based on resting-state fMRI data acquired from 281 individuals. Each region of interest (ROI) comprises voxels with homogeneous intrinsic activity, and has a contralateral homotopic counterpart, which makes this atlas a good tool for studying hemispherical asymmetries. The ROIs are rather small, allowing us to combine them to form our macro-ROIs. To extract the amyloid load, metabolism, thickness and surface of AICHA ROIs, we used Clinica, a software platform developed by the ARAMISLab, Paris Brain Institute (<https://www.clinica.run/>) for clinical research that involves the acquisition of multimodal data.

Amyloid load and brain metabolism were calculated by applying the pet-volume pipeline to PET scans acquired with ^{18}F -AV-45 (for amyloid load) and ^{18}F -FDG (for metabolism) tracers. The pipeline first performs intra-subject registration of the PET image into the space of the subject's T1-weighted MR image using SPM (<https://www.fil.ion.ucl.ac.uk/spm/>). The PET image is corrected for partial volume effects using the PETPVC toolbox (<https://github.com/UCL/PETPV>). The image is then spatially normalized into MNI space using SPM DARTEL deformation model, and intensity is normalized using the average PET uptake in a reference region (pons + cerebellum for ^{18}F -AV-45, and pons for ^{18}F -FDG). Finally, the average ^{18}F -AV-45 and ^{18}F -FDG uptake values are computed for AICHA ROIs. Regarding thickness and surface, they were calculated for each region from T1-weighted MR images with the t1-freesurfer pipeline, which is a wrapper of FreeSurfer's recon-all command (<http://surfer.nmr.mgh.harvard.edu/>). This processing includes segmentation of subcortical structures, extraction of cortical surfaces, estimation of cortical thickness, spatial normalization onto the FreeSurfer surface template (FsAverage), and parcellation of cortical regions. Since the AICHA atlas is not integrated in FreeSurfer, we relied on the converted version in FreeSurfer format provided by Faskowitz (2019).

Second, based on previous literature findings on neural correlates of self-awareness in AD dementia (see 2.2.2), we focused our analyses on three brain areas: bilateral prefrontal cortex (PFC), inferior parietal lobe (IPL), and medial temporal lobe (MTL). We then selected

three sets of AICHA ROIs to form these areas (meta-ROIs, Figure 1). A complete list of the AICHA ROIs that we have selected is presented in the supplementary material.

Third, the amyloid load, metabolism and cortical thickness of the 3 bilateral meta-ROIs (PFC, IPL, MTL) was calculated by means of a weighted average for the size of each AICHA ROI. For each meta-ROI, we computed baseline amyloid, metabolism and thickness (Amyloid_BL, Metabolism_BL and Thickness_BL) and the rate of variation in metabolism and thickness. Metabolism_var and Thickness_var represent the variation in metabolism and cortical thickness from baseline to the 2-year visit (we subtracted the baseline value from that measured at 2 years, and then divided the result by the baseline value).

We also included a measure of tau pathology, i.e., the level of phosphorylated tau in cerebrospinal fluid (CSF pTau, see <http://adni.loni.usc.edu/methods/> for CSF analysis procedures in ADNI). pTau > 23 pg/ml indicated a positive status (T+), while pTau < 23 pg/ml indicated negative status (T-) (Shaw et al., 2009). Many participants had not undergone a lumbar puncture and therefore had an unknown Tau status (Tu), which led us to consider this measure only for the purposes of describing the sample, and not for the selection of subjects or for the study of neuronal correlates.

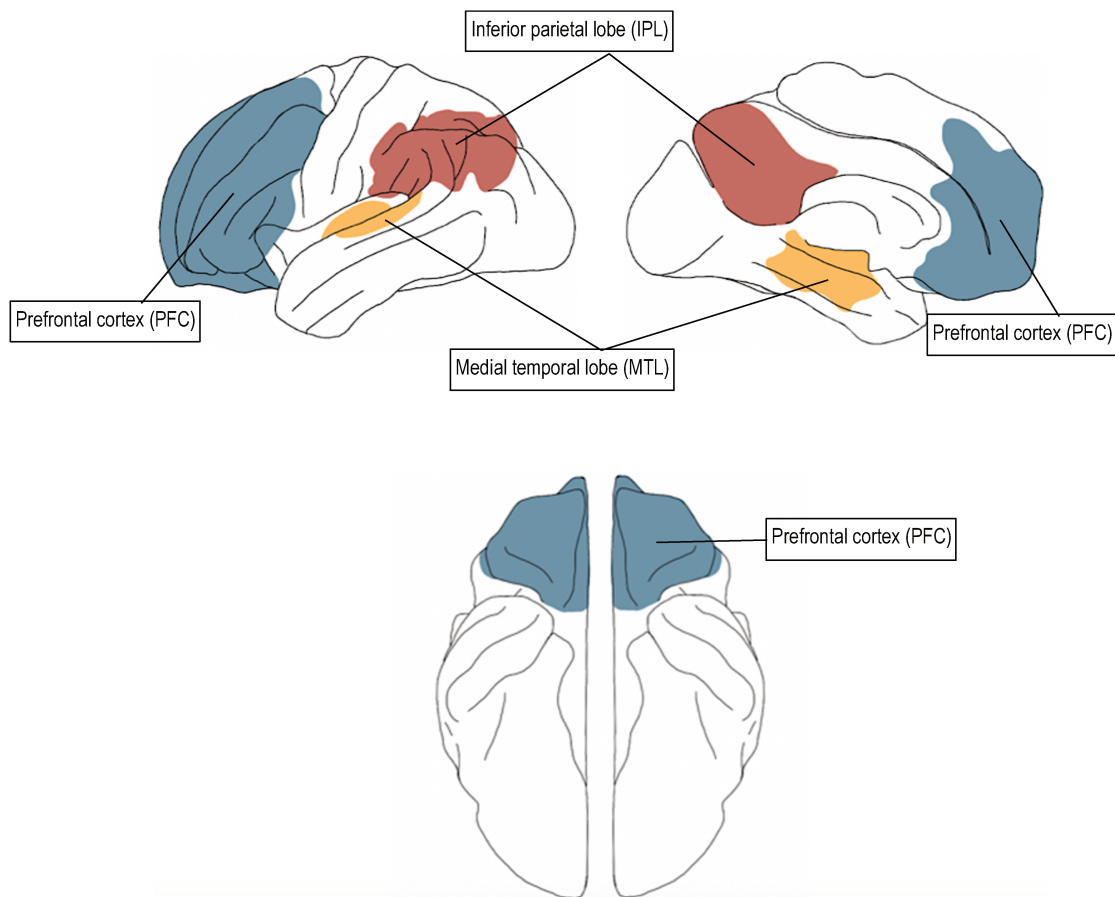
10.2.3 Statistical analysis

Statistical analyses were performed using R 3.6.1. (R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org/>).

Sample description

We performed between-group comparisons (i.e., CN/A-, CN/A+, and MCI/A+) of baseline demographical and clinical data, using Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. When significant, pairwise Mann-Whitney-Wilcoxon tests for continuous variables, and pairwise Fisher's exact tests for categorical variables, both with Benjamini-Hochberg correction, were performed for pairwise comparisons.

Figure 1. Prefrontal, medial temporal and inferior parietal meta-ROIs in lateral, sagittal and inferior view.



Note. The 3 bilateral meta-ROIs used in this study were created by averaging selected ROIs from the AICHA atlas.

Linear Mixed Models (LMM)

We performed a linear mixed model (LMM) for each of the 6 meta-ROIs (bilateral PFC, IPL, MTL). In each LMM, the participant ID was the random intercept. The ACDI was the dependent variable. As fixed effects, we used: age at baseline, gender, education, the three-way interactions between Time(in months)*Group*biomarker at baseline and its rate of variation, and their main effects and two-way interactions. For each meta-ROI, only the higher significant interaction(s) or main effect(s) will be presented in the Results section.

The metabolism and cortical thickness indices, both at baseline and their variation in 2 years, were multiplied by -1 to make them easier to interpret in relation to the amyloid load,

so that higher values meant greater damage. For Metabolism_var and Thickness_var, all changes in periods of less than 24 months have been set at 0.

To manage the issue of multiple comparisons related to the 6 meta-ROIs, the Benjamini-Hochberg procedure was applied.

Type II Wald chi-square tests were used to test the significance of the effects. Cohen's f^2 were calculated using the marginal R^2 (Nakagawa, Schielzeth, O'Hara, 2013) to assess effect sizes. Whenever the main effect of Group or an interaction involving the Group effect were significant, we performed post-hoc tests for pairwise comparisons. Normality of residuals and random effects, as well as heteroskedasticity, were checked visually. Cook's distances and hat values were computed to investigate potential influencers and outliers.

10.3 Results

10.3.1 Study population description

One subject (ADNI0099S4086) has been excluded due to the low quality of gray matter segmentation. Among the 729 visits available, 36 were excluded due to unavailable ACDI, and a total of 693 visits remained. Therefore, 113 subjects were eligible for this study. Of these, at baseline, approximately half ($n = 56$) were CN/A- (controls), 25% ($n = 28$) were CN/A+, and 25% ($n = 29$) were MCI/A+. Of the CN/A+ subjects, 18 were CN at all visits, 7 were diagnosed with MCI during follow-up, 1 was diagnosed with AD, and 2 were diagnosed first with MCI and then with AD. Of the MCI/A+ subjects, 24 had MCI at all visits, and 5 were diagnosed with AD during follow-up.

Between-group comparisons are shown in Table 1. Twenty-five percent of CN/A- controls had at least 96 months of follow-up, while 25% of CN/A+ and of MCI/A+ subjects had at least 84 months of follow-up (the difference being significant when comparing CN/A- and MCI/A+ subjects, pairwise Mann-Whitney-Wilcoxon corrected $p = 0.045$). CN/A+ subjects were older at baseline than the other groups ($p = 0.017$). Among the CN/A+ and MCI/A+ subjects there were more APOE- $\epsilon 4$ carriers (46% and 59% respectively) than among the

CN/A- controls (16%, $p < 0.001$). There was no other difference in terms of demographic characteristics, tau pathology and number of visits available. The ACDI was lower in MCI subjects than in the two CN groups, but this result did not survive correction for multiple comparisons.

Table 1. Between-group comparisons of demographic and clinical characteristics

	CN/A- ^(a) N=56 (49.56%)	CN/A+ ^(b) N=28 (24.78%)	MCI/A+ ^(c) N=29 (25.66%)	p [‡]
Number of visits	6.00 [5.00, 7.00]	6.00 [5.00, 7.00]	6.00 [6.00, 7.00]	0.228
Follow-up (months)	84.00 [48.00, 96.00] ^c	72.00 [48.00, 84.00]	60.00 [48.00, 84.00] ^a	0.031*
Age at baseline (years)	71.40 [67.70, 76.32] ^b	75.25 [70.80, 80.40] ^{a, c}	71.40 [66.60, 74.80] ^b	0.017*
Gender, women	26 (46.43%)	17 (60.71%)	16 (55.17%)	0.431
Education in years	17.50 [16.00, 19.00]	16.00 [14.75, 18.00]	16.00 [13.00, 18.00]	0.360
Tau status				0.129
T-	34 (60.71%)	12 (42.86%)	13 (44.83%)	
T+	14 (25.00%)	14 (50.00%)	14 (48.28%)	
Tu	8 (14.29%)	2 (7.14%)	2 (6.90%)	
APOE ϵ 4 copies				<0.01*
0	47 (83.93%) ^{b, c}	15 (53.57%) ^a	12 (41.38%) ^a	
1 or 2	9 (16.07%)	13 (46.43%)	17 (58.62%)	
ACDI at baseline	0.08 [0.02, 0.18]	0.23 [-0.02, 0.28]	-0.08 [-0.41, 0.28]	0.041*

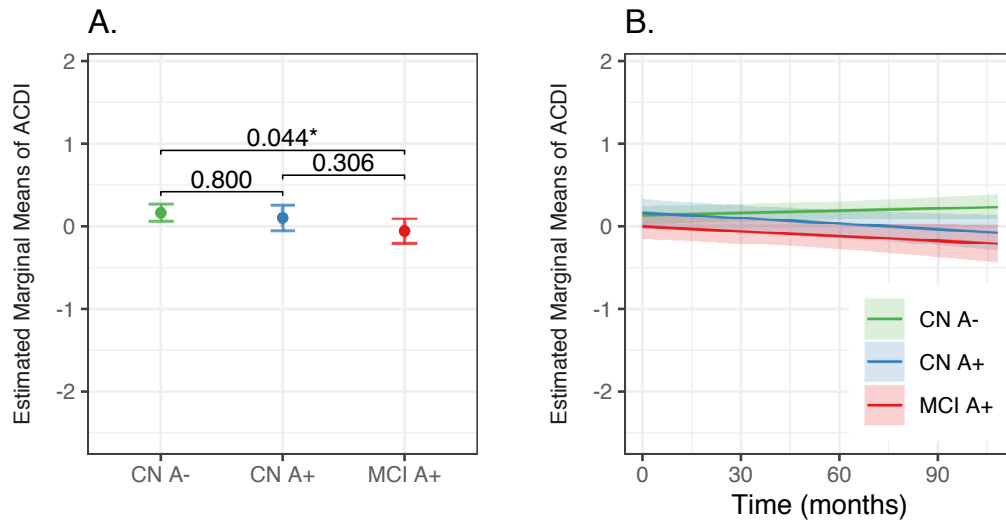
Note. Data are given as median [1st quartile, 3rd quartile] for continuous variables, as count (percentages) for categorical variables. [‡] Kruskal-Wallis test was used to compare groups for continuous variables and Fisher's exact test for categorical variables. Pairwise Mann-Whitney-Wilcoxon tests for continuous variables, and pairwise Fisher's exact tests for categorical variables, both with Benjamini-Hochberg correction were performed for pairwise comparison.

10.3.2 Linear Mixed Models

The results of the linear mixed models are presented in Figure 2 and Table 2.

The ACDI was not different between the three groups (main effect of Group, all $p > 0.523$), nor were their longitudinal trajectories (Time*Group interaction, all $p > 0.347$) (Figure 2).

Figure 2. ACD at baseline in the three clinical groups (A) and their longitudinal changes (B).



Note. Estimated Marginal Means of ACDI were computed on LMM without the 3 biomarkers at baseline and their rates of variation. Abscissa and ordinate limits are the minimum and maximum values observed in the data. * Indicates statistically significant differences

Effect of amyloid load on the ACD

The amyloid load in bilateral PFC and IPL at baseline had a statistically significant effect on ACD (main effect of Amyloid_{BL}; all Cohen's $f^2 > 0.026$, all $p_{\text{corrected}} = 0.039$). More specifically, subjects who had greater amyloid accumulation in bilateral PFC and IPL were more anosognostic. No difference between groups was observed in this pattern (non-significant Group**Amyloid_{BL}* interaction; all $p > 0.740$).

On the contrary, amyloid at baseline had no effect on the evolution of ACD, neither in the whole sample nor in the three groups taken separately (non-significant Time**Amyloid_{BL}* and Group*Time**Amyloid_{BL}* interactions; all $p > 0.282$).

Effect of hypometabolism on the ACD

Baseline metabolism had no effect on ACD (see Table 2 for more details).

On the contrary, the variation in metabolism in the right MTL had a different effect on ACD evolution according to the group (Group*Time*Metabolism_var interaction; Cohen's $f^2 = 0.007$, $p_{\text{corrected}} = 0.025$). More specifically, the more the metabolism decreased in the first two years in the CN/A+ subjects, the more they showed an increase in ACDI over time. There was no impact of Metabolism_var on the evolution of ACD in CN/A- and MCI/A+ subjects.

Effect of atrophy on the ACD

Cortical thickness at baseline had a different effect on ACD evolution according to the group (Group*Time*Thickness_BL interaction; all Cohen's $f^2 > 0.008$, all $p_{\text{corrected}} < 0.038$). More specifically, greater atrophy in the left MTL at baseline caused CN/A+ subjects to have increasing ACD over time, and MCI/A+ subjects to have decreasing ACD over time. No effect was observed for CN/A- controls. In addition, greater atrophy in the right PFC and bilateral IPL at baseline caused MCI/A+ subjects to have decreasing ACD over time, compared to both CN/A- and CN/A+ for which no impact was found.

The variation in cortical thickness had a different effect on the ACD according to the group (Group*Thickness_var interaction, all Cohen's $f^2 > 0.003$, all $p_{\text{corrected}} < 0.045$). Greater atrophy over time in left PFC and bilateral IPL caused MCI/A+ subjects to have low ACD, compared to both CN/A- and CN/A+ for which no impact was found.

The variation in cortical thickness also had a different effect on the evolution of the ACD according to the group (Group*Time*Thickness_var interaction, all Cohen's $f^2 > 0.004$, $p_{\text{corrected}} < 0.038$). The more the atrophy increased in the right MTL, the more the ACDI of the CN/A+ subjects decreased over time, compared to both CN/A- and CN/A+ subjects for which no impact was found. An increase in atrophy in the left MTL was associated with an increase in ACDI over time in CN/A+ subjects, a decrease in ACDI over time in MCI/A+ subjects, while it has no impact in CN/A- subjects. The more the atrophy increased in the right PFC, the more the ACDI of MCI/A+ subjects increased over time, compared to CN/A- controls for which no impact was found.

Table 2. Results of the linear mixed models

		Right PFC	Left PFC	Right IPL	Left IPL	Right MTL	Left MTL
Time	Cohen's f^2	0.001	0.001	0.001	0.001	0.001	0.001
	$p_{corrected}$	0.349	0.349	0.349	0.349	0.349	0.349
Group	Cohen's f^2	0.011	0.010	0.007	0.010	0.011	0.011
	$p_{corrected}$	0.523	0.523	0.603	0.523	0.523	0.523
Time*Group	Cohen's f^2	0.003	0.002	0.003	0.001	0.004	0.006
	$p_{corrected}$	0.691	0.691	0.551	0.875	0.551	0.347
Amyloid_BL	Cohen's f^2	0.033	0.023	0.026	0.029	0.015	0.003
	$p_{corrected}$	0.039*	0.039*	0.039*	0.039*	0.121	0.313
Group*Amyloid_BL	Cohen's f^2	0.012	0.005	0.007	0.005	0.006	<0.001
	$p_{corrected}$	0.740	0.740	0.740	0.740	0.740	0.969
Time*Amyloid_BL	Cohen's f^2	<0.001	<0.001	<0.001	0.003	0.001	0.002
	$p_{corrected}$	0.282	0.402	0.890	0.282	0.282	0.282
Group*Time*Amyloid_BL	Cohen's f^2	<0.001	<0.001	0.004	0.001	<0.001	0.005
	$p_{corrected}$	0.919	0.919	0.413	0.690	0.812	0.413
Metabolism_BL	Cohen's f^2	0.005	0.003	0.004	0.004	0.008	0.003
	$p_{corrected}$	0.359	0.359	0.359	0.359	0.359	0.359
Group*Metabolism_BL	Cohen's f^2	0.017	0.014	0.004	0.007	0.022	0.020
	$p_{corrected}$	0.435	0.435	0.713	0.698	0.435	0.435
Time*Metabolism_BL	Cohen's f^2	0.001	<0.001	0.002	0.001	<0.001	<0.001
	$p_{corrected}$	0.644	0.644	0.644	0.644	0.644	0.644
Group*Time*Metabolism_BL	Cohen's f^2	0.003	0.001	0.002	0.005	0.007	0.004
	$p_{corrected}$	0.415	0.655	0.659	0.439	0.256	0.439
Metabolism_var	Cohen's f^2	<0.001	0.003	<0.001	0.001	0.002	0.007
	$p_{corrected}$	0.516	0.301	0.882	0.583	0.301	0.301

Table 2. Results of the linear mixed models (Continued)

		Right PFC	Left PFC	Right IPL	Left IPL	Right MTL	Left MTL
Group*Metabolism_var	Cohen's f^2	0.009	0.004	0.005	0.001	0.007	0.019
	$p_{corrected}$	0.249	0.249	0.249	0.249	0.249	0.061
Time*Metabolism_var	Cohen's f^2	0.002	0.001	0.003	0.002	0.009	0.005
	$p_{corrected}$	0.188	0.209	0.161	0.225	0.031*	0.161
Group*Time*Metabolism_var	Cohen's f^2	0.005	0.001	<0.001	0.001	0.007	0.005
	$p_{corrected}$	0.194	0.738	0.738	0.433	0.025*	0.125
Thickness_BL	Cohen's f^2	<0.001	0.004	0.003	0.001	0.004	0.000
	$p_{corrected}$	0.921	0.708	0.708	0.708	0.708	0.921
Group*Thickness_BL	Cohen's f^2	0.009	0.010	0.006	0.004	0.017	0.026
	$p_{corrected}$	0.672	0.672	0.739	0.739	0.672	0.622
Time*Thickness_BL	Cohen's f^2	<0.001	<0.001	0.002	<0.001	0.003	0.002
	$p_{corrected}$	0.327	0.521	0.011*	0.327	0.327	0.327
Group*Time*Thickness_BL	Cohen's f^2	0.008	0.003	0.018	0.009	0.003	0.019
	$p_{corrected}$	0.038*	0.130	<0.001*	0.001*	0.451	0.001*
Thickness_var	Cohen's f^2	<0.001	<0.001	0.001	0.015	<0.001	0.007
	$p_{corrected}$	0.928	0.920	0.322	0.041*	0.507	0.322
Group*Thickness_var	Cohen's f^2	<0.001	0.003	0.027	0.023	0.001	0.006
	$p_{corrected}$	0.470	0.027*	0.027*	0.045*	0.589	0.203
Time*Thickness_var	Cohen's f^2	0.001	0.004	<0.001	<0.001	<0.001	<0.001
	$p_{corrected}$	0.533	0.407	0.460	0.171	0.366	0.476
Group*Time*Thickness_var	Cohen's f^2	0.013	0.008	<0.001	0.008	0.011	0.004
	$p_{corrected}$	0.038*	0.074	0.593	0.067	0.002*	0.002*

Note. In the LMM, the participant ID was the random intercept and the ACIDI was the dependent variable. A LMM was performed for each meta-ROI. P-values are adjusted for age at baseline, gender, education and corrected using Benjamini-Hochberg procedure.

Using multiple neuroimaging techniques, we investigated regional levels of amyloid accumulation, hypometabolism and atrophy to provide a more complete understanding of neural correlates of changes in ACD in pre-dementia AD.

10.4.1 Degree of ACD in pre-dementia AD

First, amyloid-positive, MCI subjects as a group, had poorer ACD than amyloid-negative controls. Literature results on ACD in prodromal AD are contradictory, suggesting that some of them are well aware of their decline, while others are not. In the present study, ACD is on average already reduced in prodromal AD, according to our recent meta-analysis (Chapter 7). In our meta-analysis, participants with MCI had a mild form of anosognosia because their ACD level was lower than in healthy controls, but higher than in patients with mild dementia.

ACD remained stable over time in A- controls, increased slightly in CN/A+ subjects, and decreased slightly in MCI subjects, but these two trends were not significant. We believe that with a longer follow-up and a larger sample, these would have been statistically significant. In fact, the median duration of follow-up was 5 years for the CN/A+ subjects and 6 years for the MCI/A+ subjects. Cognitive and functional decline in AD is known to be non-linear, as it accelerates over time, especially when objective deficits appear (Cloutier et al., 2015; Dubbelman et al., 2020). This means that disease progresses at a slow rate in the initial stages, and the 5-6 year follow-up of our CN and MCI participants may not have been enough to find clear changes in ACD. The slight longitudinal increase in ACD found in CN/A+ subjects indicates that subjects may first report difficulties that their informant does not notice (i.e., hyperanosognosia, Vannini et al. 2017). In the MCI stage, on the other hand, subjects would gradually show anosognosia (as in Hanseeuw et al., 2020).

10.4.2 Brain areas associated to ACD in AD

In our study, the neural correlate of ACD in pre-dementia AD was a fronto-temporo-parietal network with no clear predominance of frontal, temporal or parietal areas (Mondragón, 2019). Each of these regions could contribute to the phenomenon of anosognosia in a different way. The prefrontal cortex is known to be involved in cognitive control processes (Miller, 2000). It is involved in error detection (Stemmer, Segalowitz, Witzke, & Schönle, Invalid date) and in the prediction of the likelihood of making an error (Brown & Braver, 2005), among others. The median temporal structures, for their part, have a well-known role in episodic memory and more particularly in the creation of new memory traces, that is the storage of new memories in the brain. This is the typical damaged region in AD (see 2.3.2). It would therefore seem that another mechanism involved in anosognosia in AD is an alteration of memory for which the patient forgets to forget. Finally, the lower parietal lobe is an associative cortex involved in self-representation, including, for example, recognition of one's own face (Uddin et al., 2005), visuospatial perspective taking and self-localization (Lenggenhager et al., 2006). This suggests that AD patients with parietal damage would not be able to take a third-person perspective to assess their cognitive performance.

The network associated with the ACD was not clearly right-sided but bilateral. In the first studies on the subject, anosognosia for hemiplegia was the result of a right parietal lesions due to stroke (Langer & Levine, 2014). But later studies have shown that the left hemisphere is also involved. Cocchini et al. suggests that the prevalence of anosognosia in left stroke cases may have been underestimated due to the associated language deficits that could have induced bias. The prevalence of anosognosia detected would be affected by the measure of awareness used, verbal or visual (Cocchini et al., 2009). In the context of AD, some studies have indeed identified an association between anosognosia and left brain damage such that functional or structural damage in the left hemisphere was associated with greater anosognosia (Bertrand, E., 2021; Fujimoto et al., 2017; Shibata, 2008; Stemmer et al., Invalid date).

10.4.3 Association between ACD and pathological processes occurring in AD

Importantly, we found that greater accumulation of fronto-parietal amyloid was associated with reduced ACD in CN/A+ and MCI/A+ subjects, as well as in amyloid-negative controls.

This means that amyloid alone, even when it does not reach the value conventionally considered to be pathological, could lead to the emergence of certain cognitive-behavioral changes (in ACD in this case), against the common opinion that symptoms are mediated by tau pathology (Braak & Braak, 1991). However, it was not possible to include measurements of tau pathology in our models due to the unavailability of such data. It would therefore be interesting to understand whether the association between amyloid and ACD is direct, or mediated by tau pathology. In this study, amyloid was associated with ACD at baseline, but was not associated with longitudinal changes in ACD. It therefore seems that the accumulation of amyloid would trigger the changes in ACD but then other mechanisms would take over. Alternatively, it is possible that amyloid did not affect the longitudinal changes in ACD in our study because follow-up was too short and therefore ACD was generally little changed.

We also found that increasingly marked right medial temporal hypometabolism induces hypernosognosia in CN/A+ subjects. This term, previously proposed by Vannini et al. (2017), indicates the condition in which a subject expresses a cognitive complaint that the study-partner or tests do not detect. In the study by Vannini et al, this condition was typical of subjects who were developing the disease, without it being manifest yet. Likewise, in our study those subjects with a high amyloid load and increasing hypometabolism in the right medial temporal lobe appeared to have a subtle cognitive decline, not marked enough to be classified as MCI, but enough for the subject to perceive it and report it to the examiner.

Finally, we found that left medial temporal atrophy led CN/A+ subjects to report more cognitive impairment than their study-partner (hypernosognosia), while right medial temporal atrophy that worsened over time resulted in the same group (CN/A+) to be poorly aware. MCI subjects with greater temporal, parietal and frontal atrophy are increasingly anosognostic over time.

10.4.4 Limitations and future perspectives

We acknowledge some limitations in this study. First, the strict inclusion criteria (especially the availability of biomarkers) reduced our sample size, and therefore we could have had

greater statistic power with a greater number of participants. Second, we used amyloid status to define the condition of an individual at risk because tau status was unknown for most subjects, and according to Dubois et al. the condition of preclinical AD is referred to cognitively-intact individuals with at least one positive pathophysiological marker between amyloid and tau (Dubois et al., 2016). However, this may be less specific than considering both amyloid and tau. Further studies could also attempt to understand whether the regional level of tau pathology is related to hypernosognosia and anosognosia. Third, we chose to study three specific macro regions already known to be associated with anosognosia in AD because this allowed us to simplify the analyzes and clarify the discussion around the three biomarkers (amyloid, metabolism, atrophy). However, this could prevent the discovery of as yet undescribed regions involved in self-awareness. In addition, there may be some heterogeneity among the participants. Some subjects may have more frontal damage, others more temporal damage, and still others more parietal damage. Studying these subjects as a group may have masked such inter-individual differences. Finally, future studies could explore the hypothesis already supported by Perrotin et al. according to which there would be a disconnection between the medial temporal regions, a system linked to memory, and the fronto-parietal network, which is part of the default mode network and underlies the processes linked to the self (Perrotin et al., 2015).

IV

Further considerations and implications

Implications of the study of ACD and SCD in early-stage AD 11

The studies described above have shown that individuals with early-stage AD tend at first to complain of a subclinical decline in their cognitive performance (Jack et al., 2018) not yet detected by tests or by the people around them. This condition has been called *hypermnesia* (Vannini et al., 2017). However, it should be noted that elderly individuals with negative AD biomarkers also exhibited this behaviour in our studies, making us question its specificity and usefulness for diagnosis.

The hypermnesia ended approximately at the time of progression from preclinical to prodromal AD, when the assessment patients made of their own cognitive efficiency coincided with that made by their study-partner or by cognitive tests. Then, there was a ceiling effect, whereby subjective cognitive complaints did not increase in intensity as the disease progressed (or increased slightly) as a result of what has been called *petrified self* (see 2.2.2). During the prodromal phase, patients began to considerably underestimate the severity of their disorders (although they may continue to report some degree of cognitive difficulty), and clear anosognosia was observed in the dementia phase.

This pattern is not supposed to be detected in all Alzheimer's patients. A variability may be ascribed to inter-individual differences in clinical phenotype of AD (and therefore in brain damage), premorbid personality traits, levels of anxiety, depression and nosophobia, comorbidity, cognitive reserve, among other factors (Alladi et al., 2006; Stern, 2012). Individual variability may range from severely decreased ACD since early pathological changes, to preserved ACD throughout the disease.

We also described a second scenario (e.g., as in Chapter 4) which refers to individuals with persistent complaints not confirmed by tests or an informant. These individuals did not have an underlying AD pathology in our studies. This behavior is typical of worried-well individuals, defined by the International Classification of Diseases (ICD-10, code Z71.1), as "Individuals with feared complaint in whom no diagnosis is made" (World Health Organization (WHO), 1993), or of individuals with hypochondria, when the concern is such as to represent a psychiatric disorder.

11.1 Implications for clinical practice

11.1.1 Early diagnosis of AD: the role of an informant

Our ability to detect AD in an individual and make an accurate diagnosis has improved dramatically over the past decades. Since the 1990s and 2000s and thanks to technical and scientific progress, we now have increasingly precise diagnostic techniques which allow, for example, to visualize the patient's brain *in vivo* or to measure the presence of abnormal proteins characteristic of the disease (Gustaw-Rothenberg, 2010). The discovery of biological markers of the disease was therefore crucial for the description of its early stages, and it still is for individuals for whom the diagnostic process is undertaken and the risk of progression to dementia is intended to be established. However, biomarkers are not the optimal candidate for large-scale prevention, mainly because they are high-cost and sometimes invasive (Levy, 2016). Parallel to the attempts to identify new and more sensitive and specific biomarkers, it

is also necessary to identify cognitive indicators of the disease. They would evaluate the core clinical feature that biomarkers basically only predict (Levy, 2016), with the important advantages of being faster, less expensive and less invasive than imaging or CSF analysis. The description of the typical hippocampal amnesic profile of AD is an example (Sarazin et al., 2010), and rapid screening tests, such as the '5 words' test (Dubois et al., 2002), have been developed to early detect this syndrome in patients, as well as more comprehensive neuropsychological tests, such as the FCSRT (Grober & Buschke, 1987).

The study of SCD and ACD, their evolution and neural correlates, is a piece of the broader understanding of pre-dementia stages and a potential early cognitive indicators of AD pathology. Understanding how patients harboring AD perceive their decline, how they (and/or their family) first refer to a doctor, and what difficulties they tend to report most frequently, is of particular importance especially for general practitioners (GPs) who are mostly of cases the first doctor that the patient and his/her caregiver meet (Iliffe et al., 2004). Characterizing the SCD and ACD of patients with AD (and other neurological diseases) can provide the GP with a tool that allows him/her (i) either to refer the patient to a specialist doctor and performing examinations such as neuropsychological testing or imaging, or (ii) to reassure the patient and avoid the costs and psychological burden associated with the aforementioned specialist visits.

A first key conclusion that can be drawn from the studies above is that the subject's cognitive complaint taken individually may not be specific enough to guide the diagnosis.

Consequently, a second critical implication to retain from these studies is that the confirmation by an informant (or by the tests) is one of the most important factors to consider when a patient seeks medical advice for a cognitive complaint. Patients seeking medical help for a purely subjective cognitive complaint not confirmed by tests or the informant may have AD, but also other pathological conditions, or may be

simply reporting cognitive changes associated with normal aging. In addition, when the individual complains of a decline greater than that detected by the informant or by the tests for a long time (3 years in our study), he/she is probably not affected by AD (see Chapter 4), because ACD usually gradually decrease in AD.

The ultimate goal is to become sufficiently accurate in early diagnostic procedures to avoid false positives and associated anxiety and worry (Merckelbach, 2012), and false negatives, preventing them from taking advantage of the benefits of early diagnosis listed below.

11.1.2 Benefits of early diagnosis of AD

More independent choices

First, when a diagnosis of AD is established at the predementia stage, the patient and his/her family will be informed of the expected progression of the disease, its duration and the symptoms that will occur, and will be able to plan his/her future. Early diagnosis allows the patient to make independent choices when he/she still has the cognitive abilities to do so. This may include the administration of his/her assets, the decision-making for a possible future institutionalization and for the end of life, interrupting or modulating their professional activity, and driving license suspension may also be considered at this stage (Fuermaier, 2019). The primary caregiver will know in advance the role he/she will play and will be able to plan ahead, manage his/her time and work, and make decisions for the years to come.

Second, the scientific literature shows that in most patients the diagnosis does not cause a catastrophic emotional reaction, even in those who are at the beginning of the disease, but on the contrary may substantially reduce their level of anxiety and depression (Carpenter, 2008). It answers the doubts and questions of the patient who perceives changes in mental faculties and reduces his/her feeling of uncertainty. AD patients who are aware of their disease may have thoughts of death after the diagnosis, especially when they have depression or other psychiatric symptoms that

are not necessarily related to the diagnosis but may be pre-existing. Patients with AD rarely commit suicide (Conejero, 2018). Conversely, the risk of death by suicide is higher in other neurological diseases such as amyotrophic lateral sclerosis or Huntington's disease. The impact of the diagnosis also strongly depends on how it is made and communicated. It should also be noted that currently an early diagnosis is made as soon as the patient and/or those around him/her ask for medical help, because they realize that cognitive changes are occurring in the patient. In the absence of disease-modifying treatments, indeed, the tendency is not to detect AD as soon as possible in a certain individual, but to make a diagnosis as soon as the patient comes to the attention of the clinician (Dubois et al., 2011), seeking medical help (although this specific point might change in the future depending on the impact of upcoming disease-modifying treatments). This clearly shows the importance of characterizing ACD in AD: the presence of early poor ACD can delay seeking help and prevent an early diagnosis from being made.

Finally, there is a strong economic argument in favour of an early diagnosis of AD. The 2011 Alzheimer's Disease International report shows that each dementia patient costs society an average of \$ 32,865 per year in high-income countries. If we look at the cost of a high-quality diagnostic process, it is reported to be around \$ 5,000. Although the diagnostic and patient management process entails high initial costs, this still saves at least \$ 10,000 per subject in the long term as institutionalization has been delayed.

Greater therapeutic possibilities

Listening carefully to the patient's and informant's cognitive complaints and assessing the patient's degree of ACD is also important in defining the treatment plan. Because if this makes possible to make an early diagnosis, the patient will be able to benefit from various therapeutic possibilities which would not be possible if the diagnosis were made in the advanced stage.

First of all, and as explained in the Introduction (see 2.4.2), the cognitive decline that individuals complain of is not always due to AD. It can be due to normal age-related changes, or to a pathological condition other than AD. AD is in fact only one of the many conditions that cause cognitive impairment and complaints, despite being the most frequent. Some of these conditions are completely reversible (Day, 2019). In any case, medical advice should be sought as soon as the patient (and/or those around him/her) perceives cognitive changes, in order to immediately exclude other potentially curable medical conditions. In this context, it is therefore important to characterize the SCD typical of the patient with early-stage AD in order to make him/her undertake more in-depth examinations, but also to characterize the SCD suggestive of other pathologies for which the patient may need to consult a specialist. Anosognosia in diseases other than Alzheimer's is discussed below (Chapter 12).

The patient who is diagnosed with AD early will benefit most from the treatment. As with many other diseases, treatment options for AD are most effective when used when symptoms are mild. Conversely, most of the currently available pharmacological and non-pharmacological therapies lose their effectiveness if administered late.

To date, there is no treatment that can stop the course of the disease or return the patient to a normal cognitive state. However, some medications exist, such as cholinesterase inhibitors or the newly approved drug by the FDA (aducanumab) and can relieve and help manage the symptoms of the disease (Marasco, 2020). We also have non-pharmacological therapies (Zucchella et al., 2018), such as group cognitive stimulation or occupational therapy, which have been shown to be effective in improving the patient's quality of life. The patient could also participate in a clinical trial that involves the intake of experimental drugs not yet available on the market.

Development of territorial networks of assistance

Finally, and on a larger scale, if early diagnosis becomes usual in a given territory, then the development of a territorial network of assistance and treatment will be stimulated. This network would bring together general practitioners, specialists (e.g.,

neurologists, psychiatrists, geriatricians, etc.), paramedical professionals (neuropsychologists, speech therapists, occupational therapists), social services, etc., allowing for an interdisciplinary care plan, which is the most effective.

11.2 Implications for research

In recent years, several cohort studies involving cognitive-complainers have been created to target preclinical AD (a non-exhaustive list is presented in Table 1). However, the comparability of the results from these studies would be optimized if we could achieve a better harmonization of SCD research criteria. Moreover, a prevailing concept in the SCD literature is that SCD could be an entry condition for large-scale prevention studies. The results of the studies described above lead us to think that the presence of SCD, at least as it is currently defined, may not be an optimal inclusion criterion.

In addition, if the study focuses on MCI or prodromal AD, it should be noted that subjects may be partially anosognostic, and therefore the expression of a cognitive complaint may be an inclusion criterion leading to erroneous results.

Table 1. Inclusion criteria of studies enrolling cognitive-complainers.

	Criterion for cognitive complaints	Criterion for normal cognition	Presence of a study-partner	Exclusion criteria
INSIGHT-PreAD Cohort (Dubois et al., 2018)	Answer “yes” to: - Are you complaining about your memory? - Is it a regular complaint which lasts more than 6 months?	MMSE > 27 FCSRT TR ≥ 44 CDR = 0	Yes, but the informant-rating was not considered as an inclusion criterion	Having a neurological disease. Stroke that has occurred in the last three months
ADNI, Significant Memory Concern (SMC) group (http://adni.loni.usc.edu/)	Cognitive Change Index (CCI) ≥ 16	CDR = 0	Yes. The informant-rating was an inclusion criterion (i.e., it did not equate patient’s concern with progressive memory impairment)	MCI, dementia, psychiatric disorders, neurological diseases known to cause memory complaints, HIV, abuse of alcohol or other substances, language barrier
AIBL, SMC group (Ellis et al., 2019)	Answer “yes” to the following question: “Do you have difficulties with your memory?”	No test (or one test at most) at more than 1.5 SD below the age-adjusted mean	Yes, but the informant-rating was not considered as an inclusion criterion	Non-AD dementia, psychiatric disorders, PD, cancer within the last 2 years, symptomatic stroke, uncontrolled diabetes, current alcohol abuse
SCIENCE (Slot et al., 2018)	Cognitive Change Index (CCI-I) score > 16/80	no diagnosis of MCI, dementia, or any other disease known to cause memory complaints	Yes, but the informant-rating was not considered as an inclusion criterion	MCI, dementia, major psychiatric disorder, neurological diseases known to cause memory complaints (i.e., Parkinson’s disease, epilepsy), HIV, abuse of alcohol or other substances, and language barrier
DELCODE (Jessen et al., 2018)	subjectively reported decline in cognitive functioning with concerns as expressed to the physician of the memory center	better than -1.5 SDs below normal performance on all CERAD subtests	Not for the SCD group	Major psychiatric disorders, neurodegenerative disorder other than AD, vascular dementia, history of stroke, malignant disease, severe medical condition

Specificity of decreased awareness for Alzheimer's disease 12

In the years since Babinski's seminal description, anosognosia has been the focus of much scientific research, leaving the specific field of hemiplegia. Indeed, it has been studied in the context of many pathological conditions. We present below a sample of studies on anosognosia in three non-Alzheimer's neurodegenerative diseases.

12.1 Anosognosia in frontotemporal dementia

The term *frontotemporal dementia* encompasses a cluster of progressive cognitive disorders due to a neuronal loss in the frontal and temporal lobes (Young, 2018). There are few different clinical manifestations, which may also differ in the underlying pathology. FTD is highly heritable, although we probably know only a fraction of the genes involved (Le Ber, 2013). The most interesting variant of FTD to discuss in the context of anosognosia is the behavioural one (bvFTD), which is also the most common profile of FTD. Its clinical manifestation includes disinhibition, impulsiveness, inappropriateness in social contexts, or apathy and listlessness. In this variant, the involvement of the prefrontal cortex is more marked than in the other forms of FTD (Gordon et al., 2016). BvFTD is more frequently associated with a genetic mutation than other forms of FTD. Two examples of genes involved

are the progranulin gene (PGRN) associated with a TDP-43 pathology, and the C9orf72 gene is found in the majority of FTDs associated with amyotrophic lateral sclerosis with a TDP-43 pathology (Le Ber, 2013).

Anosognosia is one of the main features of bvFTD (Zamboni, Grafman, Krueger, Knutson, & Huey, 2010), especially in patients with significant impairment in social cognition and executive functions (Eslinger, 2005). They significantly overestimated themselves in several social, emotional and cognitive domains, and failed to recognize that a change in behaviour had occurred. This pattern of anosognosia has been described to be more prominent and diffuse than in the aphasic variants of FTD and patients with AD (Salmon et al., 2008; Eslinger et al., 2005).

During the PhD, we collaborated with Dr Isabelle Le Ber's team (Paris Brain Institute). Dr Le Ber is the coordinator of two cohort studies on the presymptomatic phase of genetic FTD: Predict-PGRN (PHRC Predict-PGRN 2008-2021) and PrevDemALS (ANR PRTS PrevDemALS 2015-2019). These studies include patients with GRN or C9orf72 mutations, respectively. More specifically, 75 participants were included in the Predict-PGRN cohort at baseline (including 8 symptomatic GRN carriers, 31 asymptomatic GRN carriers, and 36 at risk non-carrier relatives as controls). As for the PrevDemALS cohort, 113 participants were enrolled (including 19 symptomatic c9orf72 carriers, 46 asymptomatic c9orf72 carriers, and 44 at risk non-carrier relatives as controls). The studies had 3 time-points, at baseline, at 20, and 36 or 50 months (for PrevDemALS and Predict-PGRN, respectively). During their last visit between 2020 and 2021 (still ongoing), we asked participants to complete the HABCM questionnaire, where the participant and an informant compare the participant's cognitive functioning to that of 10 years ago (more details on the questionnaire are in Chapter 4).

To date (October 2021), we have collected data from 10 non-symptomatic at-risk parents (and their study-partners) from the Predict-PGRN cohort, and 24 non-symptomatic at-risk parents (and their study-partners) from the PrevDemALS study. The mean age was 51.6 years (SD = 11.84), 18 were men (52.9%) and 26 (76%) had a high level of education (high school or university). The study-partners were mainly the spouse (n = 27, 79.5%) and a minority were a child (n = 2), a parent (n = 3), or a friend (n = 4). Sixteen study-partners

were men (47%) and 28 (82%) had a high level of education (high school or university). We do not report here the analysis of these data, given that observations are still few in number and that data collection is still ongoing.

12.2 Anosognosia in Huntington's disease

Huntington's disease (HD) is a rare and inherited genetic neurodegenerative disease that causes motor disorders (chorea - that is, saccades or involuntary spasms - is the most characteristic symptom), cognitive and psychiatric disorders. Damage in the striatum has been observed in post-mortem examinations of individuals with HD, together with a substantial neuronal loss in white and grey matter in the frontal, temporal, parietal, and insular lobes (approximately 30% reduction in total brain weight) (de la Monte, S M, Vonsattel, & Richardson, 1988; Mann, 1993). The structures of the medial temporal lobe including the hippocampus are generally well preserved. Cognitive decline due to HD is progressive, eventually culminating in dementia, and characterized by a subcortico-frontal profile, including a dysexecutive syndrome, slowing of information processing and difficulties in memory retrieval (Rohrer D, 1999).

There exist far fewer studies on anosognosia in HD than in AD and FTD. Denial was initially described in these patients and often interpreted as a coping strategy (Hans & Gilmore, 1968; Mendez, Adams and Lewandowski, 1989). However, such denial behaviours may actually have a neurological nature. Unawareness has been observed across all disease domains. Patients may be unaware of their motor (Snowden et al., 1998; Vitale et al., 2001; Sitek et al., 2011), cognitive and psychiatric disorders (Ho, Robbins and Barker, 2006; Hoth et al., 2007). Poor awareness was also detected prior to the clinical diagnosis of HD (Duff et al., 2010). However, not all patients show anosognosia. In a study by McCusker et al. (2013) anosognosia for motor symptoms had a prevalence of 50%. In some studies, it has been shown that those who are more aware also report more depressive symptoms (Hoth et al., 2007). The difference in anosognosia may be linked to different patterns of impaired

connectivity between the striatum and the cortex, but comprehensive neuroimaging studies are still lacking.

12.3 Anosognosia in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized primarily by motor symptoms such as distal rest tremor, rigidity, bradykinesia, and frank asymmetry. The characteristic pathophysiological process of PD is the deregulation of the dopaminergic system due to the degeneration of the substantia nigra. This dopamine depletion deprives the prefrontal cortex of its extrinsic supply of dopamine (Scatton, 1982), leading to frontal lobe dysfunction. Another process that appears in PD patients is the accumulation of an abnormal protein, α -synuclein, which forms Lewy bodies. If at the beginning of the disease the Lewy bodies are generally limited in number and localized especially at a subcortical level, in some patients they can multiply to invade the cerebral cortex. When this happens, the clinical manifestation is difficult to distinguish from Lewy body dementia (Gomperts, 2016). Comorbidity with AD is also possible. The appearance of a storage disorder in episodic memory (hippocampal type amnesia) could indicate a comorbidity with AD.

MCI is common in PD (Litvan, 2012). MCI due to PD has a predominantly subcortical profile.

Although there are few studies on the subject, anosognosia is considered to be a rare symptom in PD. Non-demented patients usually express cognitive complaints (Hong, 2018) that are similar in intensity to the informant report and to the objective cognitive scores (Seltzer, Vasterling, Mathias, & Brennan, 2001). As for patients with dementia, they may show instead unawareness (Del Ser, Hachinski, Merskey, & Munoz, 2001), which correlated with lower levels of depression (Seltzer, Vasterling, Mathias, & Brennan, 2001). However, the studies do not clarify the dementia profile in these patients, not allowing to understand whether anosognosia can be associated with the advanced stages of PD itself, or with a comorbidity with AD or Lewy body disease.

12.4 Conclusion

In summary, among neurodegenerative conditions, impaired awareness is not specific to one particular disease, but rather seems to be associated with a progressive frontal, temporal and parietal damage, including cortical damage in these regions or in the connection of these cortical areas. However, while anosognosia is extensively studied in AD and especially in AD dementia, studies on clinical groups with different diagnoses are very few. Comparative studies could help clarify which brain regions are involved in self-awareness, regardless of the specific pathology in progress. A better description of how patients with neurodegenerative diseases perceive their cognitive, behavioural or motor changes, especially in the early stages of the disease, can help us make a more accurate differential diagnosis.

Is it advisable to treat anosognosia? 13

13.1 Rationale for the treatment of anosognosia

We are currently entering a new era in AD treatment as anti-amyloid antibodies are more and more recognized as having a disease-modifying effect (Mintun, 2021). On one hand, it seems reasonable to act on decreased ACD in preclinical AD so that patients might seek the required medical help they need. On the other hand, some may think that anosognosia serves as a protective mechanism that helps the patient cope with dementia, as awareness of being affected by a neurodegenerative disease would likely lead to a catastrophic emotional reaction. Greater awareness is indeed associated with depressed mood and anxiety (Horning et al., 2014).

However, the relationship between awareness and mood disorders is more complex than it appears. The depression exhibited by those most aware of the disease may also depend on their level of premorbid depression, their personality traits, social factors, as well as their co-morbidities. It can also be a symptom of AD and not necessarily related to the patient being disease-aware.

Anosognosia, whether partial or complete, has consequences on the patient's behaviour, which could make the treatment of anosognosia advisable, despite the risk of depression.

13.1.1 Delayed diagnosis

A first reason why it may be necessary to treat anosognosia is that reduced awareness often delays diagnosis (Castrillo Sanz et al., 2016). A patient who does not believe he/she has cognitive impairment will not seek medical help. Many, in fact, come to the doctor's attention because they have been convinced by family members to be examined. It is likely that he/she does not want to undergo specialized medical examinations, such as a lumbar puncture. The GP may find him/herself in the situation of having to make the patient more aware of his/her deficits in order to persuade him/her to consult a specialist doctor and to undergo further investigations.

13.1.2 Consequences of anosognosia on treatment

Also, anosognosia makes the patient unwilling to take medications, to participate in cognitive stimulation sessions and more generally to adhere the therapeutic plan, because he/she does not see the need for it. In Babinski's seminal description of anosognosia, we can already find that his hemiplegic and anosognostic patient, after listening to her doctors explain the treatment plan, said, "Why should I have electrical treatment? I am not paralyzed". It is known that anosognosia, as part of any underlying pathology, results in lower adherence to treatment, earlier institutionalization or more frequent hospitalizations (Amador & David, 2004). The association between anosognosia and compliance has been demonstrated in many scientific studies enrolling individuals with different diagnoses. For example, in Amador et al., the severity of anosognosia negatively correlated with treatment adherence in a group of patients with schizophrenia.

Another aspect to discuss is that an anosognostic patient who is motivated enough to adhere to treatment may assume to be able to achieve goals which are unrealistic in the context of AD: for example, the regression of cognitive impairment or the recovery of lost abilities. Failure to meet these goals can lead to feelings of frustration, anger, low self-esteem, and a lack of motivation to continue treatment.

Finally, in line with the general trend in medicine on “patient empowerment”, all patients should be given the opportunity to decide whether or not to undergo a medical or therapeutic measure, expressing their informed consent, weighing the benefits and risks of the procedure. When patients present with anosognosia, due to AD or other conditions, it may be unavoidable to resort to coercive measures, that is, implemented despite the verbal refusal or physical resistance of the patient, being the only way not to violate his/her right to health.

13.1.3 Dangerous behaviors

A third reason for increasing patient's self-awareness is that this could reduce the engagement in dangerous behaviors. Risky or dangerous behaviors can be common in people with AD. Certainly, such behaviors may be the direct consequence of their cognitive deficits. For example, patients can get lost due to their spatial disorientation. Or they may make poor financial decisions due to their executive dysfunction. The amnesic deficit often leads the patient to forget shutting off the stove or the tap, or to take the same medication twice. Attention disorders can adversely affect their driving skills. In a study by Hunt et al. (1993) a professional driving instructor judged 40% of the patients to be unsafe drivers, despite the fact that they and their study-partners found them to be safe. Anosognosia can play an important role in engaging in dangerous behaviors. Patients with anosognosia may initiate activities that are far more complex than their actual abilities, with the risk of hurting themselves or others. In a study by Starkstein et al., the frequency of dangerous behaviors during the previous month was 16% in patients with AD (at different stages of the disease) vs 2% in the control group. Patients with anosognosia were 3 times more likely to engage in dangerous behaviors. In contrast, the frequency of dangerous behaviors was not associated with age, education, and level of depression (Starkestein et al., 2007).

13.1.4 Caregiver burden

A fourth reason why one may consider intervening on anosognosia is that caregivers' sense of responsibility and commitment may be higher in the presence of reduced ACD or anosognosia, consequently having more chances to feel depressed and alienated (Jacus

et al., 2015; Mak, Chin, Ng, Yeo, & Hameed, 2015; Spalletta et al., 2012; Starkstein, Brockman, Bruce, & Petracca, 2010). Although caregivers acknowledge the patient's memory disorder, they are often puzzled by anosognosia and do not understand that their spouse or parent is no longer able to accomplish some tasks despite saying otherwise. Informing the caregivers about the nature of anosognosia and proper behavior towards it is already acting on anosognosia and alleviates the burden that it generates.

13.2 Existing methods for the management and treatment of anosognosia

It is therefore clear that the treatment of anosognosia can have positive implications despite the risk of depression or suicidal ideation. However, some recommendations on how anosognosia in AD might be treated are essential as it is a peculiar symptom and the aim of this treatment is not the same as for other symptoms of AD such as memory loss.

To our knowledge, there is currently no validated intervention to treat anosognosia due to AD or increase ACD. Methods developed in the context of other pathologies (brain injury, schizophrenia, etc.) could be used but patients with AD may present certain peculiarities that should be taken into consideration. To give an example, patients with hippocampal amnesic syndrome who are unable to learn new information need to be told repeatedly that they have memory problems requiring intervention. This may not be necessary in patients with other conditions who are still able to effectively store new information in memory. In addition to their applicability in AD, the interventions for anosognosia proposed in the literature also often lack a theoretical basis, the methods are often not very detailed and difficult to reproduce, and the results are seldom supported by a clinical trial with a large sample and a control group (Fleming, 2006).

In the context of brain injury, some authors have proposed neuropsychological rehabilitation programs as a possible treatment for anosognosia, with the idea that an improvement in neurocognitive disorders would lead the patient to be less anosognostic. Procedures such as cognitive remediation, cognitive exercises in small groups, and occupational therapy

have been shown to be effective on anosognosia in approximately 50% of patients (Prigatano, 1986). But it is crucial to stress that a considerable improvement in cognitive functions using neuropsychological rehabilitation is not expected in AD as in acquired brain injury, so the efficacy of these methods still needs to be clarified in patients with AD.

Another therapeutic technique for anosognosia, particularly used in the context of brain injury, is psychotherapy (Ownsworth et al., 2000). The objective is essentially to help the patient become more aware of the disease by accompanying him/her in the management of the feeling of helplessness, bitterness, fear that he/she may feel, and to help the patient build a new sense of self that includes awareness of illness (Prigatano, 1986). A team from the University Hospital of Marburg, Germany (Buchwitz et al., 2020), is developing an 8-week mindfulness-based program to increase the degree of awareness of patients with PD (IPSUM, "Insight into Parkinson's Disease Symptoms by using Mindfulness"). Patients are first informed of the objective of the program and its theoretical basis. They are taught mindfulness techniques, such as breathing techniques and how the latter can control behavior. This is followed by emotional education and the teaching of problem solving and stress reduction techniques, yoga and meditation. The efficacy of this method remains to be studied.

Finally, anosognosia could be treated by directly confronting the patients with their deficits. This method has its roots in occupational therapy (Katz et al., 2002) and consists in asking them to carry out activities of daily life, for example cooking, to try to make them more aware of their disabilities. However, the efficacy of this technique is limited. For example, increased awareness of difficulty in a certain task tends not to be generalized to other tasks, and overall awareness of the disease does not increase (Ownsworth, T., 2006b).

One way to give direct feedback to the patient on his/her cognitive difficulties can be by using a video recording. A camera captures the patient performing a task of daily living, and a healthy individual performing the same task may also be included, to facilitate comparison with premorbid abilities. In studies from the 80s and the 90s (Alexy, 1983; Mateer C A, 1999), it was already seen how the patient became aware of his/her deficits by watching the video and this awareness was still present a week later. A more recent study

compared the effect of watching the video on a patient 7 days after a stroke and on another patient 72 days after the stroke (Besharati, 2015). In both cases, seeing their disability in the brief video reduced their anosognosia for hemiplegia. It improved the adherence to the treatment, because after watching the video, they would say, for example, "We have to work hard". The fact that the intervention is effective both when it is performed in the acute and chronic phase means that the improvement is not due to the spontaneous remission of symptoms. This is important to emphasize when discussing the applicability of these methods to patients with AD, since remission of cognitive impairment is not expected in AD. The reason this method can be effective is that anosognostic patients generally have no difficulty judging the performance of others, while failing to evaluate their own (Marcel et al., 2004).

13.3 Specificities of the treatment of anosognosia in Alzheimer's disease

The literature on how to increase AD patients' awareness is very scarce. When increasing the patient's self-awareness is necessary, the clinician should follow the recommendations below, based on the biopsychosocial treatment for anosognosia by Ownsworth, Clare and Morris.

- Methods that involve direct feedback, such as watching a video, can be effective and easy to implement. On the contrary, all attempts to verbally convince the patient of his/her disability are futile, if not counterproductive and frustrating. Although the goal is to make the patient aware of his/her deficits, his/her point of view has to be respected. This will create a good alliance with the clinician or caregiver on which to base the intervention.
- The intervention should be done on multiple fronts:
 - 1) Neurocognitive: The patient should perform the tasks at an increasing level of difficulty according to his/her cognitive capacity to gradually become aware of his/her disorders. Bandura and later Togliatti & Kirk proposed the technique of *guided*

mastery: have the patient perform a task of the right level of difficulty so that he/she makes enough mistakes to realize that there is something wrong, but not too many to avoid excessive catastrophic reactions (Bandura, 1997; Togliola, 2000). It is also necessary to understand which cognitive functions are most important for him/her in everyday life. For example, if the patient with significant attention and visuospatial disorders persists in wanting to continue driving, it will be a priority to make him/her aware of these difficulties.

2) Psychological: it is important to understand the psychology of the patient before engaging in the treatment of his/her anosognosia. How does he/she usually react to failure and error? Furthermore, the patient must be accompanied in the identification of coping strategies in order to avoid a catastrophic emotional reaction following the awareness of the disease. He/she should establish a new sense of self by processing and accepting his/her losses (of capacity, of autonomy) and by promoting the acceptance of change.

3) Social: educate those around the patient in appropriate ways of communicating with him/her. Promote family understanding of the patient's disease and anosognosia. Help ensure that they represent a support system for the patient.

- When engaging in cognitive stimulation with an Alzheimer's patient, the intended purpose is to improve his/her memory or other cognitive functions as far as possible, or to slow his/her decline as far as possible. This is also the intended purpose of disease-modifying drugs currently being tested. On the contrary, the desired goal of treating anosognosia is not to make the patient fully aware of the diagnosis and what it implies for his/her future. Treatment of anosognosia should be done in moderation. It is advisable not to mention the diagnosis of AD whenever possible, so as not to elicit negative associations in the patient. The clinician could also focus only on the areas of concern: for example, the unawareness of attention disorders which make the patient an unsafe driver. In addition, situations that are suboptimal for the patient should be identified and they may serve as a pretext. For example, if the patient perceives that he/she needs a caregiver more than before and is bothered by this, he/she may be persuaded to take medications or perform tests

using the pretext that it will help him/her be more independent. Awareness is therefore not an all or nothing concept (Hart, 1998). Also, one should take into account the dynamic nature of anosognosia in AD.

These suggestions arise mainly thanks to our clinical experience and do not always find a counterpart in the scientific literature, because this subject is little studied. More structured studies should be conducted to objectively and rigorously assess the efficacy of intervention methods for anosognosia in patients with AD, especially at the beginning of the disease.

Conclusion 14

The aim of this thesis was to investigate the usefulness of a new potential early indicator of AD, that is reduced patient's awareness of his/her cognitive decline.

In summary, we have identified two scenarios for awareness of cognitive changes in the elderly through the 6 studies described above.

The first scenario concerns individuals at high risk for AD (in its typical amnesic variant). They present a subtle cognitive and functional decline in the preclinical phase of the disease which they are the only ones to notice (i.e., hyperanosognosia) and which they can report to their doctor. However, cognitive complaint not confirmed by an informant or tests is common in older adults, therefore its diagnostic utility is limited. Thereafter, patients begin to have abnormal scores on neuropsychological tests, and they soon begin to minimize the severity of their impairment compared to what a spouse, relative, or close friend reports. They continue to report a cognitive complaint, but this no longer matches the actual severity of their impairment. This behavior can be seen as an initial decline in self-awareness, which will gradually lead to frank anosognosia.

The second scenario concerns individuals who complain systematically and for a long period of cognitive difficulties with which neither their informant's opinion nor cognitive scores concur. These individuals are usually not affected by AD, and can be considered as "worried-well". We believe, but could not demonstrate due to the unavailability of this data, that this type of complaint refers to a benign decline in attention span impacting memory capacity, or in memory retrieval strategy, and probably due to normal aging, anxiety or depression (even subclinical).

The subjective cognitive decline itself would therefore not be specific enough to be of real use in the diagnostic process. Based on subjective complaints alone, people in the first scenario would not have received sufficient medical attention, while those in the second would have been mistakenly considered to be at high risk for AD. The clinician should carefully consider the patient's complaint, but also compare it to other more reliable sources of information, such as informant's complaint or cognitive scores. We demonstrated that the informant complaint was a valuable measure of cognitive decline. In research, these results may aid in a better selection of subjects to include in trials targeting pre-dementia AD.

A future research objective is to study the informant's complaint in more detail, and in particular in relation to his/her characteristics such as age, level of education, relationship with the patient. Indeed, we hypothesize that although the informant is generally a very useful source of information, his/her judgment could be biased by these characteristics. This would allow better selection of the patient's primary informant (or study-partner) when more than one is available.

We would also like to investigate the utility of ACD measures for AD differential diagnosis, since changes in ACD are not a specific feature of AD, but may still allow AD to be distinguished from other conditions that present with similar clinical features.

It would also be interesting to study how these new findings may have an impact on the attitude of individuals (patients and families) towards AD and early diagnosis. This could

possibly help minimize delays in medical help seeking by strengthening family's determination to see a memory specialist.

Finally, individual assistance to improve ACD through innovative digital or psychological means may also be considered a valuable research program.

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SCIENTIFIC PRODUCTION

Scientific articles published during the PhD and included in this thesis:

1. Cacciamani, F., Houot, M., Gagliardi, G., Dubois, B., Sikkes, S., Sánchez-Benavides, G., Denicolò, E., Molinuevo, J. L., Vannini, P., & Epelbaum, S. (2021). Awareness of Cognitive Decline in Patients With Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Frontiers in aging neuroscience*, 13, 697234. <https://doi.org/10.3389/fnagi.2021.697234>
2. Cacciamani, F., Sambati, L., Houot, M., Habert, M. O., Dubois, B., Epelbaum, S., & INSIGHT-PreAD study group (2020). Awareness of cognitive decline trajectories in asymptomatic individuals at risk for AD. *Alzheimer's research & therapy*, 12(1), 129. <https://doi.org/10.1186/s13195-020-00700-8>
3. Gagliardi, G., Houot, M., Cacciamani, F., Habert, M. O., Dubois, B., Epelbaum, S., & for ADNI; for the INSIGHT-preAD study group (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 research & therapy*, 12(1), 57. <https://doi.org/10.1186/s13195-020-00626-1>
4. Villeneuve, S. C., Houot, M., Cacciamani, F., Verrijp, M., Dubois, B., Sikkes, S., Epelbaum, S., & MEMENTO study group and the INSIGHT-preAD study group (2019). Latent class analysis identifies functional decline with Amsterdam IADL in preclinical Alzheimer's disease. *Alzheimer's & dementia (New York, N. Y.)*, 5, 553–562. <https://doi.org/10.1016/j.trci.2019.08.009>

Scientific articles published during the PhD and excluded from this thesis:

1. Mantoux, C., Couvy-Duchesne, B., Cacciamani, F., Epelbaum, S., Durrleman, S., & Allasonnière, S. (2021). Understanding the Variability in Graph Data Sets through Statistical Modeling on the Stiefel Manifold. *Entropy (Basel, Switzerland)*, 23(4), 490. <https://doi.org/10.3390/e23040490>

2. Gnassounou, R., Défontaines, B., Denolle, S., Brun, S., Schück, S., Germain, R., Schwartz, D., Cacciamani, F., Michon, A., Belin, C. and Mailler, D. (2020), Validation of a videoconference-based neuropsychological assessment: The e-COG study. *Alzheimer's Dement.*, 16: e047330. <https://doi.org/10.1002/alz.047330>

Book chapters in preparation:

1. Migliaccio, R. and Cacciamani, F. (Invited) The temporal lobe in typical and atypical Alzheimer's disease. In Miceli, Bartolomeo, and Navarro (Eds.), *The temporal lobe* (Elsevier).
2. Epelbaum, S. and Cacciamani, F., (Invited) Clinical Evaluations. In *Machine Learning for Brain Disorders*, Neuromethods series (Springer).

Scientific articles in preparation or under review:

1. Cacciamani, F., Houot, M., Thibeau-Sutre, E., Migliaccio, R., Epelbaum, S. (In preparation) Neural Correlates of Awareness of Cognitive Decline in Pre-Dementia Alzheimer's Disease: a Multimodal Study
2. Cacciamani, F., Koval, I., Valladier, A., Maheux, E., Durrleman, S., Epelbaum, S. (In preparation) Timing and order of pathological events in Alzheimer's disease: focus on the trajectory of the awareness of cognitive decline
3. Cacciamani, F., Godefroy, V., Brambati, S.M., Migliaccio, R., Epelbaum, S., Montembeault, M. (Submitted to *Frontiers in Aging Neuroscience*) Differential patterns of domain-specific cognitive complaints and awareness across the Alzheimer's disease spectrum

Scientific articles published before the PhD:

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Oral or poster presentations at congress or conferences:

1. Alzheimer's Association International Conference (AAIC), July 2021, *Changes in the awareness of cognitive decline across the course of Alzheimer's disease: comparison of two assessment methods*
2. AD / PD, March 2021, *Timing and order of pathological events in Alzheimer's disease: focus on the trajectory of the awareness of cognitive decline*
3. Alzheimer's Association International Conference (AAIC), July 2021, *Alzheimer's Association International Conference (AAIC), July 2021, Changes in the awareness of cognitive decline across the course of Alzheimer's disease: comparison of two assessment methods*
4. VIII Congress of the Italian Society of Neuropsychology (SINP), December 2019, *Consapevolezza del declino cognitivo lungo il decorso della malattia di Alzheimer: Revisione della letteratura, meta-analisi e proposta di un nuovo modello concettuale*

5. Alzheimer's Association International Conference (AAIC), July 2019, *The MEMOWAVE project: A phase I/II clinical trial targeting at treatment of MCI through sound stimulation during slow-wave sleep*
 6. Alzheimer's Association International Conference (AAIC), July 2019, *Unawareness of Cognitive Impairment in Alzheimer's Disease: A Review of the Current State of Art*
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