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Neuropsychology and neuroimaging profiles of amyloid-positive versus amyloid-negative amnestic mild cognitive impairment patients

Clémence Tomadesso[a,b], Vincent de La Sayette[a,c], Robin de Flores[b], Pierrick Bourgeat[d], Victor L. Villemagne[e,f], Stéphanie Egret[b], Francis Eustache[a], Gaël Chételat[b,*]

[a]*Inserm, Inserm U1077, Université de Caen Normandie, Ecole Pratique des Hautes Etudes, Caen, France*
[b]*Inserm, Inserm UMR-S U1237, Université de Caen-Normandie, GIP Cyceron, Boulevard H. Becquerel, Caen, France*
[c]*CHU de Caen, Service de Neurologie, Caen, France*
[d]*CSIRO Digital Productivity Flagship, The Australian e-Health Research Centre–BioMedIA, Herston, Queensland, Australia*
[e]*Department of Molecular Imaging and Therapy, Centre for PET, Austin Health, Heidelberg, Victoria, Australia*
[f]*The Florey Institute for Neuroscience and Mental Health, The University of Melbourne, Victoria, Australia*

Abstract

Introduction: Patients with amnestic mild cognitive impairment (aMCI) are heterogeneous as regard to their amyloid status. The present study aimed at highlighting the neuropsychological, brain atrophy, and hypometabolism profiles of amyloid-positive (Aβpos) versus amyloid-negative (Aβneg) aMCI patients.

Methods: Forty-four aMCI patients and 24 Aβneg healthy controls underwent neuropsychological, structural MRI, and fluoro-2-deoxy-D-glucose–positron emission tomography examinations. Data were compared between groups in specific regions of interest and voxelwise with SPM.

Results: When directly comparing Aβpos to Aβneg aMCI, the former had lower performances in episodic memory tests ($P = .02$ to $P < .001$) while the latter had worse scores in working memory ($P = .01$) and language ($P < .005$). Compared to Aβneg healthy controls, both aMCI subgroups showed similar profiles of atrophy and hypometabolism, with no difference between both aMCI subgroups.

Conclusion: In a sample of aMCI patients recruited and scanned in the same center, the main difference at baseline between Aβpos and Aβneg aMCI concerned the neuropsychological profile, but not the structural MRI or fluoro-2-deoxy-D-glucose–positron emission tomography profiles of brain alterations.

Keywords: Amyloid status; Amnestic mild cognitive impairment; Alzheimer's disease; Cognition; Glucose metabolism; Gray matter volume

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder defined pathologically by the presence of amyloid β (Aβ) plaques and tau-rich neurofibrillary tangles [1–4]. Cerebral Aβ pathology can be visualized in vivo using positron emission tomography (PET) imaging coupled with Aβ radioligands. Studies have shown increased brain Aβ load in AD patients compared to healthy elderly, with about 90% of patients with a clinical diagnosis of AD being classified as amyloid positive based on the PET scan [5]. Aβ is known to accumulate progressively 15 to 20 years before dementia and even years before the detection of clinical deficits [6]. Mild cognitive impairment refers to the clinical stage of cognitive decline that is greater than expected for a given age and educational attainment but does not interfere activities of daily living; such patients are generally considered to be in a predementia stage [7].

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*Corresponding author. Tel.: (+33) 2 3147 0173; Fax: (+33) 2 3147 0275.
E-mail address: chetelat@cyceron.fr

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When memory deficits are predominant, patients are called as amnestic mild cognitive impairment (aMCI) and thought to be more specifically at the prodromal stage of AD [8,9]. Yet, aMCI patients will not all progress to AD dementia [10], and they do not all present with an amyloid-positive PET scan [11–15]. Thus, 47%–75% of aMCI patients present with high cortical Aβ retention on amyloid PET [11,13,16–19]. aMCI patients with an amyloid-positive PET scan are more likely to convert to AD dementia: the percentage of progression to AD dementia over 2 to 3 years is 45% to 82% within the amyloid-positive aMCI (Aβpos aMCI) patients versus 0% to 11% within the amyloid-negative aMCI (Aβneg aMCI) [11,13,16–19]. A more extensive appraisal of aMCI patients who present with the same symptoms but differ as regard to the presence or absence of abnormal levels of amyloid deposition would help understanding the specific cognitive and brain changes associated with a particular molecular phenotype. This is of high relevance for clinical diagnosis, to screen patients for anti-amyloid clinical trials, and to improve our understanding of the role of amyloid deposition in the pathophysiology of AD.

Previous studies assessing differences in cognitive performances between Aβpos aMCI and Aβneg aMCI have consistently reported greater deficits in episodic memory in Aβpos patients [11,12,15]. Aβneg aMCI patients have been shown to be more impaired in nonepisodic memory domains compared to Aβpos aMCI [12,20], although this was not found in all studies [11,15]. As regard to brain atrophy, greater hippocampal atrophy in Aβpos aMCI than Aβneg aMCI was found in some [12,14,21] but not all [11,22] studies. Cerebral [18F] fluoro-2-deoxy-D-glucose (FDG) metabolism has been studied only in three studies that found differences between Aβpos and Aβneg aMCI but in different regions according to the study. Thus, a decrease was reported in Aβpos aMCI compared to Aβneg aMCI in the temporoparietal or only in the precuneus [15] or in the inferior parietal, inferior temporal, and precuneus [14]. However, cognition, atrophy, and hypometabolism were assessed separately in these previous studies therefore not allowing to identify which changes are the most specific, within a population presenting with the same symptoms, to a particular molecular phenotype—that is, the presence of amyloid deposition.

Landau et al.'s study [13] is the only previous study providing an overall picture of the profiles of neuropsychological changes, brain atrophy, and brain hypometabolism in Aβpos versus Aβneg aMCI patients. They reported higher hippocampal atrophy and temporoparietal hypometabolism in Aβpos compared to Aβneg aMCI. Moreover, Aβneg aMCI had higher performances than Aβpos aMCI on global cognition and on episodic memory. The present study is complementary as it compares neuropsychological, atrophy, and hypometabolism profiles between Aβpos and Aβneg aMCI from a more restricted but monocentric sample and also includes a group of healthy controls so that each subgroup of patients could also be compared to a same control group (see the Supplementary Material for further details). This comprehensive picture is yet needed to identify which changes are the most specific, within a population presenting with the same symptoms, to a particular molecular phenotype—that is, the presence of amyloid deposition.

2. Material and methods

2.1. Participants

All participants were included in the Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce (IMAP+) study (Caen, France), and the inclusion and exclusion criteria are detailed in the Supplementary Materials and the previous publication [23–26]. For the Q4 sake of the present study, 68 right-handed native French-speaking participants were included, comprising 44 patients with aMCI (20 Aβneg aMCI and 24 Aβpos aMCI; see below) and 24 Aβneg healthy controls (HCs) (all amyloid negative; see below). Participants were selected from the IMAP+ study database, if they were older than 55 years (inclusive), and had MRI, FDG-PET, and florbetapir-PET imaging. We included in the present study Q5 all aMCI patients from the IMAP database meeting these criteria, but only the HCs who met these criteria and whose florbetapir PET scan was classified as amyloid negative (see below). The two groups of participants were matched for age, gender, and education (Table 1).

Within a few days from recruitment, each participant underwent (1) a detailed neuropsychological battery detailed below, (2) a structural magnetic resonance imaging scan, (3) a PET scan using [18F] fluoro-2-deoxy-D-glucose, and (4) a PET scan using [18F] florbetapir (AV45). All participants were scanned on the same MRI and PET cameras. The IMAP study was approved by regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and registered with ClinicalTrial.gov (number NCT01638949). All participants gave written informed consent to the study before the investigation.

2.2. Neuropsychological assessment

Neuropsychological tests and scores have been selected among a more detailed neuropsychological battery that covered the main domains of cognition that are affected by AD and other dementias. All continuous raw scores were transformed into W-scores, that is, age- and education-adjusted Z-scores [27]. Eight different W-scores or composite W-scores were used to measure the following cognitive areas: episodic memory (free recall and recognition), verbal fluency, language, short-term memory, working memory, executive function, and visuospatial functions (see the Supplementary Material for further details).