# Associations between cognitive complaints, memory performance, mood and amyloid-β accumulation in healthy amyloid negative late-midlife individuals

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**Running Title:** CORRELATES OF COGNITIVE COMPLAINTS IN AGING

**ABSTRACT**

***Background***. Cognitive complaints are gaining more attention as they may represent an early marker of increased risk for AD in individuals without objective decline at standard neuropsychological examination.

***Objective***. Our aim was to assess whether cognitive complaints in late middle-aged individuals not seeking medical help are related to objective cognitive outcomes known as early markers for AD risk, concomitant affective state, and amyloid-β (Aβ) burden.

***Methods***. Eighty-seven community-based cognitively normal individuals aged 50-69 years underwent neuropsychological assessment for global cognition, using Preclinical Alzheimer's Cognitive Composite 5 (PACC5) score, and a more specific episodic memory measure. Affective state was based on self-assessment questionnaires for depression and anxiety. Aβ PET burden was assessed via [18F]Flutemetamol (N=84) and [18F]Florbetapir (N=3) uptake. Cognitive complaints were evaluated using Cognitive Difficulties Scale.

***Results***. Higher cognitive complaints were significantly associated with lower episodic memory performance and worse affective state. Moreover, higher level of cognitive complaints was related to higher (but still sub-clinical) global Aβ accumulation (at uncorrected significance level). Importantly, all three aspects remained significant when taken together in the same statistical model, indicating that they explained distinct parts of variance.

***Conclusion***. In healthy Aβ negative late middle-aged individuals, a higher degree of cognitive complaints is associated with lower episodic memory efficiency, more anxiety and depression, as well as, potentially, with higher Aβ burden, suggesting that complaints might signal subtle decline. Future studies should untangle how cognitive complaints in healthy aging populations are related to longitudinal changes in objective cognition and AD biomarker correlates.

***Keywords***: Cognitive Decline; Cognition; Episodic Memory; Affective Disorders; Amyloid; Middle-age

## INTRODUCTION

Preclinical Alzheimer's disease (AD) is characterized by normal cognition on standard neuropsychological tests and the presence of AD-related biomarkers referring to pathological protein accumulation in the brain, i.e., amyloid-β (Aβ) plaques and tau neurofibrillary tangles, irrespective of the status of neurodegeneration [1–3]. However, measurement of AD biomarkers using cerebrospinal fluid (CSF) assessment or positron emission tomography (PET) is invasive, demanding and costly. In addition, the abnormal value for these biomarkers in cognitively normal individuals does not predict AD symptom outbreak but rather represents a marker of increased risk for developing AD [4]. Therefore, the identification of other less invasive markers, which could help to detect individuals with a higher risk for AD-related pathologies in the general population without initial invasive assessment, is of particular importance.

The concept of Subjective Cognitive Decline (SCD) has been developed in that framework [5–7]. SCD might be described as a broad spectrum of cognitive complaints reported by individuals without objective decline at neuropsychological examination [5]. Although not specific, SCD is associated with an increased risk for subsequently developing AD, and may also be considered as a preclinical AD stage preceding mild cognitive impairment (MCI) [7]. According to its definition, the presence of SCD is not linked to impaired objective cognition. Nevertheless, in most cases, cognitive scores match patients' complaints, such that higher level of SCD is related to lower (but still normal) performance on global cognition [8,9], episodic memory or executive tasks [10].

A series of self and informant based questionnaires have been developed to quantify cognitive difficulties experienced by individuals in the general population or memory clinics [7,11–16]. Unfortunately, there is no consensus about which questionnaire and cut-off differentiate best SCD individuals from those without SCD. The SCD-Initiative [17] recommended the use of two main criteria for SCD diagnosis in clinical settings: (1) self-experience of persistent decline in cognition compared to previous normal status, a condition which is not related to an acute event; (2) normal performance on standardized neuropsychological tests, adjusted for sex, age, and education. The latter criterion, i.e., lack of objective cognitive decline, is the reason why SCD is not considered as a clinical category in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). In contrast, medical conditions characterized by objective cognitive decline, such as MCI and Alzheimer's disease correspond to mild and major neurocognitive disorder respectively (mild NCD or major NCD) in DSM-5 classification [18]. It is also important to note, that one diagnostic criterion of mild NCD includes "concern of the individual, a knowledgeable informant, or the clinician" for "evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains" [19]. Therefore, in terms of DSM-5, SCD could sometimes, but not always, be a precursor to mild NCD. Furthermore, active medical help seeking is considered as an additional risk factor of future objective cognitive decline [17,20]. Only a fraction of individuals with cognitive concerns seek for medical help, however [21].

Age-related brain changes associated with AD, including deposits of Aβ and tau proteins, begin as early as in late middle-age (i.e., ~ 50 y) [22–25]. Similarly, several cognitive functions such as processing speed, episodic memory and executive functions begin to decline already in midlife [26–31]. Previous studies focusing on SCD included patients that were usually 70 years or older [32–38], whereas middle-aged cohorts remain underrepresented [39,40], and only few studies took Apolipoprotein E (*APOE*) polymorphism, the most

important AD-related genetic risk factor, into account [34,39]. Consequently, participants included in these studies may represent a group with a higher AD risk [17]. Furthermore, the link between SCD and affective state is not well understood and whether affective issues can be observed beyond objective cognitive difficulties is not established [41–43]. Therefore, assessing whether cognitive complaints in late midlife are related to AD-related features both at the cognitive and brain level is of prime importance to further establish SCD as an early marker for AD risk, that could provide a large time window for prevention strategies [44,45].

Consequently, the present study aimed to explore whether cognitive complaints in late middle-aged individuals (50-69 years) not seeking medical help are related to objective cognitive outcomes known as early markers for AD risk, or if other variables associated to increased risk for AD (depression and anxiety status, Aβ PET burden) explain the subjective feeling of cognitive decline. Objective cognitive measures, affective state and continuous Aβ PET values were considered jointly to assess whether they differentially explain cognitive complaints, including APOE genotype as a covariate. Given the good health status and relatively young age of our target population, we expected that Aβ burden would remain low (or sub-clinical). Our hypothesis was that higher level of cognitive complaints would be related to lower (but still within normal range) scores for global cognition and episodic memory, worse subclinical affective state, and higher global Aβ burden.

## MATERIALS AND METHODS

***Experimental design***. Participants were enrolled in a multi-modal study designed to identify biomarkers and lifestyle factors associated with normal cognitive aging in the context of preclinical dementia (the Cognitive Fitness in Aging study, COFITAGE, with trial registration number EudraCT 2016-001436-35; see [46]). In that context, we assessed objective

cognition through neuropsychological examination, cognitive complaints and affective state via self-report questionnaires, and we also assessed Aβ via PET imaging. All participants also underwent quantitative multi-parametric magnetic resonance imaging (MRI) acquisitions for subsequent pre-processing of PET data.

***Participants*** were healthy late middle-aged (50 to 69 y.) community-dwelling French speaking men and women (**Table 1**; N = 87; 60 women [69%]) not actively seeking for help in memory clinics. They were recruited in social events for seniors, by advertising in local newspapers and by word of mouth. The study was presented as an exploration of the biological and psychological mechanisms implicated in sleep, cognition and aging. No participants reported any recent history of neurological or psychiatric disease, or were taking medication likely to affect the central nervous system. All had normal or corrected-to-normal vision and hearing. Other exclusion criteria were sleep disorders, assessed during an in-lab night of sleep under polysomnography, body mass index < 18 and > 31 kg/m², smoking, psychoactive drug consumption, excessive consumption of caffeine (> 4 cups/day) or alcohol (> 14 units/week), diabetes, and shift-work. Participants with clinical levels of depression or anxiety as assessed by the Beck Depression Inventory [47] and by the Beck Anxiety Inventory [48], respectively, and/or with ongoing pharmacological treatment were excluded. A few participants reached mild depression and/or anxiety levels according to Beck scales but this was not considered as clinical. Participants with treated (> 6 months) hypertension and hypothyroidism were included. All participants showed normal performance on the Mattis Dementia Rating Scale [49] [i.e., score > 130/144]. The procedures involving experiments on human subjects were in accordance with guidelines on human experimentation and were approved by the local Ethics Committee of the Faculty of Medicine (University of Liege). All participants gave their signed informed consent prior to the experiment and received a financial compensation..

***Neuropsychological examination*** consisted of a battery of cognitive tasks assessing short-term and episodic memory, executive and attentional functions. Original Preclinical Alzheimer's Cognitive Composite 5 (PACC5) score [50,51] was computed as the sum of z-scores of the following cognitive measures: *Free and Total Recall in the Free and Cued Selective Reminding Test (FCSRT)* [52], Delayed Recall in the *Logical Memory Test* [53], Total score in the *Digit Symbol Substitution Test* [54], scores in the *Verbal Fluency Test* for the categories of Animals, Fruits and Vegetables (1 min each), and *Mini Mental State Examination* [55]. Here we introduced three changes to the initial PACC5: Mini Mental State Examination was replaced by the score from the Mattis Dementia Rating Scale, the Verbal Fluency Test score was calculated for the animal category only, and a more recent version of the Digit Symbol Substitution Test having a larger range of scores was used [56].

The episodic memory score was assessed through *the Free and Cued Selective Reminding Test* [52], which, as a list learning test, was proposed by the European Prevention of Alzheimer's Dementia (EPAD) program as a sensitive measure for early cognitive decline [57]. The raw score of episodic memory, i.e., the sum of free recall and total recall, was converted to z-scores for our analyses.

Neuropsychological evaluation was performed during 2 sessions taking approximately 75 min each. As our study was designed for several research objectives, additional neuropsychological tasks were included in the assessment, which are not mentioned here.

***Cognitive complaint scores*** were obtained with the Cognitive Difficulties Scale (CDS; [11]). In this questionnaire, participants had to evaluate their cognitive difficulties during the last 3 weeks. There were 39 statements (e.g., "I have trouble recalling frequently used phone numbers"), where individuals had to indicate their cognitive difficulties on a 5-point Likert scale between 0 ("never") and 4 ("very often"), with higher value meaning more cognitive

complaints. This questionnaire was already shown to be a sensitive measure of cognitive complaints in studies seeking associations with Aβ burden [58,59].

***Affective state*** was based on two questionnaires collected after one of the neuropsychological evaluation sessions, the Beck Depression Inventory (BDI) [47], and the Beck Anxiety Inventory (BAI) [48]. We computed a composite score for affective state based on the average of z-scores of total scores for each questionnaire, and final score was itself converted to z-scores. Higher value means worse affective state (i.e., more depression and more anxiety).

***Quantitative multi-parametric MRI acquisition*** was performed on a 3-Tesla MR scanner (Siemens MAGNETOM Prisma, Siemens Healthineers, Erlangen, Germany). Quantitative maps were obtained by combining images using different parameters sensitive to distinct tissue properties. Multi-parameter mapping was based on multi-echo 3D fast low angle shot at 1 mm isotropic resolution [60]. This included three datasets with T1, proton density (PD), and magnetization transfer (MT)–weighted contrasts imposed by the choice of the flip angle (FA = 6° for PD & MT, 21° for T1) and the application of an additional off-resonance Gaussian-shaped RF pulse for the MT-weighted acquisition. Fieldmap data for the correction of B1 transmit and receiver fields, and B0 inhomogeneity were also acquired.

***Quantitative multi-parametric MRI processing***. MRI multi-parameter maps were processed with the hMRI toolbox [61] (http://hmri.info) and SPM12 (Welcome Trust Centre for Neuroimaging, London, UK) to obtain notably a quantitative MT map as well as segmented tissue maps (grey matter, white matter, CSF), using the "unified segmentation" approach. [62]. Inter-subject alignment into the standard MNI space was performed with diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL), providing subject specific deformation flow-fields.

***PET acquisition and processing***. Aβ PET imaging was performed with radiotracers [18F]Flutemetamol for 97 participants and with [18F]Florbetapir for 3 participants on an ECAT EXACT HR+ scanner (Siemens, Erlangen, Germany). For all radiotracers, participants received a single dose of the respective radio-ligands in an antecubital vein (target dose 185 ± 10% MBq). Aβ-PET image acquisitions started 85 minutes after injection, and 4 frames of 5 minutes were obtained. All PET images were reconstructed using filtered back-projection algorithm including corrections for measured attenuation (10 min transmission scan using three retractable 68Ge line sources), dead time, random events, and scatter using standard software (Siemens ECAT - HR+ V7.1, Siemens/CTI, Knoxville, TN, USA).

Before proceeding with further PET processing, a PET average image was created using all frames. Averaged PET images were first manually reoriented then automatically co-registered to the structural MT map in subject space. Then, deformation flow-fields derived by DARTEL from the MT maps were applied to averaged co-registered PET images [63]. Standardized uptake value ratio (SUVR) was calculated using the whole cerebellum as the reference region for Aβ-PET [64]. Volumes of interest (VOIs) were determined using the masks provided by automated anatomical labelling (AAL) atlas [65]. As Aβ-PET images were obtained using 2 radiotracers, their SUVR values were scaled to Centiloid units (CL) for common scale [64,66–68]. Finally, we applied two masks for the estimations of Aβ uptake. One mask considered global brain Aβ burden and included lateral and medial cortices in frontal, parietal, temporal, occipital brain regions, and basal ganglia together with anterior and posterior cingulate cortex. Another, more specific mask, considered brain regions which show early and rapid Aβ increase in Aβ negative individuals [69], and included posterior cingulate cortex (PCC) and precuneus. Given the relatively young age and good health of participants, they were all Aβ negative (Table 1).

***APOE genotyping*** was performed based on blood sample DNA extraction. Common Single Nucleotide Polymorphisms (SNPs) were assessed using Infinium OmniExpress-24 BeadChip (Illumina, San Diego, CA, USA) based on human genome build hg19 (GRCh37). Genotype imputation was performed using the "Sanger Imputation Server" (https://imputation.sanger.ac.uk/) by choosing Haplotype Reference Consortium (release 1.1) (HRC) [70] as reference panel and the pre-phasing algorithm Eagle2 [71]. *APOE* ε variants were determined by rs7412 and rs429358 SNPs. Participants were classified into ε4 carriers (heterozygous and homozygous) and non-carriers, based on their APOE status.

***Statistical analyses***. All statistical analyses were performed with SAS 9.4 for Windows (SAS Institute, Cary, NC, USA). Generalized linear mixed models (GLMM; PROC GLIMMIX) were applied to compute all statistics. Dependent variable distributions were estimated using allfitdist function in MATLAB (developed by Mike Sheppard, part of the MvCAT package [72]) and set accordingly for each GLMM. Collinearity diagnosis was performed on all predictors using Tolerance (TOL) and Variance Inflation Factors (VIF) as criteria via PROC REG function on SAS. Degrees of freedom (DF) were estimated using Kenward-Roger's correction. Subject (intercept) effect was included as a random factor. Since we computed 5 separate models (prior to the composite model), we defined $p\text{-}value \leq 0.01$ as significant following the Bonferroni correction for multiple comparisons.

All models included cognitive complaints as the dependent variable, and controlled for sex, age, education, and *APOE* status. GLMM first evaluated the association with cognitive performance in two different models, one with PACC5 values, and another with the episodic memory score from the PACC5. Then, models sought to evaluate the link between cognitive complaints and subclinical affective state. Next GLMMs evaluated the association between subjective cognition and AD biomarker (Aβ) in two separate models, one with Aβ burden in global brain mask, whereas another one with the more specific mask targeting regions related

to early Aβ pathophysiology. A final GLMM sought to evaluate if the significant predictors of cognitive complaints that were identified in each previous step (episodic memory, affective state, and Aβ) remained significant when assessed simultaneously in one model. Semi-partial $R^2$ ($R_{sp}^2$) was reported for each significant effect as described previously [73].

## RESULTS

Descriptive statistics about demographic data, cognitive complaints, affective status, cognitive performance, Aβ and APOE status are presented in **Table 1**.

### *Links between cognitive complaints and cognitive performance*

We tested whether CDS score was linked to PACC5 and episodic memory measure in two separate models. The first GLMM showed no significant association between CDS score and PACC5 (**Table 2A**). The second model revealed a significant negative association between CDS score and episodic memory measure, indicating that a higher level of cognitive complaints is linked to worse performance on the FCSRT task, as well as an uncorrected positive association between education and CDS in the second model, such that higher education may be associated with higher cognitive concerns (**Table 2B; Figure 1A and 1D**). Sex, age and APOE allele (i.e., ε4 carriers vs. non-carriers) were not associated with cognitive complaints in either models.

### *Association between level of cognitive complaints and affective state*

GLMM showed that the level of cognitive complaints was positively associated with affective state, at uncorrected p-value level but, though close to it, did not reach corrected level.

(**Table 3; Figure 1B**). In contrast, sex, age, education and APOE genotype were not associated with cognitive complaints.

***Relationship between level of cognitive complaints and Aβ burden***

Then, we tested whether CDS score was associated to global Aβ burden (i.e., using a brain mask covering the entire brain, except the cerebellum) and to early amyloid pathophysiology regions (i.e., posterior cingulate cortex and precuneus, see [69]). The first GLMM yielded a positive association between CDS score and global Aβ accumulation (**Table 4A; Figure 1C**), but at uncorrected p value level only. In contrast, the second GLMM did not show any significant association between CDS score and Aβ over early AD pathophysiology regions (**Table 4B**). Again, sex, age, education and APOE genotype were not associated with cognitive complaints.

***Simultaneous associations between level of cognitive complaints and episodic memory, affective state, and Aβ burden***

In our final step, we considered jointly the single parameters significantly related to CDS score at uncorrected (or corrected in case of FCSRT score) p values in the previous models. This final GLMM revealed that episodic memory performance, affective state, and global Aβ remained associated at similar significance level with subjective cognitive score (**Table 5; Figure 1**). Moreover, education was significantly positively linked to CDS, indicating that higher education may be associated with higher cognitive concerns (**Table 5; Figure 1D**). As for the previous models, sex, age and APOE genotype were not associated with cognitive complaints.

## DISCUSSION

SCD is a recent concept that might represent a preclinical stage within AD pathophysiology indicative of an increased risk for developing AD [7]. Its links with various cognitive or physiological aspects have been assessed multiple times already, but the simultaneous association with several behavioral and brain aspects remains scarce, especially in individuals not seeking for clinical help. The main objective of this study was therefore to assess how subjective feeling of one's own cognitive abilities is related to objective cognitive outcomes known as early markers of AD (global cognitive outcome using PACC5 measure, and verbal episodic memory performance for a list learning task), concomitant subclinical affective state, and in-vivo Aβ PET global brain uptake (taken as a continuous value) in cognitively normal and amyloid-β negative late middle-aged individuals, controlling for sex, age, education and APOE status.

To evaluate cognitive complaints we used the Cognitive Difficulties Scale [11], which meets current consensus as the optimal method to assess one's perception of cognitive status [6,58,59]. Our analyses revealed that a higher level of cognitive complaints was related to a worse score on the episodic memory task, but not to PACC5 outcome. We further report that cognitive complaints may also be linked to worse subjective affective state, while they were also potentially associated with a higher Aβ brain accumulation when considered over the entire brain, but not when focusing only on the brain regions considered to be first affected by Aβ accumulation over the course of AD pathophysiology. Since these correlates of cognitive complaints remained similarly associated with CDS when included together in a single statistical model, we further suggest that episodic memory, together with a potential contribution of affective state and whole-brain Aβ burden, explain at least partially distinct parts of variance in cognitive complaints.

It is important to note that the definition of SCD posits that cognitive complaints are not necessarily limited to the memory domain, but may also include other cognitive domains [5,74]. Previous cross-sectional studies have also reported that, while remaining clinically normal, a higher SCD level is related to lower performance on global cognition [8,9,75,76], and more specific cognitive functions, including verbal episodic memory and executive functions [10]. Our results show that, in late midlife, cognitive complaints in cognitively normal individuals are associated with episodic memory functioning, but not with a global measure of cognition known to be sensitive to the earliest AD-related cognitive changes. We may therefore extend previous findings by showing that if cognitive complaints do not reach a status leading to help seeking, which would allow formal clinical SCD diagnosis, we presume that episodic memory performance may be the main indicator one uses to judge his/her cognitive status.

This link must have underlying neural correlates, including changes in brain structural and functional integrity. Atrophy in the regions of medial temporal lobe (MTL) is often viewed as the primary target to account for alterations in episodic memory. For example, Perrotin and colleagues have reported that higher level of self-reported cognitive difficulties among seniors was associated with hippocampal atrophy, at least in a group seeking medical help [58]. The decline in verbal episodic memory, measured using the same FCSRT task as in our study, was also related to MTL atrophy in healthy seniors (mean age 72.7 years) in a longitudinal study [77]. Episodic memory functioning is not only limited to MTL integrity, but also includes medial and lateral prefrontal cortex, precuneus, posterior cingulate cortex [78], regions which were included in our global brain Aβ PET estimation.

Our analyses revealed that cognitive complaints are weakly related to a higher global Aβ burden (at uncorrected significance level), but not in the specific mask related to early Aβ pathophysiology. Whereas previously some negative findings were reported [79], most of the

previous studies reported that a higher level of SCD is related to a higher Aβ PET accumulation [32–34,37,58,59,80–83]. Most of previous studies have included, however, older participants (around 70 years) from both the general community and memory clinic, thus concentrating on SCD individuals with increased risk for AD [17]. Here, we add therefore that cognitive complaints in healthy midlife (mean age 59 years) community-based individuals, not seeking for medical help, could also correspond to a higher global Aβ concentration, even when the values of the latter biomarker remain in sub-threshold level for amyloid positivity. Our attempt to investigate the regional specificity of the association lead to a negative result when including the brain regions first affected by Aβ plaque progression. It seems therefore that cognitive complaints may reflect somehow the diffused global low level of Aβ rather the initial step of Aβ brain pathology. Furthermore, our results related to Aβ may be also affected by PET processing method. We used two radiotracers to estimate Aβ burden in global and specific brain masks. In order to standardize uptake values of two different radiotracers, we have validated standardized Centiloid pipeline according to our particular data [64,66,67] and computed scaling equations allowing to convert SUVR of two radiotracers into common Centiloid units (CL). However, this standardized pipeline has one possible limitation, as it does not include partial volume correction (PVC) as a PET pre-processing step, which is often used to correct for spill-in effects from adjacent tissue classes [84]. Therefore, in Supplementary Material, we have repeated our statistical analyses with Aβ data using PVC, but only with one radiotracer (Flutemetamol), as inclusion of this pre-processing step does not allow to apply Centiloid scaling equations to convert the SUVR values of two radiotracers into CL. Our statistical models in Supplementary Material showed that Aβ was no longer a significant predictor of cognitive complaints. These results may be explained by a smaller sample size than the main sample, or by the fact that PVC can sometimes increase sensitivity to inaccuracy in image registration and segmentation [85]. Thus, these last results do not allow us to imply

firm conclusions about the exact role of Aβ burden in the context of cognitive complaints. Yet, further investigations are needed to confirm our relatively weak association and establish whether the regional distribution of Aβ matters in its association with cognitive complaints using voxel-based analyses.

Surprisingly and contrary to our hypothesis, we found no associations between PACC5 score and cognitive complaints. It might be that PACC5, while considered as a sensitive measure, is limited by one of its components, the Mini Mental State Examination (MMSE) score, which in our study was replaced by the Mattis Dementia Rating Scale. Both scores are designed as short dementia screening tests, but display a ceiling effect in cognitively healthy individuals [86], and it was even suggested that PACC score should be computed without such a measure [87]. In addition, our study did not assess the associations of cognitive complaints with other specific cognitive domains (e.g., processing speed, attention, executive functions, language, visuospatial abilities), thus, we cannot dismiss the possibility of other cognitive correlates of cognitive complaints.

On top of the link between memory performance and Aβ burden, and not surprisingly, we found that cognitive complaints may be linked (at relatively low but still uncorrected p value level) to worse affective state in a healthy study sample that do not meet criteria for a clinical affective condition. Previous studies have also reported that SCD individuals show higher levels of depressive symptoms [8,33,40,42] and anxiety [43,58,88] than healthy controls. According to current views, worse affective state may reflect reaction to cognitive complaints [42], or may have a common or a separate underlying cause [17], such as hypothalamic-pituitary-adrenal axis hyperactivity [89].

While it was not our main goal, we found that higher education is potentially related to more cognitive complaints. These results are in line with previous studies reporting that better

education is linked to SCD [8,90,91]. Interestingly, it was also shown that when better educated individuals reached objective cognitive decline, they reported more self-perceived difficulties, whereas lower educated seniors did not show concomitant cognitive complaints when reaching objective cognitive decline [92]. It may be that individuals with a higher educational status have also a better self-perception of their cognitive status. Alternatively, it may also be that high cognitive efficiency in better educated individuals is more important to them due to professional or more personal reasons. The concept of cognitive reserve also suggests that in the presence of brain pathology, persons with lower education would reach clinically significant cognitive impairment faster than individuals with better education, who may be able to compensate for longer time but can sometimes express higher level of cognitive complaints [93]. For example, one study demonstrated that the link between SCD and amyloid level becomes stronger with greater educational attainment [94].

We neither observed an effect of APOE ε4 status for the level of cognitive complaints. A systematic review [95] reported APOE ε4 allele frequency is comparable between SCD individuals and healthy controls (see however [96]). Nonetheless, it seems that APOE ε4 carrier status in SCD individuals increases the probability for clinical progression to MCI [97]. These results come from studies which mostly studied clinically defined SCD individuals, and not cognitive complaint in a healthy population, as it was in our case.

While previous data indicate that age is associated to the level of memory complaints [33], and that the age for onset of SCD [17] can even be more predictive of dementia risk [34,98], we did not observe an association between age and level of cognitive complaints. However, the age range was between 50 and 69 years in our study, thus limiting the possible age effect for cognitive complaints..

From a more clinical viewpoint, it seems important to emphasize that the symptom of subjective cognitive complaints as risk factor for AD is rather unspecific and should be

associated to other minimally invasive biomarkers to identify high-risk individuals in primary care setting. For example, MRI-based lower hippocampal volume was related to poorer memory performance in a group of elderly individuals with subjective memory complaints [99]. Blood-based biomarkers are also gaining attention, as it was reported that high folate and low bilirubin levels in SCD individuals were related to cognitive decline at 3-year follow-up [100], while decreased total antioxidant and increased serum homocysteine levels were related to more subjective memory complaints [101]. Moreover, tau protein burden is also a main AD-related biomarkers [4]. Interestingly, blood-based tau biomarker (plasma tau phosphorylated at threonine 181; P-tau 181) was recently suggested as an early AD biomarker, even preceding PET-tau [102]. Furthermore, the presence of cardiovascular disease and depressive symptoms history may also indicate about possible progression or reverting in cognitive decline [103].

We stress that our study bears some limitations, the first one being its cross-sectional nature which controls less efficiently for different environmental effects or life experiences, and, therefore, does not allow to approach causal interpretation as longitudinal approaches would do. For instance, the increase in Aβ over time may be more important for cognitive decline than baseline amyloid level [104]. Another possible limitation in our study is selection bias due to the requirements of the larger project in which our volunteers were enrolled. Our participants underwent quite extensive screening for health and affective status, consumption of psychoactive substances (e.g., alcohol, drugs, caffeine), and their educational level was high. This type of selection bias is however also present in SCD studies, sometimes including highly educated volunteers from academic memory clinic or community [33,80]. In addition, we did find a weak behavioral and Aβ correlates of cognitive complaints despite this rather excellent health status, preventing any bias from potential comorbidities or unspecific heath conditions. Finally, our study did not include the evaluation of worry associated with subjective cognitive complaints. In fact, SCD accompanied with worry can greatly increase dementia risk, and was

therefore included in SCD plus category [7,17]. As we evaluated healthy volunteers from general population and many of them had quite low level of cognitive complaints (see Table 1), we did not ask a question about possible worry over their cognitive status. Future studies assessing similar population may particularly consider inclusion of the question about worry, as it might better characterize cognitive complaints.

To sum up, our results provides new insights about the associations between cognitive complaints, objective cognition and AD biomarker status. We demonstrate that as early as in late midlife, cognitive complaints may be considered as an important marker for higher sub-threshold amyloid accumulation. Moreover, we show that, beyond brain integrity, perception of cognitive status has some actual ground which relies mostly on the episodic memory and affective domains. Future studies are needed to untangle how cognitive complaints in community-based late middle-aged population is related to longitudinal changes in objective cognition and AD biomarker correlates.



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## CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

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**TABLES**

| | Mean | SD | Min | Max |
|---|---|---|---|---|
| **Demographical data** | | | | |
| Age, *years* | 59.16 | 5.22 | 50.00 | 69.00 |
| Sex, *female, n (%)* | | | | 60 (69%) |
| Ethnic status, *Caucasian, n (%)* | | | | 87 (100%) |
| Education, *years* | 15.10 | 3.07 | 9.00 | 25.00 |
| Educational level: | | | | |
| Primary School, *n (%)* | | | | .0 (0%) |
| Secondary School, *n (%)* | | | | 23 (26.4%) |
| Bachelor degree, *n (%)* | | | | 33 (37.9%) |
| Master degree, *n (%)* | | | | 25 (28.7%) |
| PhD or higher, *n (%)* | | | | 6 (6.9%) |
| **Subjective factors** | | | | |
| Subjective cognitive complaints (CDS) | 28.77 | 19.42 | .0 | 95.00 |
| Depression (BDI) | 5.21 | 4.53 | .0 | 17.00 |
| Anxiety (BAI) | 2.98 | 3.34 | .0 | 17.00 |
| **Objective cognition** | | | | |
| PACC5 score | .0 | 2.93 | -7.92 | 8.21 |
| FCSRT, *Free and Total recall* | 81.09 | 6.63 | 66.00 | 92.00 |
| Logical Memory Task, *delayed recall* | 12.26 | 3.79 | 3.00 | 22.00 |
| DSST, *total 2 min score* | 73.10 | 12.66 | 39.00 | 99.00 |
| Semantic Fluency Test, *1 min score* | 20.41 | 4.21 | 13.00 | 37.00 |
| Mattis Dementia Rating Scale | 142.48 | 1.92 | 134.00 | 144.00 |
| **Aβ accumulation** | | | | |
| Global Mask, *CL* | -5.15 | 5.65 | -15.85 | 7.36 |
| PCC and Precuneus Mask, *CL* | -.10 | 7.89 | -23.93 | 20.72 |
| **APOE** | | | | |
| APOE ε4 carriers, n (%) | | | | 16 (18.4%) |
| APOE ε4 non-carriers, n (%) | | | | 71 (81.6%) |

**Table 1.** *Descriptive statistics of demographical data, subjective factors, objective cognition, Aβ and APOE (N = 87).*

SD, Standard Deviation; CDS, Cognitive Difficulties Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; FCSRT, Free and Cued Selective Reminding Test; DSST, Digit Symbol Substitution Test; Aβ, amyloid-β; CL, Centiloid units; PCC, posterior cingulate cortex; APOE, Apolipoprotein E. See Methods section for the references of the tests.

| **Model A** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
|---|---|---|---|---|
| Sex* | -.13 ± .21 | .38 (1,81) | .542 | [-.54 .29] |
| Age | -.03 ± .09 | .13 (1,81) | .720 | [-.21 .15] |
| Education | .18 ± .10 | 3.34 (1,81) | .071 | [-.02 .37] |
| APOE | -.06 ± .23 | .06 (1,81) | .801 | [-.52 .40] |
| PACC5 | -.15 ± .10 | 2.42 (1,81) | .124 | [-.35 .04] |
| **Model B** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
| Sex* | -.18 ± .20 | .80 (1,81) | .373 | [-.56 .21] |
| Age | -.02 ± .09 | .04 (1,81) | .851 | [-.19 .16] |
| Education | .18 ± .09 | 4.11 (1,81) | *.046 ($R_{sp}^2$=.05)* | [.003 .36] |
| APOE | -.10 ± .22 | .22 (1,81) | .644 | [-.55 .34] |
| Episodic memory (FCSRT) | -.28 ± .09 | 9.67 (1,81) | **.003 ($R_{sp}^2$=.11)** | [-.46 -.10] |

**Table 2.** *Statistical outcome of the GLMM seeking for associations between cognitive complaint level (dependent variable), and:* ***A:*** *PACC5;* ***B:*** *episodic memory measure*.

SE, Standard Error; df, degrees of freedom; CI, confidence interval of 95%; APOE, Apolipoprotein E; FCSRT, Free and Cued Selective Reminding Test. Grey background represents control variables included in all GLMM. Significant associations at uncorrected level are in italic, while those meeting criteria of correction for multiple tests are in bold.

*Sex: 1 = male; 2 = female.

| | Estimate ± SE | F value (df) | P | CI |
|---|---|---|---|---|
| Sex* | .04 ± .19 | .05 (1,81) | .825 | [-.34 .43] |
| Age | -.01 ± .09 | .02 (1,81) | .876 | [-.19 .16] |
| Education | .14 ± .09 | 2.54 (1,81) | .115 | [-.04 .32] |
| APOE | -.04 ± .23 | .04 (1,81) | .844 | [-.50 .41] |
| Affective state[1] | .22 ± .09 | 6.26 (1,81) | *.014 ($R_{sp}^2$=.07)* | [.05 .40] |

**Table 3.** *Statistical outcome of the GLMM seeking for associations between cognitive complaint level (dependent variable) and affective state*.

SE, Standard Error; df, degrees of freedom; CI, confidence interval of 95%; $Rsp^2$, Semi-partial $R^2$; APOE, Apolipoprotein E. Grey background represents control variables included in all GLMM. Significant associations at uncorrected level are in italic, while those meeting criteria of correction for multiple tests are in bold.

*Sex: 1 = male; 2 = female.

[1] Higher value means worse affective state.

| **Model A** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
|---|---|---|---|---|
| Sex* | .04 ± .20 | .03 (1,81) | .853 | [-.36 .43] |
| Age | -.04 ± .09 | .19 (1,81) | .665 | [-.22 .14] |
| Education | .16 ± .09 | 3.07 (1,81) | .083 | [-.02 .34] |
| APOE | .04 ± .24 | .04 (1,81) | .849 | [-.42 .51] |
| Aβ (global) | .19 ± .09 | 4.02 (1,81) | *.048 ($R_{sp}^2$=.05)* | [.001 .38] |
| **Model B** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
| Sex* | -.01 ± .20 | .0 (1,81) | .977 | [-.41 .40] |
| Age | -.03 ± .09 | .14 (1,81) | .708 | [-.22 .15] |
| Education | .14 ± .10 | 2.10 (1,81) | .152 | [-.05 .33] |
| APOE | -.04 ± .24 | .03 (1,81) | .859 | [-.52 .43] |
| Aβ (specific) | .03 ± .10 | .11 (1,81) | .737 | [-.16 .23] |

**Table 4.** *Statistical outcome of the GLMM seeking for associations between cognitive complaint level (dependent variable) and:* ***A:*** *Aβ global mask;* ***B:*** *Aβ specific mask.*

SE, Standard Error; df, degrees of freedom; CI, confidence interval of 95%; $Rsp^2$, Semi-partial $R^2$; APOE, Apolipoprotein E; Aβ, amyloid-β. Grey background represents control variables included in all GLMM. Significant associations at uncorrected level are in italic, while those meeting criteria of correction for multiple tests are in bold.

*Sex: 1 = male; 2 = female.

| | Estimate ± SE | F value (df) | P | CI |
|---|---|---|---|---|
| Sex* | -.05 ± .19 | .06 (1,79) | .812 | [-.43 .34] |
| Age | -.003 ± .08 | .0 (1,79) | .971 | [-.17 .16] |
| Education | .21 ± .09 | 6.07 (1,79) | **.016 ($R_{sp}^2$=.07)** | [.04 .39] |
| APOE | .0004 ± .22 | .0 (1,79) | .999 | [-.44 .44] |
| Episodic memory (FCSRT) | -.24 ± .09 | 7.59 (1,79) | **.007 ($R_{sp}^2$=.09)** | [-.42 -.07] |
| Affective state[1] | .20 ± .08 | 5.50 (1,79) | **.022 ($R_{sp}^2$=.06)** | [.03 .37] |
| Aβ (global) | .18 ± .09 | 4.10 (1,79) | **.046 ($R_{sp}^2$=.05)** | [.003 .35] |

**Table 5.** *Statistical outcome of the GLMM seeking for associations between cognitive complaint level (dependent variable), episodic memory, affective state, and Aβ global mask.*

SE, Standard Error; df, degrees of freedom; CI, confidence interval of 95%; $Rsp^2$, Semi-partial $R^2$; APOE, Apolipoprotein E; FCSRT, Free and Cued Selective Reminding Test; Aβ, amyloid-β. Grey background represents control variables included in all GLMM.

*Sex: 1 = male; 2 = female.

[1] Higher value means worse affective state.

**FIGURES**

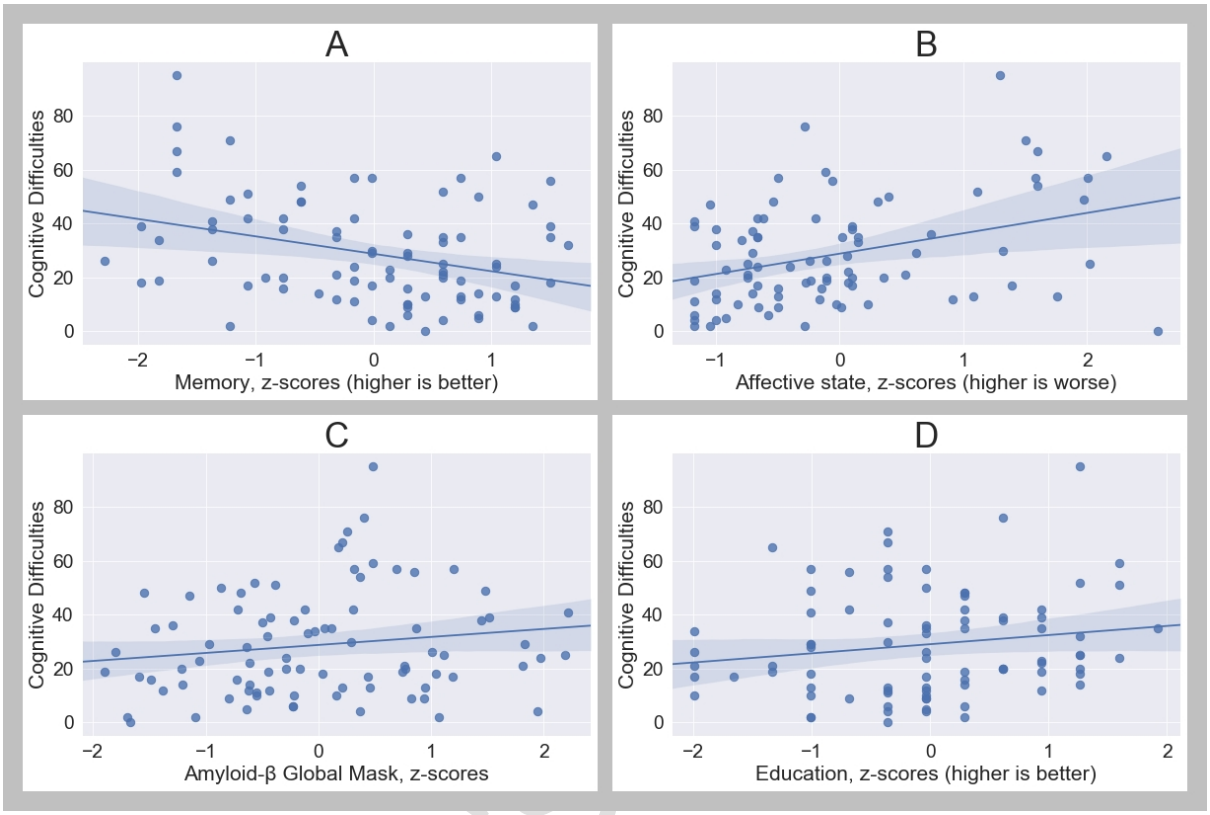


**Figure 1.** *Scatter plots visualizing the associations between cognitive complaints (higher score refers to worse cognitive difficulties) and* ***A:*** *Memory performance (higher is better);* ***B:*** *Affective state (higher is worse);* ***C:*** *Aβ accumulation in global brain mask (higher means worse);* ***D:*** *Education (higher is better). Simple regressions were used for visual display only, and not as a substitute for the full GLMM statistics.*

**SUPPLEMENTARY MATERIAL**

***Statistical models having Aβ burden estimation with PET PVC and the gray matter of the cerebellum as the reference region (N = 84)***

| **Model A** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
|---|---|---|---|---|
| Sex* | .07 ± .20 | .12 (1,78) | .732 | [-.33 .46] |
| Age | -.04 ± .09 | .22 (1,78) | .639 | [-.23 .14] |
| Education | .14 ± .09 | 2.28 (1,78) | .135 | [-.04 .32] |
| APOE | .04 ± .25 | .02 (1,78) | .878 | [-.45 .52] |
| Aβ (global), with PVE correction | .08 ± .09 | .67 (1,78) | .416 | [-.11 .26] |
| **Model B** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
| Sex* | .06 ± .20 | .09 (1,78) | .768 | [-.34 .45] |
| Age | -.03 ± .09 | .14 (1,78) | .708 | [-.22 .15] |
| Education | .12 ± .09 | 1.74 (1,78) | .192 | [-.06 .31] |
| APOE | -.03 ± .24 | .02 (1,78) | .892 | [-.51 .44] |
| Aβ (specific), with PVE correction | -.07 ± .09 | .51 (1,78) | .479 | [-.26 .12] |

**Supplementary Table 1.** *Statistical outcome of the GLMM seeking for associations between cognitive complaint level (dependent variable) and:* ***A:*** *Aβ global mask;* ***B:*** *Aβ specific mask.*

SE, Standard Error; df, degrees of freedom; CI, confidence interval of 95%; $Rsp^2$, Semi-partial $R^2$; APOE, Apolipoprotein E; Aβ, amyloid-β; PVE, partial volume effect. Grey background represents control variables included in all GLMM. For PET PVC, we have used Müller-Gärtner method on PETPVE12 toolbox [84] running in SPM12 environment.

*Sex: 1 = male; 2 = female.

***Statistical models having Aβ burden estimation without PET PVC but with the gray matter of the cerebellum as the reference region (N = 84)***

| **Model A** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
|---|---|---|---|---|
| Sex* | .10 ± .20 | .25 (1,78) | .620 | [-.29 .49] |
| Age | -.05 ± .09 | .26 (1,78) | .613 | [-.23 .13] |
| Education | .15 ± .09 | 2.64 (1,78) | .108 | [-.03 .33] |
| APOE | .05 ± .24 | .04 (1,78) | .843 | [-.43 .52] |
| Aβ (global), without PVE correction | .12 ± .09 | 1.81 (1,78) | .182 | [-.06 .31] |
| **Model B** | **Estimate ± SE** | **F value (df)** | **P** | **CI** |
| Sex* | .07 ± .20 | .13 (1,78) | .715 | [-.33 .48] |
| Age | -.04 ± .09 | .17 (1,78) | .683 | [-.22 .14] |
| Education | .14 ± .09 | 2.21 (1,78) | .141 | [-.05 .32] |
| APOE | -.01 ± .24 | .0 (1,78) | .980 | [-.48 .47] |
| Aβ (specific), without PVE correction | .01 ± .10 | .01 (1,78) | .907 | [-.18 .20] |

**Supplementary Table 2.** *Statistical outcome of the GLMM seeking for associations between cognitive complaint level (dependent variable) and:* ***A:*** *Aβ global mask;* ***B:*** *Aβ specific mask.*

SE, Standard Error; df, degrees of freedom; CI, confidence interval of 95%; $Rsp^2$, Semi-partial $R^2$; APOE, Apolipoprotein E; Aβ, amyloid-β; PVE, partial volume effect. Grey background represents control variables included in all GLMM.

*Sex: 1 = male; 2 = female.