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Memory Correlates of Alzheimer’s Disease Cerebrospinal Fluid Markers: A Longitudinal Cohort Study


aDepartment of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, The Netherlands
bNeurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, The Netherlands
cDepartment of Psychiatry, University of Cambridge, UK
dSchool of Psychological Sciences, Monash University, Melbourne, Australia
eAristotle University of Thessaloniki, Thessaloniki, Greece
fKarolinska Institutet, Karolinska University Hospital, Huddinge, Sweden
gDanish Dementia Research Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
hDepartment of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty of Mannheim, Heidelberg University, Germany
iUniversity Hospital Leuven, Leuven, Belgium
jCambridge Cognition, Cambridge, UK
kADx NeuroSciences, Gent, Belgium
lDepartment of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands

Handling Associate Editor: Adrian Ivanoie

Accepted 6 August 2017

Abstract

Background: Performance on episodic, semantic, and working memory tests is impaired in Alzheimer’s disease (AD)-type dementia, but it is unclear which type of memory test is most strongly associated with early AD biomarkers in cerebrospinal fluid (CSF), and most useful for monitoring disease progression.

Objective: To examine the association between amyloid-β 1-42 (Aβ1-42) and tau in CSF with performance on different memory domains at baseline, and how these CSF markers are related with memory decline.

Methods: We included 263 individuals with normal cognition, mild cognitive impairment, AD-type dementia, and non-AD dementia from the European EDAR study. Assessment included CSF Aβ1-42 and t-tau analyses with INNO-BIA AlzBio3 Luminex assay, the CERAD wordlist learning and delayed recall, animal fluency test, and the CANTAB Paired Associates Learning (PAL) and Spatial Working Memory tasks. Follow-up assessments were performed within 3 years after baseline.

*Correspondence to: Babette L.R. Reijs and Pieter Jelle Visser, Department of Psychiatry and Neuropsychology, Maastricht University, School for Mental Health and Neuroscience, Alzheimer Center Limburg, P.O. Box 616, 6200 MD Maastricht, the Netherlands. Tel.: +31 0 43 38 81841; Fax: +31 0 43 38 84092; E-mails: babette.reijs@maastrichtuniversity.nl (B.L.R. Reijs), pj.visser@maastrichtuniversity.nl (P. J. Visser).
Results: At baseline, decreased CSF Aβ42 correlated most strongly with the PAL total errors adjusted and the wordlist delayed recall and increased CSF t-tau with the wordlist delayed recall. Over time, decreased CSF Aβ42 was associated with decline on the wordlist learning, whereas increased CSF t-tau were associated with decline in scores on the wordlist learning, wordlist delayed recall, and animal fluency. Associations were independent of baseline diagnosis.

Conclusion: Tests assessing episodic verbal and visuospatial memory are most useful for detection of AD pathology. Tests for episodic verbal memory and semantic memory are most useful for tracking memory decline.

Keywords: Alzheimer’s disease, amyloid-β, biomarkers, cerebrospinal fluid, episodic memory, spatial memory, working memory

INTRODUCTION

Alzheimer’s disease (AD) is the most common cause of dementia. Due to increased life expectancy, the number of dementia cases is expected to grow and this will pose medical and socioeconomic problems [1]. Early detection of AD pathology is important to facilitate care and is a necessity for when effective disease-modifying medications become available. Memory dysfunction is an early and the most prominent clinical sign of AD [2], which makes memory assessment useful to detect AD at an early symptomatic stage but also to track disease progression. Memory domains that are known to be impaired in AD-type dementia include episodic memory [3], in which a specific event is consciously remembered; semantic memory, in which conceptual knowledge of facts is stored [4]; and working memory, in which recently stored memory is manipulated [5, 6]. In addition, the modality in which memory is presented may be impaired differentially in AD. Research shows that verbal and visual/spatial information are processed in different brain regions [7–9].

Key characteristics of AD pathology are amyloid-β 1-42 (Aβ42) plaques and tau neurofibrillary tangles accumulating in the brain [10, 11]. These abnormalities already occur decades before the clinical onset of AD-type dementia [12]. Previous research found that tau pathology markers measured in cerebrospinal fluid (CSF) were associated with episodic memory impairment [11, 13, 14], but information is limited whether the association is similar across different memory domains. A better understanding of the relation between CSF markers with impairment in the different memory domains may aid to select memory tests that are most sensitive to the early identification of individuals with AD pathology.

In this study, we examined the relation between AD-related amyloid and tau pathology in CSF and performance on tests for episodic, semantic, and working memory. In addition, we investigated how AD pathology was associated with decline over time on these tests. Since tau has been more closely associated with cognition than Aβ42 [13, 15], supporting the assumption that Aβ42 is abnormal before the increase in tau concentrations, we expect to find a stronger association of tau with memory tests than with Aβ42. Furthermore, since episodic memory is often first impaired in AD [16, 17], we expect to find the strongest associations between CSF markers and episodic memory. To examine whether the association between AD markers and memory performance is different along the AD continuum, we test whether the relation was dependent on diagnostic group.

MATERIALS AND METHODS

Individuals

We selected 263 individuals from the European study “Beta amyloid oligomers in the early diagnosis of AD and as marker for treatment response” (acronym: EDAR) based on the availability of both CSF and memory test performance results at baseline. Individuals were recruited from seven memory clinics across Europe between 2008 and 2010 and represented individuals with normal cognition (n = 46), mild cognitive impairment (MCI) (n = 73), AD-type dementia (n = 80), non-AD dementia (n = 47, frontotemporal dementia (FTD, n = 25), dementia with Lewy bodies (DLB, n = 11), vascular dementia (VaD, n = 10), and posterior cortical atrophy (n = 1)), and 17 unclassified individuals without dementia (see below). Follow-up assessments were performed in 120 individuals within three years after baseline.

Individuals with normal cognition were recruited among patients attending the memory clinic (n = 20) or from other settings (partners from patients or via advertisements, n = 26). Inclusion criteria for individuals with normal cognition were: age above 40 years,
a Mini-Mental State Examination score (MMSE [18]) above the 10th percentile according to age and education adjusted local norms (unpublished data from Maastricht Aging Study), and no cognitive impairment on neuropsychological tests (see below for a definition of cognitive impairment). Individuals with normal cognition from outside the memory clinic did not differ from individuals with normal cognition from the memory clinic with respect to age, gender, educational level, MMSE score, CSF markers, and neuropsychological test scores. Inclusion criteria for individuals with MCI were: memory clinic referral for the evaluation of cognitive complaints, age above 60 years, a MMSE-score above 19, one or more cognitive impairments (see below) on neuropsychological tests according to Petersen’s criteria [19], and absence of a clinical diagnosis of dementia. Inclusion criteria for individuals with dementia were: age above 40 years, a MMSE-score above 18 and a clinical diagnosis of probable or possible AD according to the NINCDS-ADRDA criteria [20], FTD [21], VaD according to the NINDS-AIREN criteria [22], or DLB [23]. Exclusion criteria for all individuals were contraindications for lumbar puncture or any disorder probably related to cognitive impairment other than neurodegeneration.

A total of 17 individuals without dementia could not be classified to a diagnostic subgroup because they had no cognitive complaints but showed cognitive impairment on one or more cognitive tests with a z-score below minus two (ten individuals) or because of missing test scores (seven individuals). They were included in the total group analyses only. All individuals provided informed consent and the medical ethics committee at each center approved the study.

Follow-up data was available for 120 individuals, representing 26 individuals with normal cognition, 43 with MCI, 42 with AD-type dementia at baseline, and 9 individuals without dementia who could not be classified to a diagnostic group. Individuals with non-AD dementia \( (n = 6) \) were excluded in the longitudinal analyses due to the small sample size.

**Definition cognitive impairment**

Cognitive impairment was defined as a z-score corrected for age, gender, and education below 1.5 (or above 1.5 for timed tasks) of a reference population on at least one of the following tests: the one-minute animal fluency test [24], wordlist learning and delayed recall of the Consortium to Establish a Registry for Alzheimer’s Disease neuropsychological battery (CERAD) [25], Trail Making Test (TMT) part A and B [24], and figures copy test of the CERAD [25]. Z-scores for the CERAD learning and delayed recall, TMT A and B and copy figures were calculated according to the CERAD-Plus norms [25, 26]. For the animal fluency test, z-scores were calculated according to the norms by van der Elst et al. [27].

**Baseline and follow-up assessment**

Baseline assessments included clinical history, physical examination, neuroimaging, routine laboratory tests for blood and CSF, the MMSE and the Clinical Dementia Rating scale (CDR [28]), Functional Assessment Questionnaire (FAQ [29]) and a neuropsychological examination consisting of standard psychometric paper-and-pencil tests and two Cambridge Neuropsychological Test Automated Battery (CANTAB) tests. Follow-up assessments were similar to baseline, excluding laboratory tests and neuroimaging. They were performed once or twice within three years after baseline at individually varying time points. In the analysis follow-up visits were categorized in six-months intervals (6 months, 12 months, up to 36 months). Follow-up was not planned for control individuals and for individuals with a non-AD type dementia in the original study plan, but a selection of centers performed follow-up in these individuals.

**Memory tests**

Performances on a variety of memory domains were measured using paper-and-pencil tests as well as computerized tests of the CANTAB. The paper-and-pencil based verbal learning task of the CERAD [25] is a verbal episodic memory and learning task in which a list of 10 unrelated words were visually presented and repeated over three trials. Outcome measures were the total number of words recalled across three trials with a maximum of 30 (i.e., wordlist learning) and the total number of words recalled after a ten-minutes interval (i.e., wordlist delayed recall) and recognized (i.e., wordlist recognition). The animal fluency [27] is a categorical semantic memory task for which the outcome measure is the number of animal names generated in one-minute.

The Paired Associates Learning (PAL) of the computerized CANTAB [30, 31] is a visuospatial episodic memory task in which individuals were asked to pair
polypropylene tubes, centrifuged at 4°C for a better fit according to likelihood ratio tests, intercepts within center (nested design). If required and education and with random effects for individual mixed models analyses corrected for age, gender, decline over time (outcome) were analyzed by linear and memory performance at baseline and memory between CSF concentrations at baseline (predictor).

A reagents. CSF concentrations below 389 (pg/ml) for Amsterdam in the Netherlands using the same batch of the VU University Medical Centre (VUmc) in Amsterdam, Belgium). All CSF analyses were performed at the end of the study at this assay at the VUmc. Investigators that collected the clinical data were blinded to the CSF results. APOE genotype was determined by Polymerase Chain Reaction (PCR) of genomic DNA extracted from EDTA anticoagulated blood.

**CSF and DNA collection, storage, and analysis**

CSF was collected via a lumbar puncture in 10 mL polypropylene tubes, centrifuged at 4°C at 2000 × g and stored at −80°C within 1 h after collection. Aβ42 and total tau (t-tau) concentrations were measured with INNO-BIA AlzBio3 Luminex assay (Fujirebio, formerly Innogenetics, Gent, Belgium). All CSF analyses were performed at the end of the study at the VU University Medical Centre (VUmc) in Amsterdam in the Netherlands using the same batch of reagents. CSF concentrations below 389 (pg/ml) for Aβ42 and above 98 (pg/ml) for t-tau were considered abnormal according to local cut-off values for this assay at the VUmc. Investigators that collected the clinical data were blinded to the CSF results. APOE genotype was determined by Polymerase Chain Reaction (PCR) of genomic DNA extracted from EDTA anticoagulated blood.

**Statistical analyses**

Data was analyzed with IBM SPSS statistics version 22. Baseline characteristics were examined with one-way ANOVAs for continuous variables and χ²-tests for categorical variables. The relationship between CSF concentrations at baseline (predictor) and memory performance at baseline and memory decline over time (outcome) were analyzed by linear mixed models analyses corrected for age, gender, and education and with random effects for individual intercepts within center (nested design). If required for a better fit according to likelihood ratio tests, random slopes were also included to allow for heterogeneity in individual trajectories over time. An interaction effect of diagnosis at baseline was included in a second model to examine a possible moderator effect. For the main analyses, raw memory scores were used in order to preserve the initial scale for better interpretability. To allow for direct comparison between tests, i.e., which memory test was most strongly associated with CSF markers, z-scores were calculated for each test based on the mean and standard deviation of the total group multiplied by 100. Furthermore, in individuals without dementia (i.e., normal cognition and MCI group) we tested the association of low memory scores (below 10th percentile for verbal memory tests and above 90th percentile for CANTAB tests based on the normal cognition group and amyloid pathology (score below 389), tau pathology (score above 98) and combined pathology (both abnormal versus at least one normal) with logistic regression. A p-value of <0.05 for two-sided tests was considered statistically significant.

**RESULTS**

Baseline characteristics for the total group and the diagnostic subgroups are presented in Table 1. Individuals were on average 68 years old, had 10 years of education, and the majority was male (56%). Individuals with MCI and AD-type dementia were older and less educated than individuals with normal cognition. Females were more common in the MCI group than in the normal cognition and non-AD type dementia group. As expected, individuals with AD-type dementia scored poorer on the MMSE, CDR, FAQ, and memory tests than individuals with MCI and normal cognition; and individuals with MCI or non-AD dementia scored poorer on these measures than individuals with normal cognition. Differences in CSF Aβ42 and t-tau concentrations were as expected (Table 1). APOE genotyping was available for 237 individuals (90%). The number of carriers of one or more APOE ε4 alleles was higher in the AD-type dementia (58%) and MCI (52%) group than in the non-AD dementia group (30%), but it did not differ from the normal cognition group (43%).

The average follow-up interval was 1.35 (SD = 0.54) years. Individuals with follow-up in the total group and in the subgroups did not differ on age, gender, education, and MMSE score from individuals with only baseline data. Twenty-six percent of individuals with MCI at baseline converted to...
dementia (i.e., 32 non-converters, 10 to AD-type dementia, 1 to vascular dementia).

**CSF markers and memory performance at baseline**

In the total group, decreased CSF Aβ42 and increased CSF t-tau concentrations were associated with poorer performances on the wordlist learning, wordlist delayed recall, wordlist recognition, and the PAL total errors adjusted (Table 2). Decreased CSF Aβ42 concentrations were also associated with poorer performance on the SWM between errors. The association between CSF Aβ42 and memory performance was strongest for the PAL total errors adjusted (z-scores, Table 2, Figure 1), whereas for CSF t-tau the association was strongest for the wordlist delayed recall (z-scores, Table 2, Figure 1). The association between Aβ42 and memory performance was independent of t-tau concentrations and vice versa, and independent of diagnostic subgroup.

**Post hoc** analyses revealed that in individuals without dementia, the wordlist immediate and delayed recall were predictive of abnormal amyloid and tau concentrations (Table 3).

**CSF markers and memory decline over time**

In the total group, lower CSF Aβ42 concentrations at baseline were associated with faster decline in performance over time on the wordlist learning, whereas higher CSF t-tau concentrations were associated with faster decline in performance on the wordlist learning, wordlist delayed recall and animal fluency (Table 4). The strength of association between CSF t-tau and memory decline was similar between the wordlist learning, wordlist delayed recall and animal fluency (z-scores, Table 4).

The association between baseline CSF concentrations and decline in memory performances over time did not differ between diagnostic groups, except for the SWM between errors. For this test, decreased CSF Aβ42 and increased t-tau concentrations were more strongly associated with decline in performance in the MCI group than in the AD-type dementia group (slope difference raw scores: Aβ42 β = −0.019, p = 0.022; t-tau β = 0.073, p = 0.002).

### Table 1

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n = 263)</th>
<th>Normal cognition (n = 46)</th>
<th>MCI (n = 73)</th>
<th>AD-type dementia (n = 80)</th>
<th>non-AD dementia (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>68.3 (9.1)</td>
<td>64.7 (9.4)</td>
<td>69.9 (8.1)</td>
<td>70.7 (8.9)</td>
<td>66.7 (9.5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>147 (56)</td>
<td>29 (63)</td>
<td>31 (43)</td>
<td>42 (53)</td>
<td>34 (72)</td>
</tr>
<tr>
<td>Education, mean y (SD)</td>
<td>10.4 (4.5)</td>
<td>13.0 (3.2)</td>
<td>9.4 (4.1)</td>
<td>9.9 (4.8)</td>
<td>10.6 (4.9)</td>
</tr>
<tr>
<td>FAQ, n</td>
<td>210</td>
<td>40</td>
<td>59</td>
<td>61</td>
<td>37</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.6 (7.2)</td>
<td>2.0 (3.3)</td>
<td>4.5 (6.2)</td>
<td>10.1 (7.0)</td>
<td>11.0 (7.8)</td>
</tr>
<tr>
<td>MMSE, n</td>
<td>261</td>
<td>45</td>
<td>73</td>
<td>80</td>
<td>46</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25.5 (3.9)</td>
<td>29.1 (1.3)</td>
<td>26.8 (2.1)</td>
<td>22.9 (3.7)</td>
<td>23.8 (4.5)</td>
</tr>
<tr>
<td>CDR-SOB, n</td>
<td>240</td>
<td>44</td>
<td>71</td>
<td>71</td>
<td>39</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.6 (2.6)</td>
<td>0.5 (0.9)</td>
<td>1.7 (1.5)</td>
<td>4.2 (2.4)</td>
<td>4.3 (3.0)</td>
</tr>
<tr>
<td>Carrier APOE e4, n (%)</td>
<td>115 (49)</td>
<td>16 (43)</td>
<td>34 (52)</td>
<td>44 (58)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Aβ42 (pg/ml), mean (SD)</td>
<td>372.2 (151.1)</td>
<td>438.4 (139.5)</td>
<td>375.3 (137.2)</td>
<td>302.8 (137.8)</td>
<td>400.2 (167.7)</td>
</tr>
<tr>
<td>Abnormal Aβ42, n (%)</td>
<td>145 (55)</td>
<td>15 (33)</td>
<td>43 (59)</td>
<td>60 (75)</td>
<td>42 (47)</td>
</tr>
<tr>
<td>t-tau (pg/ml), mean (SD)</td>
<td>106.0 (59.4)</td>
<td>79.0 (31.4)</td>
<td>104.7 (56.6)</td>
<td>141.8 (70.2)</td>
<td>82.7 (37.7)</td>
</tr>
<tr>
<td>Abnormal t-tau, n (%)</td>
<td>131 (50)</td>
<td>10 (22)</td>
<td>38 (49)</td>
<td>64 (80)</td>
<td>15 (32)</td>
</tr>
<tr>
<td>Wordlist learning, mean (SD)</td>
<td>14.6 (6.1)</td>
<td>11.1 (4.4)</td>
<td>14.4 (6.4)</td>
<td>15.1 (4.1)</td>
<td>13.0 (5.9)</td>
</tr>
<tr>
<td>Wordlist delayed recall, mean (SD)</td>
<td>4.1 (2.9)</td>
<td>7.2 (1.1)</td>
<td>4.3 (2.3)</td>
<td>1.8 (1.9)</td>
<td>3.6 (3.0)</td>
</tr>
<tr>
<td>Wordlist recognition, mean (SD)</td>
<td>17.4 (3.4)</td>
<td>19.8 (0.9)</td>
<td>17.4 (3.8)</td>
<td>15.6 (3.4)</td>
<td>16.9 (3.3)</td>
</tr>
<tr>
<td>Animal fluency, mean (SD)</td>
<td>15.0 (6.8)</td>
<td>22.0 (4.6)</td>
<td>16.2 (5.3)</td>
<td>12.0 (5.8)</td>
<td>10.9 (6.6)</td>
</tr>
<tr>
<td>PAL total errors adjusted, mean (SD)</td>
<td>61.1 (27.7)</td>
<td>30.9 (18.5)</td>
<td>55.8 (24.5)</td>
<td>76.4 (20.8)</td>
<td>69.6 (26.0)</td>
</tr>
<tr>
<td>SWM between errors, mean (SD)</td>
<td>30.0 (11.8)</td>
<td>19.2 (10.0)</td>
<td>29.6 (8.8)</td>
<td>33.9 (10.6)</td>
<td>30.6 (13.3)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or valid percent of individuals with CSF and at least one neuropsychological test available. FAQ, Functional Assessment Questionnaire; MMSE, Mini-Mental State Examination; CDR-SOB, Clinical dementia Rating; Sum of Boxes; APOE, apolipoprotein E; CSF, cerebrospinal fluid; Aβ42, amyloid-β 1-42; t-tau, total tau; PAL, Paired Associates Learning; SWM, Spatial Working Memory; MCI, mild cognitive impairment; AD, Alzheimer’s disease. *p < 0.05 compared with normal cognition. ^p < 0.05 compared with MCI, §compared with AD-type dementia, †compared with non-AD type dementia.
Table 2

Association between CSF markers and memory performance at baseline

<table>
<thead>
<tr>
<th></th>
<th>Aβ42 diagnosis</th>
<th>t-tau diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>t</strong> (z-score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wordlist learning</td>
<td>0.008**</td>
<td>-0.050***</td>
</tr>
<tr>
<td>(raw score)</td>
<td>(0.003 to 0.013)</td>
<td>(–0.074 to –0.027)</td>
</tr>
<tr>
<td>Wordlist delayed recall</td>
<td>0.002 to 0.008</td>
<td>(–0.035 to 0.008)</td>
</tr>
<tr>
<td>(raw score)</td>
<td>0.008 to 0.007</td>
<td>(–0.035 to 0.008)</td>
</tr>
<tr>
<td>Wordlist recognition</td>
<td>0.000 to 0.005</td>
<td>(–0.035 to 0.008)</td>
</tr>
<tr>
<td>(raw score)</td>
<td>0.005 to 0.007</td>
<td>(–0.035 to 0.008)</td>
</tr>
<tr>
<td>Animal Fluency</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>(raw score)</td>
<td>0.005 to 0.007</td>
<td>0.005 to 0.007</td>
</tr>
<tr>
<td>PAL total errors</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>adjusted</td>
<td>0.005 to 0.007</td>
<td>0.005 to 0.007</td>
</tr>
<tr>
<td>SWM between errors</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>0.005 to 0.007</td>
<td>0.005 to 0.007</td>
</tr>
</tbody>
</table>

Numbers are beta coefficients with 95% confidence intervals between brackets for raw scores and for z-scores (based on the mean and standard deviation of the total group multiplied by 100).

DISCUSSION

The present study revealed differential associations between AD markers in CSF and performance on several memory domains. In all individuals, CSF markers correlated with poorer performance on nearly all memory domains at baseline, but most strongly with episodic verbal and visuospatial memory. CSF Aβ42 at baseline was associated with decline on episodic verbal memory, whereas CSF t-tau correlated with decline in performance on episodic verbal and semantic memory.

The observation that CSF markers were cross-sectionally related to memory function is in line with previous studies [13–15, 36, 37], while there were also some differences. For example, Rolstad et al. [37] found an association between CSF tau and working memory and semantic memory in individuals with various levels of impairment; while in our study working memory was associated with Aβ42 and not with tau. Also, in our study no association between CSF markers and semantic memory was found, but these results were just above threshold of statistical significance. In addition, we found that the association between CSF markers and memory performance was similar across diagnostic groups, while other studies reported that some of the associations between CSF markers and memory performance were observed in specific diagnostic groups only [15, 36, 37]. These differences may be explained by the statistical approach. Unlike previous studies, we first tested the interaction between clinical diagnosis and the predictor variable and only performed analysis in separate diagnostic groups if this interaction was statistically significant.

When memory scores were dichotomized, we found that in individuals without dementia abnormal verbal episodic memory was associated with abnormal CSF Aβ42 and tau, although the odds ratio were moderately high. This indicates that memory has limited value to pre-screen individuals with underlying AD pathology.

The association between CSF markers and memory decline over time was weaker than the association with baseline scores. For CSF Aβ42, a weak correlation was found with decline on a single episodic verbal memory task. Some other studies also found no or only a weak association between CSF Aβ42 and cognitive decline [11, 38]. Others found that abnormal amyloid was associated with greater decline on the ‘Preclinical Alzheimer Cognitive Composite (PACC), which is a compound score that includes...
tests for episodic verbal memory, attention, and global cognitive functioning [39, 40]. An early decline in the verbal fluency has been reported in individuals in predementia phase of AD [41]. We did find an association between CSF tau but not Aβ42 on decline in the fluency. Previous studies did report an association of abnormal Aβ42 with decline in fluency, and that addition of a fluency measure in a cognitive compound score increased the sensitivity to detect cognitive decline in cognitively normal Aβ42-positives [42–44].

CSF Aβ42 has been found abnormal even decades before the onset of clinical symptoms [12]. Conceivably, with a longer follow-up time the association...
Table 4

<table>
<thead>
<tr>
<th>Time</th>
<th>Time* t-tau diagnosis</th>
<th>Time* Aβ42 diagnosis</th>
<th>Time* Ab42 diagnosis</th>
<th>Time Ab42 diagnosis</th>
<th>Time Ab42 diagnosis</th>
<th>Time* Ab42 diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>(raw score)</td>
<td>(z-score)</td>
<td>(raw score)</td>
<td>(z-score)</td>
<td>(raw score)</td>
<td>(z-score)</td>
</tr>
<tr>
<td></td>
<td>F (2, 101.748) = 2.39</td>
<td></td>
<td>F (2, 101.528) = 0.22</td>
<td></td>
<td>F (2, 101.528) = 0.22</td>
<td></td>
</tr>
<tr>
<td>Wordlist learning</td>
<td>–0.08</td>
<td></td>
<td>–0.01</td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Wordlist delayed recall</td>
<td>–0.26</td>
<td></td>
<td>–0.01</td>
<td></td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Wordlist recognition</td>
<td>–0.18</td>
<td></td>
<td>–0.01</td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Animal fluency</td>
<td>–0.17</td>
<td></td>
<td>–0.01</td>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>PAL total errors adjusted</td>
<td>0.01</td>
<td></td>
<td>0.00</td>
<td></td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>SWM between errors</td>
<td>–0.79</td>
<td></td>
<td>–0.06</td>
<td></td>
<td>–0.003</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are beta coefficients with 95% confidence intervals between brackets for raw scores and for z-scores (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term). The slope for time indicates change in cognitive score per 6-months follow-up (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term). The slope for time indicates change in cognitive score per 6-months follow-up (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term). The slope for time indicates change in cognitive score per 6-months follow-up (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term). The slope for time indicates change in cognitive score per 6-months follow-up (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term). The slope for time indicates change in cognitive score per 6-months follow-up (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term). The slope for time indicates change in cognitive score per 6-months follow-up (based on mean and standard deviation of the total group, which have been multiplied by 100 in case of the interaction term).
pathology differently. Moreover, CSF markers correlated less strongly with decline on the PAL total errors adjusted than on verbal episodic memory tests.

In conclusion, CSF markers correlated most strongly with tests assessing verbal and visuospatial episodic memory. Over time, CSF tau correlated with decline on episodic verbal and semantic memory tests. This implies that memory tests may have some value as a screen for the presence of abnormal CSF biomarkers. In addition, verbal episodic and semantic memory tests may be useful to track disease progression, for example in drug trials. Future studies with a longer follow-up time are recommended to examine the long-term prognostic value of these CSF markers for detecting memory decline. In addition, it would be of interest to test how AD CSF markers relate to decline on functional and non-memory measures relative to memory tests.

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REFERENCES


