Memory Correlates of Alzheimer's Disease Cerebrospinal Fluid Markers

Journal of Alzheimer's Disease 60 (2017) 1119–1128
DOI 10.3233/JAD-160766
IOS Press

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

Babette L.R. Reijs[a,*], Inez H.G.B. Ramakers[a], Sebastian Köhler[a], Charlotte E. Teunissen[b], Marleen Koel-Simmelink[b], Pradeep J. Nathan[c,d], Magda Tsolaki[e], Lars-Olof Wahlund[f], Gunhild Waldemar[g], Lucrezia Hausner[h], Rik Vandenberghe[i], Peter Johannsen[g], Andrew Blackwell[j], Hugo Vanderstichele[k], Frans Verhey[a] and Pieter Jelle Visser[a,l,*]

[a]*Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Alzheimer Center Limburg, Maastricht University, Maastricht, The Netherlands*
[b]*Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, The Netherlands*
[c]*Department of Psychiatry, University of Cambridge, UK*
[d]*School of Psychological Sciences, Monash University, Melbourne, Australia*
[e]*Aristotle University of Thessaloniki, Thessaloniki, Greece*
[f]*Karolinska Institutet, Karolinska University Hospital, Huddinge, Sweden*
[g]*Danish Dementia Research Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[h]*Department of Geriatric Psychiatry, Central Institute of Mental Health, Medical Faculty of Mannheim, Heidelberg University, Germany*
[i]*University Hospital Leuven, Leuven, Belgium*
[j]*Cambridge Cognition, Cambridge, UK*
[k]*ADx NeuroSciences, Gent, Belgium*
[l]*Department 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 ($A\beta_{42}$) 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 $A\beta_{42}$ 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 $A\beta_{42}$ 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 $A\beta_{42}$ 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 ($A\beta_{42}$) 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 $A\beta_{42}$ [13, 15], supporting the assumption that $A\beta_{42}$ is abnormal before the increase in tau concentrations, we expect to find a stronger association of tau with memory tests than with $A\beta_{42}$. 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

a token with its location as follows. One or more white boxes revealed a unique token. Subsequently, a target token was presented in the center of the screen and the individual was asked to click on its corresponding box location. Task difficulty gradually increased from two to eight tokens and box locations. Outcome measure was the total number of errors made across all difficulty stages adjusted for the stages not attempted due to previous failure, which has been found a promising marker for early AD [30, 32].

In the *Spatial Working Memory (SWM)* task of the CANTAB [33, 34], individuals had to search for one blue token in a number of boxes. The token appeared in a new location each time and the individual was asked not to return to a box where a token has already been found. The latter is called a between-search error and was the outcome measure. Task difficulty gradually increased from three to eight boxes.

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. $A\beta_{42}$ 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 $A\beta_{42}$ and above 98 (pg/ml) for t-tau were considered abnormal according to local cut-off values for this assay at the VUmc [35]. 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 χ^2 –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 $A\beta_{42}$ 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 $\varepsilon 4$ 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 $A\beta_{42}$ 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 $A\beta_{42}$ concentrations were also associated with poorer performance on the SWM between errors. The association between CSF $A\beta_{42}$ and memory performance was strongest for the PAL total errors adjusted and the wordlist delayed recall (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 $A\beta_{42}$ 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 $A\beta_{42}$ 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 $A\beta_{42}$ 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: $A\beta_{42}$ $\beta = -0.019$, $p = 0.022$; t-tau $\beta = 0.073$, $p = 0.002$).

Table 1
Baseline characteristics

	All ($n = 263$)	Normal cognition ($n = 46$)	MCI ($n = 73$)	AD-type dementia ($n = 80$)	non-AD dementia ($n = 47$)
Age, mean (SD)	68.3 (9.1)	64.7 (9.4)$^{\wedge\S}$	69.9 (8.1)$^{\#}$	70.7 (8.9)$^{\#+}$	66.7 (9.5)§
Male, *n* (%)	147 (56)	29 (63)$^{\wedge}$	31 (43)$^{\#+}$	42 (53)$^{+}$	34 (72)$^{\wedge\S}$
Education, mean y (SD)	10.4 (4.5)	13.0 (3.2)$^{\wedge\S+}$	9.4 (4.1)$^{\#}$	9.9 (4.8)$^{\#}$	10.6 (4.9)$^{\#}$
FAQ, *n*	210	40	59	61	37
Mean (SD)	6.6 (7.2)	2.0 (3.3)$^{\S+}$	4.5 (6.2)$^{\S+}$	10.1 (7.0)$^{\#\wedge}$	11.0 (7.8)$^{\#\wedge}$
MMSE, *n*	261	45	73	80	46
Mean (SD)	25.5 (3.9)	29.1 (1.3)$^{\wedge\S+}$	26.8 (2.1)$^{\#\S+}$	22.9 (3.7)$^{\#\wedge}$	23.8 (4.5)$^{\#\wedge}$
CDR-SOB, *n*	240	44	71	71	39
Mean (SD)	2.6 (2.6)	0.5 (0.9)$^{\wedge\S+}$	1.7 (1.5)$^{\#\S+}$	4.2 (2.4)$^{\#\wedge}$	4.3 (3.0)$^{\#\wedge}$
Carrier APOE ε4, *n* (%)	115 (49)	16 (43)	34 (52)$^{+}$	44 (58)$^{+}$	13 (30)$^{\wedge\S}$
$A\beta_{42}$ (pg/ml), mean (SD)	372.2 (151.1)	438.4 (139.5)$^{\wedge\S}$	375.3 (137.2)$^{\#\S}$	302.8 (137.8)$^{\#\wedge+}$	400.2 (167.7)§
Abnormal $A\beta_{42}$, *n* (%)	145 (55)	15 (33)$^{\wedge\S}$	43 (59)$^{\#\S}$	60 (75)$^{\#\wedge+}$	22 (47)§
t-tau (pg/ml), mean (SD)	106.0 (59.4)	79.0 (31.4)$^{\wedge\S}$	104.7 (56.6)$^{\#\S+}$	141.8 (70.2)$^{\#\wedge+}$	82.7 (37.7)$^{\wedge\S}$
Abnormal t-tau, *n* (%)	131 (50)	10 (22)$^{\wedge\S}$	36 (49)$^{\#\S}$	64 (80)$^{\#\wedge+}$	15 (32)§
Wordlist learning, mean (SD)	14.6 (6.1)	21.8 (4.1)$^{\wedge\S+}$	14.4 (4.6)$^{\#\S}$	10.5 (4.1)$^{\#\wedge+}$	13.0 (5.9)$^{\#\S}$
Wordlist delayed recall, mean (SD)	4.1 (2.9)	7.2 (1.9)$^{\wedge\S+}$	4.3 (2.3)$^{\#\S}$	1.8 (1.9)$^{\#\wedge+}$	3.6 (3.0)$^{\#\S}$
Wordlist recognition, mean (SD)	17.4 (3.4)	19.8 (0.9)$^{\wedge\S+}$	17.4 (3.8)$^{\#\S}$	15.6 (3.4)$^{\#\wedge+}$	16.9 (3.3)$^{\#\S}$
Animal fluency, mean (SD)	15.0 (6.8)	22.0 (4.9)$^{\wedge\S+}$	16.2 (5.3)$^{\#\S+}$	12.0 (5.8)$^{\#\wedge}$	10.9 (6.6)$^{\#\wedge}$
PAL total errors adjusted, mean (SD)	61.1 (27.7)	30.9 (18.5)$^{\wedge\S+}$	55.8 (24.5)$^{\#\S+}$	76.4 (20.8)$^{\#\wedge}$	69.6 (26.0)$^{\#\wedge}$
SWM between errors, mean (SD)	30.0 (11.8)	19.2 (10.0)$^{\wedge\S+}$	29.6 (8.8)$^{\#\S}$	33.9 (10.6)$^{\#\wedge}$	30.6 (13.3)$^{\#}$

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; $A\beta_{42}$, 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, $^{\wedge}p < 0.05$ 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

	$A\beta_{42}$ (raw score)	$A\beta_{42}$ (z-score)	$A\beta_{42}$*diagnosis	t-tau (raw score)	t-tau (z-score)	t-tau*diagnosis
Wordlist learning	0.008** (0.003 to 0.013)	0.131** (0.053 to 0.210)	F (3, 207.000) = 0.587	–0.023*** (–0.035 to –0.010)	–0.372*** (–0.574 to –0.170)	F (3, 207.000) = 0.089
Wordlist delayed recall	0.005*** (0.003 to 0.007)	0.174*** (0.092 to 0.256)	F (3, 205.393) = 1.018	–0.016*** (–0.022 to 0.010)	–0.559*** (–0.766 to –0.353)	F (3, 203.855) = 0.928
Wordlist recognition	0.005** (0.002 to 0.008)	0.155** (0.067 to 0.243)	F (3, 204.592) = 0.628	–0.008* (–0.016 to –0.001)	–0.250* (–0.482 to –0.018)	F (3, 202.959) = 1.587
Animal Fluency	0.003 (–0.003 to 0.008)	0.040 (–0.040 to 0.120)	F (3, 224.868) = 0.487	–0.014 (–0.027 to 0.000)	–0.199 (–0.404 to 0.006)	F (3, 222.100) = 0.429
PAL total errors adjusted	–0.050*** (–0.074 to –0.027)	–0.182*** (–0.267 to –0.096)	F (3, 186.000) = 0.538	0.074* (0.012 to 0.136)	0.267* (0.044 to 0.491)	F (3, 184.812) = 2.232
SWM between errors	–0.017** (–0.027 to –0.006)	–0.140** (–0.232 to –0.049)	F (3, 180.934) = 1.239	0.011 (–0.016 to 0.039)	0.097 (–0.135 to 0.329)	F (3, 179.931) = 2.420

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). Better memory performance is indicated by higher scores on the wordlist learning, wordlist delayed recall and animal fluency, and by lower scores on the PAL total errors adjusted and SWM between errors. $A\beta_{42}$, amyloid-β 1-42; t-tau, total tau; PAL, Paired Associates Learning; SWM, Spatial Working. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

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 $A\beta_{42}$ 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 $A\beta_{42}$ 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 $A\beta_{42}$ 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 $A\beta_{42}$, 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 $A\beta_{42}$ 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

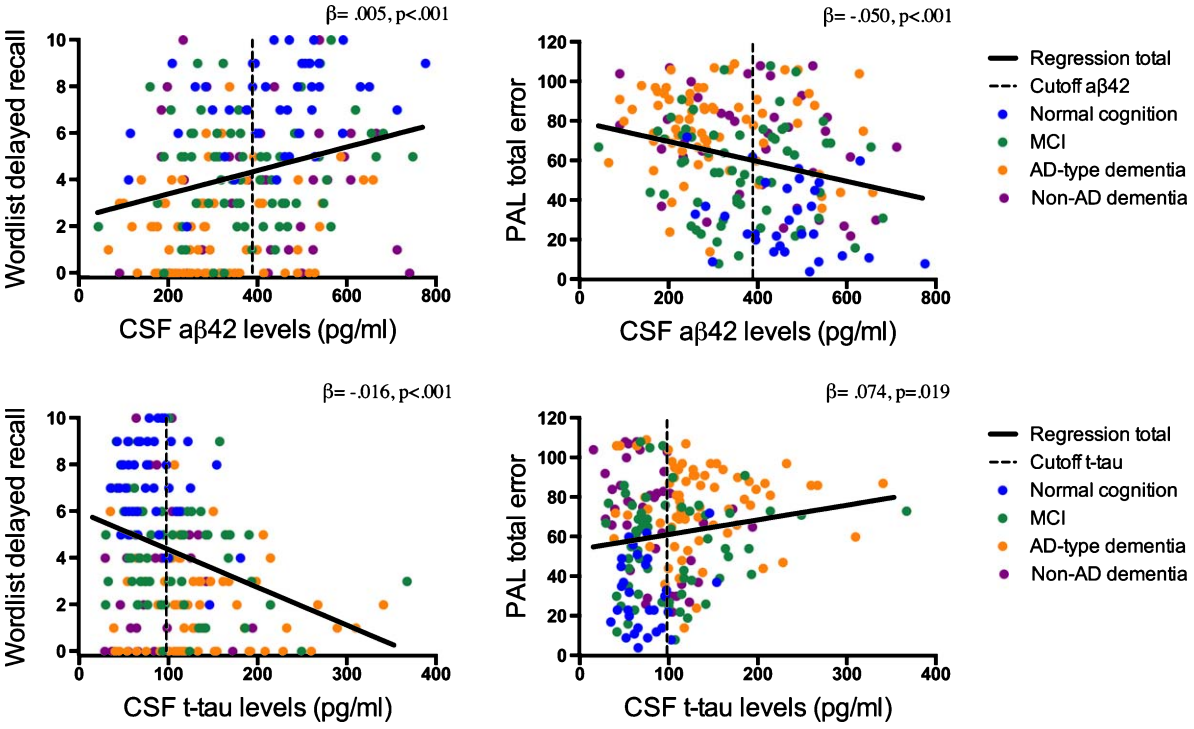

Fig. 1. Associations at baseline between CSF markers and wordlist delayed recall and PAL total errors adjusted. Figure displays count of individuals with normal cognition (blue), MCI (Green), AD-type dementia (Orange), and non-AD dementia (purple), cut-off lines for $A\beta_{42}$ and t-tau, and regression lines corrected for age, education, gender, and center.

Table 3
Association of low memory scores with presence of CSF pathology at baseline in individuals without dementia

	n	$A\beta_{42}$+	t-tau+	$A\beta_{42}$ + and t-tau+
Wordlist learning	110	2.24*	2.96**	2.98*
		(1.05 to 4.81)	(1.32 to 6.64)	(1.20 to 7.38)
Wordlist delayed recall	110	2.18	2.36*	3.35**
		(0.97 to 4.92)	(1.04 to 5.38)	(1.37 to 8.19)
Wordlist recognition	111	1.18	1.11	1.23
		(0.51 to 2.70)	(0.47 to 0.260)	(0.49 to 3.10)
Animal Fluency	116	0.78	1.59	1.36
		(0.34 to 1.76)	(0.70 to 3.63)	(0.56 to 3.34)
PAL total errors adjusted	89	1.60	1.18	1.60
		(0.68 to 3.77)	(0.49 to 2.88)	(0.62 to 4.19)
SWM between errors	89	1.32	1.49	1.03
		(0.48 to 3.64)	(0.53 to 4.20)	(0.33 to 3.27)

Numbers are odds ratios with 95% confidence intervals between brackets. $A\beta_{42}$ + is defined as an abnormal score below 389 and tau+as an abnormal score above 98. For $A\beta_{42}$ + and t-tau+both biomarkers are abnormal (versus at least one normal). For the memory tests, impairment is defined as a score below the 10th percentile for verbal tasks or above the 90th percentile for CANTAB tasks based on the normal cognition group. $A\beta_{42}$, amyloid-β 1-42; t-tau, total tau. $^*p < 0.05$, $^{**}p < 0.01$.

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 $A\beta_{42}$ on decline in the fluency. Previous studies did report an association of abnormal $A\beta_{42}$ 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 $A\beta_{42}$-postives [42–44].

CSF $A\beta_{42}$ has been found abnormal even decades before the onset of clinical symptoms [12]. Conceivably, with a longer follow-up time the association

Table 4
Association between CSF markers at baseline and memory decline during follow-up

	Time (raw score)	Time (z-score)	Time*$A\beta_{42}$ (raw score)	Time*$A\beta_{42}$ (z-score)	Time*$A\beta_{42}$* diagnosis	Time*t-tau (raw score)	Time*t-tau (z-score)	Time*t-tau* diagnosis
Wordlist learning	–0.008	–0.013	0.002*	0.035*	F (2, 94.530) = 0.382	–0.005*	–0.091*	F (2, 101.748) = 2.539
	(–0.315 to 0.160)	(–0.052 to 0.026)	(0.000 to 0.004)	(0.006 to 0.065)		(–0.010 to –0.001)	(–0.169 to –0.0013)	
Wordlist delayed recall	–0.026	–0.009	0.001	0.023	F (2, 103.952) = 0.343	–0.002*	–0.082*	F (2, 109.509) = 1.375
	(–0.139 to 0.087)	(–0.048 to 0.030)	(0.000 to 0.002)	(–0.008 to 0.053)		(–0.005 to 0.000)	(–0.162 to –0.002)	
Wordlist recognition	–0.181*	–0.049*	0.000	0.004	F (2, 184.085) = 1.022	–0.003	–0.082	F (2, 190.650) = 1.003
	(–0.357 to –0.005)	(–0.092 to –0.006)	(–0.001 to 0.002)	(–0.031 to 0.040)		(–0.007 to 0.001)	(–0.178 to 0.013)	
Animal fluency	–0.178	–0.026	0.002	0.032	F (2, 100.994) = 1.859	–0.007*	–0.097*	F (2, 101.204) = 0.875
	(–0.453 to 0.098)	(–0.067 to 0.014)	(0.000 to 0.004)	(–0.001 to 0.065)		(–0.013 to 0.000)	(–0.186 to –0.007)	
PAL total errors adjusted	0.015	0.001	–0.010	–0.038	F (2, 99.724) = 0.741	0.022	0.079	F (2, 117.570) = 1.470
	(–1.458 to 1.489)	(–0.053 to 0.054)	(–0.022 to 0.002)	(–0.081 to 0.006)		(–0.012 to 0.056)	(–0.042 to 0.200)	
SWM between errors	–0.792*	–0.067*	–0.003	–0.026	F (2, 103.610) = 3.473*	–0.010	–0.034	F (2, 112.252) = 5.413**
	(–1.578 to –0.007)	(–0.134 to –0.001)	(–0.010 to 0.003)	(–0.081 to 0.029)		(–0.004 to 0.009)	(–0.185 to 0.118)	

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 terms). The slope for time indicates the change in cognitive score per 6-months follow-up in the total group. The time-by- $A\beta_{42}$ and time-by-t-tau interaction indicates how the slope differs from the time slope as a function of the CSF marker. For example, on average the decline in wordlist learning in the total group was 0.008 words per 6-months follow-up. An individual with one CSF $A\beta_{42}$ unit below average would be expected to have an accelerated decline of 0.002 words, and an individual with one CSF tau unit above the average would be expected to have an accelerated decline of 0.005 words. $A\beta_{42}$, amyloid-β 1-42; t-tau, total tau; PAL, Paired Associates Learning; SWM, Spatial Working Memory. *$p<0.05$ **$p<0.01$.

between CSF $A\beta_{42}$ and episodic memory might have been stronger in individuals in milder disease stages. Increased CSF t-tau correlated with decline in performance on episodic verbal and semantic memory. Although the strength of the association of CSF tau with decline on episodic spatial memory was similar to that of performance on the verbal tests, there was greater heterogeneity (the standard deviation was larger) such that the association was not statistically significant.

Our finding that both cross-sectional and longitudinal associations of memory performance were stronger for CSF tau than for CSF $A\beta_{42}$ suggests that alterations in tau concentrations reflect neuronal damage better and are in closer temporal proximity to alterations in memory function as opposed to CSF $A\beta_{42}$, which is consistent with previous findings [11, 45, 46]. In particular, tau pathology in temporal and basal frontal brain regions has been associated with episodic memory, semantic memory, working memory, and visuospatial processing [46].

The present study has a few limitations. First, the relatively small sample size of the subgroups may have resulted in a type II error. Second, the follow-up time was relatively short, which limits the interpretation of the data. Possibly, with a longer follow-up time a different association between AD pathology markers and change in memory scores would have become apparent. Another limitation is that we did not have follow-up data available for all individuals. However, as individuals with follow-up data did not differ on age, education, or MMSE scores from individuals with only baseline data, we expect no selection bias. Third, differences between tests may not only due to type of memory domain tested but also by way of administration (paper pencil versus computerized) and difficulty of the test. Finally, individuals without dementia referred to the memory clinic for an evaluation of their complaints were in our study classified as MCI or normal cognition based on z-scores on neuropsychological tests, which included the wordlist learning, wordlist delayed recall and animal fluency, limiting the range of scores in this group.

This is the first time that the relationships were examined of CSF markers with the computerized PAL total errors adjusted and the SWM between errors of the CANTAB, which have both been found useful for detecting cognitive decline [30, 32, 47, 48]. The correlation of the PAL total errors adjusted with CSF $A\beta_{42}$ was similar to that of the paper-and–pencil memory tests, while the association with CSF tau was somewhat weaker suggesting that the tests reflect AD

pathology differently. Moreover, CSF markers correlated less strong 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.

ACKNOWLEDGMENTS

The EDAR study was funded by the European Commission as part of the 6th Framework Programme (contract # 37670). We thank Nico Rozendaal for the provision of the IT infrastructure, Innogenetics for the provision of INNO-BIA AlzBio3 kits, and Cambridge Cognition for the provision of CANTAB tests.

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/16-0766r2).

REFERENCES

[1] Prince M, Wimo A, Guerchet M, Ali GC, WU Y-T, Prina M (2015) *World Alzheimer Report 2015: The global impact of dementia. An analysis of prevalence, incidence, costs and trends*, Alzheimer's Disease International, London.

[2] Cummings JL (2004) Alzheimer's disease. *N Engl J Med* **351**, 56-67.

[3] Hodges JR (2000) Memory in dementias. In *The Oxford Handbook of Memory*, Tulving E, Craik FIM, eds. Oxford University Press, NY, USA.

[4] Verma M, Howard RJ (2012) Semantic memory and language dysfunction in early Alzheimer's disease: A review. *Int J Geriatr Psychiatry* **27**, 1209-1217.

[5] Belleville S, Peretz I, Malenfant D (1996) Examination of the working memory components in normal aging and in dementia of the Alzheimer type. *Neuropsychologia* **34**, 195-207.

[6] Gold CA, Budson AE (2008) Memory loss in Alzheimer's disease: Implications for development of therapeutics. *Expert Rev Neurother* **8**, 1879-1891.

[7] Bonner-Jackson A, Mahmoud S, Miller J, Banks SJ (2015) Verbal and non-verbal memory and hippocampal volumes in a memory clinic population. *Alzheimers Res Ther* **7**, 61.

[8] Budson AE (2009) Understanding memory dysfunction. *Neurologist* **15**, 71-79.

[9] Budson AE, Price BH (2005) Memory dysfunction. *N Engl J Med* **352**, 692-699.

[10] Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* **18**, 351-357.

[11] Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216.

[12] Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FR, Visser PJ, Amyloid Biomarker Study, Group (2015) Prevalence of cerebral amyloid pathology in persons without dementia: A meta-analysis. *JAMA* **313**, 1924-1938.

[13] Wagner M, Wolf S, Reischies FM, Daerr M, Wolfsgruber S, Jessen F, Popp J, Maier W, Hull M, Frolich L, Hampel H, Perneczky R, Peters O, Jahn H, Luckhaus C, Gertz HJ, Schroder J, Pantel J, Lewczuk P, Kornhuber J, Wiltfang J (2012) Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. *Neurology* **78**, 379-386.

[14] Ivanoiu A, Sindic CJ (2005) Cerebrospinal fluid tau protein and amyloid beta42 in mild cognitive impairment: Prediction of progression to Alzheimer's disease and correlation with the neuropsychological examination. *Neurocase* **11**, 32-39.

[15] Rami L, Fortea J, Bosch B, Sole-Padulles C, Llado A, Iranzo A, Sanchez-Valle R, Molinuevo JL (2011) Cerebrospinal fluid biomarkers and memory present distinct associations along the continuum from healthy subjects to AD patients. *J Alzheimers Dis* **23**, 319-326.

[16] Backman L, Jones S, Berger AK, Laukka EJ, Small BJ (2005) Cognitive impairment in preclinical Alzheimer's disease: A meta-analysis. *Neuropsychology* **19**, 520-531.

[17] Rabin LA, Pare N, Saykin AJ, Brown MJ, Wishart HA, Flashman LA, Santulli RB (2009) Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* **16**, 357-376.

[18] Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[19] Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. *J Intern Med* **256**, 183-194.

[20] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[21] Neary D, Snowden JS, Northen B, Goulding P (1988) Dementia of frontal lobe type. *J Neurol Neurosurg Psychiatry* **51**, 353-361.

[22] Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A et al. (1993) Vascular dementia: Diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* **43**, 250-260.

[23] McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH

(1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): Report of the consortium on DLB international workshop. *Neurology* **47**, 1113-1124.

[24] Lezak MD, Howieson DB, Bigler ED, Tranel D (2012) *Neuropsychological assessment*, Oxford University Press, New York.

[25] Morris JC, Mohs RC, Rogers H, Fillenbaum G, Heyman A (1988) Consortium to establish a registry for Alzheimer's disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull* **24**, 641-652.

[26] Pflüger M, Aebi C, Monsch AU (2003) Klinische untersuchungsverfahren. *Z Klin Psychol Psychother* **32**, 64-67.

[27] van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J (2006) Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. *J Int Neuropsychol Soc* **12**, 80-89.

[28] Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. *Br J Psychiatry* **140**, 566-572.

[29] Pfeffer RI, Kurosaki TT, Harrah CH Jr, Chance JM, Filos S (1982) Measurement of functional activities in older adults in the community. *J Gerontol* **37**, 323-329.

[30] Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ (2002) Paired associate performance in the early detection of DAT. *J Int Neuropsychol Soc* **8**, 58-71.

[31] Swainson R, Hodges JR, Galton CJ, Semple J, Michael A, Dunn BD, Iddon JL, Robbins TW, Sahakian BJ (2001) Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dement Geriatr Cogn Disord* **12**, 265-280.

[32] Junkkila J, Oja S, Laine M, Karrasch M (2012) Applicability of the CANTAB-PAL computerized memory test in identifying amnestic mild cognitive impairment and Alzheimer's disease. *Dement Geriatr Cogn Disord* **34**, 83-89.

[33] Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW (1990) Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28**, 1021-1034.

[34] Robbins TW, James M, Owen AM, Sahakian BJ, Lawrence AD, McInnes L, Rabbitt PM (1998) A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: Implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *J Int Neuropsychol Soc* **4**, 474-490.

[35] Jongbloed W, Kester MI, van der Flier WM, Veerhuis R, Scheltens P, Blankenstein MA, Teunissen CE (2013) Discriminatory and predictive capabilities of enzyme-linked immunosorbent assay and multiplex platforms in a longitudinal Alzheimer's disease study. *Alzheimers Dement* **9**, 276-283.

[36] Grambaite R, Hessen E, Auning E, Aarsland D, Selnes P, Fladby T (2013) Correlates of subjective and mild cognitive impairment: Depressive symptoms and CSF biomarkers. *Dement Geriatr Cogn Dis Extra* **3**, 291-300.

[37] Rolstad S, Berg AI, Bjerke M, Blennow K, Johansson B, Zetterberg H, Wallin A (2011) Amyloid-beta(4)(2) is associated with cognitive impairment in healthy elderly and subjective cognitive impairment. *J Alzheimers Dis* **26**, 135-142.

[38] Wallin AK, Blennow K, Andreasen N, Minthon L (2006) CSF biomarkers for Alzheimer's Disease: Levels of beta-amyloid, tau, phosphorylated tau relate to clinical symptoms and survival. *Dement Geriatr Cogn Disord* **21**, 131-138.

[39] Donohue MC, Sperling RA, Salmon DP, Rentz DM, Raman R, Thomas RG, Weiner M, Aisen PS; Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Ageing; Alzheimer's Disease Neuroimaging Initiative; Alzheimer's Disease Cooperative Study (2014) The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. *JAMA Neurol* **71**, 961-970.

[40] Mormino EC, Papp KV, Rentz DM, Donohue MC, Amariglio R, Quiroz YT, Chhatwal J, Marshall GA, Donovan N, Jackson J, Gatchel JR, Hanseeuw BJ, Schultz AP, Aisen PS, Johnson KA, Sperling RA (2017) Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated amyloid-beta. *Alzheimers Dement* **13**, 1004–1012.

[41] Raoux N, Amieva H, Le Goff M, Auriacombe S, Carcaillon L, Letenneur L, Dartigues JF (2008) Clustering and switching processes in semantic verbal fluency in the course of Alzheimer's disease subjects: Results from the PAQUID longitudinal study. *Cortex* **44**, 1188-1196.

[42] Burnham SC, Raghavan N, Wilson W, Baker D, Ropacki MT, Novak G, Ames D, Ellis K, Martins RN, Maruff P, Masters CL, Romano G, Rowe CC, Savage G, Macaulay SL, Narayan VA, Alzheimer's Disease Neuroimaging Initiative AIBL Research Group (2015) Novel statistically-derived composite measures for assessing the efficacy of disease-modifying therapies in prodromal Alzheimer's disease trials: An AIBL study. *J Alzheimers Dis* **46**, 1079-1089.

[43] Lim YY, Snyder PJ, Pietrzak RH, Ukiqi A, Villemagne VL, Ames D, Salvado O, Bourgeat P, Martins RN, Masters CL, Rowe CC, Maruff P (2016) Sensitivity of composite scores to amyloid burden in preclinical Alzheimer's disease: Introducing the Z-scores of Attention, Verbal fluency, and Episodic memory for Nondemented older adults composite score. *Alzheimers Dement (Amst)* **2**, 19-26.

[44] Saxton J, Lopez OL, Ratcliff G, Dulberg C, Fried LP, Carlson MC, Newman AB, Kuller L (2004) Preclinical Alzheimer disease: Neuropsychological test performance 1.5 to 8 years prior to onset. *Neurology* **63**, 2341-2347.

[45] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**, 119-128.

[46] Brier MR, Gordon B, Friedrichsen K, McCarthy J, Stern A, Christensen J, Owen C, Aldea P, Su Y, Hassenstab J, Cairns NJ, Holtzman DM, Fagan AM, Morris JC, Benzinger TL, Ances BM (2016) Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. *Sci Transl Med* **8**, 338ra366.

[47] Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR (2004) Detecting dementia: Novel neuropsychological markers of preclinical Alzheimer's disease. *Dement Geriatr Cogn Disord* **17**, 42-48.

[48] Egerhazi A, Berecz R, Bartok E, Degrell I (2007) Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* **31**, 746-751.