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Relationship between cerebrospinal fluid biomarkers of Alzheimer's disease and cognition in cognitively normal older adults

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ABSTRACT

The pathophysiological processes underlying Alzheimer's disease (AD) are hypothesized to begin years to decades before clinical symptom onset, while individuals are still cognitively normal. Although many studies have examined the effect of biomarkers of amyloid pathology on measures of cognitive performance, less is known about the effect of tau pathology on cognitive performance. The present study examined the association between cerebrospinal fluid (CSF) biomarkers of AD pathology (amyloid, total tau (t-tau), and phosphorylated tau (p-tau)) and cognition in a large sample of cognitively normal middle-aged and older adults. Associations were examined with multivariate regressions, in which either amyloid and t-tau or amyloid and p-tau were included as simultaneous predictors of cognitive performance. Cognitive performance was measured with three composite scores assessing working memory, verbal episodic memory, and visuospatial episodic memory. In their respective models, CSF measures of both t-tau and p-tau were associated with the visuospatial episodic memory composite score ($p < .001$ and $p = .02$, respectively), but not with the other measures of cognition. In contrast, CSF amyloid was not significantly associated with cognitive performance, raising the possibility that measures of tau pathology have a more direct relationship with cognition in cognitively normal individuals. These results also suggest that tau pathology may have effects on visuospatial episodic memory during preclinical AD that precede alterations in other cognitive domains.

1. Introduction

Several lines of evidence suggest there is a preclinical phase of Alzheimer's disease (AD) during which AD pathology is accumulating (i.e., amyloid plaques and tau neurofibrillary tangles), in the absence of clinical symptoms (Sperling et al., 2011). These pathophysiological processes are thought to begin years to decades before the onset of clinical symptoms of AD, when individuals are still cognitively normal. This conclusion is primarily based on evidence that a subset of older individuals who are cognitively normal have AD pathology in their brains, based on both autopsy findings (Bennett et al., 2006; Hulette et al., 1998; Knopman et al., 2003) and amyloid imaging studies (Morris et al., 2010; Rowe et al., 2010; Reiman et al., 2009).

Moreover, recent studies suggest that cognitively normal individuals with biomarker evidence of AD pathology are at increased risk for developing cognitive decline over time. For example, cerebrospinal fluid (CSF) biomarkers of AD pathology (e.g., decreased levels of amyloid-beta ($A\beta_{1-42}$) and increased levels of total tau (t-tau) and phosphorylated tau (p-tau)) are associated with increased amyloid plaque burden and neurofibrillary tangle load at autopsy (Strozyk et al., 2003; Tapiola et al., 2009). Measured in cognitively normal individuals, these biomarkers are associated with increased risk for the development of clinical symptoms of AD (Fagan et al., 2007; Li et al., 2007; Roe et al., 2013; Moghekar et al., 2013). Cognitively normal individuals who subsequently develop clinical symptoms of AD also tend to perform more poorly on cognitive tests prior to symptom onset than individuals who remain cognitively normal (Albert et al., 2014; Howieson et al., 2008; for a discussion, see Sperling et al., 2011). This likely reflects the negative effect of AD pathology on cognition

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among those who subsequently progress, suggesting there should be a relationship between cognitive test performance and biomarker measures of AD pathology. While a number of previous studies have supported this hypothesis, and reported lower cross-sectional cognitive performance among cognitively normal individuals with higher biomarker levels of amyloid and tau pathology, findings are unusually mixed.

Most prior studies on this topic have evaluated biomarkers of amyloid pathology, measured either through CSF or positron emission tomography (PET). Several studies have reported cross-sectional associations between amyloid levels and episodic memory in cognitively normal older adults (e.g., using CSF amyloid: Stomrud et al., 2010; using amyloid imaging: Hedden et al., 2012; Kantarci et al., 2012; Pike et al., 2007, 2011; Rentz et al., 2011; Sperling et al., 2013; Villemagne et al., 2011), though others have not found these associations (e.g., using CSF amyloid: Li et al., 2014; Glodzik et al., 2011; Rami et al., 2011; Rolstad et al., 2011; Schott et al., 2010; Vemuri et al., 2011; using amyloid imaging: Aizenstein et al., 2008; Rodrigue et al., 2012; Rowe et al., 2010; Storandt et al., 2009). Additionally, while some studies have reported cross-sectional associations between amyloid levels and other domains of cognition, such as working memory, processing speed, and language (using CSF amyloid: Rolstad et al., 2011; Stomrud et al., 2010; using amyloid imaging: Kantarci et al., 2012; Rodrigue et al., 2012), findings from other groups have been negative (e.g., using CSF amyloid: Li et al., 2014; Rami et al., 2011; Sperling et al., 2013; Vemuri et al., 2011; using amyloid imaging: Aizenstein et al., 2008; Hedden et al., 2012; Pike et al., 2007, 2011; Rentz et al., 2011; Storandt et al., 2009). Despite these inconsistencies, a recent meta-analysis found small, but non-trivial, associations between biomarkers of amyloid pathology and cognition in cognitively normal older adults (Hedden et al., 2013).

Fewer studies have examined the relationship between biomarkers of tau pathology and cognition in cognitively normal adults, as the collection of cerebrospinal fluid biomarkers involves an invasive procedure and tau PET imaging has only recently become available. With one exception, the CSF studies have failed to find cross-sectional associations between biomarkers of tau pathology and cognitive performance (Glodzik et al., 2011; Rami et al., 2011; Rolstad et al., 2011; Stomrud et al., 2010; Vemuri et al., 2011). As the exception, Schott et al. (2010) reported an association between CSF t-tau and p-tau and performance on an individual task measuring executive function.

The variability of findings in these previous studies may be the result of several factors. First, the groups of cognitively normal individuals studied may have varied in the proportion of individuals who were destined to develop clinical symptoms over time, therefore varying in the amount of AD pathology present; this is a particular problem in studies with modest sample sizes. It is possible, therefore, that studies not finding associations between cognition and biomarkers of amyloid or tau pathology consisted of fewer individuals in the preclinical phase of AD, or with less advanced pathology. Second, differences in the genetic composition of the groups studied may also have contributed to variability of prior findings. For example, Kantarci et al. (2012) found that amyloid-cognition associations were stronger in ε4 allele carriers of the apolipoprotein E (APOE) gene (relative to non-carriers), a well-known genetic risk factor for AD (Farrer et al., 1997) that is associated with increased amyloid accumulation (e.g., Reiman et al., 2009; for a review, see Kim et al., 2009). However, with a few exceptions (e.g., Kantarci et al., 2012; Li et al., 2014; Pike et al., 2011), previous studies have generally not included APOE carrier status in their analyses. Third, the cognitive measures have varied among prior studies, consisting of either individual cognitive scores or cognitive composite scores. Prior evidence suggests that cognitive composite scores may be more sensitive measures of cognition because they reduce type 1 error, variability attributable to idiosyncratic task demands, measurement error, or other sources of error (Gross et al., 2014; Nunnally, 1978). It is noteworthy that many of the studies that found significant amyloid-cognition associations used cognitive composite scores (e.g., Hedden et al., 2012; Kantarci et al., 2012; Pike et al., 2007, 2011; Rentz et al., 2011; Rodrigue et al., 2012; Rolstad et al., 2011; Villemagne et al., 2011), as opposed to individual task scores.

In addition, previous studies left unresolved the degree to which amyloid-cognition associations are independent of the effects of t-tau or p-tau pathology, as the effects of amyloid and tau biomarkers have rarely been examined together (see Li et al., 2014, as an exception). It is possible, for example, that in studies finding associations between amyloid burden and cognition, those individuals with the highest levels of amyloid burden also had high levels of tau biomarkers. The associations reported between amyloid and cognition, therefore, may reflect concomitant associations with tau pathology. Lastly, most previous studies have consisted of cognitively normal individuals in their mid-70s and 80s when first examined. Since evidence suggests that older individuals are more likely to have concomitant pathologies (Petersen et al., 2006; Schneider et al., 2009; Sonnen et al., 2007), it is possible that examination of a younger cohort will reveal associations obscured by the complexity of pathologies more common in older individuals.

The goal of the present study was to address some of the questions left open by previous reports, utilizing data from a large sample ($N \approx 200$) of prospectively followed, middle-aged and older adults (mean age at baseline = 57 years), with both AD biomarker data and cognitive test scores, who have been followed for up to 19 years. These data allow us to test the hypothesis that higher baseline levels of AD pathology (as measured by CSF levels of $A\beta_{1-42}$, t-tau, and p-tau) are associated with lower baseline cognitive performance (measured by composite test scores) among cognitively normal individuals. Importantly, we examined whether CSF amyloid, tau and p-tau levels confer independent effects on cognition, as would be predicted if AD pathology accumulates years prior to symptom onset. Additionally, our analyses examined whether associations between CSF measures of AD pathology and cognition are modified by APOE-4 genetic risk.

2. Materials and methods

2.1. Participants and study design

The present study consists of individuals from the BIOCARD study, a prospectively followed cohort of 349 individuals. This study was designed to recruit and follow a cohort of cognitively normal individuals who were primarily middle aged at baseline ($M = 57.2$, $SD = 10.3$, range = 20–85). By design, approximately 75% of the cohort had a first degree relative with dementia of the Alzheimer's type. The overall goal of the BIOCARD study was to identify variables among cognitively normal individuals that predict the subsequent development of mild to moderate symptoms of Alzheimer's disease. This study was initiated in 1995 at the NIH, with recruitment occurring by the staff of the Geriatric Psychiatry Branch of the intramural program of the National Institute of Mental Health. Various sources were used for recruitment, including printed advertisements, informational lectures, articles in local or national media, and word-of-mouth. Individuals were excluded from participation if they were cognitively impaired, as determined by cognitive testing, or had significant medical problems such as severe cardiovascular disease, epilepsy, or drug or alcohol abuse. Participants were enrolled over time, beginning in 1995 and ending in 2005; all participants provided informed

consent.

At baseline, participants completed a comprehensive evaluation that included a physical and neurological exam, an electrocardiogram, standard laboratory studies, neuropsychological testing, magnetic resonance imaging (MRI) scans, CSF from lumbar puncture, and blood specimens. APOE genotyping was established on all but one participant after enrollment. In 2005, this study was stopped for administrative reasons. In 2009, a research team from Johns Hopkins School of Medicine was funded to re-establish the cohort and continue annual clinical and cognitive assessments, collect blood, and evaluate previously acquired MRI scans, CSF, and blood specimens.

Details of this consensus diagnosis process have been described elsewhere (Albert et al., 2014); briefly, the diagnostic process can be summarized as follows: (1) clinical data were examined pertaining to the medical, neurologic and psychiatric status of the subject, (2) reports of changes in cognition by the subject and by collateral sources were examined, and (3) decline in cognitive performance was established on the basis of neuropsychological testing. Subjects received consensus diagnoses by the staff of the BIOCARD Clinical Core for each annual assessment, including those conducted at the NIH. For individuals with evidence of cognitive impairment, the age at which the clinical symptoms began was estimated (for details, see Albert et al., 2014).

Subjects included in the present study were cognitively normal at baseline, based on the consensus diagnosis procedures described above, and had appropriate cognitive, CSF and genetic data available, as outlined below. Of the 349 individuals in the BIOCARD cohort, data from 47 subjects were not considered for analysis ($n=33$ have not yet re-enrolled in or withdrawn from the study and $n=14$ had clinical symptom onset at or before baseline, as per their consensus diagnosis).

Of the 302 individuals who were cognitively normal at their baseline visit and have re-enrolled in the study (M follow-up = 11.8 years, $SD=3.9$, range = 0–19 years) (Table 1), 62 have developed mild to moderate clinical symptoms of AD on follow-up, resulting in a diagnosis of either Mild Cognitive Impairment (MCI) or dementia due to AD (Albert et al., 2011; McKhann et al., 2011) (described here as 'progressors'). Of the 240 individuals who have remained cognitively normal as of their last available consensus diagnosis ('non-progressors'), a subset were excluded from the follow-up analyses (see below) due to the fact that some had no additional follow-up data since their last NIH visit ($n=28$) and some had a diagnosis of Impaired not MCI ($n=35$) (i.e., they had evidence of cognitive change as indicated by either self and/or informant reported complaints of worsening cognition OR slight changes on longitudinal neuropsychological testing, but not both) (Albert et al., 2011; Petersen, 2004). All living subjects included in the present study provided informed consent in accordance with the IRB at the Johns Hopkins University School of Medicine.

2.2. Neuropsychological tasks composing cognitive composite scores

Data from baseline cognitive tests were used to create three

Table 1
Baseline demographic and descriptive statistics for all subjects and by follow-up diagnosis. All means (standard deviations) are from raw data (i.e., not z-scored).

N (maximum)	All cognitively normal subjects		Non-progressors		Progressors	
	N	302	*n*	240	*n*	62
Demographics						
Age (years)	302	56.6 (10.2)	240	55.0 (9.5)	62	62.6 (10.7) *
Education (years)	302	17.0 (2.4)	240	17.1 (2.3)	62	16.6 (2.5)
Gender (% female)	302	60%	240	62%	62	52%
MMSE[a]	297	29.5 (0.8)	237	29.6 (0.8)	60	29.4 (1.0)
APOE-4 carriers (% total)[b]	293	32%	234	31%	59	36%
Working memory tasks (with data on all 3 tasks)						
Backwards digit span	269	7.7 (2.3)	212	8.0 (2.2)	57	6.7 (2.2) *
Digit-symbol substitution	269	53.0 (11.9)	212	55.1 (11.8)	57	45.4 (8.6) *
Supermarket fluency	269	30.4 (7.3)	212	31.2 (7.3)	57	27.4 (6.8) *
Verbal episodic memory tasks (with data on all 3 tasks)						
Logical memory (immediate)	290	14.8 (2.9)	230	15.1 (2.9)	60	13.7 (2.7) *
Logical memory (delayed)	290	12.9 (3.4)	230	13.2 (3.4)	60	11.7 (3.2) *
Paired associates (immediate)	290	20.5 (3.0)	230	20.9 (2.9)	60	19.2 (3.1) *
Visuospatial episodic memory tasks (with data on all 3 tasks)						
Rey recall	284	18.2 (6.5)	225	19.0 (6.3)	59	15.1 (6.5) *
Figural memory	284	7.2 (1.4)	225	7.4 (1.4)	59	6.6 (1.4) *
Visual reproduction (delayed)	284	28.8 (7.1)	225	29.7 (6.9)	59	25.6 (7.0) *
Weighted composite scores						
Working memory	269	0.01 (0.99)	212	0.21 (0.94)	57	−0.73 (0.80) *
Verbal episodic	290	0.01 (1.4)	230	0.18 (1.34)	60	−0.66 (1.35) *
Visuospatial episodic	284	−0.01 (1.39)	225	0.20 (1.35)	59	−0.83 (1.23) *
CSF biomarkers (pg/ml)						
AB_{1-42}	225	400.8 (97.3)	180	407.8 (92.7)	45	372.9 (110.6)
Tau	225	69.1 (31.1)	180	65.2 (26.8)	45	85.1 (40.9) *
P-tau	225	35.8 (16.1)	180	33.9 (13.6)	45	43.4 (22.1) *

[a] MMSE = Mini-Mental State Examination (Folstein et al., 1975).
[b] Excludes $n=1$ with no APOE genotyping and $n=8$ with one $\varepsilon 2$ and one $\varepsilon 4$ allele.
* Significant difference between non-progressors and progressors by univariate ANOVA for continuous variables or chi-square tests for dichotomous variables, $p < .05$. Cognition and CSF group comparisons included age as a covariate.

summary factor scores, referred to here as cognitive 'composite scores': working memory, verbal episodic memory, and visuospatial episodic memory. These domains were selected because they are hypothesized to be affected early in the course of AD. We selected nine tasks that were (a) hypothesized to load on these three cognitive constructs and (b) had data available from at least 250 subjects. Working memory/executive function was measured with the backwards digit span from the Wechsler Memory Scale-Revised (WMS-R) ($n=294$; Wechsler, 1987), category fluency (number of supermarket items generated in 60 s; $n=278$; Mattis, 1976), and digit-symbol substitution of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) ($n=289$; Wechsler, 1981). Verbal episodic memory was measured with logical memory immediate recall ($n=292$), logical memory delayed recall ($n=292$), and paired associates immediate recall ($n=290$) subtests of the WMS-R (Wechsler, 1987). Visuospatial episodic memory was measured with recall of the Rey-Osterreith Complex Figure ($n=298$; Rey, 1941), the WMS-R figural memory subtest ($n=287$; Wechsler, 1987), which assesses recognition memory for unfamiliar figures, and the WMS-R delayed visual reproduction subtest ($n=288$; Wechsler, 1987), which assesses the accuracy of reproduction of unfamiliar figures.

2.3. Application of confirmatory factor analysis for composite scores

We used confirmatory factor analysis (CFA), a type of latent variable modeling, to (a) confirm that the nine neuropsychological tasks used to create the composite scores loaded on their hypothesized cognitive constructs and (b) establish task weights for creating composite scores (described below). Error variance of the immediate and delayed versions of the logical memory task were allowed to correlate given these variables reflect two measures from the same task. Model fit was evaluated with the chi-square goodness-of-fit statistic to assess the discrepancy between the sample and fitted covariance matrices (Hu and Bentler, 1998, p. 426); for this index, small, non-significant values indicate good fit. Model fit was also evaluated with Bentler's comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root-mean-square residual (SRMR). CFI is an incremental fit index that ranges from 0–1 and compares the fitted model to a restricted baseline model; values $>.95$ indicate good fit (Blunch, 2008). Both RMSEA and SRMR are absolute-fit indices based on residuals. For both, lower values ($<.05$) indicate good fit, and RMSEA should also be accompanied by a non-significant p-value. CFA models were estimated with the lavaan (*la*tent *va*riable *an*alysis) package (Rosseel, 2012) in R.

The hypothesized three-factor model was compared to the nested two- and one-factor models to determine whether the nested models provided a more plausible fit to the data. Nested models were compared by the change in chi-square across models. The fuller, more complex model was accepted as having better fit if the change in chi-square was significant given the loss of degrees of freedom. The CFA analyses included all cognitively normal individuals who had data on the 9 tasks, regardless of whether they had CSF data ($n=262$).

The factor loadings from the final CFA model were also used to create composite scores in which individual z-scored task scores were weighted by their standardized factor loadings (Fig. 1). The weighted task scores within each cognitive domain were then summed to create the composite score for that domain. Composite scores were created for all individuals who had scores on the three tasks within an individual cognitive domain (even if they did not have data for all nine tasks), to ensure we had as much power as possible in the analyses.

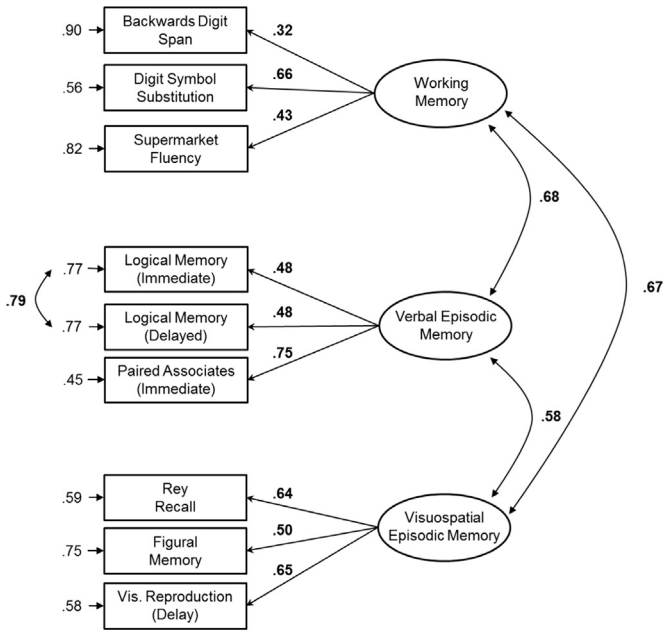

Fig. 1. Three-factor cognitive model. Numbers next to curved arrows are correlations. Numbers above left-pointing arrows are standardized factor loadings. Numbers adjacent to right-pointing arrows are residual error variances. Significant values are indicated in bold.

2.4. CSF assessments

CSF measures were available for 225 participants who underwent lumbar puncture within 150 days of their baseline cognitive testing ($M=5.3$ days between CSF draw and cognitive testing, $SD=17.8$). CSF specimens were analyzed by the current group of investigators using the Alzheimer's Disease Neuroimaging Initiative protocol. As reported in Moghekar et al. (2013), this protocol used the xMAP-based AlzBio3 kit (Innogenetics, Ghent, Belgium) run on the Bioplex 200 system. The kit contains monoclonal antibodies specific for $A\beta_{1-42}$ (4D7A3), t-tau (AT120), and p-tau_{181p} (AT270), each chemically bonded to unique sets of color-coded beads, and analyte-specific detector antibodies (HT7 and 3D6). Calibration curves were produced for each biomarker using aqueous buffered solutions that contained the combination of 3 biomarkers at concentrations ranging from 25 to 1555 pg/mL for recombinant tau, 54–1799 pg/mL for synthetic $A\beta_{1-42}$ peptide, and 15–258 pg/mL for a tau synthetic peptide phosphorylated at the threonine 181 position (i.e., the p-tau_{181p} standard). All samples for each participant were analyzed on the same plate and run in triplicate. See Moghekar et al. (2012) for additional details regarding these procedures. Although p-tau is considered a more direct measure of AD pathology (i.e., neurofibrillary tangles), t-tau has commonly been used as a biomarker of neuronal injury (e.g., Rolstad et al., 2011; Stomrud et al., 2010; Vemuri et al., 2009, 2011). Given the role of tau pathology in preclinical AD is not well understood, both t-tau and p-tau were included in the present study.

2.5. APOE genetic status

APOE genotyping was determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (Hixson and Vernier, 1990) (performed by Athena Diagnostics, Worcester, MA) and was unavailable for only 1 participant. The regression analyses described below excluded 8 individuals with an ε2/ε4 genotype, given the ε4 allele increases AD dementia risk (Corder et al., 1994), whereas the ε2 allele decreases AD dementia

risk (Farrer et al., 1997). Of the 293 participants with eligible genotyping, 12.6% ($n=37$) had at least one ε2 allele, 55.6% ($n=163$) had two ε3 alleles, and 31.7% ($n=93$) had at least one ε4 allele. Of those with at least one ε4 allele, 16.1% ($n=15$) had two ε4 alleles. For all analyses, APOE-4 carrier status was denoted by an indicator variable coding the number of ε4 alleles (0, 1, 2), referred to below as APOE load.

2.6. Statistical analyses

Associations between baseline cognitive composite scores and baseline CSF measures were examined with multivariate linear regression. For each composite score, we ran two sets of linear regression models: the first set examined the association of $A\beta_{1\text{-}42}$ and t-tau with cognition, and the second set examined the association of $A\beta_{1\text{-}42}$ and p-tau with cognition. $A\beta_{1\text{-}42}$ and t-tau (and similarly, $A\beta_{1\text{-}42}$ and p-tau) values were simultaneously entered into the models to examine each variable's association with cognition, independent of the other. For all models, cognitive composite scores served as the dependent variable, with CSF measures, age, years of education, gender (1 = male), APOE load, and the CSF measure by APOE load interactions (product) included as independent variables. CSF values by APOE interactions were included to determine whether the effect of a biomarker on cognition differed by APOE-4 carrier status. Given amyloid and tau pathology increase with age, the age variable was residually centered such that it reflected age orthogonalized for the CSF variables included in that model (i.e., the standardized residuals of regressing age on CSF $A\beta_{1\text{-}42}$ and t-tau OR age on CSF $A\beta_{1\text{-}42}$ and p-tau; Geldhof et al., 2013). All other continuous independent variables were standardized. Non-significant interaction terms were removed from the models and models were re-run without these terms. Analyses were corrected for multiple comparisons using false discovery rate (FDR) method with a q value of 0.05 (Benjamini and Hochberg, 1995). The number of subjects included in each regression analysis is shown in Table 4.

3. Results

Baseline demographic and descriptive statistics are shown in Table 1, divided into three groups: (1) all cognitively normal subjects with baseline cognitive and CSF data, meeting the criteria outlined above, (2) the subset of individuals who remained cognitively normal over time (i.e., non-progressors, as defined above), and (3) those who were cognitively normal at baseline but have since progressed to clinical symptoms of MCI or dementia due to AD. Though all individuals were cognitively normal at baseline, those who have since progressed to clinical symptoms of MCI or AD dementia tended to be slightly older, have worse performance on the cognitive testing, and more abnormal CSF levels of AD pathology, including significantly higher levels of CSF t-tau and p-tau and numerically lower levels of CSF $A\beta_{1\text{-}42}$ (see Table 1).

3.1. Evaluation of cognitive composite scores

Each z-scored cognitive variable was examined for distributional normality; all measures had skew and kurtosis values acceptable for psychometric purposes (largest skew = |.89|; largest kurtosis = |.73|). Correlations among cognitive tasks are shown in Table 2.

We first tested the fit of the hypothesized three-factor model that consisted of three distinct cognitive domains: working memory, verbal episodic memory, and visuospatial episodic memory. This model (Model 1) provided a good fit to the data ($\chi^2(23)=29.09$, $p=.18$; CFI = .989; RMSEA = .03, $p=.80$; SRMR = .04). The fit of Model 1 was compared to the two- and one-factor nested models (Models 2–5 in the Appendix; see Table A.1). Although these nested models tended to fit the data well, all provided a worse fit to the data than Model 1, as indicated by a significant change in chi-square (Table A.1, right). The three-factor model was therefore accepted as providing the best fit to the data (Fig. 1).

Table 2
Pairwise correlations among standardized cognitive task scores ($n=262$).

	1	2	3	4	5	6	7	8	9
1. Backwards digit span	–	.18**	.05	.15*	.12	.24**	.14*	.17**	.19**
2. Digit-symbol substitution		–	.33**	.17*	.18**	.32**	.25**	.23**	.34**
3. Supermarket fluency			–	.11	.07	.26**	.13*	.13*	.14*
4. Logical memory (immediate)				–	.84**	.35**	.23**	.21**	.17*
5. Logical memory (delayed)					–	.36**	.23**	.19**	.22**
6. Paired associates (immediate)						–	.22**	.26**	.27**
7. Rey recall							–	.35**	.44**
8. Figural memory								–	.27**
9. Visual reproduction (delayed)									–

* $p \le .05$, ** $p \le .005$.

3.2. Relationship between cognitive composite scores and CSF biomarkers

Correlations among demographic characteristics, CSF values, and cognitive composite scores are shown in Table 3. The results of the regression analyses are shown in Table 4. These results exclude the CSF biomarker by APOE interaction terms, as all interactions were non-significant (data not shown; all p's $> .29$); these non-significant interactions suggest that CSF-cognition associations do not vary by APOE-4 allele carrier status.

For the CSF biomarker-cognition associations, the first set of models included both CSF $A\beta_{1\text{-}42}$ and t-tau. In these models, t-tau, but not $A\beta_{1\text{-}42}$, was significantly associated with the composite score for visuospatial episodic memory ($p < .001$). In contrast, neither CSF t-tau nor $A\beta_{1\text{-}42}$ was associated with the working memory or verbal episodic memory composite scores. The second set of models included both CSF $A\beta_{1\text{-}42}$ and p-tau. In these models, p-tau was significantly associated with the composite score for visuospatial episodic memory ($p=.02$; Fig. 2), though CSF $A\beta_{1\text{-}42}$ was not. Again, neither CSF p-tau nor $A\beta_{1\text{-}42}$ were associated with the composite scores for working memory or verbal episodic memory. The negative regression weights for both t-tau and p-tau

Table 3
Correlations among demographic characteristics, CSF measures, and cognitive composite scores ($n=194$).

	1	2	3	4	5	6	7	8
1. Age	–	.11	−.17*	.30**	.16*	−.27**	−.15*	−.34**
2. Education		–	.07	−.04	−.03	.17*	.12	.04
3. CSF amyloid			–	−.004	−.27**	.11	.12	.12
4. CSF tau				–	.67**	−.04	−.04	−.22**
5. CSF p-tau					–	−.08	−.09	−.19*
6. Working memory composite						–	.36**	.39**
7. Verbal episodic memory composite							–	.40**
8. Visuospatial episodic memory composite								–

* $p \le .05$, ** $p \le .005$.

Table 4
Regression results examining the association between CSF biomarkers (amyloid and t-tau; amyloid and p-tau) and cognitive composite scores (working memory, verbal episodic memory, visuospatial episodic memory). Significant values are indicated in bold and *p*-values are corrected for multiple comparisons.

Set I: Relationship of CSF amyloid and t-tau with cognition

Outcome: working memory (n=193)				
	B	S.E. B	Beta	*p*
CSF amyloid	.08	.07	.09	.31
CSF t-tau	−.07	.06	−.08	.27
Outcome: verbal episodic memory (n=213)				
	B	S.E. B	Beta	*p*
CSF amyloid	.15	.10	.10	.37
CSF t-tau	−.13	.09	−.09	.24
Outcome: visuospatial episodic memory (n=208)				
	B	S.E. B	Beta	*p*
CSF amyloid	.20	.09	.14	.17
CSF t-tau	**−.37**	**.09**	**−.26**	**<.001**

Set II: Relationship of CSF amyloid and p-tau with cognition

Outcome: working memory (n = 193)				
	B	S.E. B	Beta	*p*
CSF amyloid	.07	.07	.08	.29
CSF p-tau	−.05	.07	−.05	.48
Outcome: verbal episodic memory (n=213)				
	B	S.E. B	Beta	*p*
CSF amyloid	.12	.10	.09	.25
CSF p-tau	−.10	.10	−.07	.42
Outcome: visuospatial episodic memory (n=208)				
	B	S.E. B	Beta	*p*
CSF amyloid	.14	.10	.10	.26
CSF p-tau	**−.24**	**.09**	**−.17**	**.02**

*S.E.=standard error.

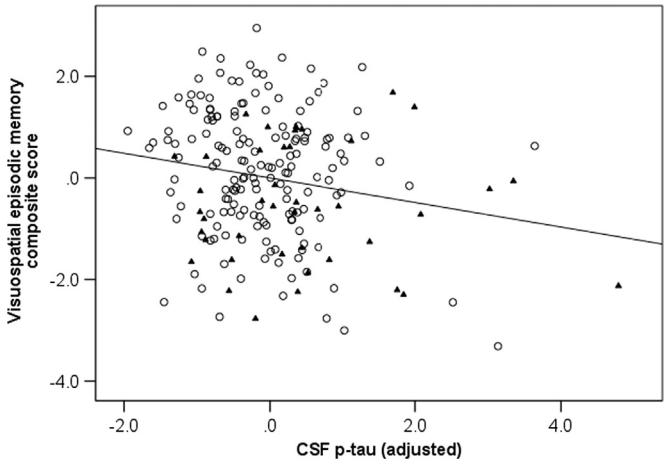

Fig. 2. Partial correlation between the visuospatial episodic memory composite score and CSF p-tau in all subjects, adjusted for covariates. For visualization purposes, non-progressors are depicted by open circles and progressors by filled triangles.

indicate that individuals with higher CSF levels of tau pathology performed worse on measures of visuospatial episodic memory, independent of CSF levels of amyloid pathology.

Of the covariates, it is notable that years of education was positively associated with the composite scores of working memory and verbal episodic memory (β's=.24, p's < .005 and β's=.18, p's < .03, respectively), but not visuospatial episodic memory (β's < .01, p's > .90). Similarly, gender was negatively associated with the composites scores of working memory and verbal episodic memory (β's ≈ −.21, p's=.004 and β's=−.22, p's < .007, respectively) with females outperforming males, but gender was not associated with the composite score of visuospatial episodic memory (β's=−.01, p's > .85). The APOE indicator variable was not associated with any of the cognitive composite scores, suggesting little difference in cognitive performance between APOE-4 carriers and non-carriers (all β's < |.08|).

Since the participants in this study have been followed for many years, consensus diagnoses are now available regarding their current status. We were therefore able to conduct follow-up analyses on the significant visuospatial findings described above. We examined the main effects of CSF levels on cognition in the subset of individuals who have demonstrated no evidence of cognitive decline to date. The goal of this follow-up analysis was to determine whether associations between baseline CSF levels and visuospatial episodic memory were present in the subset of individuals who have remained cognitively normal over time and were therefore unlikely to have AD pathology at baseline (n=127; M follow-up time=12.5 years, SD=2.9, range=8–19 years). The absence of an association in this subgroup would support the hypothesis that the significant associations in the full sample reflect variability contributed by the preclinical AD group. These follow-up analyses excluded individuals with no follow-up since their last NIH visit (as we do not have a current clinical diagnosis for them) and individuals with a current diagnosis of 'Impaired not MCI'. Age residuals were re-calculated to reflect the subset of individuals included. There were no significant main effects of CSF amyloid, CSF t-tau, or CSF p-tau on the visuospatial episodic memory composite score. As an additional follow-up, we tested whether the relationship between CSF and visuospatial episodic memory differed in those who have remained cognitively normal to date (as just described) relative to those who have since progressed. To do so, we re-ran our original models (described in Section 2.6), including interaction terms for CSF biomarker by follow-up diagnosis status (dichotomous: progressor vs. non-progressor) in place of the CSF biomarker by APOE interaction terms. There were no significant CSF biomarker by follow-up diagnosis interactions in either model (all p's > .30).

4. Conclusions

The present study examined the association between cerebrospinal fluid measures of amyloid and tau pathology and cognitive test scores in a large cohort of cognitively normal, middle-aged and older adults. Cognition was assessed by performance on three composite scores measuring working memory/executive function, verbal episodic memory, and visuospatial episodic memory. Our analyses included both CSF amyloid and CSF t-tau (first set of models), and CSF amyloid and CSF p-tau (second set of models), as simultaneous predictors of cognitive performance to determine whether the two sets of CSF measures incurred independent associations with cognition.

We found significant associations between CSF t-tau and CSF p-tau levels and visuospatial episodic memory, such that individuals with higher biomarker levels of tau pathology performed worse on the visuospatial episodic memory tests. In contrast, CSF $A\beta_{1-42}$ was not significantly associated with cognition. These findings suggest that CSF levels of tau pathology have a more direct association with cognition than levels of amyloid, and raise the possibility that previously reported relationships between amyloid and cognition may be due to concomitant tau pathology. CSF biomarkers were not associated with measures of working or verbal episodic memory. Additionally, these associations did not vary as a function of APOE-4 carrier status.

These results extend previous work in three key ways. First, we examined CSF biomarker and cognition relationships in a longitudinally followed cohort of cognitively normal individuals, and included biomarkers of both amyloid and tau pathology as

simultaneous predictors of cognitive performance. Second, this approach, in combination with our large sample size, allowed us to examine the effect of ApoE-4 carrier status in a more definitive manner. Third, we used composite scores to assess cognition, which may have provided more precise estimates of cognitive performance. In particular, the inclusion of a visuospatial episodic memory composite score permitted us to examine relationships with this cognitive domain more directly than has previously been done, either because such measures were not available in earlier studies or were included in composites not specific to memory.

Only one previous study to our knowledge has assessed whether associations between biomarkers of amyloid pathology were independent of biomarkers of tau pathology (Li et al., 2014), likely due to the fact that imaging studies have lacked measures of tau pathology until recently. In a lifespan sample of cognitively normal adults, Li et al. (2014) found no associations between biomarkers of tau pathology and cognition, though measures of visuospatial episodic memory were not included. Although a number of previous studies have found an association between biomarkers of amyloid pathology and episodic memory (e.g., Hedden et al., 2012; Kantarci et al., 2012; Pike et al., 2007; Villemagne et al., 2011), we found no significant amyloid-cognition associations with t-tau or p-tau in the regression models. We cannot rule out the possibility that the observed amyloid-cognition effect sizes, which are in the same range as previous observations (e.g., Hedden et al., 2013), may have been significant with a larger sample. However, our findings suggest biomarkers sensitive to alterations in tau pathology may be a primary influence on individual differences in cognition during preclinical AD. In line with this, a recent study found that [^{11}C] Pittsburgh compound B (PiB) PET measures of amyloid are more strongly correlated with the ratio of CSF tau/Aβ_{1-42} (or p-tau/Aβ_{1-42}), rather than CSF amyloid alone (Roe et al., 2013), also raising the possibility that alterations in tau levels contributed to previously reported amyloid imaging-cognition associations. Our findings are also consistent with preliminary data emerging from one of the first T807 tau PET imaging studies measuring both amyloid and tau levels in cognitively normal adults (Sperling et al., 2015). Consistent with our CSF results, this study reported an association between inferior temporal tau levels (but not amyloid) and episodic memory performance when both tau and amyloid served as simultaneous predictors of cognition.

The stronger effects for biomarkers of tau pathology, rather than amyloid pathology, are likely related to findings indicating that increases in tau and p-tau in the CSF may be due to the combined effect of synaptic injury, neuronal loss, and the presence of neurofibrillary tangles (Holtzman, 2011). Numerous studies from different laboratories have demonstrated a significant decrease in synaptic density in neocortical association areas and the hippocampus in patients with AD (see reviews by Scheff and Price, 2003; Scheff et al., 2014), and these studies have shown that the strongest correlation with cognitive decline is with synaptic number and regional neuronal loss (DeKosky and Scheff, 1990; Terry et al., 1991; Sze et al., 1997; Masliah et al., 2001). Although the CSF tau measures used in the present study reflect aggregate (rather than regionally specific) measures of neuronal injury and tau pathology, future studies measuring tau accumulation with PET tracers should be able to address tau-cognition associations among cognitively normal older adults in a regionally specific manner.

The specificity of the relationship between CSF t-tau and p-tau and visuospatial – but not verbal – episodic memory is also of interest. Pathological studies in cognitively normal adults have suggested that the accumulation of AD-related tau pathology begins in medial temporal regions, with later dispersion to other brain regions (Braak and Braak, 1991, 1997; Price and Morris, 1999). These same medial temporal regions are also important for episodic memory (for a review, see, e.g., Burgess et al., 2002; Squire, 1992). The visuospatial episodic memory tasks included in these analyses involved predominantly unfamiliar stimuli that were difficult to verbalize. In contrast, verbal episodic memory tasks may allow one to compensate for early medial temporal lobe pathology through the use of cortically mediated memory strategies, including verbal coding (e.g., the use of language/semantics) and the use of well-practiced heuristics in learning and retention (e.g., verbal associations). In line with this, level of education was associated with the composite score of verbal episodic memory (as well as working memory), but not visuospatial episodic memory. While prior studies have not reported a disproportional impairment on individual nonverbal memory tasks in preclinical AD (e.g., Albert et al., 2014), the present findings suggest a visuospatial episodic memory composite may be useful as a cognitive marker of preclinical AD. It should be noted that associations between CSF biomarkers and other domains of cognition (e.g., verbal episodic memory or working memory) may become apparent as the individuals age and accumulate additional AD pathology.

The finding that the tests of visuospatial episodic memory employed in the current study were not associated with level of education may also be of relevance to clinical trials. Such nonverbal tests may be less biased by educational and linguistic variables and thereby permit the selection of participants from a broad range of socioeconomic backgrounds with less adjustment for these cultural factors.

In the follow-up analyses, we found no significant interactions between CSF biomarkers and prospective clinical diagnosis. One possible interpretation for this finding is that the association between CSF biomarkers of AD pathology and measures of visuospatial episodic memory are the same for cognitively normal individuals who develop cognitive impairment over time and those who remain normal, reflecting age-related, rather than disease-related processes. However, we also found no significant biomarker-cognition associations in the subset of individuals who have remained cognitively normal to date. While this may simply reflect the reduction in power for the sub-group analyses, an alternative interpretation is that variability in cognitive scores and CSF protein levels across both groups of cognitively normal individuals is needed in order to detect associations between CSF biomarkers of AD and cognition. Supporting this view, the group who developed clinical symptoms of MCI or dementia at follow-up had higher baseline levels of both CSF t-tau and p-tau and lower cognitive test scores (Table 1). However, these follow-up analyses should be interpreted with caution. For example, the interaction terms do not account for time between baseline and clinical symptom onset, an important caveat given some subjects progressed to clinical symptoms within a few years of baseline while others progressed more than a decade later (mean time from baseline to clinical symptom onset=7 years, range=1–14). Nonetheless, our findings raise the possibility that the associations found in the entire sample of individuals who were cognitively normal at baseline were driven by variability contributed by individuals in the preclinical phase of AD (i.e., the progressors). Variability in the amount of AD pathology across samples of cognitively normal individuals may also help explain prior inconsistencies in the literature.

Additionally we found that APOE-4 carrier status was not directly associated with cognitive performance in the participants, in line with a number of previous studies finding no effect of APOE on cognition in cognitively normal adults (e.g., Li et al., 2014; Small et al., 2000; Smith et al., 1998). Furthermore, we found no differences in CSF biomarker-cognition associations between APOE-4 carriers and non-carriers (i.e., no biomarker by APOE interactions). This finding is in contrast to that of Kantarci et al. (2012), who reported stronger amyloid-cognition associations in APOE-4

Table A.1
Confirmatory factor analysis model fit indices and change in chi-square across models (relative to Model 1).

Hypothesized factor structure	χ^2	CFI	RMSEA	SRMR	$\Delta\chi^2$	Δdf	*p*-Value
(1) 3-factor model	$\chi^2(23)=29.09$, $p=.18$	.989	.03 ($p=.80$)	.04	–	–	–
Nested models							
(2) 2-factors (vsEM=vEM)	$\chi^2(25)=48.46$, $p=.003$	.959	.06 ($p=.24$)	.05	19.37	2	<.001
(3) 2-factors (vsEM=WM)	$\chi^2(25)=42.92$, $p=.01$	.969	.05 ($p=.41$)	.04	13.83	2	.001
(4) 2-factors (vEM=WM)	$\chi^2(25)=37.48$, $p=.052$	.978	.04 ($p=.62$)	.05	8.39	2	.02
(5) 1-factor	$\chi^2(26)=54.12$, $p=.001$	.951	.06 ($p=.16$)	.05	25.03	3	<.001

CFI=comparative fit index. RMSEA=root mean square error of approximation. SRMR=standardized root-mean-square residual. df=degrees of freedom. WM=working memory. vEM=verbal episodic memory. vsEM=visuospatial episodic memory.

carriers relative to non-carriers. However, the results of Kantarci et al. (2012) are difficult to compare to our own, given biomarkers of tau pathology were not included (and thus not controlled) and their participants were substantially older (mean age, 79 years) than those in the present study. Because amyloid deposition increases with age, with greater accumulation in APOE-4 carriers (Morris et al., 2010), the participants in the Kantarci et al. study may have had increased levels of amyloid deposition relative to our participants.

The present study has several limitations. The BIOCARD cohort is highly educated and primarily Caucasian, limiting the generalizability of these findings to more diverse, community populations. Additionally, many participants have a family history of dementia. These findings should be replicated in more diverse samples. Future studies could also examine whether CSF biomarkers of AD pathology are associated with other measures of verbal episodic memory, as our composite measure of verbal episodic memory consisted of both immediate and delayed recall measures. Although previous research has suggested that both types of episodic memory measures are sensitive predictors of clinical symptom onset among cognitively normal older adults (e.g., Albert et al., 2014), more challenging measures of verbal episodic memory may be more sensitive to preclinical levels of AD pathology cross-sectionally (e.g., Rentz et al., 2011). Lastly, we emphasize that the lack of a significant association among the non-progressors may be due to a reduction in sample size when compared with the first analysis; nevertheless, these results suggest that the inclusion of pre-symptomatic individuals may drive the associations between cognition and biomarkers of AD neuropathology in cognitively normal adults.

Hypothetical models of AD have described the order and pattern of biomarker accumulation over preclinical and clinical disease phases (Jack et al., 2013; Sperling et al., 2011). Though recent research has tried to address and validate these hypothetical models, the timing and consequences of preclinical AD pathology are not well understood. The present study suggests that biomarkers of tau pathology have early effects on cognition, as reflected by lower performance on measures of visuospatial episodic memory. As discussed above, this association demonstrates neuroanatomical consistency, given that visuospatial episodic memory utilizes medial temporal regions that are also some of the earliest regions affected by AD-related tau pathology.

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Appendix

See Table A.1.

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