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Cerebrospinal fluid amyloid levels are associated with delayed memory retention in cognitively normal biomarker-negative older adults

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ABSTRACT

Alzheimer's disease is defined by abnormal levels of amyloid and tau biomarkers. Even cognitively normal older adults with clinically relevant amyloid and tau levels perform worse on memory tests. However, it is unclear if the relationship between biomarker level and memory extends below clinical thresholds. We hypothesized that even subclinical biomarker levels are associated with memory when measured with neuropsychological tests designed to detect dysfunction in preclinical disease states. In a group of cognitively normal, "biomarker-negative" older men and women, we investigated the relationship between cerebrospinal fluid biomarker levels and memory measured with the ModRey, a list-learning task designed to assess memory in preclinical and cognitively normal adults. Cerebrospinal amyloid levels were associated with ModRey memory retention, the proportion of information retained after a delay period. When older adults with mild impairment were included, cerebrospinal fluid tau levels were also associated with ModRey retention. The association of amyloid and tau levels with memory was independent of each other. These results suggest cognitive changes associated with Alzheimer's disease pathology might occur earlier than currently thought.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized clinically by memory loss. Neuropathologically, AD is defined by the presence of protein aggregates comprising amyloid beta (i.e., neuritic plaques) and hyperphosphorylated tau (i.e., neurofibrillary tangles) (Jack et al., 2018; McKhann et al., 2011). The presence of amyloid beta and tau can be measured in vivo either through assays of the cerebrospinal fluid (CSF) (Fagan et al., 2007; Motter et al., 1995; Sjögren et al., 2001; Vandermeeren et al., 1993) or via positron emission tomography (PET) (Chien et al., 2013; Johnson et al., 2016; Klunk et al., 2004; Ossenkoppele et al., 2016; Resnick et al., 2010; Schöll et al., 2016). These measurements are used as biomarkers of AD. Indeed, a new diagnostic framework for AD (Jack et al., 2018) requires patients to have biomarker evidence to meet criteria for AD.

Tau and amyloid have different relationships with the cognitive and neurodegenerative trajectory of AD. Abnormal levels of either biomarker can predict future development of dementia, even in cognitively normal older adults. Tau deposition more closely matches the spatial pattern of AD-related neurodegeneration than amyloid deposition (Bennett et al., 2004; Herukka et al., 2008; Johnson et al., 2016; Ossenkoppele et al., 2016; Schöll et al., 2016). However, longitudinal studies of dominantly inherited AD suggest that amyloid accumulation precedes future cognitive decline earlier than tau accumulation in cognitively normal older adults (Bateman et al., 2012; Buchhave et al., 2012; McDade et al., 2018). Indeed, consistent with current models of disease pathogenesis (Hardy and Selkoe, 2002; Tanzi and Bertram, 2005; for review, Small and Duff,

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2008), the presence of amyloid predicts future tau deposition (Leal et al., 2018; Pontecorvo et al., 2019). An emerging narrative from recent molecular PET imaging studies suggests that amyloid potentiates the spread of autogenic tau into neocortical regions (Schwarz et al., 2016), and that association between amyloid and subsequent cognitive decline is mediated by the later presence of both biomarkers (Hanseeuw et al., 2019). It is important to note that tau deposition in the absence of amyloid is also common, although there is some debate about whether this form of tauopathy is necessarily AD related or an effect of aging (Crary et al., 2014; Duyckaerts et al., 2015).

Clinically relevant levels of amyloid and tau are linked to memory deficits, even in cognitively normal older adults; such individuals are said to be "biomarker positive." "Amyloid positivity" in cognitively normal older adults is related to lower episodic memory scores (e.g., Bilgel et al., 2018; Papp et al., 2015; Petersen et al., 2016; Pike et al., 2011; Sperling et al., 2013; Wirth et al., 2013) and a greater probability of subsequent memory decline and progression to clinical AD (e.g., Farrell et al., 2017; Lim et al., 2013; Mormino et al., 2017; Papp et al., 2017; Petersen et al., 2016; Vemuri et al., 2015; Villemagne et al., 2011). Treating amyloid as a continuous measure, several studies showed that amyloid levels and memory performance are correlated in cognitively normal, amyloid-positive older adults (e.g., Amariglio et al., 2012; Hedden et al., 2012; Sperling et al., 2013, 2018; Stomrud et al., 2010). Furthermore, 2 different large-scale meta-analyses that considered PET-derived amyloid levels showed a weak association with episodic memory in cognitively normal, amyloid-positive older adults (Hedden et al., 2013; Jansen et al., 2018). A number of studies also reported that abnormal levels of tau ("tau positivity") is related to memory both cross-sectionally (Insel et al., 2015; Pettigrew et al., 2015) and longitudinally (Glodzik et al., 2011; Moghekar et al., 2013; Soldan et al., 2016; Steenland et al., 2014) in cognitively normal older adults.

Does the relationship between amyloid or tau and memory extend to subclinical levels of biomarkers (i.e., in biomarker-negative individuals)? Few studies examined this question directly, but there are hints that amyloid levels might affect memory, even in ostensibly healthy amyloid-negative older adults. Amyloid levels are related to memory even in presumably amyloid-negative middle-aged participants (Bischof et al., 2016; Farrell et al., 2017), and amyloid levels in the amyloid-negative range are associated with greater longitudinal decline in episodic memory in older adults without dementia (Landau et al., 2018; Leal et al., 2018). In contrast, no studies to date have reported an association between tau levels and memory in a sample of only tau-negative individuals, although medial temporal lobe tau levels are associated with memory in amyloid-negative participants (Maass et al., 2018).

To maximize the likelihood of detecting memory effects in a cognitively normal, biomarker-negative older adult population, we used the Modified Rey Auditory Verbal Learning Test ("ModRey", Hale et al., 2017) to investigate the relationship of CSF amyloid and tau with memory. The ModRey is a free-recall learning and memory task designed to be more sensitive to individual differences in memory among preclinical and nonclinical participants than standard clinical neuropsychological instruments. In particular, it avoids ceiling effects by increasing the number of test items and by reducing the number of study trials compared with standard verbal learning and memory tests and has good test-retest reliability (Hale et al., 2017). Furthermore, we previously showed that memory retention, and specifically memory retention on the ModRey, is related specifically to cerebral blood volume in the entorhinal cortex (Brickman et al., 2014), where AD-related neurodegeneration occurs earliest, and that cerebral blood volume in the entorhinal cortex is related to subsequent progression to clinical AD (Khan et al., 2014). Therefore, the ModRey may be able to detect subtle variability in memory associated with levels of amyloid and tau below established clinical thresholds for AD biomarkers.

The present study focuses primarily on addressing the question of whether CSF amyloid and tau concentrations are related to ModRey memory retention in cognitively normal, biomarker-negative older adults. We additionally address the question of whether CSF amyloid and tau have independent relationships with cognition in cognitively normal/mild cognitive impairment (MCI) participants.

2. Methods

2.1. Participants

Fifty-two cognitively normal (Clinical Dementia Rating [CDR] = 0) older adult participants (27 women) were recruited through the Columbia University Alzheimer's Disease Research Center. Thirty-nine participants (75.0%) were non-Hispanic whites, 9 participants (17.3%) were African-Americans, 3 participants (5.8%) were Asian/Pacific Islander-Americans, and 1 participant (1.9%) was Hispanic white.

An additional 9 older adult participants with MCI (CDR = 0.5) were included in an augmented sample for the purposes of the secondary analysis that examined the independence of CSF amyloid and tau effects on cognition. Of these 9 additional participants, 7 were non-Hispanic whites and 2 participants were African-American.

Demographic information about the participants is displayed in Table 1. Participants were screened for English comprehension, neurological disease, as well as contraindications for magnetic resonance imaging and gadolinium injection. All participants gave informed consent to participate in this study, and the institutional review board of Columbia University approved all procedures used in this study.

2.2. ModRey

Participants were administered the ModRey, a list-learning test of learning and declarative memory. The design of the ModRey is illustrated in Fig. 1. In brief, participants first receive 3 learning trials, where they were read 20 unique, semantically and phonetically unrelated words (list A) and are asked to freely recall these words after each trial. These trials are immediately followed by a 4th learning trial, where participants are read a distractor list of 20 additional semantically and phonetically unrelated words (list B). Subsequently, participants are asked to freely recall as many words as possible from list A (the "short-delay free recall"). After an approximately 40-minute delay, during which unrelated cognitive

Table 1
Participant demographics

Group	N	Sex (F/M)	Age (y)			Education (y)		
			Mean	SD	Range	Mean	SD	Range
CDR = 0								
All	52	27/25	70.1	7.6	56–93	16.5	1.9	12–20
A- only	45	27/18	69.7	7.9	56–93	16.2	1.7	12–20
T- only	46	23/23	69.2	6.9	56–88	16.6	2.0	12–20
A- and T-	39	23/16	68.6	7.0	56–88	16.2	1.8	12–20
CDR = 0 + 0.5								
All	61	29/32	70.4	7.5	56–93	16.6	2.1	12–20
A- only	53	29/24	69.8	7.6	56–93	16.2	2.0	12–20
T- only	51	25/26	69.1	6.7	56–88	16.6	2.0	12–20
A- and T-	44	25/19	68.5	6.8	56–88	16.2	1.9	12–20

Key: CDR, Clinical Dementia Rating.

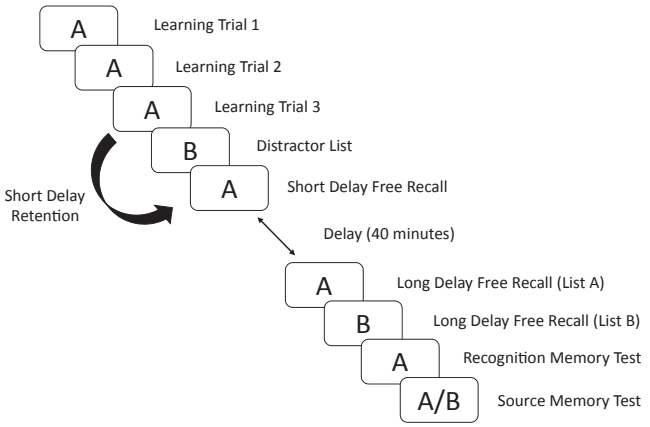

Fig. 1. The design of the ModRey. "A" and "B" refer to lists A and B, respectively. The short-delay retention (SDR) is the ratio of words recalled at the short-delay free recall to the number of word recalled at the 3rd (and last) learning trial.

testing occurred, participants are asked to freely recall as many words as possible from both list A and list B separately ("long-delay free recall"). These trials are followed by a 66-item forced-choice recognition test where participants are asked to decide if a presented word belongs to list A (distractors came from both list B and a selection of phonetically/semantically related words). Finally, source memory is assessed by asking the participant to match words on a list to either list A or list B.

The primary outcome variable of interest is the "short-delay retention" (SDR) score: the ratio of the number of items from list A correctly recalled freely at the short delay to the number of items correctly recalled freely during the last list A learning trial. This variable was chosen because it is tightly linked to function of the entorhinal cortex (Brickman et al., 2014).

Two psychometrically similar (Hale et al., 2017) versions of the ModRey were used, each with its own unique lists A and B. Half of the participants received one version of the ModRey, and the other half received the other. There were no differences in SDR between the 2 versions, $t(60) = 0.050$, $p = 0.960$. All analyses collapse across the 2 versions.

2.3. CSF biomarkers

CSF was obtained via lumbar puncture, performed with standard clinical research methods in aseptic fashion by a board-certified neurologist. CSF was always collected during a separate session from testing to avoid influencing performance on cognitive testing. The median delay between ModRey testing and CSF collection was 3 days.

Up to 15 cc of CSF was removed using a Sprotte 24G spinal needle and placed in two 12 cc polypropylene tubes. All samples were centrifuged briefly, aliquoted using polypropylene pipettes within 30 minutes, and stored for both biomarker analysis and CSF banking at −80 °C. Levels of 3 CSF biomarkers (Aβ42, phosphorylated tau, total tau) were analyzed in duplicate by a bead-based multiplex method using the Innogenetics Alz-Bio3 kits on a Luminex (LS-100) platform with 96-well plates. Coefficient of variation was generally less than 10% (samples with higher coefficient of variation were repeat analyzed). Phosphorylated tau concentrations failed measurement for 5 participants. Within our sample, Aβ42 levels were not correlated with phosphorylated tau levels, $r(46) = 0.016$, $p = 0.917$, but Aβ42 levels were correlated with total tau, $r(51) = 0.325$, $p = 0.019$. Phosphorylated tau and total tau levels were strongly correlated, $r(46) = 0.518$, $p < 0.001$.

Cutpoints for Aβ42, phosphorylated tau, and total tau "positivity" were generated using an independent set of 80 samples including only clinically probable AD and healthy controls (excluding MCI). Cutpoints were chosen with specificity of about 90% and sensitivity of 60%–70% (area under the receiver operating characteristic curve about 0.8). See supplementary table 1 for more details.

2.4. Additional neuropsychological testing

Fifty-one of the 52 participants previously received the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) neuropsychological battery, version 3 (NACC UDS-3, Weintraub et al., 2018). This is a standardized set of neuropsychological tests used by Alzheimer's Disease Centers across the United States. The battery includes the Montreal Cognitive Assessment (Nasreddine et al., 2005), Craft Story (Craft et al., 1996), Digit Span (Weschler, 1987), Semantic and Verbal Fluency (Morris et al., 1989), Trail making Test Parts A and B (Reitan and Wolfson, 1985), Benson Complex Figure Test (Possin et al., 2011), and the Multilingual Naming Task (Gollan et al., 2012).

2.5. Statistical analyses

Bivariate Pearson correlations were used to examine the relationship of CSF Aβ42, phosphorylated tau, and total tau concentrations with ModRey SDR. Age was partialed out of all correlations in our analyses. These correlations were conducted (1) on the entire sample of CDR = 0 participants, (2) using only those participants who were amyloid negative (Aβ42 concentration >325 pg/mL), (3) using only those participants who were tau-negative (t-tau concentration <72 pg/mL), and (4) using only those participants who were both amyloid negative and tau negative. Additional post hoc analyses examined the correlations when years of education, race/ethnicity, and sex/gender were included as additional covariates and if tau status was defined using phospho-tau instead of total tau (tau negativity was defined with the CSF total tau concentration in earlier analyses because CSF phosphotau levels were unavailable for 5 participants).

In the event that amyloid and tau were not correlated with memory in the cognitively normal (CDR = 0) sample—which precludes the possibility of investigating if amyloid and tau effects on memory are independent—the correlational analyses were repeated with an augmented sample that included additional participants (n = 9) with MCI (CDR = 0.5). To examine the independence of amyloid and tau effects on short-delay ModRey retention, amyloid and tau concentrations were entered as predictors for ModRey retention in multiple regression models (along with age as a covariate), both with and without interaction terms. Multiple regressions were tested for multicollinearity; residual plots were inspected to check for nonlinearity and heteroscedasticity.

As additional post hoc tests, bivariate Pearson's correlations were used to examine if (1) CSF biomarkers were additionally associated with other cognitive domains, as assessed by the NACC UDS-3 battery, and (2) with other ModRey outcome measures.

3. Results

Descriptive statistics about ModRey SDR performance and CSF biomarker concentrations are presented in Table 2.

3.1. CSF amyloid/tau—ModRey correlational analyses

Table 3 presents all 4 sets of correlational analyses run on subsets of participants, defined by biomarker status, see also Fig. 2. Of

Table 2
Descriptive statistics about memory performance and CSF concentrations

Group	N	ModRey SDR			Aβ42 concentration			P-tau concentration			T-tau concentration		
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
CDR = 0													
All	52	0.72	0.21	0.13–1.08	501.1	161.4	113.1–776.6	22.3	9.6	7.0–52.4	51.4	17.4	25.8–99.3
A- only	45	0.73	0.20	0.13–1.08	544.4	122.5	328.3–776.6	22.7	10.1	7.0–52.4	53.0	17.7	25.8–99.3
T- only	46	0.71	0.22	0.13–1.08	494.9	168.7	113.1–776.6	20.8	8.0	7.0–36.5	47.1	12.9	25.8–71.9
A- and T-	39	0.72	0.21	0.13–1.08	543.8	128.5	328.3–776.6	20.9	8.4	7.0–36.5	48.2	12.8	25.8–71.9
CDR = 0 + 0.5													
All	61	0.68	0.24	0–1.08	492.2	160.6	71.2–776.6	22.5	9.5	7.0–52.4	54.2	20.3	25.8–113.1
A- only	53	0.70	0.23	0–1.08	535.8	117.6	328.3–776.6	22.6	9.8	7.0–52.4	55.4	20.4	25.8–113.1
T- only	51	0.70	0.22	0.13–1.08	494.0	160.9	113.1–776.6	20.7	8.2	7.0–37.6	47.3	12.8	25.8–71.9
A- and T-	44	0.71	0.21	0.13–1.08	537.2	123.5	328.3–776.6	20.9	8.5	7.0–37.6	48.3	12.8	25.8–71.9

Key: CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; SDR, short-delay retention.

particular interest, we note that in the entire group of cognitively normal participants (i.e., including only the CDR = 0 participants), better ModRey SDR performance was associated with higher Aβ42 concentration, $r(49) = 0.304$, $p = 0.03$, but not with p-tau concentration, $r(44) = -0.068$, $p = 0.65$, or t-tau concentration, $r(49) = 0.123$, $p = 0.39$. Second, the association of ModRey SDR and Aβ42 concentration remained when considering only the subset of participants who were amyloid negative, $r(42) = 0.324$, $p = 0.03$. Third, this association also remained when considering only the subset of participants who were tau negative, $r(43) = 0.311$, $p = 0.04$. Finally, there was also an association between better ModRey SDR performance and higher Aβ42 concentration in the subset of participants who were both amyloid negative and tau negative concurrently, $r(36) = 0.399$, $p = 0.01$. We note that even if we take a dramatically more conservative CSF Aβ42 threshold of >500 pg/mL, this association remains, $r(22) = 0.550$, $p = 0.005$.

When the effects of race/ethnicity, education, and sex/gender were additionally partialed out, better ModRey SDR performance continued to be correlated with higher Aβ42 concentration in participants who were amyloid negative, $r(38) = 0.367$, $p = 0.02$, and participants who were both amyloid negative and tau negative, $r(32) = 0.466$, $p = 0.005$.

The correlation between ModRey SDR and CSF amyloid remained in amyloid-negative and tau-negative participants when using CSF phospho-tau instead of CSF total tau to define tau status, $r(30) = 0.408$, $p = 0.02$ and also when additionally controlling for years of education, sex/gender, and race/ethnicity, $r(25) = 0.501$, $p = 0.008$. This correlation remained even when we considered tau status with CSF tau biomarker (i.e., defining participants as being tau positive when their CSF tau exceeded either total tau or phospho-tau thresholds), $r(27) = 0.490$, $p = 0.007$, and when additionally controlling for years of education, gender, and race/ethnicity, $r(22) = 0.609$, $p = 0.002$.

3.2. CSF amyloid/tau–ModRey independence analyses

Because neither CSF tau measure was correlated with ModRey SDR performance in the cognitively normal (CDR = 0) group, it was not possible to test whether Aβ42 and tau are independently associated with memory function with data from this group alone. Accordingly, we enriched our sample with 9 additional participants with MCI (CDR = 0.5; see Table 4) and repeated the correlational analyses. In this augmented sample, better ModRey SDR performance was again associated with higher Aβ42 concentration, $r(59) = 0.329$, $p = 0.010$, and with lower t-tau concentration, $r(59) = -0.257$, $p = 0.045$, but was not associated with p-tau concentration, $r(53) = 0.060$, $p = 0.662$. When considering only amyloid-negative participants in the augmented sample (i.e., excluding one of the 9 CDR = 0.5 participants who was amyloid-positive), ModRey SDR performance correlated with both Aβ42 concentration, $r(51) = 0.335$, $p = 0.014$, and t-tau concentration, $r(51) = -0.294$, $p = 0.033$. For the tau-negative participants in the augmented sample (i.e., excluding 4 of the CDR = 0.5 participants who were tau positive), ModRey SDR was associated with Aβ42 concentrations, $r(49) = 0.310$, $p = 0.027$, but not t-tau concentrations, $r(49) = -0.085$, $p = 0.555$. Finally, considering only the participants in the augmented sample who were both amyloid negative and tau negative, ModRey SDR was associated with only Aβ42 concentration, $r(42) = 0.349$, $p = 0.020$.

Table 3
Pearson's correlations between ModRey SDR and CSF biomarker concentrations (CDR = 0 only, effects of age removed using partial correlation)

Group		Aβ42 concentration	P-tau concentration	T-tau concentration
All CDR = 0 participants	r	0.304	−0.068	0.123
	95% CI	(0.025, 0.539)	(−0.357, 0.233)	(−0.163, 0.390)
	p	0.030[a]	0.652	0.392
	df	49	44	49
Amyloid-negative only (A > 325)	r	0.324	−0.085	0.061
	95% CI	(0.023, 0.571)	(−0.398, 0.245)	(−0.247, 0.358)
	p	0.032[a]	0.608	0.695
	df	42	37	42
Tau-negative only (T-tau < 72)	r	0.311	−0.163	−0.024
	95% CI	(0.012, 0.559)	(−0.458, 0.165)	(−0.322, 0.278)
	p	0.037[a]	0.316	0.876
	df	43	38	43
Both amyloid and tau negative	r	0.399	−0.168	−0.106
	95% CI	(0.082, 0.643)	(−0.492, 0.198)	(−0.419, 0.230)
	p	0.013[a]	0.349	0.527
	Df	36	31	36

Key: CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; SDR, short-delay retention.
[a] $p < 0.05$.

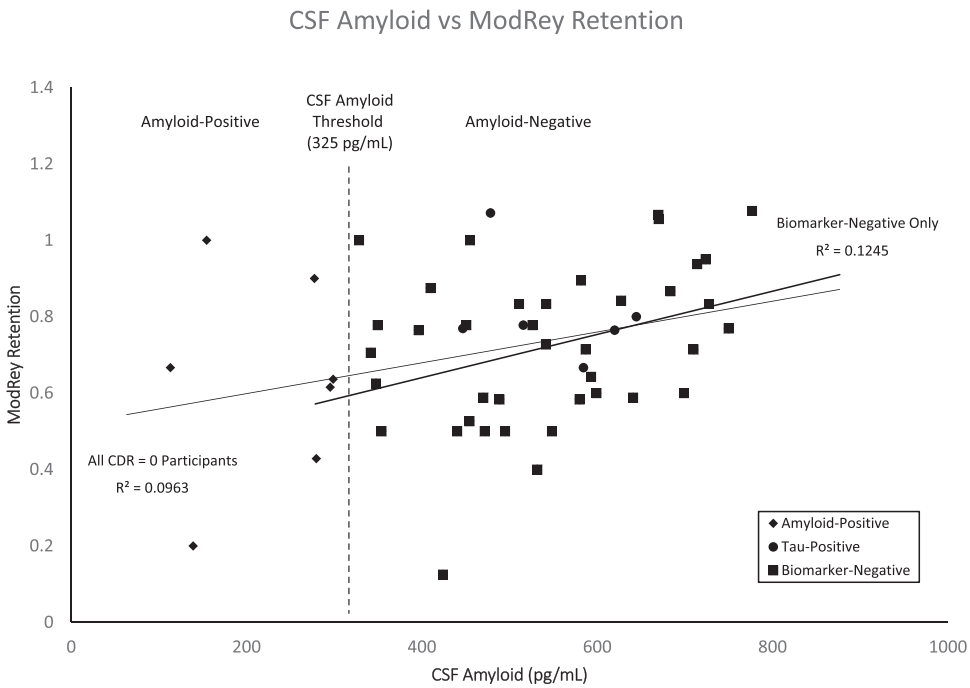

Fig. 2. Correlation between ModRey retention and CSF amyloid in all CDR = 0 participants, and only biomarker-negative CDR = 0 participants. Abbreviations: CSF, cerebrospinal fluid; CDR, Clinical Dementia Rating.

The multiple regression model to evaluate the independence of the relationships between the ModRey SDR and each of the 2 biomarkers (omnibus test, $F(3,57) = 5.102$, $p = 0.003$) showed that both CSF biomarkers were associated with SDR independently (Aβ42: $t(57) = 2.915$, $p = 0.005$, $\beta = 0.358$, $sr = 0.343$; t-tau: $t(57) = -2.060$, $p = 0.044$, $\beta = -0.275$, $sr = -0.242$). Using stepwise entry, CSF amyloid accounted for more variance than CSF tau ($R^2 = 0.359$ vs. $R^2 = 0.257$). Post hoc follow-up regression models adding an interaction term revealed no Aβ42 by t-tau interactions.

3.3. Post hoc analyses

Additional post hoc analysis was performed to assess how CSF amyloid concentrations correlated with performance on neuropsychological tests in the NACC UDS-3 battery. Controlling for age, there were no associations between CSF amyloid concentrations and scores on any of the NACC UDS-3 tests (Table 5), either in the entire cognitively normal (CDR = 0) sample, or in subsamples of cognitively normal participants who were amyloid-negative only, or both amyloid- and tau-negative only.

Post hoc analyses examining other ModRey measures showed that among cognitively normal (CDR = 0) older adults who are both amyloid negative and tau negative, Aβ42 concentration were related to both short-delay recall, $r(36) = 0.375$, $p = 0.020$, and marginally related to long-delay recall, $r(36) = 0.302$, $p = 0.066$. In contrast, t-tau was negatively associated with recognition discrimination, $r(36) = -0.333$, $p = 0.041$. This effect was accounted for by increases in false-positive responses on the recognition trials, which correlated with increases in t-tau concentration, $r(36) = 0.350$, $p = 0.031$, rather than in differences associated with true recognition, which did not, $r(36) = -0.067$, $p = 0.689$.

4. Discussion

In a sample of cognitively normal older adults, we found that the CSF concentration of amyloid is correlated with memory retention when probed with the ModRey, a test designed for preclinical and normal populations, even when considering only amyloid-negative participants (i.e., cognitively normal participants without clinically significant levels of AD amyloid biomarkers). This effect held even when the participant group was also tau negative (i.e., cognitively normal participants without clinically significant levels of either AD biomarker). Although other studies reported that amyloid levels in amyloid-negative participants were associated with future memory decline (Landau et al., 2018) and future tau deposition (Leal et al., 2018), here we demonstrate a relationship between amyloid levels and memory in a purely "biomarker-negative" and cognitively normal older adult participant group. Furthermore, this effect remained even when age, education, sex/gender, and race were covaried out. We note that while ModRey SDR correlated with CSF amyloid in both the entire cognitively normal sample and specifically biomarker-negative samples, post hoc analyses showed that performance on the other neuropsychological tests in the NACC UDS-3 did not correlated with CSF amyloid levels. These data suggest that the ModRey might be more sensitive to early AD-related cognitive changes than other instruments. Consistent with models of AD biomarker progression (Jack et al., 2013; Small and Duff, 2008), we find amyloid-ModRey associations occur among both the cognitively normal sample and in the enriched sample, whereas tau-ModRey associations appear only when our sample included participants with some cognitive impairment.

Our findings support the idea that amyloid burden should be conceptualized on a continuum with a progressively increasing risk of cognitive decline rather than as a rigid dichotomy greater than and less than a specified cutoff value. The new National Institute on Aging—Alzheimer's Association Research framework (Jack et al., 2018) notes that an explicit cut point is necessary to identify inclusion criteria for clinical trials. Our data suggest that the cut point for CSF amyloid in such studies might need to be much higher (i.e., more conservative, or less abnormal) than values currently used for this purpose or that such cutpoints may not be possible to define clearly at all. These results also suggest that early screening for amyloid burden is more valuable than previously believed: some variance in memory among individuals within the amyloid-

Table 4
Pearson's correlations between ModRey SDR and CSF biomarker concentrations (CDR = 0 + 0.5)

Group		Aβ42 concentration	P-tau concentration	T-tau concentration
All participants	r	0.329	0.060	−0.257
	95% CI	(0.085, 0.536)	(−0.208, 0.320)	(−0.477, −0.006)
	p	0.010[a]	0.662	0.045[a]
	df	59	53	59
Amyloid-negative only (A > 325)	r	0.335	0.005	−0.294
	95% CI	(0.072, 0.555)	(−0.282, 0.291)	(−0.522, −0.026)
	p	0.014[a]	0.972	0.033[a]
	df	51	47	51
Tau-negative only (T-tau < 72)	r	0.310	0.034	−0.085
	95% CI	(0.038, 0.539)	(−0.262, 0.324)	(−0.352, 0.195)
	p	0.027[a]	0.823	0.555
	df	49	43	49
Both amyloid and tau negative	r	0.349	−0.054	−0.153
	95% CI	(0.059, 0.585)	(−0.367, 0.270)	(−0.430, 0.150)
	p	0.020[a]	0.747	0.320
	df	42	36	42

Key: CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; SDR, short-delay retention.
[a] $p < 0.05$.

negative range may be attributable to amyloidosis. Furthermore, previous studies that compared cognition between an amyloid-positive experimental group and an amyloid-negative control group may need to be reassessed as their control group may already be affected by some degree of amyloid-related cognitive decline.

There is some uncertainty about the neural basis of the amyloid-cognition correlations we describe here. We showed previously that delayed retention performance on the ModRey (Brickman et al., 2014) is related to entorhinal cortex cerebral blood volume, a correlate of metabolism, and reductions in entorhinal cortex cerebral blood volume also predict future development of clinical AD (Khan et al., 2014). It is well established that the entorhinal cortex is the first cortical area where AD-related tau aggregates appear (Braak et al., 2006), and the first to experience AD-related neurodegeneration (Whitwell et al., 2007). However, our data show that ModRey retention is correlated with both CSF amyloid and CSF tau independently in our enriched, nondemented sample. The question thus arises about how and where CSF amyloid might be influencing ModRey retention. It is possible that the CSF amyloid is somehow related to entorhinal-based tau pathology in some fashion that is unconnected with CSF tau measures. Alternatively, CSF amyloid might cause changes elsewhere in the brain that also underlies ModRey retention or they might both reflect changes in some third variable related to both. As CSF biomarker levels cannot ascertain the specific spatial distribution of amyloid and tau in the brain, further work is necessary to identify the neural bases of the amyloid-cognition effect we report here.

Table 5
Pearson's correlations between CSF amyloid concentrations and cognitive performance on tasks in the National Alzheimer's Coordinating Center Uniform Data Set (UDS) neuropsychological battery, version 3 (effects of age removed using partial correlation)

Task		All participants (N = 51)	A- participants (N = 45)	A- and T- participants (N = 39)
MoCA	r	0.023	0.190	0.265
	p	0.874	0.216	0.107
Craft: Immediate Verbatim	r	−0.085	−0.022	0.019
	p	0.557	0.886	0.912
Craft: Delayed Verbatim	r	−0.072	−0.018	0.035
	p	0.621	0.907	0.835
Craft: Verbatim Retention	r	0.039	0.036	0.098
	p	0.790	0.816	0.556
Digit Span Forward	r	0.076	0.136	0.130
	p	0.599	0.380	0.438
Digit Span Backward	r	−0.044	0.113	0.103
	p	0.759	0.463	0.540
Semantic Fluency	r	−0.024	−0.086	−0.069
	p	0.869	0.580	0.681
Verbal Fluency	r	−0.153	−0.140	−0.137
	p	0.289	0.363	0.412
Trails A	r	0.130	0.229	0.220
	p	0.373	0.142	0.190
Trails B	r	0.028	−0.041	−0.067
	p	0.849	0.793	0.687
Benton Copy	r	0.044	0.141	0.141
	p	0.761	0.361	0.400
Benton Delayed	r	−0.100	−0.021	0.012
	p	0.491	0.892	0.944
MINT	r	−0.173	−0.101	−0.055
	p	0.230	0.515	0.742

Key: CSF, cerebrospinal fluid; MINT, Multilingual Naming Task; MoCA, Montreal Cognitive Assessment.

Our post hoc analyses might provide some insight into the nature of the independent cognitive contributions of the 2 CSF biomarkers on the ModRey. They suggest that among cognitively normal older adults, CSF amyloid is more related to recall, whereas CSF tau is more related to false recognition. This relationship between CSF tau and false recognition in our data might underlie earlier reports of false recognition in patients with AD (e.g., Budson et al., 2000; Gallo et al., 2004) and amnestic MCI (e.g., Yassa et al., 2010). In this regard, the 2 biomarkers might be influencing cognition through 2 distinctly different pathways, which manifest differently behaviorally.

Our results should be evaluated cautiously in light of several design limitations. We note that our sample size was small. We cannot exclude the possibility that our results reflect sources of amyloid or tau hypothesized to be non-AD related, such as primary age-related tauopathy (Crary et al., 2014; Duyckaerts et al., 2015). Furthermore, our participant sample consisted of mostly white, highly educated individuals from a major urban center. Although the effects we show survive correction for race and education, the degree of racial and educational diversity was small compared with the general population. Despite our results showing that even low levels of CSF amyloid correlate with memory performance, there are numerous additional factors (e.g., genetic, biological, behavioral, etc.), many of which have not been fully examined in the literature, that might explain the individual differences in cognitive performance in the face of elevated amyloid burden. We also note that the study design was cross-sectional, and the data do not speak to the question of whether biomarker-negative levels of CSF amyloid might predict future cognitive decline or whether individuals with biomarker-positive levels but relatively high memory functioning will not experience future cognitive decline.

Due to the progressive and irreversible nature of AD, the ability to detect cognitive impairment as early as possible is of great clinical relevance. If ModRey memory retention is reliably associated with the presence of an AD biomarker (i.e., amyloid) before it reaches a threshold of clinical significance, ModRey memory retention may be able to identify subsequent AD-related cognitive decline earlier than is currently possible. As such, the ModRey could be helpful as an early detection test for AD or as an outcome measure in intervention studies.

Disclosure

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.08.010.

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