Hale, MR, Langhough, R, Du, L, Hermann, BP, Van Hulle, CA, Carboni, M, Kollmorgen, G, Basche, KE, Bruno, D, Sanson-Miles, L, Jonaitis, EM, Chin, NA, Okonkwo, OC, Bendlin, BB, Carlsson, CM, Zetterberg, H, Blennow, K, Betthauser, TJ, Johnson, SC and Mueller, KD

Associations between recall of proper names in story recall and CSF amyloid and tau in adults without cognitive impairment

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Abstract

Neuropsychological measures sensitive to decline in the preclinical phase of Alzheimer's disease (AD) are needed. We previously demonstrated that higher amyloid-beta (Aβ) assessed by positron emission tomography in adults without cognitive impairment was associated with recall of fewer proper names in Logical Memory story recall. The current study investigated the association between proper names and cerebrospinal fluid (CSF) biomarkers ($A\beta_{42/40,}$ phosphorylated $tau_{181,}$ ($pTau_{181}$), neurofilament light) in 223 participants from the Wisconsin Registry for Alzheimer's Prevention. We assessed associations between biomarkers and delayed Logical Memory total score and proper names using binary logistic regressions. Sensitivity analyses used multinomial logistic regression and stratified biomarker groups. Lower Logical Memory total score and proper names scores from most recent visit were associated with biomarker positivity. Relatedly, there was a 27% decreased risk of being classified $A\beta_{42/40}$+/$pTau_{181}$+ for each additional proper name recalled. A linear mixed effects model found that longitudinal change in proper names recall was predicted by biomarker status. These results demonstrate a novel relationship between proper names and AD-CSF pathology.

Keywords: Preclinical Alzheimer's disease; Cerebrospinal fluid; Story recall; Proper names; Early detection

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition defined by the presence of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tau tangles. The accumulation of these proteins leads to cell death and ultimately cognitive decline and dementia (Braak and Braak, 1991; Jack Jr. et al., 2018). Cognitive decline in AD dementia is a gradual process often beginning with noticeable changes in episodic and semantic memory. However, the characteristic Aβ and tau build-up in AD has been shown to begin years before noticeable cognitive decline (i.e., prodromal AD) using neuroimaging techniques and collection of cerebrospinal fluid (CSF) biomarkers of amyloid and tau pathology. Studies suggest that the first detectable pathologic changes in AD occur in CSF $A\beta_{42}$, followed by positron emission tomography (PET) Aβ then CSF tau (Jack et al., 2013; Jack Jr. et al., 2018). These biomarkers, such as CSF Aβ, tau, and neurofilament light (NfL; marker of neuronal degeneration), can be used to differentiate typical aging from various dementia etiologies (Paterson et al., 2018; Wallin et al., 2011). The National Institute on Aging-Alzheimer's Association (NIA-AA) research framework for Alzheimer's proposes staging AD from the prodromal stage to dementia using these same in vivo AD biomarkers to determine an individual's Aβ, tau, and neurodegeneration status, known as the ATN framework (Jack Jr. et al., 2018). Neurodegeneration status in particular can be identified with anatomic MRI imaging or the CSF biomarker, NfL (Dhiman et al., 2020; Jin et al., 2019). Identifying individuals with in vivo biomarkers before they reach clinical impairment provides the opportunity to initiate intervention at an earlier AD stage when it is expected to be more beneficial (Budd et al., 2011). Correlating measures of early cognitive change in prodromal AD with these biomarkers is crucial to determining which individuals are most likely to benefit from AD-specific neuropharmacological or other forms of interventions.

In vivo AD biomarkers are also associated with prodromal cognitive decline, although findings have been mixed (Betthauser et al., 2020; Eren et al., 2020; Hu et al., 2010; McConathy and Sheline, 2015; Olsson et al., 2016). Specifically, significantly low $A\beta_{42}$ (indicating higher amyloid plaque burden) and high tau, including total tau and phosphorylated tau_{181} ($pTau_{181}$), in CSF predict the conversion of individuals with mild cognitive impairment (MCI) to dementia (Andreasen et al., 2003; Hampel et al., 2004; Monge-Argilés et al., 2011). High levels of NfL, collected via CSF, plasma, or serum, are associated with decline across various cognitive domains (e.g., memory, attention, language, executive function) (Ramani et al., 2021). Although these CSF

biomarkers have demonstrated sensitivity to AD-specific cognitive impairment, the specialized resources required make this testing inaccessible to a large portion of the population. Additionally, the perceived invasiveness and risks associated with current methods for measuring these biomarkers, such as radiation exposure in PET or CSF leak from lumbar punctures, is a barrier to research participation (Howell et al., 2016). As such, validating inexpensive and less invasive markers of early decline is a crucial step in making prodromal AD detection more accessible to the public. One such possible cognitive marker is speech and language, as it can be quickly collected with minimal and inexpensive materials and risk.

Cognitive testing often focuses on episodic memory, but inherent in these tasks is the reliance on semantic memory, a type of long-term declarative memory specific to lexical and concept-based information (Venneri et al., 2016). Whereas episodic memory has been shown to decline across the lifespan in the absence of pathology, semantic memory in contrast remains relatively stable in cognitively healthy individuals (Nilsson et al., 1997). This phenomenon however does not appear to hold true for individuals with cognitive impairment or amyloid positivity, as declines in category fluency, naming, and specific words use in discourse have been well-documented in the literature (Verfaillie et al., 2019; Wakefield et al., 2014). This ability of semantic memory to differentiate adults without cognitive impairment from cognitively declining adults may be because neuronal damage in early AD occurs in the transentorhinal and mediotemporal tissues, areas correlated with semantic memory (Braak and Braak, 1991; Venneri et al., 2016). Thus, incorporating more nuanced language measures that evaluate the semantic memory requirement of episodic memory tasks may be sensitive to early AD pathology.

Story recall is a common task that necessitates the use of both episodic and semantic memory, demonstrated in the Logical Memory subtest of the Weschler Memory Scale – Revised (WMS-R) (Wechsler, 1987). This task involves reading two short stories and then asking participants to recall the stories both immediately and after a 30-minute delay. Performance on Logical Memory has been linked to AD pathology such that cognitive healthy, middle-aged or older adults with $A\beta_{42}+/pTau_{181}-$ or $A\beta_{42}+/pTau_{181}+$ CSF biomarker profiles exhibited greater rates of decline on delayed recall than $A\beta_{42}-/pTau_{181}-$ adults (Clark et al., 2018). However, a separate study of participants without cognitive impairment, found no association between a

delayed recall composite (including Logical Memory) and CSF biomarker positivity (Trelle et al., 2021). Due to these conflicting results, relationships between story recall and AD-CSF biomarkers are unclear.

The aforementioned studies relied on calculating the conventional total Logical Memory score from the number of idea units expressed. However, the language captured in story recall tasks can be broken down to assess specific linguistic aspects such as proper names, verbs, numerical expressions, etc. The retrieval of proper names (e.g., the specific names of people and places) in particular is a common complaint among older adults and has been shown to decline as a function of typical aging (Cohen, 1990). However, evidence suggests that these difficulties are temporary and are due to deficits in retrieving the complete phonology of the target word (Shafto et al., 2007), and are therefore responsive to phonological cuing (Delazer et al., 2003). Conversely, in AD dementia, the severity of proper name retrieval is greater than in typical aging (Semenza et al., 2003), is thought to reflect degradation of both phonological and semantic stores, and individuals with AD dementia do not benefit from phonological cuing (Delazer et al., 2003). This decline is additionally thought to occur due to the decreased semantic characteristics associated with proper names defining a single entity and utilizing a different processing pathway from common names, making proper names especially susceptible to disruption from brain injury or cognitive changes (Desai et al., 2023; Lucchelli and De Renzi, 1992; Martins and Farrajota, 2007; Semenza, 2009, 2006). One study investigating the effect of cognitive impairment on recall of proper versus common names used individuals with hypoxia provoked by lengthy exposure to high altitude and found that common names were recalled better than proper names, leading the authors to postulate that the lack of semantic associations with their referent caused increased difficulty for proper names to be encoded (Pelamatti et al., 2003). This decline in

the retrieval of proper names due to MCI or AD has been demonstrated in several studies (Ahmed et al., 2008; De Jager and Budge, 2005; Delazer et al., 2003; Juncos-Rabadán et al., 2013; Thompson et al., 2002). Further, recall of proper names was in fact a more sensitive measure for detecting early AD dementia than traditional neuropsychological test batteries, such as the Mini Mental State Exam (MMSE) (Semenza et al., 2003). A possible biological basis for this finding can be rooted in evidence from lesion studies and functional magnetic resonance imaging showing that proper names retrieval is mediated by the left and right anterior temporal lobe and parahippocampal gyri, sites of early neuropathology and neurodegeneration in Alzheimer's

disease (Aminoff et al., 2013; Braak and Braak, 1996; Damasio et al., 1996; Papagno and Capitani, 1998). Relatedly, Mueller and colleagues found that only proper names from delayed Logical Memory story recall were associated with PET Aβ, such that participants who recalled more proper names were less likely to be Aβ+ (Mueller et al., 2020). In contrast, delayed Logical Memory total score was not associated with biomarker status, indicating that proper names may be a more sensitive measure of very early cognitive change (Mueller et al., 2020). This study demonstrates that investigating measures reflecting not just episodic, but also semantic memory, may be especially sensitive to the early underlying neuropathologic changes of AD.

Thus, while it has been demonstrated that CSF biomarkers are associated with declining performance on story recall and that PET Aβ+ is associated with recall of fewer proper names in Logical Memory, the relationship between proper names and AD-CSF biomarkers is unknown (Clark et al., 2018; Mueller et al., 2020). Validating the measure of proper names with additional AD biomarkers and at a theoretically earlier stage in the disease process is a critical step to establishing this cognitive marker as a predictor of AD pathology (Jack Jr. et al., 2018). In the current study, we investigated whether proper names were associated with CSF amyloid or tau positivity in late middle-aged adults, and whether the association was stronger than associations with Logical Memory total score. CSF biomarker status has been demonstrated to be consistent with PET status (Fagan et al., 2011; Hansson et al., 2018), and based on the findings in Mueller et al. (2020), we hypothesized that proper names from two time points (baseline and most recent visit) would be associated with most recent CSF biomarker positivity. We used item-level data from Logical Memory to measure delayed recall of proper names and total score scores and investigated their cross-sectional associations with three CSF biomarkers ($A\beta_{42/40}$, $pTau_{181}$, and NfL) or their corresponding biomarker status, mirroring the NIA-AA ATN model. In sensitivity analyses, we investigated cross-sectional associations between delayed proper names and total score and biomarker staging profiles representing amyloid and tau statuses, and we examined whether these profiles were associated with retrospective delayed proper names or total score trajectories.

2.Materials and methods

2.1 Study Sample

The study sample was taken from the Wisconsin Registry for Alzheimer's Prevention, a longitudinal cohort study established in 2001 that examines risk factors, lifestyle factors, and cognition in late middle-aged

participants who are at increased risk of developing AD due to parental history of dementia (Johnson et al., 2018). Participants attend a baseline visit and then follow-up visits every two years thereafter. A subset of the cohort participates in biomarker data collection through imaging and CSF studies. For detailed information on the participants and study visits, see Johnson et al. (2018).

Logical Memory was first added to baseline and follow-up neuropsychological testing in 2007, which was visit 2 for most participants. Wisconsin Registry for Alzheimer's Prevention participants were selected for the current study if they had at least one Logical Memory assessment, were cognitively unimpaired at Logical Memory baseline (per criteria described in Langhough Koscik et al., 2021), and had CSF assayed from at least one biomarker visit (n=242). Participants with a neurological diagnosis (n=4) including meningitis, stroke, multiple sclerosis, epilepsy, and Parkinson's disease, or a clinical diagnosis of MCI at Logical Memory baseline (n=4) were excluded. Participants with a CSF biomarker profile of A-/T+ (n=11) were also excluded, as these profiles may indicate non-AD pathology (Jack Jr. et al., 2018), or a benign CSF dynamics disturbance (unpublished observation). Of the 223 participants meeting these criteria, four were excluded because only NfL was available for them. The final n=219 had CSF $pTau_{181}$ and NfL data, while 218 had $A\beta_{42/40.}$ All activities for this study were approved by the University of Wisconsin – Madison Institutional Review Board and completed in accordance with the Helsinki Declaration.

2.2 Logical Memory variables

As part of the neuropsychological testing battery, Wisconsin Registry for Alzheimer's Prevention participants completed the Logical Memory subtest from the WMS-R, a standardized, norm-referenced test examining episodic memory. Standard procedures from the WMS-R manuals were followed by testers. Participants were read a short story (Story A) aloud and were immediately asked to recall the story aloud, with the instructions to "[use] as close to the same words as you can remember." These steps were repeated for a second story (Story B). After a 25-35 minute delay, participants were asked to recall both Story A and B again. Participants' immediate and delayed recalls were given a total score (Logical Memory total score) of 1-50 based on 25 idea units contained in each story following the standard scoring procedures in the WMS-R manual. A lexical category score of 1-9 for proper names from stories A and B was calculated using item-level analysis as previously described by Mueller et al. (2020). Each of the 25 idea units was made into a separate

variable in a data base and coded as 1 (accurately recalled) or 0 (not accurately recalled). Each idea unit was then assigned to a lexical category (proper names, verbs, numerical expressions) by running a transcript of the Logical memory stories through CLAN (Computerized Language Analysis Program), a part-of-speech tagger (MacWhinney, 2014). Idea units identified as proper names were then summed for stories A and B to create a proper names score. For the purposes of the current study, only Logical Memory total score and proper names from the delayed story recall were included in analyses, as prior research showed no association between proper names and immediate Logical Memory recall. Pearson product-moment correlation was used to assess correlation between Logical Memory total and proper names scores.

2.3 CSF biomarker collection

The current study considered three biomarkers from participants' CSF collection: $A\beta_{42/40}$ as a measure of amyloid plaques, $pTau_{181}$ as a measure of tau tangles, and NfL as a measure of axonal degeneration. $A\beta_{42/40}$ is defined as the ratio of $A\beta_{42}$ to $A\beta_{40.}$ CSF collection and assay processes for the Wisconsin Registry for Alzheimer's Prevention cohort are described by Van Hulle and colleagues (2021), with analyte concentrations assayed using the NeuroToolKit panel of robust prototype assays from Roche Diagnostics International Ltd (Rotkreuz, Switzerland). For participants with multiple lumbar punctures, the most recently assayed CSF available was used. Binary $A\beta_{42/40}$ and $pTau_{181}$ statuses, represented as A+/- and T+/- respectively, were determined using published cutoffs for CSF $A\beta_{42/40}$ (A+ = $A\beta_{42/40} \leq 0.046$ s) and $pTau_{181}$ (T+ = $pTau_{181} \geq 24.8$ pg/mL) (Van Hulle et al., 2021). NfL concentration was reported as a continuous value.

2.4 Statistical analyses

All statistical analyses were performed with R. Multinomial models were run with the package 'nnet,' ANCOVA models with 'aov', receiver operating characteristic (ROC) curves with 'ROCR', and longitudinal mixed effects models with 'lme4' (Bates et al., 2015; Faraway, 2002; Ripley and Venables, 2022). Significance level was set at $p<05$. For the purposes of sensitivity testing, proper names and Logical Memory total score scores were converted to z-scores.

2.4.1 Descriptive statistics and assumption testing

Descriptive statistics were calculated using SPSS and assumptions were tested in R. Three high outliers were noted for the continuous variable of NfL. However, removing these outliers did not change significance patterns of the NfL models.

2.4.2 Logical Memory variables as predictors of CSF biomarkers and biomarker statuses

The relationship between Logical Memory measures and CSF biomarker status was investigated at two time points (baseline and most recent Logical Memory administration) to mirror the analyses performed by Mueller and colleagues (Mueller et al., 2020).

2.4.2.1 Baseline delayed Logical Memory measures

We used binomial logistic regression to test whether baseline delayed Logical Memory scores (total score and proper names) were associated with increased odds of A+ or T+. An ANCOVA model was used to examine this relationship with continuous NfL values. For both model types, covariates included age at lumbar puncture, sex, literacy as measured by the Wide-Range Achievement Test – 3 (WRAT-3) (Wilkinson, 1993), time between baseline Logical Memory and lumbar puncture, and apolipoprotein E (*APOE*) ε4 status (*APOE* ε4-positive was defined as having at least one allele). Each binomial logistic regression was repeated without *APOE* ε4 status as a covariate, to ensure that genetic risk was not driving the relationship between Logical Memory performance and biomarker status (Koch et al., 2017). Akaike information criterion (AIC) values were obtained to compare model fits between proper names and the traditional Logical Memory total score baseline. A difference in AICs of +/- 2 or greater was considered significant (Cavanaugh and Neath, 2019).

For descriptive purposes related to the logistic regression results, biomarker positive vs negative differences for Logical Memory measures were estimated as follows. We ran flipped ANCOVA models, with either proper names or total score as outcome and A+/- or T+/- as the predictor with the same covariates listed above. Effect size estimates for biomarker positive vs negative were then obtained for A and T by calculating the pairwise differences of adjusted means divided by the pooled standard deviation.

2.4.2.2 Most recent Logical Memory measures

The analyses described in 2.4.2.1 were repeated using delayed Logical Memory scores (total score and proper names) from each participant's most recent neuropsychological testing. The mean(standard deviation [SD]) time between baseline and most recent administrations was 8.1(2.5) years. Five participants only had

one Logical Memory visit, meaning that their baseline and most recent proper names and Logical Memory total score scores were identical. We repeated analyses removing these five participants.

2.4.3 Sensitivity analyses

2.4.3.1 Additional lexical categories as predictors of biomarker positivity

We hypothesized that other lexical categories (verbs and numerical expressions) would not be associated with CSF biomarkers since they were not associated with PET amyloid (Mueller et al., 2020). To confirm this hypothesis, we ran the major analyses (as seen in 2.4.2.1) with verbs and numeric expressions from the most recent Logical Memory administration as predictors.

2.4.3.2 Logical Memory variables as predictors of CSF biomarker profiles

To investigate associations between Logical Memory predictors and combined A/T status, a three-level categorical variable was made based on the NIA-AA AD research framework biomarker profiles (n=157 A-/T-, n=31 A+/T-, n=30 A+T+; n=11 A-/T+ were excluded) (Jack Jr. et al., 2018). Two multinomial logistic regression models were run with most recent Logical Memory measure (proper names or total score) as the predictor and biomarker profile as the outcome (reference group=A-/T-); covariates were identical to those used in the binomial models. To describe how the biomarker trajectory profiles differed on proper names and total scores, adjusted means and effect sizes were obtained by performing flipped ANCOVA models as described in 2.4.2.1; to put Logical Memory total and proper names scores on the same scale, we converted these measures to z-scores.

2.4.3.3 CSF biomarker profiles as predictors of longitudinal Logical Memory variables

In complementary analyses, we used linear mixed effects models to examine whether biomarker profiles were associated with decline on delayed proper names and Logical Memory total score; linear mixed effects modelling allowed us to examine proper names and total scores performance for participants as a group (fixed effects), while accounting for variation with individuals' differences (i.e. random effect of subject-specific intercept) (Laird and Ware, 1982). Logical Memory scores were converted to z-scores to account for the differences in score ranges. "Time" was operationalized as age at each visit to account for differences in baseline ages and time intervals between visits. We centered age at the baseline average of 58 years for ease of interpretation, and sex, *APOE* ε4, and literacy were included as fixed effects covariates. Biomarker profile was

modeled as three-level variable dividing participants by CSF A+/- and T+/- status (A-/T-, A+/T-, A+/T+). These models were repeated using continuous NfL as a predictor instead of biomarker profile status.

2.4.4 ROC curves

ROC curves were run to determine the predictive strength of binomial models (2.4.2.1 and 2.4.2.2) for A and T status by comparing area under the curve (AUC) across proper names and total score (Sing et al., 2020). Confidence intervals (CIs) for the AUCs were obtained using the 'pROC' package in R (Robin et al., 2011). Additionally, ROC curves were run in the same fashion for the multinomial model in 2.4.4.1. Following this ROC analysis, we used the "cutpointr" package in R to obtain optimal cutpoints for both proper names and total score for the best discrimination between A-/T- and A+/T+ (Thiele and Hirschfeld, 2021). Optimal cutpoints were determined using Youden's index and subsequently validated using bootstrapping (n=1000 repetitions).

2.4.5 Post-hoc Analyses

The above analyses were repeated with a new Logical Memory measure to investigate the impact of proper names on total score. This measure was calculated for each participant by subtracting their proper names sub-score from their total score using their most recent Logical Memory administration. Pearson product-moment correlation was used to assess correlation between Logical Memory total score minus proper names and proper names scores. Additionally, the same analyses were repeated with most recent proper names and total score measures and an added covariate to investigate practice effects. This covariate was calculated by subtracting 1 from the visit number of the most recent Logical Memory administration (Jonaitis et al., 2015). Lastly, we investigated the variance in association between biomarkers and Logical Memory measures by using stepwise regressions with continuous measures of $A\beta_{42/40}$ and $pTau_{181}$.

3.0 Results

3.1 Description of study participant characteristics

Participant characteristics are displayed in Table 1 by A and T status. The 219 participants had a mean baseline age of 58.1 with a SD of 6.3; 59 (26.9%) were A+ and 29 (13.2%) were T+. The mean(SD) time between lumber puncture and baseline neuropsychological testing was 7.2(2.9) years post baseline, while the number of years between lumbar puncture and most recent Logical Memory testing was 1.6(1.6) years.

3.2 Story recall variables and CSF biomarker status

NfL was not associated with either Logical Memory story recall measure at baseline or most recent neuropsychological visit and was thus excluded from subsequent analyses. Baseline proper names and total score were not significantly associated with A+ (odds ratio (OR)=0.88, CI=0.74-1.05, p=0.154 and OR=1.02, CI=0.96-1.07, p=0.548, respectively) or T+ (OR=0.94, CI=0.76-1.16 ,p=0.561 and OR=1.02, CI=0.96-1.09, p=0.523, respectively; see Supplementary Table 1). Proper names and total score from each participant's most recent visit were both associated with A+ (OR=0.81, CI=0.96-1.09, p=0.013 and OR=0.95, CI=0.90-0.99, p=0.029, respectively) and T+ (OR=0.78, CI=0.63-0.95, p=0.014 and OR=0.92, CI=.86-0.98, p= 0.0009, respectively) (Table 2). AICs indicated similar fits between proper names and total score at both timepoints, and better fits with most recent versus baseline proper names (A+ 222.8 vs. 227.1; T+: 162.0 vs. 168.0) and Logical Memory total score scores (A+: 224.2 vs. 228.8; T+: 161.0 vs. 167.9). Relatedly, effect sizes for biomarker positive vs negative proper names and total score differences were higher for most recent Logical Memory metrics compared to baseline (Figure 1). No statistical difference was found between most recent Logical Memory total and proper names scores. Removing APOE ε4 status as a covariate did not change the significance patterns observed (Supplementary Tables 2 and 3). ROC curves for baseline and most recent Logical Memory measures (Logical Memory total score and proper names) predicting A+/- or T+/- all had AUCs between 0.74 and 0.78 with 95% CIs between 0.65 and 0.86. The correlation between most recent Logical Memory total score and proper names score is 0.73 (Supplementary Figure 1).

3.3 Sensitivity and post-hoc analyses

There were no significant relationships between CSF amyloid or tau and verbs or numeric expressions. Table 3 shows detailed results from the multinomial logistic regression analyses that allowed us to distinguish results between three biomarker profiles. The odds of being A+/T+ decreased with increases in Logical Memory measures (total score and proper names) at the most recent time point. The risk of being classified A+/T+ decreased more for each unit increase in proper names (27%) than Logical Memory total score (8%). For the ROC curves of the A+/T+ profile against the reference level, similar AUCs were found for both proper names (0.815, CI=0.73-0.89) and total score (0.811, CI=0.72-0.89) predicting A+/T+, indicating a high level of discrimination between biomarker positive and negative individuals for both Logical Memory measures (Mandrekar, 2010). The bootstrapped cutpoint was ≤ 2.8 for proper names for determining A+/T+ (sensitivity 0.37 and specificity 0.85). For total score, the optimal cutpoint for

determining A+/T+ was ≤ 23.3 (sensitivity 0.50 and specificity 0.73). Adjusted means and effect sizes of Logical Memory delayed recall of proper names and total score at most recent visit according to biomarker profile from the flipped ANCOVA model are displayed in Figure 2. Using z-scores for proper names and total score, this model highlighted that for participants with A+/T+, there was a 0.63 decrease in proper names (R^2=0.16) and 0.55 decrease in total score (R^2=0.11) versus the A-/T- group.

Results from the linear mixed effects regression models examining the relationship between Logical Memory trends (total and proper names scores) and CSF biomarker profile are presented in Table 4. A significant interaction between time (centered age) and biomarker profile status indicated that individuals who were A+/T+ declined faster than the A-/T- group on proper names score (β=-0.02, p=0.003) and total score (β=-0.04, p=<0.001). This interaction is displayed in Figure 3. AICs indicated a better model fit for the regression predicting Logical Memory total score (2183.0) than proper names (2382.2). No association was found for the longitudinal model using continuous NfL.

Repeating the models above with the new Logical Memory measure of total score minus proper names score did not affect the significance patterns observed in the binomial model investigating associations with CSF tau positivity. However, in the second binomial model total score minus proper names was not associated with amyloid positivity. Additionally, the significance patterns observed in the multinomial model investigating the association biomarker profile with total score minus proper names was unchanged. Linear mixed effects models investigating the association of biomarker profile and longitudinal total score minus proper names resulted in a similar p-value as the model with total score including proper names (p<0.001), but with a higher AIC (5490) and lower coefficient of determination (R^2=0.05). The correlation between most recent Logical Memory total score minus proper names and proper names score is 0.544 (Supplementary Figure 1). Models including practice effects as a covariate did not affect significance patterns of the variables of interest for any model. Lastly, no significant association was found for continuous measures of $A\beta_{42/40}$ and $pTau_{181}$ predicting Logical Memory total or proper names scores. Scatterplots depicting the relationship between the continuous CSF biomarkers and Logical Memory measures are shown in Supplementary Figure 2.

4.0 Discussion

In this study, we used cross-sectional analyses at two different timepoints and demonstrated a novel relationship between proper names from Logical Memory and AD-CSF biomarkers, making it one of the few studies exploring proper name recall in prodromal AD. We confirmed this association with the follow-up multinomial analyses that found a greater risk of being A+/T+ with a lower proper names score than a lower total score. Additionally, a longitudinal linear mixed effects model found that total and proper names scores are predicted by AD-CSF biomarker status.

The cross-sectional and longitudinal associations between most recent Logical Memory total score and CSF biomarkers, particularly $A\beta_{42/40}$, supports the linear decline seen in longitudinal story memory in CSF $A\beta_{42}$ positive individuals from the same cohort (Clark et al., 2018). However, the current study extends these findings by establishing a relationship with CSF biomarkers and a lexical category from this subtest, proper names. Similar to the decline seen in total score over time by Clark and colleagues, a decline in proper names recalled over time was found in the longitudinal model of the present study. Further, AIC, effect size, and AUC data indicate that proper names may be a sensitive predictor of AD-biomarker positivity.

The current study also extends the findings from our previous work on proper names by confirming a relationship between this lexical category and an additional biomarker of AD at a theoretically earlier stage in the disease process (Jack et al., 2013; Jack Jr. et al., 2018; Mueller et al., 2020). However, whereas an association was found for most recent PET Aβ status and both baseline and most recent proper names, in the current study an association was only found between most recent CSF biomarker status and most recent proper names. A possible explanation for this difference is that CSF Aβ and PET Aβ development are hypothesized to follow each other consecutively, with CSF Aβ being the first detectable AD biomarker (Jack et al., 2013). Therefore, if an individual is PET A+ they may be more advanced in the AD disease course and likely have additional years of biomarker accumulation than someone who is the same age and only CSF A+. Following this rationale, the baseline time point 7 years prior to CSF collection may have been too early to detect a measurable change in this language measure.

However, in sensitivity analyses we did not observe an association between continuous measures of CSF $A\beta_{42/40}$ and $pTau_{181}$ and either Logical Memory measure (total score and proper names score) (Supplemental Table 3; Supplemental Figure 2). This contrasts with the associations observed between the same Logical

Memory measures and binomial representations of CSF $A\beta_{42/40}$ and $pTau_{181}$. A possible explanation for this pattern of results observed could be due to the cognitively unimpaired status and relatively young age of the participants in the current study. The variability of biomarker values, especially that of $pTau_{181}$, is limited and skewed toward normal. Previous literature suggests that continuous measures of CSF biomarkers are a better predictor for cognitively impaired individuals than individuals with no impairment, like in the current study (Mattsson-Carlgren et al., 2020).

In the current study, we did not find an association between NfL and Logical Memory measures at either the time point or longitudinally. Conversely, Cody and colleagues found an association between CSF NfL and cognitive decline, as measured by the preclinical Alzheimer's Cognitive Composite (PACC-3), in a sample from the Wisconsin Registry for Alzheimer's Prevention (Cody et al., 2021). This difference is likely due to Cody and colleagues' inclusion of additional participants from the Wisconsin Alzheimer's Disease Research Center, which enrolls individuals with diagnoses of MCI and dementia. This inclusion of individuals further along the AD continuum differentiates the sample from that of the current study which focused solely on individuals without cognitive impairment. Furthermore, the PACC-3 composite score includes multiple cognitive domains, including executive function, which may also partially explain the differences in findings.

In a sensitivity analysis, we divided participants into biomarker profile groups (A-/T-, A+/T-, A+/T+) and performed multinomial logistic regression analyses examining the relationship between most recent Logical Memory measures and biomarker profile. We found that participants with the A+/T+ profile earned lower Logical Memory total and proper names scores than the A-/T- group, providing a more detailed look at the association between CSF biomarkers and Logical Memory measures. Our finding that lower proper names and lower total scores were associated with increased risk of being classified as A+T+ mirrors similar results found in a subset of Wisconsin Registry for Alzheimer's Prevention participants with PET Aβ and tau data (Betthauser et al., 2020). Betthauser et al. (2020) found that A+/T+ participants declined faster than A-/T- participants on the PACC-3. By focusing the investigation on a singular lexical category (proper names) within an episodic memory task that is relatively quick to administer and sensitive to the semantic memory involvement inherent in the task, the current study was similarly able to discern between the A+/T+ and A-/T- groups without administering a longer battery of neuropsychological tests.

The multinomial analysis from the present study demonstrated differences in semantic and episodic memory across the biomarker profile groups with similarly large effect sizes and odds ratios for both proper names and total score, indicating that proper names, a measure of only 9 items, may be just as sensitive to underlying AD pathology as total score, a measure of 50 items. The longitudinal analysis found that negative change in both proper names and total scores were predicted by A+/T+ status. These results are consistent with the theoretical progression of AD pathology in that as AD pathology accumulates in the brain, as time increases, cognitive impairment also worsens (Jack et al., 2013). Studies have shown that CSF biomarker positivity predicts not only greater cognitive decline on specific neuropsychological tests, but also eventual conversion from MCI to AD (Andreasen et al., 2003; Hansson et al., 2018). However, AICs from the longitudinal linear mixed effects model indicate that biomarker status is a better predictor of total score over time. This longitudinal relationship changed when proper names score was subtracted from total score with AICs indicating biomarker status was worse predictor of total score minus proper names over time than only proper names score over time. This finding could be due the larger range of items in the total score (0-50) vs. proper names (0-9), and/or to the additional lexical categories that are captured in Logical Memory total score (e.g., verbs, numerical expressions, etc.). Although we did not find an association between verbs and numerical expressions and CSF biomarker status in the current paper, these may contribute to lower total score as the disease progresses. Future directions in our work include examining different lexical categories and items by level of difficulty and AD biomarkers (Mueller et al., 2022), as well as designing a new task with a greater balance of sensitive lexical categories.

For both the cross-sectional and longitudinal multinomial models investigating biomarker profile associations with Logical Memory scores, individuals with A-/T- profiles could not be distinguished from/had similar declines on scores as A+/T- individuals, while those with A-/T- could be distinguished from those with A+/T+ profiles. These findings indicate that the associations in the current study between Logical Memory scores and biomarker status are largely driven by both amyloid and tau status, which is consistent with both the hypothetical AD biomarker framework (Jack et al., 2013), as well as empirical evidence showing that the combination of Aβ and pTau is a stronger predictor of cognitive decline than CSF Aβ alone. This, in turn, may

indicate that the development of abnormal tau represents a later stage on the AD continuum (Fagan et al., 2011; Guo et al., 2020; Mattsson-Carlgren et al., 2020; Pichet Binette et al., 2022).

As discussed previously, more accessible prodromal AD markers with minimal risk to participants are needed in the field. In the future, testing for early AD could be performed in a consecutive series from least invasive to most invasive. In this design, a story recall task could be performed prior to and as a trigger for AD biomarker testing using the calculated cutoff proper names score, making the cross-sectional analysis a more appropriate model. Similar analyses could be conducted to identify sub-scores from other commonly used neuropsychological tests that are particularly sensitive to prodromal AD. A new composite made up of sub-scores could be administered in a shorter time frame than existing composites. This would put a lower burden on participants, as well as present the possibility to increase accessibility by administering the evaluation over the phone or through video conferencing.

Future work could focus on developing a novel story recall task with a larger number of proper names and other lexical-semantic targets carefully chosen for people in the early stages of the AD continuum. This could produce a more ecologically valid measure of early cognitive decline, as story recall is a task often performed in social interactions. Functional measures such as these are crucial for early identification of potential problems in everyday life, as well as for disease monitoring and response to treatment in clinical trials (Snyder et al., 2014). Additionally, since the completion of the current study our group has begun to audio record and transcribe participants from the Wisconsin Registry from Alzheimer's Prevention completing the Logical Memory story recall task. With these transcripts we can investigate the association of more nuanced aspects of this task with AD biomarkers.

4.1 Strengths and limitations

Inherent in the present study are several strengths and limitations. First, a significant strength is the utilization of Logical Memory to analyze connected speech. This WMS-R subtest, is widely given across the world, meaning that there is both a wealth of existing data to replicate these findings and widespread access to the materials needed to implement this protocol in future studies. Second, Logical Memory, and particularly delayed recall, mimics an everyday social task of repeating a story previously heard that includes events with proper names, giving this task ecological validity that could more closely demonstrate how individuals in the

prodromal AD stage perform in a functional task. Third, the speech and language data analyzed in this study were collected in a quick, efficient manner with relatively low participant burden. Fourth, including AD-CSF biomarker data allowed us to extend our previous investigation of the association between proper names and PET Aβ in an additional AD biomarker.

A limitation of the current study is the generalizability of the cohort. As the Wisconsin Registry for Alzheimer's Prevention is a self-selected cohort with most individuals living in the upper Midwest, the sample is predominantly non-Hispanic White and highly educated. Therefore, the sample is not representative of the overall population of the United States, or the clinical population diagnosed with AD. In addition, this study did not investigate the relationship between proper names and participants that go on to receive an MCI or AD diagnosis due to the relatively young age of the sample. Further, the proper names within the Logical Memory task may favor high frequency names used in English. Accordingly, this study did not investigate recall of novel proper names. An additional limitation includes that we did not run a priori power calculations, due to the fact that these measures from story recall have not been explored with CSF AD biomarkers, which represent a theoretically earlier stage of disease progression than PET AD biomarkers (Jack et al., 2018). Therefore, it is possible that our study was underpowered to detect associations with CSF amyloid. Lastly, the use of binary variables to determine biomarker positivity means that some individuals with biomarker accumulation may have been missed as they did not reach the threshold for positivity. These limitations highlight the importance of replicating this study in more diverse cohorts.

4.2 Conclusions

Our data suggest that metrics from story recall tasks are associated with increased risk of CSF AD biomarker positivity and that proper names from story recall may be sensitive to early AD biomarker changes. Validation by replication in additional cohorts and additional methods (e.g., picture naming) is required.

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Table 1. Demographics and clinical characteristics

		Biomarker status			Biomarker status		
	Overall	A-	A+	*p*	T-	T+	*p*
N	219	187	59		190	29	
Age at baseline, mean (SD)	58.13 (6.31)	57.19 (6.61)	60.51 (4.59)	**<0.001**	57.65 (6.48)	61.07 (3.91)	**0.005**
Age at lumbar puncture*, mean (SD)	65.34 (7.02)	64.08 (7.29)	68.50 (5.03)	**<0.001**	64.66 (7.09)	69.40 (5.02)	**0.001**
Age at lumbar puncture – age baseline, mean (SD)	7.22 (2.96)	6.89 (2.98)	7.99 (2.80)	**0.014**	7.01 (2.91)	8.33 (3.10)	**0.023**
Years between lumbar puncture and most recent Logical Memory, mean (SD)	1.65 (1.62)	1.71 (1.71)	1.53 (1.38)	0.464	1.75 (1.69)	1.14 (1.04)	0.055
Female, n (%)	142 (65.5)	134 (66.9)	37(62.7)	0.678	124 (65.3)	20 (70.0)	0.763
Race, n (%)				0.82			0.484
American Indian or Alaska Native	1 (0.4)	1 (0.6)	0 (0.0)		1 (0.5)	0 (0.0)	
Asian	1 (0.4)	1 (0.6)	0 (0.0)		1 (0.5)	0 (0.0)	
Black or African American	5 (2.2)	3 (1.9)	2 (3.4)		3 (1.6)	2 (6.7)	
Non-Hispanic White	215 (96.4)	154 (96.2)	57 (96.6)		184 (96.8)	28 (93.3)	
Other	1 (0.4)	1 (0.6)	0 (0.0)		1 (0.5)	0 (0.0)	
Family history positive, n (%)	169 (75.8)	118 (73.8)	48 (81.4)	0.323	143 (75.3)	24 (80.0)	0.738
Years of follow-up cognitive testing	8.16 (2.57)	7.87 (2.63)	8.88 (2.27)	**0.01**	8.07 (2.58)	8.70 (2.51)	0.213
WRAT-3 Reading Standard Score, mean (SD)	106.91 (9.27)	106.32 (9.72)	108.32 (8.00)	0.158	106.55 (9.53)	108.77 (7.47)	0.225
Total years of education, mean (SD)	16.19 (2.04)	16.19 (2.04)	16.22 (2.03)	0.916	16.13 (2.05)	16.57 (1.91)	0.272
APOE ε4 carrier, n (%)	80 (36.0)	45 (28.3)	34 (57.6)	**<0.001**	64 (33.9)	16 (53.3)	0.064
Baseline MMSE, mean (SD)	29.53 (0.76)	29.53 (0.77)	29.51 (0.75)	0.845	29.54 (0.77)	29.40 (0.72)	0.343
Baseline R-AVLT, mean (SD)	51.52 (8.43)	51.74 (8.59)	51.15 (8.15)	0.647	52.02 (8.50)	48.97 (7.73)	0.066
Baseline Logical Memory delayed total, mean (SD)	26.91 (6.74)	26.74 (6.91)	27.36 (6.46)	0.555	26.74 (6.75)	27.93 (6.91)	0.369
Baseline Proper Name delayed total, mean (SD)	5.23 (1.97)	5.33 (1.94)	4.95 (2.05)	0.204	5.25 (1.93)	5.10 (2.23)	0.704

*Data from the most recent lumbar puncture was used. Sample characteristics of +/- groups for A and T were compared using t-tests or chi-square tests. Items in bold are statistically significant at $p < .05$ (unadjusted means). "Baseline" = collected at the first visit at which Logical Memory was administered, median = visit 2. "Most recent" = data collected from each participant's last Logical Memory visit, median = visit 6. One participant had data for $pTau_{181}$ only; individuals who were A-/T+ were excluded from these analyses. *Abbreviations*: A- = $A\beta_{42/40}$ CSF value greater than the cutoff score of 0.046; A+ = $A\beta_{42/40}$ CSF value less than or equal to the cutoff score; *APOE* ε4 = apolipoprotein E ε4 allele; Logical Memory = subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987); MMSE = Mini-Mental Status Examination (Folstein et al., 1983); R-AVLT = Rey Auditory Verbal Learning Test (Schmidt, 1996); SD = standard deviation; T- = $pTau_{181}$ CSF value less than the cutoff score of 24.8 pg/mL (Van Hulle et al., 2021); T+ = $pTau_{181}$ CSF value greater than or equal to the cutoff score; WRAT-3 = Wide Range Achievement Test-3 Reading Subtest (Wilkinson, 1993).

Table 2. Logistic regression results for most recent story recall variables predicting amyloid-beta and tau status

	A (+/-)			A (+/-)			T (+/-)			T (+/-)		
Predictors	*Odds ratios*	*CI*	*p*	*Odds ratios*	*CI*	*p*	*Odds ratios*	*CI*	*p*	*Odds ratios*	*CI*	*p*
Intercept	0.00	0.00 – 0.00	**<0.001**	0.00	0.00 – 0.00	**<0.001**	0.00	0.00 – 0.01	**0.002**	0.00	0.00 – 0.02	**0.004**
Age at CSF collection	1.09	1.02 – 1.16	**0.009**	1.09	1.03 – 1.17	**0.004**	1.08	1.00 – 1.18	0.053	1.09	1.01 – 1.19	**0.033**
Age difference between CSF collection and baseline Logical Memory test	1.07	0.93 – 1.22	0.353	1.07	0.94 – 1.22	0.335	1.10	0.93 – 1.32	0.284	1.10	0.93 – 1.32	0.259
WRAT-3 Reading	1.05	1.00 – 1.10	**0.038**	1.04	1.00 – 1.09	0.059	1.05	0.99 – 1.11	0.103	1.04	0.99 – 1.11	0.133
Sex (reference group: male)	1.01	0.49 – 2.04	0.976	1.06	0.52 – 2.14	0.864	0.63	0.24 – 1.50	0.311	0.63	0.24 – 1.52	0.322
APOE ε4 carrier	4.51	2.26 – 9.33	**<0.001**	4.68	2.35 – 9.70	**<0.001**	2.56	1.10 – 6.11	**0.031**	2.79	1.19 – 6.74	**0.020**
Most recent Proper Name delayed total	0.81	0.68 – 0.95	**0.013**				0.78	0.63 – 0.95	**0.014**			
Most recent Logical Memory delayed total				0.95	0.90 – 0.99	**0.029**				0.92	0.86 – 0.98	**0.009**
Observations	218			218			219			219		
R^2 Tjur	0.213			0.206			0.133			0.134		
AIC	222.803			224.206			162.038			161.078		

The CSF collection date was the most recent for each participant. Items in bold are statistically significant at $p < .05$. The threshold of 0.046 was used for $A\beta_{42/40}$ positivity and 24.8 pg/mL was used for $pTau_{181}$ positivity (VanHulle et al., 2021 (e.g. A+= $A\beta_{42/40}$ at or below 0.046 and T+= $pTau_{181}$ at or above 24.8 pg/mL). AIC differences greater than 2 for a pair of models suggests that the model with the lower AIC had a better fit. "Baseline" = collected at the first visit at which Logical Memory was administered, median = visit 2. "Most recent" = Logical Memory (Logical Memory) data collected from each participant's last Logical Memory visit, median = visit 6. Abbreviations: AIC = Akaike information criterion; *APOE* ε4 = apolipoprotein E ε4 allele; CSF = cerebrospinal fluid; Logical Memory = subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987); R^2 Tjur = the coefficient of determination as suggested by Tjur (2009)WRAT-3 = Wide Range Achievement Test-3 Reading Subtest (Wilkinson, 1993).

Table 3. Multinomial logistic regression results for most recent story recall variables predicting amyloid-beta and tau status

	A+/T-			A+/T+								
Predictors	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*	*Odds Ratios*	*CI*	*p*
(Intercept)	0.00	0.00 – 0.01	**0.001**	0.00	0.00 – 0.01	**0.002**	0.00	0.00 – 0.00	**0.001**	0.00	0.00 – 0.01	**0.002**
Age at lumbar puncture	1.08	1.00 – 1.16	0.055	1.08	1.00 – 1.16	**0.045**	1.08	0.99 – 1.17	0.071	1.09	1.01 – 1.18	**0.036**
Age at lumbar puncture – age at baseline	1.08	0.91 – 1.27	0.390	1.07	0.91 – 1.27	0.392	1.11	0.93 – 1.33	0.246	1.11	0.93 – 1.32	0.231
WRAT-3 Reading	1.04	0.99 – 1.10	0.125	1.04	0.99 – 1.09	0.144	1.06	1.00 – 1.13	**0.042**	1.06	1.00 – 1.12	0.068
Sex (reference group: male)	1.31	0.55 – 3.09	0.538	1.36	0.58 – 3.17	0.479	0.66	0.26 – 1.69	0.389	0.70	0.28 – 1.77	0.446
APOE ε4 carrier	4.45	1.88 – 10.54	**0.001**	4.47	1.89 – 10.57	**0.001**	3.69	1.50 – 9.06	**0.005**	3.94	1.60 – 9.70	**0.003**
Most recent Proper Name score	0.93	0.75 – 1.14	0.475				0.74	0.60 – 0.91	**0.005**			
Most recent Total Score				0.99	0.93 – 1.05	0.659				0.92	0.86 – 0.98	**0.009**
Observations	218											
R^2 Nagelkerke PNs	0.253	AIC PNs	322.7									
R^2 Nagelkerke Logical Memory total score	0.247	AIC Logical Memory total score	324.1									

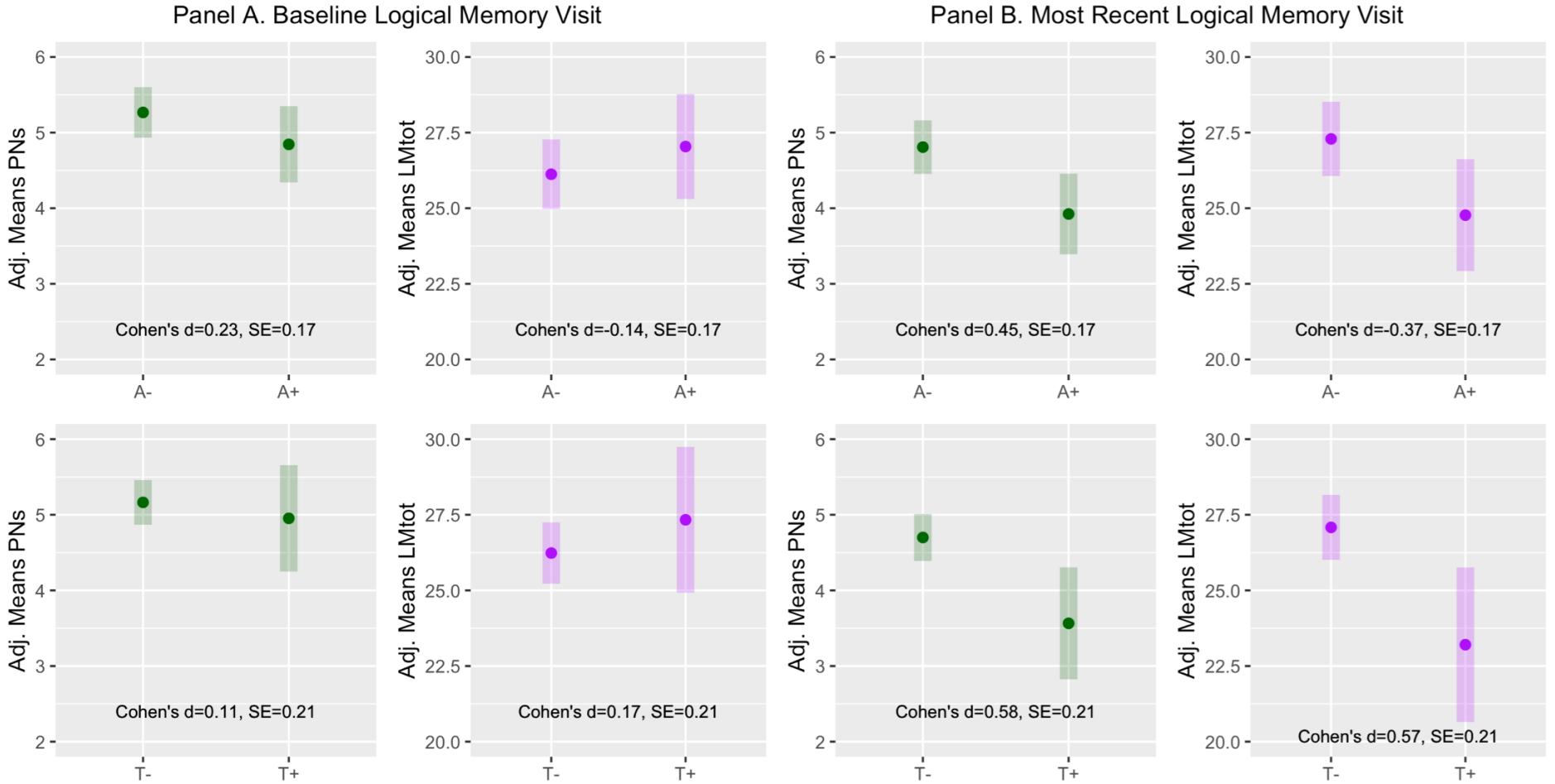
The CSF collection date was the most recent for each participant. Items in **bold** are statistically significant at $p < .05$. The threshold of 0.046 was used for $A\beta_{42/40}$ positivity and 24.8 pg/mL was used for $pTau_{181}$ positivity (VanHulle et al., 2021). AIC differences greater than 2 for a pair of models suggests that the model with the lower AIC had a better fit. "Baseline" = collected at the first visit at which Logical Memory was administered, median = visit 2. "Most recent" = Logical Memory (Logical Memory) data collected from each participant's last Logical Memory visit, median = visit 6. A-/T- (n=157) participants were used as the reference group in multinomial logistic regression models. *Abbreviations*: A+ = $A\beta_{42/40}$ at or below 0.046; AIC = Akaike information criterion; *APOE* ε4 = apolipoprotein E ε4 allele; CSF = cerebrospinal fluid; Logical Memory = subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987); T- = $pTau_{181}$ below 24.8 pg/mL; T+= $pTau_{181}$ at or above 24.8 pg/mL; WRAT-3 = Wide Range Achievement Test-3 Reading Subtest (Wilkinson, 1993).

Table 4. Longitudinal linear mixed effects model predicting delayed Logical Memory proper names and total score

	Proper Names Z-score			Total Score Z-score		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	-3.26	-4.38 – -2.14	**<0.001**	-2.47	-3.81 – -1.13	**<0.001**
Age at baseline visit centered	-0.03	-0.04 – -0.02	**<0.001**	0.01	-0.01 – 0.02	0.300
Sex (reference group: male)	-0.25	-0.45 – -0.05	**0.012**	-0.36	-0.60 – -0.12	**0.003**
WRAT-3 Reading	0.03	0.02 – 0.04	**<0.001**	0.02	0.01 – 0.04	**<0.001**
APOE ε4 carrier	0.02	-0.18 – 0.23	0.843	-0.00	-0.25 – 0.24	0.993
A+/T-	-0.08	-0.36 – 0.20	0.587	-0.01	-0.35 – 0.33	0.971
A+/T+	-0.18	-0.47 – 0.11	0.228	-0.08	-0.42 – 0.27	0.656
Age at NP visit centered * A+/T-	-0.01	-0.04 – 0.02	0.622	-0.01	-0.04 – 0.01	0.299
Age at NP visit centered * A+/T+	-0.05	-0.08 – -0.02	**0.002**	-0.08	-0.11 – -0.05	**<0.001**
Random Effects						
σ^2		0.48			0.33	
τ_{00}		0.38_{WRAPNo}			0.64_{WRAPNo}	
ICC		0.44			0.66	
N		218_{WRAPNo}			218_{WRAPNo}	
Observations		954			953	
Marginal R^2 / Conditional R^2		0.155 / 0.529			0.107 / 0.695	
AIC		2390.693			2188.930	

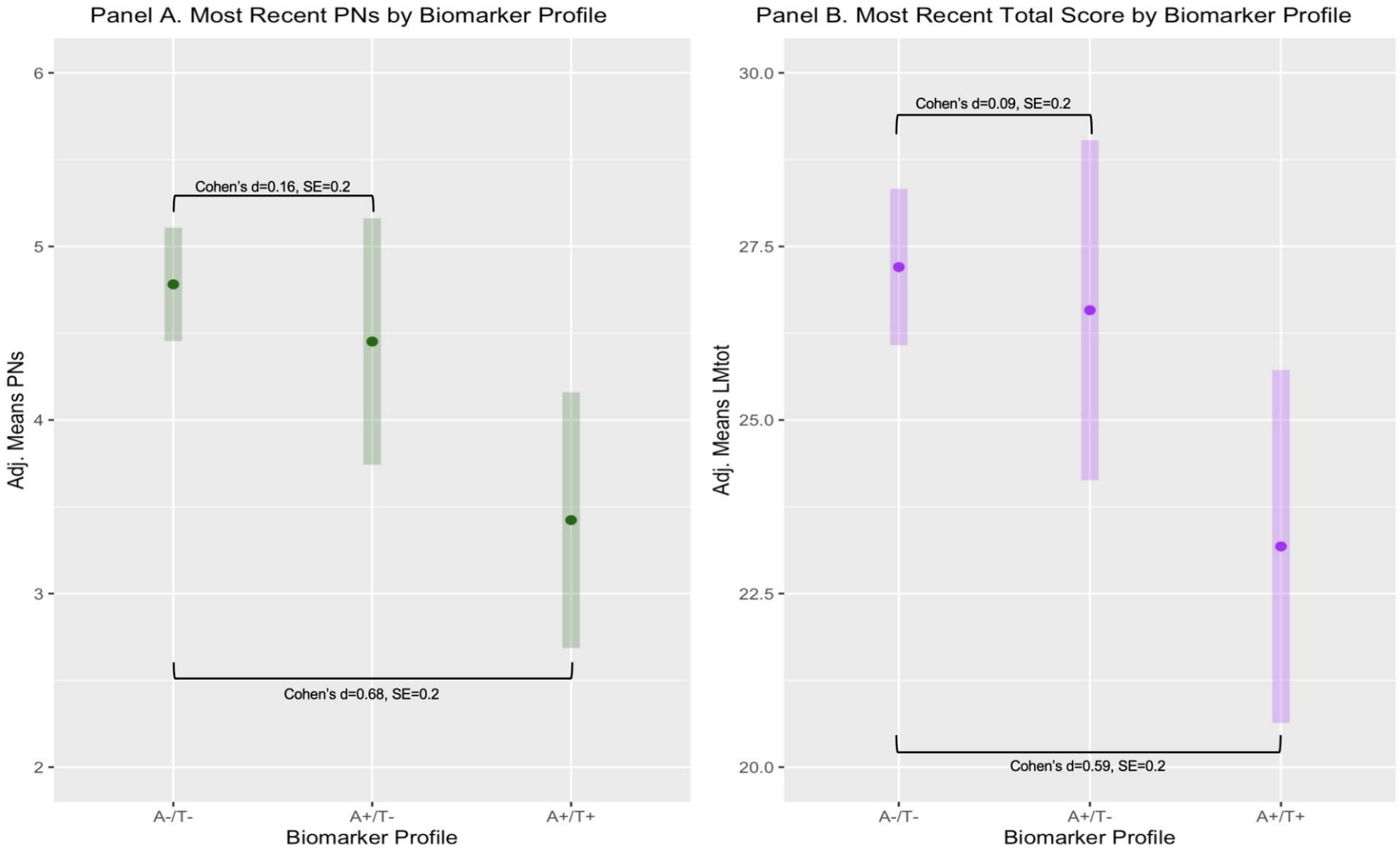
The CSF collection date was the most recent for each participant. Items in **bold** are statistically significant at $p < .05$. AIC differences greater than 2 for a pair of models suggests that the model with the lower AIC had a better fit. Biomarker profile is a 3-level variable dividing participants by CSF A+/- and T+/- status (A-/T-, A+/T-, A+/T+) treated as a categorical variable with biomarker negative profile (A-/T-) as the reference group. *Abbreviations*: A+= $A\beta_{42/40}$ at or below 0.046 (VanHulle et al., 2021) ; AIC = Akaike information criterion; *APOE* ε4 = apolipoprotein E ε4 allele; CSF = cerebrospinal fluid; Logical Memory = subtest from the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987); NP = neuropsychological visit; T- = $pTau_{181}$ below 24.8 pg/mL; T+= $pTau_{181}$ at or above 24.8 pg/mL (VanHulle et al., 2021); WRAPNo = participant ID from the Wisconsin Registry for Alzheimer's Prevention; WRAT-3 = Wide Range Achievement Test-3 Reading Subtest (Wilkinson, 1993).

Figure 1. Adjusted means and effect sizes of Logical Memory delayed recall of proper names and total score from the baseline (Panel A) vs. most recent visit (Panel B)



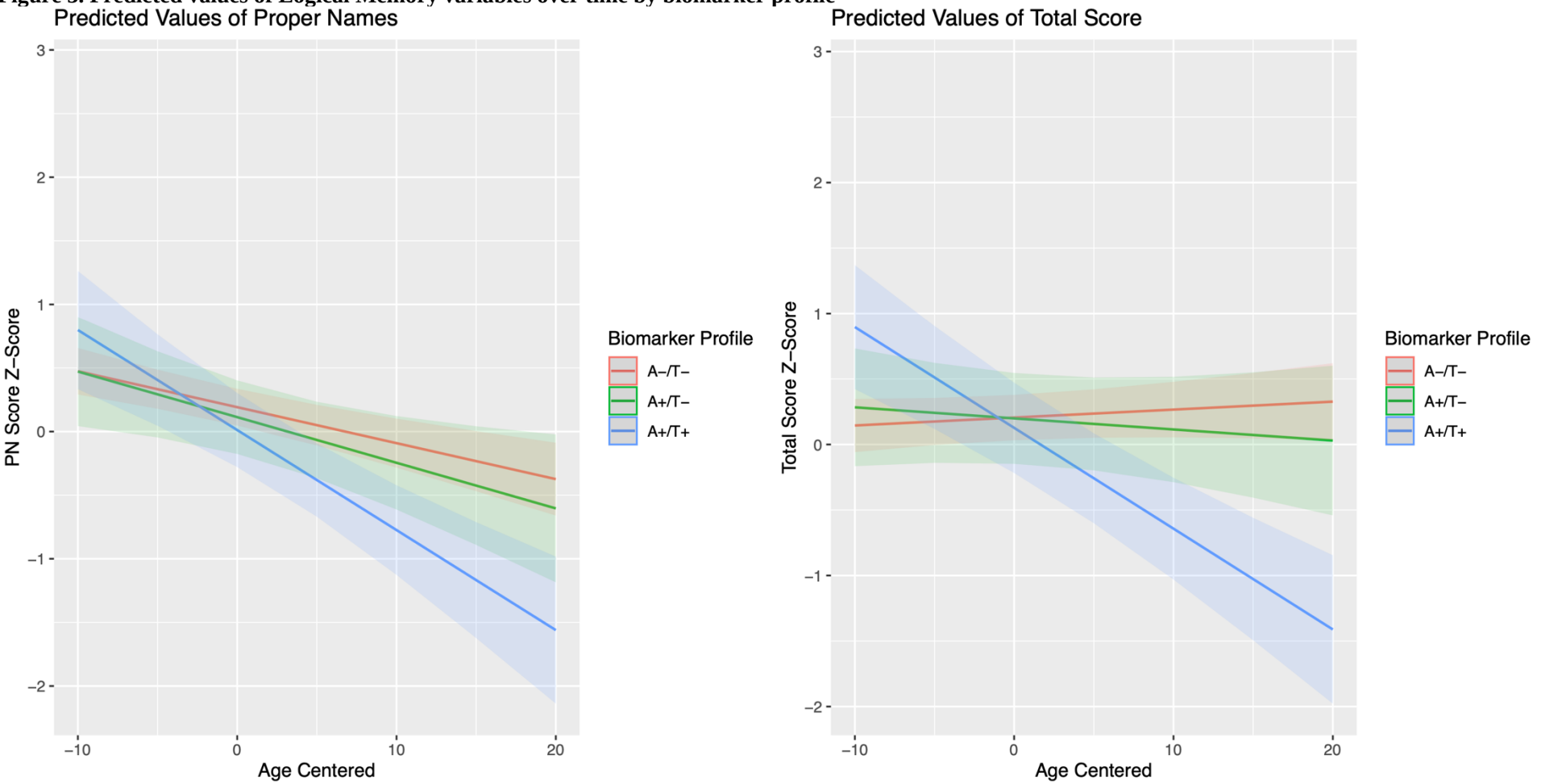
Adjusted means were calculated by performing ANCOVA models, with story recall variable (proper names or total score) as outcome, A+/- or T+/- as predictor, covarying for age, gender, WRAT-3 Reading, and *APOE* ε4 status. Effect sizes were obtained by calculating the pairwise differences of estimates divided by the pooled standard deviation. The mean (SD) years between baseline and logical memory visit is 8.16 years (SD = 2.57). *Abbreviations*: A+/- = $A\beta_{42/40}$ positive/negative; ANCOVA = analysis of covariance; *APOE* ε4 = apolipoprotein E ε4 allele; Cohen's d = effect size; LMtot = total delayed recall score from Logical Memory testing; PNs = proper names composite score from delayed recall Logical Memory testing; SD = standard deviation; SE = standard error; T+/- = $pTau_{181}$ positive/negative; WRAT-3 = Wide Range Achievement Test-3 Reading Subtest (Wilkinson, 1993).

Figure 2. Adjusted means and effect sizes of Logical Memory delayed recall of proper names (Panel A) and total score (Panel B) at most recent visit according to biomarker profile



Adjusted means were calculated by performing ANCOVA models, with story recall variable (proper names or total score) as outcome, biomarker profile as predictor, covarying for age, gender, WRAT-3 Reading, and *APOE* ε4 status. Effect sizes were obtained by calculating the pairwise differences of estimates divided by the pooled standard deviation. *Abbreviations*: A+/- = $A\beta_{42/40}$ positive/negative; Adj. = adjusted; ANCOVA = analysis of covariance; *APOE* ε4 = apolipoprotein E ε4 allele; Cohen's d = effect size; LMtot = total delayed recall score from Logical Memory testing; PNs = proper names composite score from delayed recall Logical Memory testing; SE = standard error; T+/- = $pTau_{181}$ positive/negative; WRAT-3 = Wide Range Achievement Test-3 Reading Subtest (Wilkinson, 1993).

Figure 3. Predicted values of Logical Memory variables over time by biomarker profile



Predicted values were calculated using linear mixed effects models using a predictor of interest of standardized version (calculated z-scores) of Logical Memory proper names and total score by centered age across neuropsychological visits. Abbreviations: A+/- = $A\beta_{42/40}$ positive/negative; PN = proper names composite score from delayed recall Logical Memory testing; T+/- = $pTau_{181}$ positive/negative.