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Spatial Navigation Ability as a Predictor of Increased Clinical Impairment

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by

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ABSTRACT OF THE THESIS

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Professor Denise Head, Chair

Professor Jeffrey Zacks

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Spatial navigation deficits are observed in Alzheimer disease (AD) cross-sectionally, but prediction of longitudinal clinical decline has been less examined. Cognitive mapping (CM) was assessed in 95 participants and route Learning (RL) was assessed in 65 participants at baseline. Clinical progression over an average of 4.16 years was assessed using the Clinical Dementia Rating scale. Relative predictive ability of these tasks was compared to episodic memory, hippocampal volume and cerebrospinal fluid (CSF) biomarkers ($ptau_{181}/A\beta_{42}$ ratio). CM and RL were significant predictors of clinical progression (ps<.032). All measures, except RL-Learning, remained significant predictors with episodic memory in the models (ps<.048). CM interacted with the hippocampus and $ptau_{181}/A\beta_{42}$ in prediction (ps<.013). CM, RL and episodic memory evidenced strong diagnostic accuracy (AUCs=.894, .794 and .735, respectively) with CM tending to perform better than episodic memory (p=.056). Taken together the results suggest that baseline spatial navigation performance may be appropriate for assessing risk of clinical progression.

Chapter 1: Introduction

There is a current research emphasis on developing cognitive measures that are sensitive to preclinical Alzheimer disease (AD), which is associated with an increased risk of developing symptomatic AD (Jack et al., 2018; Vos et al., 2013). During preclinical AD, individuals are clinically normal but evidence AD-related pathological changes, determined using biomarkers for beta-amyloid deposition and neurofibrillary tangles (Bloom et al., 2014; Jack et al., 2018; Price et al., 2009; Price & Morris, 1999). Thus, preclinical AD is associated with decreased cerebrospinal fluid (CSF) $A\beta_{42}$, increased CSF phosphorylated tau ($ptau_{181}$), and elevations in Positron Emission Tomography (PET) measures of amyloid and tau (e.g., Brier et al., 2016; Roe et al., 2013). Additionally, smaller brain volumes have been reported in preclinical AD, including smaller hippocampal volumes (Bernard et al., 2014; Storandt et al., 2009; Gordon et al., 2016; but see Clark et al., 2018; Schoonenboom et al., 2008). Sensitive cognitive measures for the preclinical phase are important for determining trajectories of cognitive decline and response to intervention, as future disease modifying treatments may be most effective if administered during the earliest stages of AD (Garcia-Alloza et al., 2009). Considering the expense and/or invasiveness of current methods in identifying preclinical AD (i.e., lumbar puncture, PET), cognitive tasks may represent an opportunity for a more accessible and lower risk initial screening procedure (Jack et al., 2018).

Existing methods for delineating cognitive deficits in mild cognitive impairment (MCI) and symptomatic AD tend to focus on traditional psychometric measures, with an emphasis on episodic memory. However, these may not be sufficiently sensitive to more subtle cognitive difficulties present in preclinical AD (Hedden et al., 2013; Loweinstein et al., 2018; Rentz et al., 2013). There is emerging interest in targeting spatial navigation abilities that may prove more

sensitive to the preclinical phase than current psychometric measures used in identifying MCI and symptomatic AD (Ritchie et al., 2017; Weintraub et al., 2018). The interest in spatial navigation is consistent with amyloid and tau deposition, as well as volumetric declines, occurring early in brain regions that subserve this function (e.g., hippocampus, entorhinal cortex, inferior parietal lobule, precuneus) (Braak et al., 2015; Coughlan et al., 2018; Storandt et al., 2009; Thal et al., 2002).

Deficits in multiple aspects of spatial navigation are consistently observed in MCI and symptomatic AD (Lithfous et al., 2013; Coughlan et al., 2018), including impairments in both route learning and cognitive mapping. Route learning is based on an egocentric representation and a sequence of body-turns in relation to environmental features. Cognitive mapping involves navigating based on a world-centered representation that incorporates inter-relationships amongst environmental features. Route learning involves striatal circuits whereas cognitive mapping involves hippocampal circuits (de Bruin et al., 1997; Iaria et al., 2003; O'Keefe and Nadel, 1978). Importantly, recent work suggests that individuals in the preclinical AD continuum (i.e., low CSF $A\beta_{42}$,) have differential deficits in cognitive map formation relative to route learning (Allison et al., 2016). This cognitive mapping task demonstrated high sensitivity (92%; 57% specificity) in detecting the preclinical AD continuum (Allison et al., 2016), was more sensitive than a standard episodic memory task or route learning (Allison et al., 2016), and had strong psychometric properties (Allison et al., accepted).

This past work was cross-sectional and longitudinal investigations are necessary to confirm the utility of spatial navigation tasks for predicting clinical progression. Thus, the current study examined whether spatial navigation tasks were significant predictors of clinical progression

with the hypothesis that the cognitive mapping task would be a more robust predictor than route learning. We also examined the relative predictive ability of these tasks in comparison to previously reported predictors of clinical progression, including AD biomarkers (CSF $ptau_{181}/A\beta_{42}$ ratio), hippocampal volume and standard measures of episodic memory. Lastly, we examined the diagnostic accuracy of the cognitive measures.

Chapter 2: Method

2.1 Participants

Participants were recruited from the Knight Alzheimer Disease Research Center (ADRC) at Washington University and initially participated in previous studies on spatial navigation (Allison et al., 2016; Allison et al., accepted). A total of ninety-eight participants completed the cognitive mapping (CM) task and sixty-seven completed the route learning (RL) task. Three individuals who completed the CM task and two individuals who completed the RL task did not have longitudinal data. Thus, the final sample for the current study was ninety-five for the CM cohort and sixty-five for the RL cohort with sixty-three individuals who completed both tasks (see Tables 1 and 2 for sample descriptions). Three individuals were in both initial studies; data from initial administration are included here.

Participants were screened for major medical conditions, including Parkinson's disease, Huntington's disease, stroke, seizures, and major head injury. Participants had normal vision or wore corrective lenses. Participants consented to participation in accordance with Washington University Human Research Protection Office guidelines.

2.2 Clinical Dementia Rating Scale (CDR)

The CDR global score was used to determine the absence or presence, as well as the severity, of dementia (CDR of 0=clinical normality; 0.5=very mild dementia; 1= mild dementia; 2=moderate dementia; 3=severe dementia; Morris, 1993). Clinical diagnosis of symptomatic AD for individuals with a CDR>0 is made in accordance with criteria reported by the NINCDS-ADRDA (McKhann et al., 1984). Individuals clinically diagnosed with AD at the Knight ADRC,

including those meeting MCI criteria, have AD pathology in 93% of cases (Berg et al., 1998; Storandt et al., 2006).

The CDR-Sum of Boxes score (CDR-SB; range: 0-18) provides a more quantitative estimate of clinical impairment and is based on scores in six cognitive and functional domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care) used to generate the global CDR score. The larger range of CDR-SB (vs. global CDR) score allows for increased precision and additional information regarding cognitive impairment, especially for mild impairment (Lynch et al., 2006; O'Bryant et al., 2010; Williams et al., 2013).

In the current study, clinical progression was defined as: a) an increase in global CDR score from the time of the spatial navigation tasks to the most recent follow-up; and b) change in CDR-SB across measurement occasion. CDR global scores collected between baseline and most recent follow-up were not used in determining clinical progression.

2.3 Virtual Navigation Tasks

Administration of navigation tasks are described more fully in prior work (Allison et al., 2016; Allison et al., accepted). The experimental maze environments consisted of a series of interconnected hallways with landmarks and wallpapers that differed in color. A joystick was used to maneuver through the environment. Participants completed both practice and a visuomotor expertise test in separate virtual environments.

2.3.1 Cognitive Mapping Task

A CM task was administered in prior studies (Allison et al., 2016; Allison et al., accepted) using similar procedures with differences in administration noted below. Across both studies, the task involved learning and retrieval phases. There were three study-test trials during the learning

phase. During study, participants freely explored the environment for 7 (Allison et al., 2016) or 4 minutes (Allison et al., accepted). Participants were then given a blank 2D map of the environment and asked to place Xs at landmark locations. The learning score (CM-Learning) was the average number of landmarks correctly recalled across trials (range=0-20 for Allison et al., 2016; range=0-18 for Allison et al., accepted). After a 10-minute (Allison et al., 2016) or 15-minute delay (Allison et al., accepted), participants completed 12 (Allison et al., 2016) or 6 trials (Allison et al., accepted) in which they were presented with a picture of a landmark and instructed to navigate to the landmark using the shortest path possible as quickly as possible. The retrieval score (CM-Retrieval) was the average amount of time taken to find each landmark. Because of study differences, scores on the variables within each sample were standardized (z-transformed) to obtain an estimate of each individual's relative ranking.

2.3.2 Route Learning Task

The RL task included both learning and delayed retrieval phases (Allison et al. 2016). During the learning phase, participants followed the same route marked by arrows repeatedly for 5 minutes. Next, participants drew the learned path on a blank 2D map of the environment. The study-test trials were completed four times. The learning score (RL-Learning) was the average proportion of correctly drawn turns at intersections relative to the total number of intersections along the route over the four trials (range=0-1). After a 10-minute delay, participants traversed the designated route without arrows three times. The average amount of time taken to traverse the route across trials was the retrieval phase variable (RL-Retrieval).

2.4 Episodic Memory Composite Score

A memory composite was created using free recall from the Selective Reminding Task (Grober et al. 1988), immediate and delayed recall on the Logical Memory Test from the Wechsler

Memory Scale (Wechsler & Stone, 1973) or Wechsler Memory Scale-III (Wechsler, 1997), and total score on the Associate Learning Task from the Wechsler Memory Scale (Wechsler & Stone, 1973) or Wechsler Memory Scale-III (Wechsler, 1997). All test scores were standardized (z-scored); standardized scores for each participant were averaged to create the composite score. In the case of multiple versions of a test, raw scores from each subsample were standardized separately and then combined across data sets.

2.5 CSF Collection and Processing

CSF collection has been previously described (Fagan et al., 2006). All CSF samples were analyzed using next generation Elecsys electrochemiluminescent immunoassays for $A\beta_{42}$ and $ptau_{181}$ developed by Roche Diagnostics (Basel, Switzerland) and run on the automated Roche Cobas e 601 analyzer (Bittner, Zetterberg et al., 2016). Values for $A\beta_{42}$ above 1,700 pg/ml have not been validated and are not to be used in clinical decision making. The ratio between $ptau_{181}$ and $A\beta_{42}$ was used as the AD biomarker measure because it has been found to best map onto PET imaging results (Schindler et al., 2018).

2.6 Structural MRI Acquisition and Processing

MRI scans were acquired using one of two Siemens 3T scanners (TIM Trio: TE=3ms, TR=2400ms, TI=1000ms, FA=8°, 256x256 mm acquisition matrix, 1x1x1mm voxels; BioGraph scanner: TE=2.95ms, TR=2300ms, TI=900ms, FA=9°, 240x256 mm acquisition matrix, 1x1x1.2mm voxels). The FreeSurfer image analysis suite v5.3 was used for image processing and delineation of regions of interest (Fischl et al., 2002). FreeSurfer implements an automated probabilistic labeling procedure where individual voxels in an image are assigned to a neuroanatomical label based on data from a manually labeled training set. Volumetric data

obtained through this procedure are highly correlated with manually generated volumes (Desikan et al., 2006; Fischl et al., 2002). The hippocampus was the region-of-interest for the current study. Volumes were summed across hemispheres and estimated intracranial volume was used to adjust volumes for body size differences using an analysis of covariance approach (Buckner et al., 2004).

2.7 Computer Experience

Using a Likert scale (0-7), participants self-reported their experience with computers, computer games and virtual reality games. A measure of total computer experience was created from the sum of experience scores (0-21).

2.8 Health Composite

A health composite (0-5) was created using the sum of past or present mild head trauma, heart problems, hypertension, diabetes and depression.

2.9 Statistical Analyses

2.9.1 General

CM-Learning, CM-Retrieval, RL-Learning and RL-Retrieval variables were examined in separate models. When a spatial navigation variable was a significant predictor, previously established predictors were added to the model to assess whether there was unique variance explained by the spatial navigation variable. Established predictors (CSF $ptau_{181}/A\beta_{42}$, hippocampal volume or episodic memory composite) were examined in separate models. Age, sex, education and the health composite were covariates in all analyses. For logistic and linear mixed effects models, the learning variables were reverse scored so that higher scores reflected worse performance. Standardized variables were used in all analyses.

2.9.2 CDR Progression

Logistic regression analyses were conducted using IBM SPSS Statistics 25. These analyses were used to determine whether baseline spatial navigation performance predicted global CDR progression (1=progression; 0=no-progression). Only episodic memory was additionally examined in these models considering the sample size issues with a categorical outcome.

2.9.3 Longitudinal Change in CDR-SB

Linear mixed effects models were used to determine whether spatial navigation performance predicted change in CDR-SB over time. These models were conducted using the nlme package (Pinheiro et al., 2018) in R version 3.5.1 (RStudio Team, 2005). Time (years in study) and intercept were random effects. The interaction between the spatial navigation variables and time were the independent variables of primary interest. In models examining relative predictive utility, the other predictor variable (i.e., CSF $ptau_{181}/A\beta_{42}$, hippocampal volume, episodic memory) and their interaction with time were added to the model. Finally, three-way interactions between CM variables, CSF $ptau_{181}/A\beta_{42}$ or hippocampal volume, and time were included in a model to examine whether there was moderation of any relationship observed between CM performance and CDR-SB progression. Three-way interactions were not conducted for RL variables due to the smaller sample size.

Due to the heterogeneous baseline CDR status of participants (CDR=0-1), CM models predicting CDR-SB progression including only participants with CDR=0 at baseline (n=81) were examined in order to assess whether CM task performance may be a sensitive marker of the preclinical disease stage (see Tables 3 for sample description). These analyses were not conducted in the RL cohort due to the smaller sample size of CDR=0 at baseline participants (n=50).

2.9.4 Diagnostic Accuracy

Receiver operating characteristic (ROC) analyses were conducted to assess diagnostic accuracy in predicting clinical progression according to global CDR for the sixty-three participants who completed CM, RL and episodic memory tasks. For these analyses, standardized composites were created combining the learning and retrieval phases within each task. In addition, the area under the curve (AUC) values were compared amongst the CM, RL and episodic memory composites using the method of DeLong, DeLong and Clarke-Pearson (1998) with the paired data option.

2.9.5 Outliers

Outliers were defined as values >3 STD from the group mean. All analyses were conducted with and without outliers. Unless otherwise specified, results were unchanged when outliers were removed.

Chapter 3: Results

3.1 Cognitive Mapping: Global CDR Progression

CM-Learning (OR=3.131, CI=1.376-7.123, p=.007) and CM-Retrieval (OR=2.950, CI=1.444-6.024, p=.003) significantly predicted clinical progression. These relationships remained with episodic memory added to the respective models (CM-Learning: OR=2.591, CI=1.007-6.667, p=.048; CM-Retrieval: OR=2.409, CI=1.104-5.257, p=.027). See Supplementary Table 1 for full regression results.

3.2 Cognitive Mapping: Longitudinal Change in CDR-SB

CM-Learning (β=.266, p<.001) and CM-Retrieval (β=.250, p=.002) significantly predicted clinical progression (Figure 1; Supplementary Tables 2, 3, 4). These relationships remained with episodic memory (CM-Learning: β=.216, p=.003; CM-Retrieval: β=.184, p=.021) and hippocampal volume (CM-Learning: β=.236, p=.004; CM-Retrieval: β=.233, p=.033) added to the respective models. Neither CM-Learning (β=.122, p=.197) nor CM-Retrieval (β=.123, p=.369) remained a significant predictor of clinical progression with $ptau_{181}/A\beta_{42}$ added to the respective models.

Hippocampal volume significantly moderated the association of CM-Learning (β=-.276, p<.001) and CM-Retrieval (β=-.270, p=.002) with longitudinal CDR-SB progression (Figure 2). When outliers were removed, the $ptau_{181}/A\beta_{42}$ ratio also significantly moderated the association of CM-Learning (without outliers: β=.309, p=.001; with outliers: β=.110, p=.194) and CM-Retrieval (without outliers: β=.355, p=.013; with outliers: β=.176, p=.190) with longitudinal progression (Figure 2).

3.3 Cognitive Mapping: Longitudinal Change in CDR-SB with Global CDR=0 at Baseline

In this clinically normal at baseline sample, CM-Learning (β=.155, p=.024) was a significant predictor of clinical progression (Supplementary Table 5). This remained true when episodic memory (β=.151, p=.032) was added to the model. This relationship was no longer significant when $ptau_{181}/A\beta_{42}$ (β=.105, p=.222) or hippocampal volume (β=.101, p=.206) were added to the models. CM-Retrieval (β=.121, p=.196) was not a significant predictor of clinical progression in this sample (Supplementary Table 6).

3.4 Route Learning: Global CDR Progression

RL-Learning (OR=3.293, CI=1.307-8.298, p=.011) and RL-Retrieval (OR=6.301, CI=1.941-20.461, p=.002) significantly predicted clinical progression (Supplementary Table 7). RL-Retrieval remained a significant predictor when episodic memory was added to the model (OR=4.781, CI=1.341-17.045, p=.016), but RL-Learning did not (OR=1.911, CI=.631-5.792, p=.252).

3.5 Route Learning: Longitudinal Change in CDR-SB

RL-Learning (β=.202, p=.032) and RL-Retrieval (β=.467, p<.001) significantly predicted CDR-SB progression (Figure 1; Supplementary Tables 8 and 9). RL-Learning did not remain a unique predictor in models with episodic memory (β=.015, p=.886), hippocampus (β=.040, p=.714) or $ptau_{181}/A\beta_{42}$ (β=.143, p=.086). Conversely, RL-Retrieval remained a significant predictor of CDR-SB progression when episodic memory (β=.377, p<.001), hippocampus (b=.464, p<.001) or $ptau_{181}/A\beta_{42}$ (β=.482, p<.001) were added to the model.

3.6 Diagnostic Accuracy

The AUCs for CM, RL and episodic memory were all significant (Figure 3; Table 4). The AUCs for CM and RL were not significantly different ($\chi 2=1.59$, $p=.207$). The AUC for RL was not significantly different than the AUC for episodic memory ($\chi 2=.91$, $p=.339$). There was a non-significant trend for the AUC for CM to be significantly higher than the AUC for memory ($\chi 2=3.67$, $p=.056$).

Chapter 4: Discussion

This longitudinal study examined whether tasks assessing the ability to form, retain and use a cognitive map or the ability to learn and retrieve a novel route predicted clinical progression. While a previous cross-sectional investigation observed a significant deficit in CM, but not RL, in individuals in the preclinical AD continuum (Allison et al., 2016), the current results indicated that both CM and RL were significant predictors of global CDR and CDR-SB progression. Furthermore, the prior work (Allison et al., 2016) found that the CM task evidenced significantly greater diagnostic accuracy than RL, whereas there was not a significant difference between the tasks in the current study. The differences across studies could in part relate to the inclusion of individuals with symptomatic AD in the present study as deficits in both CM and RL were observed in symptomatic AD at baseline (Allison et al., 2016; for reviews, see Coughlan et al., 2018; Lithfous et al., 2013). Thus, although CM tasks may be preferable for detecting preclinical AD cross-sectionally, when examining clinical progression using a group of individuals with varying levels of cognitive impairment (i.e., from clinical normality to symptomatic AD), baseline performance on either CM or RL tasks may serve to predict later progression of the disease.

Our findings are generally consistent with prior investigations examining the ability of spatial navigation tasks to predict clinical progression in clinically normal individuals, as well as those with MCI and symptomatic AD (Serino, Morganti, Colombo, & Riva, 2018; Verghese, Lipton, & Ayers, 2017; Wood et al., 2016; but see Weniger et al., 2011). Of note, these previous studies mainly utilized CM tasks for assessing spatial navigation, whereas the current study examined the ability of both CM and RL to predict progression. Not only did our tasks predict clinical

progression, but CM-Learning, CM-Retrieval and RL-Retrieval all predicted clinical progression with episodic memory included in the models. There was also a strong trend for overall CM performance to demonstrate greater diagnostic accuracy for CDR progression compared to episodic memory, which is consistent with prior findings demonstrating that CM was better than episodic memory at discriminating clinically normal from preclinical AD continuum individuals cross-sectionally (Allison et al., 2016). Additionally, when examining models only containing participants with CDR=0 at baseline, CM-Learning remained a significant predictor of clinical progression. Importantly, when episodic memory was added to this model, CM-Learning remained a significant predictor of clinical progression, but episodic memory did not. These findings together suggest that relative to standard psychometric tasks of memory, spatial navigation tasks, particularly CM tasks, could be useful indicators for risk of clinical progression, including during the preclinical phase.

While the CM task was a significant predictor of CDR-SB progression when hippocampal volume was added to the models, the CM task was not a unique predictor with CSF $ptau_{181}/A\beta_{42}$ in the models. Both measures interacted with hippocampal volume and with CSF $ptau_{181}/A\beta_{42}$ in predicting progression. Thus, individuals with deficits in CM, in addition to elevated AD pathology or reduced hippocampal volume, evidenced the greatest degree of clinical progression. In contrast, having only elevated AD pathology, reduced hippocampal volume or lower CM performance were each associated with slower progression over time. Thus, not only may CM measures be useful in prediction in isolation, but they may have added value when used in conjunction with hippocampal volume and/or AD biomarkers.

Regarding RL, retrieval phase performance did provide unique predictive value relative to hippocampal volume or CSF $ptau_{181}/A\beta_{42}$. Furthermore, it was a significant predictor of CDR-

SB progression, whereas episodic memory was not significant when both were in the same model. However, the learning phase was not a unique predictor in any of the models with the previously established predictors. There was some indication of a ceiling effect during the learning phase, which may have limited it as a predictor relative to other measures (20% with a score above 96%). Importantly, overall RL performance did not evidence significantly greater diagnostic accuracy compared to the episodic memory composite. The latter finding in particular does place limits on the utility of the current RL task compared to the CM task in predicting clinical progression. Furthermore, the psychometric properties of RL have yet to be established, whereas recent work has established strong psychometric properties of CM (Allison et al., accepted).

Limitations of this study include that there was an insufficient number of clinically normal individuals who converted to AD over the course of the study to fully examine whether spatial navigation measures predict conversion (i.e., n=7 of 81 for CM; n=6 of 50 for RL). In addition, the smaller size of the samples with both RL and either CSF or MRI precluded robust estimation of the 3-way interactions with time. Lastly, the sample consisted of highly educated individuals, which limits the generalizability of the results.

Collectively, current findings indicate that baseline CM and RL performance were associated with future clinical progression. These findings highlight the potential utility of spatial navigation tasks as assessment tools for identifying risk of progression to more advanced stages of dementia. Measures of CM may be particularly useful considering the evidence that these may be more powerful than standard episodic memory measures. Future work should examine whether the spatial navigation tasks predict conversion from the preclinical AD phase to symptomatic AD with a sufficiently large sample of converters. In addition, longitudinal

investigations of spatial navigation performance would be important in order to determine change over time in this critical skill.

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Tables and Figures

Table 1. Sample characteristics: cognitive mapping task

	Total Sample	*No Progression*	*Yes Progression*
N	95	78	17
Gender (M/F)	49/46	39/39	10/7
Age (years) (M, SD)*	72.10 (8.40)	70.60 (7.86)	78.94 (7.52)
Age range	50-90	50-85	66-90
Education (years) (M, SD)	16.57 (2.38)	16.40 (2.44)	17.19 (2.07)
Education (range)	12-21	12-21	13-20
Health Composite (M, SD)*	.77 (.82)	.67 (.77)	1.24 (.90)
Time in study (years) (M, SD)	4.16 (1.84)	4.11 (1.86)	4.04 (1.83)
Time in study (range)	1.02-7.07	1.19-7.07	1.02-7.02
Number CDR follow ups (M, SD)	4.40 (1.84)	4.35 (1.97)	5.00 (1.84)
Number CDR follow ups (range)	2-8	2-8	2-8
Episodic Memory (M, SD)	.04 (.86)	.13 (.69)	-.65 (1.09)
Hippocampus (cm^3) (N, M, SD)	74; 739 (111)	64; 759 (97)	10; 613 (114)
$ptau_{181}/A\beta_{42}$ (N, M, SD)	64; .026 (.022)	57; .023 (.019)	7; .049 (.031)

Notes. CDR=Clinical Dementia Rating scale; m=mean; sd=standard deviation. Time in study=years between baseline assessment and most recent CDR. At baseline, 81 participants were CDR=0, 10 were CDR=0.5, and 4 were CDR=1. Among the 17 decliners, 7 went from CDR=0 to CDR>0, 6 went from CDR=0.5 to CDR=1, 1 went from CDR=0.5 to CDR=2, 3 went from CDR=1 to CDR=2; *p<.05 difference between no progression and yes progression groups. N=67 from Allison et al., 2016; N=28 from Allison et al., accepted). Participants had CSF (M=.87, range=-1.97-1.68) and MRI (M=.90, range=-2.00-1.99) collection within 2 years of the cognitive mapping condition and memory assessment within 1.02 years (M=.47, range=.101-1.02).

Table 2. Sample characteristics: route learning task

	Total Sample	*No Progression*	*Yes Progression*
N	65	48	17
Gender (M/F)	32/33	21/27	11/6
Age (years) (M, SD)*	71.98 (9.35)	69.60 (8.82)	78.71 (7.48)
Age (range)	50-90	50-85	66-90
Education (years) (M, SD)	16.35 (2.38)	16.04 (2.41)	17.31 (2.09)
Education range	12-20	12-20	12-20
Health Composite (M, SD)*	.85 (.85)	.69 (.80)	1.29 (.85)
Time in study (years) (M, SD)*	4.95 (1.60)	5.26 (1.37)	4.06 (1.91)
Time in study (range)	1.02-7.07	1.19-7.07	1.02-7.07
Number CDR follow ups (M, SD)	5.00 (1.83)	5.19 (1.72)	4.47 (2.07)
Number CDR follow ups (range)	2-8	2-8	2-8
Episodic Memory (M, SD)*	-.03 (.88)	.19 (.72)	-.65 (.99)
Hippocampus (cm^3) (N, M, SD)*	49; 725 (131)	38; 763 (106)	11; 593 (127)
$ptau_{181}/A\beta_{42}$ ratio (N, M, SD)	41; .023 (.018)	34; .018 (.011)	7; .044 (.028)

Notes. CDR=Clinical Dementia Rating Scale; M=mean; SD=standard deviation. Time in study=years between baseline assessment and most recent CDR. At baseline, 50 participants were CDR=0, 10 were CDR=0.5, and 5 were CDR=1. Among the 17 decliners, 6 went from CDR=0 to CDR>0, 6 went from CDR=0.5 to CDR=1, 1 went from CDR=.5 to CDR=2, 4 went from CDR=1 to CDR=2; *p<.05 difference between no progression and yes progression groups. N=65 from Allison et al., 2016). Participants had CSF (M=.72, range=-1.97-1.66) and MRI (M=.90, range=-2.15-2.03) collection within 2.15 years of the route learning condition and memory assessment within 1 year (M=.42, range=.11-.92).

Table 3. Sample characteristics: cognitive mapping task with CDR=0 at baseline

	Total Sample	*No Conversion*	*Yes Conversion*
N	81	74	7
Gender (M/F)	40/41	37/37	3/4
Age (years) (M, SD)*	71.11 (7.73)	70.43 (7.59)	78.29 (5.47)
Age range	50-84	50-84	70-84
Education (years) (M, SD)	16.59 (2.40)	16.53 (2.41)	17.21 (2.38)
Education (range)	12-21	12-21	13-20
Health Composite (M, SD)*	.72 (.81)	.65 (.77)	1.43 (.98)
Time in study (years) (M, SD)	4.35 (1.84)	4.24(1.85)	5.48 (1.49)
Time in study (range)	1.33-7.07	1.33-7.07	3.05-7.02
Number CDR follow ups (M, SD)	4.54 (1.86)	4.45 (1.81)	5.57 (2.23)
Number CDR follow ups (range)	2-8	2-8	2-8
Episodic Memory (M, SD)	-.18 (.63)	-.20 (.60)	.01 (.89)
Hippocampus (cm^3) (N, M, SD)	68; 756 (92)	63; 760 (87)	5; 711 (138)
$ptau_{181}/A\beta_{42}$ (N, M, SD)	62; .025 (.02)	57; .023 (.019)	5; .046 (.030)

Notes. CDR=Clinical Dementia Rating scale; m=mean; sd=standard deviation. Time in study=years between baseline assessment and most recent CDR. Among the 7 converters, 2 went from CDR=0 to CDR=.5, 3 went from CDR=0 to CDR=1, and 2 went from CDR=0 to CDR=2; *p<.05 difference between no conversion and yes conversion groups. N=53 from Allison et al., 2016; N=28 from Allison et al., accepted). Participants had CSF (M=.87, range=-1.97-1.68) and MRI (M=.92, range=-2.00-1.99) collection within 2 years of the cognitive mapping condition and memory assessment within 1.02 years (M=.48, range=.101-1.02).

Table 4. ROC analyses

	Cognitive Mapping	*Route Learning*	*Memory*
AUC (SE)	.894 (.041)	.794 (.067)	.735 (.080)
p-value	<.001	.001	.006
Youden Index	.687	.517	.496
Sensitivity	1.00	.600	.600
Specificity	.687	.917	.896

Notes. AUC=area under the curve; SE=standard error.

Figure 1. Cognitive Mapping and Route Learning Linear Mixed Effects Models

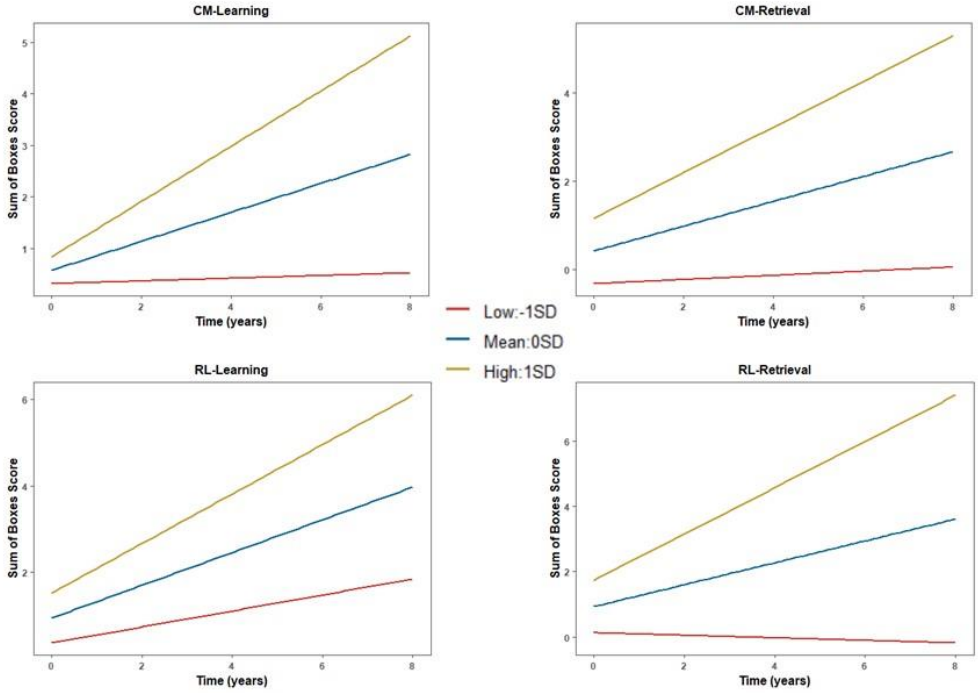

Figure 1. Relationship between spatial navigation tasks and CDR-SB change over time. Plots depict tertiles for illustration purposes. Analyses were conducted with continuous variables.

Figure 2. Cognitive Mapping Three-Way Interactions

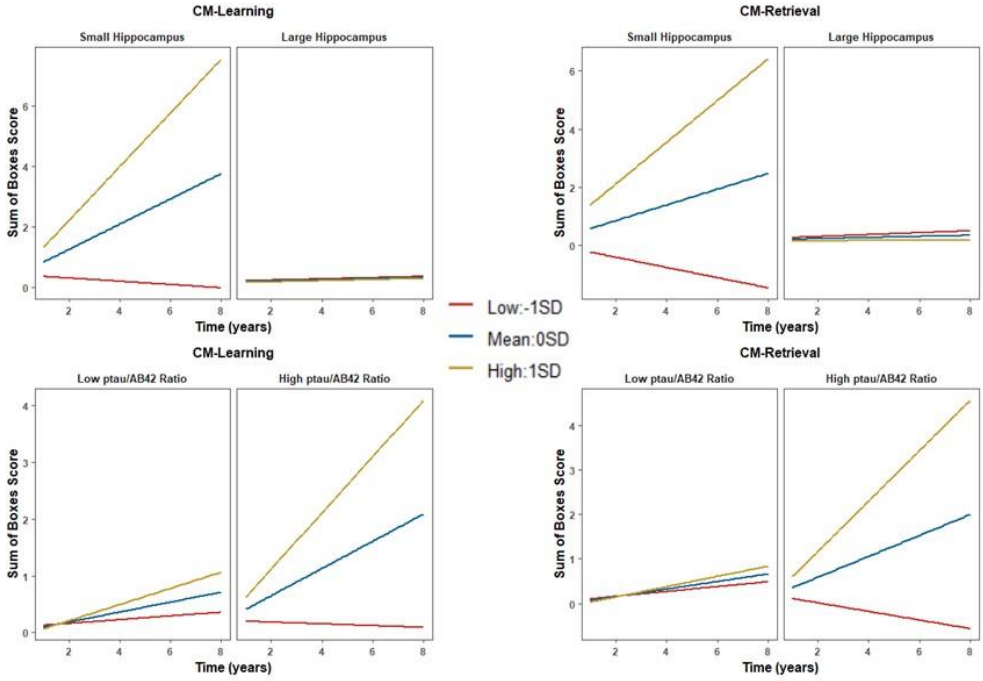

Figure 2. Interactive effects with the cognitive mapping task. Plots depict tertiles for illustration purposes. Analyses were conducted with continuous variables. $ptau_{181}/A\beta_{42}$ results are from analyses without outliers included.

Figure 3. ROC Curves

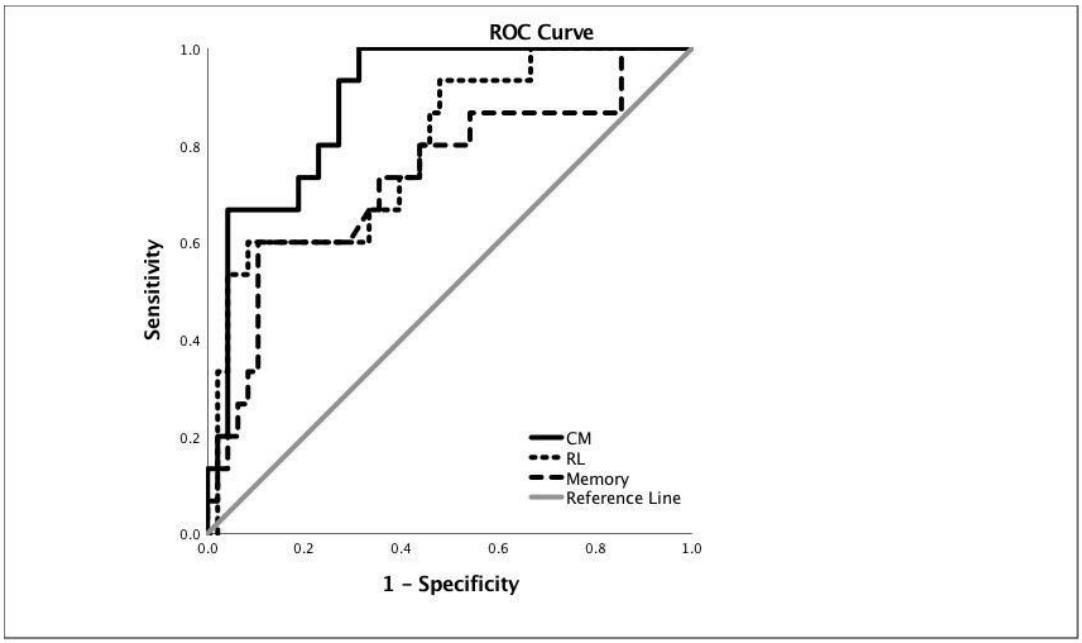

Figure 3. ROC curves for cognitive mapping, route learning and episodic memory tasks.

Supplementary Table 1. Logistic regression results: cognitive mapping task

	Odds Ratio	95% CI	*p*
	Base Model		
Age	3.799	1.435-10.059	.007
Gender	1.187	.281-5.009	.815
Education	1.590	.761-3.321	.217
Health	1.458	.784-2.712	.234
CM-Learning	3.131	1.376-7.123	.007
	Episodic Memory Model		
Age	4.177	1.278-13.658	.018
Gender	2.925	.490-17.473	.239
Education	1.988	.803-4.921	.137
Health	1.771	.820-3.824	.146
CM-Learning	2.591	1.007-6.667	.048
Memory	3.555	1.535-8.233	.003
	Base Model		
Age	5.297	1.690-16.603	.004
Gender	1.944	.440-8.590	.380
Education	2.136	.936-4.872	.071
Health	1.624	.861-3.063	.134
CM-Retrieval	2.950	1.444-6.024	.003
	Episodic Memory Model		
Age	5.191	1.464-18.411	.011
Gender	4.511	.703-28.964	.112
Education	2.730	.998-7.465	.050
Health	2.110	.975-4.565	.058
CM-Retrieval	2.409	1.104-5.257	.027
Memory	3.535	1.499-8.332	<.001

Supplementary Table 2. Linear mixed model results: cognitive mapping - learning phase

	Beta	*t*	*p*
	Base Model		
Age	.491	2.276	.025
Gender	-.146	-.383	.703
Education	-.146	-.768	.444
Health	-.304	-1.504	.136
Time	.290	4.125	<.001
CM-Learning	.260	1.296	.198
Time x CM-Learning	.266	3.635	<.001
	CSF $ptau_{181}/A\beta_{42}$ Ratio Model		
Age	.129	.730	.468
Gender	-.208	-.764	.448
Education	.075	.580	.564
Health	-.105	-.683	.497
Time	.220	2.774	.006
CM-Learning	-.077	-.408	.685
$ptau_{181}/A\beta_{42}$	-.054	-.315	.754
CM-Learning x $ptau_{181}/A\beta_{42}$	-.102	-.697	.489
Time x CM-Learning	.122	1.296	.197
Time x $ptau_{181}/A\beta_{42}$	.281	3.186	.002
Time x $ptau_{181}/ A\beta_{42}$ x CM-Learning	.110	1.304	.194
	Hippocampal Volume Model		
Age	.047	.240	.811
Gender	-.319	-1.210	.231
Education	-.023	-.175	.861
Health	-.037	-.274	.785
Time	.237	3.393	<.001
CM-Learning	-.092	-.552	.583
Hippocampus	-.448	-2.719	.008
CM-Learning x Hippocampus	-.034	-.220	.826
Time x CM- Learning	.236	2.963	.004
Time x Hippocampus	-.335	-4.687	<.001
Time x Hippocampus x CM-Learning	-.276	-4.185	<.001
	Episodic Memory Model		
Age	.566	3.084	.003
Gender	.485	1.440	.154
Education	-.051	-.313	.755
Health	-.102	-.595	.554
Time	.280	4.166	<.001

CM-Learning	-.087	-.473	.637
Memory	1.158	5.710	<.001
Time x CM-Learning	.216	2.982	.003
Time x CM-Memory	.228	2.760	.006

Supplementary Table 3. Linear mixed model results: cognitive mapping - retrieval phase

	Beta	*t*	*p*
	Base Model		
Age	.474	2.472	.015
Gender	.092	.267	.790
Education	-.078	-.469	.640
Health	-.265	-1.480	.143
Time	.290	4.042	<.001
CM-Retrieval	.793	4.582	<.001
Time x CM- Retrieval	.250	3.215	.002
	CSF $ptau_{181}/A\beta_{42}$ Ratio Model		
Age	.152	.864	.392
Gender	-.249	-.894	.375
Education	.086	.675	.502
Health	-.080	-.529	.599
Time	.193	2.147	.033
CM- Retrieval	-.027	-.110	.913
$ptau_{181}/A\beta_{42}$	-.169	-.778	.440
$ptau_{181}/A\beta_{42}$ x CM-Retrieval	.059	.246	.807
Time x CM-Retrieval	.123	.901	.369
Time x $ptau_{181}/A\beta_{42}$	.240	2.120	.036
Time x $ptau_{181}/A\beta_{42}$ x CM-Retrieval	.176	1.316	.190
	Hippocampal Volume Model		
Age	.110	.630	.531
Gender	-.268	-1.145	.256
Education	.006	.052	.959
Health	-.042	-.357	.722
Time	.194	2.550	.012
CM-Retrieval	.106	.573	.569
Hippocampus	-.371	-2.323	.023
CM-Retrieval x Hippocampus	-.360	-2.164	.034
Time x CM-Retrieval	.233	2.150	.033
Time x Hippocampus	-.277	-3.541	<.001
Time x Hippocampus x CM-Retrieval	-.270	-3.118	.002
	Episodic Memory Model		
Age	.517	3.140	.002
Gender	.605	1.995	.049
Education	-.028	-.197	.845
Health	-.089	-.575	.567

Time	.281	4.075	<.001
CM- Retrieval	.525	3.116	.003
Memory	.947	4.892	<.001
Time x CM-Retrieval	.184	2.320	.021
Time x CM-Memory	.220	2.558	.011

Supplementary Table 4. Linear mixed model results: cognitive mapping – $ptau_{181}/A\beta_{42}$ without outliers

	Beta	*t*	*p*
CSF $ptau_{181}/A\beta_{42}$ Ratio Model – CM-Learning			
Age	.127	.724	.472
Gender	-.158	-.576	.567
Education	.044	.332	.741
Health	-.091	-.590	.557
Time	.212	2.895	.004
CM-Learning	-.054	-.279	.781
$ptau_{181}/A\beta_{42}$	-.070	-.404	.688
$ptau_{181}/A\beta_{42}$ x CM-Learning	-.116	-.564	.575
Time x CM-Learning	.145	1.672	.097
Time x $ptau_{181}/A\beta_{42}$	.324	3.957	<.001
Time x $ptau_{181}/A\beta_{42}$ x CM-Learning	.309	3.322	.001
CSF $ptau_{181}/A\beta_{42}$ Ratio Model – CM-Retrieval			
Age	.152	.876	.385
Gender	-.188	-.672	.505
Education	.080	.632	.530
Health	-.010	-.065	.948
Time	.176	2.052	.042
CM-Retrieval	-.012	-.048	.962
$ptau_{181}/A\beta_{42}$	-.170	-.767	.446
$ptau_{181}/A\beta_{42}$ x CM-Retrieval	.088	.312	.756
Time x CM-Retrieval	.165	1.259	.210
Time x $ptau_{181}/A\beta_{42}$	.248	2.310	.022
Time x $ptau_{181}/A\beta_{42}$ x CM-Retrieval	.355	2.527	.013

Supplementary Table 5. Linear mixed model results: CDR=0 at baseline, CM-Learning

	Beta	*t*	*p*
	Base Model		
Age	.094	1.393	.168
Gender	.036	.405	.687
Education	-.074	-1.711	.091
Health	-.094	-2.039	.045
Time	.164	2.635	.009
CM-Learning	-.103	-1.204	.233
Time x CM-Learning	.155	2.275	.024
	CSF $ptau_{181}$/ $A\beta_{42}$ Ratio Model		
Age	.058	.697	.489
Gender	.025	.243	.809
Education	-.078	-1.581	.120
Health	-.115	-1.977	.053
Time	.198	2.729	.007
CM-Learning	-.103	-.920	.362
$ptau_{181}$/$A\beta_{42}$	-.125	-1.247	.218
Time x CM-Learning	.105	1.226	.222
Time x $ptau_{181}$/$A\beta_{42}$	.244	2.930	.004
	Hippocampal Volume Model		
Age	.084	1.007	.318
Gender	.050	.507	.614
Education	-.096	-1.874	.066
Health	-.101	-1.951	.056
Time	.180	2.538	.012
CM-Learning	-.046	-.447	.657
Hippocampus	.163	1.445	.154
Time x CM-Learning	.101	1.270	.206
Time x Hippocampus	-.185	-2.263	.025
	Episodic Memory Model		
Age	.106	1.579	.119
Gender	.076	.825	.412
Education	-.076	-1.754	.084
Health	-.083	-1.806	.075
Time	.169	2.607	.010
CM-Learning	-.117	-1.313	.193
Memory	.082	.633	.529
Time x CM-Learning	.151	2.165	.032
Time x CM-Memory	.026	.263	.793

Supplementary Table 6. Linear mixed model results: CDR=0 at baseline, CM-Retrieval

	Beta	*t*	*p*
	Base Model		
Age	.098	1.502	.137
Gender	.063	.732	.467
Education	-.070	-1.702	.093
Health	-.086	-1.934	.057
Time	.165	2.491	.014
CM-Retrieval	-.007	-.059	.953
Time x CM- Retrieval	.121	1.298	.196

Supplementary Table 7. Logistic regression results: route learning task

	Odds Ratio	*95% CI*	*p*
	Base Model		
Age	5.439	1.705-17.349	.004
Gender	1.389	.266-7.258	.697
Education	2.578	1.072-6.204	.034
Health	1.439	.666-3.109	.355
RL-Learning	3.293	1.307-8.298	.011
	Episodic Memory Model		
Age	5.101	1.401-18.571	.013
Gender	5.015	.535-46.987	.158
Education	3.536	1.247-10.029	.018
Health	1.904	.754-4.803	.173
RL-Learning	1.911	.631-5.792	.252
Memory	4.104	1.223-13.772	.022
	Base Model		
Age	9.614	1.965-47.040	.005
Gender	1.557	.246-9.875	.638
Education	3.677	1.157-11.682	.027
Health	1.762	.673-4.612	.249
RL-Retrieval	6.301	1.941-20.461	.002
	Episodic Memory Model		
Age	12.684	1.892-85.018	.009
Gender	7.632	.474-123.011	.152
Education	4.862	1.398-16.909	.013
Health	2.399	.748-7.699	.141
RL-Retrieval	4.781	1.341-17.045	.016
Memory	3.904	.946-16.117	.060

Supplementary Table 8. Linear mixed model results: route learning – learning phase

	Beta	*t*	*p*
	Base Model		
Age	.671	2.303	.025
Gender	-.378	-.759	.451
Education	-.274	-1.167	.248
Health	-.652	-2.401	.020
Time	.387	4.228	<.001
RL-Learning	.602	2.356	.022
Time x RL-Learning	.202	2.159	.032
	CSF $ptau_{181}/A\beta_{42}$ Ratio Model		
Age	.049	.184	.855
Gender	-.406	-1.069	.293
Education	.113	.616	.542
Health	-.205	-.910	.369
Time	.264	3.465	<.001
RL-Learning	.398	1.912	.064
$ptau_{181}/A\beta_{42}$	-.139	-.690	.495
Time x RL-Learning	.143	1.730	.086
Time x $ptau_{181}/A\beta_{42}$	.408	5.229	<.001
	Hippocampal Volume Model		
Age	-.123	-.429	.670
Gender	-.478	-1.222	.228
Education	-.141	-.737	.465
Health	-.397	-1.835	.074
Time	.354	3.779	<.001
RL-Learning	.374	1.775	.083
Hippocampus	-.837	-3.265	.002
Time x RL-Learning	.040	.367	.714
Time x Hippocampus	-.464	-4.108	<.001
	Episodic Memory Model		
Age	.774	3.158	.003
Gender	.556	1.192	.238
Education	-.115	-.573	.569
Health	-.402	-1.728	.089
Time	.370	4.353	<.001
RL-Learning	-.205	-.828	.411
Memory	-1.719	-5.695	<.001
Time x RL-Learning	.015	.143	.886
Time x Memory	.388	2.993	.0031

Supplementary Table 9. Linear mixed model results: route learning – retrieval phase

	Beta	*t*	*p*
	Base Model		
Age	.975	3.623	<.001
Gender	-.489	-1.022	.311
Education	-.193	-.857	.395
Health	-.670	-2.569	.013
Time	.382	5.182	<.001
RL-Retrieval	1.004	4.142	<.001
Time x RL-Retrieval	.467	5.230	<.001
	CSF $ptau_{181}/A\beta_{42}$ Ratio Model		
Age	-.020	-.071	.944
Gender	-.335	-.804	.427
Education	.143	.735	.467
Health	-.219	-.905	.372
Time	.346	4.890	<.001
RL-Retrieval	.075	.197	.845
$ptau_{181}/A\beta_{42}$	-.067	-.321	.750
Time x RL-Retrieval	.482	4.033	<.001
Time x $ptau_{181}/A\beta_{42}$	.374	5.444	<.001
	Hippocampal Volume Model		
Age	-.117	-.402	.690
Gender	-.635	-1.602	.117
Education	-.134	-.686	.497
Health	-.440	-1.967	.056
Time	.383	4.708	<.001
RL-Retrieval	.284	1.014	.316
Hippocampus	-.901	-3.363	.002
Time x RL-Retrieval	.464	3.737	<.001
Time x Hippocampus	-.286	-2.830	.005
	Episodic Memory Model		
Age	.951	4.027	<.002
Gender	.358	.779	.439
Education	-.088	-.445	.658
Health	-.440	-1.900	.063
Time	.376	5.120	<.001
RL-Retrieval	.443	1.741	.087
Memory	1.253	4.311	<.001
Time x RL-Retrieval	.377	3.693	<.001
Time x RL-Memory	.166	1.593	.113