Title: Neurodegeneration, Alzheimer's disease biomarkers, and longitudinal verbal learning and memory performance in late middle age.

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Abstract

This study examined the effect of neurodegeneration, and its interaction with Alzheimer's disease (AD) cerebrospinal fluid biomarkers, on longitudinal verbal learning and memory performance in cognitively unimpaired (CU) late middle-aged adults. Three hundred and forty-two CU adults (cognitive baseline mean age = 58.4), with cerebrospinal fluid and structural MRI, completed 2-10 (median = 5) cognitive assessments. Learning and memory were assessed using the Rey Auditory Verbal Learning Test (RAVLT). We used sequential comparison of nested linear mixed effects models to analyze the data. Model selection preserved a significant ptau181/Aβ42 × global atrophy × age interaction; individuals with less global atrophy and lower ptau181/Aβ42 levels had less learning and delayed recall decline than individuals with more global atrophy and/or higher levels of ptau181/Aβ42. The hippocampal volume × age × ptau181/Aβ42 interaction was not significant. Findings suggest that in a sample of CU late middle-aged adults, individuals with AD biomarkers, global atrophy, or both evidence greater verbal learning and memory decline than individuals without either risk factor.

1. Introduction

Considering that Alzheimer's disease (AD)-related pathological changes occur long

before the development of clinical symptoms (Price et al., 2009; Price & Morris, 1999),

biomarkers capable of measuring AD pathophysiology *in vivo* are necessary for examining the pre-symptomatic phase of the disease. Two classes of biomarkers shown to be sensitive and specific to AD are those reflecting beta-amyloid deposition and the formation of neurofibrillary tangles (NFTs) (Betthauser et al., 2018; Betthauser et al., 2019; Brier et al., 2016; Jack et al., 2018; Klunk et al., 2004; Roe et al., 2013; Strozyk, Blennow, White, & Launer, 2003; Tapiola et al., 2009; Villemagne, Doré, Burnham, Masters, & Rowe, 2018). Several studies also focus on measures of neurodegeneration as another category of biomarkers important for defining abnormal pathophysiology across the AD spectrum, particularly during preclinical AD (Jack et al., 2018, 2016, 2015; Vos et al., 2016).

A number of methods exist for detecting neurodegeneration *in vivo*, including MRI-based morphometric estimates. In terms of the specific brain regions impacted early during the course of AD, previous cross-sectional and longitudinal structural MRI studies indicate that individuals in the preclinical phase possess greater atrophy in a number of regions, including the medial temporal lobe (e.g., entorhinal cortex and hippocampus), anterior cingulate, posterior cingulate/precuneus, and inferior parietal lobe (Chételat et al., 2012, 2010; Frisoni, Fox, Jack, Scheltens, & Thompson, 2010; Pettigrew et al., 2017; Storandt, Mintun, Head, & Morris, 2009; Susanto, Pua, & Zhou, 2015; Tondelli et al., 2012; Wang et al., 2015). There is also some evidence from cross-sectional and longitudinal research to suggest that individuals with preclinical AD have greater whole brain atrophy (Allison et al., in press; Fagan et al., 2009; Fotenos et al., 2008; Fox, Warrington, & Rossor, 1999; Schott, Bartlett, Fox, & Barnes, 2010).

Unlike biomarkers reflecting beta-amyloid deposition and the formation of NFTs, measures of brain atrophy are sensitive, but not necessarily specific to AD. For example, individuals who have suffered anoxic brain injury, those with dementia due to Lewy

bodies (DLB) or Parkinson's disease, and those with hippocampal sclerosis demonstrate hippocampal atrophy (Barber et al., 1999; Camicioli et al., 2003; Di Paola et al., 2008; Jack et al., 2002). Furthermore, schizophrenia and frontotemporal lobar degeneration are both associated with atrophy in the anterior cingulate (Baiano et al., 2007; Rosen et al., 2002), and previous research indicates that atrophy of the precuneus is found in DLB and posterior cortical atrophy (Burton et al., 2002; Lehmann et al., 2011). These findings indicate that measures of neurodegeneration may reflect neuronal loss due to a number of different etiologies, one of which may be AD. Despite this lack of specificity, prior work suggests that the use of abnormal MRI markers of neurodegeneration, in combination with biomarkers reflecting beta-amyloid deposition and NFTs, improves the prediction of future cognitive decline and progression to a clinical diagnosis of dementia due to probable AD in individuals with preclinical AD and mild cognitive impairment (MCI) at baseline (Aschenbrenner, Gordon, Benzinger, Morris, & Hassenstab, 2018; Bouwman et al., 2007; Davatzikos, Bhatt, Shaw, Batmanghelich, & Trojanowski, 2011; Jack et al., 2017; Soldan et al., 2019; van Maurik et al., 2017; van Rossum et al., 2012; Vemuri et al., 2009). These results highlight the need to incorporate measures of neurodegeneration when examining cognitive decline in preclinical and prodromal AD.

Previous work by our group suggests that individuals with preclinical AD demonstrate greater verbal learning and memory decline than late middle-aged adults without evidence of AD pathophysiology (defined using biomarkers of beta-amyloid deposition) (Clark et al., 2018); however, less is known about the relationship between measures of neurodegeneration and verbal learning and memory decline in this group. Therefore, the purpose of this study was to examine the effect of neurodegeneration, and its interaction with AD pathophysiology as indexed by CSF biomarkers, on longitudinal verbal learning and memory performance in late middle age.

We defined neurodegeneration using estimates of hippocampal volume and global atrophy based on recent work by our group suggesting that these two MRI-based metrics are automated, robust, and computationally efficient for defining neurodegeneration across the AD continuum (Allison et al., 2019). We hypothesized that hippocampal and global atrophy would be related to declines in both verbal learning and memory performance, and that individuals with atrophy on structural MRI and abnormal AD biomarkers (low CSF levels of $A\beta_{42}/A\beta_{40}$, high levels of $ptau_{181}/A\beta_{42}$ or $ptau_{181}$) would evidence the greatest amount of decline on these cognitive measures.

2. Methods

2.1 Participants.

Participants included 342 late middle-aged and older adults (see Table 1 for demographic information) from the Wisconsin Registry for Alzheimer's disease Prevention (WRAP) or the Wisconsin Alzheimer's Disease Research Center (WADRC). These cohorts consist of participants enriched with a parental family history of AD (Johnson et al., 2018). Participants from WRAP and WADRC complete a baseline cognitive assessment. For the WRAP participants, a second cognitive assessment occurs four years after the baseline evaluation, and then subsequent visits occur every two years. The WADRC participants complete annual or biennial cognitive assessments. Participants in the current study completed a median of 5 (range=2-10) cognitive assessments.

To qualify for the current analysis, participants needed to have at least one structural MRI scan and one visit in which CSF levels of $ptau_{181}$, $A\beta_{42}$, and $A\beta_{40}$ were collected within 1.5 years of each other. All participants also needed to be classified as cognitively unimpaired at baseline (i.e., no clinical diagnosis of dementia or MCI) based on the National Institute on Aging-Alzheimer's Association's consensus conference criteria (Albert et al., 2011; McKhann et al.,

2011) by a team of clinicians (neuropsychologists, physician dementia specialists, and nurse

practitioners) blind to biomarker data (e.g., PET or CSF data). Exclusion criteria included

completion of only one study visit, as well as a history of neurological conditions (e.g., multiple

sclerosis, stroke/TIA, Parkinson's disease, epilepsy) or a significant psychiatric condition (e.g.,

bipolar disorder or schizophrenia). The inclusion of human participants was supported by the

University of Wisconsin-Madison Institutional Review Board. All participants provided

informed consent for this study.

2.2 Structural MRI.

MRI images were acquired in one scanning session using two identical GE 3.0 Tesla

MR750 scanners (Waukesha, WI, USA) with an 8-channel head coil (Excite HD Brain Coil; GE

Healthcare). T1-weighted brain volumes were acquired in the axial plane with a 3-D inversion-

recovery prepared fast spoiled gradient-echo sequence using the following parameters: inversion

time (TI) = 450 ms; repetition time (TR) = 8.2 ms; echo time (TE) = 3.2 ms; flip angle = 12°;

acquisition matrix = $256 \times 256 \times 156$ mm; field of view (FOV) = 256 mm; slice thickness = 1.0

mm. Additionally, 14 subjects were scanned with the same parameters, except TR = 8.1 ms.

Finally, 1 subject was scanned with a shorter sequence that was less susceptible to motion

artifacts, after it was determined their first scan would likely be unusable. The shorter sequence

parameters were: TI = 450 ms; TR = 6.0 ms; TE = 2.2 ms; flip angle = 12°; acquisition matrix =

256 x 256 x 130 mm; FOV = 256 mm; slice thickness = 1.2 mm. Cushions helped reduce head

movement during scanning. A radiologist (H.A.R.) reviewed all scans for abnormalities.

Measures of neurodegeneration included global brain atrophy and hippocampal volume.

An estimate of global brain atrophy (i.e., CSF/(total gray + total white matter volumes)) was

derived from the T1-weighted IRSPGR sequence by segmenting tissue types into CSF, as well as

gray and white matter volumes, using SPM12 (www.fil.ion.ucl.ac.uk/spm). Hippocampal volume

was calculated using FSL-FIRST (Patenaude, Smith, Kennedy, & Jenkinson, 2011), and

corrected for intracranial volume (ICV) derived using the reverse brain mask method in SPM12

(i.e., hippocampal volume/ICV) (Keihaninejad et al., 2010). One image failed based on visual

inspection of the images by S.L.A. Structural MRI data were collected, on average, 3.28 years

(SD=3.67 years) from the baseline cognitive assessment. Other information about the relative

timing of the assessments is located in Table 1.

2.3 Cerebrospinal fluid levels of Alzheimer's disease biomarkers.

CSF levels of $A\beta_{42}$ and $ptau_{181}$ were obtained via a lumbar puncture in which twenty-two

mL of CSF were removed from the L3-L4 or L4-L5 vertebral interspace. CSF samples (sent in

batches at two time points) were analyzed at the Clinical Neurochemistry Laboratory at the

Sahlgrenska Academy of the University of Gothenburg, Sweden using commercially available

enzyme-linked immunosorbent assay methods (INNOTEST assays, Fujirebio, Ghent, Belgium;

Triplex assays, MSD Human $A\beta$ peptide ultra-sensitive kit, Meso Scale Discovery, Gaithersburg,

MD). CSF samples were assayed for $A\beta_{42}$ and $ptau_{181}$. Because of widely reported batch effects

in analysis of CSF data (CITE), analyte values from the second batch were converted to the

space of the first batch based on generalized linear models. Details of this modeling process are

reported elsewhere (CITE).

2.4 Cognitive assessment.

We utilized the learning and delayed recall phases from the Rey Auditory Verbal

Learning Test (RAVLT) (Rey, 1941) on the basis of prior meta-analyses demonstrating a

significant relationship between measures of learning and memory and AD biomarkers

(Bäckman, Jones, Berger, Laukka, & Small, 2005; Baker et al., 2017; Han, Nguyen, Stricker, &

Nation, 2017; Hedden, Oh, Younger, & Patel, 2013), along with the fact that these measures were available at all study visits for both the WRAP and WADRC participants. Learning performance was defined as the number of words recalled across trials 1-5 (Total: 0-75). Delayed recall performance was defined as the number of words recalled after a thirty-minute delay (Total: 0-15).

2.5 Statistical analyses.

Statistical analyses were conducted in R version 3.4.4 (R Core Team, 2017) using the lmerTest package (Kuznetsova, Brockhoff, & Christensen, 2017), which uses the Satterthwaite approximation to compute degrees of freedom. We used sequential comparison of nested linear mixed effects models to test our hypotheses that hippocampal or global atrophy would be related to declines in RAVLT learning and memory outcomes, and that those with atrophy on structural MRI and abnormal CSF biomarkers would evidence the greatest RAVLT declines. Maximum likelihood estimation was used for model fitting. The predictors (i.e., neurodegeneration measures and CSF biomarkers) were standardized (unadjusted z-scored) prior to conducting analyses. Higher CSF levels of $ptau_{181}/A\beta_{42}$ reflect a greater degree of AD-related pathophysiology, whereas higher global atrophy and smaller hippocampi are indicative of structural changes linked to aging and disease (Jack et al., 2018). For each outcome (RAVLT verbal learning or delayed recall), the full model included: random intercept and age-related slopes; fixed effects covariates of sex, years of education, and prior exposure to the cognitive battery ("practice", visit number – 1, coded categorically); and hypothesis-related fixed effects of interest including age (centered at the mean baseline age), $ptau_{181}/A\beta_{42}$, hippocampal volume, global atrophy, and interactions between $ptau_{181}/A\beta_{42}$, each brain measure, and age. A preliminary analysis treated outcome (learning vs recall) as a fourth interacting variable to test

whether the effects of any predictors differed meaningfully between the two outcomes; following a significant four-way interaction between outcome variable, $ptau_{181}/A\beta_{42}$, hippocampal volume, and age, the two were outcomes separately (Supplementary Table S1). The four-way interaction was not significant for global atrophy.

Model selection was performed as follows. First, the relative contribution of age and practice on longitudinal trajectories was considered by comparing four simple models: linear age, no practice; quadratic age, no practice; linear age plus practice; and quadratic age plus practice. After this, the effects of the predictors of interest were examined by comparing a fully saturated model to smaller nested models on the basis of Akaike's information criterion (AIC), and in the case of ties, the Bayesian information criterion (Schwarz, 1978). The saturated model (with all interactions of interest) was run first and compared to a model with all of the two-way interactions. If the smaller model improved the fit, two-way interaction terms were removed by order of decreasing p-value until removing further terms did not improve model fit. All main effect terms were retained. If the AICs were the same for the compared models, the model with the lower Bayesian information criterion was selected (BIC).

2.5.2 Hypothesis tests. Reported p-values represent nominal probability under the null hypothesis. No adjustments were made for multiplicity due to model selection or incorporation of reviewer-suggested changes.

3. Results

3.1 Primary analysis: The effects of CSF $ptau_{181}/A\beta_{42}$, global atrophy, and hippocampal volume on RAVLT learning and delayed recall. The initial mixed effects model treating cognitive outcome as a fixed effect resulted in a significant four-way interaction, indicating that the three-way interaction between $ptau_{181}/A\beta_{42}$, hippocampal volume, and age differed for the

learning and delayed recall outcomes. Model fit statistics are displayed in Table 2. Therefore, follow-up models were fit separately for these two outcomes.

3.1.1. RAVLT Learning: Model selection preserved a significant $ptau_{181}/A\beta_{42} \times$ global atrophy $\times$ age interaction, indicating that age trajectories in RAVLT learning depended both on CSF markers of AD and on global atrophy. A significant hippocampal volume $\times$ age interaction was also retained. Simple slopes for three levels each of global atrophy (columns), hippocampal volume (rows), and $ptau_{181}/A\beta_{42}$ (lines) are plotted in Figure 1. Briefly, the deleterious effect of $ptau_{181}/A\beta_{42}$ is most pronounced in those with larger global brain volumes (i.e., lower levels of global atrophy; left column of panels), whereas those with higher levels of atrophy evidence similar decline regardless of $ptau_{181}/A\beta_{42}$. Those with larger hippocampal volumes (bottom row of panels) showed slightly less steep age-related cognitive decline than those with smaller hippocampal volumes (top row of panels). Model parameters and fit statistics are displayed in Table 3A-B.

3.1.2. RAVLT Delayed Recall: In the initial model fit, the two highest-order interactions had p-values < .10; therefore, no further selection was performed. Results suggested both a significant $ptau_{181}/A\beta_{42} \times$ global atrophy $\times$ age interaction, indicating that age trajectories in RAVLT delayed recall depended both on CSF markers of AD and on global atrophy, and a nonsignificant $ptau_{181}/A\beta_{42} \times$ hippocampal volume $\times$ age interaction, indicating a weaker dependence between these variables. Simple slopes for three levels each of global atrophy (columns), hippocampal volume (rows), and $ptau_{181}/A\beta_{42}$ (lines) are plotted in Figure 1. Briefly, the deleterious effect of $ptau_{181}/A\beta_{42}$ is most pronounced in those with lower levels of global atrophy (left column of panels), and to a weaker degree, those with smaller hippocampal volumes (top row of panels). Model parameters are displayed in Table 4.

4. Discussion

The current study examined the effect of neurodegeneration (as assessed with volumetric indices of hippocampal volume and global atrophy) and its interaction with CSF AD biomarkers on longitudinal verbal learning and memory performance in late middle age. Previous research by our group indicates that CU late middle-aged individuals with evidence of beta-amyloid deposition (defined using available PET and/or CSF data) exhibit greater rates of decline on tasks of verbal learning and memory than their counterparts without biomarker evidence of AD (Clark et al., 2018), which is consistent with the larger literature examining these relationships in older adults (Bäckman et al., 2005; Baker et al., 2017; Han et al., 2017; Hedden et al., 2013). Of note, our prior study found that amyloid deposition was associated with greater rates of cognitive decline regardless of whether individuals also had elevated levels of CSF tau.

The present study adds to our prior work by demonstrating that the deleterious effects of AD-related pathophysiology (i.e., higher levels of CSF $ptau_{181}/A\beta_{42}$) on verbal learning and memory performance depend on the degree of global atrophy present. More specifically, individuals with a greater degree of global atrophy evidenced similar rates of decline regardless of the degree of AD pathophysiology present. In contrast, in individuals with larger global brain volumes, the presence of preclinical Alzheimer's disease was associated with steeper declines in verbal learning and memory. These findings suggest that the presence of AD biomarkers, global atrophy, or both global atrophy and AD biomarkers are all associated with greater verbal learning and memory decline in a sample of late middle-aged adults.

In contrast to the global atrophy findings, the $ptau_{181}/A\beta_{42} \times$ hippocampal volume $\times$ age interaction was not a significant predictor of either outcome, although it was retained in the model of delayed recall (p<.10). This discrepancy may be due to methodological reasons. More

specifically, in contrast to global atrophy, the estimation of hippocampal volume requires differentiation of gray from white matter structures. This difference may result in less accurate estimates for hippocampal volumes than those obtained for global atrophy measures, which do not necessitate segmentation of white from gray matter volumes (Fischl et al., 2002). This is particularly relevant when examining a population consisting of late middle-aged and older adults given that white matter signal intensity declines with age (Salat et al., 2009). This difference in reliability may have accounted for the discrepant findings for hippocampal volume vs global atrophy in the current investigation.

Another reason for the discrepant findings in the current study may be that global atrophy is a better metric of brain reserve than hippocampal volume. The concept behind brain reserve suggests that some individuals evidence less cognitive decline than their peers, and that this may be due to differences in brain structure or function (Stern, 2018). Previous investigations have used a number of neuroimaging methods for defining brain reserve, including cortical thickness, gray matter volume, white matter hyperintensity burden, resting cerebral blood flow, as well as both total brain volume and hippocampal volume (for reviews on both cognitive reserve and brain reserve, see: Fratiglioni & Wang, 2007; Stern, 2018). A measure of global atrophy may be more reflective of neuronal loss due to a number of different etiologies, whereas hippocampal volume loss may be more related to changes due to AD (e.g., Henneman et al., 2009; Jack et al., 2000). Additional research is needed, but this may have accounted for the fact that only individuals with less global atrophy and lower levels of AD biomarkers demonstrated less steep decline over time on measures of verbal learning and memory in the current study.

The findings from the current study are similar to previous research in that we too observed a three-way interaction (i.e., neurodegeneration x AD biomarker x age); however, the

existing literature has found that the greatest degree of decline in cognition is observed in individuals with both atrophy and the presence of AD pathophysiology (Aschenbrenner et al., 2018; Bilgel et al., 2018; Mormino et al., 2014; Soldan et al., 2016). In contrast, the present work found that AD biomarkers interacted with a measure of global atrophy such that trajectories were fairly similar in those carrying at least one of these risk factors (i.e., global atrophy, presence of AD biomarkers, or both global atrophy and AD biomarkers), whereas less verbal learning and memory decline was evident in those with both normal AD biomarker levels and larger brain volumes. The average age of participants in these past investigations was at least 70 years old at baseline (Aschenbrenner et al., 2018; Bilgel et al., 2018; Mormino et al., 2014), with the exception that the Soldan et al. (2016) subsample with the presence of both neurodegeneration and AD biomarkers was 64. In contrast, the average baseline age in the current study was 58. This difference in age may have accounted for the discrepant findings.

Our conclusions here should be considered in light of a few design limitations. First, our analyses were limited to a single episodic learning and memory neuropsychological test because of the in-common availability of the RAVLT. To limit the analytical complexity of our analyses, as well as the inferential problems associated with multiple testing (Gelman & Geurts, 2017), we also considered only a subset of the possible measures of neurodegeneration (Frisoni et al., 2010) and CSF biomarkers (Merluzzi et al., 2019; Olsson et al., 2016). Future analyses in other cohorts should examine the conceptual replicability of these findings using different measures. The homogeneity of the sample is also a weakness, as both cohorts consisted largely of late middle-aged adults with a relatively high level of education (average of 16 years). Our center is currently recruiting a more diverse sample to establish the robustness of our findings to differences in demographic background.

Conclusions. This study joins a growing body of research that is empirically

characterizing the pre-symptomatic biomarker profile in AD. Our results suggest that AD

biomarkers are associated with verbal learning and memory decline, and that the impact of AD

biomarkers on verbal learning and memory performance is greatest in those with larger total

brain volumes. Future research would benefit from following this cohort overtime, as well as

examining the interaction between additional measures of neurodegeneration (e.g., CSF NfL or

neurogranin) and AD pathophysiology (e.g., PET measures of beta-amyloid and neurofibrillary

tangles) on cognitive performance, defined using verbal learning and memory measures, as well

as measures of other cognitive functions (e.g., executive function).

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7. References

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8. Figure Captions

Figure 1: Immediate recall (sum of learning trials 1 through 5) from the Rey Auditory Verbal Learning Test. Lines depict model-predicted age trajectories for three values of $ptau_{181}/A\beta_{42}$: red represents -1 standard deviation from the mean; gray represents the mean value; blue represents +1 standard deviation from the mean. Each panel reflects the model fit at a particular value of global atrophy (columns; -1, 0, +1 SD from the mean) and hippocampal volume (rows; sim.). Model predictions were made assuming a male participant with 16.15 years of education (the mean level) and no prior exposure to the battery. Confidence bands reflect the standard error of prediction for each line. The overlaid scatter represents raw individual test score measurements within nine predictor value bins, grouped such that $Z_{predictor} \leq -0.5$ (top/left), $-0.5 < Z_{predictor} \leq 0.5$ (center/center), and $Z predictor > 0.5$ (bottom/right).

Figure 2: Delayed recall from the Rey Auditory Verbal Learning Test. Lines depict model-predicted age trajectories for three values of $ptau_{181}/A\beta_{42}$: red represents -1 standard deviation from the mean; gray represents the mean value; blue represents +1 standard deviation from the mean. Each panel reflects the model fit at a particular value of global atrophy (columns; -1, 0, +1 SD from the mean) and hippocampal volume (rows; sim.). Model predictions were made assuming a male participant with 16.15 years of education (the mean level) and no prior exposure to the battery. Confidence bands reflect the standard error of prediction for each line. The overlaid scatter represents raw individual test score measurements within nine predictor value bins, grouped such that $Z_{predictor} \leq -0.5$ (top/left), $-0.5 < Z_{predictor} \leq 0.5$ (center/center), and $Z_{predictor} > 0.5$ (bottom/right).