ARTICLE

# Cross-sectional associations of tau-PET signal with cognition in cognitively unimpaired adults

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## Abstract

### Objective

To assess cross-sectional associations of neurofibrillary tangles, measured by tau-PET, with cognitive performance in cognitively unimpaired (CU) adults.

### Methods

Tau- and amyloid-PET were performed in 579 CU participants aged 50–98 from the population-based Mayo Clinic Study of Aging. Associations between tau-PET signal in 43 brain regions and cognitive test scores were assessed using penalized linear regression. In additional models, participants were classified by normal/abnormal global amyloid-PET (A+/A−) and normal/abnormal regional tau-PET (T+/T−). Regional tau-PET cutpoints were defined as standardized uptake value ratio (SUVR) greater than the 95th percentile of tau-PET SUVR in that region among 117 CU participants aged 30–49.

### Results

Higher tau-PET signal was associated with poorer memory performance in all medial temporal lobe (MTL) regions and also in the middle temporal pole and frontal olfactory regions. The largest association with tau-PET and memory *z* scores was seen in the entorhinal cortex; this association was independent of tau-PET signal in other brain regions. Tau-PET in the entorhinal cortex was also associated with poorer global and language performance. In the entorhinal cortex, T+ was associated with lower memory performance among both A− and A+.

### Conclusions

Tau deposition in MTL regions, as reflected by tau-PET signal, was associated with poorer performance on memory tests in CU participants. The association with entorhinal cortex tau-PET was independent of tau-PET signal in other brain regions. Longitudinal studies are needed to understand the fate of CU participants with elevated medial temporal tau-PET signal.

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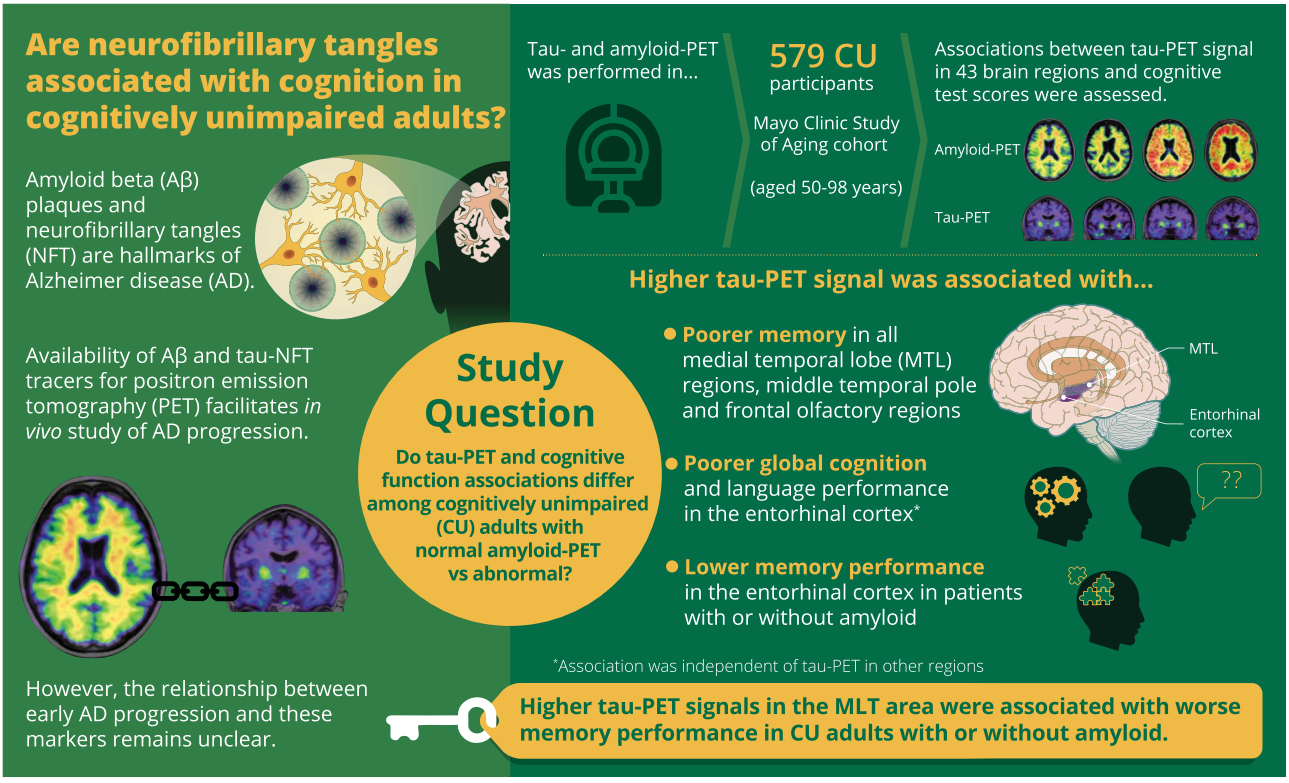
## Glossary

**Aβ** = β-amyloid; **AD** = Alzheimer disease; **CU** = cognitively unimpaired; **MCALT** = Mayo Clinic Adult Lifespan Template; **MCSA** = Mayo Clinic Study of Aging; **MTL** = medial temporal lobe; **NFT** = neurofibrillary tangle; **PART** = primary age-related tauopathy; **PVC** = partial volume correction; **ROI** = region of interest; **SUVR** = standardized uptake value ratio.

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Alzheimer disease (AD) is clinically characterized by a progressive decline in cognitive function beyond that of normal aging. Neuropsychological analysis of cognitive decline in those who are cognitively unimpaired or mildly impaired is possible and regularly implemented through numerous well-validated clinical tests.[1,2] AD is pathologically characterized by the distribution of β-amyloid (Aβ) and neurofibrillary tangles (NFT). The gold standard of AD diagnosis relies on autopsy data quantifying Aβ and NFT load throughout the brain.[3] The relationship of cognitive decline to these pathologies as seen at autopsy is well-described[4,5]; however, the relationship of cognitive decline and these 2 pathologies early in the disease process is not clearly understood.

The advent of Aβ and tau-NFT tracers for PET has facilitated in vivo study of AD pathologic progression in normal aging. Amyloid-PET can identify Aβ plaques[6–10] and is an important tool for understanding AD pathogenisis.[11,12] Tau-PET using AV-1451 identifies AD NFT burden throughout disease progression.[13] Initial reports indicate that tau-PET closely resembles Braak staging of AD.[14–16]

In cognitively unimpaired (CU) participants, there are small cohort studies that describe an association of memory with tau-PET signal primarily in Braak stage I/II (entorhinal and CA1 of the hippocampus) regions that can be independent of amyloid-PET signal[17] and show the strongest effect in the entorhinal cortex even in participants without Aβ.[18] While regional and global amyloid-PET is strongly associated with tau-PET in CUs,[19] a better understanding of the relationship between tau and Aβ and their effects on cognition in normal aging and disease in the whole brain is needed.

In the current study, we evaluated the associations between tau-PET in 43 brain regions and cognition among 579 CU participants aged 50–98 from a population-based aging study. Our study had 2 objectives: (1) to determine the extent of associations between regional tau-PET signal and cognitive function and (2) to assess if the associations of tau-PET and cognitive function were different among CU participants with normal vs abnormal amyloid-PET.

# Methods

## Participants

In this cross-sectional study, participants were enrolled in the Mayo Clinic Study of Aging (MCSA), a population-based study of aging in Olmsted County, Minnesota.[20] Tau-PET was added to the MCSA in 2015 and all participants were asked to participate in tau-PET, amyloid-PET, and MRI scanning. There were 696 CU participants who completed tau-PET, amyloid-PET, and MRI studies between May 14, 2015, and December 1, 2017. Of these, 117 were aged 30–49 years and used as a reference sample to determine regional tau-PET abnormality cutpoints while 579 aged 50–98 years were included in the main analysis. All participants were determined to be CU by a concordant diagnosis: both a nurse and clinician independently determined their diagnosis to be CU after thorough clinical and cognitive assessment without the input of neuropsychological data. Our aim was to compare tau-PET signal to neuropsychological data comprehensively; therefore, neuropsychological data were not used to characterize the participants as CU.[21]

## Standard protocol approvals, registrations, and patient consents

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written consent in accordance with the Mayo Clinic Foundation and Olmsted Medical Center Institutional Review Boards. All potential conflicts of interest and sources of funding are disclosed herein.

## Cognitive testing

Cognitive testing was completed within 6 months of the PET scans. All tests were administered by experienced psychometrists and supervised by board-certified clinical neuropsychologists. Four cognitive domains were assessed by a battery of neuropsychological tests[28]: memory (Auditory Verbal Learning Test delayed recall, Wechsler Memory Scale–Revised, Logical Memory–II and Visual Reproduction–II subtests), attention (Trail-making Test Part B, Wechsler Adult Intelligence Scale–Revised Digit Symbol), language (Boston Naming Test, category fluency), and visuospatial (Wechsler Adult Intelligence Scale–Revised Picture Completion and Block Design subtests). Individual test scores were first converted to $z$ scores using the mean and SD from the MCSA 2004–2012 CU cohorts and weighted to the 2013 Olmsted County, Minnesota, population. Therefore, a participant's $z$ score reflects how many standard deviations away he or she is from the 2013 Olmsted County, Minnesota, population mean. The individual $z$ scores were averaged to create 4 cognitive-domain $z$ scores. A global cognitive $z$ score was obtained from the average of the 4 cognitive domain $z$ scores.

## Multimodality neuroimaging

Participants were injected with 370 MBq (range 333–407) of F-18-AV-1451, 80 minutes prior to imaging for 20 minutes. Amyloid-PET imaging was performed using Pittsburgh compound B, using an injection of 550 MBq (range 292–729). After a 40-minute uptake period, amyloid-PET imaging was performed for a period of 20 minutes. PET image acquisition consisted of four 5-minute dynamic frames to allow for motion correction. A CT image was obtained for attenuation correction. Standard corrections were applied. An MRI scan was performed as previously described for anatomic brain region definition.[22]

## Image analysis

PET cortical regions of interest (ROIs) were defined using the Mayo Clinic Adult Lifespan Template (MCALT) atlas (nitrc.org/projects/mcalt/) (figure 1). Each participant's high-resolution T1-weighted brain MRI was segmented and bias corrected using Unified Segmentation[23] in SPM12 with MCALT tissue priors and settings. Warping parameters were calculated between this MRI and the MCALT template using advanced normalization tools.[24] These were used to automatically localize the MCALT ROIs on the participant MRI, excluding any voxels that were segmented as CSF. The static tau-PET and amyloid-PET image volumes of each participant were each rigidly coregistered and resampled to the corresponding MRI. Tau-PET data with and without partial volume correction (PVC) employing the 2-compartment method were evaluated as previously described.[25] In short, a brain tissue segmentation mask from a coregistered MRI was blurred by 6 mm to estimate the fraction of brain tissue vs CSF in each image voxel under the PET point spread function. Each PET image voxel was then divided by its estimated tissue fraction to correct the signal for partial volume.

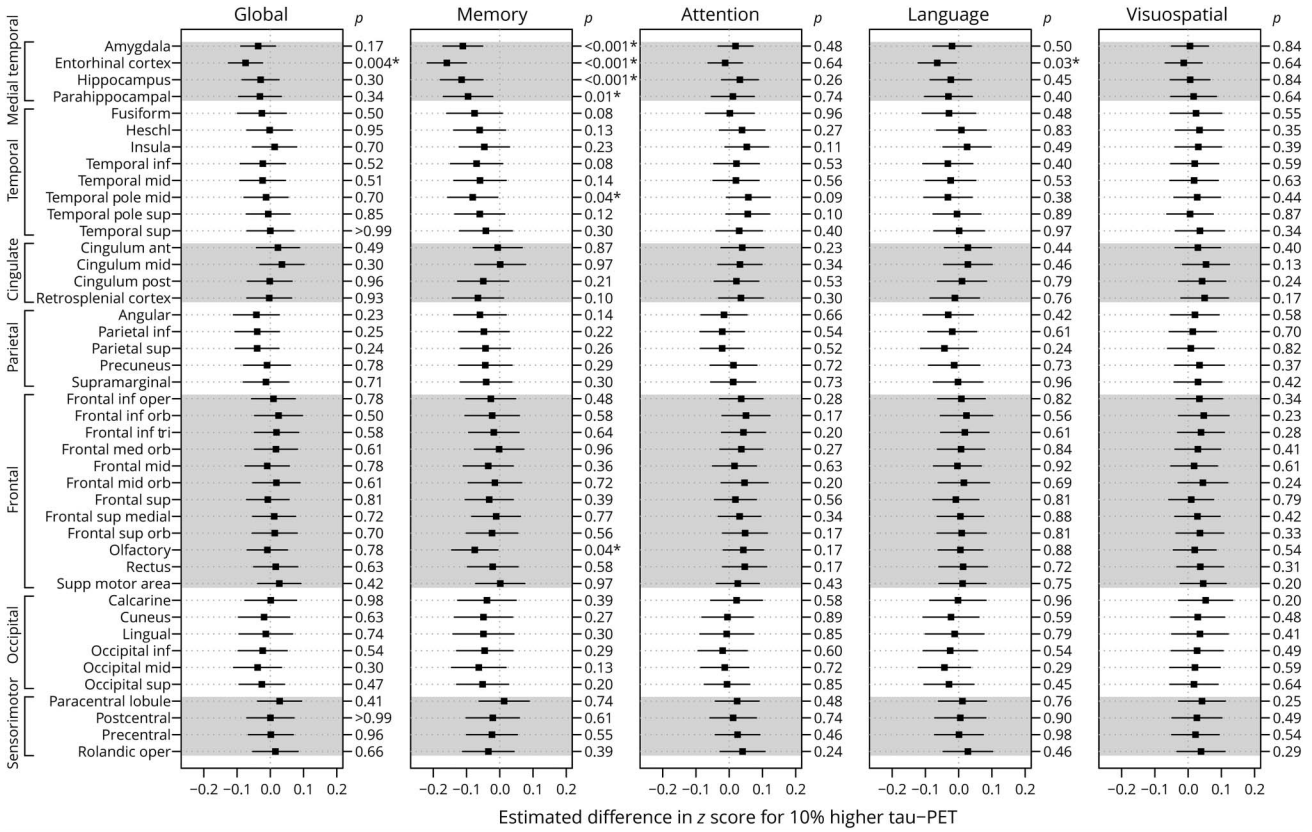
## Standardized uptake value ratio determination and PET thresholds

Participants' tau-PET ROI median values were normalized to cerebellar crus (bilateral crus 1 and 2) to calculate regional standardized uptake value ratios (SUVR) as described previously.[26] The crus regions were selected to provide a normalization option with relative isolation from CSF spaces (inferiorly) and to avoid adjacency to parahippocampal, fusiform, and lingual gyri, relative to tau pathology. Participants were classified as having abnormal tau-PET (T+) within each ROI if their tau-PET SUVR was greater than the 95th percentile of tau-PET SUVR in that region among 117 CU participants aged 30–49 years (all with normal amyloid-PET [A–]), giving an ROI-based different threshold as previously described.[26] Global cortical amyloid-PET SUVR was computed as previously described.[23,27] A+ or A– status was based on a cutpoint of 1.48 using the previously described reliable worsening method[23] but updated for SPM12.

## Statistical methods

For each ROI, we fit a linear regression model with cognitive $z$ score as the outcome and tau-PET as the primary predictor. All models included CU participants aged 50 or older and were adjusted for age, sex, and education, all 3 of which are associated with cognition and are potential confounders. Because tau-PET was only recently introduced in the MCSA,

**Figure 1** Association between regional tau-PET signal and cognition




Mean (95% confidence interval) difference in cognitive *z* scores for a 10% increase in tau-PET estimated from penalized linear regression models. Significant findings at $p < 0.05$ are shown with asterisks. These estimates are adjusted for age, sex, education, and the number of previous exposures to cognitive testing. Tau-PET was modeled with a log transformation and the reported estimates are log (1.1) × β to represent the effect on *z* score of a 10% higher tau PET standardized uptake value ratio. The estimates in this figure are based on penalized maximum likelihood, which stabilizes coefficients and accounts for multiple comparisons.

participants with tau-PET scanning may have been in the study for varying amounts of time. Therefore, we also adjusted for the number of previous exposures to the cognitive testing battery to account for possible learning effects. Tau-PET was log-transformed for the analysis to account for skewed SUVR values and in order to enable us to provide readily interpretable effect sizes that are comparable across regions. In the fitted models, the regression coefficients for the tau-PET terms can be interpreted as the difference in mean *z* scores for a one-unit increase in log (SUVR). However, since a one-unit increase in log (SUVR) is difficult to interpret, we multiplied the coefficient by log (1.1) so that it represents the estimated difference in mean *z* score for a 10% increase in tau-PET SUVR. These models were fit among all CU participants and separately among A− and A+.

Because of the large number of regions and cognitive domains that were evaluated, there was the potential for sparse data bias, overfitting, and multiple comparisons issues. To address this, we used penalized maximum likelihood estimation, also known as shrinkage estimation, to stabilize the regression estimates without greatly increasing the false-negative rate.[28–30] The penalty was applied only to the tau-PET effects and was chosen based on background knowledge that tau-PET effects in this CU sample were not extreme.[30] Specifically, for the single region linear models, we added a penalty corresponding to a standard normal density. This is equivalent to a prior 95% probability that the tau-PET coefficient was between −1.96 and +1.96 and the effect on the mean *z* score for a 10% increase in SUVR was between log (1.1) (−1.96) = −0.19 and log (1.1) (1.96) = +0.19. We use the *optim* function in R to obtain estimates and SEs with *p* values based on Wald tests. These penalized estimates and corresponding *p* values are what is shown in the results and figures.

To assess in which regions tau-PET uptake was independently associated cross-sectionally with cognition, we fit linear mixed effects models with regional tau-PET data from all ROIs included in the same model treating region as a random effect. This served to shrink regional estimates toward an overall average and provide more stable regional estimates. We note that mixed models are a penalization/shrinkage-based modeling approach. Models were fit using JAGS software version 4.3.0 with diffuse priors. The results agreed with those from the lme function in the R package nlme. These models were fit among all CU participants and separately by A− and A+.

In additional analyses, participants were grouped by normal/abnormal global amyloid-PET (A−/A+) and normal/abnormal regional tau-PET (T−/T+) using the percentile-based cutpoints described above. The number of participants categorized as T+ varied across the 43 ROIs with some ROIs only having a few participants classified as T+. ROIs with fewer than 20 participants in any of the 4 A/T groups (A−T−, A−T+, A+T−, A+T+) were excluded from analysis. We fit a linear regression model in each ROI with memory *z* score as the outcome and A, T, and the interaction between A and T as the primary predictors, adjusting for age, sex, education, and number of previous exposures to the neuropsychological testing battery. Our estimation approach was similar to that used for the continuous tau-PET models using penalties of a normal distribution with a mean of zero and SD of 0.25 for each of the T ± main effect, the A ± main effect, and the AT interaction. This penalty corresponded to a 95% prior expectation that the difference between mean *z* scores for 2 AT groups that differed by one abnormality (i.e., A−T− vs A−T+ or A+T− vs A+T+) was within −1.96 (0.25) = −0.49 and +1.96 (0.25) = +0.49. Hypothesis testing was performed using Wald tests. We report pairwise differences between the A/T groups when the joint test of A, T, and the AT interaction was significant at $p < 0.05$.

## Data availability statement

Qualified researchers may obtain de-identified imaging and clinical data used for this study from the corresponding author and the study team upon reasonable request and Mayo Clinic and Olmsted Medical Center Institutional Review Board approval.

# Results

The participant characteristics are shown in the table. The median age in this CU group was 70 with a range from 50 to 98 and 28% were *APOE* ε4 carriers. The frequency of abnormal tau-PET (T+) defined by signal in the entorhinal region was 20% while 34% had abnormal global amyloid-PET (A+).

**Table** Characteristics of participants overall and by groups defined by abnormal amyloid-PET and tau-PET

| Characteristic | All, n = 579 | A−T−,[a] n = 340 (59%) | A−T+,[a] n = 45 (8%) | A + T−,[a] n = 124 (21%) | A + T+,[a] n = 70 (12%) |
|---|---|---|---|---|---|
| **Age, y** | | | | | |
| **Median (IQR)** | 70 (63, 79) | 66 (59, 73) | 78 (71, 82) | 76 (68, 83) | 79 (74, 86) |
| **Min, max** | 50, 98 | 50, 98 | 54, 94 | 52, 94 | 55, 91 |
| **Male sex, n (%)** | 315 (54) | 185 (54) | 28 (62) | 63 (51) | 39 (56) |
| **Education, y, median (IQR)** | 16 (13, 16) | 16 (13, 16) | 14 (12, 16) | 14 (13, 17) | 15 (12, 16) |
| ***APOE* ε4 carrier, n (%)** | 156 (28) | 76 (23) | 4 (9) | 46 (38) | 30 (43) |
| **Short Test of Mental Status score, median (IQR)** | 36 (35, 37) | 37 (35, 38) | 36 (35, 37) | 36 (35, 37) | 36 (35, 37) |
| **Cognitive *z* scores,[b] median (IQR)** | | | | | |
| **Global** | 0.54 (−0.03, 1.10) | 0.78 (0.22, 1.28) | 0.45 (−0.18, 0.89) | 0.30 (−0.25, 0.74) | 0.11 (−0.63, 0.69) |
| **Memory** | 0.53 (−0.21, 1.22) | 0.74 (0.06, 1.44) | 0.02 (−0.92, 0.83) | 0.30 (−0.26, 0.97) | −0.01 (−0.87, 0.89) |
| **Attention** | 0.30 (−0.30, 0.86) | 0.54 (−0.11, 1.04) | 0.30 (−0.33, 0.76) | 0.04 (−0.36, 0.59) | −0.29 (−0.81, 0.20) |
| **Language** | 0.29 (−0.27, 0.87) | 0.44 (−0.16, 1.11) | 0.20 (−0.46, 0.64) | 0.20 (−0.51, 0.70) | −0.00 (−0.36, 0.47) |
| **Visuospatial** | 0.59 (0.00, 1.15) | 0.70 (0.20, 1.28) | 0.45 (0.07, 0.88) | 0.30 (−0.23, 0.82) | 0.45 (−0.50, 0.96) |
| **Tau-PET, SUVR** | | | | | |
| **Median (IQR)** | 1.09 (1.02, 1.15) | 1.06 (1.00, 1.10) | 1.24 (1.20, 1.29) | 1.08 (1.03, 1.12) | 1.28 (1.22, 1.40) |
| **>1.17, n (%)** | 115 (20) | 0 (0) | 45 (100) | 0 (0) | 70 (100) |
| **Amyloid-PET, SUVR** | | | | | |
| **Median (IQR)** | 1.41 (1.34, 1.54) | 1.36 (1.31, 1.40) | 1.39 (1.34, 1.42) | 1.63 (1.52, 1.88) | 2.17 (1.70, 2.43) |
| **>1.48, n (%)** | 194 (34) | 0 (0) | 0 (0) | 124 (100) | 70 (100) |

Abbreviations: IQR = interquartile range; SUVR = standardized uptake value ratio.
[a] Where T+ is defined by signal in the entorhinal region and tau-PET SUVR is shown for the entorhinal cortex region.
[b] Cognitive *z* scores were referenced to the Mayo Clinic Study of Aging 50+ and 70+ 2004–2012 cognitively unimpaired participant enrollment visits and weighted to the 2013 Olmsted County population. The number of participants missing cognitive *z* scores was 41 for global, 21 for attention, 8 for language, and 29 for visuospatial. Everyone was required to have memory *z* score for inclusion in this study.

## Cognitive associations with continuous regional tau-PET

Tau-PET signal in several brain regions was associated with worse memory performance (figure 1). The strongest observed association between tau-PET signal and memory was in the entorhinal cortex, where a 10% increase in tau-PET signal was associated with a mean memory *z* score 0.16 units lower ($p < 0.001$). In addition, having a 10% increase in tau-PET signal in the amygdala, hippocampal, parahippocampal, middle temporal pole, and frontal olfactory regions was associated with a memory *z* score that was 0.07–0.11 units lower ($p < 0.05$ for all). Tau-PET signal in several other regions (fusiform, Heschl, inferior temporal, middle temporal, superior temporal pole, retrosplenial cortex, angular, and occipital mid) showed similar but somewhat smaller effect sizes with memory but these were not significant (est = −0.06 to −0.08, $p = 0.08–0.14$). Higher entorhinal tau-PET signal was also associated with lower global (est = −0.07, $p = 0.004$) and language (est = −0.06, $p = 0.03$) cognitive performance. No other regions showed significant associations between tau-PET and global or language cognition; tau-PET was not significantly associated with attention or visuospatial cognitive domains in any regions. The association with memory and entorhinal cortex tau-PET is shown in figure 2 along with a scatterplot of the raw data. The precentral region is also shown as an example of a region with no association with memory.

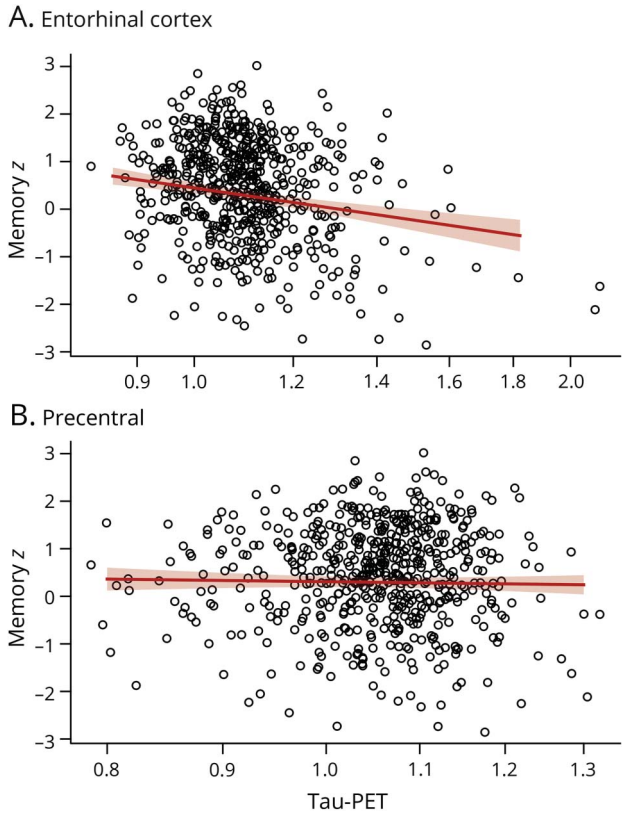
We repeated the analyses shown in figure 1 using tau-PET SUVR with PVC (results not shown). Tau-PET SUVR values with PVC were correlated strongly with noncorrected SUVR values (Spearman $r = 0.86–0.98$ depending on the region). Not surprisingly, the associations with tau-PET signal and cognition were similar when using PVC to those when using noncorrected SUVR values. In addition to the regions that were significantly associated with cognition in the non-PVC results above, the fusiform showed a significant association with a memory *z* score with PVC (est = −0.08, $p = 0.05$) and the middle and superior temporal pole regions showed a significant association with increased attention *z* score with PVC (est = 0.07 and 0.08, $p = 0.04$ and 0.02, respectively). Given the similar results with tau-PET with or without PVC correction, we further report only the non-PVC-corrected data as the most conservative approach.

We also assessed in which brain regions tau-PET signal was independently associated with cognition as compared to signal in other tau-PET regions. When including tau-PET from all 43 ROIs in the same mixed effects model, the entorhinal cortex was the only region that remained independently associated with memory (est = −0.19, $p = 0.004$) and global (est = −0.11, $p = 0.04$) cognition. No regions were independently associated with the other domains.

## Cognitive associations with continuous regional tau-PET stratified by amyloid status

Associations with tau-PET SUVR and cognition stratified by normal/abnormal amyloid status are shown in figure 3. There was no clear pattern across the domains and no significant evidence that amyloid modified the effect of regional tau-PET on memory or visuospatial cognitive performance. However, there were several regions where the effect of tau differed by A. For the global and language domains, A+ participants had a stronger tau effect in the amygdala and hippocampal regions ($p = 0.05$ and $p = 0.03$). For attention, the association between tau-PET and cognition differed by amyloid status in the entorhinal cortex, hippocampal, parahippocampal, and fusiform regions ($p \leq 0.05$). Interestingly, among the A− participants, higher tau-PET was associated with better attention *z* scores in these regions.

**Figure 2** Scatterplots of association between regional tau-PET signal and cognition

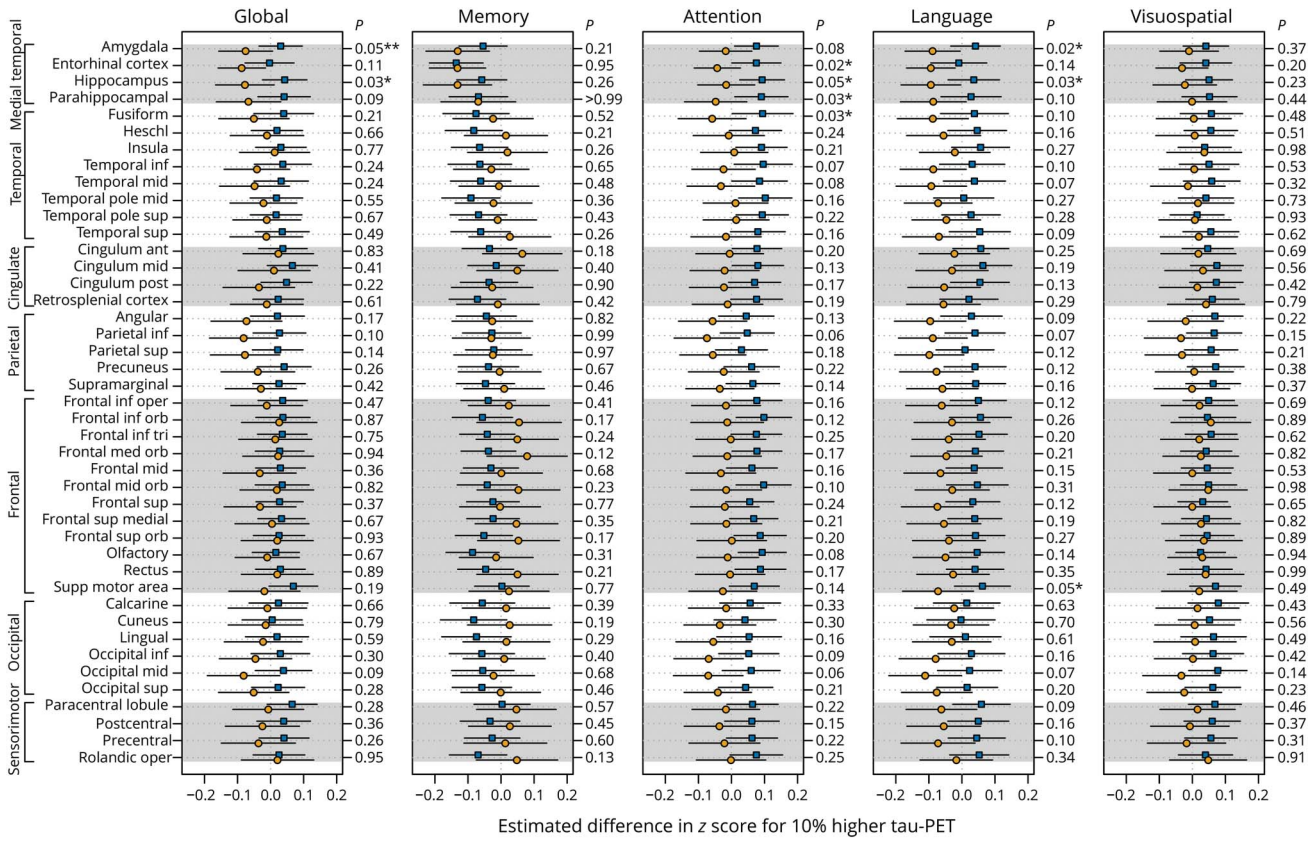



(A) Memory *z* score by tau-PET standardized uptake value ratio (SUVR) in the entorhinal cortex. (B) Memory *z* score by tau-PET SUVR in the precentral region. The regression line and 95% confidence interval are from a penalized linear regression model and correspond to the mean memory *z* assuming a 70-year-old man with 16 years of education and 2 prior exposures to the Mayo Clinic Study of Aging cognitive battery. Due to the large sample size, the 2 participants with entorhinal cortex tau-PET SUVR above 2.0 have little influence on the overall fit.

## Joint effect of regional tau-PET and global amyloid-PET status on memory

We further evaluated the joint effects of tau-PET and amyloid-PET on memory *z* scores by grouping participants according to global amyloid-PET and regional tau-PET status (A−T−, A−T+, A−T+, A+T+, figure 4). Image examples of participants in these groups are shown in figure 5. Notably, the A+ categorization was based on a global SUVR cutpoint because

**Figure 3** Association between regional tau-PET signal and cognition stratified by A− and A+ status




Mean (95% confidence interval) difference in cognitive *z* scores for a 10% increase in tau-PET estimated from penalized linear regression models. Blue squares indicate A− while orange circles indicate A+. *p* Values are from a test of whether the tau effect differed by a status. These estimates are adjusted for age, sex, education, and the number of previous exposures to cognitive testing. Tau-PET was modeled with a log transformation and the reported estimates are log (1.1) × β to represent the effect on *z* score of a 10% higher tau PET standardized uptake value ratio. The estimates in this figure are based on penalized maximum likelihood, which stabilizes coefficients and accounts for multiple comparisons.

participants who have elevated amyloid tend to have it across regions and we focus here on regional tau-PET.

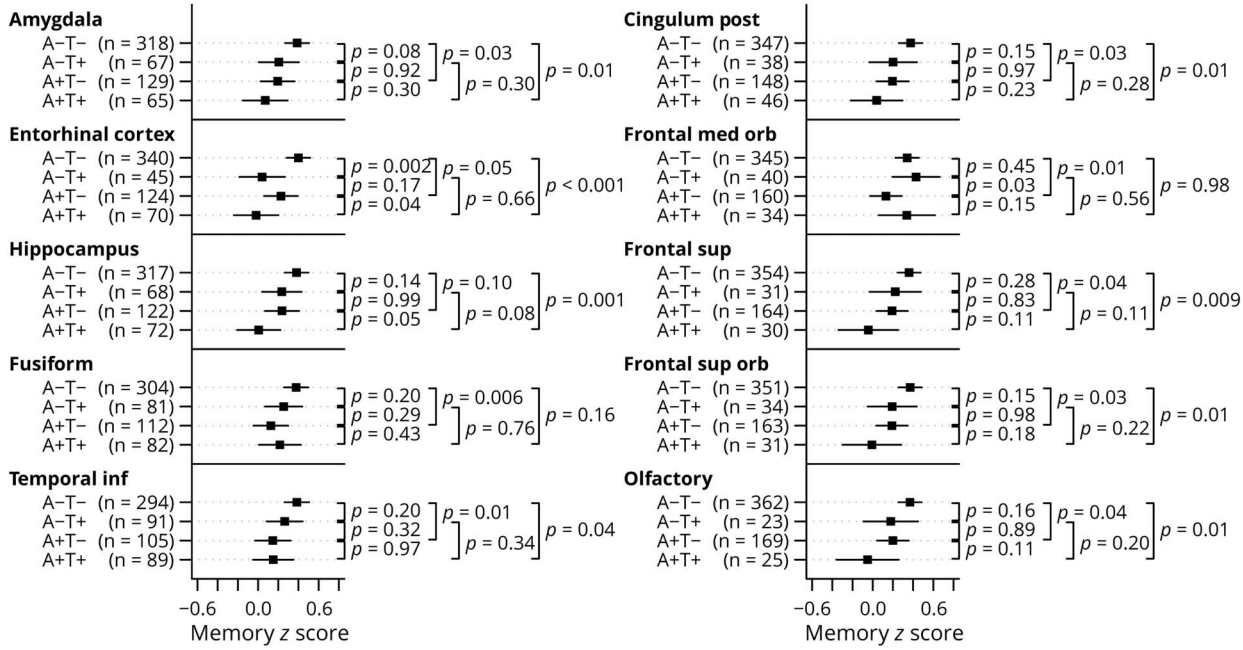
In all, there were 10 regions in which memory z score varied by AT group at the $p < 0.05$ level. In pairwise comparisons, the A−T+ group generally had 0.1–0.2 lower memory *z* scores than the A−T− group. These differences were not significant except in the entorhinal cortex, where the effect size was larger (est = −0.36, $p = 0.002$). Memory *z* score was significantly lower by about 0.2 *z* score units in A+T− vs A−T− in all regions except the hippocampus, which had a marginally smaller effect size (est = −0.14, $p = 0.10$). No A/T group had significantly lower *z* scores than the respective A+T+ in any brain region. We note that the number of T+ participants varied by region and the number of participants in the A−T+ and A+T+ groups were much smaller in some regions. It may be possible that even though mean memory scores were sometimes similar or greater in the A−T+ group than the A+T− group, for some regions (amygdala, hippocampus, posterior cingulum, frontal superior, frontal superior orbital, and olfactory) the A−T+ groups may have had nonsignificant *p* values as compared to A−T− because of smaller group sizes.

## Discussion

We evaluated cross-sectional associations between regional tau-PET and cognitive test performance among CU participants and demonstrated several interesting findings. First, associations with global cognition, memory, and language were seen with tau-PET signal in the entorhinal cortex. Second, associations of memory and regional tau-PET were seen most strongly within medial temporal lobe (MTL) regions but also in midtemporal pole and olfactory regions. Third, the entorhinal cortex was the only region in which tau-PET was independently associated with memory. Fourth, for the entorhinal cortex, T+ was associated with lower memory performance among both A− and A+.

Memory *z* scores and tau-PET signal were prominently associated in MTL regions. Many structures in the MTL including the hippocampus, amygdala, and entorhinal cortex are important for memory.[31] Both in vitro and in vivo animal data have described the pivotal role of the entorhinal cortex in memory formation.[32,33] Our findings of an association between memory performance and tau-PET in the entorhinal

**Figure 4** Pairwise analysis of memory cognition by amyloid-PET and tau-PET abnormality status

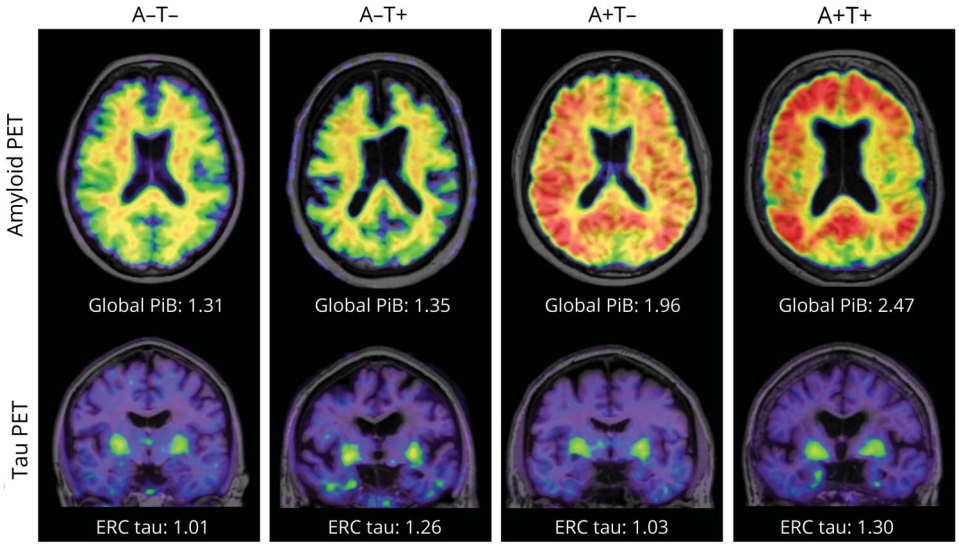



Estimated mean (95% confidence interval) memory *z* score by amyloid-PET and tau-PET groups from a penalized linear regression model adjusting for age, sex, education, and number of previous exposures to cognitive testing. Estimates are shown for a 70-year-old man with 16 years of education and 2 prior exposures to cognitive testing; differences between groups do not depend on these covariates. *p* Values indicate pairwise test results between individual A and T groups. This figure is limited to regions where memory *z* varied by AT group at the $p \leq 0.05$ level.

cortex and other medial temporal regions are consistent with this previous research.

Similar tau-PET findings have been previously published. In a cohort of 86 CU older adults, investigators found significant associations between tau-PET SUVR and memory in a meta-ROI that included Braak stage I/II regions (entorhinal cortex and hippocampus).[18] Others have shown very broad cortical tau-PET signal associated with episodic memory when assessing CU and mild AD dementia together.[34] While our findings are consistent with some of the prior findings, we report additional associations among only CU participants between memory and all MTL regions (amygdala, parahippocampal gyrus, entorhinal cortex, and hippocampus) as

**Figure 5** Tau-PET image examples in each AT group




Representative amyloid and tau-PET images in each group of A–T–, A–T+, A+T–, and A+T+. Global Pittsburgh compound B (PiB) standardized uptake value ratio (SUVR) and entorhinal cortex (ERC) tau-PET SUVR values are listed for an individual participant in each group.

well as with the middle temporal pole and frontal olfactory regions. Interesting nonsignificant memory associations of similar magnitude were also seen in other regions (fusiform, Heschl, inferior temporal, middle temporal, superior temporal pole, retrosplenial cortex, angular, and occipital mid) with several of these biologic memory underpinnings as described above. We controlled for age, sex, education, and number of exposures to cognitive testing and corrected for multiple comparisons. Some prior studies did not correct for these confounders,[18] indicating the strength of the association in the present work. We also report a novel association between global cognition and language performance with tau-PET signal in the entorhinal cortex. This finding expands upon prior studies that found associations between entorhinal tau-PET signal and memory test performance.[18] We identified an association of tau-PET signal in the entorhinal cortex and language. This observation could be explained by the influence of tau pathology on verbal retrieval and learning in the entorhinal cortex.[35] Longitudinal data will be helpful to further explore this finding. The significant effect of tau deposition in the entorhinal region, particularly in this CU population, supports the early pathologic deposition of tau as described by Braak and Braak.[3] Further study in cognitively impaired populations and longitudinal data in unimpaired populations may provide additional insight into the implication of this finding relative to the development of AD or other dementia types.

We found memory associations in a few extra medial temporal regions. Superior and inferior subregions of the temporal pole play an important role in auditory memory processing and formation.[36,37] Other extramedial temporal lobe regions such as the inferior temporal lobe[38] and the fusiform gyrus[39] also play an important role in memory. The association of memory with tau-PET in the fusiform gyrus and the inferior temporal lobe did not reach statistical significance in our study ($p = 0.08$). The posterior cingulate is involved early in memory processing but we saw no association.[40] The frontal olfactory region functions as a component of emotion-related learning[41] and it demonstrated an association between memory and tau-PET signal. More data and longitudinal follow-up may help to assess if these regions continue to show significance and what other regions could become important.

Regional tau-PET stratified by amyloid status showed no clear pattern across the domains and no significant evidence that amyloid modified the effect of regional tau-PET on memory or visuospatial cognitive performance. For the global and language domains, A+ participants had a stronger tau effect in the amygdala and hippocampal regions. For attention, the association between tau-PET and cognition differed by amyloid status in the entorhinal cortex, hippocampal, parahippocampal, and fusiform regions, with higher tau-PET being associated with better attention $z$ scores in these regions. We are uncertain of the reason for this latter finding as it is opposite to the general concept of cognitive decline with tau accumulation. In the raw cognitive score in the table, the A−T+ group has a better attention $z$ score than A+T− but still lower than A−T−, so we could not show this attention improvement effect solely by elevation of tau-PET signal. Further, the mixed model showing independent associations between ROIs show no association of tau-PET signal and attention (data not shown). We will investigate this finding further in additional follow-up studies.

We found that mean memory $z$ scores were similar in T+ participants with normal (A−) or abnormal (A+) amyloid in several brain regions and this is comparable to prior reports.[15,17,18,42] Others have also reported associations of episodic memory with tau-PET signal in CU among A+ and A− in the entorhinal cortex and hippocampus.[17,18] Our data support tau-only or amyloid-only related memory $z$ score reduction and no synergist effect (i.e., interaction) in additional worsening of early memory impairment when both amyloid and tau are present in CU participants. These findings imply that there could be a tau-first pathologic pathway that leads to worse memory performance in AD prior to the presence of amyloid. An amyloid-first pathologic pathway seems equally plausible with amyloid-positive status being associated with worse memory scores but this is less specific regionally given that our data used a global amyloid measure. In all, these data support possible independent pathways for initial AD pathologic development with either pathology possibly occurring first.

These findings are supported by prior autopsy data. In the 1996 publication by Braak et al.,[43] amyloid deposition did not always precede NFT deposition and variable spatial distribution between amyloid and NFT was still reported.[44] While the tau-PET findings we describe could represent pathologic NFT deposition before amyloid in limited regions in people on an AD pathway, it is also consistent with the understood pathologic development of primary age-related tauopathy (PART).[45] The finding of important tau-PET signal outside of the MTL would be a departure from the prior notion of PART involvement exclusively in the MTL. Notably, the NFT type found in PART is 3R/4R and should be identified by tau-PET.[46] Smaller autopsy studies showing that advanced NFT stages (IV–VI) are seen in CUs and participants with dementia with considerable overlap,[47] that widespread isocortical NFTs were less frequent but present in CU,[48] and that a few isolated (stage II) or a few scattered (stage III) NFTs are seen in isocortex in CU, support the present findings.[3] Autopsy data also supports a progressive increase in NFT frequency with age at least in limited extratemporal regions.[43] Our findings present suggestive, but not conclusive, evidence that NFT in some extratemporal regions of the brain may play a role in memory. Serial follow-up beyond the scope of this work may help to further assess the progression of NFT pathology throughout the brain and any related worsening of cognitive impairment among CU participants.

The strengths of our study include its population-based cohort, which is less likely than memory clinic populations to

bias the sample toward genetically predisposed participants (*APOE* ε4 carriers) and in that sense would be more generalizable to the overall population. Our analysis methods were not limited to regional selections tailored to the pathologically described end-of-life NFT pathology findings but provided a whole brain assessment of tau-PET signal in CU participants. This is a large group of CU participants and the wider age range of our population (>50 years) as compared to other smaller studies allows for more detailed examination of early tau development and cognition. Nevertheless, for some regions the number of A–T+ participants was relatively small and this limited statistical power. Other limitations include the difficulty of separating the effects increasing disease burden on PET and aging. Further, we lack autopsy data from the cohort to validate tau-PET findings. Tau-PET is relatively specific for AD NFT but we have shown that tau-PET signal can be seen in off-target sites and other tauopathies.[46] An example of off-target AV-1451 binding that could possibly affect our results is tau-PET signal that can be seen in the choroid plexus. While this has the potential to add bleed-in signal to the hippocampus, we found no hippocampal associations that were inconsistent with the other MTL region findings and therefore doubt this had a significant role. Bone or areas of bone mineralization[46] and brain infarcts[49] can also have off-target tau-PET signal and can be near enough to cortex to bleed-in to multiple cortical regions. Autopsy data correlated with antemortem imaging will be needed for verification of the role of off-target binding. We selected a group of participants <50 years old to determine tau-PET normality; however, early tau deposition may be present in some young people. In any case, this would likely conservatively bias our results. On the other hand, our definition of tau-PET abnormality is more sensitive than using a cutpoint derived from optimizing the group separation of CU and cognitively impaired participants. Serial tau-PET imaging will be needed to confirm that abnormalities classified by comparison with a normal young group are indeed indicative, or at least predictive, of pathologic NFT.

## Author contributions

V.J. Lowe: conception and design of the study, acquisition and analysis of data, and drafting the manuscript and figures. T.J. Bruinsma: drafting the manuscript and figures. H.J. Wiste: analysis of data and drafting the manuscript and figures. H.-K. Min: drafting and critically reviewed the manuscript. P. Fang: acquisition and analysis of data and critically reviewed the manuscript. M.L. Senjem: acquisition and analysis of data and drafting the manuscript and figures. S.D. Weigand: analysis of data and drafting the manuscript and figures. T.M. Therneau: analysis of data and critically reviewed the manuscript. B.F. Boeve: acquisition and analysis of data and critically reviewed the manuscript. K.A. Josephs: acquisition and analysis of data and critically reviewed the manuscript. M.K. Pandey: acquisition and analysis of data and critically reviewed the manuscript. M.E. Murray: acquisition and analysis of data and critically reviewed the manuscript. K. Kantarci: acquisition and analysis of data and critically reviewed the manuscript. D.T. Jones: conception and design of the study, acquisition and analysis of data, and critically reviewed the manuscript. P. Vemuri: acquisition and analysis of data and critically reviewed the manuscript. J. Graff-Radford: acquisition and analysis of data and critically reviewed the manuscript. C.G. Schwarz: acquisition and analysis of data and critically reviewed the manuscript. M.M. Machulda: acquisition and analysis of data and critically reviewed the manuscript. M.M. Mielke: acquisition and analysis of data and critically reviewed the manuscript. R.O. Roberts: acquisition and analysis of data and critically reviewed the manuscript. D.S. Knopman: acquisition and analysis of data and critically reviewed the manuscript. R.C. Petersen: acquisition and analysis of data and critically reviewed the manuscript. C.R. Jack: conception and design of the study, acquisition and analysis of data, and critically reviewed the manuscript.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