

BRAIN COMMUNICATIONS

Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity

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The amyloid cascade model of Alzheimer's disease posits the primacy of amyloid beta deposition preceding tau-mediated neurofibrillary tangle formation. The amyloid-tau-neurodegeneration biomarker-only diagnostic framework similarly requires the presence of amyloid beta for a diagnosis on the Alzheimer's continuum. However, medial temporal lobe tau pathology in the absence of amyloid beta is frequently observed at autopsy in cognitively normal individuals, a phenomenon that may reflect a consequence of aging and has been labelled 'primary age-related tauopathy'. Alternatively, others argue that this tauopathy reflects an early stage of the developmental continuum leading to Alzheimer's disease. We used positron emission tomography imaging to investigate amyloid beta and tau positivity and associations with cognition to better inform the conceptualization of biomarker changes in Alzheimer's pathogenesis. Five hundred twenty-three individuals from the Alzheimer's Disease Neuroimaging Initiative who had undergone flortaucipir positron emission tomography imaging were selected to derive positron emission tomography positivity thresholds using conditional inference decision tree regression. A subsample of 301 individuals without dementia (i.e. those with normal cognition or mild cognitive impairment) had also undergone florbetapir positron emission tomography imaging within 12 months and were categorized into one of the four groups based on cortical amyloid and Braak stage I/II tau positivity: A-/T-, A+/T-, A-/T+, or A+/T+. Tau positivity in the absence of amyloid beta positivity (i.e. A-/T+) comprised the largest group, representing 45% of the sample. In contrast, only 6% of the sample was identified as A+/T-, and the remainder of the sample fell into A-/T- (22%) or A+/T+ (27%) categories. A-/T- and A+/T- groups had the best cognitive performances across memory, language and executive function; the A-/T+ group showed small-to-moderate relative decreases in cognition; and the A+/T+ group had the worst cognitive performances. Furthermore, there were negative associations between Braak stage I/II tau values and all cognitive domains only in the A-/T+ and A+/T+ groups, with strongest associations for the A+/T+ group. Among our sample of older adults across the Alzheimer's pathological spectrum, 7-fold fewer individuals have positron emission tomography evidence of amyloid beta pathology in the absence of tau pathology than the converse, challenging prevailing models of amyloid beta's primacy in Alzheimer's pathogenesis. Given that cognitive performance in the A-/T+ group was poorer than in individuals without either pathology, our results suggest that medial temporal lobe tau without cortical amyloid beta may reflect an early stage on the Alzheimer's pathological continuum.

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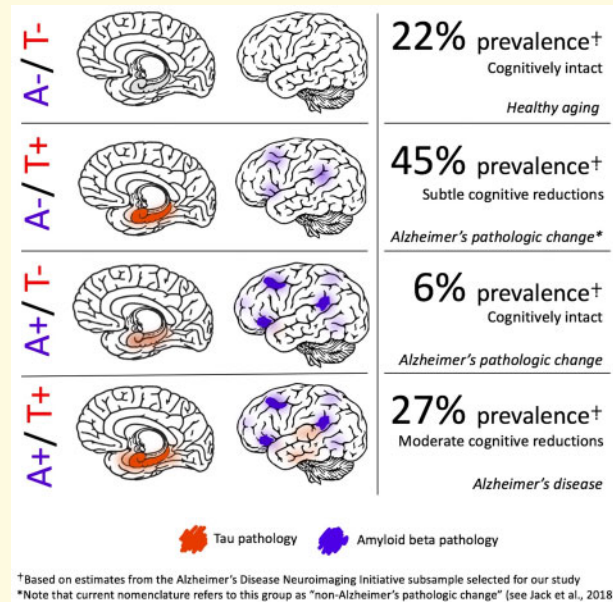
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Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; AT(N) = amyloid-tau-neurodegeneration; $A\beta$ = amyloid beta; APOE = apolipoprotein E; CN = cognitively normal; MTL = medial temporal lobe; MCI = mild cognitive impairment; PART = primary age-related tauopathy; SUVR = standardized uptake variable ratio

Graphical Abstract



Introduction

Amyloid beta ($A\beta$) plaques and tau neurofibrillary tangles represent two of the original defining neuropathological features of Alzheimer's disease (AD; [Alzheimer, 1907](#)). Although initially no distinction was made in the relative causal contributions of these two pathologies, the prevailing view of Alzheimer's disease pathogenesis later shifted to an $A\beta$ -centric perspective that considered $A\beta$ to be the primary harbinger of the disease state, referred to as the amyloid cascade model ([Glennner and Wong, 1984](#); [Hardy, 2017](#)). The deterministic gene mutations for AD result in increased accumulation of the $A\beta$ protein ([Blacker and Tanzi, 1998](#)) and are generally regarded as confirmatory of the primacy of beta-amyloidosis in AD pathogenesis, although a study by [Oxtoby et al. \(2018\)](#) in early-onset familial AD gene mutation carriers demonstrated identical cortical PiB $A\beta$ and CSF p-tau abnormality rates. Furthermore, the recent failures of large-scale clinical trials targeting $A\beta$ have called into question the verity of the amyloid cascade model ([Egan et al., 2018](#); [Honig et al., 2018](#); [Selkoe, 2019](#)). Consequently, the role of $A\beta$ as the primary driving force in the pathogenesis of

AD has recently come under scrutiny ([Ricciarelli and Fedele, 2017](#); [Morris et al., 2018](#)).

A recent re-conceptualization of the AD diagnostic framework has built upon the amyloid cascade hypothesis by proposing a biomarker characterization of the disease in terms of $A\beta$ pathology (A), tau pathology (T), and neurodegeneration (N), thus comprising the amyloid-tau-neurodegeneration or 'AT(N)' framework ([Jack et al., 2016, 2018a,b](#)). Although this framework purports agnosticism with regard to the temporal emergence of abnormal biomarkers, it retains an $A\beta$ -centric perspective by necessitating that abnormal $A\beta$ must be present to constitute 'Alzheimer's pathologic change' (A+/T-), followed by a subsequent pathological change in tau that transitions the diagnosis to 'Alzheimer's disease' (A+/T+). In contrast, tau in the absence of $A\beta$ (A-/T+), either with or without neurodegeneration, is labelled as 'non-Alzheimer's pathologic change' within this framework. Such nomenclature suggests that individuals in this category are not on the Alzheimer's continuum but rather on an alternative pathological trajectory ([Burnham et al., 2016](#); [Gordon et al., 2016](#); [Mormino et al., 2016](#)). Controversy remains over the designation of tau in the

absence of $A\beta$ as a non-Alzheimer's disease process, however, as some studies indicate that this group (A-/T+) is indistinguishable from $A\beta$ -positive groups on a host of purportedly 'non-Alzheimer's disease' clinical and biological factors (Knopman *et al.*, 2013).

Analogous to the AT(N) framework's 'non-Alzheimer's disease pathologic change' is the concept of primary age-related tauopathy (PART), which postulates that medial temporal lobe (MTL) tau in the absence of $A\beta$ reflects a feature of aging separate from the Alzheimer's continuum that is 'observed in cognitively normal individuals', with 'severe PART' associated with amnesic changes only (Crary *et al.*, 2014). Similar controversy exists as to whether PART should be considered a distinct pathological entity (Crary, 2016; Bell *et al.*, 2019) or whether it is better represented as an early Alzheimer's process given its phenomenological similarity to AD (Braak and Del Tredici, 2014; Duyckaerts *et al.*, 2015) and evidence of cognitive decline despite the absence of $A\beta$ -positivity (Jefferson-George *et al.*, 2017; Josephs *et al.*, 2017). Although PART has typically been studied using post-mortem histopathology, recent advances in positron emission tomography (PET) imaging for tau (Jagust, 2018) now allow for *in vivo* investigation of MTL tau in the absence of $A\beta$ that can clarify the characteristics of PART and its separability from—or inclusion on—the Alzheimer's continuum.

Accordingly, we examined the proportion of older adults without dementia [i.e. cognitively normal (CN) and mild cognitive impairment (MCI)] who had MTL tau in the absence of $A\beta$ (A-/T+) relative to individuals with $A\beta$ in the absence of tau (A+/T-), with the expectation that there will be a higher prevalence of A-/T+ individuals based on the neuropathological staging studies of Braak and Del Tredici (2014, 2015). Furthermore, given prior suggestions by Crary *et al.* (2014) that A-/T+ represents a common feature of aging in primarily CN individuals (i.e. PART), we explored this notion by comparing the biomarker groupings on neuropsychological function. In concert with findings from Braak and colleagues, our results may have implications for the amyloid cascade hypothesis and AT(N) framework by indicating the need for the recognition of MTL tauopathy as a primary substrate of the Alzheimer's continuum or, at the very least, agnosticism regarding the temporal sequence of pathological events in AD.

Materials and methods

Participants

Initially, data were assessed from 523 participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI) who had flortaucipir data available to create tau standardized uptake variable ratio (SUVR) positivity thresholds. Of these 523 participants with available flortaucipir data,

350 participants also had available florbetapir data acquired within 12 months of the flortaucipir data to create $A\beta$ SUVR positivity thresholds. Subsequently, a subset of 301 individuals without dementia (i.e. CN and MCI) who had data from both PET measures acquired within 12 months of one another were included in analyses investigating the concurrence of $A\beta$ and tau positivity (i.e. A/T grouping) and subsequent group comparisons in clinical and cognitive characteristics.

Amyloid positron emission tomography processing

Processing methods for ADNI florbetapir (^{18}F -AV-45) data have been previously described (Landau *et al.*, 2013; Landau and Jagust, 2015). Briefly, all PET images were smoothed to the resolution of the lowest resolution scanners (8-mm full-width half-maximum; see <http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/> for a detailed description of PET preprocessing methods). Preprocessed PET images were co-registered with the individual's native-space structural magnetic resonance imaging that was collected within the closest proximity to the PET scan (typically 3 months or less) to obtain Freesurfer-defined regional standardized uptake variable values. A cortical summary measure was derived by calculating a volume-weighted average across frontal, cingulate, lateral parietal and lateral temporal regions. All SUVs were intensity normalized by dividing each value by the whole cerebellum to derive SUVRs, as recommended in ADNI's florbetapir processing methods (Landau and Jagust, 2015). Although a positivity threshold of 1.11 is recommended for the intensity normalized cortical summary measure (Joshi *et al.*, 2012; Landau and Jagust, 2015), we derived a new threshold using the procedures described below to maintain methodological consistency with the derivation of a tau positivity threshold (see also below). Notably, florbetapir data were selected based on the acquisition date closest in time to the baseline flortaucipir scan acquisition date within a 12-month period. On average, acquisition of the florbetapir scan followed the flortaucipir scan by 0.54 months with an SD of 1.69 months in either direction.

Tau positron emission tomography processing

Processing methods for ADNI flortaucipir (^{18}F -AV-1451) data have been previously described (Landau and Jagust, 2016; Maass *et al.*, 2017). As above, preprocessed PET images were smoothed to 8-mm full-width half-maximum and co-registered with the structural magnetic resonance imaging to obtain Freesurfer-defined regional standardized uptake variable values. Flortaucipir data were partial volume-corrected using the Geometric Transfer Matrix approach (Baker *et al.*, 2017). Regional partial volume-corrected SUVR values were combined to approximate

Braak stages I/II, III/IV and V/VI; specific Freesurfer-defined regions included within each Braak stage can be found in [Maass et al. \(2017\)](#). Lastly, partial volume-corrected Braak stage composite ROIs were intensity normalized using the inferior cerebellar grey matter as a reference region to create SUVRs, as recommended in ADNI's flortaucipir processing methods ([Landau and Jagust, 2016](#)).

Amyloid and tau positivity thresholding

Thresholds for the determination of $A\beta$ and tau positivity were derived with conditional inference classification trees using the `ctree()` function from the `party` package in R version 3.5.0 (<https://cran.r-project.org/>), similar to methods used in previous ADNI studies of tau PET ([Schöll et al., 2016](#); [Maass et al., 2017](#)). Mini-Mental State Examination total score was used to drive the classification algorithm separately for both $A\beta$ and tau data to obtain thresholds that (i) are consistent between both $A\beta$ and tau PET data (i.e. to avoid an $A\beta$ threshold defined on pathologically confirmed diagnoses versus a tau threshold that is not validated in this way) and (ii) use a global cognitive measure independent from neuropsychological outcome variables used in later group comparisons. Analyses for each Braak composite stage were conducted in a hierarchical manner: first, thresholds were determined for Braak V/VI; individuals positive for Braak V/VI were then removed from subsequent analyses prior to the determination of Braak III/IV thresholds; and finally, following the removal of individuals positive for Braak III/IV, thresholds for Braak I/II were determined. Analyses were conducted in a single algorithm for $A\beta$ using the cortical summary measure, given the more spatially diffuse emergence of $A\beta$ deposits relative to the consistent hierarchical spatiotemporal progression of tau pathology. Thresholds were taken at the lowest bifurcation in the tree, unless otherwise noted; if two bifurcations were made at the same level, the threshold was instead taken from the level above. Importantly, unlike prior studies that have thresholded tau conditionally on $A\beta$ ([Wang et al., 2016](#); [Mishra et al., 2017](#); [Jack et al., 2019](#)), thresholds for $A\beta$ and tau positivity were derived independently of the other to avoid bias in the prevalence estimates of A/T groups.

Diagnostic classification

Individuals with dementia were included only during derivation of the SUVR thresholds. Clinical diagnosis of dementia was made based on the following criteria utilized by ADNI (<http://adni.loni.usc.edu/>): (i) subjective memory complaint reported by the participant, study partner or clinician; (ii) objective memory impairment defined by a score below education-adjusted cut-offs on Logical Memory Delayed Recall, Story A of the Wechsler

Memory Scale—Revised; (iii) score between 20 and 26 on the Mini-Mental State Examination; (iv) score 0.5 or 1.0 on the Clinical Dementia Rating Scale; and (v) met NINCDS/ADRDA criteria ([McKhann et al., 1984](#)) for probable Alzheimer's disease.

Clinical diagnosis of MCI was determined using comprehensive neuropsychological criteria ([Jak et al., 2009](#); [Bondi et al., 2014](#)). Regression-based z -scores adjusting for age, sex and education were derived for all participants for the following measures: Trail Making Test Parts A and B (attention/executive domain); confrontation naming (i.e. Boston Naming Test or Multilingual Naming Test) and Animal Fluency (language domain); and Rey Auditory Verbal Learning Recall and Recognition (memory domain). Participants' observed scores were compared with the predicted scores for a group of 'robust' CN participants (i.e. maintained CN status throughout the duration of their participation in ADNI) and standardized to create z -scores. A diagnosis of MCI was made for any participant with z -scores >1 SD below the mean for either (i) both tests within a domain or (ii) at least one test across all three domains. All other participants with scores above these cut-points were considered CN.

Clinical and cognitive variables

Demographic variables including age, sex and education were measured for all participants and adjusted for within the cognitive z -scores. Apolipoprotein E (APOE) $\epsilon 4$ positivity was determined by the presence of at least one APOE $\epsilon 4$ allele. Cardiovascular risk was assessed using pulse pressure and calculated as systolic minus diastolic blood pressure, to ascertain the possible contribution of vascular pathology to group differences in cognition given that pulse pressure has been associated with post-mortem cerebrovascular disease ([Nation et al., 2012](#)). For a subset of individuals ($n=76$) with Hachinski ischemic scale scores, an aggregate measure of vascular risk, group differences in this measure are also reported to further rule out vascular contributions to cognitive differences.

Neuropsychological composite scores were created by calculating z -scores for individual measures, as described in the previous section, and averaging within the following domains: memory recall (Logical Memory Immediate Recall, Logical Memory Delayed Recall and Rey Auditory Verbal Learning Delayed Recall), attention/executive function (Trail Making Test Parts A and B) and language [confrontation naming (Boston Naming Test or Multilingual Naming Test) and animal fluency]. For the creation of domain composites, all observations indicating discontinuation of the test due to failure were retained as meaningful values [i.e. maximum raw score of 300 s on Trails B ($n=7$) or 0 on confrontation naming ($n=7$)].

Statistical analyses

Individuals were first assigned to one of the four A/T groups based on A β and tau PET positivity (i.e. A-/T-, A-/T+, A+/T- or A+/T+). Group comparisons on demographic, clinical, and PET SUVR data were conducted using chi-square tests for independence for categorical variables and one-way ANOVAs for continuous variables. Analyses assessing group differences in neuropsychological composite scores were conducted using ANCOVAs adjusting for APOE ϵ 4 positivity with four observations (one per group) deleted due to missing APOE ϵ 4 data. To assess the effect of using a newly derived A β PET threshold, we additionally ran these analyses using the conventional 1.11 threshold for A β . Residuals for all three domain composite scores indicated a moderate-to-strong negative skew; therefore, prior to data analysis, these variables were shifted to a positive scale $[1 + x - \min(x)]$ and normalized using Box-Cox transformation $[(x^2 - 1)/\lambda]$ where $\lambda = 1.7$ for memory, 4.2 for executive, and 3.4 for language]. Reported statistics of interest includes F -ratios and partial eta-squares (η_p^2 s) for omnibus tests and t -ratios and Cohen's d statistics for all pairwise contrasts. P -values were also reported for all statistical tests with Tukey adjustment for pairwise contrasts within each domain. Effect sizes were interpreted as per convention: $\eta_p^2 = 0.01$ (small effect), $\eta_p^2 = 0.09$ (medium effect), $\eta_p^2 = 0.25$ (large effect); Cohen's $d = 0.2$ (small effect), Cohen's $d = 0.5$ (medium effect), Cohen's $d = 0.8$ (large effect). All 95% confidence intervals were included with effect size statistics. Although the reported statistics reflect the difference between estimated marginal means of Box-Cox transformed values, untransformed and unadjusted z -score means for each group are presented in tables and figures to facilitate interpretation. Finally, within-group assessment of associations between transformed neuropsychological domain scores and continuous cortical A β and Braak I/II SUVR levels were conducted using Pearson partial correlations controlling for APOE ϵ 4 positivity, with partial r s and unadjusted P -values as the reported statistics. Effect sizes were again interpreted as per convention: $r = 0.1$ (small effect), $r = 0.3$ (moderate effect), $r = 0.5$ (large effect). Scatterplots include Box-Cox transformed and residualized values to depict tau PET and cognitive associations as modelled. Hypothesis tests were two-sided and considered statistically significant at $\alpha = 0.05$ unless otherwise noted. All analyses and figures were generated in R version 3.5.0 (R Core Team, 2017), including the following extension packages: MASS, dplyr, car, emmeans, sjstats, compute.es, psych, and ggplot2. Raincloud plots were generated from code supplied in Allen *et al.* (2019).

Data availability

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership.

The primary goal of ADNI has been to test whether serial magnetic resonance imaging, PET, other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early Alzheimer's disease. This research was approved by the Institutional Review Boards of all participating sites, and written informed consent was obtained for all study participants.

Results

Amyloid and tau positivity

Thresholds were determined using a sample of 523 individuals (355 CN, 122 MCI, and 46 with dementia) with tau PET data and 350 individuals (219 CN, 95 MCI and 36 with dementia) who additionally had A β PET data. [Supplementary Figs. 1 and 2](#) depict decision tree outputs from the conditional inference classification algorithm with Mini-Mental State Examination score as the response variable. A positivity threshold of >1.14 was derived for the intensity normalized A β summary SUVR ($P < 0.001$), resulting in 140 individuals [40% overall; 59 CN (26.9%), 47 MCI (49.5%), 34 Alzheimer's disease (94.4%)] classified as A+. Although there was a lower-level bifurcation in the tree at a value of 0.95 ($P = 0.03$), the first bifurcation value of 1.14 was chosen to maintain consistency with prior conventional positivity thresholds (i.e. 1.11; Joshi *et al.*, 2012; Landau and Jagust, 2015) and because selection of the lower threshold would have resulted in 90% of individuals without dementia categorized as A+, which does not comport with prior PET studies (10–30% in CN using k-means cluster methods in Cohen *et al.*, 2013; 29% in CN and 43% in early MCI in Landau *et al.*, 2012; 25% in CN and abnormal in Lewczuk *et al.*, 2017) nor with neuropathological studies (e.g. Arriagada *et al.*, 1992; Braak and Del Tredici, 2015).

Braak stage thresholding began with the intensity normalized Braak V/VI SUVR, for which a positivity threshold of >1.96 was derived ($P < 0.001$); 22 individuals [3 CN (0.8%), 7 MCI (5.7%), 12 with dementia (26.0%)] were classified as Braak V/VI+ and were removed from subsequent Braak staging classifications (Schöll *et al.*, 2016). For the remaining 501 Braak V/VI- individuals, a positivity threshold of >1.51 was derived for the intensity normalized Braak III/IV SUVR ($P < 0.001$); 101 individuals [37 CN (10.5%), 42 MCI (41.7%), 22 with dementia (64.7%)] were classified as Braak III/IV+ and were removed from the final Braak staging classification. Finally, for the remaining 400 Braak III/IV- individuals, a positivity threshold of >1.18 was derived for the intensity normalized Braak I/II+ SUVR ($P = 0.02$); 278 individuals [210 CN (66.7%), 56 MCI (76.7%), 12 with dementia (100%)] were classified as Braak I/II+ and the remaining 122 individuals [105 CN (33.3%), 17 MCI

(23.3%)] were classified as Braak I/II–. Braak III/IV+ and Braak V/VI+ individuals iteratively removed during the classification process were also assigned positivity for lower Braak stages. Any individual classified as Braak I/II+ was considered T+. Notably, there were no individuals classified as Braak III/IV+ who were not also Braak I/II+.

A/T group classification

Three hundred one individuals without dementia (212 CN, 89 MCI) who had florbetapir and flortaucipir PET data obtained within 12 months of one another were assigned to one of the four groups to investigate the concurrence of A β and tau positivity: A–/T–, A–/T+, A+/T– or A+/T+. Table 1 depicts a cross-tabulation of A β and tau positivity. The largest group of individuals [135 total (45%); 103 CN, 32 MCI] had evidence of prominent tau in the absence of A β (A–/T+). In contrast, only 18 individuals (6%; 14 CN, 4 MCI) had evidence of prominent A β in the absence of tau (A+/T–); 81 individuals (27%; 42 CN, 39 MCI) were positive for both A β and tau (A+/T+); and 67 individuals (22%; 53 CN, 14 MCI) were negative for both pathologies (A–/T–).

Notably, when the conventional 1.11 threshold for A β was used to categorize groups, group proportions largely remained the same with the A–/T– group at 21%, A–/T+ at 40%, A+/T– at 7% and A+/T+ at 32% (see Supplementary Table 1). For completeness, classification of the 36 excluded individuals with dementia with the original 1.14 threshold for A β resulted in the following: 1 individual was A–/T–, 1 individual was A–/T+, 1 individual was A+/T–, and 33 individuals were A+/T+.

Florbetapir/flortaucipir PET summary statistics

The means and standard deviations for cortical A β , Braak I/II and Braak III/IV SUVR levels across the four A/T groups are reported in Supplementary Table 2, and distributions of these variables are displayed Fig. 1. One individual in the A–/T+ group had an SUVR value of 3.46 for Braak I/II that was suppressed in Fig. 1 to improve visualization of the rest of the data; given that this value is physiologically plausible and the Braak III/IV value for this individual was well within the range of the sample (1.89), this individual was not excluded from any analyses. Notably, as indicated by Fig. 1C, individuals in the A–/T+ group had a range of A β SUVR values and were not clustered just below the threshold for A β

positivity. Furthermore, some individuals in the A–/T+ group exhibited notable flortaucipir binding in Braak III/IV regions typically considered free from tau pathology in the absence of significant cortical A β (see Fig. 1B; mean SUVR = 1.42; 18 individuals Braak III/IV+).

Demographic and clinical comparisons

Stratification of demographic and clinical characteristics by A/T group can be found in Table 2. Groups statistically differed in age ($F=13.6$, $\eta_p^2 = 0.12$, $P < 0.001$) such that the A–/T– group was younger than all other groups. The A+/T+ group had the largest proportion of individuals with MCI (48.1%), whereas all other groups consisted of 20–24% individuals with MCI ($\chi^2 = 18.50$, $\eta_p^2 = 0.10$, $P < 0.001$). Groups also differed in genetic risk ($\chi^2 = 29.60$, $\eta_p^2 = 0.15$, $P < 0.001$), with a higher proportion of APOE $\epsilon 4$ carriers in the A+/T+ groups relative to the A–/T– and A–/T+ groups. The A+/T– group did not statistically differ from any other groups, although it is notable that there were no $\epsilon 4/\epsilon 4$ homozygotes in this group. There was no difference in vascular risk between groups as indexed by pulse pressure, although the A+/T– group had a numerically lower pulse pressure by an average of ~ 8 mmHg. Furthermore, for a subset of individuals with Hachinski ischemic scale scores, there were no group differences in this measure of vascular risk.

Cognitive comparisons

Memory recall

ANCOVAs assessing differences in memory domain scores between A/T groups yielded a statistically significant omnibus effect of moderate size ($F=5.55$, $\eta_p^2 = 0.06$, $P = 0.001$; see Table 3 and Fig. 2; see also Supplementary Table 3 for all pairwise contrasts including Tukey-adjusted P -values). Follow-up pairwise contrasts revealed large effects for differences between the A+/T+ group and the A–/T– (Cohen's $d = 0.84$, 95% CI = [0.33, 1.33]) and A+/T– (Cohen's $d = 1.32$, 95% CI = [0.28, 2.34]) groups, with lower scores observed for the A+/T+ group. There was also a moderate effect for the difference between A+/T+ and A–/T+ groups (Cohen's $d = 0.55$, 95% CI = [0.20, 0.89]) with lower scores again observed for the A+/T+ group. Lastly, there was a small effect for the difference between A–/T– and A–/T+ groups (Cohen's $d = 0.18$, 95% CI = [–0.30, 0.66]), with lower scores observed for the A–/T+ group. Results remained largely the same when group comparisons were made using the 1.11 threshold.

Attention/executive function

ANCOVAs assessing differences in executive domain scores between A/T groups yielded a statistically significant omnibus effect of moderate size ($F=4.15$, $\eta_p^2 =$

Table 1 Cross-tabulation of amyloid and tau positivity resulting in four group classifications

| | T– | T+ |
|----|--------------------------|----------------------------|
| A– | 67 (22%) (53 CN, 14 MCI) | 135 (45%) (103 CN, 32 MCI) |
| A+ | 18 (6%) (14 CN, 4 MCI) | 81 (27%) (42 CN, 39 MCI) |

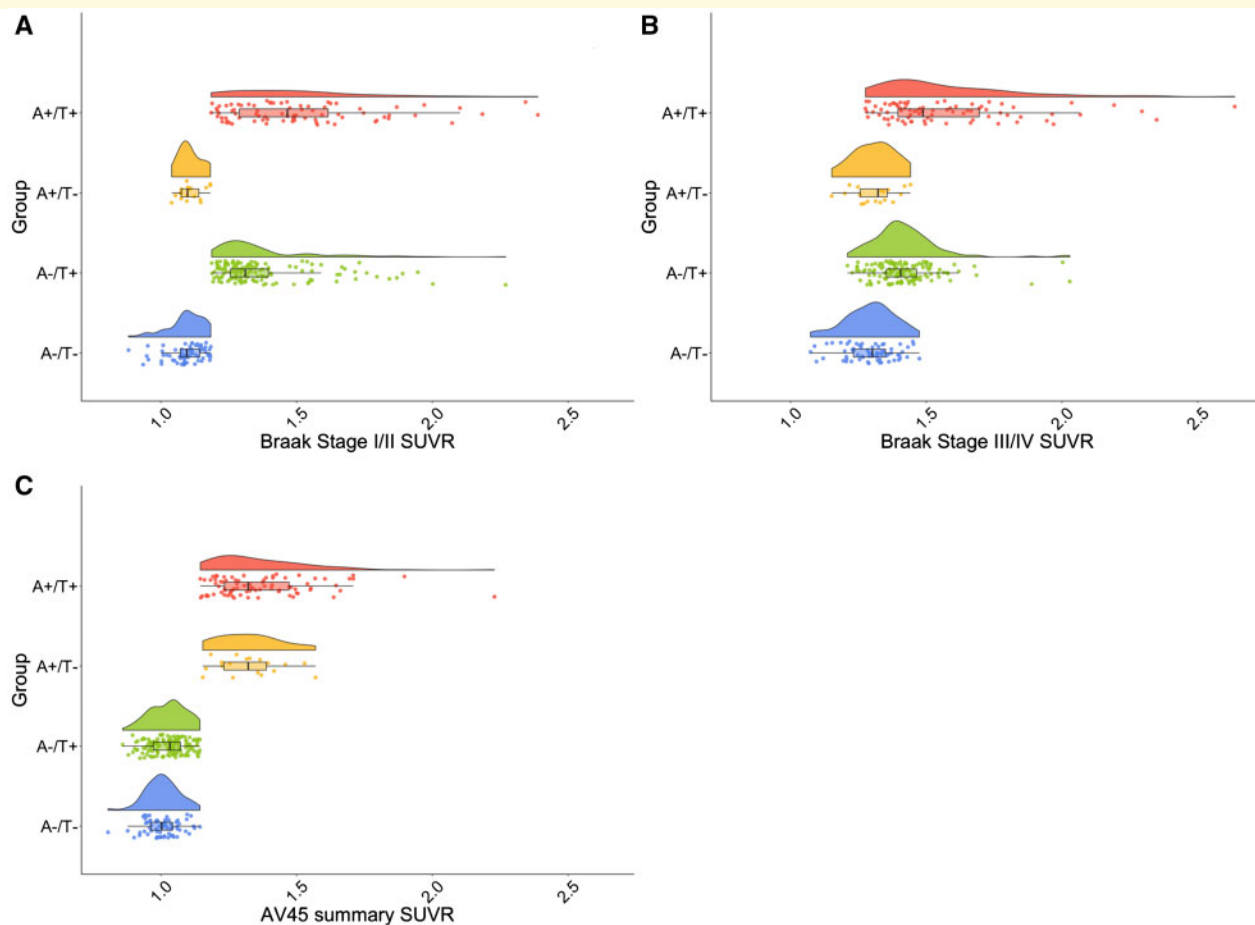


Figure 1 PET SUVR distributions by A/T group. Raincloud plots depicting distributions of SUVR values for AV1451 Braak stage I/II (**A**), AV1451 Braak stage III/IV (**B**) and AV45 cortical summary index (**C**) across all A/T groups. A-/T- is denoted in blue, A-/T+ is denoted in green, A+/T- is denoted in orange and A+/T+ is denoted in red. One individual had an SUVR value of 3.46 for Braak I/II that was suppressed in all panels to improve the visualization of the rest of the data.

Table 2 A/T group differences in demographic and clinical characteristics

| | Group, mean (SD) | | | | Group differences | | |
|--|----------------------|----------------------|---------------------|----------------------|-------------------|----------|---------|
| | A-/T- | A-/T+ | A+/T- | A+/T+ | For χ^2 | η^2 | P-value |
| n (%) | 67 (22.2) | 135 (44.9) | 18 (6.0) | 81 (26.9) | | | |
| Age | 71.13 (6.28) | 76.50 (7.21) | 75.39 (4.85) | 78.06 (7.17) | 13.60 | 0.12 | <0.001 |
| Sex (% female) | 46.3 | 49.6 | 38.9 | 53.1 | 1.50 | 0.01 | 0.68 |
| Education (years) | 16.55 (2.43) | 16.95 (2.56) | 16.28 (2.45) | 16.48 (2.61) | 0.87 | 0.01 | 0.46 |
| Diagnosis (% MCI) | 20.9 | 23.7 | 22.2 | 48.1 | 18.50 | 0.10 | <0.001 |
| APOE risk (n 0/1/2 ϵ 4 alleles) | 46/19/1 | 105/23/6 | 10/7/0 | 37/33/10 | 29.60 | 0.15 | <0.001 |
| Pulse pressure | 57.93 (14.01) | 59.18 (16.30) | 51.28 (11.06) | 62.19 (16.24) | 2.69 | 0.03 | 0.05 |
| Hachinski risk score | 0.58 (0.93) (n = 24) | 0.53 (0.73) (n = 30) | 0.60 (0.55) (n = 5) | 0.35 (0.61) (n = 17) | 0.34 | 0.01 | 0.79 |

0.05, $P = 0.007$; see [Table 3](#) and [Fig. 2](#); see also [Supplementary Table 4](#) for all pairwise contrasts including Tukey-adjusted P -values). Follow-up pairwise contrasts revealed large effects for differences between the A+/T+ group and the A-/T- (Cohen's $d = 0.80$, 95% CI = [0.30, 1.29]) and A+/T- (Cohen's $d = 0.96$, 95%

CI = [-0.03, 1.93]) groups, with lower scores observed for the A+/T+ group. There was also a moderate effect for the difference between A+/T+ and A-/T+ groups (Cohen's $d = 0.44$, 95% CI = [0.10, 0.78]) with lower scores again observed for the A+/T+ group. Lastly, there was a small-to-moderate effect for the difference between

Table 3 A/T group differences in neuropsychological domain performance

| | Group, mean (SD) | | | | Group differences | | |
|-----------|------------------|----------------|---------------|---------------|-------------------|------------|---------|
| | A-/T-, n = 67 | A-/T+, n = 135 | A+/T-, n = 18 | A+/T+, n = 81 | F-ratio | η_p^2 | P-value |
| Memory | -0.24 (0.85) | -0.35 (0.99) | -0.07 (0.73) | -0.96 (1.30) | 5.55 | 0.06 | 0.001 |
| Executive | -0.005 (0.64) | -0.21 (0.94) | -0.05 (0.77) | -0.78 (1.69) | 4.15 | 0.05 | 0.007 |
| Language | -0.14 (0.86) | -0.48 (1.62) | 0.07 (0.67) | -0.59 (1.25) | 2.51 | 0.03 | 0.06 |

Note: Reported values reflect untransformed and unadjusted z-score means to facilitate the interpretation of group differences; these values were not used in models from which statistics were derived.

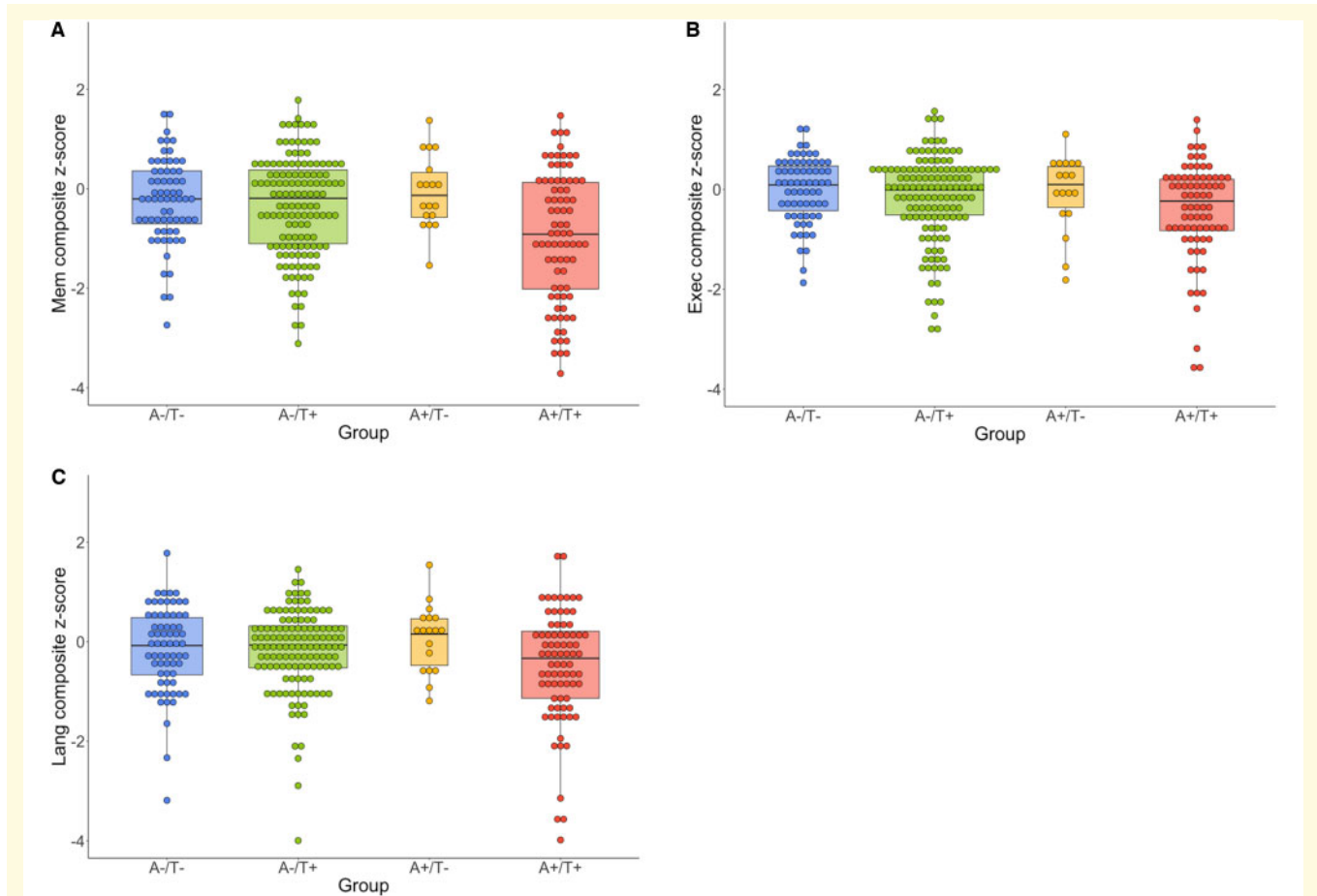


Figure 2 Cognitive z-score distributions by A/T group. Dot-boxplots depicting cognitive domain scores for memory (A), executive function (B) and language (C) composites across all A/T groups. A-/T- is denoted in blue, A-/T+ is denoted in green, A+/T- is denoted in orange and A+/T+ is denoted in red. Values reflect untransformed and unadjusted z-scores.

A-/T- and A-/T+ groups (Cohen's $d = 0.28$, 95% CI = [-0.20, 0.76]), with lower scores observed for the A-/T+ group. Results remained largely the same when group comparisons were made using the 1.11 threshold.

Language

ANCOVAs assessing differences in language domain scores between A/T groups yielded an omnibus effect of small size ($F = 2.51$, $\eta_p^2 = 0.03$, $P = 0.06$; see Table 3 and Fig. 2; see also Supplementary Table 5 for all

pairwise contrasts including Tukey-adjusted P -values). Follow-up pairwise contrasts revealed a large effect for the difference between A+/T+ and A+/T- groups (Cohen's $d = 1.05$, 95% CI = [0.04, 2.03]), with lower scores observed for the A+/T+ group. There was also a moderate effect for the difference between A+/T+ and A-/T- groups (Cohen's $d = 0.52$, 95% CI = [0.03, 1.01]) with lower scores again observed for the A+/T+ group. No notable difference was observed between A+/T+ and A-/T+ groups. However, there were small-to-

moderate effects for the difference between the A-/T+ group and the A-/T- (Cohen's $d = 0.29$, 95% CI = [-0.19, 0.77]) and A+/T- (Cohen's $d = 0.27$, 95% CI = [-0.07, 0.61]) groups, with lower scores observed for the A-/T+ group. Results remained largely the same when group comparisons were made using the 1.11 threshold.

Cognition and PET SUVR associations

Partial correlations controlling for APOE $\epsilon 4$ positivity revealed negative associations between Braak I/II SUVR levels and all neuropsychological domain scores for only the A-/T+ (small-to-moderate r s from -0.18 to -0.27) and A+/T+ (moderate-to-large r s from -0.29 to -0.48) groups (see Table 4). Effect sizes were considerably larger for the A+/T+ group across all domains and most notably within the memory domain. The A+/T- group exhibited a moderately strong association within the executive domain ($r = -0.30$), with an effect as large as that of the A+/T+ group. Notably, when one observation from the A-/T+ group was excluded due to an outlier of 3.46 in Braak I/II SUVR (6 SD above sample mean), all results were retained with similar effects. In contrast, there were no associations between cortical A β SUVR levels and any neuropsychological domain score, although a moderate effect was again observed for the A+/T- group within the executive domain ($r = -0.37$). Table 4 displays partial r s with confidence intervals for all correlations and P -values, and Fig. 3 displays scatterplots for these associations.

Discussion

Despite the primacy of A β over tau postulated by the amyloid cascade model and AT(N) framework for AD pathological progression, our investigation of discrepancies in A β and tau PET positivity revealed that the largest

proportion of our sample (45%) had MTL tau accumulation in the absence of A β (A-/T+). In contrast, only 6% of the sample had evidence of A β in the absence of tau (A+/T-), despite the use of equivalent methods for deriving positivity thresholds. The A-/T+ group tended to perform more poorly across memory, executive function, and language domains relative to the A-/T- and A+/T- groups, although not as poorly as the A+/T+ group. Only the A-/T+ and A+/T+ groups exhibited associations between tau SUVR levels and all cognitive domains, with stronger effects observed for the A+/T+ group. Importantly, our results provide preliminary evidence to suggest that tau pathology may emerge independent of beta-amyloidosis and that A-/T+ individuals, given their widespread early cognitive compromises, may be best represented on the Alzheimer's continuum. These findings are critically important in the conceptualization and treatment of AD because they suggest a wider spectrum of individuals as part of the AD prodrome, as well as provide further evidence that tau represents a relevant and promising treatment target for Alzheimer's disease.

Although there has been a recent surge of research utilizing tau PET imaging in the context of Alzheimer's disease, many studies have focused on tau only in the presence of A β , rather than assessing them independently (Vemuri *et al.*, 2016; Bejanin *et al.*, 2017; Ossenkoppele *et al.*, 2019a,b). In addition, positivity for tau PET is often determined conditionally based on A β (Wang *et al.*, 2016; Mishra *et al.*, 2017; Jack *et al.*, 2019). Importantly, this strategy obviates the possibility of assessing discordance between A β and tau positivities and offers incomplete conclusions about the respective roles of these pathologies in the Alzheimer's disease clinical continuum. It is for this reason that we derived thresholds for A β and tau independently of one another and independent of our clinical and cognitive outcome variables, by using Mini-Mental State Examination as a global index of cognition to drive the classification algorithm. This process yielded tau positivity thresholds that were similar to, albeit more conservative than, those

Table 4 Correlations between cortical amyloid/tau Braak I/II SUVR levels and neuropsychological domain performance, stratified by A/T group

| | Partial correlation coefficients with 95% confidence intervals [LB, r , UB] | | | |
|--------------------|---|---|---|--|
| | A-/T-, $n = 67$ | A-/T+, $n = 135$ | A+/T-, $n = 18$ | A+/T+, $n = 81$ |
| Tau, memory | [-0.28, -0.04 , 0.20] $P = 0.75$ | [-0.42, -0.27 , -0.11]* $P = 0.001$ | [-0.63, -0.21 , 0.30] $P = 0.41$ | [-0.63, -0.48 , -0.29]* $P < 0.001$ |
| Tau, executive | [-0.19, 0.06 , 0.29] $P = 0.65$ | [-0.34, -0.18 , -0.01]* $P = 0.04$ | [-0.68, -0.30 , 0.22] $P = 0.25$ | [-0.48, -0.29 , -0.07]* $P = 0.01$ |
| Tau, language | [-0.06, 0.18 , 0.41] $P = 0.14$ | [-0.38, -0.22 , -0.05]* $P = 0.01$ | [-0.55, -0.10 , 0.40] $P = 0.71$ | [-0.56, -0.38 , -0.18]* $P < 0.001$ |
| Amyloid, memory | [-0.15, 0.09 , 0.33] $P = 0.45$ | [-0.14, 0.03 , 0.20] $P = 0.76$ | [-0.53, -0.07 , 0.42] $P = 0.79$ | [-0.18, 0.04 , 0.26] $P = 0.74$ |
| Amyloid, executive | [-0.35, -0.12 , 0.13] $P = 0.34$ | [-0.04, 0.13 , 0.30] $P = 0.12$ | [-0.72, -0.37 , 0.13] $P = 0.14$ | [-0.32, -0.11 , 0.11] $P = 0.32$ |
| Amyloid, language | [-0.13, 0.12 , 0.35] $P = 0.34$ | [-0.11, 0.06 , 0.22] $P = 0.52$ | [-0.64, -0.23 , 0.28] $P = 0.37$ | [-0.20, 0.02 , 0.24] $P = 0.83$ |

LB = 95% CI lower bound; UB = 95% CI upper bound. r values are given in bold.

*Statistically significant association at $P < 0.05$.

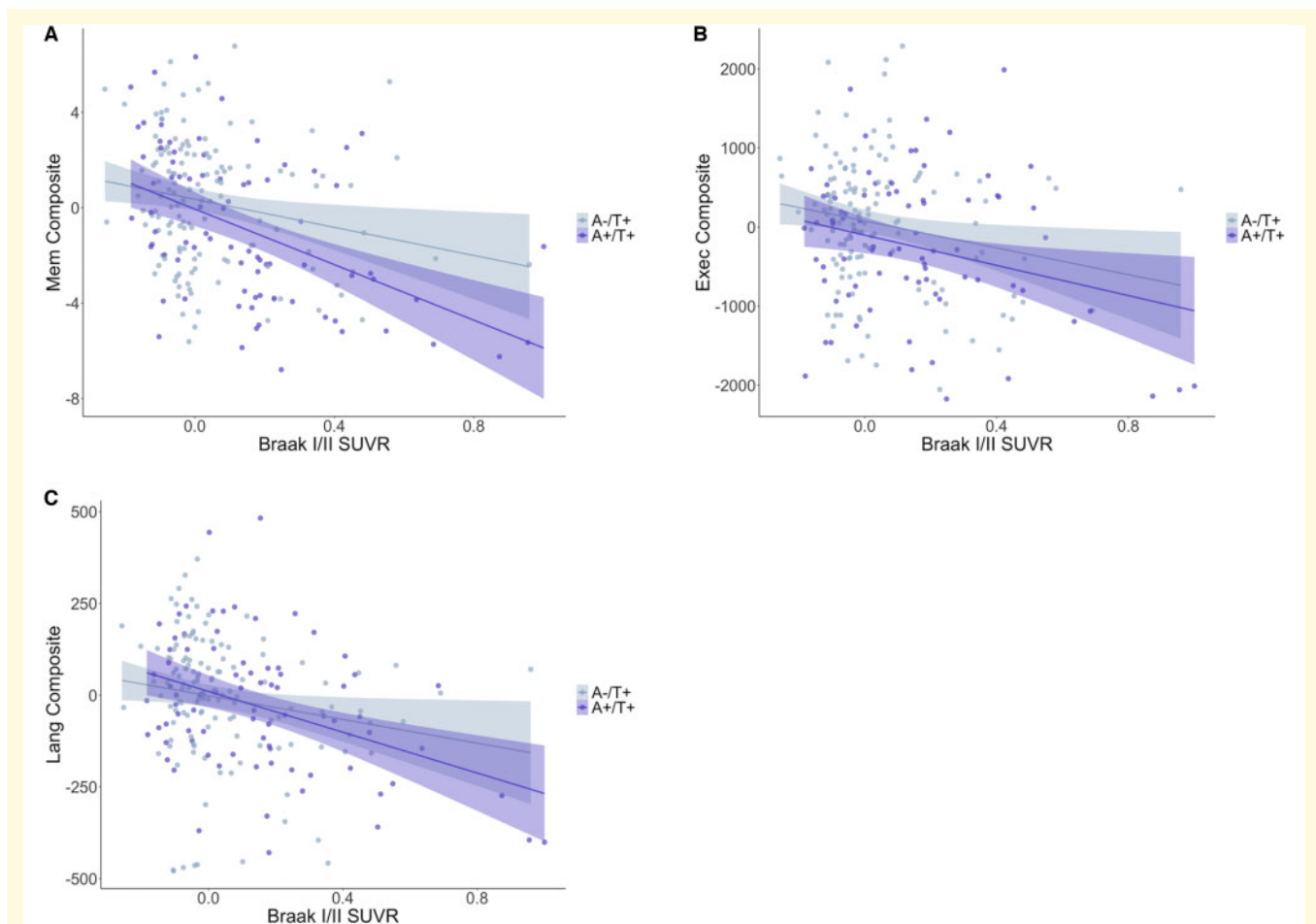


Figure 3 Tau PET and cognition associations for T+ groups. Scatterplots depicting the association between Braak I/II SUVR and memory (A), executive function (B) and language (C) composites. A-/T+ is denoted in gray and A+/T+ is denoted in purple. Values have been residualized with respect to APOE ϵ 4 positivity and cognitive composites transformed to meet normality assumptions. Figures exclude one outlier with a residualized Braak I/II SUVR of 2.14 to improve visualization, but effects remained statistically and qualitatively similar.

previously reported using analogous methods in a more heterogeneous sample (Schöll *et al.*, 2016; Maass *et al.*, 2017), providing convergent validity for the values derived in this study. Notably, although the value we derived for the $A\beta$ positivity threshold (>1.14) was slightly more liberal than the conventional threshold using pathologically confirmed data (>1.11 ; Landau and Jagust, 2015), a reanalysis of the data with the conventional 1.11 threshold revealed that group classifications remained largely the same (see Supplementary Table 1) and cognitive comparisons did not notably differ from the results reported above. Thus, we believe that the methods used for threshold derivation in this study provide valid and reliable biomarker categorizations.

Applying these newly derived positivity thresholds to examine discrepancies in $A\beta$ and tau positivity, we found that the A-/T+ group represented the largest proportion of the sample (45%), whereas more than a 7-fold lower proportion (6%) were categorized as A+/T-. Notably, these proportions differ substantially from a recent study

of AT(N) categorizations, which found only 11.5% to be classified as A-/T+/(N- or +) using PET methods (Jack *et al.*, 2019). Importantly, this prior study derived a threshold for tau positivity that was contingent on $A\beta$ status, with the tau SUVR threshold determined based on optimal discriminability of young CN A- individuals from older cognitively impaired A+ individuals. Using a model based on discrimination of A- and A+ groups necessarily yields a threshold value that will maximally group high tau SUVRs with the A+ category and low tau SUVRs with the A- category, thus increasing the likelihood of producing A+/T+ and A-/T- groups with fewer individuals falling into discrepant groups. We, in contrast, derived A+ and T+ threshold independently of one another by fitting our model to a global cognitive outcome regardless of PET status for the other biomarker to reduce bias.

Our resultant classifications of 45% A-/T+ and 6% A+/T- differ from the temporal sequence of pathological events anticipated by the amyloid cascade model and

AT(N) framework, both of which purport that A β is the primary pathological substrate of Alzheimer's disease that emerges some years prior to the tauopathy of Alzheimer's disease. However, post-mortem histopathological studies of Alzheimer's disease have indicated early pathological tau changes that occur in the brainstem, specifically the locus coeruleus, which subsequently propagate to medial temporal regions encompassing Braak stage I/II. These events largely occur before the evidence of A β accumulation (Braak *et al.*, 2011; Braak and Del Tredici, 2015; Ehrenberg *et al.*, 2017), in accord with the high proportion of A-/T+ observed in our study. Furthermore, our findings of a high prevalence of T+ in the context of A-comport with the post-mortem pathological findings of Braak and Del Tredici (2015). In their study, ~75–80% of individuals aged 70–80 years had evidence of Braak stages I–II tau pathology, whereas only ~10–35% over that same age range had evidence of A β phases 1–3 (note that the average age of our study participants was 75.6 years). Moreover, across all ages, 953 (61%) of the autopsied subjects with Braak stage I/II tau pathology had A β phase 0 pathology. In a separate study, Braak and Del Tredici (2014) further demonstrated that, of the 80% of individuals between the ages of 70–80 years with neuropathological evidence of Braak stages I–II tau pathology, only half also had evidence of A β (including phase 1), which again aligns with our findings of 45% A-/T+ prevalence.

Prior research has acknowledged this group of A-/T+ individuals, although historically they have not been considered part of the Alzheimer's developmental continuum. Instead, individuals with this pathological presentation of MTL tau in the absence of A β have been relegated to alternative categorizations such as PART, which views medial temporal tauopathy in the absence of A β as a feature of aging separate from AD (Crary *et al.*, 2014; Jellinger *et al.*, 2015). Individuals under the PART designation have been characterized as older, having lower APOE ϵ 4 allelic frequencies, and typically more cognitively intact with only localized amnesic changes observed in severe cases (Crary *et al.*, 2014). However, other groups contend that PART itself is a developmental stage (i.e. Braak I/II) of Alzheimer's disease pathogenesis (Braak and Del Tredici, 2014; Duyckaerts *et al.*, 2015; Josephs *et al.*, 2017). Most investigations into PART have been conducted using post-mortem histopathological data, which limits the ability to assess cognitive status in close temporal proximity to the pathological determinants due to the use of retrospective cognitive data that often varies on the order of years in its proximity to the time of autopsy. In contrast, our study was able to investigate these groupings using *in vivo* PET markers of A β and tau pathology that more closely coincided with the administration of a neuropsychological battery, allowing for an improved cognitive characterization of A-/T+ individuals.

Importantly, our results do not recapitulate the usual demographic and clinical features of the A-/T+ group proposed by proponents of PART (Crary *et al.*, 2014). For example, our A-/T+ group did not differ from the non-pathological A-/T- group in terms of APOE ϵ 4 allelic frequency. Furthermore, although the A-/T+ group was older than the A-/T- group, they did not differ from the other groups (A+/T- and A+/T+). Notably, vascular risk assessed through multiple indices did not differ between the groups and therefore any group differences in cognition are likely not attributable to vascular differences. The proportion of individuals with MCI did not differ among the A-/T-, A-/T+ and A+/T- groups (21–24%), but it was twice as high in the A+/T+ group (48%). Significantly, the A-/T+ group had an MCI rate of 24%, which conflicts with the claim that PART is a condition observed primarily in CN individuals (Crary *et al.*, 2014). However, given that this rate did not statistically differ from the A-/T- group, we also examined differences in neuropsychological domain scores to further explore the pattern of cognitive performance across groups.

From the amyloid cascade and PART perspectives, one would predict similar cognitive performances between the A-/T- and A-/T+ groups, particularly in non-amnesic domains, followed by a lower-performing A+/T- group, followed by the lowest-performing A+/T+ group. This pattern was not observed across any of the three cognitive domains. Instead, the A-/T- and A+/T- groups performed most similarly, often with the A+/T- group demonstrating the best performances of all groups. In contrast, the A-/T+ group exhibited small-to-moderate decreases in performance relative to the A-/T- group across all domains. The A+/T+ group had the poorest performances in all domains with the exception of language, for which the A-/T+ group performed equally as poorly. Furthermore, examination of partial correlations between domain performance and Braak stage I/II SUVR levels revealed associations only for the A-/T+ and A+/T+ groups, with stronger effects for the latter. Despite its confinement to the MTL in Braak stage I/II, tau appears to have widespread effects on cognition across memory, executive, and language domains, even in the absence of A β positivity. The cognitive differences and associations in executive and language domains in the A-/T+ group are particularly noteworthy given that PART purports to impart only amnesic cognitive changes in the most severe cases. Thus, tau appears to be exerting deleterious effects on cognition within the MTL and beyond even in A- individuals, possibly through network changes to broader association cortices associated with language and executive functions (Ossenkoppele *et al.*, 2019a,b). Notably, the reported effect sizes for group differences in cognition are relatively small and the conclusions drawn should be interpreted cautiously in the absence of further longitudinal research. Nevertheless, these preliminary findings suggest that MTL tau pathology in the absence of A β

may not be an anticipated consequence of aging, as the PART hypothesis implies.

Given these findings, we propose that prominent MTL tau pathology itself is sufficient to be considered part of the Alzheimer's continuum, rather than the distinct entity of PART, with subsequent beta-amyloidosis accelerating the disease stage. These data indicate that a revision to the AT(N) nomenclature (Jack *et al.*, 2016, 2018a,b) is also warranted such that A−/T+ profiles should fall under the category of 'Alzheimer's pathologic change' rather than 'non-Alzheimer's pathologic change,' with the term 'Alzheimer's disease' reserved for A+/T+. If an individual falls into one of these categories in the context of intact cognition, they would be considered in a preclinical stage (i.e. preclinical Alzheimer's pathologic change or preclinical Alzheimer's disease; see Fig. 4). Interestingly, a prior study investigating the prevalence of abnormal biomarkers without regard to their temporal ordering noted that neurodegeneration (possibly due to MTL tau pathology) was more likely to be the first abnormal biomarker than Aβ (Edmonds *et al.*, 2015); perhaps the most appropriate staging model for Alzheimer's pathology would follow this 'tally' system to maintain agnosticism with regard to the temporal emergence of these biomarkers, given the continued uncertainty over the developmental cascade leading to

AD. Such a reframing in nosology would also have critical implications for drug discovery and clinical trials. As our findings suggest, waiting for Aβ positivity to become evident before attempting its clearance, particularly in those with MTL tau positivity, would negate the opportunity to clear pathological tau before it begins to affect cognition broadly across memory, language and executive functions.

Prevailing theory postulates that tau pathology migrates from the brainstem to the MTL as part of the aging process and remains in this region until sufficient Aβ pathology has accumulated to drive it out to adjacent neocortical regions (Bennett *et al.*, 2017). Our data showed that within the A−/T+ group, all of whom were Braak stage I/II+ (i.e. confined to MTL), 18 individuals (13% of the A−/T+ group) were also Braak stage III/IV+ despite their Aβ negativity. These data suggest that, in some cases, tau pathology may extend beyond the MTL independent of the influence of Aβ. Nonetheless, it remains unclear whether Aβ is needed to further the spread of tau beyond the MTL and the literature offers conflicting evidence. On the one hand, several studies have demonstrated that tau accumulates at a faster rate in the presence of Aβ (Lockhart *et al.*, 2017; Jack *et al.*, 2018b; Leal *et al.*, 2018; Schultz *et al.*, 2018) and our results indicated a stronger association between tau and

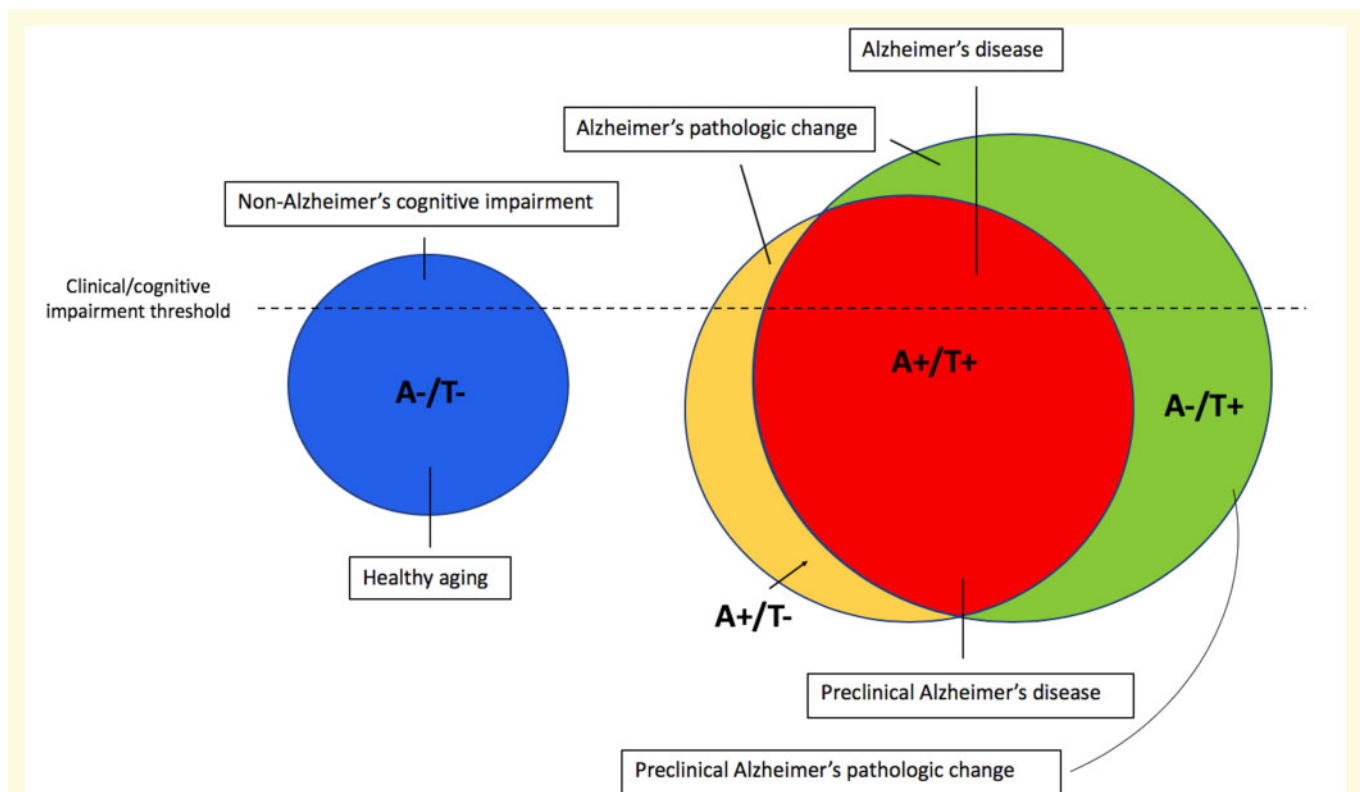


Figure 4 Suggested nomenclature for the Alzheimer's pathological continuum. Theoretical model of Alzheimer's nomenclature based on A/T group and cognitive status, including relative group proportions based on A/T positivity prevalence findings in the current sample.

cognitive performance, as well as generally poorer performance, in the A+/T+ group relative to the A-/T+ group. On the other hand, other studies show that tau has the ability to spread beyond the MTL to adjacent cortical regions in the absence of A β , both in animal models (Kaufman *et al.*, 2018) and human PET studies (Lowe *et al.*, 2018). Further post-mortem evidence demonstrates the continued progression of tau pathology despite the enduring clearance of A β from anti-A β therapies administered prior to death, suggesting an A β -independent mechanism of tau propagation (Nicoll *et al.*, 2019).

Notably, there are several other pathologies in addition to A β and tau that comprise the Alzheimer's syndrome, and the majority of individuals with Alzheimer's disease have multiple pathologies (Schneider *et al.*, 2009; Boyle *et al.*, 2018). Cerebrovascular pathology has proven to be a prominent and early contributor to Alzheimer's processes, with neuroimaging markers of small-vessel disease emerging as early as 22 years prior to symptom onset in autosomal-dominant AD (Lee *et al.*, 2016). Data further indicate synergistic interactions between cerebrovascular pathology and hallmark Alzheimer's pathologies, such that cerebrovascular dysfunction may accelerate A β and tau pathological progression, and vice versa (Blair *et al.*, 2015; Nation *et al.*, 2015; Rabin *et al.*, 2019). Another important pathological feature in older adults is TDP-43, which defines the new conceptualization of limbic-predominant age-related TDP-43 encephalopathy (i.e. LATE; Nelson *et al.*, 2019) and is often comorbid with A β and tau pathologies (James *et al.*, 2016). As research progresses, a polypathologic staging scheme for AD that extends beyond A β and tau may be warranted. As previously suggested, a 'tally' system for these multiple pathologies (which also includes the presence of subtle or mild cognitive declines) may be the best nosology for representing their cumulative contributions to the Alzheimer's dementia syndrome (see Edmonds *et al.*, 2015).

There are several notable strengths of the current study. First, the measurement of A β and tau positivity with PET imaging allowed for perhaps the first *in vivo* investigation of PART, with improved temporal proximity between the assessment of cognition and the measurement of pathology relative to previous post-mortem studies. The independent derivation of positivity thresholds for A β and tau is also a unique feature of our study relative to prior studies and ensured any potential A-/T+ individuals could accurately be detected, given that A β positivity was not considered in the determination of T- and T+ groups. Furthermore, the use of neuropsychological measures sensitive to early AD provided a multi-domain assessment of cognition, rather than relying on brief cognitive screening or rating measures insensitive to the AD prodrome and not validated outside of clinic settings (see De Roeck *et al.*, 2019 for a review). These methodological strengths allowed for an improved examination of the concept of PART, leading to the conclusion that this A-/T+ pathological profile has deleterious effects on cognition and may be better considered as a stage of the Alzheimer's continuum.

Despite its strengths, we also acknowledge that this study is not without its limitations. Importantly, the homogeneity of the ADNI sample may limit generalizability to more representative community-based samples and further studies sampling from a diverse population are needed to ensure that these effects persist among individuals of underrepresented races/ethnicities, socioeconomic strata and comorbid medical or mental health conditions. Furthermore, our study's cross-sectional analyses limited our ability to directly examine within-subject temporal emergence of A β and tau pathologies as well as cognitive change over time across the A/T groups, and longitudinal investigations of such phenomena will be an important next step to corroborate the preliminary findings presented in this study and further our understanding of pathological progression along the Alzheimer's continuum within individuals over time. It is also noteworthy that the florbetapir PET tracer for A β has a high affinity for neuritic plaques, but it may not detect diffuse plaques or soluble oligomers (Beach *et al.*, 2014); thus, we cannot rule out that these other forms of A β pathology are present in A- individuals and contribute to neurofibrillary tangle formation (Koss *et al.*, 2016; Abner *et al.*, 2018). That said, proponents of PART allow for the presence of diffuse plaques in addition to MTL tau (Crary *et al.*, 2014) and, therefore, the detection of these diffuse plaques would not change the categorization of this group.

One may also question the decision to restrict the definition of tau positivity based on spatial location (i.e. MTL) while instead using a broader cortical summary measure for A β positivity. Importantly, the use of a composite across diffuse cortical regions may dilute sensitivity of the detection of pathology in any single region. However, given that A β pathology presents diffusely and variably throughout cortex (Braak and Braak, 1995; Lockhart *et al.*, 2017), a composite region may better capture the presence of this accumulated pathology given that measurement of a single region may produce false negatives if A β has instead accumulated in other unsampled cortical regions. Conversely, tau pathology emerges in a specific spatiotemporal sequence across the Alzheimer's continuum (Braak and Braak, 1991), which increases our sensitivity for the detection of tau pathology if we select these regions predicted by neuropathological staging (e.g. MTL regions for early detection). For this reason, we and other representative PET studies (see Maass *et al.*, 2017) have determined tau positivity based on SUVR level within the MTL (i.e. Braak stage I/II). Notably, selection of this approach likely contributed to our relatively high prevalence of T+ within this study (Braak *et al.*, 2011), whereas a composite of Braak stages I-IV would be more conservative in detecting T+. However, given that we observed subtle cognitive deficits among A-/T+ individuals (with tau largely confined to the MTL), this finding suggests that the observed highly prevalent MTL tau in the absence of amyloid is an important pathological grouping that may be considered part of the Alzheimer's continuum rather than a feature of normal aging.

That said, other approaches to thresholding or staging of tau PET are worth considering and may yield different prevalence rates of A−/T+. For example, one study derived a composite summary measure, which included four regions that maximally separated low and high levels of flortaucipir binding, and proceeded to define a positivity threshold based on discrimination of Aβ− and Aβ+ older adults (Mishra *et al.*, 2017). Another approach taken by Ossenkoppele *et al.* (2018) selected regions of interest across Braak stages I–IV and defined a positivity threshold that was 2 SD above the mean for cognitively healthy older adults. We recognize that selection of a thresholding approach is highly influential to the resultant positivity groupings and, therefore, future studies investigating alternative methods for the determination of PET positivity and resultant A/T groupings are critically needed to inform our understanding of pathological changes along the Alzheimer's disease continuum. However, regardless of the selection of regions or thresholding method, we believe that it is important to determine tau positivity independently of Aβ, given the emerging early and independent role of tau within the Alzheimer's disease prodrome (Jefferson-George *et al.*, 2017; Aschenbrenner *et al.*, 2018; Maass *et al.*, 2018; Nicoll *et al.*, 2019).

In summary, our analyses of PET data within the ADNI cohort suggest that tau pathology is common among individuals without significant beta-amyloidosis, given that 45% of the sample was categorized as A−/T+ relative to 6% as A+/T−, contrary to prevailing amyloid cascade and AT(N) frameworks. Furthermore, the relatively poor cognitive performances of the A−/T+ group, as well as the associations between Braak III tau levels and cognition in this group, support the notion that tau pathology confined to the MTL and, in the absence of Aβ, may be part of the Alzheimer's developmental cascade rather than a feature of aging with few-to-no circumscribed cognitive deficits (i.e. PART). Future studies using longitudinal PET and cognitive data will provide an improved characterization of cognitive change within these A/T groups and better profile how they may transition over time. If realized, this work will lead to a better understanding of the respective spatiotemporal relationships between Aβ and tau in the AD prodrome and offer important implications for person-specific interventions in future anti-Aβ and anti-tau treatment efforts.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

A.J.W., K.J.B., K.R.T., L.D.-W., P.E.G., and A.M.B. report no competing interests. M.W.B. receives royalties from Oxford University Press and serves as a consultant for Eisai, Novartis and Roche Pharmaceutical companies.

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Appendix I: ADNI study investigators

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