Optimal Combinations of Biomarkers to Determine AT(N) in the Alzheimer's Disease

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Research

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Abstract

Background: National Institute on Aging—Alzheimer's Association (NIA-AA) proposed the AT(N) system based on β-amyloid deposition, pathologic tau, and neurodegeneration, which considered the definition of Alzheimer's disease (AD) as a biological construct. However, the associations between different AT(N) combinations and clinical stage and progression have been poorly explored systematically. The aim of this study is to compare different AT(N) combinations using recognized biomarkers within the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort.

Methods: A total of 341 participants from ADNI cohort were classified into AT(N) groups, including 200 cognitively unimpaired (CU) participants and 141 cognitively impaired (CI) participants (101 mild cognitive impairment [MCI] and 40 Alzheimer's disease [AD]). CSF Aβ42 and amyloid-PET ([18F]flutemetamol) were used as biomarkers for A; CSF phosphorylated tau (p-tau) and tau-PET ([18F]flortaucipir) were used as biomarkers for T; CSF total tau (t-tau), FDG-PET, hippocampal volume, temporal cortical thickness and plasma neurofilament light (NfL) were used as biomarkers for (N). Binarization of biomarkers was acquired from Youden index and public cutoffs. The relationship between different AT(N) biomarkers combinations and cognitive changes (longitudinal Mini-Mental State Examination scores and Clinical Dementia Rating Sum of Boxes) was examined using linear mixed modeling and coefficient of variation.

Results: Among CU participants, A−T−(N)− variants were most common. More T+ cases were shown using p-tau than tau PET, and more N+ cases were shown using fluid biomarkers than neuroimaging. Among CI participants, A+T+(N)+ was more common. Tau PET combined with cortical thickness best predicted longitudinal cognitive decline in CI and MRI measurements in CU participants.

Conclusion: These findings suggest that optimal combinations of biomarkers to determine AT(N) are differed by clinical stage. Different biomarkers within a specific component for defining AT(N) cannot be used identically. Furthermore, different strategies for discontinuous biomarkers will be an important area for the future studies.

Background

Alzheimer's disease (AD) is the most common cause of dementia, and one of the main causes of complications and death in the aging population. A series of complex pathobiology are involved in the pathogenesis of AD, including the deposition of extracellular amyloid plaque, tau-related intracellular neurofibrillary tangles (NFTs), neuronal loss and atrophy[1]. Recently, National Institute on Aging—Alzheimer's Association (NIA-AA) proposed a research framework based on the pathological characteristics mentioned above[2]. The framework establishes a classification system consisted of biomarkers of Aβ (A), tau (T), and neurodegeneration (N), and lists a classic AD biomarker grouping including CSF, MRI and PET. However, it's not perfect concordant among biomarkers within a specific component (A, T, or N)[2-3], and it's usually difficult to perform all examinations on patients, which may limit its clinical application. Therefore, how to choose AT(N) biomarkers for patients with different clinical stages is an urgent problem to be solved. Though a lot of researches compared different biomarkers in a certain component[4-6], only one study assessed different combinations of AT(N) using BioFINDER participants[7]. Here, we use a more comprehensive biomarkers group and suppose that AT(N) category prevalence and cognitive prediction would vary by combinations of different biomarkers and clinical stage.

Methods

Participants

All participants in this study were from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which is a longitudinal multicenter study designed to develop clinical, imaging, genetic, and biospecimen biomarkers for tracking the progression of AD. Cognitively unimpaired (CU) participants must be free of memory complaints and cognitively normal. And

cognitively impaired (CI) participants must have a subjective memory concern, including mild cognitively impaired (MCI) participants, whose general cognition and functional performance sufficiently preserved, and AD dementia participants according to NINCDS/ADRDA criteria for probable AD[8]. Demographic and clinical information, neuroimaging, and biomarkers data were downloaded from the ADNI data repository (adni.loni.usc.edu).

CSF and plasma biomarkers analysis

CSF β-Amyloid (1-42), phospho-tau (181P), and total tau were analyzed by the electrochemiluminescence immunoassays (ECLIA) Elecsys following a Roche Study Protocol[4]. Plasma neurofilament light (NfL) was obtained by the Single Molecule Array (Simoa) technique. This assay used a combination of monoclonal antibodies and purified bovine NfL as a calibrator.

Neuroimaging acquisition and processing

3T MRI scans were processed before download as previously described[9-10]. FreeSurfer (ADNI phase 1, grand opportunity and phase 2 data was run with FreeSurfer version 5.1, while phase 3 with version 6.0) was used for further analysis. Regions of interest (ROIs) were extracted, including the bilateral hippocampal volumes (adjusted for intracranial volume [ICV] by calculating the residual term from a linear regression of hippocampal volume versus ICV among ApoE negatively CU participants) and an AD signature cortical thickness (mean thickness in the entorhinal, inferior temporal, middle temporal, and fusiform cortices)[11]. Amyloid, tau and metabolic imaging were performed using [18F]florbetapir, [18F]flortaucipir and [18F]fluorodeoxyglucose (FDG) PET respectively. [18F]florbetapir standardized uptake value ratios (SUVRs) were calculated by averaging the 4 cortical regions: frontal, anterior/posterior cingulate, lateral parietal and lateral temporal, and dividing the ROIs by the whole cerebellum reference region. For tau PET, the inferior temporal cortex (ITC) and the region of Braak V/VI were selected as target ROIs[12]. ITC and Braak V/VI indicated early and late stage of tangle pathology respectively. [18F]flortaucipir data were corrected for partial volume effects using the Geometric Transfer Matrix (GTM) approach and divided by the inferior cerebellar GM reference region[13]. The pre-defined meta-ROIs in FDG PET of AD were composed of the angular gyrus, posterior cingulate, and inferior temporal cortical normalized to pons and vermis[14].

Cognition assessment

Cognition was assessed using longitudinal Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Sum of Boxes (CDRSB). According to the interquartile range (IQR 6-8 years), we selected 7-time points from the baseline to 12 years for longitudinal cognitive assessment.

AT(N) definitions

AT(N) biomarkers included CSF Aβ42 (A1), amyloid PET ([18F]florbetapir) (A2), CSF p-tau (T1), tau PET ([18F]flortaucipir) SUVR in the ITC (T2) and Braak V/VI region (T3), hippocampal volume ([N]1), temporal meta-ROI cortical thickness ([N]2), CSF t-tau ([N]3), AD-characteristic FDG PET SUVR ([N]4), and plasma NfL ([N]5). Binarization of biomarkers (+/-, normal/abnormal) was done using cut-points established by Youden index (Aβ-positive MCI vs Aβ-negative CU, with Aβ status defined by the CSF Aβ42) except for A biomarkers. For CSF Aβ positivity, we used a published cut-point (CSF Aβ42 level, <880 ng/L)[4]. And for amyloid PET, we selected a cutoff of 1.11, which is the upper 95% confidence interval above the mean of a young normal control group[15]. Furthermore, mean ±2 SD from Aβ-negative CU controls (+2 SD for amyloid PET, tau PET, CSF tau, and plasma NfL; -2 SD for CSF Aβ42, hippocampal volume, temporal cortical thickness, and FDG PET), along with 90% sensitivity for AD were used as a sensitivity analysis.

Statistical analyses

Demographics and continuous biomarkers between different groups were compared using Kruskal-Wallis test, and binary biomarkers using Fisher exact test. Associations between biomarkers were analyzed using Spearman rank correlation (ρ), Cohen's kappa coefficient (κ), and percentage agreement (concordance). Prevalence estimates for AT(N) categories were calculated in CU, CI, MCI and AD participants with 95% confidence intervals generated using bootstrap resampling (n=1,000). The relationship between AT(N) variants and cognitive trajectories (longitudinal MMSE and CDRSB) was examined by linear mixed-effects (LME) model (including age, sex and education as covariates, and time as a categorical variable) with subject-specific intercepts and slopes. The goodness of LME models with different AT(N) variants was assessed by marginal R^2. All analyses were performed in IBM SPSS Statistics 20, with significance set at $p<0.05$, 2-tailed.

Results

Study participants

Demographics are presented in **Table 1**, more detailed information are shown in **Supplement Table 1**. Between CU and CI participants, there was no significant difference in age, while there were more females, longer time for education, and less prevalence of *APOE* e4 in the CU group. No significant differences were found between MCI and AD (subgroups of CI) in age, gender, education, or *APOE* e4. MMSE, Aβ42, hippocampal volume, temporal cortical thickness and FDG PET decreased sequentially, while CDRSB, amyloid and tau PET, CSF tau and NfL increased sequentially among CU, MCI, CI and AD groups. However, there was no significance in NfL between MCI and AD. As plasma NfL level was reported to be positively associated with age (ρ=0.471, p<0.01)[16-17], we divided participants into younger and older groups using a median split (age=72.25y) and found there was a significant difference in NfL levels between the resulting groups (p<0.001). Therefore the prevalence of (N)+ using NfL was likely to vary by age in the present cohort, so we calculated the cut-point based on age stratification.

Biomarker relationships

Cut-points were defined as CSF Aβ42 <880 ng/L (A1), amyloid PET >1.1 SUVR (A2), p-tau > 21.11 ng/L (T1), ITC tau PET >2.122 SUVR (T2), Braak V/VI tau PET >1.938 SUVR (T3), adjusted hippocampal volume <-0.4477 cm^3 (N1), temporal meta-ROI thickness <2.9214 mm (N2), CSF t-tau > 233.6 ng/L (N3), FDG PET meta-ROIs <1.2599 SUVR (N4), plasma NfL in younger participants >30.35 ng/L and in older participants >36.45 ng/L. Similar cutoffs were obtained using the 90% sensitivity for AD, while mean ± 2 SD from Aβ-negative CU controls resulted in more conservative cutoffs (**Supplement Table 2**).

Continuous biomarkers within each component were correlated: CSF Aβ42 vs amyloid PET (ρ=-0.671; **Figure 1A**), p-tau vs ITC tau PET (ρ=0.379) and Braak V/VI (ρ=0.380), as well as between the 2 tau PET measures (ρ=0.851; **Figure 1B–D**); hippocampal volume vs temporal cortical thickness (ρ=0.584), vs FDG PET (ρ=0.448), and vs NfL (ρ=-0.395); temporal cortical thickness vs FDG PET (ρ=0.426), and vs NfL (ρ=-0.321); and FDG PET vs NfL (ρ=-0.326). There were weak correlations between CSF t-tau and other neurodegeneration biomarkers: CSF t-tau vs hippocampal volume (ρ=-0.239), vs temporal cortical thickness (ρ=-0.215), vs FDG PET (ρ=-0.145, p<0.05) and vs NfL (ρ=0.188; all p<0.001 except as specially marked; **Figure 1E–N**).

Using binary data, there was a substantial agreement between amyloid biomarkers (**Figure 1A**), between the 2 tau PET measures (**Figure 1B-D**); and a moderate agreement between the 2 MRI imaging measures (**Figure 1E**). Fair agreement was seen between p-tau and tau PET (**Figure 1B-C**), between MRI imaging measures, FDG PET and NfL (**Figure 1G, H, J, K, N**), while slight agreement between CSF t-tau and other neurodegeneration biomarkers (**Figure 1F, I, L, M**).

Prevalence measures in CU participants

Prevalence for AT(N) categories in CU and CI participants are summarized in **Figure 2**, **Figure 3** and **Supplement Table 3-4**. When only considering A and T in CU, A-T- were the most common categories (range 43.5% [A1T1; 95% confidence interval, 36.6%-50.5%] to 62.0% [A2T2; 95% confidence interval, 55.0%-68.8%]). Comparing A biomarkers, slightly more were negative when using CSF Aβ42 than amyloid PET. Positivity in T was highest when using CSF p-tau both in the case of A+ or A-, while the prevalence of T+ was much less when using tau PET (**Figure 2A**). These results indicate that using CSF p-tau may greatly increase the positive rate of T component compared to tau PET in CU participants.

When adding (N) biomarkers, the most prevalent categories was A-T-(N)- (range 26.1% [A2T1(N)5; 95% confidence interval, 18.7%-33.3%] to 50.8% [A2T2(N)2; 95% confidence interval, 44.1%-58.0%]). Although there were 8 possible categories in each AT(N) variants, several categories were lacking or had very low frequencies (**Figure 3A**), including A+T+(N)+, A+T-(N)+ and A-T+(N)+ when using MRI imaging and FDG PET, as well as A+T+(N)-, A+T-(N)+ and A-T+(N)- in the combination of CSF p-tau and t-tau, since strong correlation (ρ=0.980, p<0.001) and almost perfect agreement (κ=0.876; concordance=93.8%) between them[18]. Among the different biomarkers for (N), CSF t-tau and plasma NfL were the most prevalent biomarkers resulting in (N)+ cases (**Figure 3A**).

Prevalence measures in CI participants

A+T+ was the main category when only using A and T biomarkers in CI (range 39.7% [A1T3; 95% confidence interval, 31.8%-48.4%] to 54.6% [A2T1; 95% confidence interval, 45.7%-63.5%]). A and T categories of different AT(N) variants in CI demonstrated similar trends to CU (i.e., higher prevalence of A+ using amyloid PET and lower prevalence of T+ using tau PET) (**Figure 2B**). There were significant differences in A and T categories between 2 subgroups of CI (Fisher exact test, all p <0.001). In MCI, A-T- were the most common categories when using tau PET in Braak V/VI (**Figure 2C**). In AD, A+T+N+ accounted for about 75% (range 70% [A1T3; 95% confidence interval, 55.8%-85.3%] to 82.5% [A2T1; 95% confidence interval, 69.8%-93.3%]); the difference from other groups was the lower prevalence of T+ using CSF p-tau than tau PET in the case of A- (**Figure 2D**).

When adding (N) biomarkers, the most prevalent categories was A+T+(N)+ (range 29.9% [A1T3(N)4; 95% confidence interval, 23.3%-38.6%] to 51.8% [A2T1(N)3; 95% confidence interval, 43.2%-60.3%]), and the frequencies of T+(N)- and T-(N)+ in the combination of CSF p-tau and t-tau were relatively low (**Figure 3B**). As mentioned above, A-T-N- was the main category when using tau PET in Braak V/VI combined with some N biomarkers (A1T3[N]1, A1T3[N]2, A1T3[N]4, A1T3[N]5 and A2T3[N]4) in MCI (**Supplement Figure 1A**). AD group had the most A+T+N+ (range 60.6% [A1T3(N)5; 95% confidence interval, 44.1%-76%] to 80% [A2T1(N)3; 95% confidence interval, 67.6%-92.1%]) among 3 groups. Again, several categories were lacking or had low frequencies (A-T+N-, A-T-N+ when using tau PET) (**Supplement Figure 1B**). The prevalence of all the (N) biomarkers resulting in (N)+ cases was approximative, except it was relatively low when using FDG PET in CI (**Figure 3B**).

Longitudinal cognition

Overall findings for longitudinal cognition using continuous predictors are summarized in **Figure 4**, **Figure 5** and **Supplement Table 5-7**. In CU participants, age and education significantly affected cognition (age, p=0.027 and education, p=0.048 in CDRSB; age, p=0.025 and education, p<0.001 in MMSE), consistent with previous findings[19-20]. When using a single AT(N) biomarker to predict cognitive changes, exclusively MRI imaging contributed significantly ([N]2 in CDRSB, [N]1 in MMSE; **Figure 4G, H**). The best AT(N) variants capturing changes in cognition in CDRSB and MMSE were A2T3[N]2 (R^2=7.84%) and A2T1[N]1 (R^2=12.29%) respectively, but not all included biomarkers contributed significantly (**Figure 4B, E**). For the marginal R^2 in CU participants relatively low, we considered whether random effects (i.e., individual heterogeneity) accounted for more variance. Then we calculated conditional R^2 using MRI imaging biomarkers ([N]2 for CDRSB and [N]1 for MMSE). Adding individual heterogeneity and slope for time as the random effect, conditional R^2 increased to 19.32% and 33.55% in CDRSB and MMSE respectively. These results indicated that

longitudinal cognition in CU participants was mainly associated with individual characteristics; and MRI imaging measurements were the best biomarkers to predict cognitive changes.

In CI participants, individual characteristics were not significantly associated with cognitive decline. Almost all single AT(N) biomarkers could predict longitudinal cognition except CSF p-tau (p=0.061) and t-tau (p=0.051) in CDRSB, and marginal R^2 using MRI imaging and tau PET was relatively higher than others. The AT(N) variants combining CSF Aβ42, tau PET, and temporal cortical thickness were the best predictors in both CDRSB and MMSE, and almost all included variables contributed significantly (**Figure 5B, C, E, F**). Then we found the interaction between time and AT(N) variants significantly improved the goodness of model fit (AIC and BIC) using paired t test (p<0.001 in CDRSB and MMSE), and interactions dominated the main effects. Again, CSF Aβ42, tau PET, and temporal cortical thickness were the best in both scales (CDRSB: A1T2[N]2, R^2=52.76%; A1T3[N]2, R^2=52.24%; MMSE: A1T3[N]2, R^2=50.84%; A1T2[N]2, R^2=50.25%) and all interactions were significant (**Figure 5, G-J**).

Sensitivity analyses

We repeated the AT(N) prevalence analyses using alternative cut-points (**Supplement Table 8**). Using cutoffs from 90% sensitivity for AD, except for more amyloid positivity using CSF Aβ42 in CU participants, other results were in concordance with main cutoffs. However, cut-points defined by mean ± 2 SD from Aβ-negative CU controls were more conservative. There was the least tau positivity using CSF rather than PET, and temporal cortical thickness in all participants was negative.

Discussion

In this study, we found that different combinations of AT(N) biomarkers have different effects on category prevalence and predictions of cognitive decline. First, it is not surprising that the composition of AT(N) categories is different between CU and CI. Categories representing AD continuum was the most common in CI while more subjects with non-AD pathologic change were observed in CU[2]. Moreover, different AT(N) variants give considerable differences in prevalence, such as less prevalence of T+ when using tau PET than CSF p-tau in all groups, and more prevalence of N+ using fluid biomarkers in CU. Finally, different AT(N) combinations have different associations with cognitive changes, with differences between CU and CI (MRI imaging was more influential in CU participants, and tau PET in CI participants). Taken together, these results indicate that different combinations lead to different AT(N) classifications of individuals and different predictions of longitudinal cognition. Our results have important implications for how to choose AT(N) combinations according to different needs of research or clinical applications. For instance, we tend to use dynamic fluid examinations for early screening and prevention, and cognition may be predicted by non-invasive MRI imaging in CU; while for accurate clinical staging and prognosis of patients with cognitive impairment, imaging measures that represent the magnitude of the neuropathologic load or damage accumulated over time may help a lot, especially tau PET.

Biomarkers of AD mainly include fluids and imaging, here we chose 7 classic biomarkers mentioned in NIA-AA Research Framework 2018[2, 21], and plasma NfL, a candidate neurodegeneration marker found recently[16-17]. However, different biomarkers in the specific AT(N) component may discordant[2,22], because of cut-point strategies, characteristics of pathological progression and limitations of methods, etc. In our study, the continuous relationship between CSF Ab42 and amyloid PET is “L-shaped” rather than linear (**Figure 1A**)[23-24]. This may be owing to a temporal offset between them[6,25-26]. And in T biomarkers, the correlation between CSF p-tau and tau PET is imperfect, because p-tau seems to plateau later in the disease[27] while the tau PET signal keeps increasing continuously[28]. Among biomarkers in the (N) component, MRI imaging tends to reflect cumulative neuron loss and shrinkage of the neuropil[29-31], CSF t-tau and plasma NfL manifest the intensity of neuronal injury dynamically[32-33], and FDG PET likely indicates both sides[34]. These differences may explain the discordance among different (N) biomarkers.

For AT(N) prevalence, we noted that both AT(N) categories and variants differ between CU and CI participants. Normal AD biomarkers (A-T-[N]-) and Non-AD pathologic change (A-T+[N]-, A-T+[N]+ and A-T-[N]+) account for the most of CU individuals, while Alzheimer's continuum (A+T+[N]-, A+T+[N]+, A+T-[N]- and A+T-[N]+) for CI individuals, especially AD (A+T+[N]-, A+T+[N]+)[2]. Still, there are about 1/4 CU individuals classified as AD continuum without cognitive symptoms. Since cognition is also a continuum and the definition of CU is independent from biomarker findings according to the NIA-AA research framework[2]. In our study, the overall prevalence of A+ in CU participants is similar, in consistent with a meta-analysis demonstrated[35]. But the increments of amyloid positivity between 2 groups were higher when using amyloid PET. This may be due to CSF analysis detecting cerebral Aβ accumulation earlier than PET[6,25-26]. Same findings were shown in tau positivity by comparing CSF and PET owing to temporal lag[28,36]. Among the neurodegeneration biomarkers, CSF t-tau and plasma NfL are more common in CU participants, while there are no evident differences in CI. These results in line with several studies that found CSF t-tau and blood NfL are increased before symptom onset[28, 37].

In order to verify the prevalence findings across AT(N) categories, we repeated prevalence calculations in different cut-points strategies and found the results were not completely consistent. This finding highlights the optimization of categorization strategies is important for future studies.

Here, we analyzed the prediction of different AT(N) variants on longitudinal cognition which evaluated by both CDRSB and MMSE. CDRSB may enable a more detailed analysis of subtle changes with different staging of dementia severity[38]. First of all, optimal variants differ by clinical stage. Only MRI imaging measures were significantly associated with cognition changes in CU participants, whereas the best model for predicting cognition in CI included CSF Aβ42, tau PET and cortical thickness. When using a single AT(N) biomarker for prediction, there was no obvious difference between CSF and PET amyloid plaque. This finding may indicate CSF Aβ42 and amyloid PET can be used interchangeably in practice as several literatures reported[4,39], which is consistent with the characteristic of "A" as state biomarkers[3]. However, CSF p-tau is increased earlier in the disease stage than tau PET[5,7,39]. Therefore, between 2 subgroups of CI, the difference of tau PET was more significant than that of CSF p-tau. This may be the reason why tau PET far exceeded CSF p-tau on longitudinal cognitive prediction in CI. And early tangle pathology of tau PET was better for prediction on CDRSB than MMSE, which is consistent with the characteristics of the scales. Compared to other N biomarkers, we found MRI imaging measures were the best, especially cortical thickness. Since the hippocampal volume is highly related to ICV[11], and differing methods of adjusted volume by ICV associated with gender, age and study populations may affect study power[40]. A study proposed to use thickness measurements rather than volumes to assess neurodegeneration in AD cohorts with a large age range[40]. Our results also suggested that cortical thickness may predict cognition more precisely. Same findings were shown when considering interactions in CI, but the interactions dominated the main effects. This result demonstrates that although AT(N) variants can predict cognitive changes, their marginal effects rely on the time level. Overall, we got relatively robust results in this cohort (MRI imaging for CU and the combination of tau PET and cortical thickness using MRI for CI). Compared to a recent study recruiting participants from Swedish BioFINDER[7], we confirmed the importance of tau PET in AD diagnosis and staging, and highlight that cortical thickness may be of great significance to cognition declines and staging severity.

Limitations

This study has several limitations. First, the sample size in our study was moderate, which may have some effects on study power. Further, the greater individual heterogeneity of CU participants may be a reason of low marginal R^2. Then, differences were observed among different cut-points strategies, and between binary or continuous biomarkers as another study reported[7]. So, more approaches to selecting normal/abnormal cutoffs or alternatives of the binarization (semicontinuous scale, i.e. the centiloid scale)[21] are needed to be tested. Finally, we only determined typical AD biomarkers in this study. With the emergence of more and more biomarkers, they may also need to be included.

Conclusions

Collectively, the proposal of the A/T/N framework makes a more precise division of the Alzheimer's continuum from the pathology[2], but different biomarkers for defining AT(N) cannot be used identically. Each component of biomarkers for AT(N) system classification plays different roles in the stating and staging of AD, and the optimal combinations for cognitive prediction may differ by clinical stage. Furthermore, different strategies for discontinuous biomarkers will be an important area for future studies.

Abbreviations

NIA-AA: National Institute on Aging—Alzheimer's Association; AT(N): β-amyloid, tau, and neurodegeneration classification system; AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; CU: cognitively unimpaired; CI: cognitively impaired; MCI: mild cognitive impairment; Aβ: β-amyloid; p-tau: tau phosphorylated at Thr181; t-tau: total tau; NfL: neurofilament light; NFTs: neurofibrillary tangles; ECLIA: electrochemiluminescence immunoassays; ROIs: regions of interest; ICV: intracranial volume; FDG: fluorodeoxyglucose; SUVRs: standardized uptake value ratios; ITC: inferior temporal cortex; GTM: Geometric Transfer Matrix; MMSE: Mini-Mental State Examination; CDRSB: Clinical Dementia Rating Sum of Boxes; IQR: interquartile range; LME: linear mixed-effects.

Declarations

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Contributors

Rong-Rong Lin: analysis and interpretation of the data, and drafting the manuscript; Yan-Yan Xue, Xiao-Yan Li, and Yi-He Chen: data acquisition, analysis and interpretation of the data; Qing-Qing Tao: funding, designed the study, critical revision of the manuscript; Zhi-Ying Wu: funding, conceptualized and designed the study, critical revision of the manuscript. All authors reviewed the manuscript. All authors have contributed to the manuscript revising and editing critically for important intellectual content and given final approval of the version and agreed to be accountable for all aspects of the work presented here. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Institutional Review Boards approved the study procedures across institutions participating in ADNI. Written informed consent to share data for scientific research purposes was obtained from each participant. A request for access to data was approved by the ADNI Data and Publication Committee (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_DSP_Policy.pdf).

Consent for publication

Not applicable.

Competing interests

None declared

Data availability statement

Data are available on reasonable request to the corresponding authors.

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Tables

Table 1 Characteristics of ADNI participants

	CU	CI	*p*	MCI	AD	*p*
No.	200	141	CU vs. CI	101	40	MCI vs. AD
Age at baseline, y	70.95±6.27	72.25±7.08	0.074417	72.47±6.69	71.72±8.06	0.57102
Female	115(57.5%)	60(42.6%)	<0.05	41(40.6%)	19(47.5%)	0.454664
Education, y	16.77±2.39	15.98±2.82	<0.05	16.21±2.98	15.40±2.31	0.089235
ApoE e4 positive	71(35.7%)	61(43.3%)	<0.01	38(37.6%)	23(57.5%)	0.097857
MMSE at baseline	29.11±1.10	27.61±2.32	<0.0001	28.15±1.74	26.28±2.99	<0.0001
CDRSB at baseline	0.13±0.47	1.32±1.11	<0.0001	0.98±0.65	2.19±1.51	<0.0001
CSF Aβ42, ng/L	1332.84±643.16	1029.24±660.36	<0.0001	1159.51±703.67	700.33±375.32	<0.0001
CSF Aβ42 positive	61(30.5%)	82(58.2%)	<0.0001	48(47.5%)	34(85.0%)	<0.0001
Amyloid PET SUVR	1.11±0.18	1.26±0.26	<0.0001	1.20±0.24	1.42±0.22	<0.0001
Amyloid PET positive	63(31.5%)	92(65.2%)	<0.0001	56(55.4%)	36(90.0%)	<0.0001
CSF p-tau, ng/L	22.21±10.85	29.65±17.95	<0.0001	26.67±15.16	37.15±22.06	<0.01
CSF p-tau positive	83(41.5%)	95(67.4%)	<0.0001	62(61.4%)	33(82.5%)	<0.05
Tau PET in ITC SUVR	1.99±0.28	2.65±1.20	<0.0001	2.28±0.74	3.60±1.57	<0.0001
Tau PET in ITC positive	41(20.5%)	80(56.7%)	<0.0001	46(45.5%)	34(85.0%)	<0.0001
Tau PET in Braak5/6 SUVR	1.81±0.19	2.17±0.70	<0.0001	1.95±0.33	2.72±1.02	<0.0001
Tau PET in Braak5/6 positive	40(20.0%)	72(51.1%)	<0.0001	40(39.6%)	32(80.0%)	<0.0001
Hippocampal volume, cm3	-0.059±0.808	-1.09±1.11	<0.0001	-0.80±1.03	-1.83±0.95	<0.0001
Hippocampal volume positive	51(25.5%)	95(67.4%)	<0.0001	60(59.4%)	35(87.5%)	<0.001
Temporal meta-ROI thickness, mm	3.01±0.15	2.80±0.28	<0.0001	2.86±0.25	2.65±0.28	<0.0001
Temporal meta-ROI	41(20.6%)	90(63.8%)	<0.0001	56(55.4%)	34(85.0%)	<0.01

thickness positive						
CSF t-tau, ng/L	244.13±98.70	306.61±152.66	<0.0001	281.77±130.47	369.34±185.41	<0.01
CSF t-tau positive	90(45.0%)	95(67.4%)	<0.0001	62(61.4%)	33(82.5%)	<0.05
FDG-PET meta-ROI SUVR	1.33±0.11	1.22±0.14	<0.0001	1.26±0.13	1.11±0.12	<0.0001
FDG-PET meta-ROI SUVR positive	34(24.1%)	85(62.0%)	<0.0001	52(52.5%)	33(86.8%)	<0.0001
plasma NfL, ng/L	35.92±15.72	43.66±20.62	<0.01	41.82±20.90	48.28±19.44	0.128508
plasma NfL positive	66(47.8%)	81(69.8%)	<0.01	52(62.7%)	29(87.9%)	<0.01

Abbreviations: Aβ = β-amyloid; amyloid PET = [18F]florbetapir PET; CDRSB = Clinical Dementia Rating Sum of Boxes；CI = cognitively impaired; CU = cognitively unimpaired; FDG-PET = [18F]fluorodeoxyglucose PET; ITC = inferior temporal cortex; MMSE = Mini-Mental State Examination; NfL = neurofilament light; p-tau = phosphorylated at Thr181; ROI = region of interest; tau PET = [18F]flortaucipir PET; SUVR = standardized uptake value ratio.

Data are presented as mean (SD) or n (%).

Figures

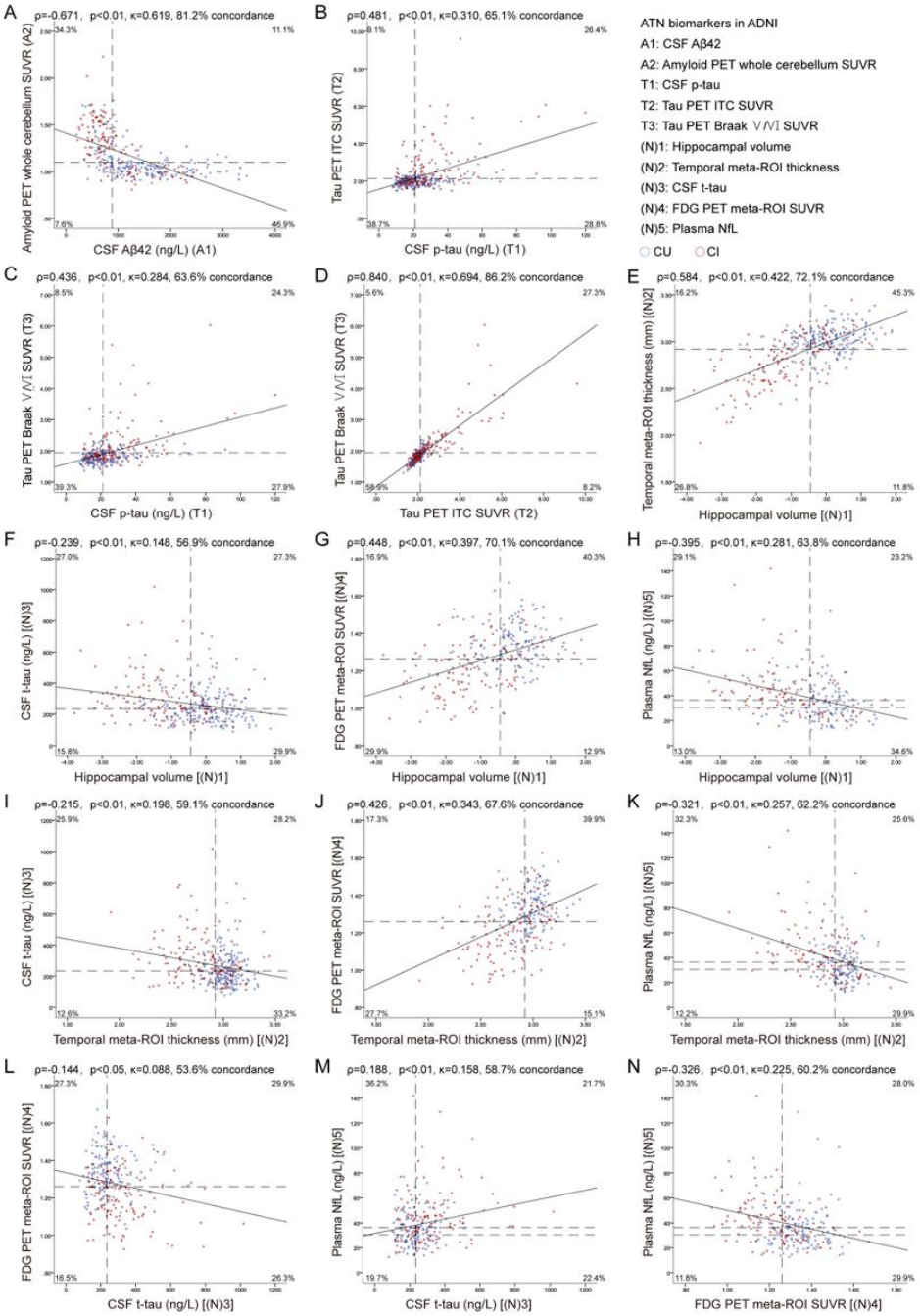
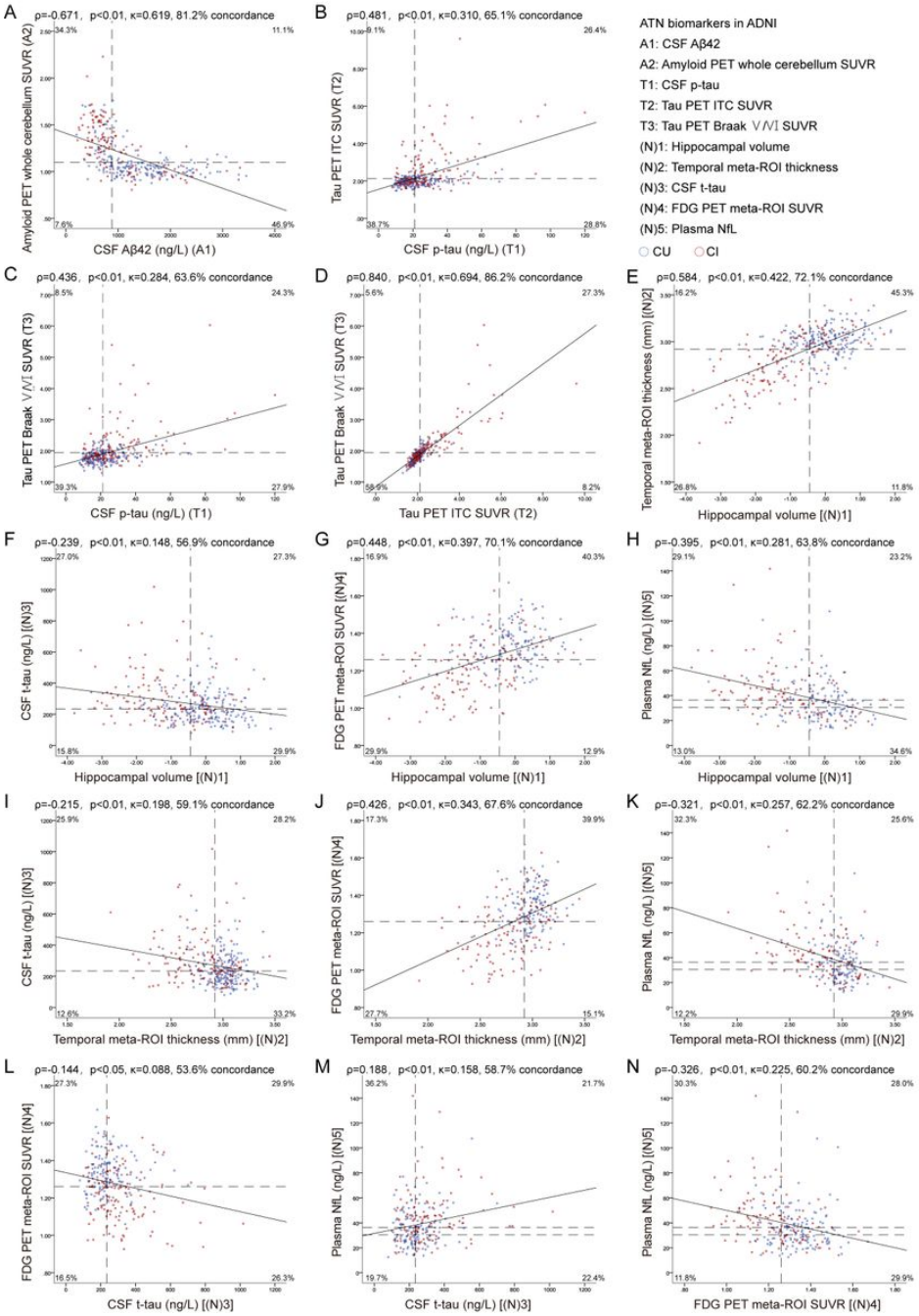


Figure 1

Relationships between biomarkers in A, T or (N) component. Scatterplots show the association between continuous measures for amyloid (A), tau (B-D) and neurodegeneration (E-N) biomarkers. Dashed lines indicate cutoff points. Spearman correlations (ρ) with p values, Cohen kappa statistic (κ), and concordance (percentage showing both biomarkers positive or negative) are shown at the top of each panel. For A comparisons, the upper left and lower right quadrants indicate concordance positive (+/+) and negative (-/-). And for T comparisons, lower left and upper right quadrants indicate concordance positive and negative, respectively. For the comparisons (N)3 vs (N)5, the upper right and lower left quadrants concordance positive and negative, respectively. For the 4 remaining (N) comparisons, concordant positive is in the upper left quadrant, while concordant negative is in the lower right. Percentage figures across quadrants indicate distribution (percentage-wise) of participants.



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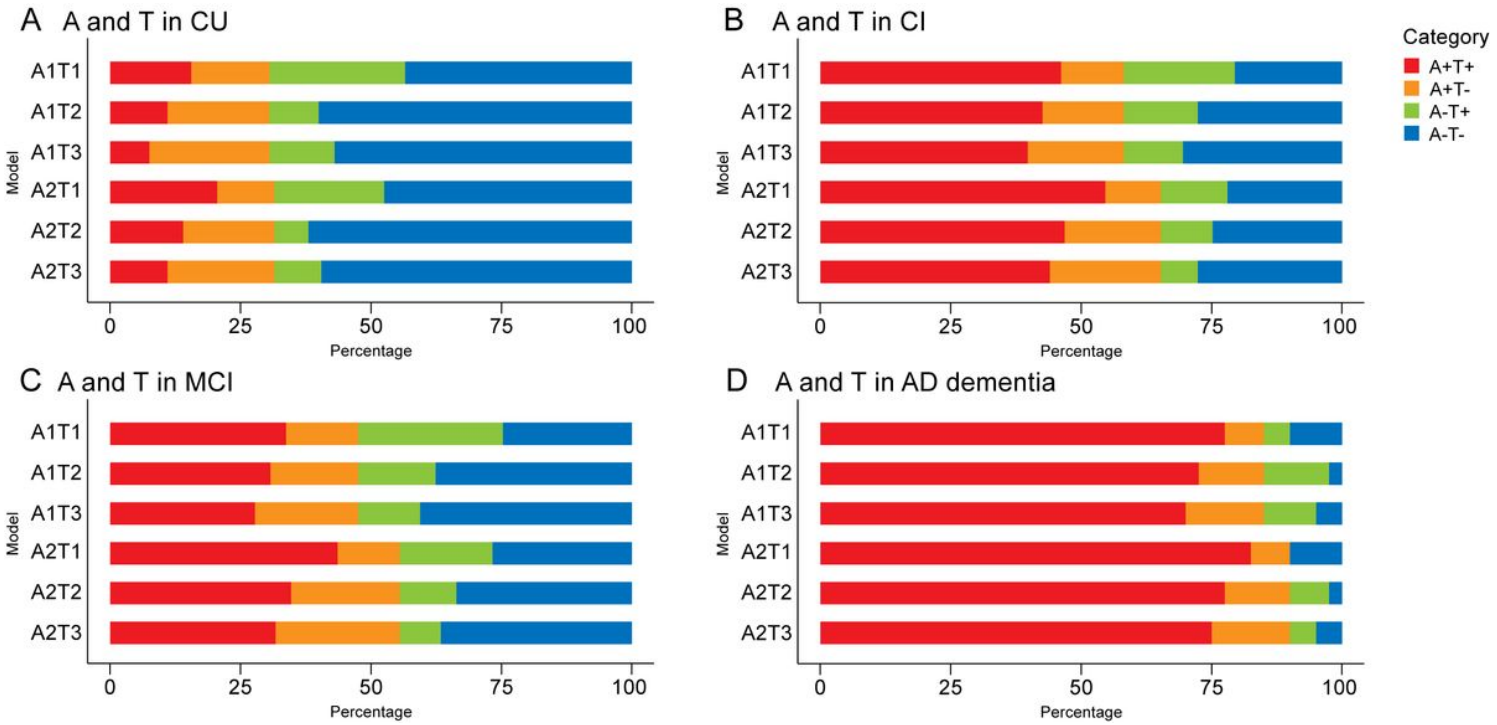
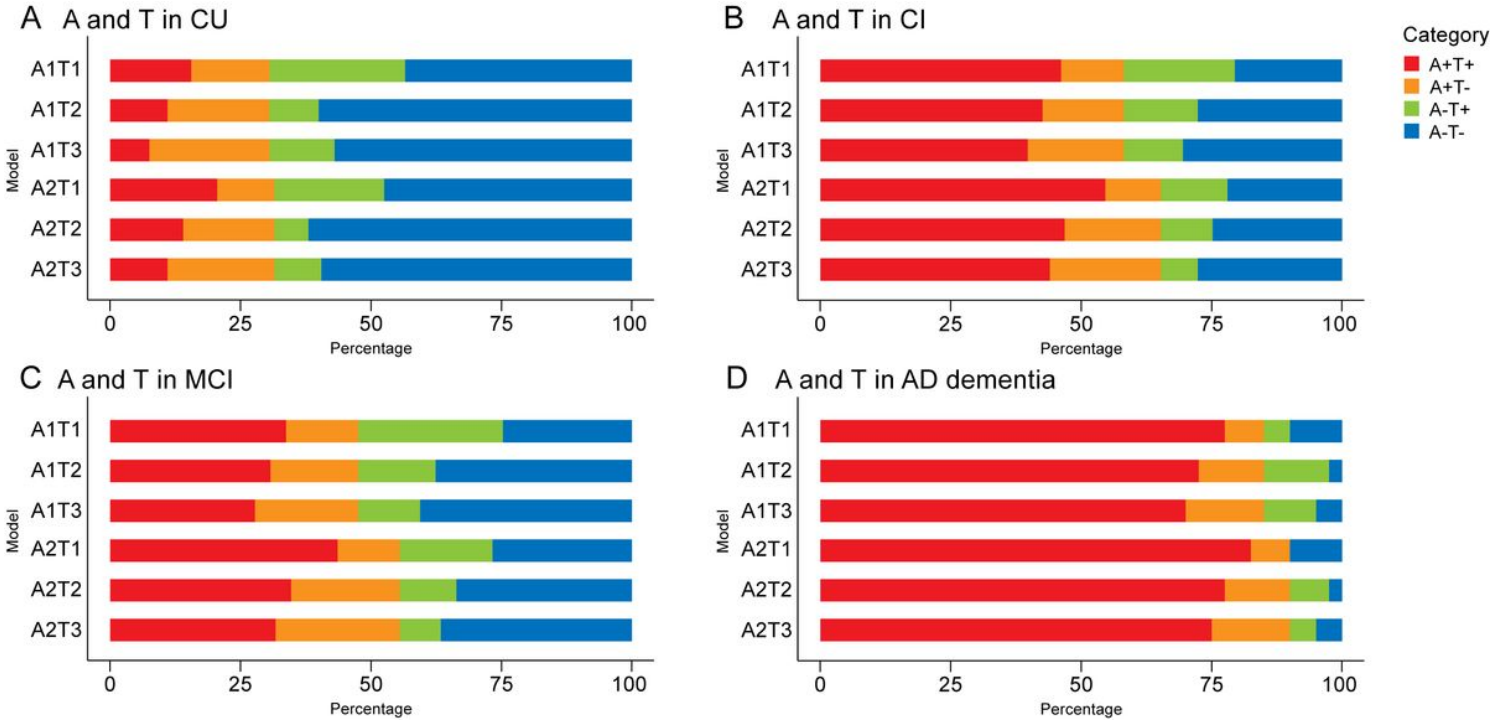


Figure 2

Prevalence of different AT(N) categories in different AT variants. Prevalence of different AT(N) categories in different AT variants among cognitively unimpaired (CU) (A) and cognitively impaired (CI) (B) participants in ADNI. Mild cognitively impaired (MCI) (C) and Alzheimer's disease (AD dementia) (D) are 2 subgroups of CI. CSF Aβ42 (A1); amyloid PET whole cerebellum standardized uptake value ratio (SUVR) (A2); CSF tau phosphorylated at Thr181 (T1); tau PET inferior temporal cortex SUVR (T2); tau PET Braak V/VI SUVR (T3).



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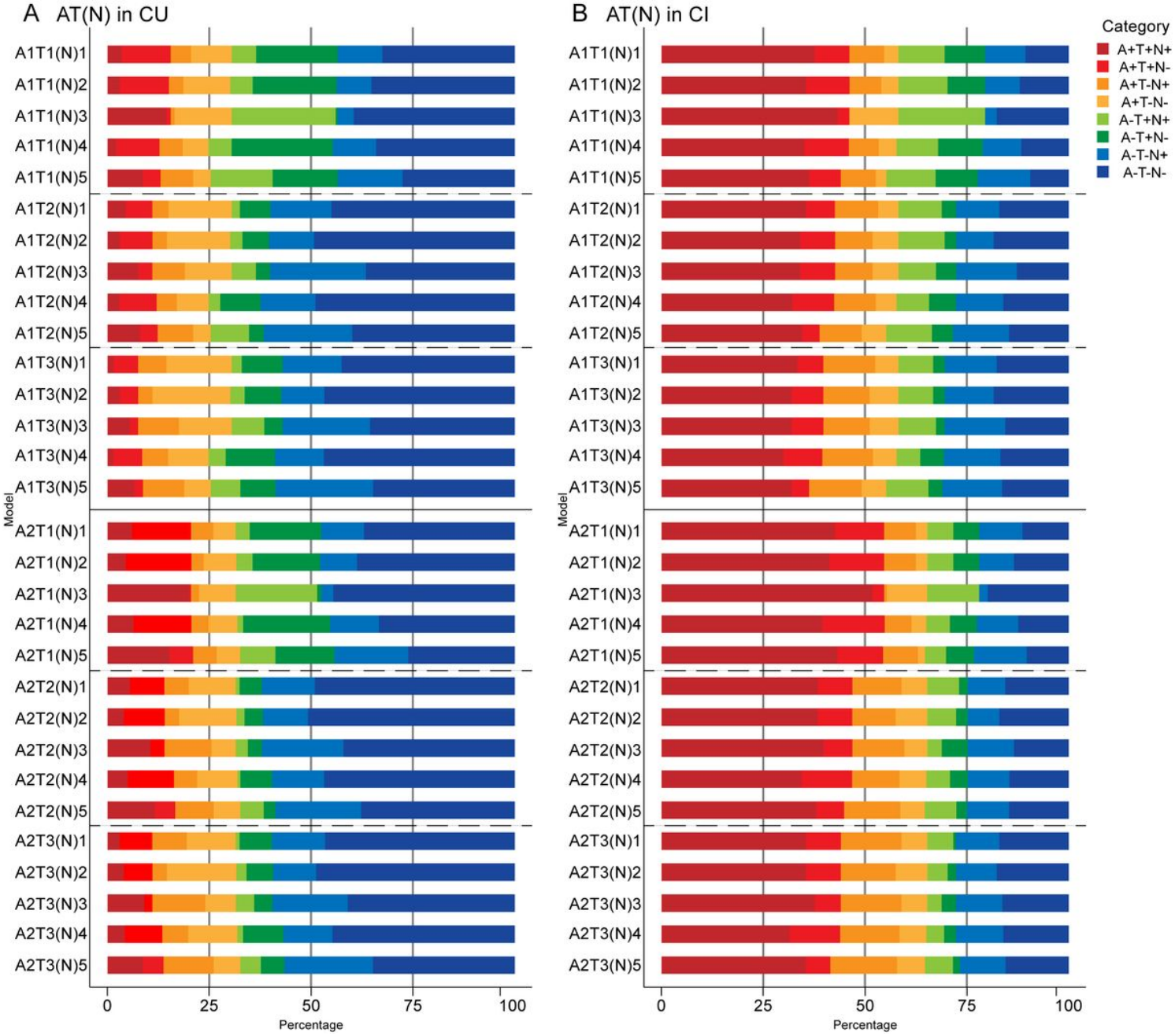
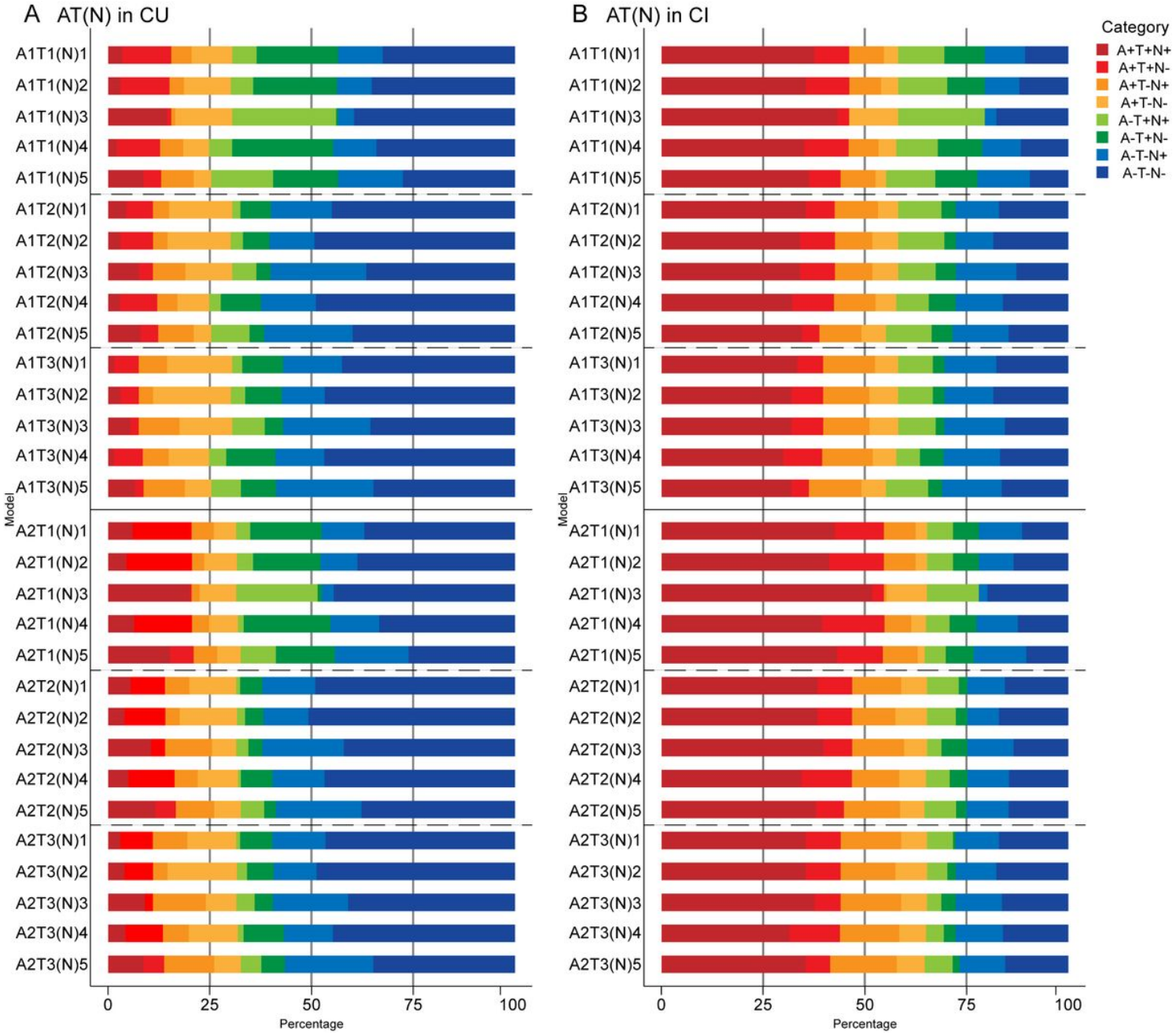


Figure 3

Prevalence of different AT(N) categories in different AT(N) variants among CU and CI participants. Prevalence of different AT(N) categories in different AT(N) variants among cognitively unimpaired (CU) (A) and cognitively impaired (CI) (B) participants in ADNI. CSF Aβ42 (A1); amyloid PET whole cerebellum standardized uptake value ratio (SUVR) (A2); CSF tau phosphorylated at Thr181 (T1); tau PET inferior temporal cortex SUVR (T2); tau PET Braak V/VI SUVR (T3); hippocampal volume [(N)1]; temporal meta-ROI thickness [(N)2]; CSF total tau [(N)3]; FDG PET meta-ROI SUVR [(N)4]; plasma neurofilament light [(N)5].



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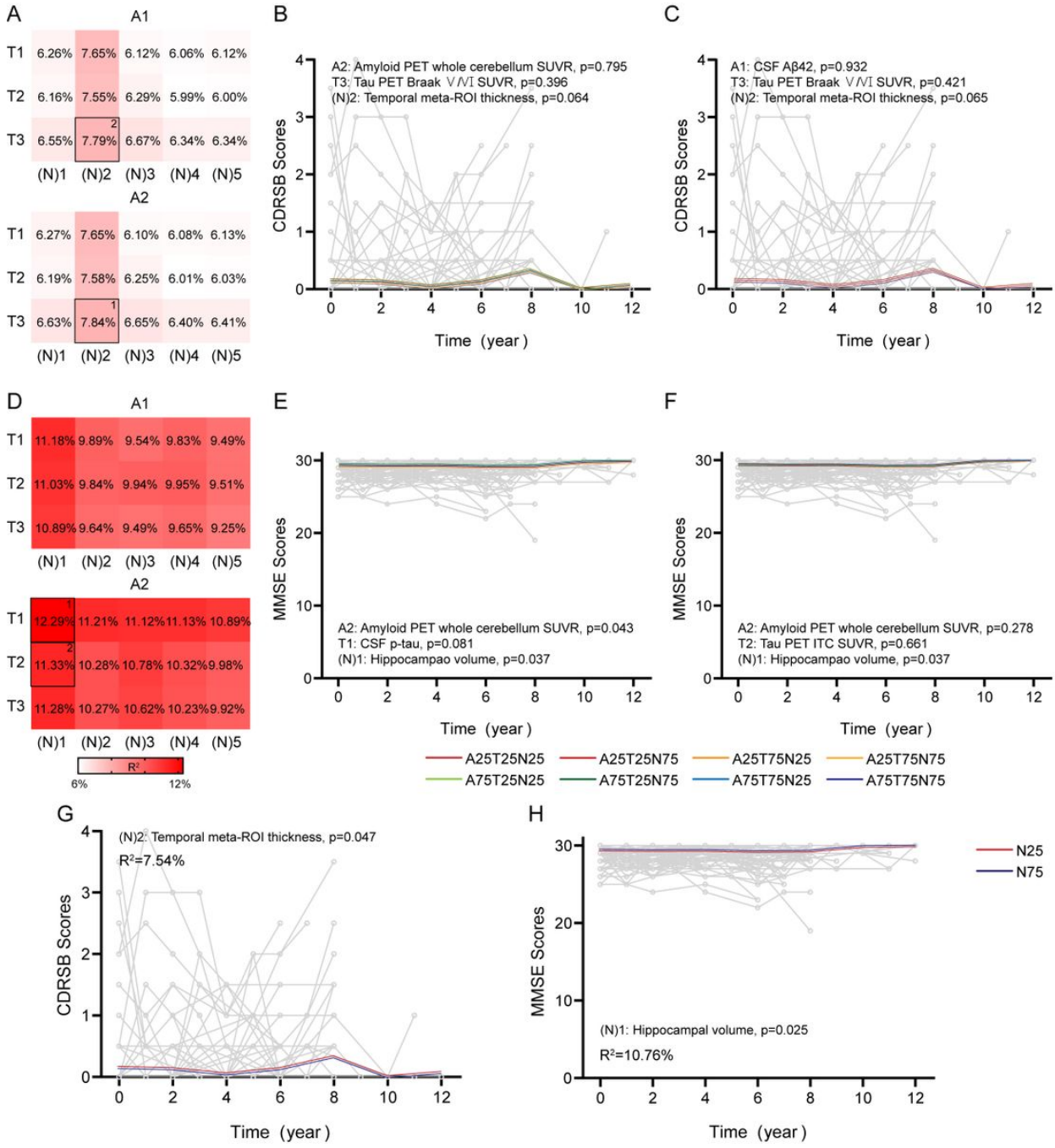
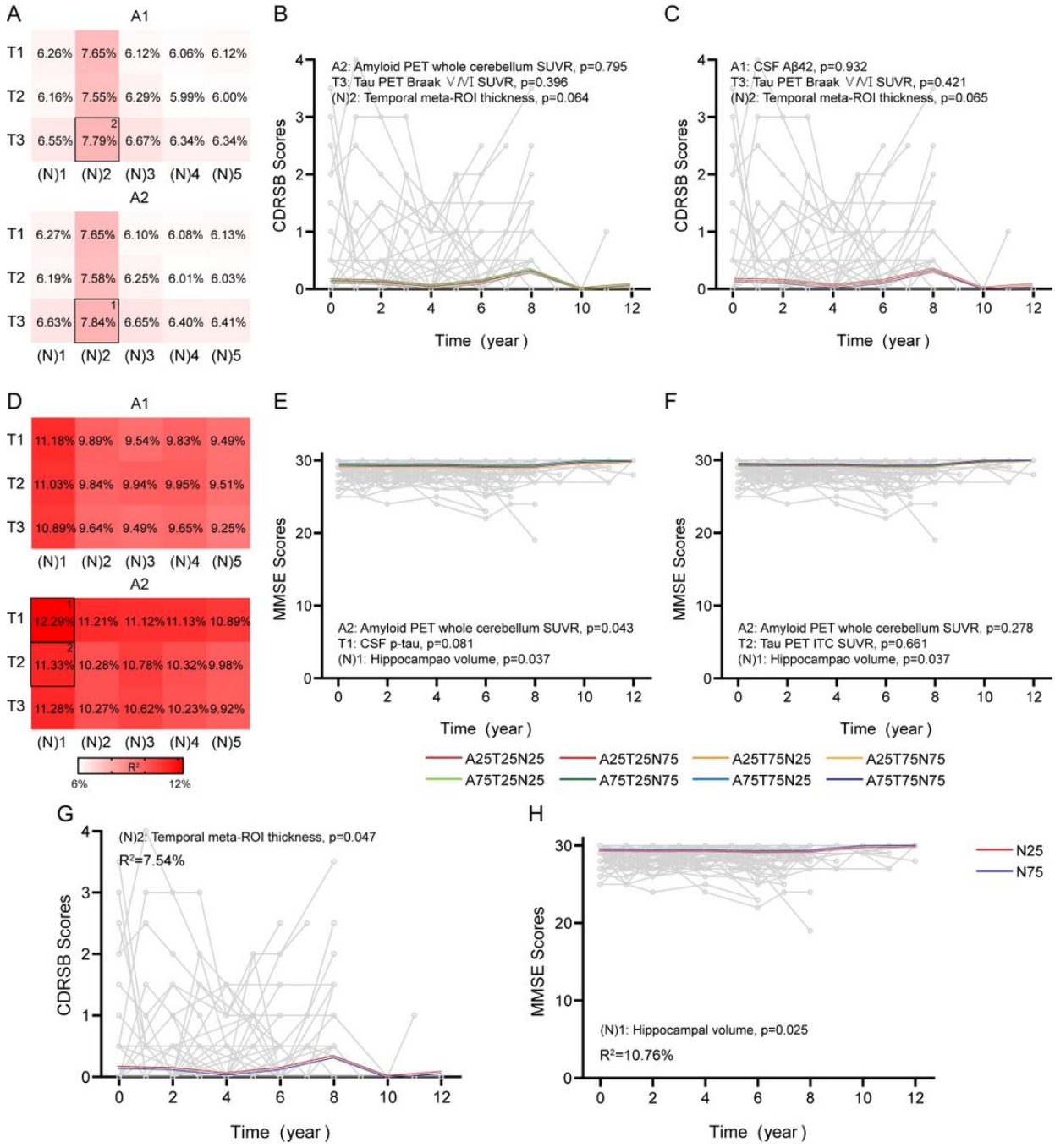


Figure 4

Associations between different AT(N) combinations and longitudinal cognition in CU group. Marginal R2 for different AT(N) variants to predict longitudinal Clinical Dementia Rating Sum of Boxes (CDRSB) and Mini-Mental State Examination (MMSE) for cognitively unimpaired (CU), respectively (divided by A biomarkers) (A, D). The selected models in (B, C) and (E, F) are the top 2 best for different cognitive scales. The LME models with significant AT(N) biomarkers to predict longitudinal CDRSB and MMSE, respectively (G, H); AT(N) variants chosen in the model and p values, and marginal R2 are shown at the top (CDRSB) or bottle (MMSE) of each panel; 25 and 75 refer to 25th and 75th quartiles, where lower indicates a more abnormal biomarker.



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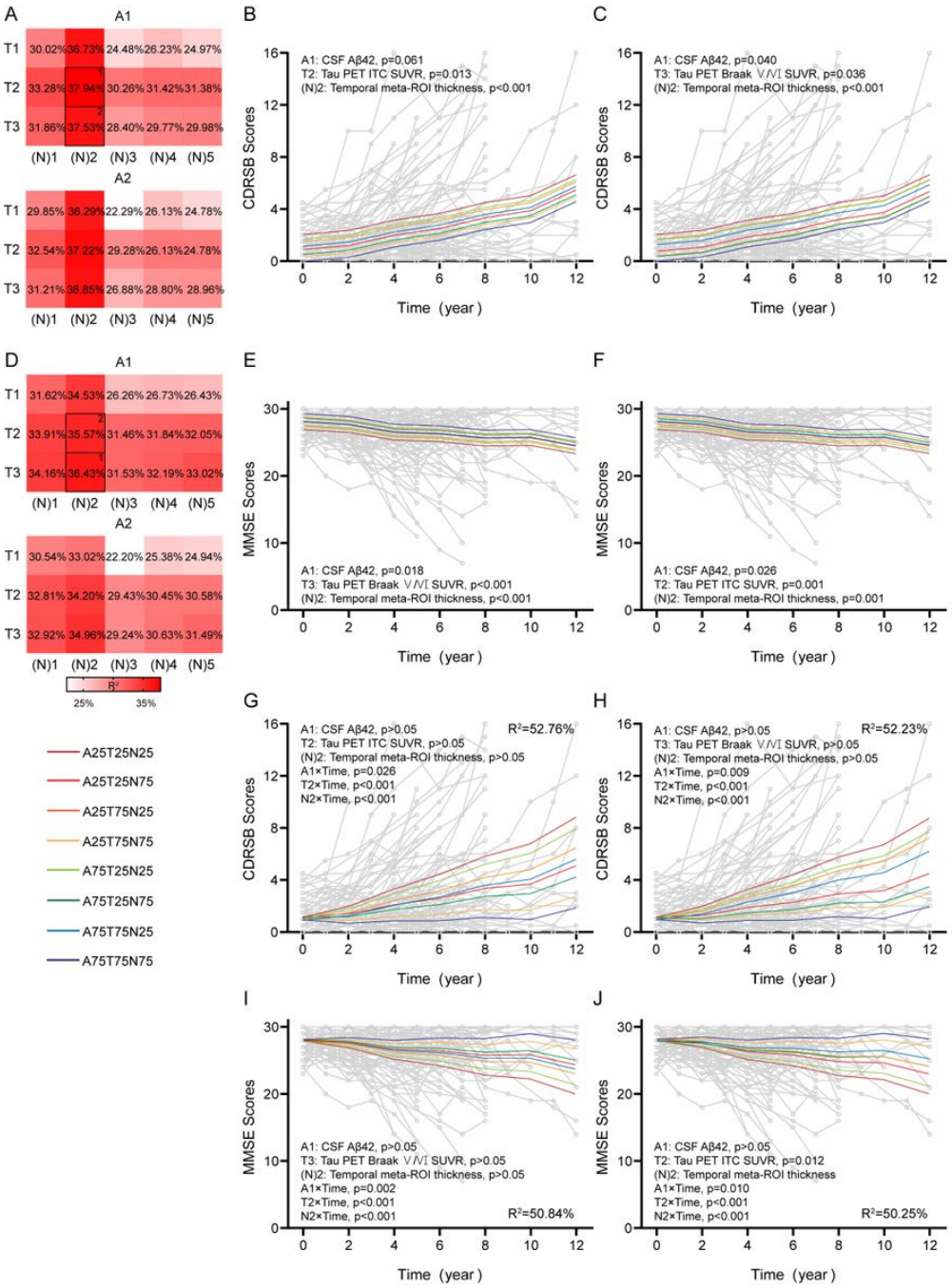

Figure 5

Associations between different AT(N) combinations and longitudinal cognition in CI group. Marginal R2 for different AT(N) variants to predict longitudinal Clinical Dementia Rating Sum of Boxes (CDRSB) and Mini-Mental State Examination (MMSE) for cognitively impaired (CI), respectively (divided by A biomarkers) (A, D). The selected models in (B,C) and (E,F) are the top 2 best for different cognitive scales. The top 2 best models with interaction between time and AT(N) variants to predict longitudinal CDRSB and MMSE, respectively (G-J); AT(N) variants chosen in the model and p values, and marginal R2 are shown at the top (CDRSB) or bottle (MMSE) of each panel; 25 and 75 refer to 25th and 75th quartiles, where lower indicates a more abnormal biomarker.

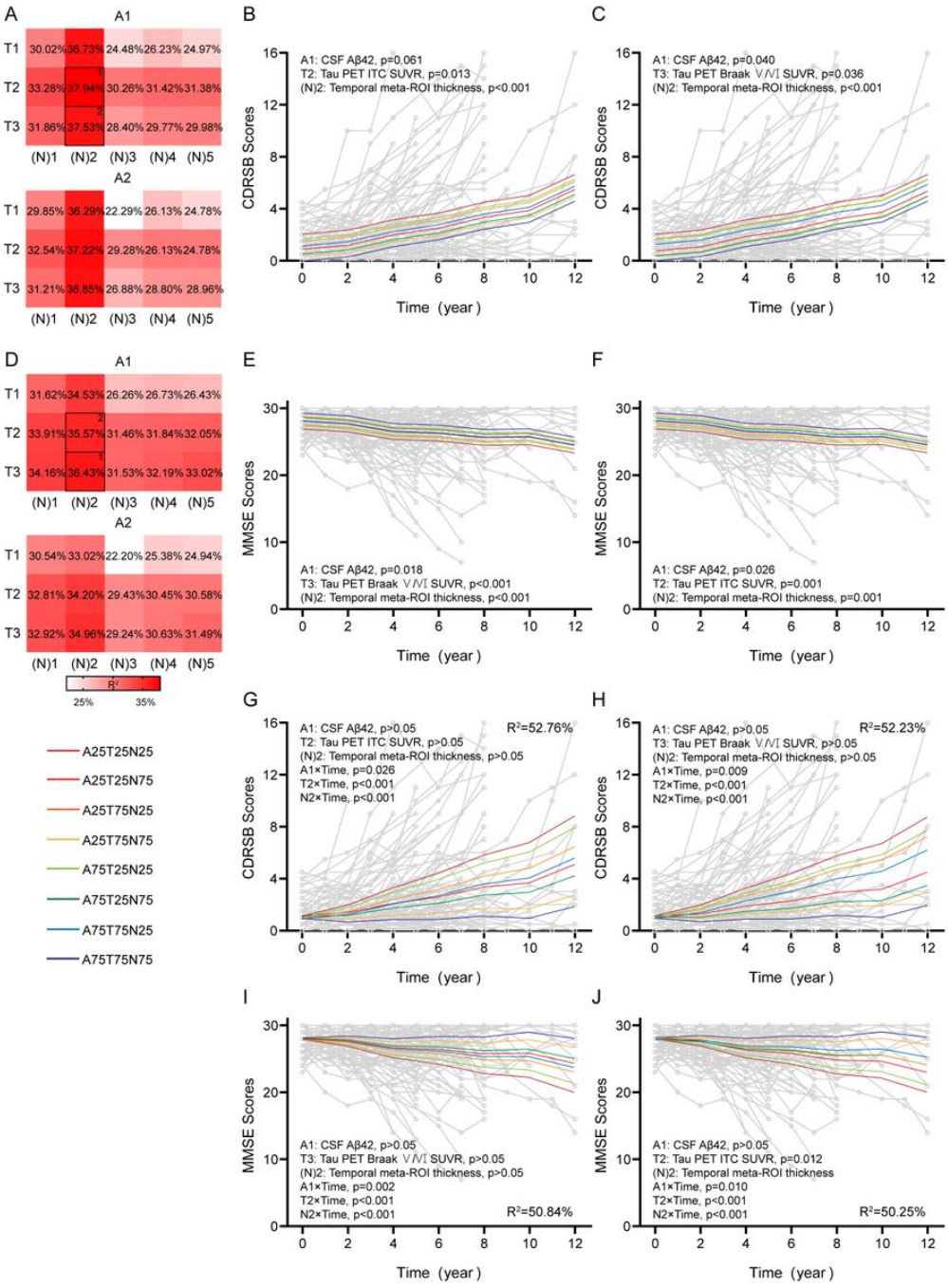

Figure 5

Associations between different AT(N) combinations and longitudinal cognition in CI group. Marginal R2 for different AT(N) variants to predict longitudinal Clinical Dementia Rating Sum of Boxes (CDRSB) and Mini-Mental State Examination (MMSE) for cognitively impaired (CI), respectively (divided by A biomarkers) (A, D). The selected models in (B,C) and (E,F) are the top 2 best for different cognitive scales. The top 2 best models with interaction between time and AT(N) variants to predict longitudinal CDRSB and MMSE, respectively (G-J); AT(N) variants chosen in the model and p values, and marginal R2 are shown at the top (CDRSB) or bottle (MMSE) of each panel; 25 and 75 refer to 25th and 75th quartiles, where lower indicates a more abnormal biomarker.

Supplementary Files

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