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RESEARCH ARTICLE

# Longitudinal changes in metabolic network activity in early Alzheimer's disease

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## Abstract

**INTRODUCTION:** The progression of Alzheimer's disease (AD) has been linked to two metabolic networks, the AD-related pattern (ADRP) and the default mode network (DMN).

**METHODS:** Converting and clinically stable cognitively normal subjects ($n = 47$) and individuals with mild cognitive impairment ($n = 96$) underwent 2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) three or more times over 6 years ($n_{scans} = 705$). Expression levels for ADRP and DMN were measured in each subject and time point, and the resulting changes were correlated with cognitive performance. The role of network expression in predicting conversion to dementia was also evaluated.

**RESULTS:** Longitudinal increases in ADRP expression were observed in converters, while age-related DMN loss was seen in converters and nonconverters. Cognitive decline correlated with increases in ADRP and declines in DMN, but conversion to dementia was predicted only by baseline ADRP levels.

**DISCUSSION:** The results point to the potential utility of ADRP as an imaging biomarker of AD progression.

KEYWORDS
Alzheimer's disease-related pattern, conversion, default mode network, FDG PET, mild cognitive impairment

## 1 | BACKGROUND

Alzheimer's disease (AD) is characterized by abnormal accumulation of amyloid $\beta$ (A$\beta$) and tau protein in the brain.[1] In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed a research framework that defines AD based solely on biomarker findings. An individual's biomarker profile is on the Alzheimer's continuum if the presence of amyloid pathology (A+) is demonstrated either with cerebrospinal fluid (CSF) analysis or positron emission tomography (PET) imaging.[2] Alzheimer's network pathology can be demonstrated using structural and functional magnetic resonance imaging (MRI) techniques[3] as well as metabolic imaging with 2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG) PET.[4,5] Spatial covariance mapping of metabolic brain images from AD patients and healthy control subjects has revealed

  

reproducible disease-related patterns characterized by reductions in the precuneus and temporoparietal regions, associated with relative increases in the cerebellum, pons, and primary sensorimotor cortex.[3,5] Indeed, a consistent AD-related metabolic pattern, termed ADRP, has been identified in multiple independent populations,[5–8] including a recent sample of biomarker-confirmed patients.[9] Of note, the covariance mapping approach allows expression levels (subject scores) for disease patterns such as ADRP to be quantified in individual subjects at multiple time points.[5,10] Indeed, ADRP expression has been found to correlate with cognitive performance in multiple AD samples.[6,7,9]

While AD patients typically exhibit significant elevations in ADRP expression, which can be helpful in differentiation from other common dementia syndromes,[11] other networks may also be involved in this disease. The default mode network (DMN) is relevant in this regard. This network is characterized by relatively increased resting state activity in the medial frontal cortex, posterior cingulate gyrus, and precuneus, and in temporal regions, which deactivates during task performance.[12,13] The DMN has been topographically linked to amyloid pathology in AD,[14] and expression levels for the corresponding metabolic network are consistently reduced in patients diagnosed with this disorder.[15] That said, the time course of ADRP and DMN expression in individuals with mild cognitive impairment (MCI) is currently unknown.

To this end, we measured longitudinal changes in ADRP and DMN expression in FDG PET scans from healthy control subjects and in MCI patients in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. In addition to assessing the effect of apolipoprotein E (*APOE*) ε4 allele and CSF amyloid status on the trajectory of the two networks, we examined the relationship of their respective time courses with cognitive change. Lastly, we determined the prognostic value of ADRP and DMN as predictors of future transition to dementia.

**RESEARCH IN CONTEXT**

1. **Systematic Review**: Alzheimer's disease is accompanied by changes in functional brain networks. Previous studies showed the appearance of a disease-related network, termed AD-related pattern (ADRP), and the loss of a major resting state network, a default mode network (DMN). The contribution of each to disease progression has not been studied in detail.
2. **Interpretation**: Our findings, based on a large longitudinal imaging dataset, show progressive increases in ADRP expression levels in cognitively normal participants who subsequently develop mild cognitive impairment (MCI) and in individuals with MCI who later develop dementia. Longitudinal loss of DMN expression was observed in stable and converting participants but was mostly related to aging. That said, changes in both networks were associated with progressive cognitive decline.
3. **Future Directions**: This study supports the use of ADRP as a metabolic imaging biomarker of disease progression and as a predictor of dementia in patients with MCI.

## 2 | METHODS

### 2.1 | Participants

Participants data and their scans were obtained from the ADNI database on December 9, 2021 (https://adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

We used the *ADNIMERGE* package[16] to extract data on age, sex, years of education, $A\beta_{42}$, total tau (tTau), and phosphorylated tau (pTau) CSF levels at baseline, Mini-Mental State Examination (MMSE) scores, and neuropsychological composite scores for memory,[17] executive function,[18] and language.[19]

We included 143 participants with three or more available FDG PET scans. The selection flowchart is presented in Figure 1. The two clinical groups were stratified based on their clinical conversion status: stable CN (sCN) and converter CN (cCN) if they developed MCI and stable MCI (sMCI) and converter MCI (cMCI) if they developed dementia during follow-up. Only amyloid positive (A+), defined as CSF $A\beta_{42} < 880$ pg/mL,[2,20] cCN, and cMCI were included. Individuals with one or more *APOE* ε4 alleles (i.e., ε2/ε4, ε3/ε4 or ε4/ε4) were considered as being *APOE* ε4 positive.

### 2.2 | Image preprocessing and analysis

Patients from the ADNI cohort underwent imaging at different sites, as described in more detail elsewhere (https://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/). Coregistered, averaged, standardized images with uniform voxel size and resolution were obtained from ADNI. The preprocessing procedure is described in more detail at the ADNI website. Coregistered, averaged scans were obtained by averaging six or four 5-min frames. Scans were then reoriented into a standard 160 × 160 × 96 voxel image grid with 1.5-mm cubic voxels. Scans were intensity normalized using a subject-specific mask so that the average of all voxels within the mask was exactly one. Lastly, each image was filtered with a scanner-specific filter function to produce images of a uniform isotropic resolution of 8 mm full width at half maximum. FDG PET scans were origin corrected and preprocessed with SPM12 (Wellcome Trust Centre for Neuroimaging, Institute of Neurology, London, UK) running on MATLAB R2019a (MathWorks Inc., Natick, MA, USA) using an in-house pipeline, as described previously.[9]

We then computed expression values (subject scores) for previously validated ADRP[9] and DMN[15] patterns for each subject and time point using the forward application routine in ScAnVP (software available from The Feinstein Institutes for Medical Research

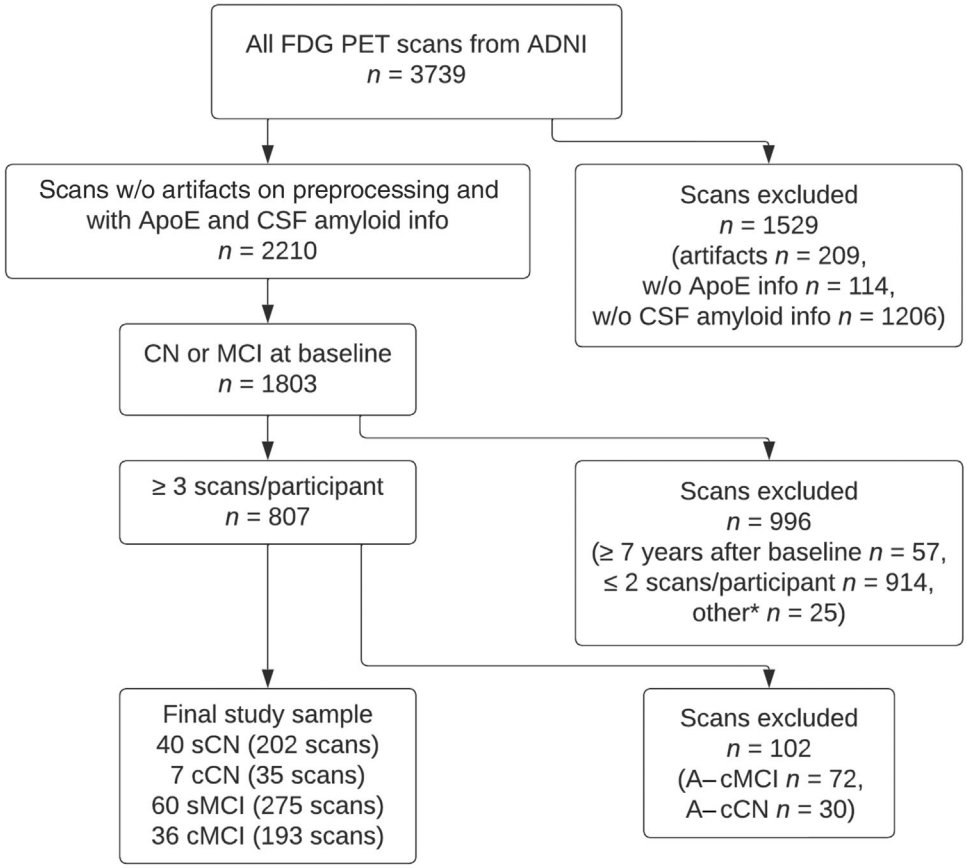


**FIGURE 1** Selection flowchart. We included participants with information available on apolipoprotein E (*APOE*) status and cerebrospinal fluid (CSF) amyloid (A) who were either cognitively normal (CN) or had mild cognitive impairment (MCI) at baseline, and with three or more longitudinal 2-[$^{18}$F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) scans without major structural changes or postprocessing artifacts. We excluded time points/scans taken 7 or more years from baseline because of the small number of such scans that were available. To reduce the biological heterogeneity, we excluded A–converters, because conversion to MCI/dementia in these subjects is unlikely to be caused by AD.[2] sCN, stable CN; cCN, converter CN; sMCI, stable MCI; cMCI, converter MCI. *Missing baseline scan or fluctuating clinical diagnosis, for example, from CN to MCI and back to CN.

at https://feinsteinneuroscience.org/). Additionally, for validation, we computed expression values for an analogous ADRP identified previously in an analysis of 20 AD patients and 20 healthy control subjects from the ADNI database[6] (Supplementary Materials A). The resulting raw scores were standardized (*z*-score) based on the distribution of values computed in an independent group of 53 CN subjects (age 73.8 ± 6.5 years, MMSE = 29.0 ± 1.2) from the ADNI database with only a single FDG PET scan, without pathological CSF changes. Additionally, we used ordinal trends/canonical variates analysis (OrT/CVA), a computational algorithm based on supervised principal component analysis[5,21] to identify consistent patterns of longitudinal change in the MCI group (Supplementary Materials B). The resulting AD progression pattern (ADPP) was compared to the ADRP and DMN topographies using voxel-wise correlations as described elsewhere.[22]

## 2.3 | Statistical analysis

We used analysis of variance (ANOVA) with post hoc pairwise *t*-tests incorporating the Holm correction for multiple comparisons for continuous variables, and for categorical variables, the Kruskal-Wallis rank-sum test and post hoc pairwise Fisher's exact test with a Holm correction for multiple comparisons were used. We used the lme4 package[23] to perform a linear mixed-effects (LME) analysis of the longitudinal relationship of conversion status, *APOE* ε4, and amyloid status, with ADRP and DMN expression values. All LME models included a group × time interaction item with random intercepts for each individual, adjusted for age, sex, and group status. To assess the relationship between cognitive changes over time and pattern expression values, we used LME models with neuropsychological performance measures such as MMSE and memory, executive function, and language composite scores as outcome variables. Pattern expression × time interaction terms were included in the models, with random intercepts for each individual, adjusted for baseline ADRP/DMN expression, age, sex, and education years. To assess the significance of the interaction term, type II ANOVA with Satterthwaite's approximation for the calculation of degrees of freedom was performed using the lmerTest package.[24] When ANOVA revealed a significant interaction effect, we computed the effect of time on pattern expression values per condition (i.e., the estimated marginal means of linear trends) and compared the

differences between slopes in a pairwise fashion with Tukey's correction for multiple comparisons using the emmeans package.[25]

To evaluate the risk of conversion from MCI to dementia, we performed Cox proportional hazard (PH) regression analyses. For converters, the time-to-event variable was in the number of months from the baseline assessment to the first assessment at which the subject received the diagnosis of dementia; for clinically stable participants, the variable was the number of months from baseline to last follow-up. Univariate and multivariate Cox PH regression was performed with age at baseline (years) and dichotomized sex (male = 1), *APOE ε4* status, pTau (> 21.8 pg/mL), and tTau (> 245 pg/mL) as predictors, along with ADRP and DMN expression dichotomized into "high" or "low" categories according to the median value for each pattern.

For validation (Supplementary Materials A), longitudinal relationships and predictions based on the recently published ADRP topography from a completely independent dataset[9] were confirmed using an analogous pattern identified previously from the ADNI database.[5,6]

All statistical analyses were conducted in RStudio version 1.3.1093, R version 3.6.0,[26] and figures were produced with the ggplot2[27] and survminer[28] packages. Results were considered significant at $p < .05$ (two-tailed).

## 3 | RESULTS

The final sample included 40 sCN (202 scans), seven A+ cCN (35 scans), 60 sMCI (275 scans), and 36 A+ cMCI (193 scans). The groups did not differ in age ($F(3, 139) = 0.9$, $p = .43$) or sex distribution ($\chi^2(3) = 0.3$, $p = .96$) but did differ significantly in CSF amyloid positivity ($\chi^2(3) = 45.1$, $p < .001$) and *APOE ε4* status ($\chi^2(3) = 15.3$, $p = .002$). Baseline demographic information for the subjects is provided in Table 1.

### 3.1 | Group differences in ADRP and DMN expression

We observed a significant group × time interaction effect on ADRP expression values adjusted for age, group status, and sex ($p < .001$). Age ($p = .02$) and group status ($p < .001$) were significant as confounders, whereas sex was not significant ($p = .95$). The rate of ADRP progression (Figure 2A, *top*) was fastest in the cMCI group ($\beta = 0.34$, 95% confidence interval (CI) [0.28, 0.39], $p < .001$), followed by cCN ($\beta = 0.18$ [0.08, 0.27], $p < .001$), sMCI ($\beta = 0.05$ [0.01, 0.10], $p = .01$), and sCN ($\beta = 0.03$ [−0.02, 0.08], $p = .26$). Pairwise comparison of the groups showed that ADRP progression was faster in cMCI compared to cCN ($p = .02$), sMCI ($p < .001$) and sCN ($p < .001$). ADRP progression was significantly faster in cCN compared to sCN ($p = .03$) but exhibited only a trend in comparison to sMCI ($p = .08$). The difference in ADRP progression rates for sCN and sMCI was not significant ($p = .81$).

The group × time interaction on DMN expression adjusted for age, group status, and sex was not significant ($p = .73$). Age was a significant confounder ($p < .001$), group status was marginal ($p = .06$), and sex was not significant ($p = .83$). Longitudinal changes in DMN expression did not reach significance in any of the groups (sCN $p = .43$; cCN $p = .09$; sMCI $p = .38$; cMCI $p = .15$). In an age-unadjusted model (Figure 2A, *bottom*), we observed a significant decline in DMN expression scores in all four groups; sCN ($\beta = -0.09$ [−0.13, −0.04], $p < .001$), cCN ($\beta = -0.15$ [−0.24, −0.06], $p = .001$), sMCI ($\beta = -0.05$ [−0.08, −0.02], $p = .003$) and cMCI ($\beta = -0.11$ [−0.15, −0.06], $p < .001$). Pairwise differences in slopes were not significant in this model ($p > .18$).

### 3.2 | Effect of *APOE ε4* allele status on longitudinal changes in ADRP and DMN expression levels

Significant *APOE ε4* status × time interaction effects were not present on either ADRP or DMN expression in the sCN, cCN, or sMCI groups

**TABLE 1** Baseline demographics.

| | Stable CN | Converter CN | Stable MCI | Converter MCI | *p* |
|---|---|---|---|---|---|
| ***N* (scans)** | 40 (202) | 7 (35) | 60 (275) | 36 (193) | |
| **Age** | 73.7 ± 6.0 | 77.3 ± 3.2 | 72.8 ± 7.4 | 73.9 ± 7.9 | .43 |
| **Sex (f/m)** | 14/26 | 3/4 | 20/40 | 13/23 | .96 |
| **MMSE** | 28.9 ± 1.2 | 29.1 ± 0.9 | 28.1 ± 1.5 | 27.0 ± 1.7 | <.001[bcef] |
| **Memory** | 0.96 ± 0.48 | 0.59 ± 0.50 | 0.28 ± 0.54 | −0.25 ± 0.43 | <.001[bcef] |
| **Executive function** | 0.64 ± 0.79 | 0.23 ± 0.52 | 0.35 ± 0.68 | −0.14 ± 0.87 | <.001[cf] |
| **Language** | 0.71 ± 0.55 | 0.28 ± 0.69 | 0.28 ± 0.58 | 0.00 ± 0.68 | <.001[bc] |
| **Amyloid (pos/total)** | 12/40 (30%) | 7/7 (100%) | 31/60 (52%) | 36/36 (100%) | .002[acdf] |
| ***APOE ε4* (pos/total)** | 11/40 (28%) | 6/7 (96%) | 24/60 (40%) | 23/36 (64%) | .001[ac] |

Abbreviations: cMCI, converter mild cognitive impairment; sMCI, stable MCI; cCN, converter cognitively normal; sCN, stable CN; MMSE, Mini-Mental State Examination; APOE, apolipoprotein E. All data presented as mean ± SD.

[a]Post hoc significant: sCN < cCN.
[b]Post hoc significant: sCN < sMCI.
[c]Post hoc significant: sCN < cMCI.
[d]Post hoc significant: cCN < sMCI.
[e]Post hoc significant: cCN < cMCI.
[f]Post hoc significant: sMCI < cMCI.

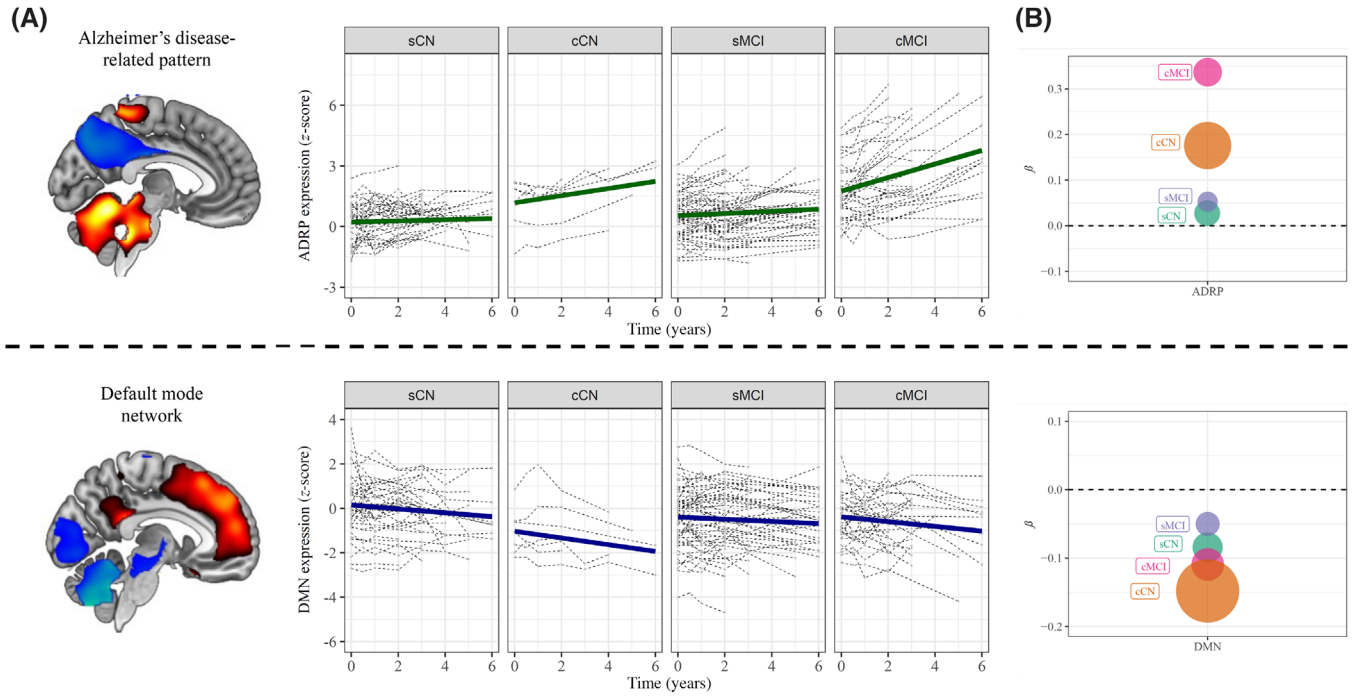


**FIGURE 2** (A) Changes in expression values over time for Alzheimer's disease-related pattern (ADRP, *top*) and metabolic default mode network (DMN, *bottom*) in cognitively normal (CN) individuals and in those with mild cognitive impairment (MCI). In both groups, individual subjects were stratified by conversion status (see Methods). (Dotted gray lines represent the time course of network expression in each subject. Green lines are ADRP × time slopes from a linear mixed-effects model adjusted for age, sex, and group status. Blue lines are DMN × time slopes from a linear mixed-effects model adjusted for sex and group status. sCN, stable CN; cCN, converter CN; sMCI, stable MCI; cMCI, converter MCI.) (B) Bubble plots of estimated rate of ADRP (*top*) and DMN (*bottom*) progression for each of the groups. In these displays, the mean rate (proportional to $\beta$) is placed at the center of the corresponding disc; the diameter is proportional to the standard error of the estimate for each group.

(Table S1, Figures SA1 and SA2). However, a significant *APOE* ε4 status × time interaction effect on ADRP expression was present in cMCI ($p < .001$), with faster progression ($p = .002$) in patients with one or more *APOE* ε4 alleles ($\beta = 0.46$ [0.38, 0.54], $p < .001$) compared to their *APOE* ε4 negative counterparts ($\beta = 0.31$ [0.22, 0.40], $p < .001$) (Table S1A). By contrast, the longitudinal decline in DMN expression in cMCI did not differ significantly ($p = .80$) for *APOE* ε4-positive and negative patients (Table S1B).

## 3.3 | Effect of amyloid on ADRP and DMN expression

Given that the converter groups included only A+ subjects (see Methods), the effects of amyloid on longitudinal changes in network expression were assessed only in the clinically stable groups. Thus, a significant amyloid × time interaction effect on ADRP expression was observed in sCN ($p = .04$), with faster progression ($p = .005$) in A+ ($\beta = 0.15$ [0.05, 0.25], $p = .004$) compared to A− ($\beta = -0.00$ [−0.06, 0.06], $p = .93$) (Table S2A, Figure SA3). Amyloid status did not affect ADRP progression in the sMCI group ($p = .226$), but we observed a significant main effect of amyloid status on ADRP expression ($p = .026$). In contrast to ADRP, amyloid status did not affect longitudinal changes in DMN expression in either group (Table S2B, Figures SA3 and SA4).

## 3.4 | Relationship of longitudinal changes in ADRP and DMN expression to neuropsychological performance

Significant group differences were observed at baseline for MMSE ($F(3, 139) = 12.1$, $p < .001$) and memory ($F(3, 138) = 38.3$, $p < .001$), executive function ($F(3, 139) = 6.9$, $p < .001$), and language composites ($F(3, 139) = 9.1$, $p < .001$) (Table 1). Over time, a significant decline in MMSE scores was noted in cMCI ($p < .001$), but not in the other groups ($p > .29$; Figure SA5). Significant declines in memory, executive function, and language composites were observed in cCN and cMCI ($p < .02$ for each group) but not in sCN and sMCI ($p > .10$; Table 2, Figure SA6).

Adjusting for age, sex, and education we found a significant main effect of ADRP on memory composite scores in the sCN group. A significant relationship between ADRP × time interaction effects and MMSE was also observed in this group ($\beta = -0.15$ [−0.24, −0.05], $p = .004$; Table S3).

Adjusting for age, sex, and education we found no main effect of ADRP and DMN expression on MMSE or neuropsychological composite measurements in the cCN (all $p > .24$). However, significant ADRP × time interaction effects were observed in this group on executive function ($\beta = -0.07$ [−0.12, −0.02], $p = .019$) and on language composite scores ($\beta = -0.06$ [−0.10, −0.02], $p = .004$). Similarly, we observed significant DMN × time interaction effects on executive function ($\beta = 0.11$

**TABLE 2** Longitudinal changes in neuropsychological test scores.

| | MMSE | | | Memory composite | | | Executive function composite | | | Language composite | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Predictors* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* |
| (Intercept) | 31.3 | 28.0 to 34.6 | <**.001** | 1.7 | 0.6 to 2.7 | **.003** | 1.7 | 0.2 to 3.2 | **.03** | 1.7 | 0.4 to 3.0 | **.009** |
| Age | −0.0 | −0.1 to −0.0 | **.02** | −0.0 | −0.0 to −0.0 | **.02** | −0.0 | −0.0 to −0.0 | **.005** | −0.0 | −0.0 to −0.0 | **.001** |
| Education | 0.1 | −0.0 to 0.2 | .13 | 0.0 | −0.0 to 0.1 | .06 | 0.1 | 0.0 to 0.1 | **.004** | 0.1 | 0.0 to 0.1 | **.004** |
| Sex [Male] | 0.1 | −0.4 to 0.7 | .67 | −0.0 | −0.2 to 0.2 | .95 | −0.0 | −0.3 to 0.2 | .85 | −0.0 | −0.2 to 0.2 | .98 |
| Group [cCN] | −0.4 | −1.8 to 1.0 | .58 | −0.4 | −0.8 to 0.0 | .08 | −0.1 | −0.8 to 0.5 | .65 | −0.2 | −0.7 to 0.3 | .43 |
| Group [sMCI] | −1.2 | −1.9 to −0.5 | **.001** | −0.7 | −0.9 to −0.5 | <**.001** | −0.4 | −0.7 to −0.1 | **.006** | −0.5 | −0.7 to −0.2 | <**.001** |
| Group [cMCI] | −2.3 | −3.1 to −1.5 | <**.001** | −1.2 | −1.5 to −1.0 | <**.001** | −0.9 | −1.2 to −0.5 | <**.001** | −0.8 | −1.1 to −0.5 | <**.001** |
| Group [sCN] × Time | −0.0 | −0.2 to 0.1 | .92 | 0.0 | −0.0 to 0.0 | .58 | 0.0 | −0.0 to 0.1 | .86 | 0.0 | −0.0 to 0.1 | .10 |
| Group [cCN] × Time | −0.2 | −0.5 to 0.2 | .29 | −0.1 | −0.2 to −0.1 | <**.001** | −0.1 | −0.2 to −0.0 | **.02** | −0.1 | −0.2 to −0.0 | **.04** |
| Group [sMCI] × Time | −0.0 | −0.2 to 0.1 | .44 | 0.0 | −0.0 to 0.0 | .73 | 0.0 | −0.0 to 0.1 | .20 | −0.0 | −0.0 to 0.0 | .76 |
| Group [cMCI] × Time | −1.2 | −1.3 to −1.0 | <**.001** | −0.1 | −0.2 to −0.1 | <**.001** | −0.2 | −0.3 to −0.2 | <**.001** | −0.2 | −0.2 to −0.1 | <**.001** |

Abbreviations: cMCI, converter mild cognitive impairment; sMCI, stable MCI; cCN, converter cognitively normal; sCN, stable CN; MMSE, Mini-Mental State Examination; CI, 95% confidence interval. Significant *p*-values are in bold.

[0.04, 0.19], $p$ =.011) and language composite scores ($\beta$ = 0.08 [0.01, 0.13], $p$ =.017) in this group (Table 3).

Adjusting for age, sex, and education we found a significant main effect of ADRP on MMSE and executive function composite scores in the sMCI. Significant relationships between ADRP × time interaction effects and composite scores for memory ($\beta$ = −0.03 [−0.05, −0.00], $p$ =.02) and language ($\beta$ = −0.03 [−0.05, −0.00], $p$ =.02) were observed in this group. Relationships between DMN × time interaction effects and cognitive function composite scores in this group (Table S4) were significant only for language composite scores ($\beta$ = 0.03 [0.01, 0.05], $p$ =.001).

We observed a significant main effect of ADRP expression on MMSE and neuropsychological composite scores in the cMCI, adjusting for age, sex, and education level (Table 4A). That said, the main effect of DMN expression on MMSE and neuropsychological composite scores, adjusted for the same variables, was non-significant (Table 4B). A significant ADRP × time interaction was observed on MMSE ($\beta$ = −0.19 [−0.28, −0.11], $p$ <.001), memory ($\beta$ = −0.03 [−0.04, −0.02], $p$ <.001), executive function ($\beta$ = −0.03 [−0.05, −0.01], $p$ =.004), and language composite scores ($\beta$ = −0.03 [−0.05, −0.01], $p$ =.014). That said, a significant DMN × time interaction effect was seen on the MMSE ($\beta$ = 0.43 [0.22, 0.65], $p$ <.001; Table 4).

### 3.5 | Survival analysis

Univariate Cox PH models showed that positive CSF levels of tTau ($p$ =.008) and pTau ($p$ =.03) and *APOE* ε4 status ($p$ =.046) were significant predictors of conversion from MCI to dementia, whereas age and sex were non-significant as predictors ($p$ >.16). MCI participants were dichotomized based on median ADRP expression at baseline, and high values (> 0.94) were significant as predictors of subsequent conversion to dementia ($p$ <.001; Figure 3A). By the same token, dichotomization of MCI participants by median DMN expression at baseline did not disclose low values (< −0.26) as predictive ($p$ =.28). Similar results were seen with a multivariate Cox PH model (Figure 3B): higher than median ADRP expression at baseline was a significant predictor of later conversion to dementia (hazard ratio = 5.5 [2.5, 12.5], $p$ <.001).

## 4 | DISCUSSION

In this study, we utilized a large longitudinal dataset to examine the time course of expression levels for established metabolic brain networks in CN subjects and in patients with MCI. In particular, we focused on the ADRP, an abnormal topography expressed in AD patients,[5,9] and on the DMN, a normal brain network with reduced expression in AD and other neurodegenerative disorders.[15,29] We observed a steady increase in ADRP expression over time in cCN and cMCI, with only marginal increases in their clinically stable counterparts. By contrast, significant declines in DMN expression were observed in stable and converting CN and MCI, consistent with a non-specific aging effect. This observation is in line with previous resting-state functional MRI (rs-fMRI) studies showing decreased functional connectivity in DMN during healthy aging.[30] Reductions in DMN connectivity have also been widely reported in AD, mainly in rs-fMRI studies.[31] A meta-analysis based largely on rs-fMRI studies of AD patients revealed consistent DMN abnormalities in individuals with clinically diagnosed dementia,[32] and steadily declining expression of the metabolic DMN was noted in this population over 2 years.[15] The results in the pre-dementia stage have been less consistent, however.[32] In the current study, we observed a significant decline in DMN expression in CN and MCI subjects over the span of 6 years. However, the rate of decline did not differ between converters and non-converters, and in the age-adjusted model, the rate was non-significant. While ADRP and DMN share several regions, such as the posterior cingulate cortex, precuneus, and parietal cortex, the two metabolic topographies are not significantly correlated ($r$ = −0.33, $p$ >.05; voxel-wise correlation, corrected for spatial autocorrelation[22]). Given the absence of a close relationship between the two patterns, increases in ADRP expression over time are not necessarily associated with concurrent declines in DMN. This accords with a recent rs-fMRI study that showed that a global functional connectivity signature was superior to individual resting-state networks, including DMN, as an indicator of conversion to dementia.[33] Likewise, using longitudinal MCI data to identify a specific disease progression pattern disclosed a significant topography that was more closely related to ADRP than DMN (Supplementary Materials B, Figures SB1 and SB2).

Along these lines, we found that cMCI subjects with one or more *APOE* ε4 alleles had faster ADRP progression than their counterparts with no *APOE* ε4 alleles, whereas the decline in DMN expression over time was similar in both subgroups. Analogous findings were not seen in cCN, indicating that the effect of *APOE* ε4 status on ADRP expression is more prominent in symptomatic individuals. Carriers of one or more *APOE* ε4 alleles are at an increased risk for the development of AD. It is believed that ApoE interacts with γ-aminobutyric acid (GABA)-expressing interneurons to cause a dysregulation of neural networks in the hippocampus and neocortex.[34] Indeed, it has been shown that MCI *APOE* ε4 carriers have faster cognitive decline and greater longitudinal decreases in FDG uptake compared to non-carriers.[35]

Conversely, the amyloid effect on ADRP expression was only seen in sCN subjects. (It was not studied in the converter groups as these were composed only of A+ individuals.) Of note, sCN participants who were A+ while remaining clinically stable during the follow-up period had slightly faster progression in ADRP expression. According to the NIA-AA research framework, these individuals are already on the Alzheimer's continuum.[2] Recent studies showed an increased risk of progression to MCI and dementia in A+ CN.[36,37] Amyloid build-up occurs up to 20 years before symptom onset.[38] It is therefore conceivable that the follow-up period in our study was long enough to capture the effects of amyloid deposition on ADRP expression, but not on cognitive functioning. Along these lines, A+ sMCI had higher ADRP expression than A− sMCI, but no difference in the ADRP progression rate.

As expected, we observed a significant decline in neuropsychological composite scores in the converters, but not in the non-converters.

**TABLE 3** Relationship of expression values for (A) ADRP and (B) DMN to neuropsychological indices in the cCN group.

| A. ADRP | MMSE | | | Memory composite | | | Executive function composite | | | Language composite | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Predictors* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* |
| (Intercept) | 21.7 | −26.5 to 69.9 | .36 | 3.3 | −9.9 to 16.6 | .61 | −10.7 | −30.1 to 8.7 | .27 | −3.0 | −16.7 to 10.7 | .66 |
| Age | 0.1 | −0.5 to 0.6 | .80 | −0.0 | −0.2 to 0.1 | .57 | 0.1 | −0.1 to 0.3 | .28 | 0.0 | −0.1 to 0.2 | .77 |
| Education | 0.1 | −0.4 to 0.6 | .76 | 0.0 | −0.1 to 0.2 | .62 | 0.1 | −0.1 to 0.4 | .28 | 0.1 | −0.1 to 0.3 | .34 |
| Sex [Male] | 0.2 | −2.2 to 2.6 | .86 | −0.3 | −1.3 to 0.7 | .58 | 0.8 | −0.4 to 2.0 | .19 | 0.1 | −1.2 to 1.3 | .91 |
| ADRP | 0.0 | −1.2 to 1.3 | .95 | −0.2 | −0.6 to 0.1 | .24 | −0.2 | −0.7 to 0.3 | .39 | 0.1 | −0.2 to 0.4 | .60 |
| ADRP × Time | −0.0 | −0.2 to 0.1 | .73 | −0.0 | −0.1 to 0.0 | .56 | −0.1 | −0.2 to −0.0 | **.019** | −0.1 | −0.1 to −0.0 | **.004** |
| **B. DMN** | **MMSE** | | | **Memory composite** | | | **Executive function composite** | | | **Language composite** | | |
| *Predictor* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* |
| (Intercept) | 10.1 | −29.2 to 49.5 | .60 | 9.5 | −3.4 to 22.4 | .14 | −13.0 | −30.2 to 4.3 | .14 | −1.7 | −14.9 to 11.5 | .79 |
| Age | 0.2 | −0.2 to 0.6 | .37 | −0.1 | −0.2 to 0.0 | .14 | 0.1 | −0.0 to 0.3 | .14 | 0.0 | −0.1 to 0.2 | .94 |
| Education | 0.2 | −0.2 to 0.5 | .35 | −0.0 | −0.2 to 0.1 | .65 | 0.1 | −0.0 to 0.3 | .14 | 0.1 | −0.1 to 0.3 | .20 |
| Sex [Male] | 0.6 | −1.3 to 2.6 | .50 | −0.5 | −1.5 to 0.5 | .29 | 0.8 | −0.2 to 1.8 | .12 | −0.0 | −1.1 to 1.1 | .99 |
| DMN | 0.2 | −0.7 to 1.1 | .70 | −0.1 | −0.4 to 0.2 | .66 | 0.3 | −0.1 to 0.7 | .10 | 0.1 | −0.2 to 0.3 | .66 |
| DMN × Time | 0.1 | −0.1 to 0.3 | .39 | 0.0 | −0.1 to 0.1 | .65 | 0.1 | 0.0 to 0.2 | **.011** | 0.1 | 0.0 to 0.1 | **.017** |

Abbreviations: ADRP, Alzheimer's disease-related pattern; DMN, default mode network; MMSE, Mini-Mental State Examination; CI, 95% confidence interval.

**TABLE 4** Relationship of expression values for (A) ADRP and (B) DMN to neuropsychological indices in the cMCI group.

| A. ADRP | MMSE | | | Memory composite | | | Executive function composite | | | Language composite | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Predictor* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* |
| (Intercept) | 35.0 | 25.1 to 44.9 | **<.001** | 1.0 | −0.9 to 3.0 | .30 | 0.1 | −2.8 to 3.0 | .95 | 1.8 | −1.1 to 4.7 | .22 |
| Age | −0.1 | −0.2 to −0.0 | **.047** | −0.0 | −0.0 to 0.0 | .33 | −0.0 | −0.0 to 0.0 | .61 | −0.0 | −0.1 to −0.0 | **.027** |
| Education | −0.0 | −0.3 to 0.2 | .75 | −0.0 | −0.1 to 0.0 | .35 | 0.1 | −0.0 to 0.1 | .17 | 0.1 | −0.0 to 0.1 | .21 |
| Sex (Male) | 0.9 | −0.6 to 2.5 | .24 | 0.1 | −0.2 to 0.4 | .58 | −0.2 | −0.7 to 0.2 | .34 | 0.0 | −0.5 to 0.5 | .91 |
| ADRP | −0.7 | −1.2 to −0.2 | **.003** | −0.1 | −0.2 to −0.0 | **.002** | −0.3 | −0.4 to −0.1 | **<.001** | −0.3 | −0.4 to −0.1 | **<.001** |
| ADRP × Time | −0.2 | −0.3 to −0.1 | **<.001** | −0.03 | −0.04 to −0.02 | **<.001** | −0.03 | −0.1 to −0.01 | **.004** | −0.03 | −0.05 to −0.01 | **.014** |
| **B. DMN** | **MMSE** | | | **Memory composite** | | | **Executive function composite** | | | **Language composite** | | |
| *Predictors* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* | *β* | CI | *p* |
| (Intercept) | 24.9 | 14.1 to 35.7 | **<.001** | −0.4 | −2.5 to 1.6 | .68 | −2.0 | −6.5 to 2.4 | .37 | 0.8 | −2.7 to 4.2 | .65 |
| Age | −0.0 | −0.1 to 0.1 | .74 | 0.0 | −0.0 to 0.0 | .88 | 0.0 | −0.0 to 0.0 | .98 | −0.0 | −0.1 to 0.0 | .12 |
| Education | 0.1 | −0.2 to 0.4 | .64 | −0.0 | −0.1 to 0.0 | .69 | 0.1 | −0.0 to 0.2 | .16 | 0.1 | −0.0 to 0.2 | .23 |
| Sex [Male] | −0.0 | −1.8 to 1.7 | .96 | −0.0 | −0.4 to 0.3 | .80 | −0.4 | −1.1 to 0.4 | .32 | −0.1 | −0.7 to 0.5 | .69 |
| DMN | 0.3 | −0.5 to 1.0 | .49 | 0.1 | −0.0 to 0.2 | .15 | −0.0 | −0.2 to 0.2 | .66 | 0.2 | −0.0 to 0.3 | .08 |
| DMN × Time | 0.4 | 0.2 to 0.6 | **<.001** | 0.0 | −0.0 to 0.0 | .12 | 0.0 | −0.0 to 0.0 | .92 | 0.0 | −0.0 to 0.1 | .37 |

Abbreviations: ADRP, Alzheimer's disease-related pattern; DMN, default mode network; MMSE, Mini-Mental State Examination; CI, 95% confidence interval.

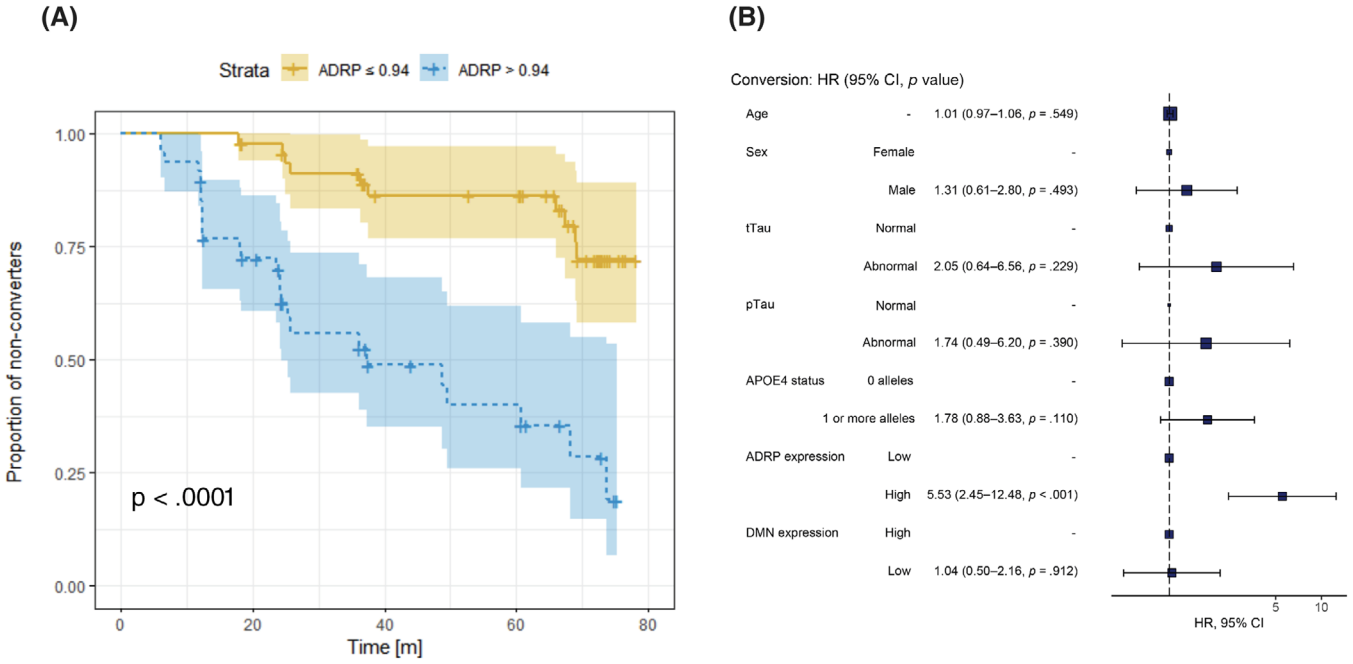


**FIGURE 3** (A) Estimated survival curves for mild cognitive impairment (MCI) patients with high or low baseline Alzheimer's disease-related pattern (ADRP) expression determined by median value (see text). (B) Hazard ratios from multivariate Cox proportional hazard model. In both models, high baseline ADRP expression (>0.94) in MCI patients was associated with greater likelihood of subsequent conversion to dementia.

In cCN, expression levels for ADRP, a disease-related network, and reductions in expression levels for DMN, a normal network, together contributed to the decline in executive function and language composite scores. In cMCI, by contrast, ADRP progression alone contributed to further declines in neuropsychological performance. This suggests that declining DMN activity may be more relevant at early disease stages, whereas increasing ADRP expression has a greater role in mediating further cognitive decline. This is in line with previous cross-sectional studies showing inverse correlations between ADRP expression and composite scores for memory, executive function, visuospatial performance, and language in patients with dementia due to AD.[6,7,9] Comparison of the two MCI groups shows that relationships of ADRP with memory and executive function are specific for the cMCI group. That said, significant relationships between ADRP and language composite scores were noted for both sMCI and cMCI. Interestingly, a significant relationship between DMN and language was seen for sMCI but not cMCI. Thus, in sMCI, language function is associated with changes in both ADRP and DMN, but these relationships were comparatively stronger for the latter network.

We also compared the predictive value of ADRP and DMN expression in a survival analysis. This analysis was restricted to the MCI group, as the cCN group was too small. In the univariate survival model, CSF biomarkers and ADRP were both significant predictors of subsequent conversion. However, in the multivariate Cox regression model, only high (i.e., greater than median) ADRP expression survived as significant predictor. We note that a recently identified metabolic covariance pattern, termed the AD conversion-related pattern (ADCRP), was also useful as a predictor of dementia in MCI patients.[39] This pattern had topographic features similar to ADRP and was derived using a related computational algorithm. ADCRP expression has been shown to be a better predictor of conversion than genetic biomarkers, CSF measurements, regional glucose uptake measures from FDG PET, or amyloid PET.[40,41] While previous studies showed that ADRP expression was higher in individuals with MCI than CN[42] and in A+ MCI than A− MCI,[9] it remains unclear how this network compares with ADCRP in this regard. That said, given that ADRP topographies may vary to a degree across patient samples, we repeated the LME analyses using a previously reported AD pattern derived from a different population.[6] As with the first ADRP, we observed a monotonic increase in expression in converters but not in stable subjects (Figure SA7), along with similar interaction effects (Supplementary Materials A). However, to highlight the robustness of the ADRP network as biomarker, we focused on the disease-related topography that was identified in scan data from a completely unrelated population.[9]

We note several limitations to this study. The presence of amyloid pathology was shown using in vivo biomarkers and not *post-mortem* examination, which could introduce an additional source of heterogeneity to our cohorts. However, CSF biomarkers closely reflect neuropathological findings.[43] Because of the limited availability of tau PET data in this longitudinal sample, we could not assess the importance of tau pathology on ADRP expression. This remains to be addressed in future studies. Though we had access to the information on CSF pTau levels, recent studies showed that these biomarkers are more closely related to amyloid than to tau PET.[44] Therefore, we did not use this information as a substitute for tau PET. Lastly, in this study we focused on the previously validated AD network and DMN, and we did not study the changes in the expression of other major resting-state networks. While we cannot exclude the role of other resting-state

networks in the pathogenesis of AD, the metabolic DMN is among the first affected by the disease process.[15]

## 5 | CONCLUSION

Elevated ADRP expression is seen in CN and MCI individuals before conversion to MCI or dementia, respectively. Longitudinal changes in ADRP expression relate to decline in cognitive performance. The presence of the *APOE ε*4 allele and amyloid positivity in CSF are associated with faster ADRP progression. This study supports the use of ADRP expression as a marker of disease progression and a potential predictor of conversion to dementia in MCI patients.

Furthermore, ADRP expression can be measured longitudinally to monitor the effect of potential new therapies in blinded clinical trials of early stage patients. Network expression may provide a useful secondary outcome variable in such studies.

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### CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest. Author disclosures are available in the supporting information.

### CONSENT STATEMENT

For patients and healthy volunteers participating in ADNI protocols, written informed consent was obtained after approval was granted by the institutional review board of the collaborating institutions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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