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Original Article

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New Trajectory of Clinical and Biomarker Changes in Sporadic Alzheimer's Disease

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Abstract

Identifying dynamic changes in biomarkers and clinical profiles is essential for understanding the progression of Alzheimer's disease (AD). The relevant studies have primarily relied on patients with autosomal dominant AD; however, relevant studies in sporadic AD are poorly understood. Here, we analyzed longitudinal data from 665 participants (mean follow-up 4.90 ± 2.83 years). By aligning normal cognition (CN) baseline with a clinical diagnosis of mild cognitive impairment (MCI) or AD, we studied the progression of AD using a linear mixed model to estimate the clinical and biomarker changes from stable CN to MCI to AD. The results showed that the trajectory of hippocampal volume and fluorodeoxyglucose (FDG) was consistent with the clinical measures in that they did not follow a hypothetical sigmoid curve but rather showed a slow change in the initial stage and accelerated changes in the later stage from MCI conversion to AD. Dramatic hippocampal atrophy and the ADAS13 increase were, respectively, 2.5 and 1 years earlier than the MCI onset. Besides, cognitively normal people with elevated and normal amyloid showed no significant differences in clinical measures, hippocampal volume, or FDG. These results reveal that pre-MCI to pre-AD may be a better time window for future clinical trial design.

Key words: β-amyloid, biomarker trajectories, hippocampal volume, mild cognitive impairment, sporadic Alzheimer's disease

Introduction

The diagnostic guidelines for Alzheimer's disease (AD) (McKhann et al. 2011; Dubois et al. 2014) provide a clinical-pathological framework. The National Institute on Aging-Alzheimer's Association (NIA-AA), in line with the amyloid hypothesis (Hardy and Higgins 1992; Selkoe and Hardy 2016), defines AD on the basis of biomarkers, rather than by clinical symptoms (Jack Jr et al. 2018). However, two observations, the failure of all antiamyloid-β (Aβ) drugs (Honig et al. 2018; Wessels et al. 2020; Panza et al. 2019a; Panza et al. 2019b) to show clinical efficacy and the discovery that amyloid plaques are not unique to AD (Jack Jr et al. 2018; Morris et al. 2018), have led to a debate about the central role of amyloid in the etiology of the disease and its usefulness as a diagnostic marker of AD.

To address this debate, identifying which dynamic changes in biomarkers and clinical profiles correlate directly with the progression of AD is essential. The relevant studies have primarily relied on patients with autosomal dominant AD (ADAD), who often have a predictable age at onset (Bateman et al. 2012; Yau et al. 2015; McDade et al. 2018). In contrast, the precise timing of the disease for patients with sporadic AD (SAD) is difficult to predict (Gordon et al. 2018). Because the ADAD genetic mutations (*APP, PSEN1,* and *PSEN2*) cause alterations in Aβ processing, ADAD studies have consistently found that Aβ is the first and key biomarker, followed by changes in other biomarkers and clinical profiles (Bateman et al. 2012; Yau et al. 2015; McDade et al. 2018). However, increasing evidence has shown that patients with SAD are associated with multiple gene factors, which affect more than Aβ processing (Ryan et al. 2015; Morris et al. 2018; Heart et al. 2019; Jansen et al. 2019). Since ADAD only accounts for a very small proportion (~1%) of AD (Bateman et al. 2012), how widely applicable the findings obtained from ADAD to SAD remains a question (Morris et al. 2018).

A previous prospective SAD study based the stage of AD on the level of accumulation of amyloid and found, consistent with ADAD studies, that the Aβ abnormality appeared first, followed by other changes (Villemagne et al. 2013). However, due to its assumption that Aβ is the etiological agent, that study does not consider the possible dynamic biomarker and clinical changes that occur in relation to symptom onset as in the previous ADAD studies (Bateman et al. 2012; Yau et al. 2015; McDade et al. 2018). Even in subjects who have over 15 years of longitudinal data, the baseline has not been aligned with the onset of clinical symptoms to investigate longitudinal changes in biomarkers and clinical profiles (Veitch et al. 2019). However, as the progression of AD has been hypothesized to be nonlinear (Jack Jr et al. 2010, 2013), simply aligning the baseline with Aβ levels or studying the longitude data is not sufficient to chart the progression of SAD. Thus, to reduce this limitation, we aligned the timepoints of the clinical diagnosis of mild cognitive impairment (MCI) or AD onset to investigate the dynamic changes that occur from cognitively normal (CN) to MCI and from MCI to AD.

Materials and Methods

Study Design

The data were obtained from the ADNI dataset (http://adni.loni.usc.edu/) and downloaded in December 2018. The 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.

To estimate the timing, order, and trajectory of clinical and biomarker changes from normal aging to AD, we labeled the data of the three subgroups as CN, subjects with normal cognition who were confirmed to convert to MCI (CN2MCI), and subjects with MCI who were confirmed to convert to AD (MCI2AD). The CN subgroup was defined as either subject who had a cognitively normal baseline, showed no significant memory concern (SMC), and had at least 2 years' follow-up without conversion to MCI or AD or as subjects with a baseline of MCI who reversed to CN within 1 year and remained stable CN for at least 2 years to the end of follow-up. The CN2MCI subgroup was defined as subjects with a baseline diagnosis of cognitively normal and a subsequent diagnosis of having converted to MCI in the follow-up or as subjects with an SMC confirmed as having converted to MCI. To increase the sample size and statistical power, the CN2MCI timepoint of subjects who converted to MCI and finally to AD were also included in the CN2MCI group. The MCI2AD subgroup was defined as subjects with a baseline diagnosis of MCI who converted to stable AD in the follow-up.

To precisely reflect the stage of the disease, we selected those subjects within the CN2MCI and MCI2AD subgroups who had 1 year or less between the initial one-time assessment before the disease onset and the disease onset of MCI or AD.

Assessments

The clinical profiles and cognitive scores used in the present study include: the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS13), Mini-Mental State Examination (MMSE), and Clinical Dementia Rating Scale-Sum of Boxes (CDRSB). The structural MRI brain scans were acquired using 1.5 T and 3 T MRI scanners. Automated volume measures of MRI structure data were performed with FreeSurfer. The quality of FreeSurfer output data has been controlled by the UCSF group. In the present study, the sum of the left and right hippocampal volume adjusted for the total intracranial volume (TIV) was used to assess the degree of brain atrophy. There are two popular methods for adjusted hippocampal volume with TIV. The first one is adjusting the hippocampal volume for TIV variation based on covariance (Bateman et al. 2012). This method needs to estimate the covariance of TIV for total group data. The second one is adjusting the hippocampal volume by direct dividing the TIV for each subject (Donohue et al. 2017). This method did not need to compute the group data and can be direct used in each individual, thus in the current study we used the second adjust method.

The fluorodeoxyglucose (FDG) PET was used to calculate cerebral metabolism. For the postcingulate region, which is known to be an area of early deposition in ADAD (Bateman et al. 2012; Gordon et al. 2018), the standardized uptake value ratio (SUVR) was normalized with the reference region for the brain stem. To improve the accuracy of the longitudinal Aβ PET changes, we measure the florbetapir PET SUVR as a weighted florbetapir mean in the frontal, cingulate, parietal, and temporal regions relative to the mean of composite reference region (average of whole cerebellum, brainstem/pons, and eroded white matter) (Landau et al. 2015). The median value for all batch of CSF tau, phosphor-tau (Ptau), and Aβ42 has been used in the present study.

Participants were categorized into elevated amyloid or normal amyloid subsets depending on their florbetapir SUVR or

CSF $A\beta_{42}$ status. Elevated amyloid was defined as a florbetapir SUVR >0.79 (Landau et al. 2018) or a CSF $A\beta_{42}$ value less than 192 pg/mL (Shaw et al. 2009). Participants were classified as having elevated amyloid if they met the cutoff threshold at any timepoint. Otherwise, they were classified as having normal amyloid. If there was no amyloid information for a participant, their data were classified as missing.

As the ADAS has usually been used to monitor the progression of AD (Egan et al. 2018; Honig et al. 2018), we calculated the correlations between the ADAS13 and each marker in the CN2MCI and MCI2AD stages separately to evaluate whether the markers could predict AD progression.

To compare the progression curve for all the markers and verify the model of the fitted results, the scaled value for each marker was defined by (raw data—mean CN baseline value)/the standard deviation (SD) of the whole dataset. To further verify the abnormal pattern of the markers in the progression of AD, we also analyzed the within-individual trajectories for all 24 subjects who were initially diagnosed as CN, subsequently converted to MCI, and then to AD (CN2MCI2AD). Each marker in these individuals was also scaled by the mean of the baseline data for the CN subgroup and for the SD of the entire dataset.

Statistical Analysis

For the longitudinal trajectory analyses of the CN2MCI and MCI2AD subgroups, the follow-up years were categorized into presymptom onset (<0 onset years) and postsymptom onset (>0 onset years). To increase model convergence, we excluded the data of timepoints for which the sample size was <3 for each clinical profile or biomarker, (See Supplementary Figure S1 for the detailed sample size for the various timepoints for each clinical profile or biomarker) Statistical analyses and plotting were performed using R (version 3.5.3, https://www.r-project.org/).

Longitudinal trajectory models were constructed for the various biomarkers using linear mixed effects models (West et al. 2014). For each marker, we started by fitting an appropriate function to the time (baseline or onset time), for example, $\text{time} + \text{time}^2 + \text{time}^3$. Disease progression (CN, CN2MCI, and MCI2AD) was included in the models to extract disease-specific biomarker trajectories. Covariates such as age at baseline or onset year, sex, APOEε4, and education were included as confounds, and a backward elimination method was used for model selection. We then selected a structure for the random effects and covariance structure for the residuals in the model. All the model selections were based on the Akaike Information Criterion (Akaike 1998), an objective model selection tool. Maximum likelihood was used to fit the mixed-effect models as it is robust to the absence of random data (Donohue et al. 2017).

We further compared the trajectories for each marker in the progression of AD to uncover differences between the elevated amyloid and normal amyloid groups. The overall amyloid effect was tested using likelihood ratio tests that compared the full model to a reduced model with no amyloid factor in each subgroup for each marker. For any subgroup that showed a significant amyloid effect as the disease progressed, a supplementary post hoc analysis was performed between the elevated amyloid and normal amyloid groups at each timepoint based on the estimated marginal means derived from the model.

To determine the timing of the dysfunctions, we fitted a linear mixed-effects model to the CN2MCI subgroup with time as a categorical variable for each biomarker. The post hoc analysis was conducted between each timepoint based on estimated marginal means derived from the model.

Results

Characteristics of Study Participants

Of the downloaded 665 subjects from the ADNI dataset, we utilized the data from 663 participants in the group analysis (CN: 294, CN2MCI: 69, and MCI2AD: 300, for more details of the participants' characteristics, see Table 1) and 24 CN2MCI2AD participants in the individual analysis (the data from the group of 22 participants in the CN2MCI stage was combined into the above CN2MCI group analysis). Some participants were followed for up to 13 years with a mean follow-up period of 4.90 ± 2.83 years.

Estimated Group Trajectories of Clinical Profiles and Biomarkers in the Progression of SAD

Figure 1 shows the trajectories of the biomarkers estimated by the linear mixed-effects models across groups (for the spaghetti plot of the raw data, see Supplementary Figure S2). Consistent with the clinical profiles of AD progression, the hippocampal volume and FDG levels remained stable throughout the CN stage followed by slow, nonlinear changes in the CN2MCI stage, and rapid nonlinear changes in the MCI2AD. Even the values of the florbetapir PET and the CSF biomarkers were normal in CN, intermediate in CN2MCI and abnormal in MCI2AD subgroups, the shape of the trajectories for florbetapir PET and the CSF biomarkers did not consistent with the clinical profile. The details of the linear mixed model for each biomarker are displayed in Supplementary Table S1–S3.

The annual change results (Table 2) consistent with Figure 1 showed that the hippocampal volume and FDG consistent with clinical measures remained stable in the CN stage followed by slow changes in the CN2MCI stage and rapid changes in the MCI2AD. Moreover, the annual changes of florbetapir PET and the CSF biomarkers are not consistent with clinical measures for which there are no significant differences among CN, CN2MCI, and MCI2AD groups.

Estimated Elevated and Normal Amyloid Group Trajectories of Clinical Profiles and Biomarkers in the Progression of SAD

Figure 2 shows the trajectories of the biomarker changes for either the normal or elevated amyloid groups. Qualitatively, the pattern remained stable in the CN, showing slow nonlinear changes in the CN2MCI and ended with a phase in which rapid nonlinear changes appeared in the MCI2AD. We found no significant differences in the clinical profiles, hippocampal volume, or FDG changes between the elevated and normal amyloid subjects at the $P < 0.05$ level. The statistical results showed no difference for CDRSB and FDG in any of the three (CN, CN2MCI, and MCI2AD) subgroups at $P < 0.05$. The ADAS13 analysis showed significant group differences for the 6–9-year time period in the CN subgroup, for the < -4.5 and > 4 years to onset time in the CN2MCI subgroup, and for the > -0.5 years to onset time in the MCI2AD subgroup at $P < 0.05$. The MMSE analysis showed a significant group difference for the time period > -1 year in the CN2MCI subgroup at $P < 0.05$. Although the likelihood ratio test showed a significant difference in hippocampal volume between the elevated and normal amyloid subjects ($P = 0.047$),

Table 1 Characteristics of study participants

	CN	CN2MCI	MCI2AD	P
	N = 294	N = 69 (22 finally to AD)	N = 300	
Sex				0.058
Female	146 (49.7%)	28 (40.6%)	121 (40.3%)	
Male	148 (50.3%)	41 (59.4%)	179 (59.7%)	
Education, mean (SD), y	16.5 (2.68)	16.1 (2.67)	15.9 (2.80)	0.032
APOE allele:				<0.001
APOEε4 noncarriers	221 (75.2%)	42 (60.9%)	98 (32.7%)	
APOEε4 carriers	73 (24.8%)	27 (39.1%)	202 (67.3%)	
Follow-up, mean (SD), y	5.33 (2.83)	5.70 (3.43)	4.07 (2.29)	<0.001
Amyloid characteristics:				<0.001
Missing amyloid information	52 (17.7%)	8 (11.6%)	75 (25.0%)	
Elevated amyloid	115 (39.1%)	41 (59.4%)	202 (67.3%)	
Normal Amyloid	127 (43.2%)	20 (29.0%)	23 (7.7%)	
	Baseline characteristics	MCI onset characteristics	AD onset characteristics	
Age, mean (SD), y	74.0 (6.18)	79.7 (5.70)	76.5 (7.39)	<0.001
ADAS13, mean (SD)	8.60 (4.04)	15.0 (6.32)	27.1 (7.36)	<0.001
CDRSB, mean (SD)	0.06 (0.26)	1.01 (0.76)	4.30 (1.59)	<0.001
MMSE, mean (SD)	29.1 (1.17)	27.6 (1.83)	23.8 (2.91)	<0.001
Hippocampal volume, mean (SD), %ICV	0.50 (0.06)	0.44 (0.05)	0.37 (0.06)	<0.001
FDG PET SUVR, mean (SD)	1.41 (0.14)	1.20 (0.15)	1.16 (0.14)	<0.001
Amyloid PET SUVR, mean (SD)	0.78 (0.09)	0.93 (0.14)	1.01 (0.12)	<0.001
CSF Aβ42, mean (SD), pg/mL	207 (49.9)	194 (79.0)	137 (35.6)	<0.001
CSF tau, mean (SD), pg/mL	63.8 (29.2)	90.4 (28.8)	130 (75.9)	<0.001
CSF ptau, mean (SD), pg/mL	29.1 (14.7)	39.2 (23.7)	55.1 (30.7)	<0.001

Note: ADASA13, the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale; CSF, cerebrospinal fluid.

the post-hoc results showed no significance at $P < 0.05$ in the CN2MCI and only showed a significant group difference for the time period <-1 year in the MCI2AD at $P < 0.05$. All subgroups showed obvious significant differences with respect to florbetapir PET and CSF Aβ_{42} between the elevated and normal amyloid subjects at $P < 0.001$. For CSF Tau and CSF Ptau, only the CN2MCI subgroup showed no amyloid effect at $P < 0.05$; the other two subgroups showed significant differences at $P < 0.05$ (Figure 2; for the post hoc analysis results, see Supplementary Table S4).

Changes in Aβ Biomarkers were not Associated with Changes in ADAS13 During the Disease Status Conversion.

We found that the changes in the CDRSB (Fig. 3.1A and 2A), MMSE (Fig. 3.1B and 2B), hippocampal volume (Fig. 3.1.C and 2.C), and FDG PET in the postcingulate cortex (Fig. 3.1.D and 2.D) were associated with the change in the ADAS13 in both the CN2MCI and MCI2AD subgroups. However, the changes in the amyloid-related biomarkers florbetapir PET and CSF Aβ_{42} were not significantly associated with the change in the ADAS13 in either group (Fig. 3.1.E, 1.F, 2.E and 2.F).

Temporal Evolution of Relative Abnormality in Clinical Measures and Biomarkers

Combining the biomarker findings, we assessed the trajectories and order of pathophysiological changes for the clinical, imaging, and biochemical measures (Fig. 4A and B). As can be seen in Figures 1 and 2, the clinical profiles, hippocampal volume, and FDG changed slowly in the initial stage of CN2MCI and accelerated in the late MCI2AD stage. The order in which these measures changed in the CN2MCI subgroup was that the hippocampus and FDG PET changed earlier than ADAS13 and that CDRSB and MMSE were the last measures to change. Further, a post hoc analysis showed that the change in hippocampal volume preceded the symptom onset of MCI by 2.5 years and ADAS13 preceded the symptom onset of MCI by 1 year. Significant changes in MMSE and CDRSB were concurrent with MCI onset (Supplementary Figure S3). Even in patients with elevated amyloid, the trajectory of the amyloid-related biomarker was not consistent with the clinical profiles, hippocampal volume, or FDG (Fig. 4B). More importantly, florbetapir PET was stable during the CN2MCI stage. Although CSF Aβ_{42} showed some nonlinear changes before MCI onset, the change was smaller than those of the other biomarkers. Thus, these results do not support previous reports (Bateman et al. 2012; Yau et al. 2015), suggesting that amyloid-related biomarker changes largely lead other biomarker changes at the onset of the disease.

Within-Individual Trajectories of Clinical Measures and Biomarkers

We further assessed each biomarker for the individuals who progressed from CN to MCI and to AD for each biomarker (Fig. 4C and Supplementary Figure S4). The mean time for conversions from MCI to AD was 2.44 ± 1.49 (range 1–7) years in these 24 subjects. The individual results were consistent with the previous group results: the trajectories of their clinical profiles changed slowly in the initial period in the CN2MCI stage and accelerated in the MCI2AD stage, the dynamic changes of hippocampal volume paralleled the disease status changes, and there were

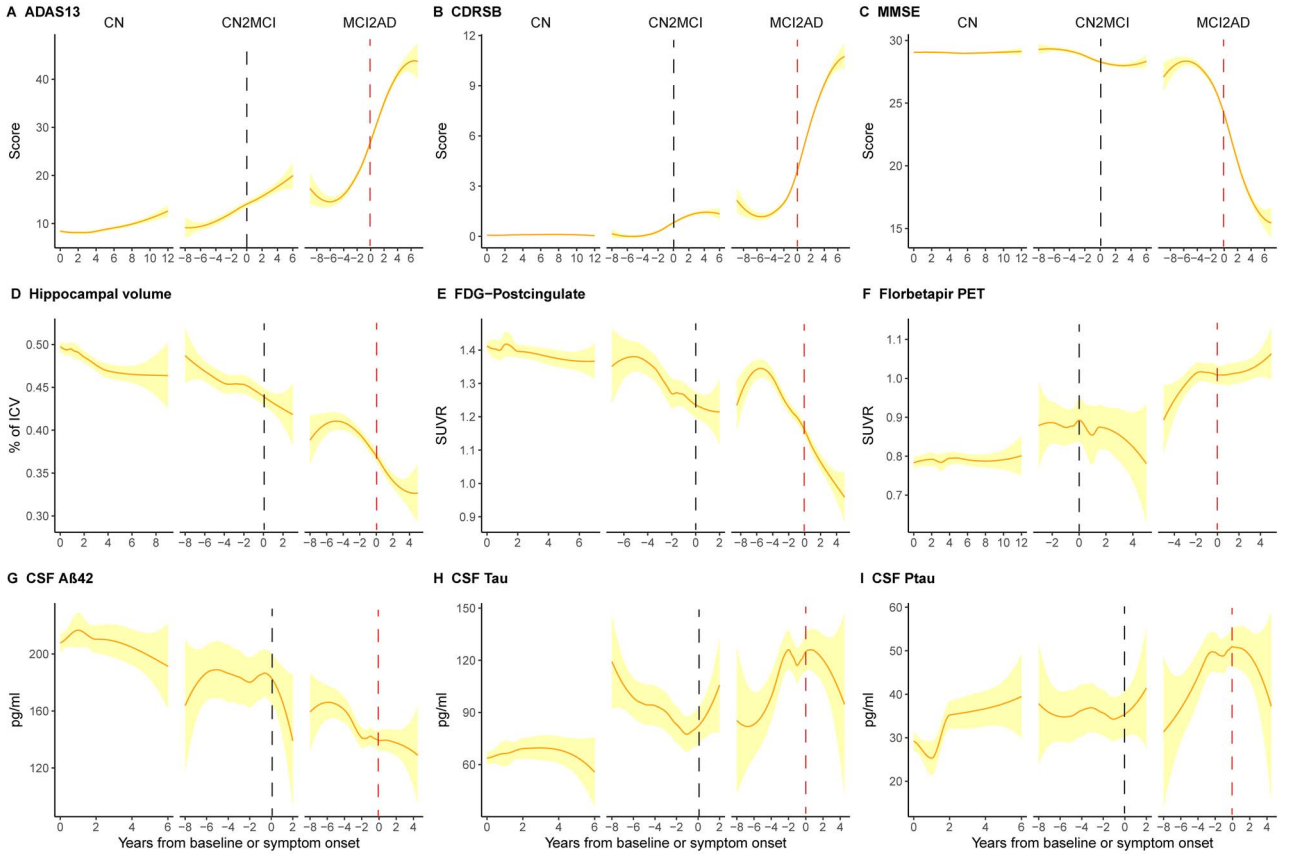

Figure 1. Estimated group trajectories of clinical profiles and biomarkers. (*A*) ADAS13; range from 0 [best] to 85 [worst], (*B*) CDRSB; range from 0 [best] to 18 [worst], (*C*) MMSE; range from 0 [worst] to 30 [best], (*D*) the MRI measures of hippocampal volumes adjusted by percent of the total intracranial volume (ICV), (*E*) the postcingulate cortex glucose metabolism measured by FDG PET consistently showed stable changes in the stable cognitive normal (CN) subgroup, slow nonlinear changes in the confirmed CN conversion to MCI (CN2MCI) subgroup, and acceleration nonlinear changes in the confirmed MCI conversion to AD (MCI2AD) subgroup. In contrast, (*F*) Florbetapir PET, (*G*) CSF Aβ_{42}, (*H*) CSF tau, and (*I*) CSF phosphor-tau (Ptau) did not show changes consistent with the clinical profiles. The estimated trajectory and 95% confidence interval from the linear mixed models (yellow line and yellow shaded area, respectively) are plotted against years from baseline or symptom (MCI or AD) onset for each marker. The black dashed line represents the MCI onset timepoint. The red dashed line represents the AD onset timepoint.

Table 2 The annual change of clinical profile and biomarkers

	CN	CN2MCI	MCI2AD	P
ADAS13, median [IQR]	0.388 [−0.278, 0.818]	1.000 [0.239, 2.330]	3.388 [1.750, 6.169]	<0.001
CDRSB, median [IQR]	0.000 [0.000, 0.000]	0.214 [0.100, 0.500]	1.250 [0.750, 2.000]	<0.001
MMSE, median [IQR]	0.000 [−0.250, 0.161]	−0.286 [−0.571, 0.000]	−1.500 [−2.775, −0.800]	<0.001
Hippocampal volume, median [IQR], %ICV	−0.005 [−0.011, −0.001]	−0.006 [−0.012, −0.002]	−0.014 [−0.021, −0.009]	<0.001
FDG PET SUVR, median [IQR]	−0.011 [−0.030, 0.010]	−0.027 [−0.056, −0.012]	−0.039 [−0.063, 0.014]	<0.001
Amyloid PET SUVR, median [IQR]	0.004 [−0.002, 0.012]	0.004 [−0.001,0.011]	0.005 [−0.006, 0.014]	0.840
CSF Aβ42, median [IQR], pg/ml	−1.500 [−6.000, 4.000]	−2.200 [−5.667, 4.000]	−2.000 [−7.000, 2.650]	0.564
CSF tau, median [IQR], pg/ml	0.775 [−1.887, 4.500]	2.150 [−0.500, 7.900]	3.000 [−3.900, 14.175]	0.121
CSF ptau, median [IQR], pg/mL	1.050 [−1.450, 4.500]	1.980 [−0.200, 5.050]	1.408 [−1.321, 8.325]	0.628

Note: IQR, interquartile range.

no significant changes in amyloid-related biomarkers in the CN to MCI to AD progression.

Discussion

Identifying the dynamic changes in clinical assessments and biomarkers during a patient's progression to AD is critical for defining the stage of the disease and its etiology and for monitoring the efficacy of potential therapies. In the present study, we avoided preconceptions about disease etiology and aligned the clinical symptom onset timepoints of the different stages from CN, through MCI, to AD using various clinical assessments and biomarkers to obtain a panorama of disease progression. The end stage of CN remained stable during the follow-up. Furthermore, the onset timepoints of clinical diagnosis were rigidly

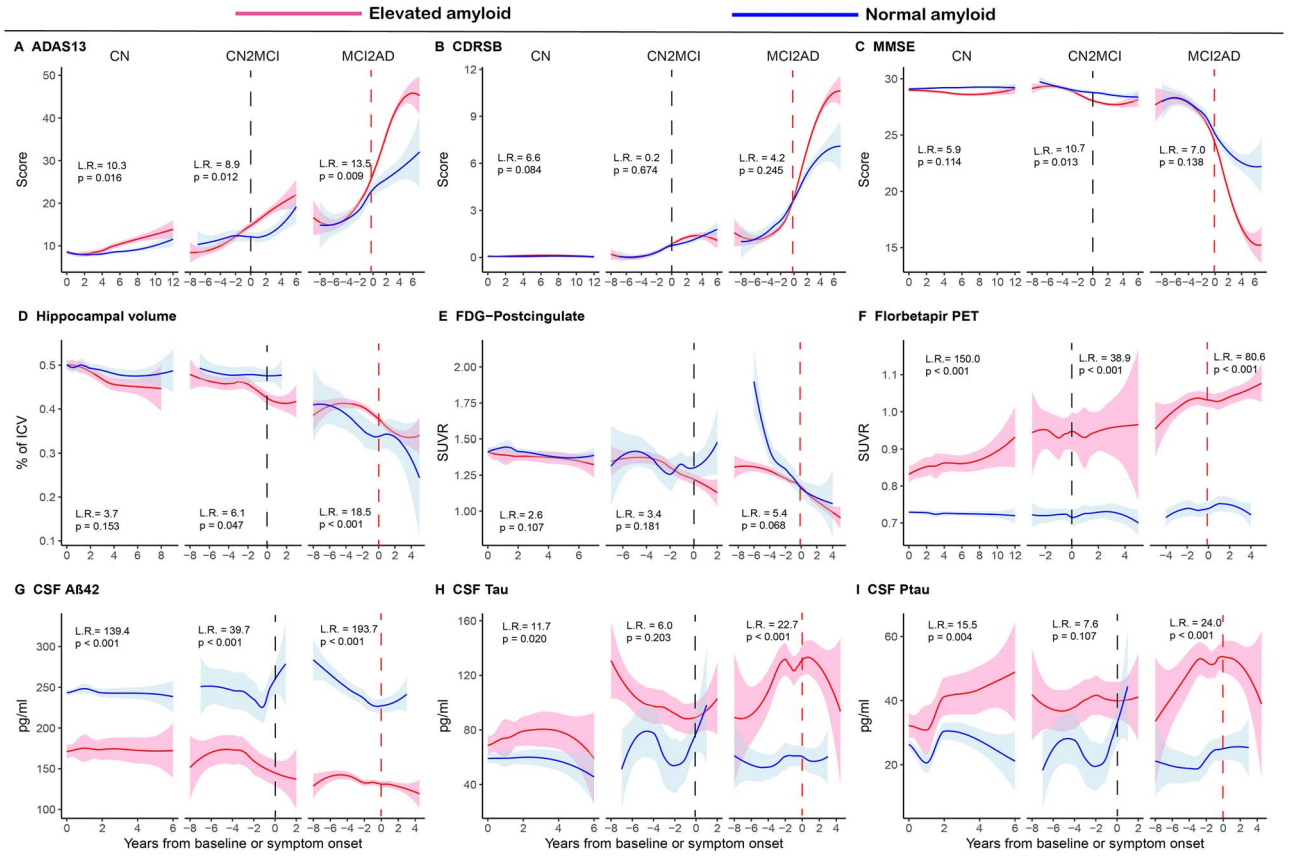

Figure 2. Estimated elevated and normal amyloid group trajectories of clinical profiles and biomarkers. The estimated trajectory and 95% confidence interval from the linear mixed models are plotted against years from baseline or symptom (MCI or AD) onset for each marker. Red line and pink shaded area represent the elevated amyloid subjects. Blue line and blue shaded area represent the normal amyloid subjects. L.R. = likelihood ratio.

aligned for CN2MCI and MCI2AD with error <1 year. In addition, we also replicated the group results using the CN2MCI2AD subjects. Thus, the study expands the current literature about the trajectory of clinical and biomarker changes in the progression of SAD.

By aligning the disease onset timepoint, we found that the trajectory of hippocampal volume and FDG were consistent with the clinical profiles in that they did not follow a sigmoid curve (Jack Jr et al. 2010, 2013) but rather showed a slow change in the initial stage and accelerated changes in the later stage from MCI to AD (Figs 1 and 4). Although previous studies based on the ADNI dataset reported that the changes in these biomarkers followed a sigmoid curve (Caroli et al. 2010; Jack Jr et al. 2012; Schuff et al. 2012), these studies did not align their findings with the stage of the disease, so they could not be considered to accurately reflect the trajectory of biomarker changes that occur in the progression of AD. In addition, we founded that the rate of changes in amyloid-related biomarkers was not associated with a change in disease status even in elevated amyloid subjects (Figs 2F, 2G and 4B and C). A previous prospective study, based on the amyloid hypothesis, reported that brain Aβ deposition continuously changed with SAD progression (Villemagne et al., 2013). However, they found that the raw data of Aβ deposition was stable and changed slowly (Villemagne et al. 2013), a finding that is in keeping with our results. Thus, these results indicated that assessment of the clinical or biomarker dynamic changes by aligning the clinical onset timepoint maybe better reflect and characterize the progress of the disease. Besides, these results will contribute to future clinical trial design. If the progression curve as sigmoid, which means that the change rate of the different disease stage is similar, and the clinical trial designed in a different stage have the same effect. However, our results revealed that the changed rate in the disease progression not similar, which will influence the clinical trial results. For example, in two recent clinical trials AMARANTH for Lanabecestat (NCT02245737) (Wessels et al. 2020) and EMERGE for Aducanumab (NCT02484547), the inclusion criteria for MMSE with 20–30 and 26–30, respectively. Our results (Figs 1 and 2) suggest that such clinical design would involve a mixture of slowly changing subjects and rapidly changing subjects, which may influence the final clinical trial results.

We found that the accumulation of amyloid in the CN did not predict future cognitive impairment in either people who maintained a stable CN or those in the pre-MCI onset stage (Fig. 2A–C). This result is consistent with recent reports that indicated that brain Aβ is not clinically relevant (Dubois et al. 2018; Jansen et al. 2018). Other studies, however, reported that elevated amyloid in CN individuals was associated with a higher likelihood of cognitive decline compared with normal amyloid CN subjects (Donohue et al. 2017; Insel et al. 2018). Although these findings are insightful, using the same ADNI dataset, we found that cognitive decline did not depend on the accumulation of amyloid but on the clinical stage of the disease. Moreover, our results were partially consistent with previous findings,

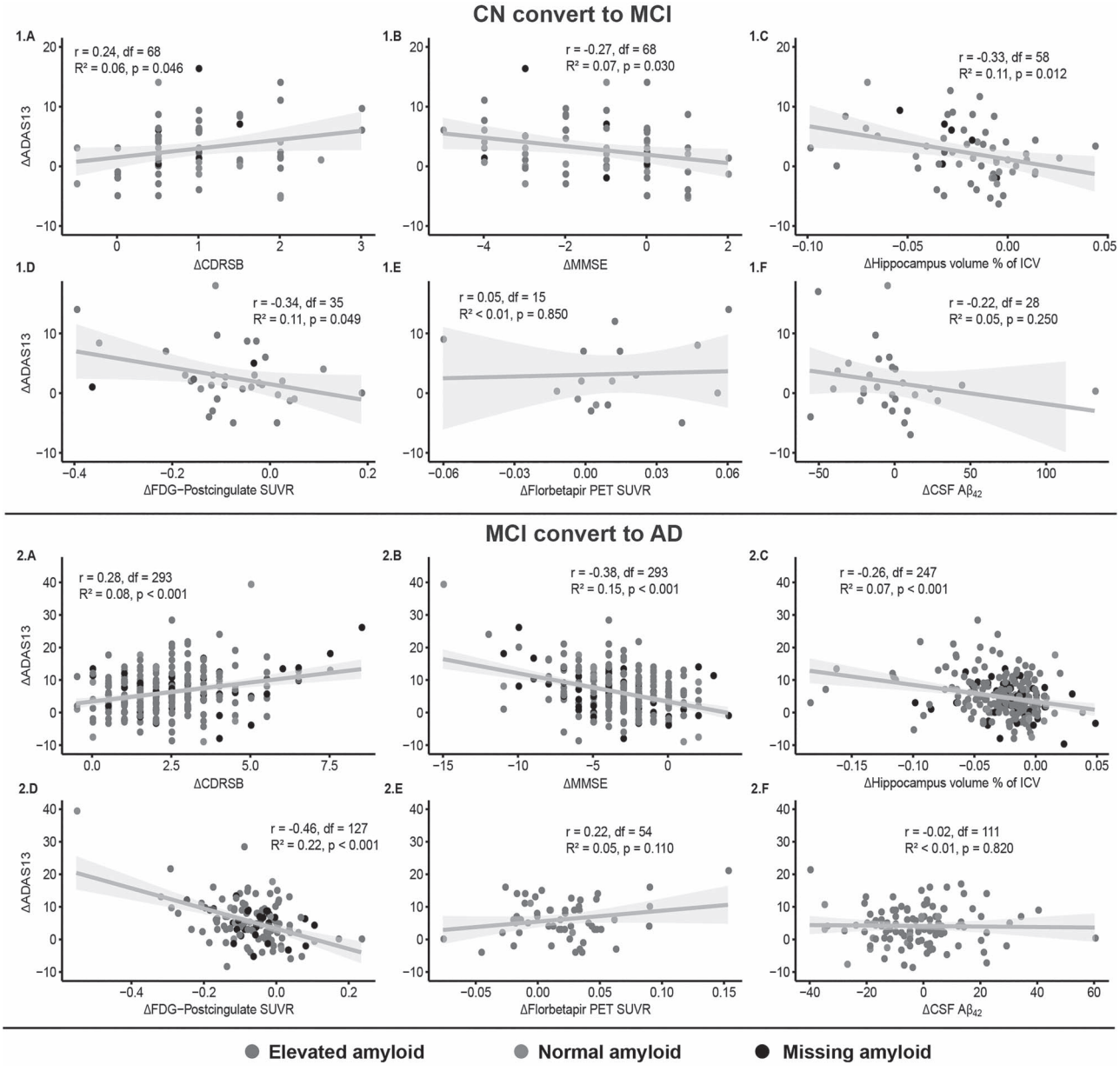

Figure 3. Relationship between the change in each biomarker and the change in ADAS13 in the CN conversion to MCI and the MCI conversion to AD subgroups. The top panels show that the changes in the (1.*A*) CDRSB score, (1.*B*) MMSE score, (1.*C*) hippocampal volume percent of ICV, and (1.*D*) postcingulate FDG SUVR value significantly correlated with the change in the ADAS13 scores in the CN conversion to MCI subgroup. However, the changes in the amyloid-related biomarkers, (1.*E*) Florbetapir PET SUVR and (1.*F*) CSF Aβ_{42}, were not significantly correlated with the change in ADAS13 scores. The bottom panels show that the change in the (2.*A*) CDRSB score, (2.*B*) MMSE score, (2.*C*) hippocampal volume percent of ICV, and (2.*D*) postcingulate FDG SUVR value significantly correlated with the change in ADAS13 scores in the MCI conversion to AD subgroup. However, the changes in amyloid-related biomarkers, (2.*E*) Florbetapir PET SUVR and (2.*F*) CSF Aβ_{42}, were not significantly correlated with the change in ADAS13 scores. df = degree of freedom.

showing that amyloid accumulation alone cannot predict the cognitive decline or disease progression, whereas the amyloid accumulation combined with tau or atrophy of some groups can predict the further cognitive decline (Bilgel et al. 2018; Zhao et al. 2018; Jack Jr et al. 2019) or disease progression in the normal adults (Vos et al. 2013, 2015; Burnham et al. 2016). These results support the recent idea about the combination therapies for future AD treatment strategies (Long and Holtzman 2019) and the widespread concern about overdiagnosis in the preclinical AD (Langa and Burke 2019).

Our finding that cognitive decline and Aβ deposition did not occur in parallel (Figs 3 and 4) is consistent with previous studies that reported that Aβ dysregulation poorly correlates with AD severity (Arriagada et al. 1992), progressive neurodegeneration (Holmes et al. 2008), cognitive dysfunction (Giannakopoulos et al. 2003), or brain atrophy (Jack Jr et al. 2009). During the rapid cognitive decline from MCI to AD, Aβ deposition only mildly increased. This may partially explain why anti-Aβ drugs have failed in clinical trials. Medications, such as solanezumab, a medication designed to clear soluble Aβ from the brain, are

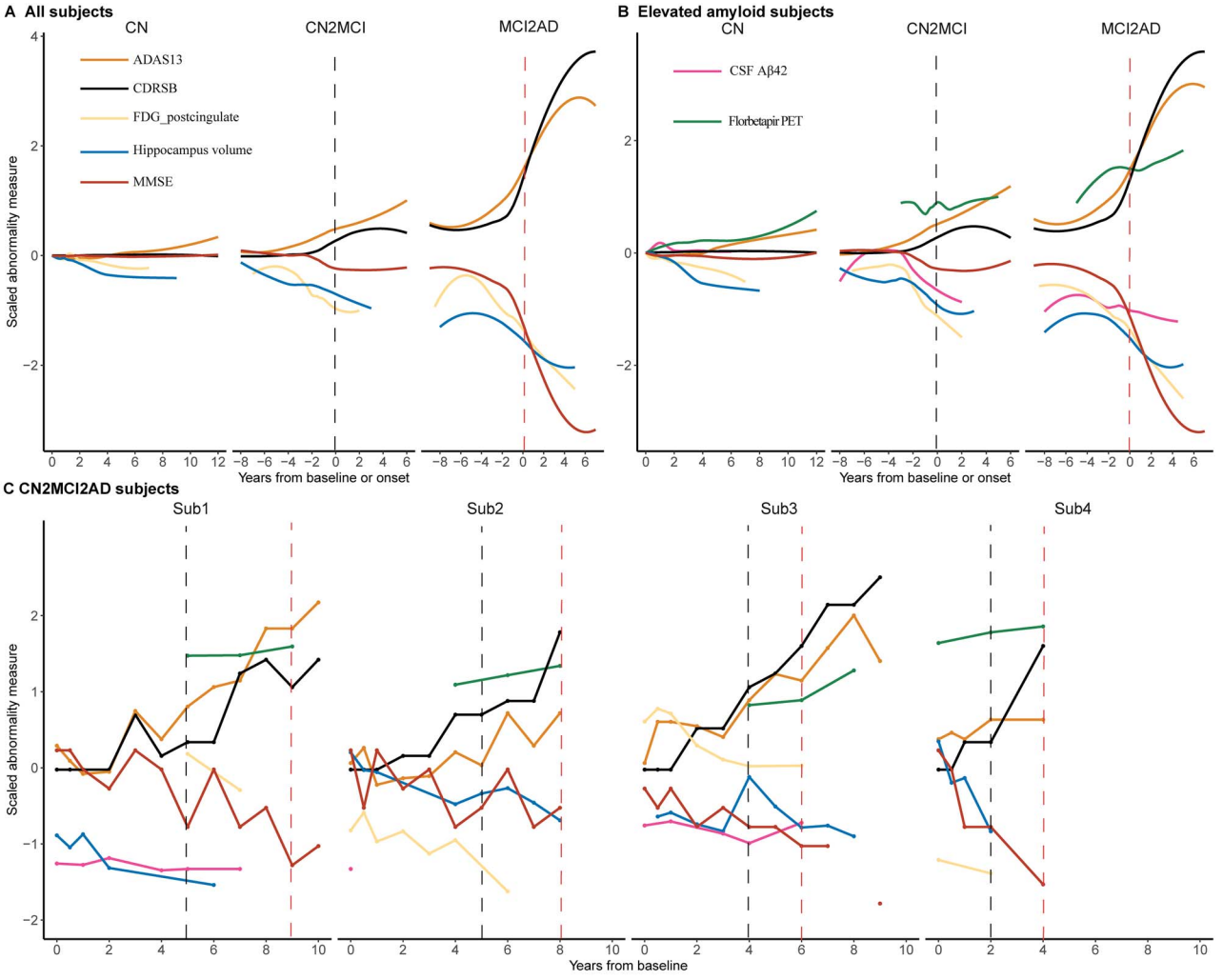

Figure 4. Temporal evolution of marker changes and within-individual trajectories of marker changes. Raw data for each biomarker and clinical profile converted to scaled values. The scaled value for each marker was defined by (raw data—mean CN baseline value)/the SD of the whole dataset. (*A*) Clinical profiles, hippocampal volume, and FDG scaled changes in all subjects; (*B*) clinical profiles and biomarkers scaled changes in the elevated amyloid subjects; (*C*) clinical profiles and biomarkers scaled changes in 4 subjects who included the entire disease process from CN conversion to MCI followed by conversion to AD (CN2MCI2AD), within-individual changes. The clinical measures and biomarker represented by the line color are consistent with (*A*) and (*B*).

used in the mild AD stage (Honig et al. 2018), which is too late to prevent rapid cognitive decline. In addition, ADAS13 showed dramatic changes about 1 year before the clinical MCI onset, a finding which was not consistent with the general concept that clinical profiles change only after the onset of MCI (Jack Jr et al. 2010, 2013). Thus, the slow stage from pre-MCI to pre-AD may be a better time window for future clinical trial design.

Our results suggest that applying ADAD results directly to SAD research may not be appropriate (Morris et al. 2018). We found that the rate of Aβ biomarker changes during CN conversion to MCI stage did not reflect those of other biomarkers and was not associated with clinical changes (Fig. 4). This result is not consistent with previous ADAD studies that found that amyloid biomarkers undergo greater changes and lead to other biomarker changes in the initial stage of symptom onset (Bateman et al. 2012; Yau et al. 2015; McDade et al. 2018). The most likely explanation for this difference is that the ADAD and SAD have different etiologies (Morris et al. 2018). In addition, we found that dramatic hippocampal atrophy starts 2.5 years prior to MCI onset, which is later than recent ADAD brain atrophy findings (Gordon et al. 2018; McDade et al. 2018). The concept that SAD involves a long presymptomatic period and is derived from ADAD studies (Ryan et al. 2015) may need to be reconsidered.

One of the limitations of the current study is that the CN2MCI subgroup was older than the MCI2AD subgroup, which may have influenced the pattern of biomarker changes. The ongoing ADNI dataset maybe resolves this limitation in future studies. Another limitation is the small sample size of the tau and Aβ biomarkers in the pre-MCI stage, which meant that we could not fully reveal the dynamic changes in these biomarkers in the preclinical stage. The ongoing collection of plasma biomarkers (Nakamura et al. 2018; Mattsson et al. 2019; Ashton et al. 2020; Janelidze et al. 2020; Thijssen et al. 2020) and ADNI3 tau-related PET data (Scholl et al. 2016) will improve the likelihood of fully understanding the preclinical stage of SAD in the future.

In conclusion, the trajectories of hippocampal volume and FDG were consistent with clinical profiles in that they did not

follow a sigmoidal curve but rather showed a slow nonlinear change in the initial stage and an acceleration in the later stage from MCI to AD. The ADAS13 increases 1 year earlier than MCI onset. In addition, Aβ alone is not associated with clinical profiles, hippocampal volume, and FDG impairment in the preclinical stage of SAD. Thus, these results after aligning the clinical onset timepoint reveal that the slow stage of pre-MCI to pre-AD may be a better time window for future clinical trial design.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Author Contributions

T.J. and P.F.B. supervised the study. J.Z., P.F.B., and T.J. were responsible for the design of the concept and the study. J.Z. contribution to the data analysis and statistical analysis; Y.Z., B.L., Y.L., and X.Z. made substantial contributions to the discussion on the results and the manuscript; J.Z., P.F.B., and T.J. wrote the manuscript.

Notes

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