Neurobiology of Disease

Reciprocal Predictive Relationships between Amyloid and Tau Biomarkers in Alzheimer's Disease Progression: An Empirical Model

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There is an urgent need to understand the relationships between amyloid-β (Aβ) and tau in the progression of Alzheimer's disease to identify treatment targets. Here we examine reciprocal predictions of brain Aβ burden quantified by positron emission tomography and CSF concentrations of Aβ42 and phosphorylated tau (p-tau). Each biomarker was examined over 48 months in two separate cross-lagged models; one in asymptomatic healthy elderly people (men and women), and one in patients with Alzheimer's disease (AD) dementia or mild cognitive impairment (MCI). The models examine predictions of each biomarker on the progression of the others, considering each previous and concurrent measure. In healthy elderly, lower CSF Aβ42 predicted Aβ deposition and reciprocally, Aβ burden predicted a decrease in CSF Aβ42. Lower CSF Aβ42 predicted an increase in CSF p-tau, and CSF p-tau predicted Aβ deposition. In AD/MCI, lower CSF Aβ42 predicted Aβ deposition and Aβ burden reciprocally predicted CSF Aβ42 changes; however, in contrast to healthy elderly, CSF p-tau concentrations did not predict Aβ biomarkers, or vice versa. In *post hoc* models examining cognitive status, CSF Aβ42 predicted Mini Mental State Examination (MMSE) scores in healthy elderly, whereas Aβ burden and CSF p-tau predicted MMSE scores in AD/MCI. The findings describe reciprocal predictions between Aβ and tau biomarkers in healthy elderly and they implicate mechanisms underlying low CSF Aβ42 in Alzheimer's disease pathogenesis and progression. In symptomatic Alzheimer's disease, CSF Aβ42 and Aβ deposition predicted each other; however, Aβ and CSF p-tau progressed independently and they independently predicted cognitive decline.

Key words: amyloid; biomarkers; CSF; PET; tau

Significance Statement

This study offers empirical evidence concerning the hypothesized "amyloid cascade", as it progressed over 4 years in healthy elderly people and in Alzheimer's disease patients. In healthy elderly, CSF amyloid changes predicted amyloid deposition, CSF phosphorylated tau concentrations, and a decline in cognitive status. Phosphorylated tau concentrations specifically predicted amyloid deposition. In Alzheimer's disease patients, although amyloid deposition and CSF amyloid changes continued to "cascade", there was no evidence to suggest that amyloid and tau biomarkers predicted each other, although both amyloid deposition and CSF tau progression predicted cognitive decline independently. Taking advantage of repeated amyloid PET and CSF measures, this dynamic view offers new insight into the progression of Alzheimer's disease biomarkers and their relationships with cognitive decline.

Introduction

Alzheimer's disease (AD) is defined by two pathological hallmarks: Aβ plaques and neurofibrillary tangles (NFTs), caused, respectively, by extracellular aggregation of Aβ and intracellular

hyperphosphorylation of tau (Ittner and Götz, 2011). A long-standing amyloid hypothesis implicates Aβ as the initiator and

driver of AD pathological progression (Hardy and Selkoe, 2002; Karran et al., 2011), although some have speculated that Aβ and tau pathologies may be driven by a common upstream pathological process (Small and Duff, 2008). The failure of several anti-amyloid therapies to improve clinical symptoms in AD dementia (Castello et al., 2014) highlights an urgency to understand the interactions between Aβ and tau, and their roles in AD progression.

Genetic evidence supports an initiatory role of Aβ dysregulation in AD; mutations in the amyloid precursor protein (*APP*) gene (Goate et al., 1991), as well as presenilin 1 (Sherrington et al., 1995) and 2 (Levy-Lahad et al., 1995), can cause autosomal dominantly inherited AD, whereas the roles of polymorphisms that increase the likelihood of late-onset AD remain incompletely understood. Tau mutations can cause frontotemporal dementia (Hutton et al., 1998), but not AD, implicating tau as a downstream effect of Aβ, common across several dementia syndromes (Karran et al., 2011).

The temporal evolution of AD biomarkers shows a characteristic decrease in CSF Aβ peptide 42 (Aβ42) concentrations, and a subsequent increase in Aβ deposition inferred from positron emission tomography (PET) scans, that precedes increases in CSF tau concentrations or tau deposition in most brain regions (Jack et al., 2013; Blennow et al., 2015). Some evidence opposes this canonical sequence of biomarker staging. Braak and Braak (1997) reported that tau pathology typically appeared at younger ages than Aβ pathology. Examining both amyloid and tau PET, Cho et al. (2018) found that tau deposition often appears in the temporal cortex, but not more broadly throughout other cortical areas, in the absence of detectable neocortical Aβ. Those findings would be consistent with the suggestion that the predominant role of Aβ may be to exacerbate tau pathology (Jack et al., 2013; Stancu et al., 2014).

To date, most biomarker studies have been adynamic, and so an amyloid "cascade" per se, involving reciprocal synergy between Aβ and tau progression, has yet to be empirically proven in living people. Moreover, existing clinical evidence fails to identify a role of Aβ beyond the initiation of AD pathogenesis, and the nature of its relationship with tau progression has been described only recently as AD symptoms develop and progress (Hanseeuw et al., 2019; Sperling et al., 2019). Possibly due in part to a previous lack of long-term clinical data, the AD cascade has remained an enigmatic target for treatment.

The present study takes advantage of repeated measurements collected by the Alzheimer's Disease Neuroimaging Initiative (ADNI) investigators to examine the dynamic interplay between biomarkers of Aβ and tau in their progression over 48 months, both in asymptomatic healthy elderly controls (HCs) and in cognitively impaired individuals with AD dementia or mild cognitive impairment (MCI) who have biomarker confirmation of amyloid positivity (AD/MCI). The predictive relationships between CSF concentrations of Aβ42, CSF concentrations of tau phosphorylated at threonine 181 (p-tau), and levels of Aβ deposition obtained from ^{18}F-florbetapir (^{18}F-AV-45) PET (Johnson et al., 2013) are examined using a cross-lagged panel model (CLPM), which offers an ideal statistical environment to dissect reciprocal predictive relationships between co-propagating factors over time. Specifically, a model was constructed to examine (1) the predictive relationships between CSF Aβ42 and CSF p-tau progression; (2) the predictive relationship between amyloid deposition and the progression of CSF Aβ42 and CSF p-tau, and the converse predictions of CSF Aβ42 and CSF p-tau on amyloid deposition; and (3) amyloid and tau progression in HC and AD/MCI separately to specify their relationships in asymptomatic and symptomatic people. *Post hoc* models were constructed including Mini-Mental State Examination (MMSE) scores to explore the predictive relationships between these biomarkers and changes in cognitive status.

Materials and Methods

Sample. Separate analyses were conducted in HC and AD/MCI participants (http://adni.loni.usc.edu/) to examine the predictive relationships between Aβ and tau biomarkers in asymptomatic elderly and in cognitively impaired biomarker-confirmed symptomatic people. Data were used from ADNI GO and 2 because ^{18}F-AV-45 PET scans on subjects began in these study phases. ADNI was launched in 2003, as a public–private partnership, with the primary goal of determining whether neuroimaging, other biomarkers, and clinical and neuropsychological assessments could be combined to measure the progression of MCI and early AD. ADNI was conducted according to Good Clinical Practice guidelines, US 21CFR Part 50–Protection of Human Subjects, and Part 56–Institutional Review Boards, and pursuant to state and federal regulations. Written informed consent and HIPAA authorizations for the study were obtained from all participants and/or authorized representatives and the study partners.

Measures. CSF p-tau concentrations, CSF Aβ42 concentrations, and Aβ deposition were included at each of the three waves (baseline, 24 months, 48 months) in the model. Two biomarkers of Aβ pathology were included because AD-related abnormalities in these biomarkers are thought to initiate at temporally distinct points in AD pathogenesis (Jack et al., 2013), and reflect changes in different forms of Aβ (soluble versus fibrillar). Longitudinal CSF p-tau concentrations were chosen over total tau (t-tau) concentrations to represent progression of tauopathy; although both t-tau and p-tau behave similarly in AD progression (Fagan et al., 2009), and both are associated with NFT burden on autopsy (Tapiola et al., 2009), p-tau has been shown to have greater specificity for AD than t-tau (Schraen-Maschke et al., 2008). Five potential confounders were introduced as covariates: baseline age, baseline MMSE score, baseline whole-brain atrophy, sex, and APOEε4 allele presence/absence.

Fully automated Roche Elecsys immunoassays were used to quantify CSF concentrations of all AD biomarkers. Aβ deposition values were obtained from ^{18}F-AV-45 cortical summary measures (SUVR) normalized by a composite reference region (made up of whole cerebellum, brainstem/pons, and eroded subcortical white matter), as white matter-containing reference regions have been shown to produce greater accuracy in longitudinal ^{18}F-AV-45 measures (Landau et al., 2015). As the PET signal was normalized to a composite reference region, the recommended cutoff value for amyloid positivity was 0.79; all AD/MCI subjects with normalized SUVR values above the cutoff at their baseline visit were

Figure 1. Flow diagram of determination of included subjects in HC and AD/MCI study groups. All AD/MCI were PET-confirmed Aβ+ (above the amyloid positivity cutoff); HC were separated into Aβ+ and Aβ− subgroups for further analyses. Groups and subgroups investigated in green.

included in the AD/MCI Aβ+ group, whereas all HC subjects were included regardless of amyloid status. Analyses were performed separately in a subgroup of HC subjects with baseline SUVR values below the cutoff (HC Aβ−), and in a subgroup of HC subjects above the SUVR cutoff (HC Aβ+). For magnetic resonance imaging data used to calculate whole-brain atrophy, 3T scans were processed with FreeSurfer 5.1. All data used for analyses were downloaded from the ADNI database in January 2019. Whole-brain atrophy was estimated by dividing the total brain parenchymal volume by intracranial volume.

Experimental design and statistical analysis. The CLPM is a statistical technique used to understand the most likely predictive relationships between variables over time (Kenny and Harackiewicz, 1979; Hamaker et al., 2015). The CLPM tests predictions of each measure on the progression of the others, considering (1) each previous measure, (2) each concurrent measure, and (3) any relevant covariates (Karran et al., 2011). Unlike univariate mediation/predictive models, the CLPM does not assume a particular order in which variables influence each other, and unlike data-driven or descriptive approaches, the CLPM, via fit indices, tests a hypothesis about how well the data fit a specific model structure that is defined a priori (Kenny and Harackiewicz, 1979; Hamaker et al., 2015). Analyses were conducted in Mplus v8, using three waves of longitudinal data (baseline, 24 months, 48 months), as both CSF and PET data were available at those time points and they are sufficiently distanced in time to detect meaningful changes in each biomarker. A robust maximum likelihood estimator was used, allowing for inclusion of participants despite missing data without imputation under the assumption of a missing at random mechanism. Standardized coefficients (β) and their significance values were estimated for each association tested.

The CLPM approach created nine grand mean centered variables (see Fig. 2 A, B, larger circles) from each of three observed variables across three waves (see Fig. 2 A, B, rectangles) as described previously (Hamaker et al., 2015). Briefly, these variables were predicted by their own antecedent measures in an autoregressive manner, and also by each of the other measures at the antecedent time point (i.e., "cross-lagged"). These effects were estimated freely. The residuals at each wave (latent variables represented by small circles) were allowed to be correlated with each other to

account for time-specific correlations between the biomarkers. Goodness of fit was assessed for all models using: root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker–Lewis index (TLI), and standardized root mean square residual (SRMR). Good fit was indicated for values of RMSEA < 0.06, CFI > 0.95, TLI > 0.90, and SRMR < 0.08.

Because of similarities in CSF p-tau and t-tau measures as AD biomarkers, *post hoc* analyses substituting longitudinal CSF t-tau for p-tau were conducted. To explore relationships between the biomarkers and changes in cognitive status over time, MMSE scores from each of the three waves were considered as a fourth cross-lagged variable (instead of as a covariate) in a second set of *post hoc* models.

Results

Sample

There were 921 subjects in ADNI GO and ADNI 2. Of these subjects, 294 were defined clinically as healthy controls, and 405 were amyloid-positive and defined clinically as having either dementia or MCI. From these groups, five subjects were excluded due to missing data at every time point for each longitudinal variable, and 31 subjects were excluded because of missing data on at least one covariate since the analytical framework required no missing data in any predictor. In two instances, the p-tau measurement at a single time point was below the detectable level of the immunoassay, so data were imputed at the sensitivity of the assay. Therefore, 276 HC and 387 AD/MCI subjects were included in analyses (Fig. 1). Characteristics of participants in both groups can be found in Table 1.

Testing the models

The data fit the models well for both HC (RMSEA = 0.038, CFI = 0.992, TLI = 0.984, SRMR = 0.020) and AD/MCI (RMSEA = 0.046, CFI = 0.983, TLI = 0.965, SRMR = 0.051) groups. The data fit the model well for the HC Aβ- subgroup (RMSEA =

Table 1. Characteristics of HC and AD/MCI subjects

Characteristic	HC ($n = 276$)	AD/MCI ($n = 387$) ($n_{AD} = 119$; $n_{MCI} = 268$)
Age, mean (SD)	73 (6)	73 (7)
Baseline MMSE, mean (SD)	29 (1)	26 (3)
No. (%) APOEε4 carriers	82 (30)	266 (69)
No. (%) male	128 (46)	215 (56)
No. with CSF Aβ42 data (baseline, 24 months, 48 months)	242, 126, 37	357, 137, 40
No. with CSF p-tau data; baseline, 24 months, 48 months	242, 126, 37	357, 137, 40
No. with 18F-AV-45 PET data; baseline, 24 months, 48 months)	271, 207, 129	387, 195, 86
No. amyloid positive/no. amyloid negative at baseline*	100/171	387

AD/MCI subjects were PET-confirmed to be above the amyloid positivity cutoff.

*271 of 276 HC subjects had baseline amyloid PET scans, 100 of whom were amyloid-positive.

0.049, CFI = 0.980, TLI = 0.958, SRMR = 0.061), but covariance coverage was insufficient to test a model for the HC Aβ+ subgroup due to small sample size. For all significant predictions, β and p values are shown in Figures 2, A and B, and 3.

Covariate effects, biomarker stability, cross-sectional correlations, and model residuals

In both HC and AD/MCI groups (Fig. 2A,B), women had a higher baseline Aβ burden, and in the AD/MCI group, women also had higher baseline CSF p-tau concentrations and higher baseline CSF Aβ42 concentrations. Older subjects in both HC and AD/MCI groups had lower CSF Aβ42 concentrations, and older subjects in the HC group also had higher baseline CSF p-tau concentrations and greater Aβ burden. APOEε4 carriers in both HC and AD/MCI groups had higher baseline Aβ burden and lower baseline CSF Aβ42 concentrations, and the in HC group APOEε4 carriers also had higher baseline CSF p-tau concentrations. In the AD/MCI group, baseline MMSE scores and whole-brain atrophy were associated with baseline biomarkers; lower MMSE scores were associated with higher baseline Aβ burden, higher CSF p-tau concentrations, and lower CSF Aβ42 concentrations, and those with greater baseline atrophy had higher baseline Aβ burden and lower baseline CSF Aβ42 concentrations.

CSF Aβ42 concentrations, CSF p-tau concentrations, and Aβ burden each displayed strong longitudinal stability (i.e., each measure strongly predicted its own measure at subsequent time points; Fig. 2A,B).

Cross-sectional correlations between cross-lagged variables are identified in the covariance and correlation matrices for HC (Fig. 2-1, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-1, and Fig. 2-2, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-2), for AD/MCI (Fig. 2-3, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-3, and Fig. 2-4, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-4), and for the HC Aβ- subgroup (Fig. 3-1, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f3-1, and Fig. 3-2, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f3-2); they are summarized in Table 2. In both models, CSF Aβ42 and CSF p-tau residuals were positively correlated, CSF and PET Aβ residuals were negatively correlated, and CSF p-tau concentrations and PET Aβ residuals were positively correlated at various times (Fig. 2A,B).

Cascade characteristics in asymptomatic elderly

In HC (Fig. 2A), lower CSF Aβ42 concentrations consistently predicted the progression of Aβ deposition and reciprocally Aβ

deposition at baseline predicted a subsequent drop in CSF Aβ42 concentrations between baseline and Month 24. Lower CSF Aβ42 concentrations at baseline also predicted an increase in CSF p-tau concentrations 24 months later. Higher CSF p-tau concentrations at baseline predicted higher Aβ burden at Month 24. CSF p-tau concentrations did not predict CSF Aβ42 concentration changes.

In the subgroup of HCs who were PET Aβ−, the same predictive relationships were observed, except that Aβ deposition did not predict CSF Aβ42 concentration changes, but instead, it predicted changes in CSF p-tau concentrations (Fig. 3).

Cascade characteristics in AD/MCI subjects

In AD/MCI (Fig. 2B), lower CSF Aβ42 concentrations consistently predicted increases in Aβ deposition across time points, as observed also in HC subjects and the reciprocal predictive effect was also observed; higher Aβ burden at Month 24 predicted a decrease in CSF Aβ42 concentrations 24 months later. Neither Aβ biomarker predicted changes in CSF p-tau concentrations, and CSF p-tau concentration changes did not significantly predict changes in either Aβ biomarker. Results in healthy elderly and AD/MCI groups are summarized in Table 2.

Post hoc analyses

Total tau versus p-tau

Post hoc analyses substituting t-tau for p-tau produced identical significant longitudinal predictions and residual correlations in the AD/MCI model (data not shown). Results were identical in the HC model, except the residual of PET and CSF Aβ biomarkers were no longer correlated at month 24, and instead the residuals of CSF Aβ42 and p-tau were correlated at month 48 (data not shown).

Progression of cognitive status

Post hoc models were tested with MMSE scores included as longitudinal variables instead of as a covariate, to discern which biomarkers predicted changes in cognitive status in HC and AD/MCI groups. The models returned good fit indices for HC (RMSEA = 0.048, CFI = 0.986, TLI = 0.966, SRMR = 0.044) and for AD/MCI (RMSEA = 0.056, CFI = 0.975, TLI = 0.940, SRMR = 0.053) groups. In both models, all covariate relationships, longitudinal predictions, cross-sectional correlations and residual correlations between biomarkers were unchanged from the previous set of models and additionally, in the AD/MCI group, APOEε4 predicted higher baseline CSF p-tau, and Aβ burden and CSF p-tau concentration at month 48 were correlated (Fig. 2A,B). In the HC group, lower baseline CSF Aβ42 concentrations predicted a subsequent decline in MMSE scores between baseline and 24 months (Fig. 4A). In the AD/MCI model, Aβ burden at both baseline and month 24, and higher CSF p-tau concentrations at month 24 (trending also at baseline; $p = 0.07$), predicted subsequent MMSE scores (Fig. 4B). The complete covariance and correlation matrices are provided in Fig. 4-1, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-1, Fig. 4-2, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-2, Fig. 4-3, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-3, and Fig. 4-4, available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-4, and the results are summarized in Table 2.

Discussion

In healthy elderly and in patients with AD or MCI, CSF and PET Aβ biomarkers demonstrated reciprocal predictive relationships,
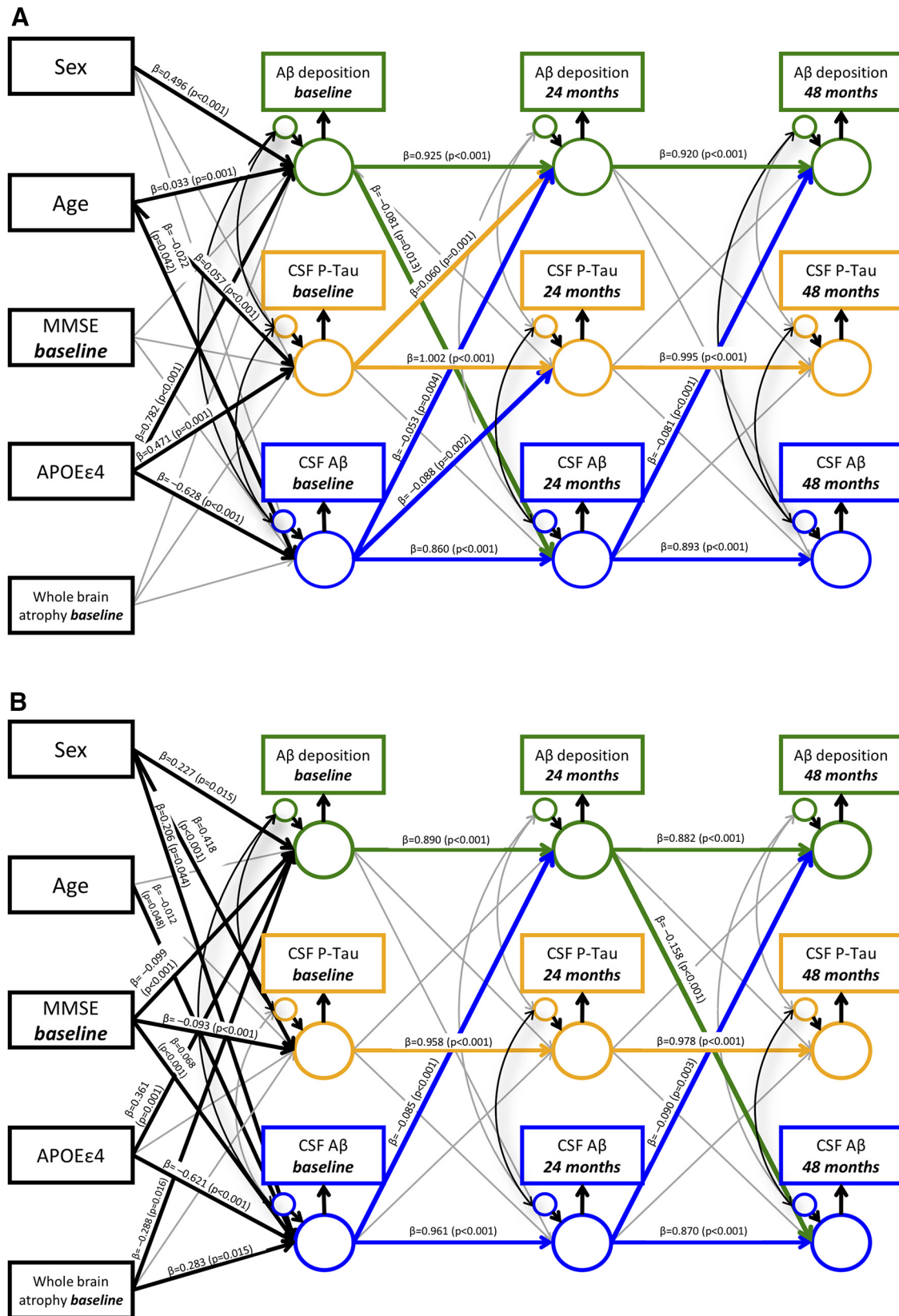
Figure 2. Cross-lagged panel model results in (**A**) HC and (**B**) AD/MCI subjects. PET-derived Aβ burden, CSF p-tau concentrations, and CSF Aβ42 concentrations are modeled across three waves (baseline, 24 months, and 48 months) with covariates sex, baseline age, baseline MMSE score, APOEε4, and baseline whole-brain atrophy. Rectangles, Observed variables; large circles, grand mean centered variables; small circles, residual variances; thin gray arrows, nonsignificant longitudinal predictions or correlations between residuals; black arrows, significant covariate associations or correlations between residuals; green arrows, significant longitudinal predictions from Aβ deposition to a variable at a subsequent time point; orange arrows, significant longitudinal predictions from CSF p-tau concentrations to a variable at a subsequent time point; blue arrows, significant longitudinal predictions from CSF Aβ concentrations to a variable at a subsequent time point. Standardized coefficients (β) and *p* values are displayed for all significant predictions. The complete covariance and correlation matrices are provided for HC in (*Figure legend continues.*)
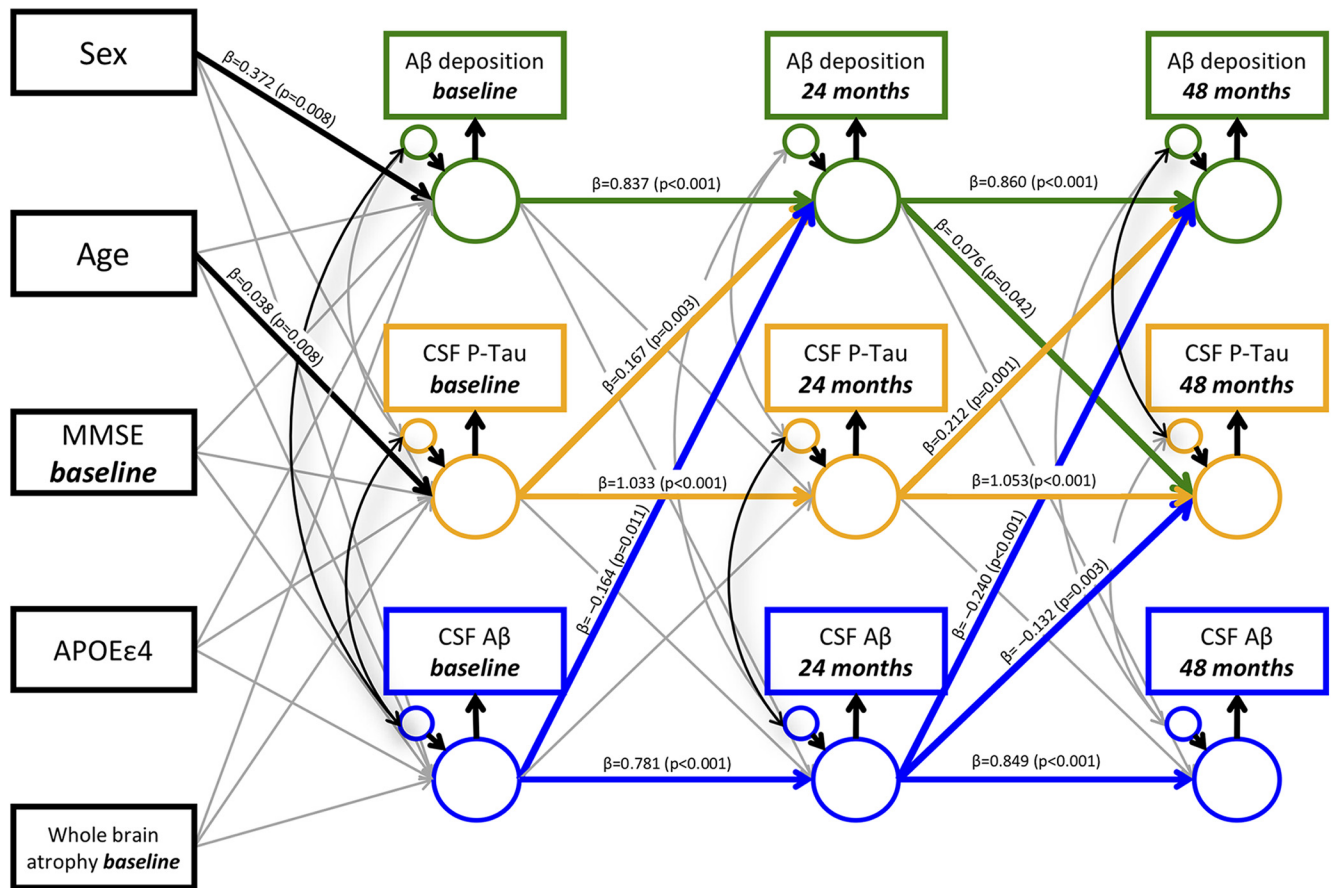
Figure 3. Cross-lagged panel model results in a subgroup of HC subjects who are Aβ−. PET-derived Aβ burden, CSF p-tau concentrations, and CSF Aβ42 concentrations are modeled across three waves (baseline, 24 months, and 48 months) with covariates sex, baseline age, baseline MMSE score, APOEε4, and baseline whole-brain atrophy. The complete covariance and correlation matrices are provided in Figure 3-1 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f3-1) and Figure 3-2 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f3-2). Figure legend as described in Figure 2.

consistent with an amyloid cascade model. Although CSF and PET Aβ biomarkers track the same protein, they relay some unique information about the processes underlying AD pathogenesis (Mattsson et al., 2015). Previous observations suggest that CSF and PET Aβ biomarkers detect different forms of the protein (i.e., soluble Aβ42 vs extracellular fibrillar Aβ), and that CSF Aβ42 changes stage earlier in AD progression (Fagan et al., 2009; Jack et al., 2013), consistent with the finding that CSF Aβ42 concentrations consistently predicted subsequent Aβ deposition in the present models. Reciprocally, the PET Aβ signal also predicted CSF Aβ42 changes, although this direction of prediction was observed only in the HC group that included PET Aβ+ people and in AD/MCI, suggesting that appreciable amyloid burden might be required before the PET Aβ signal predicts subsequent CSF Aβ42 changes. Some have attributed this to differences in biomarker sensitivity (Palmqvist et al., 2016; Schindler et al., 2018); however, recent findings argue that even subthreshold amyloid PET measures are meaningful in asymptomatic people
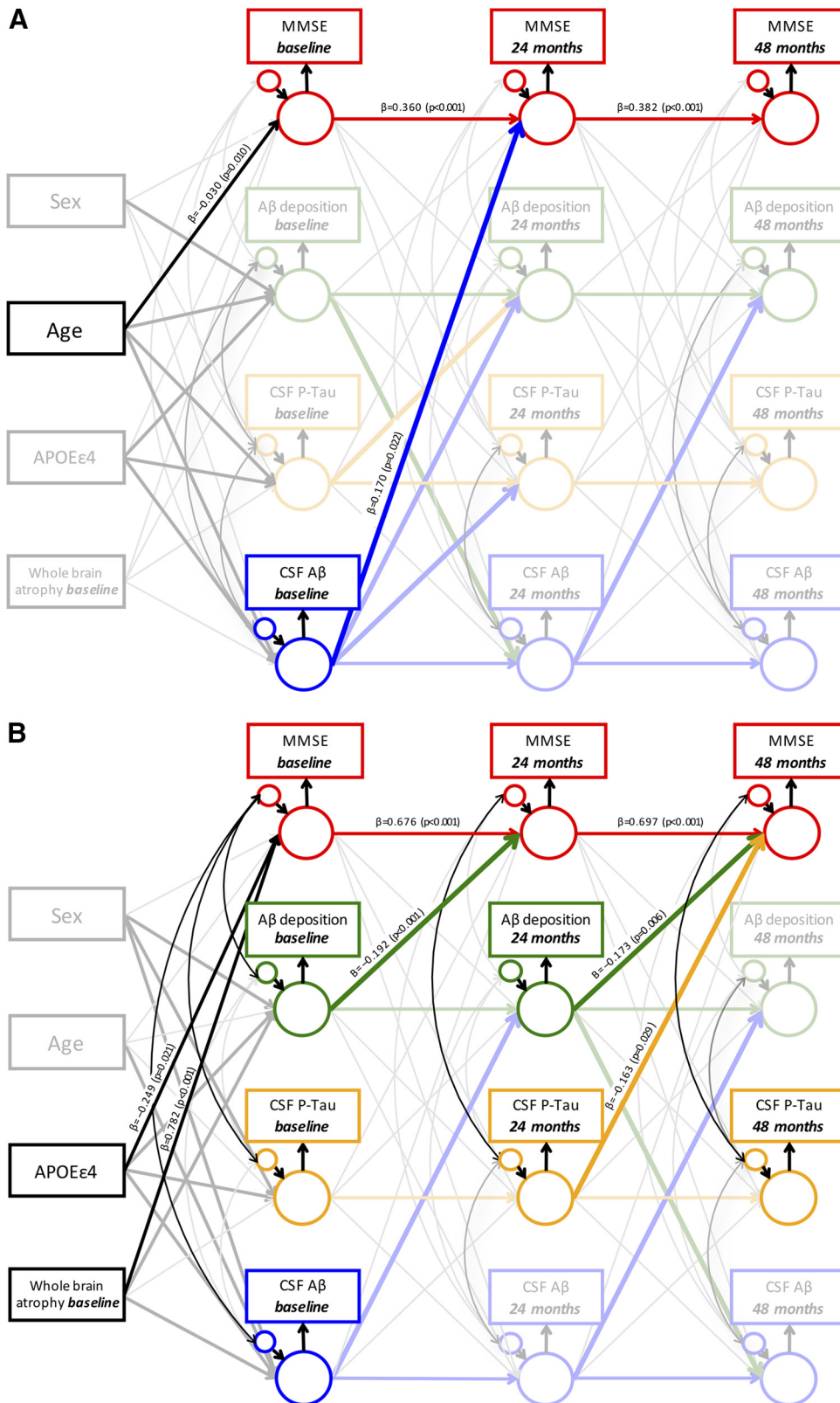
as they can predict tau accumulation and cognitive decline (Leal et al., 2018; Hanseeuw et al., 2019).

The specific mechanisms underlying the drop in CSF Aβ42 remain unclear. It has been suggested that the drop in CSF Aβ might be caused by its deposition in fibrillar/insoluble form (Motter et al., 1995; Fagan et al., 2006). In that case, the empirical model might be expected to show the PET signal to predict CSF changes more consistently. Impaired efflux or trapping of Aβ in the interstitial fluid (e.g., in oligomeric form) could also prevent movement into the CSF. If the radiotracer failed to detect oligomeric species in interstitial fluid, then a drop in CSF Aβ42 concentrations might be expected to predict changes in the PET Aβ signal. The initial change in CSF Aβ42 concentrations has also been suggested to involve defects in Aβ processing and/or intraneuronal transport related to accumulation in autophagic vesicles (possibly because of cell stress and dysfunction of the endosomal-lysosomal system), which has been shown to occur early in AD pathogenesis and to precede extracellular deposition around dystrophic neurites (Nixon, 2007).

In healthy elderly some evidence of a reciprocally predictive relationship between Aβ and tau biomarker progression was seen; lower CSF Aβ42 concentrations variably predicted subsequent increases in CSF p-tau, CSF p-tau variably predicted Aβ deposition, and Aβ deposition variably predicted subsequent increases in CSF p-tau. The results are consistent with animal studies suggesting that tau and Aβ can have co-propagating activities.

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(*Figure legend continued.*) Figure 2-1 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-1) and Figure 2-2 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-2), and for AD/MCI in Figure 2-3 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-3) and Figure 2-4 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f2-4).

Figure 4. *Post hoc* cross-lagged panel model results with longitudinal MMSE scores in (*A*) HC and (*B*) AD/MCI subjects. PET-derived Aβ burden, CSF p-tau concentration, CSF Aβ42 concentrations, and MMSE scores are modeled across three waves (baseline, 24 months, and 48 months) with covariates sex, baseline age, APOEε4, and baseline whole-brain atrophy. Legend as in Figure 2. Standardized coefficients (β) and *p* values are displayed for all significant longitudinal predictions between MMSE scores and other cross-lagged variables, and for all significant associations between baseline covariates and MMSE scores. The complete covariance and correlation matrices are provided for HC in Figure 4-1 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-1), and in Figure 4-2 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-2), and for AD/MCI in Figure 4-3 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-3) and Figure 4-4 (available at https://doi.org/10.1523/JNEUROSCI.1056-19.2019.f4-4).

Table 2. Summary of findings in healthy elderly and AD/MCI groups

	Longitudinal predictive results	Cross-sectional correlations
Healthy elderly	• Lower CSF Aβ42 predicted increased Aβ deposition • Greater Aβ burden variably predicted lower CSF Aβ42 (not in the Aβ− subgroup) • Lower CSF Aβ42 predicted increased CSF p-tau • Higher CSF p-tau predicted increased Aβ deposition • Lower CSF Aβ42 variably predicted lower MMSE scores	• Negative correlation between CSF Aβ42 and Aβ burden • Positive correlation between CSF p-tau and Aβ burden • Positive correlation between CSF Aβ42 and CSF p-tau (the Aβ− subgroup only) • Negative correlation between Aβ burden and MMSE scores at 48 months
AD/MCI	• Lower CSF Aβ42 predicted increased Aβ deposition • Greater Aβ burden predicted lower CSF Aβ42 • Greater Aβ burden predicted lower MMSE scores • Higher CSF p-tau concentrations variably predicted lower MMSE scores	• Negative correlation between CSF Aβ42 and Aβ burden • Positive correlation between CSF p-tau and Aβ burden • Positive correlation between CSF Aβ42 and MMSE scores • Negative correlation between CSF p-tau and MMSE scores • Negative correlation between Aβ burden and MMSE scores

In animals, Aβ increases tau hyperphosphorylation and NFT formation (Stancu et al., 2014). Reciprocally, overexpression of human tau in APP transgenic mice can increase Aβ deposition (Bright et al., 2015; Jackson et al., 2016), tau immunization can reduce Aβ plaque burden (Dai et al., 2017), and exogenous extracellular tau can increase Aβ production *in vitro* (Bright et al., 2015). Those studies suggest that interactions between Aβ and tau might be cyclic in nature. In the present models, CSF p-tau specifically predicted Aβ deposition, and reciprocally, there was some evidence that Aβ deposition could predict CSF p-tau progression. In cross-sectional correlations, CSF p-tau concentrations were correlated with Aβ burden but not with CSF Aβ42 concentrations, as previously reported (Mattsson et al., 2015); however, CSF Aβ42 concentrations were positively correlated with CSF p-tau uniquely in the subgroup of Aβ− HC, suggesting that in the absence of Alzheimer's disease, these markers may have different relationships.

Because of uncertainties in the neurobiological underpinnings of the biomarkers and a lack of definitive causal inferences, the implications of the present model for preventative interventions are unclear. In HC, lower CSF Aβ42 variably predicted changes in cognitive status, so it might be speculated that identifying and targeting the mechanism(s) underlying this biomarker might prevent early changes in cognitive status due to AD in healthy elderly people. The prediction of Aβ deposition by CSF p-tau seen in HC might also suggest that strategies targeting tau, either directly or indirectly via other processes that lead to tau accrual (Kim et al., 2018; Rabin et al., 2019; e.g., cerebral small vessel disease, vascular risk factors, diabetes, head trauma, etc.), might slow amyloid deposition in asymptomatic people. In a recent study, healthy elderly people with both amyloid and tau PET accrual showed greater memory decline (Sperling et al., 2019); however, CSF Aβ42 was not examined, which based on the present results might be hypothesized to predict both Aβ and tau PET signals. Further prospective studies of asymptomatic/presymptomatic people will be needed to determine how the interplay between CSF and PET biomarkers predicts the development of clinical AD.

In AD/MCI, there was no evidence to support reciprocal predictions between Aβ and tau biomarkers. The reason for this is unclear. One possibility is that the biomarkers reached plateaus before these symptomatic stages. It has been suggested that CSF Aβ42 concentrations tend to bottom-out before the onset of symptoms (Buchhave et al., 2012), and that Aβ deposition might also plateau earlier in disease progression than once thought (Leal et al., 2018). The empirical model suggests that this may not entirely account for the null findings because the amyloid biomarkers continued to exhibit dynamic interplay in AD/MCI, each predicting progression of the other. Therefore, it is possible

that amyloid and tau biomarkers progressed independently of one another in AD/MCI. It has been suggested that extracellular p-tau can spread between neurons independently of amyloid, possibly driving neuronal hyperexcitability and disease progression in symptomatic stages (Bright et al., 2015; Goedert and Spillantini, 2017). Consistent with those hypotheses, here CSF p-tau concentrations variably predicted cognitive decline in AD/MCI.

The lack of predictive relationships between tau and amyloid in AD/MCI might have therapeutic implications. Recent studies using PET-derived tau measures suggest that tau deposition mediates the relationship between Aβ burden and cognitive status (Kim et al., 2018; Hanseeuw et al., 2019), consistent with autopsy studies that showed closer correlations between cognitive status and tangles than plaques (Arriagada et al., 1992; Giannakopoulos et al., 2003). If tau progresses independently of amyloid deposition once AD/MCI is established, then therapies targeting extracellular amyloid may be insufficient to halt cognitive progression. In the present study, both Aβ burden and CSF p-tau predicted cognitive decline independently, and if true, targeting their distinct underlying molecular processes simultaneously may be necessary to halt disease progression. This would be consistent with the failure of amyloid-targeted monotherapies in AD clinical trials to date (Mehta et al., 2017). Moreover, examining CSF biomarkers together with the PET Aβ signal over time revealed that CSF Aβ42 concentrations consistently predicted Aβ deposition in AD/MCI, suggesting that mechanisms underlying the drop CSF Aβ42 were sustained throughout AD progression. It might be speculated that targeting those mechanisms, which may include but may not be limited to Aβ deposition, might be of therapeutic benefit in symptomatic stages.

This study has several limitations. As an empirical approach, the CLPM offers the advantage of making the cascade hypothesis explicitly testable; however, causality cannot be inferred explicitly, and the model is data-demanding leading to sample-size limitations; not all identified cross-lagged predictions reached significance consistently between the two lag periods, and there were insufficient data to construct the models in the subgroup of PET Aβ+ HC, an important limitation to be addressed in future studies. Because a similar independent dataset was unavailable, replication was not possible. Additional waves would be required to model explicitly interindividual differences as trait-like features, although subgroup analyses accounted meaningfully for population heterogeneity (Hamaker et al., 2015). Too few longitudinal AV-1451 PET measures were available to model in ADNI cohorts, precluding exploration of tau deposition dynamics and regional specificity in brain; however, CSF p-tau appears to correlate with tau deposition (Brier et al., 2016), making CSF p-tau a reasonable proxy of pathologic tau for the present objectives. We propose further applications of the model to establish how the

present findings link with biomarkers of neurodegeneration, and to identify pathophysiological processes that predict decreases in CSF Aβ42 as potential targets for prevention and treatment.

In conclusion, to our knowledge, this is the first empirical model to test reciprocal predictive relationships between amyloid and tau biomarkers as they progressed over time in living people. The empirical biomarker model is consistent with a hypothetical amyloid cascade involving reciprocal predictions between amyloid and tau progression in healthy elderly people, wherein tau specifically predicted amyloid deposition but not CSF Aβ42 changes. In healthy elderly people, lower CSF Aβ42 concentrations predicted subsequent amyloid deposition and CSF p-tau changes, consistent with the proposed staging of these biomarkers (Jack et al., 2013), and a decline in cognitive status. The empirical model further suggested that amyloid and tau biomarkers progressed independently in people with established AD/MCI. In AD/MCI, CSF Aβ42 concentrations predicted Aβ deposition, which predicted cognitive decline, and CSF p-tau concentrations predicted cognitive decline independently. The results provide clarification regarding the dynamics of AD biomarker progression and its relationships with cognitive decline, consistent with priorities identified by The National Institute on Aging–Alzheimer's Association updated research framework (Jack et al., 2018).

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