



The mediational effects of FDG hypometabolism on the association between cerebrospinal fluid biomarkers and neurocognitive function



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ABSTRACT

Positive cerebrospinal fluid (CSF) biomarkers of tau and amyloid beta42 suggest possible active underlying Alzheimer's disease (AD) including neurometabolic dysfunction and neurodegeneration leading to eventual cognitive decline. But the temporal relationship between CSF, imaging markers of neural function, and cognition has not been described. Using a statistical mediation model, we examined relationships between cerebrospinal fluid (CSF) analytes (hyperphosphorylated tau (p-Tau_{181p}), β -amyloid peptides 1–42 ($A\beta_{1-42}$), total tau (t-Tau), and their ratios); change in cognitive function; and change in [18F]fluorodeoxyglucose (FDG) uptake using positron emission tomography (PET). We hypothesized that a) abnormal CSF protein values at baseline, result in cognitive declines by decreasing neuronal glucose metabolism across time, and b) the role of altered glucose metabolism in the assumed causal chain varies by brain region and the nature of CSF protein alteration. Data from 412 individuals participating in Alzheimer's Disease Neuroimaging (ADNI) cohort studies were included in analyses. At baseline, individuals were cognitively normal ($N = 82$), or impaired: 241 with mild cognitive impairment, and 89 with Alzheimer's disease. A parallel-process latent growth curve model was used to test mediational effects of changes in regional FDG-PET uptake over time in relation to baseline CSF biomarkers and changes in cognition, measured with the 13-item Alzheimer Disease's Assessment Scale–cognitive subscale (ADAS–Cog).

Findings suggested a causal sequence of events; specifically, FDG hypometabolism acted as a mediator between antecedent CSF biomarker alterations and subsequent cognitive impairment. Higher baseline concentrations of t-Tau, and p-Tau_{181p} were more predictive of decline in cerebral glucose metabolism than lower baseline concentrations of $A\beta_{1-42}$. FDG-PET changes appeared to mediate t-Tau or t-Tau/ $A\beta_{1-42}$ -associated cognitive change across all brain regions examined. Significant direct effects of alterations in $A\beta_{1-42}$ levels on hypometabolism were observed in a single brain region: middle/inferior temporal gyrus.

Results support a temporal framework model in which reduced CSF amyloid-related biomarkers occur earlier in the pathogenic pathway, ultimately leading to detrimental cognitive effects. Also consistent with this temporal framework model, baseline markers of neurofibrillary degeneration predicted changes in brain glucose metabolism in turn causing longitudinal cognitive changes, suggesting that tau-related burden precedes neurometabolic dysfunction. While intriguing, the hypothesized mediational relationships require further validation.

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Abbreviations: AD, Alzheimer's disease; ADAS–Cog, Alzheimer Disease's Assessment Scale–cognitive subscale; ADNI, Alzheimer's Disease Neuroimaging; ApoE, Apolipoprotein E; $A\beta$, β -amyloid; $A\beta_{1-42}$, β -amyloid peptides 1 to 42; Bc, Bias-corrected; CFI, Comparative fit index; CI, Confidence interval; CN, Cognitively normal; CSF, Cerebrospinal fluid; FDG, [18F] fluorodeoxyglucose; LGC, Latent growth curve; MCI, Mild cognitive impairment; MMSE, Mini Mental State Examination; PET, Positron emission tomography; PPLGC, Parallel-process latent growth curve; p-Tau_{181p}, Hyperphosphorylated tau; RMSEA, Root mean square error of approximation; ROI, Region of interest; SMC, Significant memory concern; TLI, Tucker–Lewis Index; t-Tau, Total tau.

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Introduction

A number of studies have investigated the efficacy of specific potential biomarkers of Alzheimer's disease (AD) pathology in the cerebrospinal fluid (CSF) and regional cerebral glucose metabolic rate, measured by positron emission tomography (PET) imaging with [18 F]fluorodeoxyglucose uptake (FDG-PET), to predict outcomes, discriminate between disease stages, and assess prognosis (Choo et al., 2013; Herholz, 2003; Landau et al., 2010). The most frequently studied CSF analytes in AD for prognostic accuracy include markers for neurofibrillary degeneration (i.e., total tau [t-Tau] and hyperphosphorylated tau at threonine 181 [p-Tau $_{181p}$] proteins) and β -amyloid ($A\beta$) plaque pathology ($A\beta$ peptides 1 to 42 [$A\beta_{1-42}$]). Compared to individual markers, ratios combining CSF measures have been shown to be stronger predictors of cognitive decline in different populations. For example, elevated ratios of p-Tau $_{181p}/A\beta_{1-42}$ and/or t-Tau/ $A\beta_{1-42}$ predict cognitive impairment within a few years of onset in non-demented older adults (Craig-Schapiro et al., 2010; Fagan et al., 2007; Li et al., 2007; Roe et al., 2013), conversion from mild cognitive impairment (MCI) to AD (Hansson et al., 2006), and faster progression of functional and cognitive deficits in individuals with incipient dementia of the Alzheimer type (Snider et al., 2009). Similarly, in group studies FDG-PET has been consistently shown to be sensitive in detecting neurometabolic dysfunction even at the preclinical asymptomatic stage of AD, which strongly suggests its suitability as a marker to study the effect of disease pathology on brain metabolic function (de Leon et al., 2001; Drzezga et al., 2011; Jagust et al., 2006; Mosconi et al., 2013, 2010, 2009; Reiman et al., 2001). Furthermore, FDG-PET studies with cohorts of cognitively intact middle-age and young Apolipoprotein E (*ApoE*) $\epsilon 4$ carriers have also revealed MCI- and AD-like patterns of metabolic lesions in the same brain regions typically affected in clinical AD (Mosconi et al., 2008; Reiman et al., 2001, 1996). FDG PET and tau-related CSF analytes are both indicators of neural injury, but the temporal effects of these markers on each other and on cognitive decline have not been studied in a multimodal framework allowing for *formal tests* of mediational hypotheses.

Over the past decade, many studies have focused on defining the associations between symptom severity, alterations in CSF constituents or $A\beta$ deposition, and concomitant or co-occurring decreased FDG uptake in several brain regions including parietal, temporal, and posterior cingulate gyrus. These associations have been largely studied in cognitively normal individuals (Petrie et al., 2009), those with MCI and AD compared with normal controls (Arlt et al., 2009; Fellgiebel et al., 2007, 2004; Hunt et al., 2006), or asymptomatic middle-age adults at increased risk for AD (Mosconi et al., 2013, 2008). Despite the consistent longitudinal research evidence on key AD-related biological changes, only a few studies have investigated longitudinal dynamic changes in multiple biomarkers associated with AD pathology (see, for example, de Leon et al., 2006; Lo et al., 2011; Sluimer et al., 2010; Zhang and Shen, 2011, 2012). One of these studies (Lo et al., 2011) used separate models, instead of a single multiple-group growth model (Muthén and Curran, 1997), to examine the relative associations between rates of change in $A\beta_{1-42}$ levels, FDG uptake, hippocampal volume, and rates of change in cognitive function in individuals enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. The authors concluded that the pattern of changes across diagnostic groups (cognitively normal, CN; MCI; and AD) obtained in separate analyses provided evidence in support of a *sequential association* of events in which $A\beta$ amyloid deposition preceded hypometabolism or hippocampal atrophy. However, to the best of our knowledge, no studies have applied longitudinal mediation models to explicate possible causal relationships between multiple biomarkers and their effect on cognitive outcomes in a heterogeneous sporadic disease population. The application of these modeling approaches is important in exploring and testing hypotheses on the role of biological markers in the chain of events that ultimately cause axonal dysfunction and neuronal degeneration. Although the mechanisms underlying

these effects are still unknown, model-based hypothesis testing may elucidate causal relationships as possible explanations of these effects.

The present study applied a parallel-process latent growth curve (PPLGC) model (Cheong et al., 2003; MacKinnon et al., 2004) to test whether the relationship between several analytes in CSF, including p-Tau $_{181p}$, $A\beta_{1-42}$, t-Tau, and their ratios, and changes in cognitive function was mediated by changes in glucose metabolism in subjects diagnosed at baseline as CN, MCI, or AD. We hypothesized that a) abnormal CSF protein values at baseline increase the rate of decline in cognitive function by decreasing glucose metabolism across time, and b) the role of the mediator in the assumed causal chain varies across brain regions and the form of CSF protein level affected at baseline.

Materials and methods

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as to lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org. The study obtained written informed consent from all participants and was conducted with prior institutional review board approval at each participating center.

The population for this study included all participants with FDG-PET measures (up to the 24-month visit) and neuropsychological data (up to the 36-month follow-up visit) for at least two time points and available baseline CSF data. FDG measures that “failed” local quality control standards, had missing quality assessments, or obtained a “partial” assessment were excluded from the analysis. The study comprised 85.5% of the total sample in ADNI who underwent lumbar puncture at baseline. As shown in Table 1, the final analytical sample included 412 older adults with available data on variables of interest (1363 person-time observations) diagnosed at study entry as NC ($N = 82$), MCI ($N = 241$), and AD ($N = 89$). The participants were mostly male (57.5%), ranged in age from 48 to 89 years ($M = 72.28$, $SD = 7.32$), reported an average of 16.33 years of education ($SD = 2.62$; range, 8–20 years), and roughly 54% were carriers of at least one *ApoE*- $\epsilon 4$ allele. Table 1 also reports global cognition at baseline measured by the Mini Mental State Examination (MMSE; Folstein et al., 1975). As a way of evaluating the selectivity of the studied sample, we compared its demographic characteristics with those of the full ADNI participant

Table 1
Descriptive statistics of study variables at baseline.

Variable	Total	NC	MCI	AD
	(N = 412)	(N = 82)	(N = 241)	(N = 89)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Demographic characteristics^a				
Gender (male %)	57.5%	51.2%	60.2%	56.2%
ApoE ϵ 4 status (carrier %)	54.6%	34.2%	54.0%	75.3%
Age in years	72.28 (7.32)	72.45 (6.66)	71.49 (7.41)	74.25 (7.35)
Education in years	16.33 (2.62)	16.61 (2.59)	16.45 (2.59)	15.72 (2.64)
Global cognition^b				
MMSE	27.03 (2.71)	29.06 (1.18)	27.74 (1.82)	23.22 (2.00)
FDG ROI^b				
Posterior cingulate	1.30 (0.19)	1.40 (0.16)	1.33 (0.17)	1.15 (0.16)
L temporal	1.17 (0.18)	1.27 (0.13)	1.20 (0.15)	1.00 (0.18)
R temporal	1.18 (0.16)	1.25 (0.12)	1.20 (0.14)	1.06 (0.17)
L angular	1.22 (0.19)	1.32 (0.14)	1.24 (0.16)	1.05 (0.18)
R angular	1.22 (0.18)	1.32 (0.14)	1.25 (0.16)	1.07 (0.19)
Composite ROI	1.22 (0.16)	1.31 (0.12)	1.24 (0.14)	1.06 (0.15)
Neuropsychological outcome^{b,c}				
ADAS–Cog–13	17.67 (10.25)	8.67 (4.53)	15.88 (6.96)	31.22 (8.61)
CSF biomarkers^b				
A β _{1–42}	169.89 (56.39)	211.15 (51.03)	169.46 (54.95)	132.61 (34.95)
t-Tau	98.33 (59.01)	67.68 (34.21)	94.42 (54.86)	138.12 (67.12)
p-Tau _{181p}	41.54 (24.80)	31.39 (21.53)	39.85 (21.34)	55.60 (30.06)
t-Tau/A β _{1–42}	0.69 (0.56)	0.35 (0.25)	0.66 (0.50)	1.11 (0.64)
p-Tau _{181p} /A β _{1–42}	0.29 (0.23)	0.17 (0.18)	0.28 (0.19)	0.45 (0.30)

Key: NC = normal control; MCI = mild cognitive impairment; AD = Alzheimer's disease; ApoE = apolipoprotein E; CSF = cerebrospinal fluid; A β = beta amyloid; p-Tau = phosphorylated tau; t-Tau = total tau.

^a The omnibus F-test was significant for age ($F = 4.725, p = 0.009$). Hochberg-adjusted age mean difference between the MCI and AD groups was significant ($p = 0.007$). ApoE status was associated with diagnosis at baseline ($\chi^2 = 26.790, p < 0.001$).

^b The omnibus F-test was significant as well as all Hochberg-adjusted post-hoc pairwise comparisons.

^c Lower scores reflect higher functioning or better performance.

population at baseline. The analytical sample did not differ from the general participant population in terms of age ($M_{ADNI} = 72.79, SD_{ADNI} = 7.67; M_{sample} = 72.28; SD_{sample} = 7.32; p = 0.905$) and gender ($M_{ADNI} = 0.54, SD_{ADNI} = 0.49; M_{sample} = 0.58; SD_{sample} = 0.49; p = 0.063$). However, the studied sample was, on average, more educated ($M_{ADNI} = 15.80, SD_{ADNI} = 2.92; M_{sample} = 16.33; SD_{sample} = 2.62; p < 0.001$) and had a higher prevalence of ApoE- ϵ 4 carriers ($M_{ADNI} = 0.47, SD_{ADNI} = 0.49; M_{sample} = 0.55; SD_{sample} = 0.49; p = 0.003$). Therefore, results from the current data set are most applicable to a group of individuals who, on average, have a college-level degree and close to 50% have, at least, one copy of the ϵ 4 allele.

FDG-PET measures

Longitudinal summary measurements of hypometabolism were obtained from images preprocessed at the University of California, Berkeley (UC Berkeley), following a standard four-step procedure described in <http://adni.loni.usc.edu/methods/pet-analysis/pre-processing/>. Further details on the quality control analyses and procedures to enhance uniformity and reduce variability in PET images across centers are provided in Joshi et al. (2009). The full standardized protocol for image analysis is described in <http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx>. FDG-PET data analyzed at UC Berkeley used pre-specified regions of interest (ROIs) generated through a meta-analysis of PubMed longitudinal and cross-sectional studies identifying the location of FDG-PET changes in the brain most commonly affected in AD and MCI patients or that were correlated with cognitive performance. Detailed procedures for the FDG-ROI generation and subsequent smoothing and normalization of volumes are explained elsewhere (Jagust et al., 2010, 2009; Landau et al., 2010). The analytical approach resulted in a set of five regions located in bilateral posterior cingulate gyrus, right and left angular gyri, and middle/inferior temporal gyrus (denoted here as right and left temporal). Given the high bivariate correlations between the five FDG-ROIs at baseline and across assessment waves (0.425 to 0.876), a unit-weighted composite was

also generated by averaging across all five ROIs for each participant at each observation time-point. Longitudinal FDG measures collected at baseline, 6-month, 12-month, 18-month (only MCI), and 24-month were modeled as mediators in all subsequent parallel growth process models. The collection of FDG-PET images varied slightly per study protocol: ADNI 1 followed the schedule mentioned above; ADNI 1 CN and late MCI individuals meeting the follow-up eligibility criteria for inclusion in ADNI-GO, continued with yearly FDG imaging events; PET scans for early MCI subjects newly enrolled in ADNI-GO (approximately 200 in the main study) were obtained at baseline; and ADNI-2 obtained PET scans at baseline and every two years thereafter. Baseline mean values for the five FDG-ROIs and the composite ROI included in the present study are presented in Table 1.

Cognitive measures

The Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS–Cog) (Mohs et al., 1983; Rosen et al., 1984) was used as the target outcome measure. The ADAS–Cog is a rating instrument commonly used to measure cognitive dysfunction in clinical trials and for detecting, tracking, and staging AD. It was administered by trained individuals at each study site. Scores are obtained from written and verbal responses to items measuring key areas of cognition in AD including verbal episodic memory, language, comprehension, and ideomotor praxis. The standard ADAS–Cog includes 11 items and the expanded scale (ADAS–Cog-13) includes two additional items measuring visual attention and concentration (digit cancellation) and delayed verbal recall. The expanded ADAS–Cog-13 scale was selected as the longitudinal outcome measure. The 13 items were combined into a unit-weighted composite score ranging from 0 to 85 with lower scores indicating better cognitive performance. This measure was selected because it is a global cognitive scale assessing multiple domains and is more precise in measuring mild degrees of impairment than other global cognitive impairment measures such as the MMSE (Tombaugh and McIntyre, 1992; Wouters et al., 2010). The study included outcome observations from

all participants taken at five data collection time points: baseline, 6-month, 12-month, 18-month, 24-month, and 36-month. Note that compared to the FDG mediation process, assumed to unfold from baseline to month 24, the cognitive outcome change process extended the span of time to include an extra year to attenuate issues involving concurrent causation (Salthouse, 2011; Selig and Preacher, 2009).

The ADNI study administers alternate test forms at each visit in which only the word lists are varied to minimize practice effects. To insure unambiguous interpretation of changes in the ADAS-Cog-13 between time points, we conducted longitudinal measurement invariance tests over a 36-month interval to determine whether the test items assessed the same attribute across time (Horn and McArdle, 1992; Meredith, 1993). Longitudinal invariance was evaluated using a confirmatory factor analysis within the framework of structural equation modeling (SEM; Meredith, 1993; Schaie et al., 1998). We tested and compared a series of nested models that sequentially imposed more restrictive constraints on the model parameters across time. That is, we assessed the degree to which ADAS-Cog-13 factor structure (configural invariance), factor loadings (metric invariance), factor variance/covariance and item means (scalar invariance), and item error variances were similar across time. The results provided evidence in support of the test's longitudinal factorial invariance over the 36-month period. (Results are available upon request from the first author.) Means and standard deviations of the ADAS-Cog-13 at baseline are reported in Table 1. The test reliability estimate of a 12-month test-retest correlation was 0.86.

CSF biomarker measures

The standardized protocol for CSF sample collection and analysis in ADNI is available at <http://www.adni-info.org/Scientists/ADNIStudyProcedures.aspx>. Briefly, baseline CSF samples were collected at each

study center and placed in polypropylene transfer tubes followed by aliquoting, freezing at -80°C , and shipping on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center for banking, processing, and analysis (Shaw, 2008). After implementing the necessary quality control studies and establishing the validity of the analytical platform, the baseline CSF t-Tau, $A\beta_{1-42}$, and p-Tau_{181p} were measured using the multiplex xMAP Luminex platform and Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium) immunoassay kit-based reagents. This system measures the biomarkers simultaneously in the same sample aliquot in ADNI individuals and in an independent age-matched cohort of autopsy-confirmed AD cases with premortem CSF samples (Shaw et al., 2009).

As displayed in Fig. 1, the mediational process was modeled by associating baseline CSF measures (predictors) and latent growth factors for FDG-PET measures (capturing changes in the metabolic rate for glucose) and cognitive function also indexing changes over time. Baseline means and standard deviations for raw CSF variables are presented in Table 1 by clinical group. Prior to statistical modeling, CSF biomarker data were log-transformed to normalize their distribution.

To strengthen the validity of the mediation analysis, all models controlled for the following covariates: initial clinical diagnosis, age at baseline, gender (coded as 1 for Male), education level, and ApoE status coded as $\epsilon 4$ present versus absent. A contrast coding scheme was used for the three-level clinical diagnosis variable assigning “normal control” as the reference level.

Statistical analysis

A SEM approach of building and evaluating latent growth curve models (LGC; Meredith and Tisak, 1990; Muthén and Curran, 1997; Singer and Willet, 2003) was used to tease apart direct versus indirect effects of CSF biomarkers on the rate of decline in cognitive function

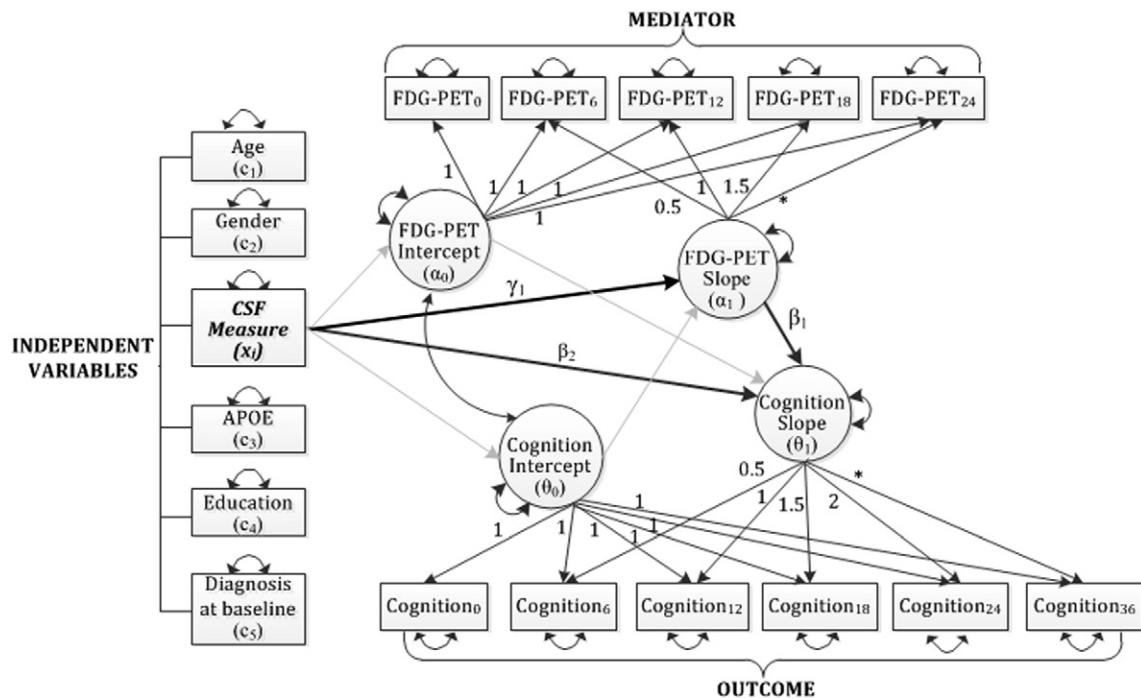


Fig. 1. Schematic representation of the parallel process growth model estimated to test the longitudinal effects of CSF measures on the rate of change in cognition via the rate of change in regional glucose metabolism over time. The model equations are notationally described in Materials and Methods section. Latent variable intercepts (α_0 and θ_0) and slopes (α_1 and θ_1), represented by circles, were regressed on six observed (squares) variables: age, gender, ApoE, education, clinical diagnosis at baseline, and CSF (x_i). Residual error variances are shown by two-headed curved arrows going towards observed and latent variables. Numbers on the arrows going from the latent growth parameters to observed measures at each time point indicate factor loadings. The asterisk (*) indicates that the loading was estimated. The CSF measures were assessed separately in the model and included: $A\beta_{1-42}$, t-Tau, p-Tau_{181p}, t-Tau/ $A\beta_{1-42}$, and p-Tau_{181p}/ $A\beta_{1-42}$. The models also included direct paths from each covariate (c_i) to all the growth parameters, but have been omitted in the figure for simplicity purposes.

and the potential mediating effects of changes in brain glucose metabolism when included in the causal pathway in a parallel change process. In the LGC model applied in this study, performance at a given measurement time-point was determined by two factors (Tucker-Drob and Salthouse, 2011): 1) an initial level factor representing baseline performance, and 2) a change or “growth” curve slope factor, which represented annual change in the outcome over the span of the study. A PPLGC model allows the simultaneous modeling of the growth trajectories of the mediator and outcome and the assessment of mediational processes (Cheong et al., 2003; MacKinnon et al., 2004). In this study, hypotheses concerning indirect or mediational effects were tested by using parameter estimates obtained from the effect of baseline CSF measures (\mathbf{x}_i) on the growth rate factor of the mediator (brain glucose metabolism) and the growth rate factor of the outcome (cognitive function). This tenable explanatory mechanism was modeled and tested using the two-wave PPLGC mediation model with non-equidistant time points shown graphically in Fig. 1. Assuming linear relationships, the growth of the measured variable for the cognitive outcome and the FDG-PET mediator (measurement models) is expressed, respectively as:

$$Y_{it} = \theta_{0i} + \theta_{1i} \text{time}_t + \varepsilon_{1i} \quad \text{and} \quad M_{it} = \alpha_{0i} + \alpha_{1i} \text{time}_t + \varepsilon_{2i} \quad (1)$$

where \mathbf{Y} and \mathbf{M} represent the vector of repeated measures for individual i over the t time points (0, 6, 12, ..., T). The growth parameters include vectors for initial status (θ_0 for cognition and α_0 for the mediator) and for the linear slope (θ_1 and α_1) (Muthén and Curran, 1997). The following regression equations are estimated to obtain the mediation-relevant portions of the model:

$$\theta_{1i} = \beta_0 + \beta_1 \alpha_{1i} + \beta_2 x_i + \beta_3 c_{i1} + \dots + \beta_7 c_{i5} + \zeta_{1i}, \quad (2)$$

$$\alpha_{1i} = \gamma_0 + \gamma_1 x_i + \gamma_2 c_{i1} + \dots + \gamma_6 c_{i5} + \zeta_{2i}. \quad (3)$$

The residuals ζ_1 and ζ_2 are assumed to be normally distributed with zero means, variances σ^2_1 and σ^2_2 are uncorrelated with each other and the covariates ($c_{ij}; j = 1, \dots, 5$) (Muthén and Asparouhov, forthcoming). Inserting Eq. (3) in Eq. (2) yields:

$$\theta_{1i} = \beta_0 + \beta_1 \gamma_0 + \beta_1 \gamma_1 x_i + \beta_1 \gamma_2 c_{i1} + \dots + \beta_1 \gamma_6 c_{i5} + \beta_1 \varepsilon_{2i} + \beta_2 x_i + \beta_3 c_{i1} + \dots + \beta_7 c_{i5} + \varepsilon_{2i}. \quad (4)$$

Eq. (4) states that the “direct” effect of CSF (x_i) (obtained at baseline) on the cognitive slope (θ_1), which captures the linear change in cognition over three years, is β_2 and the “indirect” or “mediation” effect through the FDG-PET slope, which also captures linear change but over a 2-year period, is $\beta_1 \gamma_1$. Both of these effects are conditional on the joint effect of all the predictors in the model.

Some of the advantages of using a LGC modeling framework to study individual differences in growth parameters and assess mediational mechanisms over similar approaches (e.g., hierarchical modeling or mixed effects techniques) include the capability to (1) model more complex multivariate relationships containing, for example, multiple independent measures and time-invariant or variant mediation influencing the underlying random effects of an outcome trajectory, (2) define change over time in terms of unobserved latent factors (Singer and Willet, 2003), (3) estimate model parameters simultaneously, and (4) incorporate in the model the unreliability of observed measures (measurement error) (Rovine and Molenaar, 2001).

The PPLGC modeling scheme for testing mediation proceeded in several steps. First, using a univariate two-factor LGC model, we examined the presence and type (linear, quadratic, etc.) of change in the outcome (cognitive function) and the mediator (regional brain glucose uptake) over data collection time points and whether or not change trajectories varied as a function of the type of CSF biomarker. That is, we estimated

single-outcome latent growth models for a) cognition and b) FDG-PET measures in each of six regions (bilateral posterior cingulate gyrus, right and left angular gyri, right and left temporal gyri, and the average of all regions) each with two latent factors defining, respectively, the level (intercept) and the slope of the “growth” curve. Control variables (clinical diagnosis, age at baseline, gender, education, and *ApoE*) were also included in these models. Subject-specific mean functions were plotted to explore growth shape and marginal growth trends. We used a time-based LGC model in which the rates of change were assumed to be person-specific functions of time since baseline evaluation or the number of data collection time points (for other approaches, see McArdle et al., 2002). That is, we centered time scores at time point 1. The factor loadings of the growth factor were first fixed to represent “linear” change and the fit of the model was examined. The inclusion of higher-order terms in the growth curves and freely estimated time points (represented with an asterisk * in Fig. 1) were also examined. Second, after confirming growth and examining the shape of the trajectories, we combined the models to include two outcomes at once and tested for the longitudinal mediational effects of regional FDG-PET measures estimating the parameters simultaneously.

In all PPLGC models, the significance of mediation (indirect) effects was examined using 95% bias-corrected (Bc) bootstrapped asymmetric confidence intervals (CIs) (Efron and Tibshirani, 1993; MacKinnon et al., 2004; Preacher and Hayes, 2008). Bc bootstrapped asymmetric CIs do not require normality of the sampling distribution of the indirect (mediation) effect estimates and the constituent paths of the indirect effects and coverage properties of estimates are good even in small samples (Kilian, 1998; Mackinnon et al., 2008, 2004). Additionally, Bc bootstrapped CIs take into account possible correlations among all the explanatory variables included in the model, allow dependencies between the standard error of the estimated effect and the effect parameter, and efficiently single out mediational effects, possibly improving the validity of statistical inferences. All mediational tests were performed with 10,000 bootstrap replications. If the 95% Bc CI for a given point estimate failed to include 0, the effect was said to be significant. The normal approximation CIs were provided for all the single direct paths in the model.

The fit of hypothesized models was assessed using multiple fit indexes that were sensitive to model misspecification in growth curve models and did not depend on sample size as much as the χ^2 test (Schermelleh-Engel et al., 2003; Wu et al., 2009). These included: the root mean square error of approximation (RMSEA; Browne and Cudeck, 1993), the comparative fit index (CFI; Bentler and Bonett, 1980), and the Tucker–Lewis Index (TLI; Tucker and Lewis, 1973). Models with CFI and TLI values greater than 0.95 were considered to adequately fit the data and a RMSEA less than 0.08 indicated satisfactory fit (Hu and Bentler, 1995). We also used residual diagnostics procedures to assess possible model misspecification (Wang et al., 2005). Descriptive analyses and exploration of growth trajectories were performed in R, Version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Growth model analyses were conducted in Mplus, Version 7.11 (Muthén and Muthén, 2013) using a full information maximum likelihood estimator.

Results

Table 2 reports the bivariate correlations among the baseline predictors, the mediators across five assessment points and the neuro-cognitive outcomes measured at six time points. It can be seen that FDG-PET mediators for the average measures across regions and cognitive ability outcomes were strongly and negatively correlated both within and across data collection time points. Most CSF measures were correlated with both longitudinal cognitive and FDG metabolic measures. All variables appeared to be correlated with outcomes of interest, prior to or after multiple comparison adjustments, justifying their inclusion in the analyses.

Table 2

Bivariate correlation statistics between predictors and longitudinal mediator and outcome variables.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Target outcome																						
1 ADAS-Cog M0	–																					
2 ADAS-Cog M6	0.90	–																				
3 ADAS-Cog M12	0.86	0.89	–																			
4 ADAS-Cog M18	0.73	0.82	0.75	–																		
5 ADAS-Cog M24	0.84	0.89	0.88	0.87	–																	
6 ADAS-Cog M36	0.75	0.85	0.81	0.82	0.91	–																
Mediator																						
7 Av FDG-PET M0	–0.63	–0.63	–0.58	–0.48	–0.55	–0.47	–															
8 Av FDG-PET M6	–0.52	–0.55	–0.52	–0.56	–0.59	–0.52	0.91	–														
9 Av FDG-PET M12	–0.53	–0.55	–0.49	–0.51	–0.63	–0.50	0.91	0.91	–													
10 Av FDG-PET M18	–0.33	–0.33	–0.31	–0.51	–0.50	–0.51	0.90	0.89	0.92	–												
11 Av FDG-PET M24	–0.58	–0.59	–0.56	–0.48	–0.66	–0.56	0.86	0.87	0.91	0.93	–											
CSF measures(predictor)																						
12 A β_{1-42}	–0.47	–0.51	–0.48	–0.31	–0.52	–0.53	0.40	0.26	0.33	0.22	0.35	–										
13 t-Tau	0.42	0.43	0.46	0.01	0.34	0.28	–0.29	–0.10	–0.24	–0.03	–0.17	–0.45	–									
14 p-Tau _{181p}	0.35	0.40	0.37	0.13	0.42	0.42	–0.26	–0.14	–0.25	–0.03	–0.27	–0.46	0.69	–								
15 p-Tau _{181p} /A β_{1-42}	0.40	0.46	0.43	0.23	0.44	0.52	–0.34	–0.18	–0.26	–0.05	–0.25	–0.64	0.67	0.93	–							
16 t-Tau/A β_{1-42}	0.47	0.48	0.50	0.11	0.40	0.37	–0.35	–0.16	–0.30	–0.07	–0.18	–0.65	0.93	0.69	0.78	–						
Demographics																						
17 Male	0.08	0.06	0.04	0.02	–0.01	0.04	–0.05	0.09	0.15	–0.03	0.02	–0.08	–0.22	–0.10	–0.05	–0.14	–					
18 Education	–0.13	–0.12	–0.14	–0.05	–0.08	0.02	0.10	0.10	0.11	0.03	0.03	0.08	–0.14	–0.05	–0.05	–0.13	0.21	–				
19 Age	0.22	0.21	0.20	0.07	0.08	0.15	–0.11	–0.09	0.03	–0.21	–0.31	–0.13	0.06	–0.01	0.01	0.06	0.14	–0.08	–			
20 ApoE ϵ 4	0.26	0.29	0.26	0.16	0.28	0.30	–0.17	–0.12	–0.22	–0.02	–0.15	–0.43	0.32	0.33	0.38	0.39	0.00	–0.11	–0.15	–		
21 dxMCI	–0.21	–0.19	–0.14		0.02	0.26	0.19	–0.06	–0.10		0.06	–0.01	–0.08	–0.08	–0.08	–0.07	0.06	0.06	–0.13	–0.01	–	
22 dxAD	0.68	0.67	0.63		0.64	0.35	–0.50	–0.34	–0.39		–0.40	–0.35	0.35	0.30	0.35	0.39	–0.01	–0.12	0.14	0.21	–0.62	–

Note. Correlations greater than the absolute value of $\rho = 0.19$ were significant using a per-test Sidak-adjusted $p < 0.00047$ and a family-wise alpha of 0.10.

Key. ADAS-Cog = Alzheimer's disease assessment scale-cognitive subscale-13 items; Av FDG-PET = Average or composite [18 F]fluorodeoxyglucose positron emission tomography obtained from serial measurements (baseline; M0, to Month 24; M24) in the following five brain regions: right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus. CSF = cerebrospinal fluid; A β = beta amyloid; p-Tau = phosphorylated tau; t-Tau = total tau ApoE = apolipoprotein E; MCI = mild cognitive impaired; AD = Alzheimer's disease.

Univariate growth curve models

ADAS-Cog-13 outcome

Detailed results for all univariate LGC models including ADAS-Cog-13 as the outcome are reported in the supplemental materials, Table A.1, Appendix A. All models produced a good fit according to established criteria. The CFI and TLI indices varied from 0.996 to 1 and RMSEA values ranged from 0 to 0.032. The mean “growth” trajectory or change factor estimate for the unconditional (no covariates) model was positive and highly significant ($1.87, p < 0.001$) indicating an average decline of about two units per year in the ADAS-Cog-13. All the conditional models also produced statistically significant mean growth trajectories. The variances of the intercept and growth factors exhibited statistically significant individual variability in initial status and change in cognition over time (all $ps < 0.05$). All but $A\beta_{1-42}$ CSF measures yielded a positive and statistically significant effect on both level (initial status) and change in cognitive performance over time. The effect of $A\beta_{1-42}$ on both growth factors was negative and also significant; that is, low baseline amyloid beta protein levels predicted poor baseline cognitive performance (higher scores in the test) and faster decline over time. After testing alternative models, a linear growth system with additive random coefficients was appropriate for the target cognitive outcome. A linear trend was also observed in the panel of individual plots for the response variable over the time periods included in this study.

FDG-PET mediator

Table A2, Appendix A, summarizes the results of the univariate LGC models for the FDG-PET mediator as an outcome organized by regional brain measure (posterior cingulate gyrus, right and left angular gyri, right and left temporal gyri, and the average of all regions). The overall fit indices strongly suggested that the models fit the data well (CFI, range: 0.985 to 1; TLI, range: 0.979 to 1; RMSEA, 0 to 0.035). A linear LGC model also provided a good fit and was deemed appropriate for the data. The shape of the growth curve was also inspected using individual and mean plots.

The mean of the slope growth factor for all unconditional models across brain regions was negative and statistically significant ranging from ($-0.025, p < 0.001$; Average regional FDG-PET effect) to ($-0.031, p < 0.001$; Posterior cingulate effect). The negative rate of change in the slope indicated that, on average, FDG-PET scores decreased about 0.03 points between each assessment. Statistically significant variance of intercepts and slopes suggested non-trivial individual variability in both intercept and slopes around their mean values across the five time points. Participants varied in their initial glucose metabolism scores and their rates of change over time. Interestingly, the effect of CSF measures on initial and longitudinal changes in cerebral metabolic rates of glucose utilization, varied by brain region. For example, $A\beta_{1-42}$ CSF measures had a significant positive regression coefficient for the FDG-PET slope growth factor only in the left temporal region. That is, low $A\beta_{1-42}$ levels were associated with faster decline in glucose metabolism specifically in the left temporal gyrus. The same relationship was not observed in the other brain regions under study. Notably, however, in all brain regions, low baseline levels of $A\beta_{1-42}$ were associated with low initial glucose metabolism. Similarly, the effect of higher levels of $p\text{-Tau}_{181p}/A\beta_{1-42}$ on a significant reduction of glucose uptake was observed in all but the right and left angular gyri. As shown in Table A2, all the other baseline CSF measures ($p\text{-Tau}_{181p}$, $t\text{-Tau}$, and $t\text{-Tau}/A\beta_{1-42}$) were highly predictive of changes in glucose metabolic rates over time in all five brain regions and their composite (all $ps < 0.01$).

Parallel process latent growth curve models and mediation tests

The main goal of this study was to formally test the mediational effect of changes in FDG-PET uptake in the relationship between baseline

CSF biomarkers and changes in cognitive performance. That is, we set out to test the hypothesis that altered CSF measures would result in regional glucose hypometabolism in the brain and this metabolic change, in turn, would increase cognitive decline over a three-year period. To this end, the FDG-PET mediator LGC model described above was combined with the cognitive function outcome growth model into a PPLGC model and regressed on baseline CSF biomarkers, gender, education, age, *ApoE*, and diagnosis at entry. The hypothesized relationships among the latent growth factors and predictors describing the mediational process depicted in Fig. 1 were estimated separately for each analyte and mean glucose metabolic rate in each ROI. The point estimates of these relationships and corresponding 95% CIs are reported in Table 3 by brain region and CSF biomarker predictor.

FDG-PET as mediator

The role of decline in FDG-PET metabolism as a process variable mediating the effects of alterations in baseline CSF biomarkers on changes in cognitive function varied by CSF analyte and brain region. However, the effect of changes in metabolic function on changes in cognition was statistically significant across all ROIs. That is, in all models, increased metabolic dysfunction was associated with cognitive decline over time, irrespective of the CSF biomarker predictor or measured brain region. All the direct paths from metabolic function measures to cognitive performance were significant (see Table 2). Interestingly, the estimated mediated effects of FDG uptake in the left temporal region were significant for all the CSF biomarker predictors evaluated in this study. Compared to the effect of biomarkers of $A\beta$ accumulation, such as $A\beta_{1-42}$, biomarkers of neuronal degeneration or injury ($t\text{-Tau}$, $p\text{-Tau}_{181p}$, and ratios including these analytes) had a stronger effect on changes in FDG as a mediator across all brain regions. In all ROIs, the tests of FDG-PET change rate as a mediator of the effects of $t\text{-Tau}$ and $t\text{-Tau}/A\beta_{1-42}$ on cognitive change were statistically significant. For example, in the right temporal region illustrating mediation of $t\text{-Tau}/A\beta_{1-42}$ effects, the significance of direct and indirect paths suggested a mediational process such that high baseline $Tau/A\beta_{1-42}$ levels negatively affected FDG-metabolism by decreasing glucose metabolic rate, which in turn had a detrimental effect on changes in cognitive function over the studied time period.

The effect of alterations in $A\beta_{1-42}$ as a predictor of cognitive decline was only mediated by the effect of FDG uptake assessed in the left temporal brain region. As depicted in Fig. 2, the mediational effects of metabolic function in the “composite” or average FDG uptake over five regions (middle/inferior temporal, bilateral posterior cingulate, and lateral angular) were significant for all CSF biomarker predictors except for $A\beta_{1-42}$. This finding suggests that a composite FDG score may be more reliable but not necessarily a valid or representative measure of metabolic activity in specific brain regions included in the average possibly having an important role in the causal chain (or sequence) of neuro-pathological events leading to AD.

Discussion

This study sought to investigate the mechanisms behind the dynamic association between alterations in CSF biomarkers and longitudinal changes in cognitive performance and FDG uptake over time. In our principal analysis we used a multimodal framework to simultaneously model the longitudinal changes in brain glucose metabolism, longitudinal changes in cognition, their association over time, and the impact of baseline CSF measures on these associations while controlling for demographic variables, baseline clinical diagnosis, and *ApoE* $\epsilon 4$ status. We formally tested whether the relationship between CSF analytes and the growth (change) trajectory for cognitive function was mediated by the growth (change) trajectories of glucose uptake and how the mediation process varied by target brain region. In all models, altered levels of CSF peptides were hypothesized to have a neurotoxic effect leading to decreased glucose utilization and impaired cell function, indexed at an

Table 3
Mediation tests.

Mediation process	Posterior cingulate		Temporal (right)	
	Model fit (range)		Model fit (range)	
	CFI: 0.996–1.0; TLI = 1.0; RMSEA = 0.0		CFI: 0.989–0.996; TLI = 0.987–0.992; RMSEA = 0.016–0.026	
	Estimate	95% BC bootstrap CI	Estimate	95% BC bootstrap CI
Direct paths				
$A\beta_{1-42} \rightarrow$ FDG-PET slope	0.020	(−0.005, 0.044)	0.015	(−0.012, 0.042)
FDG-PET slope \rightarrow cognitive slope	−57.883 ^a	(−93.615, −22.919)	−36.883 ^a	(−66.276, −7.490)
$A\beta_{1-42} \rightarrow$ cognitive slope	0.452	(−2.227, 4.701)	−1.22	(−2.644, 0.203)
Estimated mediational effects (indirect paths)				
$A\beta_{1-42}$ FDG-PET slope \rightarrow cognitive slope	−1.140	(−6.140, 0.161)	−0.536	(−3.556, 0.494)
Direct paths				
p-Tau _{181p} \rightarrow FDG-PET slope	−0.017	(−0.037, 0.004)	−0.018 ^a	(−0.034, −0.001)
FDG-PET slope \rightarrow cognitive slope	−74.804 ^a	(−105.175, −44.432)	−27.866 ^a	(−51.811, −3.921)
p-Tau _{181p} \rightarrow cognitive slope	−0.025	(−3.97, 0.542)	0.525	(−2.583, 1.445)
Estimated mediational effects				
p-Tau _{181p} \rightarrow FDG-PET slope \rightarrow cognitive slope	1.257	(−0.255, 4.603)	0.493 ^a	0.002, 4.276)
Direct paths				
t-Tau \rightarrow FDG-PET slope	−0.020 ^a	(−0.038, −0.002)	−0.028 ^a	(−0.044, −0.013)
FDG-PET slope \rightarrow cognitive slope	−64.539 ^a	(−92.664, −36.413)	−33.944 ^a	(−67.085, −0.804)
t-Tau \rightarrow cognitive slope	−0.698	(−3.308, 0.513)	−0.058	(−1.129, 1.333)
Estimated mediational effects (indirect paths)				
t-Tau \rightarrow FDG-PET slope \rightarrow cognitive slope	1.317 ^a	(0.117, 4.064)	0.953 ^a	(0.134, 6.727)
Direct paths				
t-Tau/ $A\beta_{1-42}$ FDG-PET slope	−0.016 ^a	(−0.027, −0.005)	−0.020 ^a	(−0.032, −0.008)
FDG-PET slope \rightarrow cognitive slope	−66.115 ^a	(−98.921, −27.028)	−28.837 ^a	(−48.818, −8.855)
t-Tau/ $A\beta_{1-42} \rightarrow$ cognitive slope	−0.354	(−1.282, 0.573)	0.214	(−0.423, 0.850)
Estimated mediational effects (indirect paths)				
t-Tau/ $A\beta_{1-42} \rightarrow$ FDG-PET slope \rightarrow cognitive slope	1.036 ^a	(0.180, 3.672)	0.570 ^a	(0.100, 1.588)
Direct paths				
p-Tau _{181p} / $A\beta_{1-42} \rightarrow$ FDG-PET slope	−0.010	(−0.023, 0.002)	−0.014	(−0.028, 0.001)
FDG-PET slope \rightarrow cognitive slope	−57.879 ^a	(−101.183, −14.576)	−25.630 ^a	(−47.969, −3.291)
p-Tau _{181p} / $A\beta_{1-42} \rightarrow$ cognitive slope	0.186	(−0.640, 1.012)	0.554	(−1.026, 1.274)
Estimated mediational effects (indirect paths)				
p-Tau _{181p} / $A\beta_{1-42} \rightarrow$ FDG-PET slope \rightarrow cognitive slope	0.589	(−0.020, 2.819)	0.356	(−0.141, 1.371)
Mediation process				
	Temporal (left)		Angular (right)	
	Model fit (range)		Model fit (range)	
	CFI: 0.996–1.0; TLI: 0.998–1.0; RMSEA: 0.011–0.0		CFI: 1.0; TLI: 1.0; RMSEA: 0.0	
	Estimate	95% BC bootstrap CI	Estimate	95% BC bootstrap CI
Direct paths				
$A\beta_{1-42} \rightarrow$ FDG-PET slope	0.027 ^a	(0.005, 0.050)	−0.012	(−0.015, 0.039)
FDG-PET slope \rightarrow cognitive slope	−43.082 ^a	(−80.079, −6.086)	−61.703 ^a	(−89.417, 33.988)
$A\beta_{1-42} \rightarrow$ cognitive slope	−0.336	(−2.211, 3.037)	−0.647	(−2.223, 0.929)
Estimated mediational effects (indirect paths)				
$A\beta_{1-42} \rightarrow$ FDG-PET slope \rightarrow cognitive slope	−1.166 ^a	(−5.166, −0.139)	−0.729	(−2.824, 1.063)
Direct paths				
p-Tau _{181p} \rightarrow FDG-PET slope	−0.023 ^a	(−0.041, −0.006)	−0.025 ^a	(−0.044, −0.006)
FDG-PET slope \rightarrow cognitive slope	−63.248 ^a	(−95.434, −31.062)	−50.894 ^a	(−73.720, −28.067)
p-Tau _{181p} \rightarrow cognitive slope	−0.796	(−2.162, 0.569)	−0.488	(−1.625, 0.649)
Estimated mediational effects (indirect paths)				
p-Tau _{181p} \rightarrow FDG-PET slope \rightarrow cognitive slope	1.474 ^a	(0.167, 5.181)	1.278 ^a	(0.109, 3.794)
Direct paths				
t-Tau \rightarrow FDG-PET slope	−0.022 ^a	(−0.036, −0.009)	−0.025 ^a	(−0.041, −0.009)
FDG-PET slope \rightarrow cognitive slope	−64.073 ^a	(−94.484, −27.840)	−53.939 ^a	(−75.890, −31.989)
t-Tau \rightarrow cognitive slope	−0.855	(−1.944, 0.234)	−0.695	(−1.637, 0.248)
Estimated mediational effects (indirect paths)				
t-Tau \rightarrow FDG-PET slope \rightarrow cognitive slope	1.441 ^a	(0.359, 5.605)	1.343 ^a	(0.340, 3.282)
Direct paths				
t-Tau/ $A\beta_{1-42}$ FDG-PET slope	−0.018 ^a	(−0.029, −0.007)	−0.017 ^a	(−0.030, −0.003)
FDG-PET slope \rightarrow cognitive slope	−49.434 ^a	(−79.774, −19.133)	−62.965 ^a	(−92.526, −33.405)
t-Tau/ $A\beta_{1-42} \rightarrow$ cognitive slope	−0.23	(−3.518, 0.648)	−0.383	(−1.289, 0.524)
Estimated mediational effects (indirect paths)				
t-Tau/ $A\beta_{1-42} \rightarrow$ FDG-PET slope \rightarrow cognitive slope	0.896 ^a	(0.155, 4.244)	1.042 ^a	(0.139, 2.749)
Direct paths				
p-Tau _{181p} / $A\beta_{1-42}$ FDG-PET slope	−0.013 ^a	(−0.023, −0.002)	−0.011	(−0.024, 0.001)
FDG-PET slope \rightarrow cognitive slope	−49.484 ^a	(−83.657, −15.321)	−65.349 ^a	(−100.101, −29.899)
p-Tau _{181p} / $A\beta_{1-42} \rightarrow$ cognitive slope	0.073	(−1.240, 1.387)	−0.126	(−0.987, 0.735)
Estimated mediational effects (indirect paths)				
p-Tau _{181p} / $A\beta_{1-42} \rightarrow$ FDG-PET slope \rightarrow cognitive slope	0.633 ^a	(0.066, 3.636)	0.736	(−0.059, 2.683)

Table 3 (continued)

Mediational process	Angular (left)		Composite ROIs	
	Model fit (range)		Model fit (range)	
	CFI: 0.996–1.0; TLI: 0.998–1.0; RMSEA: 0.012–0.0		CFI: 1.0; TLI: 1.0; RMSEA: 0.0	
	Estimate	95% BC bootstrap CI	Estimate	95% BC bootstrap CI
Direct paths				
A β_{1-42} → FDG-PET slope	0.015	(−0.006, 0.037)	0.019	(−0.002, 0.039)
FDG-PET slope → cognitive slope	−26.891 ^a	(−46.483, −7.299)	−43.825 ^a	(−68.895, −18.756)
A β_{1-42} → cognitive slope	−1.217 ^a	(−2.270, −0.163)	−0.988	(−2.309, 0.334)
Estimated mediational effects (indirect paths)				
A β_{1-42} → FDG-PET slope → cognitive slope	−0.412	(−2.175, 0.269)	−0.818	(−2.805, 0.234)
Direct paths				
p-Tau _{181p} → FDG-PET slope	−0.013	(−0.031, 0.005)	−0.021 ^a	(−0.037, −0.005)
FDG-PET slope → cognitive slope	−26.538 ^a	(−47.613, −5.462)	−36.973 ^a	(−57.285, −16.662)
p-Tau _{181p} → cognitive slope	0.651	(−0.146, 1.447)	0.14	(−0.712, 0.992)
Estimated mediational effects (indirect paths)				
p-Tau _{181p} → FDG-PET slope → cognitive slope	0.338	(−0.201, 2.791)	0.765 ^a	(−0.076, −2.448)
Direct paths				
t-Tau → FDG-PET slope	−0.023 ^a	(−0.040, −0.005)	−0.024 ^a	(−0.039, −0.009)
FDG-PET slope → cognitive slope	−38.243 ^a	(−68.157, −8.330)	−52.321 ^a	(−86.690, −17.943)
t-Tau → cognitive slope	−0.145	(−0.983, 1.273)	−0.26	(−1.418, 0.897)
Estimated mediational effects (indirect paths)				
t-Tau → FDG-PET slope → cognitive slope	0.886 ^a	(0.073, 4.528)	1.269 ^a	(0.157, 4.165)
Direct paths				
t-Tau/A β_{1-42} → FDG-PET slope	−0.016 ^a	(−0.029, −0.003)	−0.018 ^a	(−0.029, −0.007)
FDG-PET slope → cognitive slope	−26.318 ^a	(−47.407, −5.229)	−44.872 ^a	(−72.476, −17.267)
t-Tau/A β_{1-42} → cognitive slope	0.375	(−2.112, 1.009)	−0.126	(−0.613, 0.865)
Estimated mediational effects (indirect paths)				
t-Tau/A β_{1-42} → FDG-PET slope → cognitive slope	0.424 ^a	(0.046, 3.292)	0.807 ^a	(0.129, 2.971)
Direct paths				
p-Tau _{181p} /A β_{1-42} → FDG-PET slope	−0.011	(−0.025, 0.003)	−0.013 ^a	(−0.025, −0.001)
FDG-PET slope → cognitive slope	−22.578 ^a	(−40.826, −4.329)	−36.043 ^a	(−58.134, −10.484)
p-Tau _{181p} /A β_{1-42} cognitive slope	0.643	(−0.086, 1.200)	0.376	(−0.258, 1.011)
Estimated mediational effects (indirect paths)				
p-Tau _{181p} /A β_{1-42} → FDG-PET slope → cognitive slope	0.250	(−0.138, 2.013)	0.467 ^a	(0.031, 2.458)

^a Statistically significantly different from 0 based on the asymmetric 95% bias-corrected bootstrap confidence interval.

aggregate level by FDG-PET, causing in turn cognitive decline as measured by ADAS-Cog-13.

Our findings suggest a regional causal sequence of events that identifies change in FDG hypometabolism as a mediator between antecedent alterations in the production of CSF biomarkers and subsequent cognitive impairment. Reduced glucose uptake also implies either a reduction in the number of synapses or a reduced synaptic metabolic activity over time mediating the effect of early measures of CSF markers on changes in cognitive function. In all pre-defined ROIs, which were selected based on an extensive meta-analysis (Landau et al., 2011) suggesting these are commonly-implicated regions in symptomatic AD,

higher baseline concentrations of putative indicators of neuronal damage, such as t-Tau, p-Tau_{181p}, and ratios including these measures, were more predictive of decline in cerebral glucose metabolism, which caused in turn decline in cognition, than lower baseline concentrations of A β_{1-42} ; a known marker of A β sequestration in neuritic plaques. Mediational tests modeling changes in cerebral metabolic rate for glucose, as the mediator of the effect of t-Tau or t-Tau/A β_{1-42} on cognitive change across time, were significant across all brain regions. Consistent with previous findings, primarily in cross-sectional studies, a significant direct effect of alterations in A β_{1-42} levels on hypometabolism was observed in a single brain region: the middle/

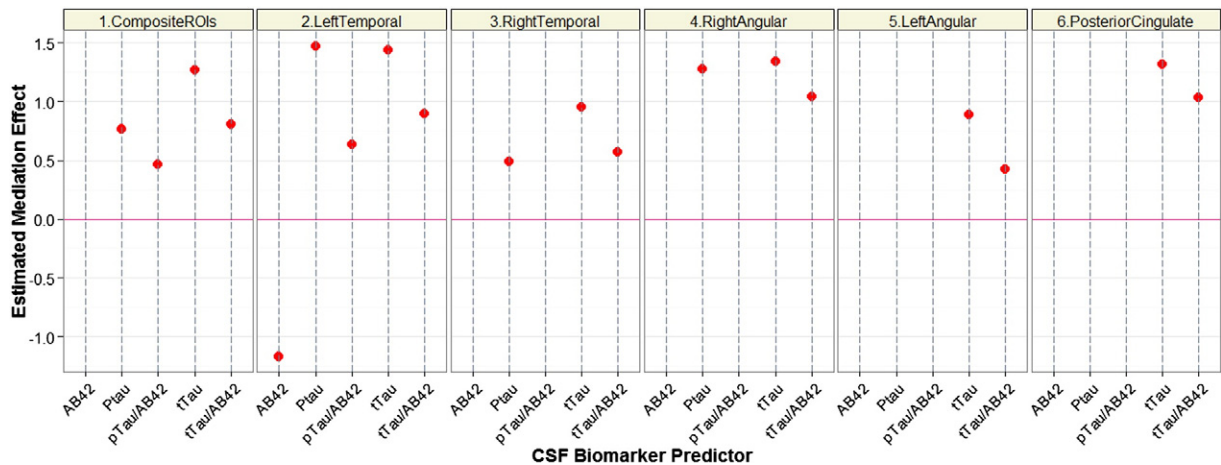


Fig. 2. Estimates of the significant mediation test results for FDG-PET change rate as the mediator of the effects of alterations in CSF measures on cognitive decline over time across 5 different brain regions.

inferior temporal gyrus (Okamura et al., 1999; Petrie et al., 2009). Similarly, after including cerebral glucose uptake as a mediator in the causal path, the association between baseline $A\beta_{1-42}$ or tau-related measures and cognitive decline observed in the univariate growth models became insignificant. These findings provide support for the revised temporal framework model posited by Jack et al. (2013) in which reduced CSF levels of the $A\beta_{1-42}$ peptide (amyloid-related biomarkers reflecting extracellular amyloid burden) may occur much earlier in the pathogenic chain of events and are thus weakly correlated with concurrent cognition, but may ultimately lead to detrimental effects on cognition. Congruent with this theory of a temporal sequence of pathological changes, we also showed that baseline markers of intra-neuronal neurofibrillary degeneration (t-Tau, p-Tau_{181p}, and ratios including these biomarkers) predicted changes in brain glucose metabolism (a biomarker of neuronal function and structure) causing in turn changes in cognitive performance across time. Using an extension of the recently-introduced event-based model (Fonteijn et al., 2012) with multimodal data, but focusing on “ordering” of events rather than longitudinal mediation, Young et al., 2014 also found a sequence of events strongly placing CSF and atrophy rates before cognitive test scores.

This study examined longitudinal data from a sample representing the full range of the AD spectrum from healthy controls to mild dementia and provided new information regarding the broad temporal chain of events across the disease continuum. The study was not designed to assess relatively early or transient nonlinear signal in presymptomatic subjects. For example, some studies (Landau et al., 2012) have shown a greater association between $A\beta$ deposition and cognitive decline in CN individuals than in individuals at later stages of the disease for whom hypometabolism may become more prominent consequently affecting cognitive abilities. Yet, other studies suggest the presence of upregulated FDG metabolism in individuals with a positive β -amyloid PET imaging result, but cognitively normal (Oh et al., 2014). The revised hypothetical biomarker curve model proposed by Jack et al. (2013) also conveys the idea that early increases in metabolism may pre-date amyloid accumulation. To formally study such early FDG changes it would be necessary to target people who will eventually develop AD and examine their serial FDG metabolic patterns in the preclinical phase. Several ongoing projects are studying this phase and the application of the types of models we have described here to establish and test competing causality hypotheses would be of interest in that phase of the disease (Johnson et al., 2014; Reiman et al., 2012; Villemagne et al., 2013).

As we have noted above, the results are highly consistent with prior work demonstrating stronger associations between cognition and tau-related pathology rather than amyloid-related pathology. Presumably this is linked to the fact that neurofibrillary tangles are intracellular and the detection of these analytes in the CSF may be from the breakdown and clearance of such affected cells. A consistently replicated finding is that a large portion of cognitively healthy older adults and people at risk harbor amyloid in the brain (Johnson et al., 2014; Villemagne et al., 2013). In a recent study of brain banked cases, Perez-Nievas et al. (2013) showed that compared to AD, cognitively normal but amyloid harboring control brains were more likely to have diffuse rather than neuritic plaques, less inflammation and microglial activation, fewer neurofibrillary tangles, and more neurons and synapses. These and other studies (Niedowicz et al., 2012) suggest that this type of amyloid formation may be predictive of subsequent neurofibrillary pathology and eventual neurometabolic decline. However, CSF amyloid analytes and amyloid imaging are not sufficiently sensitive to dissociate benign from toxic amyloid formations accruing in the brain. Tau imaging with PET (Chien et al., 2014; Okamura et al., 2014; Xia et al., 2013) is a new technique that can be done serially over time in individual patients. While, like amyloid biomarkers, the specificity to the various tau forms has not been established, such methods will likely be helpful in characterizing the accumulation and spread of fibrillary tau-related pathology in the development of AD.

This study has some limitations that should be noted. The ADNI sample used in the analysis had a larger *ApoE* $\epsilon 4$ prevalence rate (55%) than the total study population (48%). Previous research (Reiman et al., 2001, 1996; Small et al., 2000) has demonstrated a link between *ApoE* $\epsilon 4$ carriers and lower cerebral glucose metabolism as compared to *ApoE* $\epsilon 4$ non-carriers. Higher prevalence increases positive predictive value and the interpretation of findings should take into account the characteristics of the sample. It is also possible that there are other variables not measured in the present study that may be causally affecting both the brain glucose metabolism mediator and the longitudinal cognitive outcome even after conditioning on the covariates we controlled for (Imai et al., 2010). Limitations inherent to observational studies curb the ability to infer causality with the certainty of randomized or experimental designs. Sequential tests of different predictors of the mediator theory set forth in the present study (e.g., tau and amyloid imaging as described above; structural measures, such as hippocampal volume and other measures of atrophy; genetic profiles of resilience genes and susceptibility genes; markers of microglial-mediated inflammation in the brain, such as YKL-40 or plasma-based markers) may be necessary to strengthen the results of the analysis. A natural extension of this study would include a third growth process representing the longitudinal effect of changes in CSF biomarker predictors on FDG uptake changes as a mediator and cognitive changes as the outcome. To minimize issues related to “concurrent causation” and test a hypothesis of a “temporal sequence of events,” a better design would include longitudinal CSF biomarkers collected prior to the serial FDG-PET evaluations and repeated cognitive assessments after the collection of PET imaging biomarkers using time intervals that allow for the evolution of clinically meaningful disease-associated events, which, of course, may vary according to disease status. Still, advanced causal inference models may also be required to increase the evidence of a true causal mediation (Imai et al., 2010; Jo, 2008). However, despite the outlined study design limitations, the results of the present mediation analysis examining simultaneously the effect of change processes in the mediator (FDG-PET) on changes in cognition (ADAS-Cog-13) do provide information that can be utilized to increase the evidence for causal inference. Other modeling approaches using statistical machine learning techniques showing promise in optimizing classification and regression performance with multimodal baseline and longitudinal data (see, for example, Zhang & Zheng, 2012) may also be further explored to test hypotheses of temporal sequence of events in disease progression. More longitudinal studies and appropriate modeling approaches are required, as well as relevant clinical information, to examine and validate hypothesized mediational relationships explaining the complex sequence of events leading to neurodegeneration in AD.

Disclosures

There were no actual or potential conflicts of interest for any of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2014.10.050>.

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