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CSF biomarker associations with change in hippocampal volume and precuneus thickness: implications for the Alzheimer's pathological cascade

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Abstract

Neurofibrillary tangles (NFT) and amyloid plaques are hallmark neuropathological features of Alzheimer's disease (AD). There is some debate as to which neuropathological feature comes first in the disease process, with early autopsy studies suggesting that NFT develop first, and more recent neuroimaging studies supporting the early role of amyloid beta (Aβ) deposition. Cerebrospinal fluid (CSF) biomarkers of $A\beta_{42}$ and hyperphosphorylated tau (p-tau) have been shown to serve as in vivo proxy measures of amyloid plaques and NFT, respectively. The aim of this study was to examine the association between CSF biomarkers and rate of atrophy in the precuneus and hippocampus. These regions were selected because the precuneus appears to be affected early and severely by Aβ deposition, and the hippocampus similarly by NFT pathology. We predicted (1) baseline $A\beta_{42}$ would be related to accelerated rate of cortical thinning in the precuneus and volume loss in the hippocampus, with the latter relationship expected to be weaker, (2) baseline p-tau_{181p} would be related to accelerated rate of hippocampal atrophy and cortical thinning in the precuneus, with the latter relationship expected to be weaker. Using all ADNI cohorts, we fitted separate linear mixed-effects models for changes in hippocampus and precuneus longitudinal outcome measures with baseline CSF biomarkers modeled as predictors. Results partially supported our hypotheses: Both baseline p-tau_{181p} and $A\beta_{42}$ were associated with hippocampal atrophy over time. Neither p-tau_{181p} nor $A\beta_{42}$ were significantly related to cortical thinning in the precuneus over time. However, follow-up analyses demonstrated that having abnormal levels of both $A\beta_{42}$ and p-tau_{181p} was associated with an accelerated rate of atrophy in both the hippocampus and precuneus. Results support early effects of Aβ in the Alzheimer's

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disease process, which are less apparent than and perhaps dependent on p-tau effects as the disease progresses. However, amyloid deposition alone may be insufficient for emergence of significant morphometric changes and clinical symptoms.

Keywords

Biomarkers; Beta Amyloid; Phosphorylated Tau; MRI; Alzheimer's Disease; Hippocampus; Precuneus

INTRODUCTION

Neurofibrillary tangles (NFT) and amyloid plaques are the hallmark neuropathological features of Alzheimer's disease (AD). There is some debate about which neuropathological feature comes first in the disease process. Early autopsy studies suggested that NFT develop first (Braak, Braak, Bohl, & Reintjes, 1996), whereas some recent neuroimaging studies, particularly those employing ^{11}C-PiB methods, support the early role of amyloid deposition (see Jack et al., 2010 for review), in line with the amyloid cascade hypothesis (J. A. Hardy & Higgins, 1992; see J. Hardy, 2009 for a critical reappraisal of this hypothesis). CSF biomarkers of phosphorylated tau and $A\beta_{42}$ have been shown to serve as in vivo proxy measures of NFT and amyloid plaques, respectively (Buerger et al., 2006; Clark et al., 2003; Shaw et al., 2009), and improve diagnostic accuracy for AD (Hampel, Goernitz, & Buerger, 2003; Strozyk, Blennow, White, & Launer, 2003). There is evidence that as amyloid plaques develop, CSF $A\beta_{42}$ decreases (Shaw, Korecka, Clark, Lee, & Trojanowski, 2007), thus lower CSF $A\beta_{42}$ suggests increased brain amyloid deposition. Unlike total tau, which may be a general marker of neuronal damage, p-tau is likely to reflect the formation of tangles in AD (Blennow & Hampel, 2003), with increased levels of CSF p-tau thought to reflect increased NFT pathology.

Investigation of the relationship between CSF biomarkers and regional changes on structural and functional MRI may contribute to understanding the pathological mechanisms of AD. Aβ-associated neurodegeneration manifests as cortical thinning in regions vulnerable to early Aβ deposition and this may begin prior to clinically evident cognitive impairment (Becker et al., 2011). The precuneus is a site of preferential amyloid uptake in PiB studies (see Rabinovici & Jagust, 2009 for review), consistently shows hypometabolism in FDG-PET studies of AD and atrophy/cortical thinning in morphometric studies (Buckner et al., 2005), and is a key part of the default network (Buckner, Andrews-Hanna, & Schacter, 2008), which is important for memory function (Sperling et al., 2009). Relationships between CSF $A\beta_{42}$ or amyloid load as measured by PiB and the precuneus have previously been demonstrated in nondemented older adults and in MCI and AD subjects (Becker et al., 2011; Chetelat et al., 2010; Fjell et al., 2008; Tosun et al., 2010). In contrast to the precuneus, the hippocampus remains relatively free of amyloid deposition during normal aging and early to mid-stage AD (Braak et al., 1996), and there is variability in the literature as to the presence of an association between amyloid load and hippocampal atrophy, with some studies supporting at least a weak relationship (Apostolova et al., 2010; Beckett et al., 2010; Henneman et al., 2009; Mormino et al., 2009; Schuff et al., 2009), and other studies not finding a significant relationship (Becker et al., 2011; Fagan et al., 2009).

A relationship between p-tau and both baseline hippocampal volume and rate of hippocampal atrophy has been demonstrated across several studies (Apostolova et al., 2010; Beckett et al., 2010; de Leon et al., 2006; Hampel et al., 2005; Henneman et al., 2009; Tosun et al., 2010; but also see Schuff et al., 2009), consistent with the well-established finding that the hippocampus is an early site of NFT pathology in the course of AD. While a number

of studies have investigated the association of CSF biomarkers and change in selected brain regions, to our knowledge only one study to date has investigated the potential interaction of multiple CSF biomarkers on atrophy. Desikan and colleagues (2011) found an interaction between $A\beta_{42}$ and p-tau_{181p} status on entorhinal cortex atrophy over time, with elevated atrophy in individuals with abnormal levels of both $A\beta_{42}$ and p-tau_{181p}. Follow-up analyses further revealed that $A\beta_{42}$ status was associated with accelerated atrophy in entorhinal cortex only among p-tau_{181p} positive individuals in a nondemented sample. The authors demonstrated this same effect within an "AD-vulnerable" region of interest (ROI) that averaged longitudinal changes in multiple temporal and parietal regions affected subsequently to the entorhinal cortex. They did not examine this effect in the hippocampus and precuneus, and included only nondemented subjects. There has been an increasing emphasis on considering Alzheimer's disease as a continuum, with the process beginning in otherwise "normal" individuals, and progressing slowly over time, with eventual clinical expression resulting in the diagnostic classifications of MCI and eventually AD dementia. Although the use of diagnostic classification is clinically useful, when studying the effects of CSF biomarkers it is important to examine effects across the entire disease spectrum. This focus separates the current study from recent work that has examined similar questions within diagnostic subgroups (Desikan et al., 2011; Tosun et al., 2010).

The primary aim of this study was to examine the association of CSF biomarkers and rate of atrophy in the precuneus and hippocampus. These regions were selected because the precuneus appears to be affected early and severely by Aβ deposition, and the hippocampus similarly by NFT pathology. A secondary aim was to extend the findings of Desikan and colleagues by assessing the effect of a three-way interaction of $A\beta_{42}$, p-tau_{181p} and time on rates of atrophy in the precuneus and hippocampus. We predicted (1) baseline $A\beta_{42}$ would be related to accelerated rate of cortical thinning in the precuneus and volume loss in the hippocampus, with the latter relationship expected to be weaker, (2) baseline p-tau_{181p} would be related to accelerated rate of hippocampal atrophy and cortical thinning in the precuneus, with the latter relationship expected to be weaker and (3) an interaction between low $A\beta_{42}$ and high p-tau_{181p} would be associated with an accelerated rate of atrophy in both the hippocampus and precuneus. The precentral gyrus was selected as a control region because we did not predict a relationship with either CSF biomarker in this ROI as primary motor regions remain relatively free of Alzheimer's pathology until late in the disease process.

METHOD

Data used were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). 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), and private pharmaceutical companies and non-profit organizations, as a 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 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 coinvestigators 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 adults, ages 55 to 90, to participate in the research,

approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with MCI to be followed for 3 years and 200 people with early AD to be followed for 2 years (see www.adni-info.org). This study was approved by each ADNI-affiliated institution. Written informed consent was obtained from all patients or authorized representatives participating in the study.

Participants

ADNI general eligibility criteria are described at www.adni-info.org/Scientists/ADNIGrant/ProtocolSummary.aspx. Briefly, healthy controls (HC) had a Mini-Mental State Exam (MMSE; Folstein, Robins, & Helzer, 1983) score between 24–30 (inclusive), a global Clinical Dementia Rating (CDR; Morris, 1993) score of 0, and did not meet criteria for MCI or dementia (Petersen et al., 2001). MCI participants had MMSE scores between 24–30 (inclusive), a memory complaint, evidence of objective memory loss as measured by education adjusted scores on the Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Mildly demented AD participants had MMSE scores between 20–26, global CDR scores of 0.5 or 1.0, and met NINCDS/ADRDA criteria for probable AD (McKhann et al., 1984). The ADNI study collected CSF from approximately 50% of participants at baseline, and from smaller subgroups subsequently. CSF biomarker acquisition procedures for ADNI are described in detail elsewhere (Jagust et al., 2010; Petersen et al., 2010; Trojanowski et al., 2010). A measure derived from the components of the CDR known as “sum of boxes” (CDR-SB) was calculated to further estimate level of clinical impairment. The data used in the current analysis was downloaded on 6/1/2011. Participants with CSF data and baseline and follow-up MRI scans (interval info) that met global quality control criteria were used in the current analysis (see www.loni.ucla.edu/twiki/pub/ADNI/ADNIPostProc/UCSFFreeSrferMethodsSummary.pdf).

MR scanning and brain morphometry

Protocols are described in detail at http://www.loni.ucla.edu/ADNI/Research/Cores/. Two T1-weighted volumes were acquired for each participant. Volumetric (Fischl et al., 2002; Fischl, Salat et al., 2004) and cortical surface reconstruction (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl, van der Kouwe et al., 2004) methods based on FreeSurfer software, optimized for use on large, multi-site datasets, were used. To measure thickness, the cortical surface was reconstructed (Dale et al., 1999) and parcellated into distinct ROIs (Desikan et al., 2006; Fischl, van der Kouwe et al., 2004). Details of the application of these methods to the ADNI data have been described in full elsewhere (Fennema-Notestine et al., 2009). Three a priori selected ROIs were included in the present analyses: precuneus cortical thickness, precentral gyrus cortical thickness and hippocampal volume.

Statistical analyses

We used linear mixed effects (LME) multiple regression (Diggle, Heagerty, Liang, & Zeger, 2002) to model hippocampus, precuneus and precentral gyrus as three separate longitudinal outcomes. Each model included time in months (0, 6^{th}, 12^{th}, 18^{th} and 24^{th} from baseline), baseline CSF biomarkers ($A\beta_{42}$ and p-tau_{181p}) and their interactions with time as predictors, and baseline age, sex, and apoe4 status as control variables. CSF biomarkers were normalized using the Blom’s rank normalization algorithm (Conover & Inman, 1981) so that estimated effects of these two biomarkers on the outcome could be meaningfully compared. Intercept and time were treated as random effects in all models. All models assumed an unstructured within-subject error covariance structure. Restricted maximum likelihood was used for estimation. Pairwise interactions between CSF biomarkers and time were of substantive interest. That is, we were interested in examining the interplay between CSF

biomarkers at baseline and trajectories over time in outcome measures (hippocampal volume, precuneus and precentral gyrus thickness). We first carried out the LME analyses described above on the complete data set (n=342). Next, we applied the same LME models to each diagnostic group separately (normal controls, MCI, and AD) to examine the effect of baseline CSF biomarkers on longitudinal outcomes of interest within each group. Quadratic and higher order time variables did not improve the model fitness indicated by Bayesian information and log-likelihood criteria for any models and is thus not included. The overall fit of the models was examined using a combination of formal fit criteria and visual inspection of residual plots. Results were considered significant when at $p < .05$; we also provide Bonferroni-adjusted p-values in Table 2.

RESULTS

CSF measures were obtained in a subset of ADNI subjects. Out of 819 subjects enrolled in the ADNI I study, 342 subjects had information on $A\beta_{42}$, p-tau_{181p}, and valid assessment of hippocampal brain volume, precuneus and precentral gyrus measures at baseline. These subjects were included in the current analyses using their follow-up assessments up to 24 months. Demographic characteristics are presented in Table 1.

Hippocampal volume

Across all subjects, there was a main effect of time, and this effect persisted within each diagnostic subgroup. There was no main effect of $A\beta_{42}$, meaning that $A\beta_{42}$ was not associated with hippocampal volume at baseline, either across all groups or within diagnostic groups. There was a main effect of p-tau_{181p}; higher p-tau_{181p} was associated with lower hippocampal volume, and this effect persisted within the AD group. There was an interaction of time and CSF biomarkers: higher $A\beta_{42}$was associated with a smaller decline in hippocampal volume over time, and higher p-tau was associated with a larger decline in hippocampal volume over time. When running the model within subgroups, the interaction of $A\beta_{42}$ and time persisted only within the NC group, suggesting that $A\beta_{42}$ at baseline does not significantly affect change over time within MCI and AD groups. P-tau_{181p} showed the opposite pattern: baseline p-tau_{181p} does not significantly affect change in hippocampal volume over time in the NC group, whereas within the MCI and AD groups, higher p-tau_{181p} at baseline was associated with greater decline in hippocampal volume over time (Table 2). Figure 1 shows examples of the trajectories of hippocampal volume. We illustrate the effect of high/low CSF biomarkers on hippocampal volume over time for the diagnostic group where significant interactions of biomarkers and time were found using the coefficients obtained in the mixed effects models. For models where hippocampal volume is the outcome, models were ran both with and without controlling for baseline estimated total intracranial vault (eTIV) volume (Buckner et al., 2004) and the same pattern of results was obtained. We present results of models without controlling for eTIV.

Precuneus thickness

Across all subjects there was a main effect of time, and this effect persisted within each diagnostic group. There was no main effect of $A\beta_{42}$, either across all groups or within diagnostic groups. There was a main effect of p-tau_{181p}; higher p-tau_{181p} was associated with lower precuneus thickness at baseline. Within groups, this main effect was significant only within the MCI group. There were no interactions with time, either across all groups or within groups.

Precentral gyrus thickness

Across all subjects there was a main effect of time, and this effect persisted within each individual group. There was no main effect of $A\beta_{42}$, either across all groups or within

individual groups. There was a main effect of p-tau$_{181p}$ for all groups combined; higher p-tau$_{181p}$ was associated with lower precentral gyrus thickness at baseline. Within diagnostic groups, this main effect was significant only within the NC group. There were no interactions with time, either across all groups or within groups.

In a set of secondary analyses, we tested for potential interaction effects of p-tau$_{181p}$ and Aβ_{42} to determine if having both abnormal p-tau$_{181p}$ and Aβ_{42} values has an added effect on atrophy over time in our selected ROIs. We dichotomized high and low values of each CSF biomarker for the 3-way interaction to facilitate interpretation of results. Previously defined cutoffs were applied (Shaw et al., 2009): abnormal p-tau$_{181p}$ was defined as p-tau$_{181p}$ > 23pg/ml (−0.34818 using blom normalized scores), and abnormal Aβ_{42} was defined as Aβ_{42} < 192pg/ml (0.4395 using blom normalized scores). The proportion of those with both abnormal p-tau$_{181p}$ and Aβ_{42} was 81.7%, 64.0% and 21.3% among AD, MCI, and normal controls, respectively (Pearson chi-square test, $p<0.001$). In the entire sample (NC, MCI and AD), there was a 3-way interaction of abnormal p-tau$_{181p}$ and abnormal Aβ_{42} with time for each ROI (HCV $p=0.040$, precuneus $p=0.0007$, precentral gyrus $p=0.029$), after controlling for gender, Apoe4, and baseline age, p-tau and Aβ_{42} (continuous variables) and 2-way interactions of p-tau and time, and Aβ_{42} and time. That is, having the combination of both abnormal p-tau$_{181p}$ and Aβ_{42} resulted in an additional increased rate of atrophy over time beyond the additive effect of each biomarker. There was also a significant interaction of p-tau and time ($p=0.012$) when outcome was hippocampal volume (all diagnostic groups combined). Within subgroups, the 3-way interaction remained significant only for the AD group for precuneus ($p=0.005$) and precentral gyrus ($p=0.019$) thickness.

DISCUSSION

These results demonstrate that across the Alzheimer's disease spectrum from normal aging to early dementia, CSF biomarkers exert an influence on rate of atrophy, although this effect varies by region, CSF biomarker, and sample composition.

Baseline association results showed a significant relationship between p-tau$_{181p}$ and hippocampal volume, whereas the relationship between Aβ_{42} and hippocampal volume was not significant, but a trend was demonstrated. These baseline results supported our prediction that p-tau$_{181p}$ would have a stronger relationship with hippocampal volume than Aβ_{42}. The lack of baseline association of hippocampal volume and markers of amyloid burden has been demonstrated in prior PiB and CSF biomarker studies (Becker et al., 2011; Fagan et al., 2009; Fjell et al., 2010), whereas other studies have demonstrated at least a weak relationship (Apostolova et al., 2010; Henneman et al., 2009; Mormino et al., 2009). A somewhat different pattern of results was revealed for rates of change. Within the entire sample, both p-tau$_{181p}$ and Aβ_{42} were significantly associated with accelerated rates of hippocampal atrophy. Within-group results demonstrated a relationship between Aβ_{42} and accelerated rate of hippocampal atrophy within the NC group, but not within the two clinical groups. Although trajectories of change within the NC group may differ since some subjects are destined to develop AD while others are not, the early detection of effects of Aβ_{42} only in the NC group is consistent with a potential initiating role as suggested by Jack et al. (2010). In contrast, within-group results demonstrated a relationship between p-tau$_{181p}$ and accelerated rate of hippocampal atrophy within the MCI and AD groups, consistent with studies showing that rates of brain atrophy and clinical progression correlate well with pathological indices of NFT (Josephs et al., 2008). Henneman and colleagues (2009) similarly found that CSF p-tau$_{181p}$ predicted accelerated rate of hippocampal atrophy when collapsing across normal and clinical groups, but in that study results did not persist within diagnostic subgroups, potentially due to much smaller sample sizes relative to the current study: In their study, the total sample size combining normal, MCI and AD was 75 subjects.

Other studies have demonstrated a significant relationship between p-tau$_{231p}$ or p-tau$_{181p}$ and accelerated hippocampal atrophy in MCI (de Leon et al., 2006; Fjell et al., 2010; Hampel et al., 2005; Tosun et al., 2010).

Considered together, our results demonstrate that lower baseline Aβ_{42} in the NC group and higher baseline p-tau$_{181p}$ in the MCI and AD groups is associated with an accelerated rate of hippocampal atrophy over time. Our results are consistent with the biomarker model proposed by Hyman, (2011) and further supported by data from Lo et al., (2011) in which Aβ may exert an effect early in the disease, but it has relatively smaller effects later. That is, once there are clinically detectable symptoms warranting a diagnosis of MCI or AD, the downstream effects of Aβ become uncoupled from Aβ itself. Hyman's model emphasizes a two-stage process in which intervention efforts may be beneficial very early in the disease process, before there is any clinically detectable cognitive symptoms or MRI atrophy, whereas once clinical symptoms emerge, Aβ or another early initiating factor has already instigated the pathological cascade and may be less important for predicting disease progression and ineffective as a treatment target in these later stages of the disease.

Because accumulation of amyloid beta is theorized to occur prior to NFT (Jack et al., 2010), we hypothesized that baseline Aβ_{42} would be related to accelerated rates of cortical thinning in the precuneus given evidence of early amyloid deposition in this region. However, a pattern opposite to that we predicted was demonstrated: baseline Aβ_{42} did not predict accelerated rates of cortical thinning in the precuneus, whereas it did predict accelerated rate of hippocampal atrophy as discussed above. In fact, neither CSF biomarker predicted accelerated rates of cortical thinning in the precuneus. A baseline association of p-tau$_{181p}$ and precuneus thickness was demonstrated, whereas a baseline association of Aβ_{42} and precuneus was not. The precuneus is assumed to be an early site of amyloid deposition based largely on the findings of multiple PiB studies that have demonstrated preferential amyloid uptake in this region (Aizenstein et al., 2008; Mintun et al., 2006; Rowe et al., 2007) and its involvement in the default network (Buckner et al., 2008). A few PiB studies have shown a significant baseline association between amyloid uptake and hippocampal volume (Becker et al., 2011; Chetelat et al., 2010; Fjell et al., 2008), and one study has shown PiB uptake is associated with accelerated hippocampal atrophy in MCI (Tosun et al., 2010). Because PiB and CSF measures of amyloid may not be equivalent, this alone could explain our discrepant findings. Our use of an ROI analysis approach, as opposed to voxelwise analysis that may be more sensitive to localized changes within subregions of the precuneus, may also explain our findings. However, autopsy studies have not demonstrated a predilection for early amyloid plaque accumulation in the precuneus relative to other areas of the neocortex (Nelson et al., 2009), so further investigation of the relationship between amyloid and the precuneus is warranted.

We also predicted a significant relationship between p-tau$_{181p}$ and accelerated rates of precuneus thinning based on a hypothesized indirect relationship. An indirect relationship was expected due to the extensive anatomical and functional connections between posterior cortical regions including the precuneus and medial temporal lobe regions affected early in AD, including the hippocampus (Dorfel, Werner, Schaefer, von Kummer, & Karl, 2009; Kobayashi & Amaral, 2003; Teipel et al., 2010). Decreased resting state functional connectivity between the precuneus and the hippocampus (as well as other regions of the default network) has been demonstrated in patients with early AD, PiB+ normal healthy elderly and PiB− normal healthy elderly APOE4 allele carriers (Sheline, Morris et al., 2010; Sheline, Raichle et al., 2010). Results did not support this hypothesis; we found no baseline or longitudinal associations beween p-tau$_{181p}$ and precuneus thickness. To our knowledge no other studies have directly assessed this relationship.

An interaction between low $A\beta_{42}$ and high p-tau_{181p} was associated with greater cortical thinning in the precuneus and precentral gyrus and hippocampal atrophy over time, extending the findings of Desikan et al. (2011) to these additional regions in a combined NC, MCI and AD sample. This suggests that having both abnormal $A\beta_{42}$ and p-tau_{181p} leads to accelerated atrophy. The significance of this effect in our "control" region (precentral gyrus) was surprising and may point toward more diffuse effects of these combined biomarkers. Inconsistent with the results of Desikan et al. (2011), this 3-way interaction persisted only within the AD group for cortical thickness measures. Although the analyses performed on the entire sample demonstrated this effect in all regions studied, the 3-way interaction was not significant within NC or MCI groups when examined individually.

There are several limitations that must be considered when interpreting these results. First, we selected a small number of potential biomarkers to focus on in this study to maintain a narrow focus. We did not include t-tau or ratio values of $A\beta_{42}$ and tau. We also included only a small number of a priori ROIs, instead of performing exploratory voxelwise analyses. Because ROIs average across an entire region, subtle group difference that may be detected within such a region by voxelwise analysis may be missed; in other words, ROI analyses may be less sensitive. However, examining these effects using ROIs is important, as this is likely to be a widely used approach in large clinical trials applying automated neuroimaging processing techniques. Second, the primary goal of the ADNI is to optimize clinical trials, and the sample is not representative of the general population (e.g., highly educated); therefore the generalizability of the current results is limited. Third, we did not include longitudinal CSF data, thus the timing of biomarker effects cannot be fully disentangled with the current set of analyses. A longer duration of follow-up would likely be necessary to optimally complete such analyses, as there is evidence that little change in CSF biomarkers can be measured over relatively short intervals such as those included in this study (Vemuri et al., 2010). This is particularly notable for $A\beta_{42}$, as change in this CSF biomarker has not been significantly associated with annual decline in cognitive and functional scores in MCI and AD groups despite evidence of clear cognitive and functional decline (Vemuri et al., 2010), leading some to propose that CSF load is nearly disconnected from the disease stage (Caroli & Frisoni, 2010). Finally, the sample size varied across the diagnostic subgroups, with nearly twice as many subjects in the MCI sample relative to the NC and AD subgroups. This limits the extent to which we can make conclusions regarding the significance or lack thereof of effects across subgroups. Again, this is why we chose to focus primarily on the results collapsed across groups.

In summary, the current results provide at least partial support for the Jack et al. (2010) dynamic biomarker model, although the current analyses alone are insufficient to fully test this model. Results suggest that there may be an early affect of amyloid in the Alzheimer's pathological cascade process, which appears to be most detectable in its effects on the rate of hippocampal atrophy in normal older people. Despite this early effect, amyloid does not appear to directly affect atrophy in later disease stages. Results also raise questions about how the precuneus is affected by AD since evidence of relationships between Aβ and rates of atrophy are weak. Finally, in conjunction with results from Desikan and colleagues (2011), these results highlight the importance of considering the additive effect of $A\beta_{42}$ and p-tau_{181p} in the progression of atrophy over time across the Alzheimer's disease spectrum, and provide further support of the possibility that amyloid deposition alone may be insufficient for emergence of significant morphometric changes and clinical symptoms.

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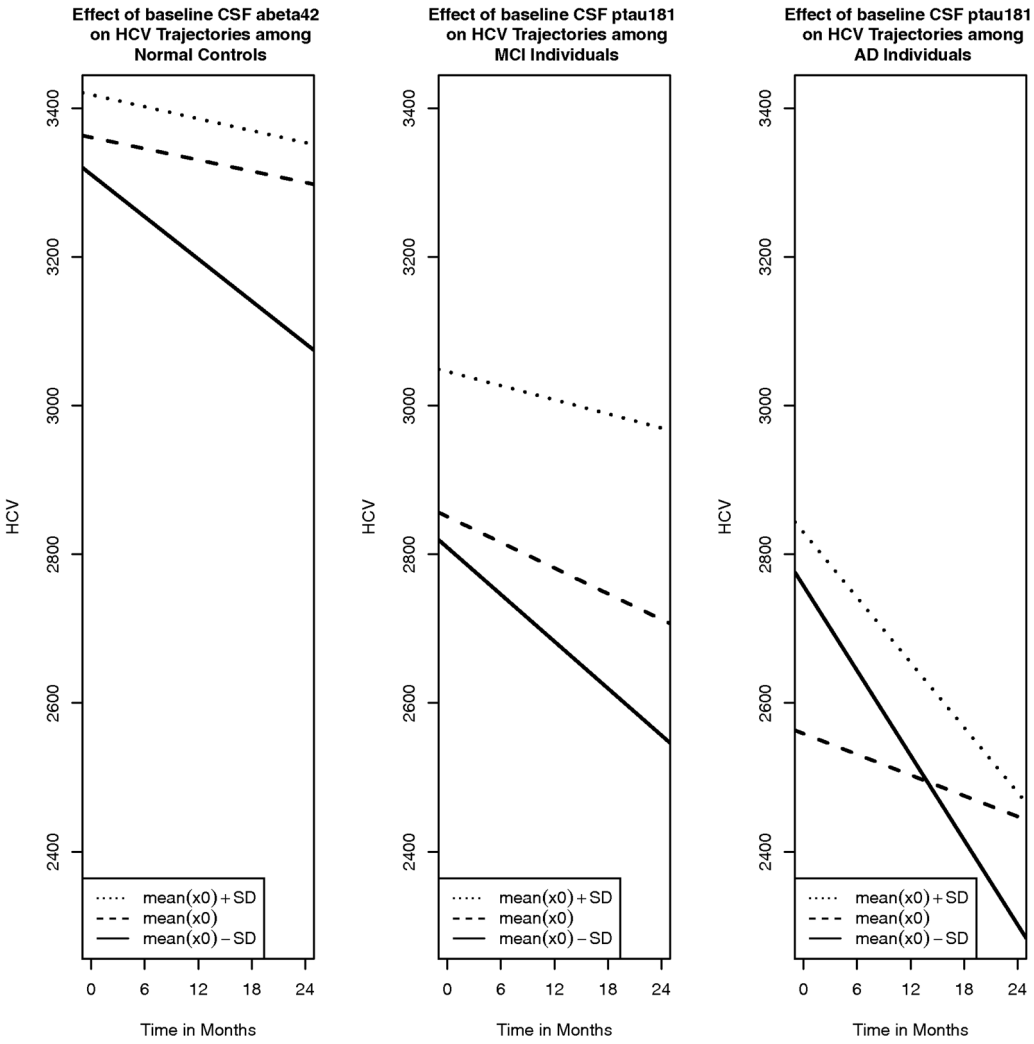

Figure 1.

Synergistic effect of CSF (P-tau$_{\mathbf{181p}}$ and Aβ_{42}) vs time on the rate of hippocampal atrophy. The plotted lines represent fitted values conditioned upon mean baseline CSF and 1SD above and below mean baseline CSF. Only interactions with an *adjusted p-value* below 0.10 are plotted.

Table 1

Baseline characteristics.

	All DX Combined N=342	Normal N=103	MCI N=163	AD N=76	Difference among DX[+]
N at each follow-up	**0/6/12/18/24 342/330/325/130/236**	**0/6/12/24 103/100/101/81**	**0/6/12/18/24 163/159/151/130/106**	**0/6/12/24 76/71/73/49**	***p-value***
Age mean (std)	74.84 (6.91)	75.52 (5.21)	74.41 (7.39)	74.86 (7.81)	0.74
Female %	40.64	46.60	35.58	43.42	0.17
Ethnicity (% Caucasian)	95.32	93.20	94.48	100.00	0.052
Years of Education: mean (std)	15.66 (2.97)	15.67(2.81)	15.86(2.96)	15.21(3.19)	0.28
Apoe4 (at least one e4 allele) %	47.95	25.24	52.15	69.74	<0.001
MMSE	26.83 (2.55)	29.07 (1.04)	26.92 (1.80)	23.59 (1.87)	<0.001
CDR-SB	1.65 (1.72)	0.02 (0.10)	1.53 (0.87)	4.11 (1.42)	<0.001
$A\beta_{42}$*	0.00 (1.00)	0.48(0.90)	−0.12(0.97)	−0.48(0.87)	<0.001
P-tau_{181p}*	0.00 (1.00)	−0.54(0.91)	0.14 (0.92)	0.48 (0.92)	<0.001
Hippocampal Volume (mm^3)	2970.06 (548.28)	3363.74 (367.42)	2880.130 (514.50)	2629.41 (513.24)	<0.001
Precuneus Thickness (mm)	4.04 (0.39)	4.23 (0.33)	4.03 (0.36)	3.83 (0.42)	<0.001
Precentral gyrus thickness (mm)	2.08 (0.21)	2.14 (0.20)	2.08 (0.21)	1.99 (0.20)	<0.001

[+] Kruskal-Wallis test for continuous variables and Pearson Chi-Square test for categorical variables; Fisher's exact test used for ethnicity due to small numbers of non-Caucasian participants.

* Normalized values using Blom's rank normalization algorithm.

Table 2

Results of Mixed Effects Models.

	ALL DX together			Normal			MCI			AD		
	coefficient	**SE**	**p-value**	**coefficient**	**SE**	**p-value**	**coefficient**	**SE**	**p-value**	**coefficient**	**SE**	**p-value**
Hippocampal Volume												
Time	−5.982	0.268	<.0001**	−4.001	0.548	<.0001**	−6.535	0.382	<.0001**	−7.172	0.758	<.0001**
$A\beta_{42}$	59.897	32.535	0.066	−56.693	46.726	0.227	70.660	44.904	0.116	23.816	65.808	0.718
P-tau$_{181p}$	−123.840	30.524	<.0001**	−58.586	42.990	0.175	−47.789	46.660	0.306	−137.410	61.365	0.027*
$A\beta_{42}$*time	0.948	0.308	0.0021**	1.135	0.547	0.040*	0.288	0.437	0.510	0.858	0.733	0.245
P-tau$_{181p}$*time	−1.545	0.308	<.0001**	−0.585	0.524	0.266	−1.454	0.465	0.0019**	−1.584	0.707	0.027*
Precuneus Thickness												
Time	−0.004	0.000	<.0001**	−0.003	0.001	<.0001**	−0.004	0.001	<.0001**	−0.008	0.001	<.0001**
$A\beta_{42}$	0.022	0.025	0.389	0.009	0.042	0.838	−0.016	0.034	0.642	0.040	0.064	0.537
P-tau$_{181p}$	−0.110	0.024	<.0001**	−0.067	0.039	0.088	−0.094	0.035	0.008*	−0.062	0.060	0.298
$A\beta_{42}$*time	0.001	0.000	0.232	0.000	0.001	0.739	0.001	0.001	0.203	−0.002	0.001	0.226
P-tau$_{181p}$*time	−0.001	0.000	0.112	0.000	0.001	0.952	−0.001	0.001	0.255	0.000	0.001	0.909
Precentral Gyrus Thickness												
Time	−0.002	0.000	<.0001**	−0.002	0.000	<.0001**	−0.002	0.000	<.0001**	−0.003	0.001	0.002**
$A\beta_{42}$	0.007	0.013	0.591	−0.022	0.023	0.343	0.002	0.018	0.933	0.020	0.029	0.477
P-tau$_{181p}$	−0.026	0.012	0.035*	−0.043	0.021	0.045*	−0.008	0.019	0.681	0.011	0.027	0.689
$A\beta_{42}$*time	0.000	0.000	0.955	0.001	0.000	0.237	0.000	0.000	0.876	−0.001	0.001	0.495
P-tau$_{181p}$*time	0.000	0.000	0.116	0.000	0.000	0.687	0.000	0.000	0.611	−0.001	0.001	0.056

In all models, the following variables are controlled: age at baseline, gender, and Apoe (at least having one e4 vs. none). Tau and a beta are normalized using Blom's rank normalization algorithm.

* $p < .05$

** significant at $p < 0.0042$, multiple comparison adjusted p-value.