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Cerebrospinal Fluid Biomarkers and Cerebral Atrophy in Distinct Clinical Variants of Probable Alzheimer's Disease

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Abstract

Different clinical variants of probable Alzheimer's disease (AD) share underlying plaques and tangles but show distinct atrophy patterns. We included 52 posterior cortical atrophy (PCA), 29 logopenic variant primary progressive aphasia (lvPPA), 53 early-onset (EOAD) and 42 late-onset AD (LOAD) patients, selected for abnormal CSF-Aβ_{42}, with CSF and MRI data available. Bootstrapping revealed no differences in the prevalence of abnormal CSF total-tau and phosphorylated-tau between probable AD variants (range total-tau: 84.9–92.3%, phosphorylated-tau: 79.2–93.1%, $p>0.05$). Voxel-wise linear regressions showed various relationships between lower CSF-Aβ_{42} and syndrome-specific atrophy, involving precuneus, posterior cingulate, and medial temporal lobe (MTL) in EOAD, occipital cortex and middle temporal gyrus in PCA; anterior cingulate, insular cortex and precentral gyrus (left>right) in lvPPA; and MTL, thalamus, and temporal pole in LOAD (all at $p<0.001$ uncorrected). In contrast, CSF-tau was not related to gray matter atrophy in any group. Our findings suggest that lower CSF-Aβ_{42} – and not increased total-tau and phosphorylated-tau – relates to reduced gray matter volumes, mostly in regions that are typically atrophied in distinct clinical variants of probable AD.

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Keywords

Alzheimer's disease; cerebrospinal fluid; magnetic resonance imaging; amyloid; tau; atrophy

1. INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that can present with a variety of clinical manifestations. Patients with late-onset AD (LOAD, defined as age-at-onset ≥65 years in most studies) typically present with memory deficits, while early-onset AD (EOAD, <65 years) patients show more impaired attention, language, visuo-spatial abilities and executive functions (Koedam, et al., 2010, Koss, et al., 1996, Smits, et al., 2012, Stopford, et al., 2008). AD can also present with focal non-amnestic syndromes, including posterior cortical atrophy (PCA) affects occipital, parietal and occipitotemporal cortices and is clinically characterized by predominant visuo-spatial and visuo-perceptive deficits (Benson, et al., 1988, Crutch, et al., 2012). Logopenic variant primary progressive aphasia (lvPPA) is associated with brain atrophy in the language-dominant left hemisphere resulting in a progressive language disorder (Gorno-Tempini, et al., 2008, Mesulam, et al., 2008). PCA and lvPPA usually manifest at a young age and are caused by AD pathology (i.e. amyloid-beta (Aβ) plaques and neurofibrillary tangles) in the majority of patients (Galton, et al., 2000, Mesulam, et al., 2014, Renner, et al., 2004). Due to their atypical, non-amnestic presentation, they may pose clinicians with great diagnostic dilemmas. In the past decades, several pathophysiological and neurodegenerative biomarkers, including $A\beta_{42}$, total-tau (t-tau) and phosphorylated-tau (p-tau) concentrations in cerebrospinal fluid (CSF) (Blennow, et al., 2010, Schoonenboom, et al., 2012), have been developed to support the clinical diagnosis of AD.

Previous studies on CSF biomarkers in distinct clinical variants of probable AD have shown that CSF $A\beta_{42}$ levels are reduced (reflecting greater amyloid burden) independent of phenotype (Baumann, et al., 2010, Bouwman, et al., 2009, Coppi, et al., 2014, de Souza, et al., 2011a, de Souza, et al., 2011b, Magnin, et al., 2014, Santangelo, et al., 2014, Seguin, et al., 2011, Teng, et al., 2014). In contrast, for CSF t-tau and p-tau results have shown discrepancies between studies. Some studies have found comparable t-tau and p-tau levels between amnestic AD and PCA (Baumann, et al., 2010, Coppi, et al., 2014, de Souza, et al., 2011a, de Souza, et al., 2011b, Seguin, et al., 2011), amnestic AD and lvPPA (Santangelo, et al., 2014, Teng, et al., 2014), and between EOAD and LOAD (Bouwman, et al., 2009). One study found lower CSF t-tau and p-tau levels in PCA than in lvPPA and amnestic AD (Teng, et al., 2014) and another study found higher CSF t-tau and p-tau levels in lvPPA compared to amnestic AD (Magnin, et al., 2014). In general, sample sizes of these studies have been small, included only two or three different clinical variants of probable AD and did not always select for patients with abnormal CSF biomarker profiles.

CSF t-tau and p-tau are believed to reflect axonal neurodegeneration and tangle pathology (Blennow, et al., 2010), and have been associated with greater rates of atrophy in AD patients (Hampel, et al., 2005, Henneman, et al., 2009). CSF tau is thus associated with neurodegeneration in AD, but in other conditions that involve massive neurodegeneration,

such as frontotemporal dementia, CSF tau is not elevated consistently (Blennow, et al., 2010, Scherling, et al., 2014, Schoonenboom, et al., 2012). One possible explanation is that the likelihood of tau spill-in into CSF is related to the site of neurodegeneration and its proximity to the ventricular space (e.g. medial temporal lobes versus neocortex (Murray et al., 2011)). To the best of our knowledge, no study has investigated the relationships between CSF biomarkers and patterns of brain atrophy at a voxelwise level across multiple probable AD variants. In this study, we aimed to determine the prevalence of abnormal CSF biomarkers and their relationships to brain atrophy in LOAD, EOAD, PCA and lvPPA patients. We hypothesized that 1) t-tau and p-tau CSF biomarkers would be comparable across probable AD variants, and 2) t-tau and p-tau, and not $A\beta_{42}$, would be associated with syndrome-specific patterns of brain atrophy.

2. METHODS

2.1 Participants

A total of 176 AD patients were included from the Amsterdam Dementia Cohort (van der Flier, et al., 2014). All patients underwent standard dementia screening that included a medical history and physical examination, a structured caregiver interview, brain MRI and neuropsychological testing. Clinical diagnosis was established by consensus in a multidisciplinary team. All patients fulfilled National Institute on Ageing-Alzheimer's Association (NIA-AA) criteria for probable AD (McKhann, et al., 2011) or mild cognitive impairment (MCI) due to AD (Albert, et al., 2011), with at least intermediate likelihood due to reduced $A\beta_{42}$ levels in CSF (see below). Patients with PCA and lvPPA additionally met specific diagnostic criteria for PCA (Mendez, et al., 2002, Tang-Wai, et al., 2004) or lvPPA (Gorno-Tempini, et al., 2011). We included all PCA and lvPPA patients in the VUMC database with available CSF and MRI data. Next, AD patients that did not meet criteria for PCA or lvPPA were categorized as EOAD (defined as <65 years at time of diagnosis) or LOAD (defined as (≥65 years at time of diagnosis). 53 EOAD patients were selected from a larger pool based on matching criteria (i.e. age, sex, disease severity (CDR and MMSE) and MRI scanner type) to the PCA and lvPPA patients. Similar matching criteria – except for age – were applied to select 42 LOAD patients. LOAD patients had predominantly memory presentations, while EOAD patients were also memory-predominant but showed more diffuse cortical symptoms in addition to their memory deficits. Informed consent was obtained from all subjects or their assigned surrogate decision-makers, and the VUMC institutional review board for human research approved the study.

2.2 Cerebrospinal Fluid Biochemical Analysis

CSF was obtained by lumbar puncture during dementia screening using a 25-gauge needle and collected in 10-mL polypropylene tubes (Sarstedt, Nümbrecht, Germany). Part of the CSF was used for routine analysis including leukocyte count, erythrocyte count, glucose concentration, and total protein concentration. Within two hours, the remaining CSF was centrifuged at 1800g for 10 minutes at 4°C, transferred to new polypropylene tubes, and stored at −20°C until biomarker analysis (within 2 months). $A\beta_{42}$, total tau (t-tau), and phosphorylated tau (p-tau) were measured with commercially available ELISAs (Innotest β-amyloid$_{(1–42)}$, Innotest hTAU-Ag and Innotest Phosphotau$_{(181P)}$, respectively; Innogenetics,

Ghent, Belgium) on a routine basis as described before (Mulder, et al., 2010). Only patients with a high likelihood of harboring amyloid pathology were included since we aimed to study patients with underlying AD pathology and a small proportion of PCA and lvPPA clinical syndromes are caused by non-AD pathologies (Crutch, et al., 2012). We used a threshold of CSF $A\beta_{42}$ <640 ng/L that showed excellent correspondence with global [^{11}C]PIB PET binding in VUMC patients (Zwan, et al., 2014). This threshold is similar to a recent independent PET-CSF study (cut-off: <647 ng/L), in which there was also excellent agreement between amyloid PET positivity and reduced CSF $A\beta_{42}$ (Palmqvist, et al., 2014).

2.3 Structural MRI Image Acquisition

Structural MRI scans were performed on a 1T (Magnetom Impact, Siemens, n=21; 8 EOAD, 7 PCA, 3 lvPPA and 3 LOAD), 1.5T (Sonata, Siemens, n=34; 10 EOAD, 10 PCA, 7 lvPPA and 7 LOAD) or 3T (SignaHDxt, GE Healtcare, n=121; 35 EOAD, 35 PCA, 19 lvPPA and 32 LOAD) unit. Acquisition parameters have been published previously (Moller, et al., 2013, Ossenkoppele, et al., 2012, Sluimer, et al., 2008). The proportion of patients scanned on each scanner was balanced across the groups and all statistical models included scanner type as nuisance variable. MRI acquisition and lumbar puncture were performed on the same day in the majority of patients (151/176, median=0, range: 0–6 months).

2.4 Structural MRI Imaging Data Processing and Analysis

MRI data were segmented using the New Segment toolbox implemented in the Statistical Parametric Mapping (SPM) 8 software (Wellcome Trust Centre for Neuroimaging, Institute of Neurology at University College London). DARTEL was used to generate a study-specific template by aligning the gray matter (GM) images non-linearly to a common space (Ashburner, 2007). Native GM and white matter (GM) images were spatially normalized to the DARTEL template using individual flow fields (modulation was applied to preserve the total amount of signal). Images were smoothed using a 8mm full width at half maximum (FWHM) isotropic Gaussian kernel. Images were inspected visually after each step in the processing pipeline and the final smoothed-modulated-warped GM images were checked for sample homogeneity using the VBM8 toolbox to identify potential outliers. Finally, we created implicit masks thresholded at GM volumes between 0.05–0.3 (at 0.05 steps), visually assessed how each of these masks overlaid on the study specific gray matter template, and finally selected an implicit mask thresholded at 0.1 as the best fit. This implicit mask was used for statistical analysis and provided the optimal balance between noise reduction and preservation of actual GM.

2.5 Statistical Analysis

Differences between groups for baseline characteristics were assessed using ANOVA with post hoc Bonferroni tests for continuous variables, X^2 tests for dichotomous data and Kruskal-Wallis tests for ordinal data. Further statistical analysis was divided into three steps. First, we investigated whether the prevalence of abnormal CSF biomarkers (t-tau and p-tau) differed among probable AD variants. $A\beta_{42}$ and tau/$A\beta_{42}$ ratios were not tested as CSF $A\beta_{42}$ was used as an inclusion criterion. We used a priori cutoffs (t-tau >375 ng/L and p-tau >52 ng/L) defined previously for clinical practice at VU University Medical Center Amsterdam

(Mulder, et al., 2010). For each biomarker and pair of probable AD variants, we calculated a 95% confidence interval (CI) by non-parametric bootstrapping for the difference in frequency of abnormal CSF biomarkers between the two diagnoses, using R version 3.0.2 (R Foundation for Statistical Computing, 2012). If the 95% CI did include zero, we concluded that the prevalence of abnormal CSF biomarkers did not differ for the probable AD variants. Note that we did not perform this comparison for CSF $A\beta_{42}$, since subjects with normal CSF $A\beta_{42}$ levels were already excluded. Second, a combined CSF-MRI analysis was performed using SPM8 software, where we tested for associations between CSF biomarkers and brain atrophy using voxel-based morphometry. We applied 3 linear regression models within each probable AD variant, using one CSF biomarker at the time ($A\beta_{42}$, t-tau, or p-tau as continuous variables) as independent variable and whole-brain gray matter volumes as dependent variable. The models further included age, sex, total intracranial volume and scanner type as nuisance variables. The statistical threshold was set at $p<0.001$, uncorrected for multiple comparisons. Third, for each probable AD variant we masked the cluster with the greatest T-value derived by the previous analysis, and calculated the mean gray matter probability within this cluster using the Marsbar ROI toolbox implemented in SPM8. We then performed linear regressions between CSF $A\beta_{42}$ levels and the mean GM probability within each cluster, and calculated both unadjusted bivariate and adjusted (for age, sex, TIV and MRI scanner type) multivariate standardized correlation coefficients (expressed as standardized β) using R version 3.0.2.

3. RESULTS

3.1 Subjects

Demographic and clinical characteristics of 52 PCA, 29 lvPPA, 53 EOAD and 42 LOAD patients are presented in Table-1. On average, patients showed mild disease severity (mean MMSE: 22.0±4.1, mean CDR: 0.8±0.2), and LOAD and lvPPA patients older than PCA and EOAD patients. There were no other significant differences between the groups. Specifically, mean $A\beta_{42}$, t-tau and p-tau levels in CSF did not differ across groups.

3.2 Prevalence of Abnormal CSF T-tau and P-tau Biomarkers

Next, we tested whether the prevalence of abnormal CSF t-tau and p-tau biomarkers (as defined by the a priori thresholds) varied between different variants of probable AD. In general, the CSF biomarker levels were comparable across the AD variants (Table-1). The only exception was that p-tau concentrations in the EOAD group were less often abnormal, although the differences were not statistically significant. Figure 1 represents boxplots of t-tau and p-tau for each probable AD variant.

3.3 Associations Between CSF biomarkers and Cerebral Atrophy

3.3.1 CSF $A\beta_{42}$—Voxelwise linear regression models with adjustment for age, sex, TIV and scanner type showed several relationships between reduced $A\beta_{42}$ levels in CSF and reduced gray matter volumes on MRI, mostly in regions that are typically atrophied in the distinct clinical of probable AD. In EOAD, lower $A\beta_{42}$ was associated with significant clusters in bilateral precuneus, posterior cingulate cortex and right hippocampus and amygdala (Figure-2A). PCA patients showed significant associations between decreased

$A\beta_{42}$ and reduced gray matter volumes in left fusiform and lingual gyri, bilateral lateral occipital cortex and left middle temporal gyrus (Figure-2B). In lvPPA, there was a positive relationship between CSF $A\beta_{42}$ and gray matter volumes in the anterior cingulate cortex (left more than right), left insular cortex and left precentral gyrus (Figure-2C). Finally, in LOAD patients lower $A\beta_{42}$ related to reduced gray matter volumes in left thalamus, and right hippocampus, amygdala and temporal pole (Figure-2D). None of those clusters survived family-wise error correction, and analyses with all AD probable variants together did not yield any significant clusters at $p<0.001$, uncorrected. Adjusting for disease severity by (additionally) entering CDR as a nuisance variable did essentially not change the results (data not shown). Figure-3 illustrates for each AD variant the relationship between CSF $A\beta_{42}$ and mean gray matter probability within the cluster showing the highest T-values in the previous analysis. Linear regression models yielded the following standardized correlation coefficients ± standard error: $\beta=0.34\pm0.08$ (unadjusted bivariate analysis) and $\beta=0.61\pm0.07$ (adjusted (for age, sex, TIV and MRI scanner type) multivariate analysis) in posterior cingulate for EOAD, $\beta=0.41\pm0.08$ and $\beta=0.85\pm0.05$ in lateral occipital cortex for PCA, $\beta=0.35\pm0.02$ and $\beta=0.77\pm0.02$ in precentral gyrus for lvPPA, and $\beta=0.29\pm0.04$ and $\beta=0.84\pm0.02$ in medial temporal lobe for LOAD.

3.3.2 CSF t-tau and p-tau—Linear regressions with t-tau and p-tau as independent variables did not reveal significant relationships with cerebral atrophy in any of the clinical variants of probable AD at $p<0.001$, uncorrected.

4. DISCUSSION

In the present study we investigated the prevalence of abnormal t-tau and p-tau concentrations in CSF of patients with LOAD, EOAD, PCA and lvPPA, and the relationships between CSF $A\beta_{42}$, t-tau and p-tau and cerebral atrophy patterns within these probable AD variants. We found that overall CSF biomarker levels were comparable across probable AD variants and CSF t-tau and p-tau showed similar sensitivity in clinical phenotypes of Alzheimer's disease according to a priori defined thresholds. Voxel-based morphometry showed relationships between lower $A\beta_{42}$ concentrations and reduced gray matter volume, mostly in regions that correspond to the symptomatology of the distinct probable AD variants. We conclude that CSF t-tau and p-tau biomarkers do not distinguish various clinical phenotypes of AD. Contrary to our expectations, in this sample of mild AD patients with biomarker evidence of amyloid pathology, lower CSF $A\beta_{42}$ levels - and not t-tau and p-tau - were associated with brain atrophy in patterns typically observed in distinct clinical phenotypes. We speculate that lower CSF $A\beta_{42}$, even within the pathological range, represents a more advanced neurobiological disease stage associated with greater syndrome-specific neurodegeneration.

A remarkable and unexpected finding of this study was that within probable AD variants, CSF $A\beta_{42}$ - and not t-tau or p-tau – related to brain atrophy in syndrome-specific patterns described in previous MRI studies on EOAD, PCA, LOAD and to a lesser extent lvPPA (Frisoni, et al., 2007, Lehmann, et al., 2012, Migliaccio, et al., 2009, Moller, et al., 2013, Ridgway, et al., 2012, Rogalski, et al., 2014). We know from neuropathological and amyloid PET studies that Aβ deposits in a relatively diffuse and symmetric fashion throughout the

neocortex (Braak and Braak, 1991, Klunk, et al., 2004), even in focal syndromes such as PCA and lvPPA (Lehmann, et al., 2013, Rosenbloom, et al., 2011). Furthermore, Aβ pathology shows only modest associations with the extent of neurodegeneration, particularly in the very earliest and latest stages of AD (Bateman, et al., 2012, Benzinger, et al., 2013, Ossenkoppele, et al., 2012). Consequently, it has been proposed that Aβ pathology is not a driver of the disease but exerts its effects by facilitating other pathogenic processes (especially spread of tau pathology) that lead to neuronal dysfunction and brain atrophy (Jack and Holtzman, 2013). Several biomarker studies have suggested that Aβ continues to accumulate over time in the MCI and early stage of AD dementia (Ossenkoppele, et al., 2011, Rinne, et al., 2010, Villain, et al., 2012, Villemagne, et al., 2011). This suggests that even within the pathological range, there is still considerable variability in early disease stages. Reduced CSF $A\beta_{42}$ concentrations in the current study may thus be reflective of a more advanced neurobiological disease stage, explaining why lower $A\beta_{42}$ correlated with greater brain atrophy. The fact that lower $A\beta_{42}$ was associated with syndrome-specific atrophy patterns further supports this notion. It is conceivable that these relationships are best captured within early clinical stages, as exemplified by patients in the present study, when Aβ deposition and brain atrophy may show dynamic changes at the same time (Jack and Holtzman, 2013).

Animal and post-mortem studies have consistently linked tau pathology to neurodegeneration and disease severity (Nelson, et al., 2012, Spires-Jones and Hyman, 2014). Furthermore, the regional distribution of tau mirrors clinical symptoms and neurodegenerative patterns in various probable AD variants (Johnson, et al., 1999, Mesulam, et al., 2014, Ossenkoppele, et al., 2014, Renner, et al., 2004, Tang-Wai, et al., 2004). Contrary to our hypothesis, however, increased t-tau and p-tau concentrations did not correlate with gray matter reductions in any of the clinical variants. A potential explanation is that CSF t-tau and p-tau may reflect processes that are not specific to AD. For instance, CSF t-tau concentrations increase rapidly in the face of acute lesions associated with Creutzfeld-Jacob disease (Skillback, et al., 2014), stroke (Hesse, et al., 2001) or traumatic brain injury (Ost, et al., 2006). Neurofibrillary tangle pathology is typically absent in those conditions, suggesting that CSF t-tau indicates axonal degeneration in general. CSF p-tau levels, on the other hand, have been proposed to reflect tangle load since CSF p-tau is increased primarily in AD and not in most non-AD dementias (Blennow, et al., 2010). However, the relationship between CSF p-tau and tangle burden has been non-existent or weak in neuropathological studies (Buerger, et al., 2006, Engelborghs, et al., 2007). The aforementioned studies suggest that more rapid cell death could result in increased release of tau proteins in CSF. CSF tau concentrations may therefore be a derivative of the rate of cerebral atrophy, rather than reflecting the current state of the brain. This is in line with previous biomarker studies showing that CSF tau is a better predictor for disease progression than for baseline brain atrophy or cognition (Kester, et al., 2009, Tosun, et al., 2011, van der Vlies, et al., 2009).

In line with previous studies (Baumann, et al., 2010, Bouwman, et al., 2009, Coppi, et al., 2014, de Souza, et al., 2011a, de Souza, et al., 2011b, Magnin, et al., 2014, Santangelo, et al., 2014, Seguin, et al., 2011, Teng, et al., 2014), we found that CSF $A\beta_{42}$ concentrations were similar across clinical variants of probable AD, although we narrowed the dynamic

range by including only patients within the pathological range for Aβ. Discrepant findings for t-tau and p-tau in probable AD variants have been reported previously (Baumann, et al., 2010, Bouwman, et al., 2009, Coppi, et al., 2014, de Souza, et al., 2011a, de Souza, et al., 2011b, Magnin, et al., 2014, Santangelo, et al., 2014, Seguin, et al., 2011, Teng, et al., 2014), but in this relatively large study we observed comparable CSF levels in all probable AD variants and the prevalence of abnormal t-tau and p-tau concentrations was essentially the same across AD phenotypes. This is an important finding as CSF biomarkers have been incorporated in research criteria for AD and are increasingly used in clinical practice (Duits, et al., 2014, Mattsson, et al., 2012). Currently there exist two different biomarker informed sets of criteria for AD: the NIA-AA criteria (McKhann, et al., 2011) and the International Working Group-2 (IWG-2) criteria (Dubois, et al., 2014). Both NIA-AA and IWG-2 discuss different subtypes of AD, but neither proposes differential usage of CSF biomarkers to diagnose AD based on the clinical phenotype. While IWG-2 requires the presence of reduced CSF $A\beta_{42}$ in combination with increased t-tau or p-tau (or a positive amyloid PET scan or the presence of an autosomal dominant mutation) for a diagnosis of AD dementia, NIA-AA proposes that the likelihood of underlying AD pathology contributing to the clinical presentation can be high (when both CSF $A\beta_{42}$ and tau are positive) or intermediate (when either CSF $A\beta_{42}$ or tau is positive). Our observation that CSF t-tau and p-tau are equally useful in all clinical phenotypes is thus compatible with both NIA-AA and IWG-2.

The strength of this study is the relatively large sample size, encompassing various clinical variants of probable AD. There are also some limitations. First, CSF samples were analyzed continuously in clinical practice rather than in one single run. This may introduce variability in biomarker levels, both due to factors related to analytical procedures and to the analytical kits used for measurements (Mattsson, et al., 2013). Because of this, the VUMC neurochemistry laboratory has implemented an elaborate quality control system in order to minimize this variability and acts as reference laboratory for the Netherlands. Second, we did not examine diagnostic sensitivity for CSF $A\beta_{42}$ concentrations or tau/$A\beta_{42}$ ratios, since we excluded patients with negative $A\beta_{42}$ markers to reduce the possibility of clinical misdiagnosis in EOAD and LOAD (Ossenkoppele, et al., 2013, Sanchez-Juan, et al., 2014) and to rule out the small proportion of PCA and lvPPA clinical syndromes that are caused by non-Aβ pathologies (Crutch, et al., 2012). This approach seems justified, as previous studies did not detect differences in CSF $A\beta_{42}$ between AD variants (Baumann, et al., 2010, Bouwman, et al., 2009, Coppi, et al., 2014, de Souza, et al., 2011a, de Souza, et al., 2011b, Magnin, et al., 2014, Santangelo, et al., 2014, Seguin, et al., 2011, Teng, et al., 2014), so we could focus on the less established diagnostic performance of t-tau and p-tau. Third, we used three different MRI scanner types. We adjusted for this by entering scanner type as a covariate in all imaging regression analyses. Fourth, although the clinical diagnosis of AD was supported by CSF $A\beta_{42}$ biomarkers, the presence of non-AD pathologies can not be excluded as autopsy data are not available. CSF $A\beta_{42}$ may be specific to amyloid pathology, it is not specific to AD as (comorbid) amyloid pathology can be present in other neurodegenerative diseases. Finally, our voxelwise regressions were performed using a liberal threshold ($p<0.001$ uncorrected) and did not survive conservative family-wise error correction for multiple comparisons. This may have induced a false positive finding in the lvPPA group, showing a less plausible atrophy pattern compared to PCA, EOAD and

LOAD. On the other hand, the lvPPA patients showed - in line with the literature (Ridgway, et al., 2012, Rogalski, et al., 2014) – left hemispheric predominant atrophy, and the most severely affected regions (i.e. left insula and anterior cingulate) were also identified in a longitudinal study (Rohrer, et al., 2013).

5. CONCLUSIONS

In this group of probable AD patients who were are all likely to harbor cerebral amyloid pathology as determined by reduced CSF $A\beta_{42}$ levels, we found that the prevalence of abnormal CSF t-tau and p-tau biomarkers was comparable across all clinical probable AD variants. We also found that CSF $A\beta_{42}$, but not CSF t-tau or p-tau, was related to regional atrophy in patterns largely corresponding to symptomatology in the different syndromes. This suggests that decreased CSF $A\beta_{42}$, even after crossing the cut-off for amyloid-positivity, represents a more advanced neurobiological disease stage associated with greater syndrome-specific neurodegeneration in distinct variants of probable AD.

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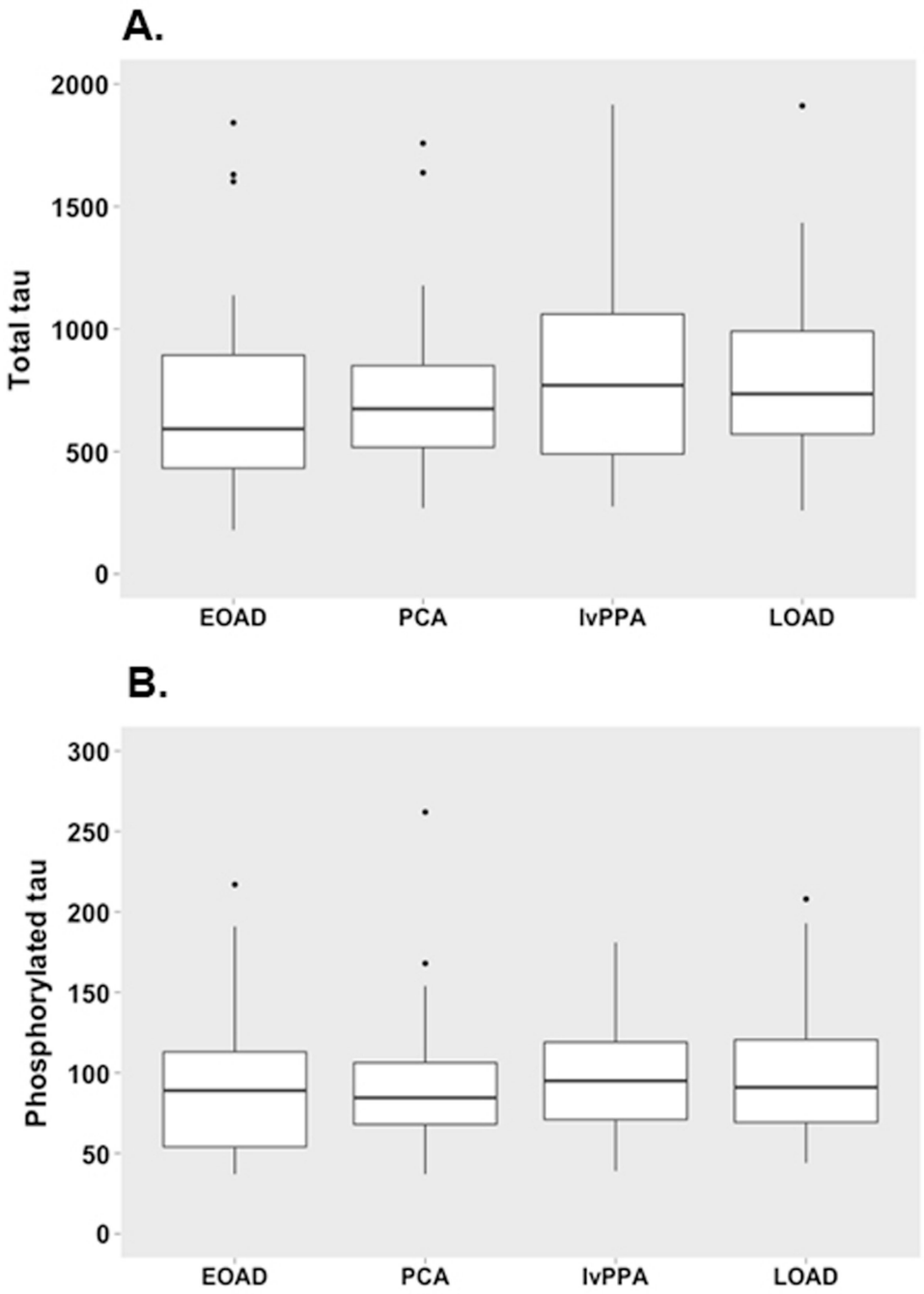

FIGURE 1.

Boxplots for CSF total tau (A) and phosphorylated tau (B) levels (ng/L) for each AD variant. ANOVA with post-hoc Bonferroni tests revealed no differences between groups.

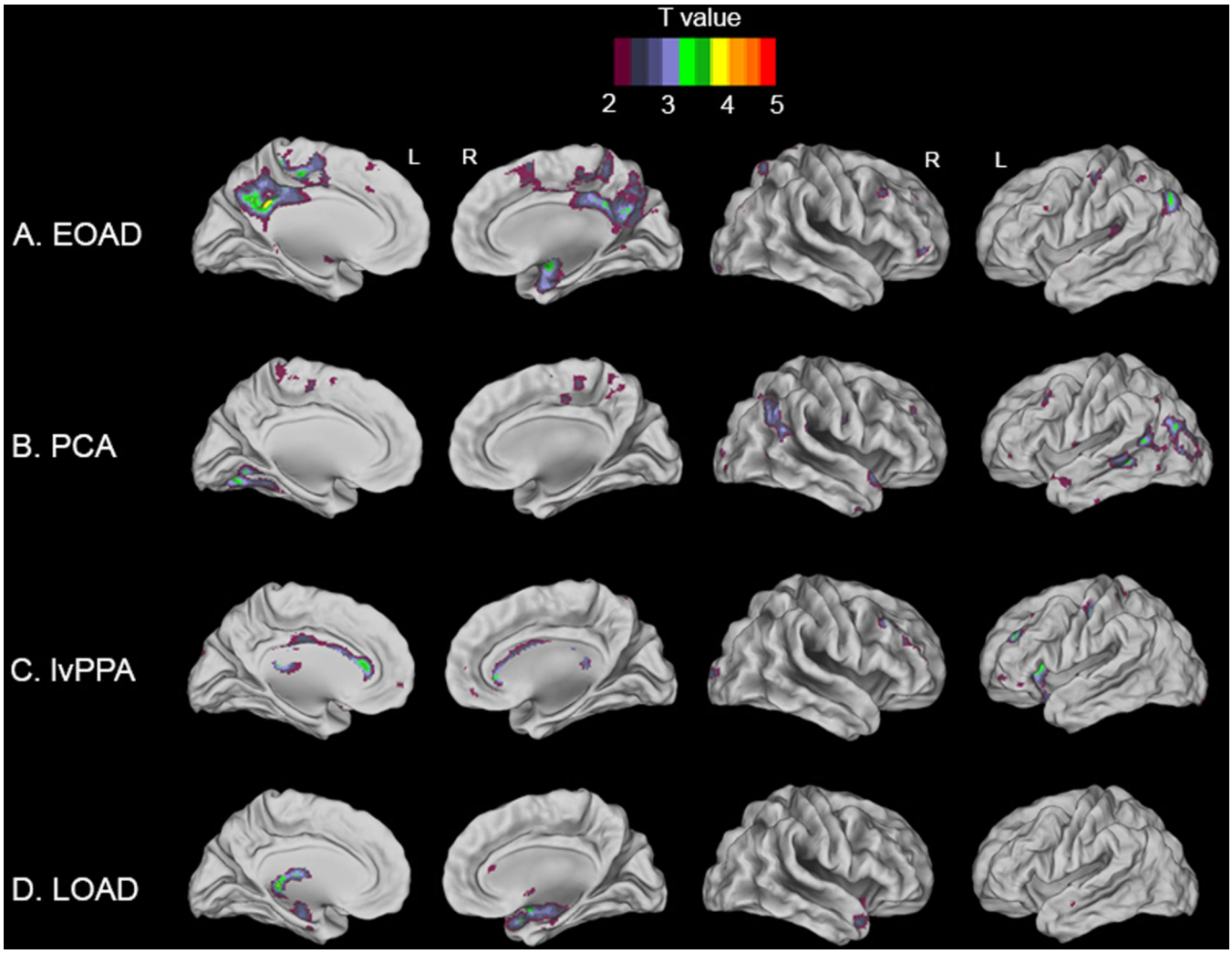

FIGURE 2.

Voxelwise linear regression analyses between CSF $A\beta_{42}$ and gray matter volume on MRI in early-onset AD (A), posterior cortical atrophy (B), logopenic variant primary progressive aphasia (C) and late-onset AD (D). T-maps are superimposed on a brain template implemented in Caret software, ranging from 2 to 5 for visualization purposes (T values of 3.27 for EOAD, 3.28 for PCA, 3.48 for lvPPA and 3.33 for LOAD correspond to the $p<0.001$ threshold; In the text only the significant regions have been reported).

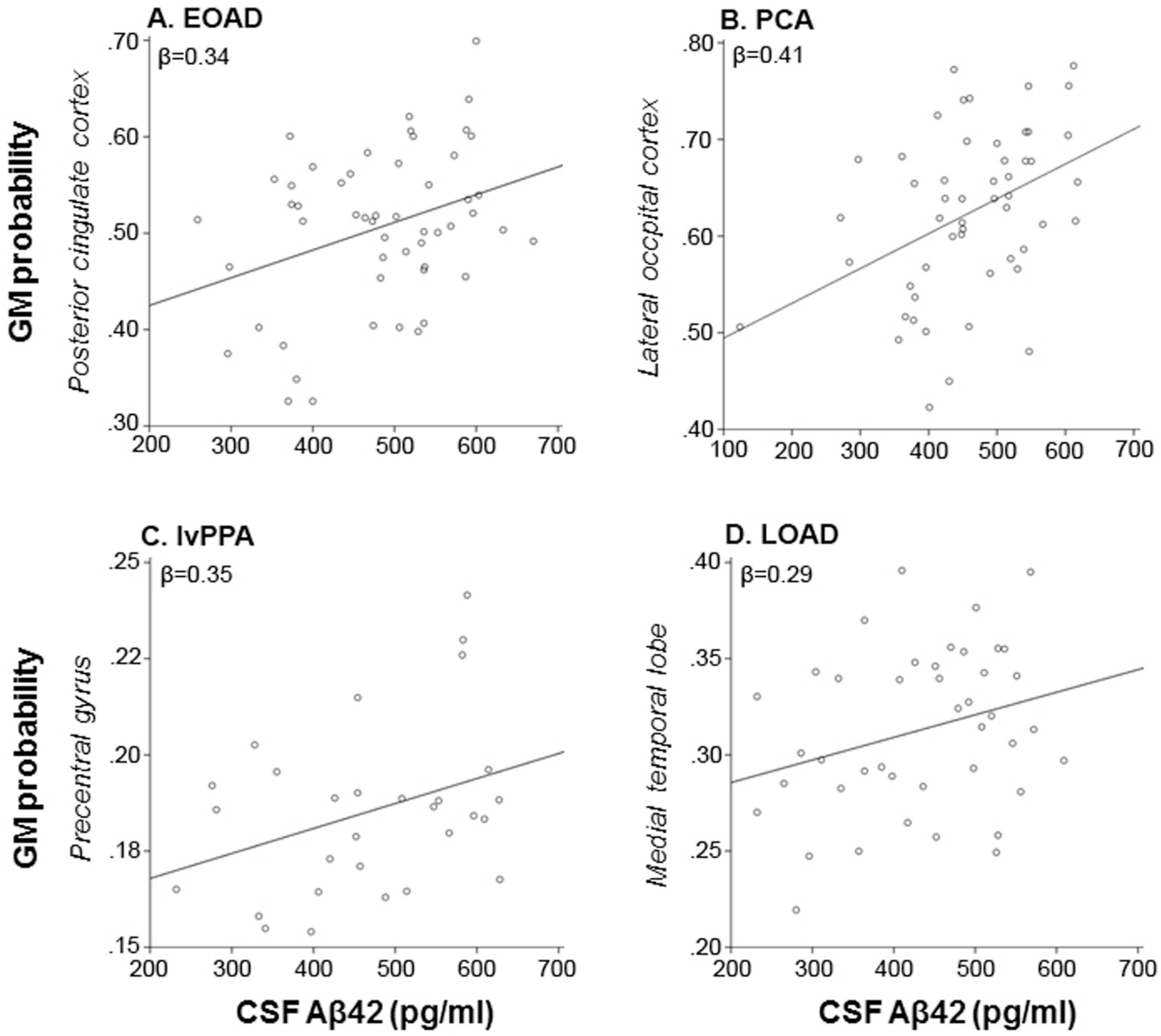

FIGURE 3.

Scatterplots for each probable AD variant of CSF $A\beta_{42}$ and gray matter probability in the cluster with the greatest T-value: Posterior cingulate cortex for EOAD (A), lateral occipital cortex for PCA (B), precentral gyrus for lvPPA (C), and medial temporal lobe for LOAD (D).

TABLE 1

Demographic and clinical characteristics according to AD phenotype

	EOAD	PCA	lvPPA	LOAD
N	53	52	29	42
Age	61.5±4.4	62.6±7.6	67.0±7.7[a]	75.8±3.0[b]
Sex (% male)	55.2	58.5	59.5	51.9
Education*	5.3±1.0	5.0±1.1	4.7±1.5	4.9±1.3
MMSE	21.5±5.4	22.2±3.4	21.8±4.3	22.1±3.9
CDR	0.7±0.3	0.8±0.2	0.9±0.2	0.8±0.2
TIV (L)	1.56±0.13	1.57±0.14	1.61±0.14	1.57±0.14
CSF $A\beta_{42}$(ng/L)**	480±90	459±98	469±117	433±103
CSF Total tau (ng/L)	695±358	728±309	788±376	785±336
% CSF total tau >375	84.9	92.3	85.7	90.5
CSF Phospho tau (ng/L)	92±40	93±38	96±34	97±39
% CSF phospho tau >52	79.2	90.4	93.1	90.5

Abbreviations: PCA = Posterior cortical atrophy; lvPPA = Logopenic variant primary progressive aphasia; EOAD = Early-onset Alzheimer's disease; LOAD = Late-onset Alzheimer's disease; MMSE = Mini-mental state examination; CDR = Clinical dementia rating scale; TIV = Total intracranial volume.

Data are presented as mean ± SD unless otherwise stated. Differences between groups were analyzed using ANOVA with post-hoc Bonferroni tests (age, MMSE, CDR, TIV, CSF), X^2 tests (sex), Kruskal-Wallis with post-hoc Mann-Whitney U-tests (education) and bootstrapping (% of suprathreshold CSF concentrations).

* using Verhage's classification (scale 1–7(Verhage, 1964)),

** Only patients with CSF $A\beta_{42}$ <640 were included,

[a] lvPPA > PCA & EOAD, p<0.01;

[b] LOAD > all other groups, p<0.001.