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Brief communication

## CSF tau markers are correlated with hippocampal volume in Alzheimer's disease

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### Abstract

Hippocampal atrophy as assessed by magnetic resonance imaging (MRI) and abnormal cerebrospinal fluid (CSF) biomarkers are supportive features for the diagnosis of Alzheimer's disease (AD) and are assumed to be indirect pathological markers of the disease. In AD patients, antemortem MRI hippocampal volumes (HVs) correlate with the density of neurofibrillary tangles (but not with senile plaques) at autopsy suggesting that HVs may better correlate with CSF tau and hyperphosphorylated tau (P-tau) levels than CSF amyloid beta protein ( $A\beta$ )<sub>42</sub> level. Here, we tested this hypothesis in a well-defined AD group. Patients were selected according to the New Research Criteria for AD, including specific episodic memory deficit and CSF AD profile (defined as abnormal ratio of  $A\beta$ <sub>42</sub>:tau). MRI was performed within 6 months of lumbar puncture. HVs were obtained using automated segmentation software. Thirty-six patients were included. Left HV correlated with CSF tau ( $R = -0.53$ ) and P-tau ( $R = -0.56$ ) levels. Mean HVs correlated with the CSF P-tau level ( $R = -0.52$ ). No correlation was found between any brain measurement and CSF  $A\beta$ <sub>42</sub> level. The CSF tau and P-tau levels, but not the CSF  $A\beta$ <sub>42</sub> level, correlated with HV, suggesting that CSF tau markers reflect the neuronal loss associated with the physiopathological process of AD. © 2011 Elsevier Inc. All rights reserved.

**Keywords:** Alzheimer's disease; CSF biomarkers; Hippocampus

### 1. Introduction

In Alzheimer's disease (AD), both hippocampal volumes (HVs) and cerebrospinal fluid (CSF) tau markers were associated with neurofibrillary tangles deposits: (1) antemortem HVs assessed by using magnetic resonance imaging

(MRI) volumetry significantly correlated with the density of neurofibrillary tangles at autopsy (Csernansky et al., 2004; Jack et al., 2002) but not with amyloid beta protein ( $A\beta$ ) plaque load (Csernansky et al., 2004), and (2) CSF tau levels correlated with the presence of neocortical neurofibrillary tangles (Tapiola et al., 2009). Therefore, levels of CSF tau and CSF hyperphosphorylated tau (P-tau) should correlate with HV. However, conflicting results have been observed in neuroimaging studies (Apostolova et al., 2010; Fagan et al., 2009; Herukka et al., 2008; Schoonenboom et al., 2008; Thomann et al., 2009) and a recent study (Fagan et al., 2009) showed no correlation between CSF biomark-

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ers and HV in AD patients. We wanted to analyze the correlations between CSF biomarkers and whole brain volume or HV in order to test the hypothesis that the levels of CSF tau and P-tau, but not CSF  $A\beta_{42}$ , are associated with hippocampal atrophy in AD patients.

## 2. Methods

### 2.1. Subjects

Patients were retrospectively recruited from the database of the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital from May 2007 to February 2010. Inclusion criteria were: (1) AD (either at prodromal or dementia stage) defined according to the New Research Criteria (Dubois et al., 2007, 2010); and (2) complete clinical and neuropsychological evaluations, brain MRI using standardized protocol and CSF marker measurements (for  $A\beta_{42}$ , total tau [T-tau], and P-tau) performed less than 6 months from 1 to another.

The New Research Criteria for AD (Dubois et al., 2007, 2010) included: (1) progressive episodic memory impairment, characterized by a low free recall not normalized with cueing; (2) CSF AD profile, defined as score below 1, calculated with the formula  $A\beta_{42}/(240 + [1.18 \times \text{T-tau}])$  (Visser et al., 2009); and (3) Clinical Dementia Rating (CDR) greater than 0. We did not include patients who presented: (1) clinical or neuroimaging evidence of focal lesions; (2) severe cortical or subcortical vascular lesions; or (3) severe depression.

All imaging and clinical data were generated during routine clinical workups of the patients in the Neurology and Neuroradiology departments and retrospectively extracted for the purpose of this study. According to French legislation, explicit informed consent was waived. However, the regulation concerning electronic filing was followed, and both patients and their relatives were informed that individual data may be used in retrospective clinical research studies.

### 2.2. Measurement of CSF biomarkers

CSF samples obtained by lumbar puncture (LP) were centrifuged for 10 minutes at 1500 rpm at 4 °C to remove cells, aliquoted into 0.4-mL polypropylene tubes, and stored at -80 °C until analysis. CSF biomarkers T-tau, tau phosphorylated at threonine 181 (P-tau), and  $A\beta_{42}$  were measured in duplicate using a double-sandwich enzyme-linked immunosorbent assay (ELISA) method (Innogenetics, Gent, Belgium) according to the manufacturer's instructions.

### 2.3. MRI acquisition

T1-weighted magnetic resonance images were acquired with standard 3-dimensional sequences (please see Supplementary data for details).

### 2.4. Automated hippocampal volumetry

Segmentation of the hippocampus was performed using an automated method, as previously described (Chupin et al., 2009). Gray matter, white matter, and whole-brain volumes (WBV) were derived from SPM5 segmentations (Wellcome Trust Centre for Neuroimaging, London, UK). HVs were adjusted for head size by correcting for total intracranial volume, derived from SPM5 segmentations.

### 2.5. Statistical analysis

All statistical analyses were performed with Statistica 5.5A (StatSoft®, Tulsa, OK, USA). Descriptive statistics were used to characterize the population. All variables tested positive for normality by the Shapiro-Wilk test. The statistical analyses were performed with parametric tests. Statistical analyses of correlations between CSF data and volumetric brain measurements were performed using Pearson correlation test and were confirmed by partial correlations controlling for age and Mini Mental State Examination (MMSE) score. The Bonferroni correction for multiple correlations was applied ( $\alpha < 0.002$ ). Only results for Pearson correlation test are presented below. Values are presented as means  $\pm$  standard deviations.

## 3. Results

Thirty-six patients were included (mean age =  $62.6 \pm 8.1$  years; Mini Mental State Examination [MMSE] score =  $19.2 \pm 6.3$ ; CDR = 0.5 for  $n = 6$  subjects, CDR = 1 for  $n = 10$ , CDR = 1.5 for  $n = 10$ , and CDR = 2 for  $n = 10$ ; please see Supplementary data for table). The mean time interval between MRI scan and LP was  $15 \pm 59$  days. All selected patients had decreased CSF  $A\beta_{42}$  concentrations ( $261 \pm 100.23$  pg/mL). Mean CSF concentrations were  $506.52 \pm 160.22$  pg/mL for T-tau (increased  $>450$  pg/mL in 23/36 patients) and  $82.42 \pm 19.59$  pg/mL for P-tau (increased  $>60$  pg/mL in 32/36 patients). There was no asymmetry between left and right mean HVs (left HV =  $2.22 \pm 0.49$  cm<sup>3</sup>; right HV =  $2.21 \pm 0.50$  cm<sup>3</sup>). The mean WBV was  $1021 \pm 140.47$  cm<sup>3</sup>.

Significant negative correlations ( $p < 0.001$ ) were found between left HV and concentrations of T-tau ( $R = -0.53$ ) and P-tau ( $R = -0.56$ ). Mean left + right HV correlated negatively with P-tau levels ( $p < 0.001$ ;  $R = -0.52$ ) (Fig. 1) but not with T-tau levels. No significant correlation was found between HV and  $A\beta_{42}$  concentration.

There was no correlation between normalized whole-brain volume and any CSF biomarker ( $A\beta_{42}$ , T-tau, or P-tau) (Table 1) or between neuroimaging parameters and CSF ratios (T-tau/ $A\beta_{42}$  or P-tau/ $A\beta_{42}$ ).

## 4. Discussion

This study explored correlations between CSF biomarkers and measurements of hippocampal atrophy in a well-

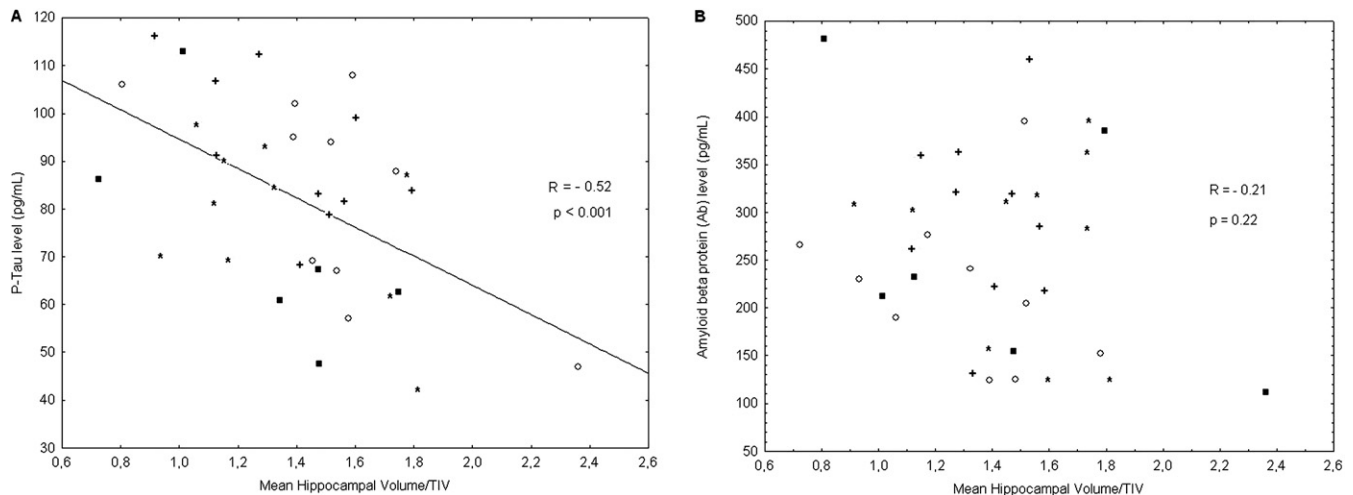


Fig. 1. Scatterplots showing the relation between normalized mean hippocampal volume and cerebrospinal fluid (CSF) hyperphosphorylated tau (P-tau) (A) and CSF amyloid beta protein ( $A\beta_{42}$ ) (B). Patients are grouped by Clinical Dementia Rating (CDR): \* CDR = 0.5; + CDR = 1; ○ CDR = 1.5; ■ CDR = 2.

defined population of AD patients (either at prodromal or dementia stage) selected according to New Research Diagnostic Criteria (Dubois et al., 2007, 2010), and had MRI and lumbar puncture performed within a short time period. Our results confirmed the hypothesis that CSF T-tau and P-tau (but not  $A\beta_{42}$ ) levels correlated with HV in AD patients. These results are in accordance with recently published data (Apostolova et al., 2010), which reported a significant correlation between HV and CSF P-tau (but not with CSF  $A\beta_{42}$  and T-tau) in a group of 95 AD patients selected according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). The reasons for the left side lateralization of correlations between HV and CSF T-tau markers and P-tau remain unclear, even though these correlations were also observed with brain perfusion on scintigraphy (Habert et al., 2010).

In contrast, previous studies of AD patients found no correlation between HV and CSF tau levels (Fagan et al.,

2009; Schoonenboom et al., 2008). This discrepancy may be due to methodological issues. Medial temporal lobe atrophy was assessed using visual estimation in one study (Schoonenboom et al., 2008). The delay between MRI and LP was long (up to 2 years) in another study (Fagan et al., 2009); brain atrophy may have progressed during this delay, and thus may have driven correlations between whole brain volume and CSF tau markers. Other studies included mixed populations of subjects with mild cognitive impairment (Herukka et al., 2008) or heterogeneous groups of patients (e.g., AD patients, normal controls, and those with age-associated cognitive decline) (Thomann et al., 2009). Therefore, the lack of correlation reported in previous studies may result from an increased variability of CSF biomarkers and HVs among normal/pathological subjects with different underlying physiopathological processes.

Our results are in accordance with previous postmortem histopathological studies that demonstrated an association between the degree of antemortem MRI hippocampal atrophy and neurofibrillary tangle burden (Jack et al., 2002) and

Table 1  
Results for correlation analyses (Pearson correlation test) between CSF biomarkers and neuroimaging variables

	CSF $A\beta_{42}$	CSF T-tau	CSF P-tau	T-tau/ $A\beta_{42}$	P-tau/ $A\beta_{42}$
Left hippocampus	$R = -0.24$ $p = 0.15$	<b><i><math>R = -0.53</math></i></b> <b><i><math>p = 0.001^a</math></i></b>	<b><i><math>R = -0.56</math></i></b> <b><i><math>p = 0.001^a</math></i></b>	$R = -0.08$ $p = 0.63$	$R = -0.004$ $p = 0.98$
Right hippocampus	$R = -0.14$ $p = 0.40$	$R = -0.31$ $p = 0.07$	$R = -0.41$ $p = 0.014$	$R = -0.02$ $p = 0.91$	$R = -0.01$ $p = 0.96$
Mean hippocampal volume	$R = -0.21$ $p = 0.22$	$R = -0.45$ $p = 0.006$	<b><i><math>R = -0.52</math></i></b> <b><i><math>p = 0.001^a</math></i></b>	$R = -0.03$ $p = 0.84$	$R = 0.003$ $p = 0.98$
Whole brain volume	$R = -0.22$ $p = 0.19$	$R = -0.03$ $p = 0.84$	$R = -0.02$ $p = 0.90$	$R = 0.16$ $p = 0.34$	$R = 0.17$ $p = 0.31$

All neuroimaging variables were normalized for total intracranial volume. Significant correlations are in bold and italics.

Key:  $A\beta$ , amyloid beta; CSF, cerebrospinal fluid; P-tau, hyperphosphorylated tau.

<sup>a</sup> Significant after Bonferroni correction ( $p < 0.002$ ).

a strong correlation between both CSF T-tau and P-tau levels and the presence of neocortical neurofibrillary tangles (Tapiola et al., 2009). Longitudinal data also showed that elevated baseline levels of CSF P-tau were associated with higher rates of hippocampal atrophy in mild cognitive impairment (MCI) (Fjell et al., 2010) and in AD patients (Hampel et al., 2005; Henneman et al., 2009). In accordance with these data, recent studies have observed that high CSF P-tau levels were predictive markers of poor clinical outcome in AD patients (Henneman et al., 2009).

CSF A $\beta_{42}$  levels did not correlate with WBV and with HV, in agreement with histopathological studies demonstrating that the rate of brain volume loss was not determined by the amount of A $\beta$  (Josephs et al., 2008), but in disagreement with longitudinal studies that found relationships between lower levels of A $\beta_{42}$  and higher rates of hippocampal and temporal atrophy in MCI patients (Fjell et al., 2010; Schuff et al., 2009). In vivo data from 11C Pittsburgh Compound B (PIB) positron emission tomography (PET) showed that amyloid load appeared early in preclinical AD patients and then remained stable over time (Jack et al., 2009; Klunk et al., 2006) and did not correlate with disease progression (Jack et al., 2009). Conflicting results have been observed on correlation analyses between measures of brain atrophy and PIB load. Some studies found correlations between PIB uptake and hippocampal atrophy in PIB-positive asymptomatic subjects (Bourgeat et al., 2010), in MCI patients (Mormino et al., 2009), and in a sample of normal controls and AD patients (Frisoni et al., 2009); or with WBV in AD patients (Archer et al., 2006). However, another study (Chételat et al., 2010) did not find any correlation between PIB-measured amyloid load and global or hippocampal gray matter volume in MCI and AD patients. These observations suggest that amyloid pathology precedes the atrophic process before the appearance of symptoms and that other pathological events such as tau pathology may also be involved in the progression of atrophy in AD.

Taken together, our results reinforce this hypothesis and support the theory that, in clinical AD, high CSF P-tau concentration reflects the process of neuronal death due to neurofibrillary tangles. The use of the New Research Criteria and the short interval between lumbar puncture and MRI may have increased the uniformity of the underlying physiopathological processes of the included patients and may therefore explain why our findings differ from recently published results (Fagan et al., 2009).

### Disclosure statement

Dr de Souza is funded by a grant from “Association France Alzheimer”. During the 2 last years, Dr de Souza has collaborated with the following pharmaceutical company: Lundbeck. During the 2 last years, Dr Chupin has collaborated with the following pharmaceutical company: EISAI.

Dr Lamari, Dr Jardel, Dr Leclercq, and Dr Colliot report no conflict of interest. During the 2 last years, Pr Lehericy has collaborated with the following pharmaceutical company: EISAI. During the 2 last years, Pr Dubois has collaborated with the following pharmaceutical companies: EISAI, Novartis, Roche, Bristol-Myers Squibb, and Servier. During the 2 last years, Dr Sarazin has collaborated with the following pharmaceutical companies: EISAI and Novartis.

According to French legislation, explicit informed consent was waived. However, the regulation concerning electronic filing was followed, and both patients and their relatives were informed that individual data may be used in retrospective clinical research studies.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.neurobiolaging.2011.02.022](https://doi.org/10.1016/j.neurobiolaging.2011.02.022).

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