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Longitudinal structural cerebral changes related to core CSF biomarkers in preclinical Alzheimer's disease: A study of two independent datasets

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ABSTRACT

Alzheimer's disease (AD) is characterized by an accumulation of β-amyloid ($A\beta_{42}$) accompanied by brain atrophy and cognitive decline. Several recent studies have shown that $A\beta_{42}$ accumulation is associated with gray matter (GM) changes prior to the development of cognitive impairment, in the so-called preclinical stage of the AD (pre-AD). It also has been proved that the GM atrophy profile is not linear, both in normal ageing but, especially, on AD. However, several other factors may influence this association and may have an impact on the generalization of results from different samples. In this work, we estimate differences in rates of GM volume change in cognitively healthy elders in association with baseline core cerebrospinal fluid (CSF) AD biomarkers, and assess to what these differences are sample dependent. We report the dependence of atrophy rates, measured in a two-year interval, on $A\beta_{42}$, computed both over continuous and categorical values of $A\beta_{42}$, at voxel-level ($p < 0.001$; $k < 100$) and corrected for sex, age and education. Analyses were performed jointly and separately, on two samples. The first sample was formed of 31 individuals (22 Ctrl and 9 pre-AD), aged 60–80 and recruited at the Hospital Clinic of Barcelona. The second sample was a replica of the first one with subjects selected from the ADNI dataset. We also investigated the dependence of the GM atrophy rate on the basal levels of continuous p-tau and on the p-tau/$A\beta_{42}$ ratio. Correlation analyses on the whole sample showed a dependence of GM atrophy rates on $A\beta_{42}$ in medial and orbital frontal, precuneus, cingulate, medial temporal regions and cerebellum. Correlations with p-tau were located in the left hippocampus, parahippocampus and striatal nuclei whereas correlation with p-tau/$A\beta_{42}$ was mainly found in ventral and medial temporal areas. Regarding analyses performed separately, we found a substantial discrepancy of results between samples, illustrating the complexities of comparing two independent datasets even when using the same inclusion criteria. Such discrepancies may lead to significant differences in the sample size needed to detect a particular reduction on cerebral atrophy rates in prevention trials. Higher cognitive reserve and more advanced pathological progression in the ADNI sample could partially account for the observed discrepancies. Taken together, our findings in these two samples highlight the importance of comparing and merging independent datasets to draw more robust and generalizable conclusions on the structural changes in the preclinical stages of AD.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that slowly progresses over decades and is characterized by progressive neuropathology, brain atrophy and, ultimately cognitive decline. The neuropathological hallmarks of AD are amyloid-β ($A\beta_{42}$) plaques and

Abbreviations: AD, Alzheimer's disease; $A\beta_{42}$, amyloid beta; p-tau, phosphorylated tau; t-tau, total tau; Ctrl, control; preAD, preclinical Alzheimer's disease; HCB, Hospital Clinic Barcelona; ADNI, Alzheimer's Disease Neuroimaging Initiative; MMSE, Mini Mental State examination; CDR, Clinical Dementia Rating; ELISA, Enzyme-Linked ImmunoSorbent Assay; VBM, voxel-based morphometry; GM, gray matter; WM, white matter; CSF, Cerebro-Spinal Fluid; PLR, pairwise longitudinal registration; DI, divergences of the longitudinal deformations; ROI, region of interest; TIV, total intracranial volume; FWE, Family Wise Error; L, left; R, right

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neurofibrillary tau tangles. Converging evidence shows that the pathophysiological process of the disease begins decades before the time of clinical diagnosis (Braak and Del Tredici, 2013; Villemagne et al., 2013). Either sampling cerebrospinal fluid (CSF) or with amyloid PET imaging (Landau et al., 2013; Tolboom et al., 2009), $A\beta_{42}$ alterations can be detected in a substantial percentage of cognitively healthy subjects (Jack et al., 2014; Morris et al., 2010). This has led to the formulation, for research purposes, of the concept of preclinical Alzheimer disease (Dubois et al., 2016; Sperling et al., 2011). While it is not yet known whether all these individuals with asymptomatic cerebral amyloidosis will eventually develop AD, there is consensus that the prognosis for amyloid-positive subjects is worse than for amyloid negative ones (Chételat et al., 2013).

By the time clinical impairment is detectable, substantial neurodegeneration has already taken place (Morris and Price, 2001). However, the relationship between $A\beta_{42}$ deposition and brain atrophy in preclinical AD is still under debate (Chételat et al., 2013; Fjell et al., 2014, 2014). In cross-sectional comparisons, amyloid positive non-demented subjects show decreased whole brain (Fagan et al., 2009) or hippocampal volumes (Bourgeat et al., 2010; Dickerson et al., 2009; Mormino et al., 2009; Storandt et al., 2009). Conversely, other studies did not found significant differences in hippocampal volume between amyloid positive and negative healthy individuals (Jack et al., 2010; Vemuri et al., 2009) but some did in parietal and posterior cingulate cortex extending into the precuneus (Becker et al., 2011), or even found increased volume in temporal regions including the hippocampus (Chételat et al., 2010) and parahippocampal areas (Gispert et al., 2015).

Longitudinal studies comparing cerebral atrophy rates have reported increased declines in whole brain, hippocampus, amygdala and posterior cingulate and in temporal parietal and frontal regions in preclinical AD (Doré et al., 2013; Insel et al., 2016; Lorenzi et al., 2015; Mattsson et al., 2014; Schott et al., 2010; Storandt et al., 2009). However, some others were unable to detect such accelerated atrophy rates (Driscoll et al., n.d.; Fotenos et al., 2008). One factor that may partially account for such discrepant results is the dichotomization of cognitively normal samples into two groups based on a threshold of amyloid abnormality. Nevertheless, studying the association between amyloid levels and atrophy rates in pooled samples of cognitively healthy subjects, again some found significant associations in the hippocampus (Andrews et al., 2013; Stricker et al., 2012) and in temporal regions (Doré et al., 2013) whereas some others did not (Driscoll et al., n.d.; Tosun et al., 2010) or the association was only evident in $A\beta_{42}$ positive subjects, after dichotomizing the sample again (Fjell et al., 2010; Schott et al., 2010). The longitudinal evolution of GM volume has been proved to be non-linear (Fjell et al., 2014, 2014; Gispert et al., 2015) so the atrophy rate is non constant over-time neither along disease progress. It is still unclear which factors affect, a part from age and gender, the GM atrophy rate progression in cognitively healthy subjects.

Taken together, these reports reflect a complex interaction between $A\beta_{42}$ levels and cerebral atrophy. Recently, it has been suggested that such an association might be better modeled using nonlinear regression techniques (Becker et al., 2011; Fjell et al., 2014, 2014; Fortea et al., 2011; Gispert et al., 2015) and that atrophy rates may greatly vary across different brain regions (Insel et al., 2014). The aim of this work is to characterize longitudinal changes, computed in a two-year period, in cognitively healthy (healthy controls and preclinical AD elders and to seek for linear associations between baseline CSF biomarker levels ($A\beta_{42}$, p-tau and p-tau/$A\beta_{42}$). The linear association of variables with atrophy rates deals with second order term of the atrophy, acceleration or restrain of atrophy, by looking for variations in the first order term (atrophy rate). We used the publicly available dataset from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to replicate the findings in our sample. Thus, a secondary purpose of the work was to check for the dependence of results on the sample, and hence, to evaluate the equivalence of datasets.

2. Material and methods

2.1. Subjects

In this work, we have studied and compared two independent samples with 2 year longitudinal MRI scans and baseline CSF measurements. The first sample, referred to as HCB, originally consisted of 34 cognitively healthy subjects recruited at Alzheimer's Disease and Other Cognitive Disorders Unit from Hospital Clinic of Barcelona. The sample was a subset of the one described in (Gispert et al., 2015) formed of those subjects who underwent to a second MRI scan in two years' time and who remained cognitively healthy by the time of the second scan. The inclusion criteria were neurologically healthy subjects, aged 60–80 years, that didn't present any evidence of cognitive impairment (Clinical Dementia Rating, CDR = 0). The sample was mostly recruited among relatives of neurological patients who voluntary agreed to take part of the study and few subjects with subjective cognitive decline (SDC) whose cognitive tests had normal scores. Almost all controls began to the first group. Participants underwent complete clinical and neuropsychological examinations and a lumbar puncture to determine CSF $A\beta_{42}$ and p-tau values. The mean time interval between the lumbar puncture and the first MRI session was 44 ± 35 days, ranged from 1 to 134 days. $A\beta_{42}$, t-tau and p-tau quantitation was performed using ELISA (Enzyme-Linked ImmunoSorbent Assay kits, Innogenetics, Ghent, Belgium). Specific details about quantitation can be found in (Gispert et al., 2016). The $A\beta_{42}$ range for abnormality, which defined preclinical AD stage, was set to ($A\beta_{42}$ < 500 pg/ml) as it was determined for ELISA in a previous work (Antonell et al., 2014). The same MRI protocol was used in both scans: High-resolution structural images by MPRAGE sequence (TR/TE/TI = 2300/2.98/900 ms, respectively, FA = 9°, 240 sagittal slices, 1 × 1 × 1 mm^3 voxel) on a 3T TIM TRIO scanner (Siemens, Erlangen, Germany) at the IDIBAPS's Imaging core facilities. Two subjects had to be removed from the sample because a very poor quality of the images (movement artefact) and one preclinical AD was removed from the sample because showing an outlier value of p-tau (213 pg/ml while the mean and standard deviation of the rest of the sample was 56.4 and 47 pg/ml respectively), what biased all the analysis in which p-tau was involved. Then, the final sample consisted of 31 individuals (22 control and 9 preclinical AD). All participants signed a written consent to take part in the study and the Ethical Committee of the hospital approved the research protocol.

The second sample was a replica selected from ADNI dataset (Alzheimer's Disease Neuroimaging Initiative database: adni.loni.usc.edu). The selection criteria were identical to the previous sample: cognitively normal individuals (MMSE > 24 and CDR = 0), aged 60 to 80 years old, who had been submitted to two sessions of MRI delayed two years on a same 3T scanner, and who had $A\beta_{42}$ value at the time of the first MRI session. The search resulted in 49 subjects, 22 controls and 17 preAD. The selection between them was done by matching age, as main confounding factor, with subjects from HCB. Although picking the youngest ones, there still was a significant difference on age between samples (Table 1). One of the firstly selected preAD subjects was removed of the sample because presenting a massive right temporal atrophy that altered all VBM analyses (outlier) and substituted by the following next in the list. The acquisition parameters depended on site/scanner, being common the matrix (256 × 256 × 240) and voxel size (1 × 1 × 1.2 mm^3) for all subjects. Subjects scanned on a Tim TRIO had been acquired with almost the same protocol that the one used in HCB (TR/TE/TI = 2300/2.98/900 ms, respectively, FA = 9°, 240 sagittal slices, 1 × 1 × 1.2 mm^3 voxel). In ADNI dataset, the quantitation of $A\beta_{42}$, p-tau and t-tau levels was performed using xMAP Luminex platform and Innogenetics/Fujirebio AlzBio3 immunoassay kits. Nine of the subjects were preclinical at the time of the first scan because their $A\beta_{42}$ level was below the threshold of pathology (192 pg/ml for this technique) (Shaw et al., 2009). According (Mattsson et al., 2013), both