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Associations between white matter hyperintensities and cognitive decline over three years in non-dementia older adults with memory complaints

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ABSTRACT

We investigated whether the baseline level and overtime changes of white matter hyperintensities (WMH) would be associated with cognitive decline over three years in non-demented older adults with memory complaints. 109 participants with baseline magnetic resonance imaging (MRI) and follow-up cognitive assessments up to 3-year were included; among them, 82 also had a follow-up MRI assessment over three years. WMH volume was obtained by an automated segmentation algorithm. Baseline WMH volumes and change between baseline and follow-up WMH were related to cognitive scores over time using mixed-effect linear regressions. Secondary stratified analyses according to Clinical Dementia Rating (CDR) status, APOE4 status, and presence of amyloid in the brain were conducted using similar regression models. Change in WMH volume overtime was associated with declines in COWAT ($\beta = -0.239$; 95% CI $= -0.381, -0.096$, $p = 0.001$). Baseline WMH was not associated to any of the cognitive tests. Secondary analysis found that baseline WMH was associated to declines in TMT-A in APOE4 non-carriers ($\beta = 0.343$; 95% CI $= 0.121, 0.564$, $p = 0.003$) and CDR 0 groups ($\beta = 0.307$; 95% CI $= 0.095, 0.519$, $p = 0.005$); in CDR 0 group, overtime changes in WMH was associated to declines on both TMT-A ($\beta = 0.698$; 95% CI $= 0.270, 1.126$, $p = 0.002$) and TMT-B ($\beta = 2.573$; 95% CI $= 1.200, 3.947$, $p < 0.001$). Changes in WMH volume are associated with declines in information processing speed and executive function in non-demented older adults with memory complaints. Overtime changes in WMH volume is probably a better determinant of cognitive function in the elderly than baseline WMH volume.

1. Introduction

White matter hyperintensities (WMH) are associated with increased risk of cognitive dysfunction [1,2]. Previous studies have shown that WMH predict an increased risk of dementia [3,4]. In addition, previous reports have revealed that WMH has been associated to cognition, with overtime progression being a better indicator of cognitive decline than baseline WMH, particularly regarding attention and executive functioning [5–9]. However, these associations have been consistent only in older people with normal cognition [3–5], but not in studies on patients with mild cognitive impairment (MCI) or dementia [3,4,10–13]. It could suggest that WMH do not influence the risk of cognitive dysfunction when memory impairment is already severe with a high probability of coincident Alzheimer's disease (AD). A previous clinicopathological study showed that only Braak and Braak stage, not cerebrovascular parenchymal pathology scores, contributed to a global

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neuropsychological measure of cognitive impairment in patients with subcortical ischemic vascular disease and AD [14]. Therefore, the effect of WMH on cognitive decline may be more revealing in earlier stages in the spectrum of cognitive impairment, such as in non-demented older adults with memory complaints who are prevalent in the community or clinics and might be correspondent to early MCI or subjective memory complaints (SMC) [15]. However, so far, there have been few studies investigating the relationship between WMH and cognitive decline in non-demented older adults with memory complaints [16,17]. The studies showed that the presence of WMH were associated with annual decline on global cognition [16] or memory, attention, executive functioning, and global cognition [17]. However, they did not investigate the relationship between the progression of WMH and cognitive decline.

Moreover, although previous studies have shown that apolipoprotein E4 (APOE4) [18,19] and β-amyloid in the brain [20] have been found to be predictors of cognitive decline in non-demented older adults with memory complaints, to the best of our knowledge, there have been no studies demonstrating these predictors modify the relationship between WMH and cognitive decline in non-demented older adults with memory complaints.

We investigated whether both baseline and overtime changes of WMH would be associated with cognitive decline in non-demented older adults with memory complaints in a 3-year observational follow-up. We also explored in secondary analysis how these associations would differ according with baseline clinical dementia severity (CDR 0 and 0.5), APOE4 status (carriers and non-carriers), or presence of amyloid in the brain (amyloid + and amyloid −).

2. Methods

Data were obtained from the MRI substudy carried out in the context of the larger phase III, multicenter, randomized, placebo controlled Multidomain Alzheimer Preventive Trial (MAPT study). MAPT methods have been described elsewhere [21,22]. In brief, the 3-year MAPT study was designed to assess the efficacy of isolated supplementation with omega-3 fatty acid, an isolated multidomain intervention (consisting of nutritional counseling, physical exercise advice, and cognitive stimulation) or a combination of the two interventions compared to placebo on the change of cognitive functions in frail subjects with memory complaints aged 70 years and older. The protocol is registered on a public-access clinical trial database (www.clinicaltrials.gov) (NCT00672685). Both the MAPT study and MRI substudy were approved by the ethical committee in Toulouse (CPP SOOM II). Written consent was obtained from all participants.

2.1. Study population

At inclusion, MAPT participants presented any of spontaneous memory complaint, limitation in one instrumental activity of daily living, or slow gait speed ≤0.8 m/s. People with dementia, severe depression, or limitations in basic activities of daily living were excluded. In order to rule out the potential effects of both the supplementation with omega-3 fatty acid and the multidomain intervention (interactions between MAPT group allocation and WMH were significantly associated with cognitive function overtime, suggesting that the WMH-cognition association were different across MAPT groups), the study population was restricted to the 109 participants from the placebo group who have undergone at least one MRI assessment; among them, 82 have received two MRI assessments.

2.2. MRI acquisition and analyses

The acquisition protocol for brain MRI has been previously described [21]. MRI measures used in this study consisted of total intracranial volume (TICV, cm^3) and WMH volume (cm^3). The TICV was measured on the baseline 3D T1-weighted sequence, and derived from the tissue volumes given by the SPM5 toolbox (http://www.fil.ion.ucl.ac.uk/spm). The volume of WMH was measured on the baseline and 36 months MRI by the WHASA software (White matter Hyperintensities Automated Segmentation Algorithm), a method designed for automatically segmenting WMH from FLAIR and 3D T1- weighted images [23]. Contrary to intensity-based approaches, this method relies on contrast. Standard preprocessing steps extracted tissue information from 3D T1-weighted images, registered it to the FLAIR image and corrected for intensity inhomogeneity. Non-linear diffusion framework enabled then to enhance contrast of WMH on the FLAIR image and obtain a piecewise constant image. Finally, tissue information obtained from preprocessing steps allowed the selection of relevant regions according to their location. The baseline WMH volume (cm^3) was obtained from the first MRI and overtime changes of WMH volume (cm^3) was computed as the difference of WMH volume between follow-up and baseline.

2.3. [18F] florbetapir PET scanning and analysis

Data were obtained from the PET substudy. The methods have previously been described in detail [24]. Among 109 participants with the baseline MRI, 36 participants took the [18F] florbetapir PET. Out of 82 participants who also performed the follow-up MRI, 28 had the [18F] florbetapir PET. Semiautomated quantitative analysis (cortical-to-cerebellar standard uptake value ratio (SUVR)) was performed using the mean signal of six predefined cortical regions of interest (regions of interest; frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate); the whotel cerebellum was the reference region. A quality control based on a semiquantification process was also performed. The positivity threshold for amyloid PET was set at the mean cortical standard uptake value ratio (SUVR) ≥ 1.17.

2.4. Cognitive outcomes

MAPT cognitive assessments were carried out at baseline, 6 months, and 1, 2, and 3 years by independent research staff blinded to the participants' treatment [21]. Five cognitive variables were used as outcome measures: first, we calculated a composite Z score (main outcome measure of the whole MAPT trial) [22], made by combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding test (FCSRT), Mini-Mental State Examination Orientation subset, Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale-Revised, and Category Fluency Test). Although this composite score was built as an outcome measure sensitive to the earliest preclinical Alzheimer disease-related changes [25] and taking into consideration the cognitive domains that composes this measure, it is acceptable to consider this score is a representative and global measure of cognition. Therefore, we chose the composite Z score as the global score. Secondly, free and total recall of the FCSRT was used for the assessment of memory function. Finally, three outcome measures encompassing the constructs of information processing speed and executive function were examined: TMT part A (time), part B (time), and COWAT (phonetic names generated in 1 min). TMT is a representative test to investigate the information processing speed [26]. In addition, we assumed that Category Fluency Test could be more affected by language function than executive function; therefore, COWAT was considered to be more appropriate than Category Fluency Test [27] to evaluate executive function. Due to the small sample size, we used only three tests to evaluate information processing speed and executive function.

2.5. Timing of assessments

Among 109 participants, 61 (55.9%) subjects took their first MRI between baseline and 6-month follow-up and 48 performed it between six and 12 months. The mean interval ± standard deviation between the first MRI and the last clinical assessments was 877.5 ± 238.4 days.