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Cross-sectional variations of white and grey matter in older hypertensive patients with subjective memory complaints

Ahmed Chetouani[a], Mohammad B. Chawki[a], Gabriela Hossu[b], Anna Kearney-Schwartz[c,d], Florence Chauveau-Beuret[e], Serge Bracard[e,f], Veronique Roch[a], Vincent Lebon[g], Pierre-Yves Marie[a,c,h], Athanase Benetos[d,f], Laure Joly[d,f], Antoine Verger[a,b,*]

[a] CHU-Nancy, Department of Nuclear Medicine & Nancyclotep Imaging platform, Nancy, F-54000, France
[b] INSERM U947, Nancy F-54000, France
[c] INSERM, Centre d'Investigation Clinique CIC-IT, 1433, Nancy F-54000, France
[d] CHU-Nancy, Department of Geriatric Medicine, Nancy, F-54000, France
[e] CHU-Nancy, Department of Neuroradiology, Nancy, F-54000, France
[f] INSERM, Centre d'Investigation Clinique CIC-P 9501, Nancy, F-54000, France
[g] Department of Nuclear Medicine Frédéric Joliot, CEA, Orsay, F-91400, France
[h] INSERM, U1116, Nancy, F-54000, France

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ABSTRACT

Mild cognitive impairment and Alzheimer's dementia involve a grey matter disease, quantifiable by ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET), but also white matter damage, evidenced by diffusion tensor magnetic resonance imaging (DTI), which may play an additional pathogenic role. This study aimed to determine whether such DTI and PET variations are also interrelated in a high-risk population of older hypertensive patients with only subjective memory complaints (SMC).

Sixty older hypertensive patients (75 ± 5 years) with SMC were referred to DTI and FDG-PET brain imaging, executive and memory tests, as well as peripheral and central blood pressure (BP) measurements. Mean apparent diffusion coefficient (ADC_{mean}) was determined in overall white matter and correlated with the grey matter distribution of the metabolic rate of glucose (CMRGlc) using whole-brain voxel-based analyses of FDG-PET images.

ADC_{mean} was variable between individuals, ranging from 0.82 to $1.01.10^{-3}$ mm^2 sec^{-1}, and mainly in relation with CMRGlc of areas involved in Alzheimer's disease such as internal temporal areas, posterior associative junctions, posterior cingulum but also insulo-opercular areas (global correlation coefficient: -0.577, $p < 0.001$). Both the ADC_{mean} and CMRGlc of the interrelated grey matter areas were additionally and concordantly linked to the results of executive and memory tests and to systolic central BP (all $p < 0.05$).

Altogether, our findings show that cross-sectional variations in overall white brain matter are linked to the metabolism of Alzheimer-like cortical areas and to cognitive performance in older hypertensive patients with only subjective memory complaints. Additional relationships with central BP strengthen the hypothesis of a contributing pathogenic role of hypertension.

1. Introduction

Subjective cognitive impairment (SCI) is common in the elderly, and may serve as a symptomatic indicator of a precursor stage of Alzheimer's dementia (AD), even if subtle cognitive decline is difficult to detect on standardized cognitive testing (Jessen et al., 2014). While this condition is not considered to be a definite neurodegenerative process such as mild cognitive impairment (MCI) or AD, it may precede a further cognitive decline and the development of dementia (Kielb et al., 2017).

In addition, impaired cognitive performance has been associated with cardiovascular (CV) risk factors such as hypertension (Ferreira et al., 2017; Muller et al., 2007; Rafnsson et al., 2007), in keeping with our recent observation that brain remodeling with age is linked to the level of central pulse pressure (Verger et al., 2015). Thus, older hypertensive patients with SCI may constitute a particularly high-risk

* Corresponding author at: CHU-Nancy, Hôpitaux de BRABOIS, Service de Médecine Nucléaire, Allée du Morvan, 54500, Vandœuvre, France.
E-mail address: a.verger@chu-nancy.fr (A. Verger).

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group for subsequent dementia and may therefore benefit from dedicated modalities of medical management and of early diagnosis.

Recent advances in MRI and PET imaging modalities can detect early changes in brain structure and/or metabolism, before the stage of dementia. Among these, diffusion tensor imaging (DTI), through the mean apparent diffusion coefficient (ADC_{mean}), may be particularly useful for the early diagnosis of neurodegenerative disorders (Sali et al., 2013). This DTI-derived parameter provides a measurement of diffusion rate and its global value is more closely linked to the neurodegenerative process than local values (Kin et al., 2006). White matter ADC_{mean} is indeed commonly increased in neurodegenerative diseases owing to the loss of axonal myelin and the disruption of cell membranes (Kin et al., 2006).

^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is also a useful imaging method in this setting, owing to its ability to quantify neuronal activity through the glycolytic metabolism of the brain grey matter (Magistretti and Allaman, 2015). ^{18}F-FDG PET is moreover increasingly used for the early diagnosis of dementia and predementia states and more precisely, for detecting the degenerative component of these diseases, in accordance with the recommendations of the international Alzheimer's Association (McKhann et al., 2011). ^{18}F-FDG PET abnormalities, which are documented in AD or MCI patients, were recently shown to correlate with the microstructural white matter changes observed with DTI (Yakushev et al., 2011a; Zimny et al., 2015; Walhovd et al., 2009). To date, however, it is not known whether these interrelated white and grey matter changes are also present in patients with only subjective memory complaints, before the stage of any objective cognitive impairment.

In light of the above, this dual DTI and ^{18}F-FDG PET study aimed to determine whether cross-sectional variations within the white and grey brain matters are also associated before the stage of any objective cognitive impairment, in a high-risk population of older hypertensive patients with only subjective memory complaints.

2. Materials and methods

2.1. Subjects

This ancillary PET/MRI study was extracted from the ADELAHYDE longitudinal single-center study, which aimed at identifying factors associated with cognitive decline and white matter diseases in older hypertensive patients with subjective memory complaints (Analyse des DEterminants génétiques et environnementaux de la Leucoaraiose dans une population de sujets Agés Hypertendus présentant des troubles cognitifs DEbutants; ClinicalTrials.gov Identifier: NCT01351961). Inclusion and exclusion criteria have already been detailed elsewhere (Kearney-Schwartz et al., 2009).

A total of 131 patients participated to the ADELAHYDE-2 study and results of the present study were extracted from the second control visit which comprised a medical examination with measurement of central blood pressure (BP), various neuropsychological tests and a brain MRI (Ferreira et al., 2017). Among these 131 patients, 71 accepted to undergo an additional investigation by brain ^{18}F-FDG-PET (local Ethics Committee (CPP) agreement no 2010-A01399-30), although the study population was finally restricted to 60 patients, 11 being excluded for technical issues at MRI (3 without any DTI acquisition and 2 with incorrect acquisitions) or for a significant cognitive impairment and a high probability of MCI (n = 4) or AD (n = 2) based on neuropsychological tests (score < 25 for Mini-Mental State Examination or < 17 for free recall or < 40 for total recall of the Grober-Buschke tests (Sarazin et al., 2007)).

All investigations were planned on the same day, except for the brain MRI, which was performed in the following 3 months.

2.2. Clinical cardiovascular and neuropsychological assessments

Peripheral brachial BP was measured in the supine position with an oscillometric semiautomatic device (Omron 705IT, Kyoto, Japan) after a minimum 10-min rest period. Systolic, diastolic, pulse and mean BPs were recorded three to four times and averaged for subsequent analyses.

Central BP was determined in 56 patients (24 women) by the transcutaneous analysis of the carotid pulse wave with an applanation tonometer (Joly et al., 2009; Salvi et al., 2004). Carotid pressures were deemed as a close surrogate of central pressures and calibrated with the diastolic and mean brachial BP values (the differences in diastolic and mean arterial pressure are minimal throughout the arterial tree) (Verger et al., 2015).

Neuropsychological assessment was comprised of: 1) a Mini-Mental State Examination test for global cognition (Folstein et al., 1975), 2) the Free and Cued recall tests (i.e. (Hofman et al., 1997) a French equivalent of the Grober-Buschke test for the capacities of encoding and consolidation, as well as for the efficiency of the recovery mechanisms (Grober et al., 1988), 3) a Benton Visual Retention Test for visuospatial capacities (Spreen and Benton, 1963), 4) the Verbal Fluency Test for executive function and long-term verbal memory (Strauss et al., 2006), and 5) the Trail Making Tests for visual attention and task switching (Ashendorf et al., 2008; Greenlief et al., 1985).

2.3. MRI acquisition and analysis

All data were acquired on a 1.5-T magnet (Signa HDxt, GE Healthcare, Milwaukee, WI, USA) with an 8-element receive head coil (Invivo Corp, Orlando, FL). The protocol involved the recording of a 3-dimensional T1-weighted sequence with the following parameters: slice thickness 1.4 mm; TE/TR/TI = 5/12/350 ms, field of view 240 mm (matrix size 256 × 256), and Fluid-Attenuated Inversion Recovery (FLAIR) images, with the following parameters: slice thickness 5 mm, TE/TR/TI = 158/10000/2300 ms, field of view 240 mm (matrix size 288 × 224). White matter hyperintensities of presumed vascular origin were assessed on the FLAIR images by a blinded experimented radiologist (SB) using the Fazekas score, corresponding to the sum of periventricular and deep white matter hyperintensity ratings (Fazekas et al., 1987).

A DTI axial acquisition was also performed with the following parameters: 15 non-collinear gradient directions with b = 1000 s/mm^2, one b = 0 reference image, contiguous slices of 5 mm thickness; TE/TR = 72–100/9.600 ms, field of view 240 mm (matrix size of 128 × 128) covering the entire brain and cerebellum.

An automated parcellation of the subcortical white matter was obtained on the 3D T1-weighted images from each patient and by using the “-recon-all” processing pipeline of the FreeSurfer software version 5.2. This parcellation was thereafter applied to the DTI images through a co-registration and a transformation in the 3D-T1 space of the DTI images (“Dt_recon” function of the FreeSurfer software). Finally, ADC_{mean} values were obtained from the total white matter and from the different lobes using a subcortical white matter parcellation atlas “wmparc” (Salat et al., 2009).

2.4. ^{18}F-FDG-PET recording and analysis

The ^{18}F-FDG-PET images were recorded on a Biograph™ 6 hybrid PET/Computed Tomography (CT) system (Siemens Medical Solutions, Erlangen, Germany). Patients were fasted for at least 6 h prior to the injection of 4 to 5 MBq/kg of ^{18}F-FDG and subsequently placed in a quiet environment with eyes closed. Fifty minutes later, a 3-dimensional Computed Tomography (CT) of the brain was recorded and immediately followed by a 3D PET brain recording over a 15 min period. Images were reconstructed with an iterative 3-dimensional Ordered Subset Expected Minimization (OSEM) method, corrected for