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DISRUPTED WHITE MATTER STRUCTURAL NETWORKS IN HEALTHY OLDER ADULTS *APOE ε4* CARRIERS – AN INTERNATIONAL MULTICENTER DTI STUDY

ENRICA CAVEDO,[a,b]* SIMONE LISTA,[a] KATRINE ROJKOVA,[a] PATRIZIA ANDREA CHIESA,[a] MARION HOUOT,[c] KATHARINA BRUEGGEN,[d] JANUSCH BLAUTZIK,[e] ARUN L. W. BOKDE,[f] BRUNO DUBOIS,[g] FREDERIK BARKHOF,[h] PETRA J. W. POUWELS,[h] STEFAN TEIPEL[d,i] AND HARALD HAMPEL[a], for the Alzheimer Precision Medicine Initiative (APMI)

[a] *AXA Research Fund & UPMC Chair, Sorbonne Universités, Université Pierre et Marie Curie (UPMC) Paris 06, Inserm, CNRS, Institut du Cerveau et de la Moelle Épinière (ICM), Département de Neurologie, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), Hôpital Pitié-Salpêtrière, Boulevard de l'hôpital, F-75013 Paris, France*

[b] *Laboratory of Alzheimer's Neuroimaging and Epidemiology, IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy*

[c] *Institute of Memory and Alzheimer's Disease (IM2A), Centre of Excellence of Neurodegenerative Disease (CoEN), ICM, APHP Department of Neurology, Hopital Pitié-Salpêtrière, University Paris 6, Paris, France*

[d] *DZNE, German Center for Neurodegenerative Diseases, Rostock, Germany*

[e] *Institute for Clinical Radiology, Department of MRI, Ludwig Maximilian University Munich, Germany*

[f] *Cognitive Systems Group, Discipline of Psychiatry, School of Medicine, Trinity College Dublin, Dublin, Ireland; and Trinity College Institute of Neuroscience (TCIN), Trinity College Dublin, Dublin, Ireland*

[g] *Sorbonne Universities, Pierre et Marie Curie University, Paris 06, Institute of Memory and Alzheimer's Disease (IM2A) & Brain and Spine Institute (ICM) UMR S 1127, Departament of Neurology, Hopital Pitié-Salpêtrière, Paris, France*

[h] *Department of Radiology and Nuclear Medicine, Neuroscience Campus Amsterdam, VU University Medical Centre, The Netherlands*

[i] *Department of Psychosomatic Medicine, University Medicine Rostock, Rostock, Germany*

Abstract—The *ε4* allelic variant of the Apolipoprotein E gene (*APOE ε4*) is the best-established genetic risk factor for late-onset Alzheimer's disease (AD). White matter (WM) microstructural damages measured with Diffusion Tensor Imaging (DTI) represent an early sign of fiber tract disconnection in AD. We examined the impact of *APOEε4 on* WM microstructure in elderly individuals from the multicenter European DTI Study on Dementia. Voxelwise statistical analysis of Fractional anisotropy (FA), mean diffusivity, radial and axial diffusivity (MD, radD and axD respectively) was carried out using Tract-Based Spatial Statistics. Seventy-four healthy elderly individuals – 31 *APOE ε4* carriers (*APOE ε4* +) and 43 *APOE ε4* non-carriers (*APOE ε4*–) –were considered for data analysis. All the results were corrected for scanner acquisition protocols, age, gender and for multiple comparisons. *APOE ε4*+ and *APOE ε4*– subjects were comparable regarding sociodemographic features and global cognition. A significant reduction of FA and increased radD was found in the *APOE ε4*+ compared to the *APOE ε4*– in the cingulum, in the corpus callosum, in the inferior fronto-occipital and in the inferior longitudinal fasciculi, internal and external capsule. *APOE ε4*+, compared to *APOE ε4*– showed higher MD in the genu, right internal capsule, superior longitudinal fasciculus and corona radiate. Comparisons stratified by center supported the results obtained on the whole sample. These findings support previous evidence in monocentric studies indicating a modulatory role of *APOE ε4* allele on WM microstructure in elderly individuals at risk for AD suggesting early vulnerability and/or reduced resilience of WM tracts involved in AD. © 2017 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: Diffusion Tensor Imaging, Apolipoprotein E, multicenter study, white matter integrity, aging.

INTRODUCTION

The *APOE* gene, located on chromosome 19q13.2, encodes for the ApoE protein (Boyles et al., 1985; Nakai et al., 1996). ApoE participates in lipid metabolism, particularly in cholesterol transport and clearance. Moreover, its activity is associated with relevant components of brain WM such as myelin, of which cholesterol is a major constituent (Westlye et al., 2012). It is also implicated in neuronal growth and repair, nerve regeneration, immune response, and activation of lipolytic enzymes (Karch et al., 2014; Yu et al., 2014). At present, the *ε4* allelic variant of *APOE* – *APOE ε4* – is the best established genetic

*Corresponding authors. Addresses: Université Pierre et Marie Curie, Paris 06, Département de Neurologie, Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), Hôpital de la Salpêtrière, 47 Bd de l'hôpital, 75013 Paris, France.
E-mail addresses: enrica.cavedo@gmail.com (E. Cavedo), harald.hampel@icm-institute.org, harald.hampel@med.uni-muenchen.de (H. Hampel).

Abbreviations: AD, Alzheimer's disease; *APOE ε4*, Apolipoprotein E gene; axD, axial diffusivity; DTI, Diffusion Tensor Imaging; EDSD, European multicenter DTI Study on Dementia; FA, Fractional anisotropy; FWE, family-wise error; MD, mean diffusivity; radD, radial diffusivity; WM, white matter.

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risk factor for the development of late-onset Alzheimer's Disease (AD) (Corder et al., 1993; Strittmatter et al., 1993). The involvement of genetic risk factors such as *APOE ε4* in sporadic late-onset AD has been profoundly demonstrated (Saunders et al., 1993; Sherrington et al., 1995; Bertram et al., 2007; Reitz et al., 2011; Lockhart and DeCarli, 2014).

Structural neuroimaging patterns related to *APOE ε4* in elderly individuals described gray matter atrophy in the medial temporal structures (Chen et al., 2007; Donix et al., 2010b; Hua et al., 2010; Risacher et al., 2010; Lu et al., 2011; Roussotte et al., 2014) such as the subiculum (Burggren et al., 2008; Suthana et al., 2010) and CA1 subfield (Kerchner et al., 2014) of the hippocampus (Donix et al., 2010a; Chiang et al., 2011; O'Dwyer et al., 2012; Taylor et al., 2014), although contrasting results were published as well (Jack et al., 1998; Du et al., 2006; Schuff et al., 2009; Taylor et al., 2014). Moreover, higher cortical beta-amyloid deposition (Reiman et al., 2009; Morris et al., 2010; Fleisher et al., 2013), glucose hypometabolism in brain regions typically impaired in AD (Rimajova et al., 2008; Protas et al., 2013; Fouquet et al., 2014) and changes in brain function during an encoding memory task (Filippini et al., 2011) were previously described in elderly cognitive intact individuals carrying the *APOE ε4* allele. No interaction effects were found of APOE *ε4* status on the relationship between brain beta-amyloid levels and gray matter network disruption (Tijms et al., 2016). So far, the exact pathophysiological mechanism through which *APOE ε4* contributes to the etiology and progression of the disease remains unclear.

In vitro and *in vivo* studies demonstrated that *APOE ε4* allele is associated with axonal degeneration (Tesseur et al., 2000) and structural modifications in intracellular microtubules (Nathan et al., 1995), thereby raising the possibility of mechanistically impacting white matter (WM) microstructure (Heise et al., 2011, 2014; Westlye et al., 2012). More than half of the individuals diagnosed with AD display WM microstructural alterations (Chalmers et al., 2005) that can be investigated *in vivo* by Diffusion Tensor Imaging (DTI).

DTI detects the amplitude and directional coherence of water molecule diffusion and, since water molecule diffusion is usually constrained along the main fiber direction by axonal membranes and myelin sheaths, this feature can be used to measure WM structural integrity (Pierpaoli and Basser, 1996; Behrens et al., 2007). In particular, Fractional Anisotropy (FA) measures are generally high in healthy, structurally intact, coherently organized WM tissues (Acosta-Cabronero and Nestor, 2014). However, there was also evidence of reduced FA in healthy cognitively intact adults in region of crossing fibers between the corticospinal tract and the superior longitudinal fasciculus (Douaud et al., 2011) as previously reported also in diseased tissue (Amlien and Fjell, 2014), whereas, high mean diffusivity (MD), radial diffusivity (radD) and axial diffusivity (axD) measures may potentially be used to detect tissue breakdown, myelin loss and axonal injury respectively (Beaulieu, 2002; Song et al., 2002, 2005; Kumar et al., 2011, 2013).

Previous studies investigating DTI indexes in AD patients showed a consistent pattern of decreased FA and increased MD, radD and axD, suggesting the presence of WM tracts disconnection in this population (Amlien and Fjell, 2014; Zhang et al., 2014). Although brain WM integrity, in older adults carrying *APOE ε4,* have been previously investigated in several monocentric studies (Gold et al., 2012; Felsky and Voineskos, 2013; Lyall et al., 2014), the reproducibility of these results in multicenter studies has not been sufficiently examined. In the present study, we investigated how the *APOE ε4* variant alters the brain WM microstructure in healthy older individuals recruited in the European multicenter DTI Study on Dementia (EDSD).

EXPERIMENTAL PROCEDURES

Participants

Sociodemographic, clinical and neuroimaging data were selected from the retrospective multicenter European Diffusion Tensor Imaging Study on Dementia (EDSD) database (Teipel et al., 2011, 2012, 2014; Fischer et al., 2012; Dyrba et al., 2013, 2014, 2015; Kilimann et al., 2014; Kljajevic et al., 2014; Tsao et al., 2014; Brueggen et al., 2015, 2016). The EDSD is a framework created to study the multicenter variability and diagnostic accuracy of DTI derived markers in patients with prodromal Alzheimer's disease (AD) and AD dementia. It was founded in 2010 and is coordinated by the German Center for Neurodegenerative Diseases (DZNE) in Rostock (Germany). Initially, MRI data, including DTI sequences of healthy control subjects (HC) and AD patients were retrospectively collected from 10 European centers leading in the field of AD research. The EDSD database has collected data from eleven European centers: Amsterdam (The Netherlands), Brescia (Italy), Cambridge (United Kingdom), Dublin (Ireland), Frankfurt (Germany), Freiburg (Germany), Milan (Italy), Mainz (Germany), Mannheim (Germany), Munich (Germany), and Rostock (Germany). As of March 2016, the EDSD sample consists of 139 Alzheimer's patients, 160 Mild Cognitive Impairment patients and 194 Healthy controls. An inclusion criterion for each center in order to upload the data of HC required that they were free of cognitive impairment. Healthy subjects were recruited via advertisement, e.g. in newspapers. During anamnesis and neuropsychological assessment it was ruled out that they had cognitive complaints or medical diseases, including neurological and psychiatric diseases (such as depression or substance abuse). In the present study, we selected 85 healthy control individuals that underwent *APOE* genotyping conducted according to the standard methods derived from Amsterdam (renamed Center 1), Dublin (Center 2), Munich (Center 3), and Rostock (Center 4). Quality control of DTI scans was done visually to exclude scans with conspicuous artifacts such as ghosting, blurring due to motion, or strong susceptibility artifacts, and scans on which the brain was not entirely delimited within the field of view. Because of poor/incomplete head coverage preventing the creation of the mean FA image and its

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