Neurobiology of Aging 35 (2014) 1103–1110

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Thalamic diffusion differences related to cognitive function in white matter lesions

Marina Fernández-Andújar [a,d,1], Juan José Soriano-Raya [a,1], Júlia Miralbell [a,d], Elena López-Cancio [c], Cynthia Cáceres [c], Núria Bargalló [e], Maite Barrios [b], Juan Francisco Arenillas [f], Pere Toran [g], Maite Alzamora [g], Imma Clemente [a,d], Antoni Dávalos [c], Maria Mataró [a,d,*]

[a] Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Barcelona, Spain
[b] Department of Methodology of Behavioral Sciences, University of Barcelona, Barcelona, Spain
[c] Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Barcelona, Spain
[d] Institute for Brain, Cognition and Behaviour (IR3C), University of Barcelona, Barcelona, Spain
[e] Image Research Platform, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[f] Hospital Clínico Universitario, Valladolid, Spain
[g] Primary Healthcare Research Support Unit Metropolitana Nord, ICS-IDIAP Jordi Gol, Mataró, Barcelona, Spain

ARTICLE INFO

Article history:
Received 23 April 2013
Received in revised form 14 October 2013
Accepted 20 October 2013
Available online 24 October 2013

Keywords:
Thalamus diffusivity
White matter lesions
Neuropsychology
Psychomotor speed
Verbal fluency
Visuospatial skills

ABSTRACT

Cerebral white matter lesions (WMLs) are related to cognitive deficits, probably due to a disruption of frontal–subcortical circuits. We explored thalamic diffusion differences related to white matter lesions (WMLs) and their association with cognitive function in middle-aged individuals. Ninety-six participants from the Barcelona-AsIA Neuropsychology Study were included. Participants were classified into groups based on low grade and high grade of periventricular hyperintensities (PVHs) and deep white matter hyperintensities (DWMHs). Tract-Based Spatial Statistics was used to study thalamic diffusion differences between groups. Mean fractional anisotropy (FA) values in significant areas were calculated for each subject and correlated with cognitive performance. Participants with high-grade PVHs and DWMHs showed lower FA thalamic values compared to those with low-grade PVHs and DWMHs, respectively. Decreased FA thalamic values in high-grade DWMHs, but not high-grade PVH, were related to lower levels of performance in psychomotor speed, verbal fluency, and visuospatial skills. Thalamic diffusion differences are related to lower cognitive function only in participants with high-grade DWMHs. These results support the hypothesis that fronto–subcortical disruption is associated with cognitive function only in DWMHs.

1. Introduction

Cerebral white matter lesions (WMLs) comprise diffuse areas of high signal intensity on T2-weighted images in magnetic resonance image (MRI), and are common findings in normal aging (de Leeuw et al., 2001; Enzinger et al., 2007; Longstreth et al., 1996). WMLs are considered an expression of cerebrovascular small vessel disease (SVD) (Pantoni et al., 2002) and are usually divided into 2 groups: those adjacent to the ventricles (periventricular hyperintensities [PVHs]) and those located in the deep white matter (deep white matter hyperintensities [DWMHs]) (Fazekas et al., 2002).

WMLs have been consistently related to cognitive dysfunction resulting from cortico-subcortical circuit disruption (Schmidt et al., 2006; Linortner et al., 2012). However, the specific contribution of PVHs or DWHMs is still controversial (Schmidt et al., 2011).

The thalamus, which is a key structure in cortico–subcortical circuits (Byne et al., 2009), is involved in cognitive functions through extensive reciprocal connections with the cerebral cortex (Alexander et al., 1986; Cummings, 1993; Leh et al., 2007). Thalamic microstructural abnormalities have been related to cognitive dysfunction in lacunar stroke patients with leukoaraiosis (Li et al., 2012), schizophrenia (Marenco et al., 2012), and attention-deficit hyperactivity disorder (Xia et al., 2012). However, thalamic diffusion differences related to WMLs and their association with cognitive function remains unknown. The aims of this study were to explore thalamic diffusivity differences associated with DWMHs and PVHs, and to examine their relationship with cognitive outcomes in middle-aged, community-dwelling individuals.

* Corresponding author at: Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Passeig de la Vall d'Hebrón 171, 08035 Barcelona, Spain. Tel.: +34 933125052; fax: +34 934021584.
E-mail address: mmataro@ub.edu (M. Mataró).
[1] M.F.-A. and J.J.S.-R. are co–first authors.

0197-4580/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.10.087

In a previous study, we found a predominant role of high-grade DWMHs in cognitive dysfunction in middle-aged individuals (Soriano-Raya et al., 2012). Accordingly, we hypothesized the following: (1) thalamic diffusion differences would be found in a greater extent in participants with high-grade DWMHs than in participants with high-grade PVHs; (2) thalamic diffusion differences related to high-grade DWMHs would be associated with lower cognitive performance; and (3) thalamic diffusion differences related to high-grade PVHs would not be associated with cognitive function.

2. Methods

2.1. Study participants

The Barcelona-AsIA (Asymptomatic Intracranial Atherosclerosis) Study is an ongoing population-based study that includes a random sample of participants more than 50 years of age without previous history of stroke or ischemic heart disease. Complete details of the Barcelona-AsIA protocol have been previously described (Lopez-Cancio et al., 2012). The Barcelona-AsIA Neuropsychology Study is a related prospective study with the following objectives: (1) to investigate the associations of vascular risk factors (VRF), asymptomatic cervicocerebral atherosclerosis, and MRI signs of SVD with cognition; and (2) to identify clinical and radiological features and biological mechanisms underlying these associations.

Our participants were recruited from the Peripheral Arterial Disease Study (PERART), a related ongoing population-based study that aims to determine the prevalence of peripheral arterial disease and to evaluate the predictive value of ankle–arm index in relation to cardiovascular morbidity and mortality (Alzamora et al., 2007). Details of the recruitment process have been previously described (Soriano-Raya et al., 2012). Briefly, a total of 132 participants were selected to undergo a comprehensive neuropsychological assessment and brain MRI. We included individuals 50–65 years of age. Exclusion criteria were as follows: history of stroke or transient ischemic attack (TIA), coronary heart disease, chronic neurological disease, or severe psychiatric disorder (n = 11); a Mini-Mental State Examination (MMSE) score of <25 or severe disability (n = 3); other medical diseases that could affect cognitive assessment and function (n = 4); contraindications to undergo MRI (n = 10); unexpected findings seen on brain MRI (n = 2); or other causes (i.e., <75% of neuropsychological assessment available) (n = 2). For the present study, we finally selected 100 participants 50–65 years of age, stratified by sex and educational level.

This study was approved by the University of Barcelona and the Hospital Germans Trias i Pujol Ethics committee. Informed consent was obtained for each participant in accordance with the Declaration of Helsinki.

2.2. Evaluation of vascular risk factors

Diagnosis of a particular vascular risk factor (arterial hypertension, dyslipidemia, diabetes mellitus, and current smoking status) was based on clinical history or use of medication for this particular condition at the time of the clinical examination.

2.3. Neuropsychological assessment

All participants completed an extensive neuropsychological assessment. Cognitive measures were grouped into 8 cognitive domains including tests that measure the same cognitive function (Lezak et al., 2004; Strauss et al., 2006): executive functioning, working memory, attention, verbal fluency, verbal memory, visual memory, visuospatial skills and psychomotor speed. The 64-item computerized version of the Wisconsin Card Sorting Test (WCST-64) (Kongs et al., 2000) and the interference score of the Color–Word Stroop Test (Golden, 1978) were used to examine executive functioning (i.e., conceptualization, planning, and inhibition). Working memory was assessed with Digit Span Backwards from the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) (Wechsler, 1997a) and part B of the Trail Making Test (Tombaugh, 2004). A computerized version of the Continuous Performance Test (Conners, 1995) and Digit Span Forward, Symbol Search, and Digit Symbol Coding subtests of the WAIS-III were used to measure attentional abilities. Verbal fluency was assessed with letter fluency (letters P, M, and R) (Artiola et al., 1999) and semantic category fluency (animals) (Strauss et al., 2006) in 60 seconds. Verbal and visual memory were examined using Word Lists and Visual Reproduction from the Wechsler Memory Scale–3rd edition (WMS-III) (Wechsler, 1997b), respectively. Evaluation of visuospatial skills was done by Visual Discrimination and the Copy from the Visual Reproduction subtest (WMS-III). Psychomotor speed was measured with part A of the Trail Making Test and Grooved Pegboard (Ruff and Parker, 1993). Participants' raw scores were normalized to z scores using the mean and standard deviation of the sample. Composite z scores for each participant in each cognitive domain were calculated by averaging the z scores of all tests within that domain. The Geriatric Depression Scale 15-item version (GDS-15) (Sheikh and Yesavage, 1986) was used to assess depressive symptoms.

2.4. MRI and analysis

MRI was performed on a 3T Siemens Magnetom Trio (Siemens Diagnostics Healthcare, Erlangen, Germany) at the Image Diagnosis Centre (Hospital Clínic, Barcelona, Spain). The MRI protocol included a set of MPRAGE T1-weighted images (repetition time [TR]: 2300 ms; echo time [TE]: 3 ms; flip angle: 15°; field of view: 245 mm; and voxel size: 1 × 1 × 1 mm), and diffusion tensor images (DTI) acquired in 30 directions with the following echoplanar acquisition protocol matrix: 120 × 120; TR: 9300 ms; TE: 94 ms; flip angle: 15°; field of view: 240 mm; no gap (2-mm thickness); voxel size: 2 × 2 × 2 mm, and b = 1000 s/mm^2. Two acquisitions of DTI were averaged. Axial fluid attenuated inversion recovery (FLAIR) images (TR: 9040 ms; TE: 85 ms; inversion time [TI]: 2500 ms; and voxel size: 1.1 × 0.9 × 5 mm, gap: 1.5 mm) and axial T2-weighted images (TR: 5520 ms; TE: 92 ms; and voxel size: 0.5 × 0.4 × 5 mm, gap: 1.5 mm) were also collected for white matter rating lesions (see below).

Individual processing of diffusion tensor data was performed using Tract-Based Spatial Statistics (TBSS), part of the FMRIB Software Library (FSL) version 5.0.1 (Smith et al., 2004). Fractional anisotropy (FA), throughout DTI indices, has been defined as a measure of tract directionality and integrity (Mori and Zhang, 2006). First, the effects of motion and eddy currents were corrected, the registration to the reference volume (b0) was made, and non-brain voxels were removed using the Brain Extraction Tool (BET). Then, FA maps were created by fitting a tensor model to the raw diffusion data using the FMRIB Diffusion Toolbox (FDT). FA data for all participants were aligned into a common space using the higher-resolution FA standard space Montreal Neurological Institute (MNI) atlas by the nonlinear registration method. The aligned FA data for each subject was then projected onto both thalami masks provided within FSL software (Smith et al., 2004), and the resulting data were fed into voxelwise statistics. We used the thalamus FSL masks to delimitate the voxelwise analysis of FA differences between WMLs groups. FA values were extracted only from thalamic areas where we found significant differences