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Structural MRI correlates of cognitive function in multiple sclerosis

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ABSTRACT

Background: Cognitive impairment (CI) has been associated with numerous magnetic resonance imaging (MRI) indices in multiple sclerosis (MS) patients. In this study we investigated the association of a large set of 2D and 3D MRI markers with cognitive function in MS.

Methods: A sample of 61 RRMS patients (mean age 41.8 ± 10.6 years old, 44 women, mean disease duration 137.9 ± 83.9 months) along with 51 age and gender matched healthy controls was used in this cross-sectional study. Neuropsychological and other tests, along with a large set of 2D/3D MRI evaluations were made.

Results: 44.3% of patients had CI. CI patients had more disability, physical fatigue than non-CI patients and more psychological distress than non-CI patients and HCs. Also, CI patients had significantly larger third ventricle width and volume, smaller coprus callosum index and larger lesion volume than non-CI patients. These MRI markers also significantly predicted cognitive scores after adjusting for age and education, explaining about 30.6% of the variance of the total cognitive score.

Conclusions: Selected linear and volumetric MRI indices predict cognitive function in MS. Future studies should expand these results by exploring longitudinal changes and producing normative data.

1. Introduction

Cognitive impairment (CI) is found in 26–56% of multiple sclerosis (MS) patients, even in the early stages of the disease (Chiaravalloti and DeLuca, 2008; Fischer et al., 2014). The cognitive domains mostly affected are information processing speed, working memory, complex attention, executive functions, verbal fluency and verbal and visuospatial learning and memory (Chiaravalloti and DeLuca, 2008). Importantly, CI has been attested as a robust predictor for conversion to clinically definite MS, disability accumulation, progression to secondary progressive MS, treatment compliance, depression, low quality of sleep, unemployment and low quality of life (Chiaravalloti and DeLuca, 2008). As such, CI monitoring has been now claiming a growing role both in MS research and in the clinical settings.

In this context, quantitative magnetic resonance imaging (MRI) assessments have been increasingly used to subserve neuropsychological testing in evaluating cognitive function (Rovaris et al., 2006). Volumetric MRI seems to reliably reflect pathogenetic processes such as neuroinflammation and neurodegeneration in MS (Lanz et al., 2007). Most importantly, MS patients have been found to lose about 0.5–1.5% of their brain volume each year which has been related to concomitant decline of their cognitive ability (Vollmer et al., 2016). Various studies using both linear non-automated two-dimensional and volumetric automated tree-dimensional MRI markers have provided useful MRI associations with cognitive function in MS (Rocca et al., 2015). Two-dimensional MRI markers like third ventricle width (Benedict et al., 2006; Sánchez et al., 2008), bicaudate ratio (Bermel et al., 2002), corpus callosum surface (Bergendal et al., 2013) and corpus callosum index (Yaldizli et al., 2014) have been related to cognitive impairment in MS. With respect to volumetric MRI, the grey and white matter volume (Sanfilipo et al., 2006), cortical lesions (Harrison et al., 2015), white matter lesion volume (Mineev et al., 2009), peripheral grey matter volume (Jonkman et al., 2015), subcortical structures' volume (Damjanovic et al., 2016) such as thalamus (Bergsland et al., 2016), hippocampus (Hulst et al., 2015), putamen (Debernard et al., 2015), caudate nucleus (Batista et al., 2012) and cerebellum (Valentino et al., 2009) and cingulate gyrus (Geisseler et al., 2016) have all been associated with cognitive function in MS. So far, it is the normalized brain volume and the lesion volume that are mainly investigated in clinical trials as an important endpoint for brain atrophy. To our knowledge, no study has examined simultaneously many two- and three-dimensional MRI markers with respect to cognitive function in the same sample of MS patients.

So, the primary aim of this study was to investigate the predictive

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ability of a large set of MRI structural markers for cognitive function in the same sample of relapsing-remitting MS (RRMS) patients. Another goal was to explore the differences between healthy controls (HCs) and MS patients with and without CI, with regards to various disease-related and psychological characteristics.

2. Materials and methods

2.1. Subjects

In this cross-sectional study, we invited 61 RRMS patients attending their follow-up outpatient visits in Aeginition and Army Share Fund Hospital (NIMTS) to participate in the study. The inclusion criteria were: (a) diagnosis of MS based on the revised 2010 McDonald criteria, (b) being over 18 years old, (c) fluency in Greek language, (d) Expanded Disability Status Scale (EDSS) below 6.0 and (e) ability to give written informed consent (Kurtzke, 1983; Polman et al., 2011). The exclusion criteria were the following: (a) major psychiatric disease (e.g. schizophrenia, drug and substance abuse etc.) or learning disability, (b) serious auditory or visual or other impairment that would affect the subject's ability to understand and perform assessments and (c) relapse and/or corticosteroid use within one month preceding the study assessments. A group of 51 healthy volunteers matched through age and gender served as HCs. The study was approved by the Hospitals' (Aeginition and Army Share Fund Hospitals) Ethics Committees and an informed consent was obtained from each participant. The study was performed in accordance with the good clinical practices and the Declaration of Helsinki.

Patient data included age, gender, education, working status, disease duration, number of relapses from onset, drugs and disability assessed with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983).

2.2. Neuropsychological testing

Patients and HCs were screened for their cognitive performance using the Brief International Cognitive Assessment for MS (BICAMS), a brief 15-min screening tool comprised of the Symbol Digits Modalities Test (SDMT), the California Verbal Learning Test II (CVLT-II) and the Brief Visuospatial Memory Test Revised (BVMT-R) (Langdon et al., 2012). The tool has been validated in Greece (Polychroniadou et al., 2016). SDMT assesses attention and information processing speed by asking the participant to voice the digit associated with each symbol presented in pseudo-random sequence of nine different symbols (after first presenting a series of nine symbols paired with a single digit each) as quickly as possible within 90 s. Score was derived by adding correct matchings within this time period. CVLT-II is a measure of verbal learning and memory testing the participant's ability to learn and recall 16 words over the course of five trials (theoretical range of score 0–80). Finally, BVMT-R evaluates visuospatial learning and memory by exposing the participants to a matrix of six simple designs for 10 s followed by an unaided drawing recall, repeated three times. Accuracy and location of each design were scored in each trial (theoretical range of score 0–36). A total cognitive score was calculated, based on the mean z scores of the three cognitive domains of BICAMS. CI was defined as deficits in at least one cognitive domain based on the lowest 5% cut-offs derived by normative age, gender and education adjusted data (i.e. using linear regression multivariate models for each cognitive score) of 207 available healthy volunteers.

2.3. Psychological assessments and Fatigue

Depression, anxiety and stress was measured using the Depression Anxiety Stress 21-item Scale (DASS-21). The responders declare the frequency of their symptoms in a Likert-type scale (from 0 = did not apply to me at all to 3 = applied to me very much, or most of the time) during the past week. Scores for each subscale each comprised by seven items were produced by summing up all items and multiplying by two (minimum score = 0, maximum score = 42). Higher scores indicate higher level of depression, anxiety or stress. The scale has been adapted in the Greek population (Lyrakos et al., 2011). In our study internal consistency was excellent (Cronbach's alphas: stress = 0.84, anxiety = 0.79 and depression = 0.84).

Visual analogue scales for physical (VAS-PF), cognitive (VAS-CF) and mental (VAS-MF) fatigue were completed by the participants. Each participant declared his/her level of fatigue during the last week by drawing a single point in a 10-cm line (from 0 no fatigue to 10 cm very much fatigue). Scores were derived by measuring the distance (in mm) from 0 to the point indicated. VAS scales for fatigue have been previously found reliable in MS patients (Kos et al., 2017).

2.4. MRI acquisition and analysis

Conventional MRI scans acquired within the last 6 months before the study assessment were available for the RRMS patients. All brain MRIs were performed at 3.0 T devices in multiple centers using the same acquisition MRI protocol: T1-weighted 3D high resolution magnetization-prepared rapid acquisition with gradient echo (3D MP-RAGE) sequence, axial T2-weighted fluid attenuated inversion recovery (FLAIR) sequence and axial proton density-weighted images. All scans were examined by an experienced observer.

On FLAIR images, lesions were identified and quantified (white matter lesion volume, WMLV) using a semi-automated local threshold technique as part of the Medical Images Processing Analysis and Visualization (MIPAV) software (https://mipav.cit.nih.gov/).

A set of two-dimensional linear manual methods of MRI assessments were used: third ventricle volume (TVV) and width (TVW), bicaudate ratio (BCR), corpus callosum index (CCI), frontal horn width (FHW) and transverse skull diameter (TSD) which is the minimum distance separating the inner tables of the skull at the level of the most rostral portion of the frontal horns (Bakshi et al., 2005; Butzkueven et al., 2008; De Stefano et al., 2007; Grassiot et al., 2009). TVV (in mm^3) was calculated by multiplying three different dimensions of the third ventricle recognized in the T1-weighted images; lamina terminalis-posterior commissure line, highest curvature of the inferior surface of fornix-upper surface of the mammillary body line and a line perpendicular to the interhemispheric fissure at third ventricle's midpoint (TVW). Normalized values were also calculated (NTVV = TVV ÷ TSD and NTVW = TVW ÷ TSD). The BCR was the minimum intercaudate distance (ICD) divided by brain width along the same line. The BCR was measured in the FLAIR axial slice where the heads of the caudate nuclei were most visible and closest to one another. Normalized ICD was also calculated (NICD = ICD ÷ TSD). CCI was obtained by drawing a straight line at greatest anteroposterior diameter of CC and a perpendicular at its midline. Anterior, posterior and medium segments of CC were measured and normalized to its greatest anteroposterior diameter. The FHW (in mm) was defined as the maximal distance between the lateral borders of the frontal horns of the lateral ventricles and was normalized (NFHW) with the TSD (NFHW = FHW ÷ TSD).

Volumetric analyses of the brain was also conducted using axial 3D MP-RAGE images and FMRI Software Library (FSL) (Smith et al., 2004). Brain tissue volume, normalized for subject head size, was estimated with SIENAX. SIENAX starts by extracting brain and skull images from the single whole-head input data (Smith, 2002). The brain image is then affine-registered to MNI152 (or Talairach) space (a reference brain map obtained from 152 healthy individuals) (using the skull image to determine the registration scaling); this is primarily in order to obtain the volumetric scaling factor, to be used as a normaliZation for head size (Jenkinson and Smith, 2001). Next, tissue-type segmentation with partial volume estimation is carried out in order to calculate normalized volumes for total normalized brain tissue (NBV), grey matter (GMV), peripheral grey matter (PGMV) and white matter (WMV) (Zhang et al.,