Journal of Neuroradiology (2015) 42, 141—149

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

ORIGINAL ARTICLE

Gray matter atrophy is associated with functional connectivity reorganization during the Paced Auditory Serial Addition Test (PASAT) execution in Multiple Sclerosis (MS)

Sabina Anna Baltruschat[a], **Noelia Ventura-Campos**[a], **Álvaro Javier Cruz-Gómez**[a], **Antonio Belenguer**[b], **Cristina Forn**[a,*]

[a] *Universitat Jaume I, Campus Riu Sec, Fac. Ciències de la Salut, Departament de Psicología Bàsica, Clínica i Psicobiología, Avd. Sos Baynat s/n, 12071 Castelló de la Plana, Spain*
[b] *Hospital General de Castellón, Servicio de Neurología, Castelló de la Plana, Spain*

Available online 6 April 2015

KEYWORDS
Multiple sclerosis (MS);
Paced Auditory Serial Addition Test (PASAT);
Gray matter (GM) atrophy;
Functional connectivity;
Compensatory processes

Summary
Background and purpose: We explored the relationship between gray matter atrophy and reorganization of functional connectivity in multiple sclerosis patients during execution of the Paced Auditory Serial Addition Test (PASAT).
Materials and methods: Seventeen patients and 15 healthy controls were selected for the study. Atrophy was determined using voxel-based morphometry, and atrophy-related connectivity changes were assessed using psychophysiological interaction analysis. Group differences, and correlations with PASAT performance and radiological variables were also examined.
Results: Gray matter atrophy in MS patients was circumscribed to the bilateral posterior cingulate gyrus/precuneus. Compared with controls, patients showed stronger connectivity between the left posterior cingulate gyrus/precuneus, and the left middle temporal gyrus and left cerebellum. A regression analysis in controls showed a negative correlation between PASAT scores and functional connectivity between: (1) the left posterior cingulate gyrus/precuneus, and left pre/postcentral gyri and left occipital gyrus, and (2) the right posterior cingulate gyrus/precuneus, and bilateral cerebellum and left pre/postcentral gyri. Patients showed a

Abbreviations: MS, multiple sclerosis; PASAT, Paced Auditory Serial Addition Test; HC, healthy controls; GM, gray matter; WM, white matter; VBM, voxel-based morphometry; AC-PC, anterior-posterior commissure; PPI, psychophysiological interaction; MNI, Montreal Neurological Institute; BPF, brain parenchymal fraction; DARTEL, diffeomorphic anatomical registration through exponential lie algebra; PCG, posterior cingulate gyrus; DMN, default mode network.

* Corresponding author. Tel.: +0034964727663.
E-mail address: forn@psb.uji.es (C. Forn).

http://dx.doi.org/10.1016/j.neurad.2015.02.006

negative correlation between brain parenchymal fraction and functional connectivity between the left posterior cingulate gyrus/precuneus and left cerebellum.
Conclusion: Patients with early MS and little brain damage presented more connectivity during PASAT execution, which may be interpreted as compensatory processes that help preserve cognitive functions.

Introduction

Cognitive deterioration is characteristic of multiple sclerosis (MS), occurring in 43—70% of patients with early MS. In this population, impairments are frequently observed in information processing speed, attention processes, working memory, long-term memory, and executive function [1]. These cognitive deficits are frequently assessed using the Paced Auditory Serial Addition Test (PASAT), which demands information processing speed and working memory resources, and is consequently very sensitive to cognitive decline in MS patients [2,3].

Neuroimaging has been important for studying functional and structural neural differences between MS patients and healthy controls (HC) [4,5], and associating them with specific cognitive deficits. Several fMRI-based studies found greater neural activation in cognitively preserved MS patients able to perform the PASAT accurately [2,6—8].

Similarly, using different connectivity analysis approaches and compared to healthy controls, several studies have observed that MS patients show enhanced connectivity between different cortical areas during execution of the PASAT [9—11]. These enhancements of activation and connectivity observed in MS patients have been interpreted as compensatory processes resulting from cortical reorganization that might dampen (at least in some stages of MS) the deficits produced by gray matter (GM) and white matter (WM) atrophy [7—12].

Although previous studies have revealed the emergence of compensatory mechanisms in MS patients that allow them to cope with brain damage, there is no information on whether or not there is colocalization of brain damage and these adaptations. To address this, we designed the present study to determine the potential influence of the location of GM atrophy on the anatomical localization of this cortical reorganization in cognitively preserved MS patients. We first used voxel-based morphometry (VBM) to locate the atrophy and then a psychophysiological interaction (PPI; [13]) analysis to study how atrophy affects functional connectivity between these areas and the rest of the brain. Following previous results, we expected active compensatory processes to be secondary to GM atrophy.

Materials and methods

Participants

Seventeen (11 females) right-handed patients from Hospital General de Castellón with relapsing-remitting MS according to McDonald criteria [14] were selected and neurologically assessed using the Expanded Disability Status Scale. Fifteen (seven females) matched HC with no history of psychiatric or neurological illness were also recruited. See Table 1 for participant characteristics.

To guarantee appropriate PASAT performance, we only enrolled participants who scored greater than 1 SD below the mean in the PASAT 3-s version in accordance with normative data established by Sepulcre et al. [15]. All participants gave written consent and the study protocol was approved by the ethics committees of Hospital General de Castellón and Universitat Jaume I.

Neuropsychological assessment

After neurological assessment and before MRI acquisition, participants were cognitively assessed using the Brief Repeatable Battery of Neuropsychological Tests validated in a Spanish population [15]. The Matrix Reasoning subtest of the Wechsler Adult Intelligence Scale (WAIS III), were used to assess intelligence quotient, and Fatigue Severity Scale were also administered.

MRI acquisition

Participants were scanned with a 1.5T scanner (Siemens Avanto, Erlangen, Germany) using a gradient-echo EPI sequence (TR/TE = 3000/30 ms, matrix = 64×64); 29 slices (voxel size $4 \times 4 \times 4.5$). Slices were acquired in the axial plane parallel to the anterior-posterior commissure (AC-PC) from bottom to top, covering the entire brain. A morphological, volumetric, sagittal T1-weighted sequence was acquired (TR/TE = 11/4.9 ms, FOV = 24 cm, matrix = $256 \times 224 \times 176$, voxel size = $1 \times 1 \times 1$ mm).

Experimental design

Participants were instructed to perform an fMRI-adapted auditory version of the PASAT [2]. A block design was used with six blocks of 1 min each, three each for the control and active conditions. During the control condition, participants were instructed to repeat the last number heard. During the active condition, participants performed the PASAT by adding up the last two numbers heard. Single-digit numbers (excluding zero) were randomly presented every 3 s. Participants were asked to give overt verbal responses, which were recorded by an observer inside the room. Task stimuli were presented using fMRI-compatible headphones (VisuaStim; Resonance Technologies, Inc., Los Angeles, California, USA). The volume was adjusted so that each participant could hear the PASAT stimuli properly. Before scanning, participants underwent a 10-min practice session involving different stimuli presented in the scanner. Foam cushioning