Hippocampal dysfunction is associated with memory impairment in multiple sclerosis: A volumetric and functional connectivity study

Julio Alberto González Torre [1] * and Álvaro Javier Cruz-Gómez [1] *; Antonio Belenguer [2], Carla Sanchis-Segura [1], César Ávila[1], Cristina Forn [1]

* These authors contributed equally to the manuscript.

1. Universitat Jaume I. Departament de Psicología Bàsica, Clínica i Psicobiología. Castelló de la Plana. Spain.
2. Servicio de Neurología. Hospital General de Castellón, Castelló de la Plana. Spain.

Corresponding Author:
Cristina Forn, PhD
forn@psb.uji.es
Dept. Psicologia Bàsica, Clínica i Psicobiologia
Campus Riu Sec
Fac. Ciències Humanes i Socials
Universitat Jaume I
E-12071 Castelló
SPAIN

BACKGROUND: Previous studies have suggested a relationship between neuroanatomical and neurofunctional hippocampal alterations and episodic memory impairments in multiple sclerosis (MS) patients

OBJECTIVE: We examined hippocampus volume and functional connectivity (FC) changes in MS patients with different episodic memory capabilities.

METHODS: hippocampal subfield volume and FC changes were compared in two subgroups of MS patients with and without episodic memory impairment (MSi and MSp, respectively) and healthy controls. A discriminant function (DF) analysis was used to identify which of these neuroanatomical and neurofunctional parameters were the most relevant components of the mnemonic profiles of HC, MSp and MSi.

RESULTS: MSi showed reduced volume in several hippocampal subfields compared to MSp and HC. Ordinal gradation (MSi>MSp>HC) was also observed for FC between the posterior hippocampus and several cortical areas. DF-based analyses revealed that reduced right fimbria volume and enhanced FC at the right posterior hippocampus were the main neural signatures of the episodic memory impairments observed in the MSi group.

CONCLUSIONS: Before any sign of episodic memory alterations (MSp), FC increased on several pathways that connect the hippocampus with cortical areas. These changes further increased when the several hippocampal volumes reduced and memory deficits appeared (MSi).

Key words: hippocampus, episodic memory, MRI, gray matter, resting state, functional connectivity.

1. Introduction

Memory deficits are commonly found in multiple sclerosis (MS), more specifically those that affect episodic memory, with prevalence rates ranging between 40-75% of patients [1]. According to current memory models, the hippocampus plays a critical role in the formation of new episodic memories [2].

Neuroimaging techniques have proven very important for studying neuroanatomical and functional changes in MS, and attempts have been made to associate them with specific cognitive deficits. Indeed some recent studies have investigated the relationship between anatomical and functional hippocampal damage and episodic memory impairment in MS patients. One of the first studies [3] revealed reduced volume in the CA1 subfield of the hippocampus in patients with relapsing-remitting (RR) MS, and a more global loss of hippocampal volume in patients with secondary progressive (SP) MS. This study also showed that reduced hippocampal volume correlated with the reduced ability to learn verbal information [3]. Susceptibility of loss of volume in the subfield of CA1 in MS patients has also been described in a more recent study [4]. The authors observed reduced volume to the left and right of the CA1 subfield in different subtypes of MS patients (RR, SP, primary progressive –PP– and benign MS), which correlated with performance in visual and verbal memory tasks. A similarly reduced hippocampal volume in MS patients with the RR and PP forms has also been reported [5], but only a statistically marginal relationship was observed between loss of hippocampus volume and memory performance.

Only two previous studies have explored hippocampal functional connectivity (FC) in the resting state and episodic memory performance in MS patients. These studies have shown apparently opposing results: while Hulst et al., (2015) [6] found increased FC in several specific hippocampal subfields in memory impaired MS patients, Roosendaal et

al., (2010) [7] reported decreased hippocampal FC. This discrepancy might be related to the cognitive status of the patients recruited in each study. It is worth noting that the MS patients in the former study presented memory impairments, while those in the second one did not.

Therefore, very few data are available that confirm a possible relationship between hippocampal alterations and episodic memory performance in MS patients. Such evidence to date is far from conclusive, and the possible relationship that links hippocampal volume, FC changes and episodic memory capabilities needs to be further investigated to clarify the mechanisms that underlie alterations in these cognitive domains that are commonly found in MS patients. For this reason, the aims of the present study were to: 1) describe possible changes in the hippocampal volume subfields in MS patients with episodic memory impairments (labeled MS impaired –MSi–) and with normal episodic memory performance (labeled MS preserved –MSp–); 2) describe FC changes observed in different hippocampal subfields in the MSi and MSp groups; 3) assess the relationship between episodic memory performance and the anatomical and FC changes observed in both patient groups (MSp and MSi).

2. Methods

2.1. Participants

Sixty-four patients diagnosed with definite MS according to the revised Mc Donald criteria [8] from the Hospital General de Castelló were enrolled in this study; 53 had the relapsing-remitting (RR) subtype of the disease, and 11 patients had the secondary-progressive (SP) subtype. In order to be included, all the patients had to be relapse- and steroid-free for at least 2 months prior to the study. Eighteen healthy volunteers with no previous history of neurologic dysfunctions were the control subjects.

All the patients were neurologically evaluated using the Expanded Disability Status Scale [9] (EDSS) and were neuropsychological assessed with memory subtests of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), validated for the Spanish population [10]. Verbal memory was assessed by the *Selective Reminding Test* (including long-term storage, retrieval and delayed recall scores), while visual memory was assessed by the *10/36 Spatial Recall Test* (including long-term storage and delayed recall scores). Subsequently, we computed the global Z scores for both the verbal and visual memory domains following the criteria developed by Sepulcre [10].

Verbal memory Z-score (Zve) = (SRT Long-Term Storage Z + SRT Consistent Long-Term Retrieval Z+ SRT Delayed Recall Z) / 3

Visual memory Z-score (Zvi) = (SPART Long-Term Storage Z + SPART Delayed Recall Z) / 2

MS patients whose scores were 1.5 standard deviations below the corresponding normative mean in at least one global memory score (verbal or visual) were considered mnemonically impaired (MSi; n=33). The rest were considered mnemonically preserved (MSp; n=31).

The *Matrix Reasoning Subtest* of the *Wechsler Adult Intelligence Scale (WAIS-III)* [11] was used to assess the intelligence quotient (IQ). The *Fatigue Severity Scale* [12] was also administered. This study was approved by the Ethics Standards Committees of the General Hospital de Castelló and the Universitat Jaume I. All the participants gave informed written consent prior to participating.

2.2. MRI acquisition

Anatomical high-resolution three-dimensional MPRAGE T1 images were acquired in a 1.5 T scanner (Siemens Avanto, Erlangen, Germany, TR = 11 ms, TE = 4.9 ms, FOV =

24 cm, matrix = 256 x 224 x 176, voxel size = 1 x 1 x 1 mm). In addition to the structural sequences, fMRI resting-state 270 volumes were recorded over 9 min using a gradient-echo T2*-weighted echo-planar imaging sequence (TR/TE = 2000/30 ms, matrix = 64 x 64 x 30, voxel size = 3.5 x 3.5 x 4.02 mm, flip angle = 90º). During the resting sequence, participants were instructed to remain motionless and to relax with their eyes closed, to not fall asleep and to think of nothing in particular.

2.3. Hippocampal Subfield Volumes

First, T1-hypointense lesions were identified and filed as previously described [13]. Total lesion volume in milliliters (ml) was obtained using JIM software (Version 5.0, Xinapse Systems, Northants, UK; http://www.xinapse.com. Structural T1-weighted images were processed by Freesurfer 5.3, a fully automated image analysis package for the volumetric segmentation of hippocampal subfields (http://surfer.nmr.mgh.harvard.edu). The technical details of these procedures are available in previous publications [14]. Briefly, the automatic reconstruction process includes motion correction, removal of non brain tissue by a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter structures, intensity normalization, tessellation of the gray matter/white matter boundary, automated topology correction, and surface deformation following gradients to place the gray/white and gray/cerebrospinal fluid borders optimally at the location where the greatest shift in intensity defines the transition to the other tissue type. Subcortical segmentation is achieved by aligning the target image with an atlas constructed from a set of labeled training images, from which gray and white matter as well as total intracranial volumes were extracted.

We specified that the automatic reconstruction command should include the hippocampal subfields segmentation. This procedure uses Bayesian inference and a

probabilistic atlas of the hippocampal formation, which is based on manual delineations of the subfields in T1-weighted MRI scans from a number of different subjects [15]. Segmentation uses a tetrahedrical mesh-based probabilistic atlas that is deformed from its original reference position of the mesh nodes. The hippocampal subfield segmentation implemented in Freesurfer segments both the hippocampi of each subject into eight subfields, including the cornu ammonis 1 (CA1), cornu ammonis 2-3 (CA2-3), cornu ammonis 4-dentade gyrus (CA4-DG), subiculum, presubiculum, fimbria, hippocampal fissure and posterior hippocampus. The technical details of these procedures have been described elsewhere [16].

We obtained two outputs from this procedure: (1) a probabilistic ROI for each subject for each hippocampal subfield in the native space (see **Figure 1 a, b**), and (2) a table of estimated volumes for each subject and each subfield in mm^3. The segmentation ROI results of the hippocampal subfields were visually inspected for errors in all the data sets. We found no errors or misclassifications.

2.4. Hippocampal subfield regions of interest

We applied the same procedure for hippocampal subfield segmentation with the "ch2" template included in MRIcron (www.sph.sc.edu/comd/rorden/mricron) to obtain the same probabilistic maps for each hippocampal structure in a standard MNI space. Each probability map was transformed into binary masks with IMcalc from SPM12 at a threshold of 95%. The correct anatomical localization of these masks in the different hippocampal sub-regions after transformation of native space MPRAGE T1 images to MNI space was visually confirmed for each single participant. Each binary mask was used as functional connectivity (FC) seeds in the subsequent analyses (see **Figure 1 c)**.

2.5. Resting state functional connectivity (rs-FC) analysis

Resting-state fMRI scans were pre-processed by the DPARSF V4.1 tool [17] and included: removing the first 10 functional scans to reach a signal equilibrium, slice timing correction, realignment to the first scan of each session, head motion correction, coregister, nuisance covariates regression to remove effects of possible artifacts (including head motion, scrubbing regressors, white matter signal and CSF signal), spatial normalization with a resampled voxel size of 3 mm^3 to the Montreal Neurological Institute (MNI) space, and spatial smoothing with an isotropic Gaussian kernel of 4-mm full width at half maximum (FWHM). Next temporal filtering (0.01 Hz - 0.08 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency noise.

Previous hippocampal subfields ROIs segmented in the MNI space were resampled to the functional data dimensions, to obtain 14 seeds that corresponded to the bilateral CA1, CA2-3, CA4-DG, Fimbria, Presubiculum, Subiculum and Posterior Hippocampus. The hippocampal fissure seed was excluded for its non brain tissue localization. Individual voxel-wise rs-FC maps were computed for each subject at each seed.

2.6. Statistical Analysis

All volumetric measures were normalized by the subject's intracranial volume (ICV), derived from Freesurfer with the following formula: $volume_{norm} = volume_{raw} \times 1000 /$ ICV in cm^3 [18].

A statistical analysis was conducted with SPSS 23. Categorical variables were inspected using a Chi square test, and continuous variables were compared using an ANCOVA with Bonferroni *post hoc* comparisons.

Hippocampal subfield volumes were compared for the three groups with an ANCOVA. Each volume was included as a dependent variable, a subgroup as the factor with three

levels (HC, MSp and MSi), and were covariated by age and gender. The statistical significance areas derived from the previous ANCOVA were included in the correlation analysis to observe the relationship between these areas and the memory Z scores.

FC differences between groups were assessed by an ANCOVA design in SPM v12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK), including age and gender as nuisance covariates. All the FC results were assessed at $p < 0.05$ FWE cluster-corrected for the multiple comparisons in a combination with a threshold of $p < 0.001$ at the uncorrected voxel level.

A step-wise discriminant function analysis was performed to identify which of all the previously described neuroanatomical (hippocampal subfield volumes) and neurofunctional (rs-FC) parameters were relevant for discriminating the three experimental groups of the present study.

3. Results

3.1 Demographic, clinical and structural results

As summarized in Table 1, the HC group showed more years of education and obtained higher IQ scores than the MSi and MSp groups (which did not differ between them). On the other hand, MSi patients displayed higher EDSS scores and longer disease duration than MSp. Similarly, MSi patients showed more lesion volume, less total gray matter and reduced hippocampal volume than MSp and HC. No differences were observed in the rest of variables.

3.2 Hippocampal subfields volume

Regarding the hippocampal subfield analyses, the volumes between the HC and MSp group did not differ in any area. Compared to the HCs and MSp groups, MSi patients showed significant volume loss in the left Presubiculum and Subiculum, left CA2-3, left

Fimbria, left CA4-DG and right Fimbria. The MSi patients also showed a smaller volume in the right posterior hippocampus compared to the HC group, but not to the MSp group (see **Table 2**). A posterior correlation analysis showed positive relationships in the MSi group, specifically between the Zvi scores and both the left and right Fimbria volumes ($r=0.41$, $p<0.05$ and $r=0.45$, $p< 0.01$, respectively). No significant correlations were found in the MSp group.

3.3 FC of hippocampi with other brain areas

FC significant differences between groups were observed, but only in the bilateral posterior hippocampus seeds, and are summarized in **Table 3.** The rest of the FC hippocampal subfield seeds showed no significant differences between groups. Both MSp and MSi exhibited a higher FC between both the posterior hippocampi and several posterior and anterior cortical areas compared with HC (see **Figure 2**). MSi displayed higher FC between the right posterior hippocampus and the left frontal areas and bilateral thalamus compared with MSp. The eigenvalues of these significant clusters were extracted and correlated negatively with the Zve and Zvi scores in the MS (MSi + MSp) patients. The Zve scores correlated negatively with the FC observed between the right posterior hippocampus and the left inferior frontal gyrus ($r=-0.34$, $p<0.01$), and between the left superior frontal gyris ($r=-0.43$, $p<0.01$) and the bilateral thalamus ($r=-0.43$, $p<0.01$). The Zvi scores correlated negatively with the FC scores between the right posterior hippocampus and the left inferior frontal gyrus ($r=0.26$, $p<0.05$) and the left superior frontal gyrus ($r=-0.33$, $p<0.01$).

3.4 Discriminant analysis

The discriminant functional analysis produced two different functions. The first (DF1) yielded statistical significance (Wilks lambda=0.524; Chi-square (4)= 50.703, $p<0.001$) and explained most of the variance (eigenvalue: 0.863; accounted variance: 97.3%), and hence satisfactorily discriminated (canonical correlation: 0.68) MSi patients from the other two groups (HC and MSp). This function was composed of two predictors of very similar importance, but with the opposite sign; the right fimbria volume (Fisher standardized coefficient: -0.720; Wilks lambda=0.699) and the FC observed between the right posterior hippocampus and the left superior frontal gyrus (Fisher standardized coefficient: 0.754; Wilks lambda=0.524). Therefore, the FC increased on this pathway but the reduced right fimbria volume resulted in positive values on the DF1 that were characteristic of MSi (group centroid: 1.1), but not of MSp patients or the HC (groups centroids -0.703 and -0.824, respectively). The second discriminant function did not achieve statistical significance (Wilks lambda= 0.976; Chi-square(1)= 1.869, p=0.172) and showed a very low canonical correlation (0.153) and eigenvalue (0.024), and was rendered to be of no further use. See Figure 3

Discussion

To investigate the underlying mechanisms related to episodic memory impairment in MS patients, we used a comprehensive combination of anatomical and functional neuroimaging methods, and focused our study on the hippocampus. More specifically to quantify the hippocampus volume, we used the Freesurfer tool. This is an automated method that produces accurate segmentation on deep GM structures in MS patients [19]. Functional hippocampal connectivity and the relationships between these two variables

and episodic memory were also assessed in two groups of MS patients, with and without episodic memory impairments (MSi and MSp, respectively).

We identified anatomical hippocampal damage in MSi patients compared to HC and MSp patients. An asymmetrical (left>right) decreased volume in different parts of the hippocampus in the patients with memory impairment (MSi) was observed compared to MSp patients, and HC was also observed. This result agrees with those reported in MS patients[3] and in other neurological populations characterized by episodic memory deficits, such as Alzheimer's disease (AD) patients [20,]. While the possible significance of this lateralization effect remains unclear, the largest differences lay between the MSi patients and HC in hippocampal volume were observed at the left presubiculum and subiculum, and in CA4-DG. The volumes of these subfields in MSi also significantly reduced compared to those of the MSp patients, but this difference was smaller than that observed in the HC comparison (see Table 2). This once again suggests a similar atrophy progression pattern to that described in AD, in which hippocampal degeneration initially affected the presubiculum and subiculum, followed by atrophy in the CA4-DG and CA3-2 and at the end of the CA 1 subfield [21].

Our study also showed increased FC between the left and right posterior areas of the hippocampus and other cortical areas in both patient groups (MSi and MSp) compared to HC. We also observed that MSi patients displayed stronger connections between the right hippocampus and some frontal areas compared to the MSp patients. In line with this, previous studies [22-24] have suggested that enhanced FC is a secondary consequence of neural atrophy which in some instances, but not always [6,] and might act as a compensatory mechanism to allow MS patients to retain normal cognitive competence. However, FC was higher in MSi than in the MSp patients, and was also higher in MSp than in HC. So in this case, increased FC did not seem to act as a compensatory

mechanism, rather as another sign of MS neuropathology progression in the hippocampus. We did not find FC differences between MSp and MSi patients regarding FC in the whole left or whole right hippocampus. This suggests that the hippocampal alterations identified in this study are highly specific and affect to a relatively small proportion of hippocampal circuits, then getting masked when global analyses are performed. This observation highlights the importance fine grain analyses at specific hippocampal sub-regions to detect correlates of subtle/ moderate deficits.

Our results revealed a solid and statistically significant relationship between memory performance and some neuroanatomical and neurofunctional parameters. More specifically, we observed statistically significant inverse correlations between FC and verbal and visual memory performance. An inverse gradation (MSi< MSp< HC) for the volume and the left and right fimbria was found, and the remaining volume in these areas correlated directly to the visual memory performance in the MSi patients. Interestingly, the combination of only two of these variables (right fimbria volume and connectivity in the posterior hippocampus) yielded a powerful discriminant function that was able to distinguish MSi from MSp and HC, which were mutually indistinguishable using these, or any other variable, measured herein.

These results extend those obtained in previous studies, which indicates that reduced hippocampal volume is associated with reduced episodic memory in MS patients [3–5]. Our results agree with a recent study that showed increased FC in specific hippocampal regions in MS patients with memory impairment [6]. Nevertheless, in this study we did not evaluate other functions that could interfere with episodic memory execution (e.g. information processing speed). Such a limitation should be explored in future studies to definitively confirm the specificity of the relationship between hippocampal alterations and mnemonic capabilities in MS patients. Similarly, the possible effect of depression and anxiety-related symptomatology with episodic memory deficits in this population should also be assessed. Finally, the spatial specificity required in this kind of studies

demands the use of small ROIs that might also potentially result in increased noise, voxel misplacement and increased chances of misregistration. However, as we have described in the methods section, ROIs localization was verified for each participant's images and additional control procedures were applied to minimize the occurrence/ impact of these potential problems.

In conclusion, the results of the present study demonstrated that, compared to HC, MS patients present stronger connectivity between the hippocampus and cortical areas. These changes even appear in patients with no episodic memory problems and before any measurable degree of atrophy. As a result, we interpret that these FC changes are an early sign of future episodic memory alterations. Nonetheless, episodic memory problems only become evident in patients that already present substantially reduced hippocampal gray matter volume. Future studies with subgroups of MS patients with different episodic memory performance are needed to clarify whether early functional hippocampal changes are a clinically useful predictor of episodic memory problems in MS patients.

This study was sponsored by grants P1-1B2014-15 awarded by Universitat Jaume I and PSI2015-67285-R awarded by MINECO to Dr. Cristina Forn.

Bibliography

1 Amato MP, Zipoli V, Portaccio E. Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *J Neurol Sci* 2006; 245:41–6.

2 Ranganath C, Ritchey M. Two cortical systems for memory-guided behaviour. *Nat Rev Neurosci* 2012;13:713–26.

3 Sicotte NL, Kern KC, Giesser BS, *et al.* Regional hippocampal atrophy in multiple sclerosis. *Brain* 2008;131:1134–41.

4 Longoni G, Rocca M a., Pagani E, *et al.* Deficits in memory and visuospatial learning correlate with regional hippocampal atrophy in MS. *Brain Struct Funct* 2015;220:435–44.

5 Anderson V, Fisniku L, Khaleeli Z, *et al.* Hippocampal atrophy in relapsing-remitting and primary progressive MS: a comparative study. *Mult Scler* 2010;16:1083–90.

6 Hulst HE, Schoonheim MM, Van Geest Q, *et al.* Memory impairment in multiple sclerosis: Relevance of hippocampal activation and hippocampal connectivity. *Mult Scler J* 2015;21:1705–12.

7 Roosendaal SD, Hulst HE, Vrenken H, *et al.* Structural and functional hippocampal changes in multiple sclerosis patients with intact memory function. *Radiology* 2010;255:595–604.

8 Polman CH, Reingold SC, Banwell B, *et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.

9 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.

10 Sepulcre J, Vanotti S, Hernández R, *et al.* Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. *Mult Scler* 2006;12:187–95.

11 Wechsler D. *Wechsler Adult Intelligence Scale (3rd edition)*. San Antonio: : TX: Psychological Corporation 1997.

12 Krupp LB, LaRocca NG, Muir-Nash J, *et al.* The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–3.

13 Gelineau-Morel R, Tomassini V, Jenkinson M, *et al.* The effect of hypointense white matter lesions on automated gray matter segmentation in multiple sclerosis. *Hum Brain Mapp* 2012;33:2802–14.

14 Fischl B. FreeSurfer. *Neuroimage* 2012;62:774–81.

15 Van Leemput K, Bakkour A, Benner T, *et al.* Automated segmentation of hippocampal subfields from ultra-high resolution in vivo MRI. *Hippocampus* 2009;19:549–57.

16 Engvig A, Fjell AM, Westlye LT, *et al.* Hippocampal subfield volumes correlate with memory training benefit in subjective memory impairment. *Neuroimage* 2012;61:188-94.

17 Chao-Gan Y, Yu-Feng Z. DPARSF: A MATLAB Toolbox for 'Pipeline' Data Analysis of Resting-State fMRI. *Front Syst Neurosci* 2010;4:13.

18 Westman E, Aguilar C, Muehlboeck J-S, *et al.* Regional Magnetic Resonance Imaging Measures for Multivariate Analysis in Alzheimer's Disease and Mild Cognitive Impairment. *Brain Topogr* 2013;26:9–23.

19 Derakhshan M, Caramanos Z, Giacomini PS, *et al.* Evaluation of automated techniques for the quantification of grey matter atrophy in patients with multiple sclerosis. *Neuroimage* 2010;52:1261–7.

20 Barnes J, Scahill RI, Schott JM, *et al.* Does Alzheimer's disease affect hippocampal asymmetry? Evidence from a cross-sectional and longitudinal volumetric MRI study. *Dement Geriatr Cogn Disord* 2005;19:338–44.

21 Carlesimo GA, Piras F, Orfei MD, *et al.* Atrophy of presubiculum and subiculum is the earliest hippocampal anatomical marker of Alzheimer's disease. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 2015;1:24–32.

22 Schoonheim MM, Geurts JJG, Barkhof F. The limits of functional reorganization in multiple sclerosis. *Neurology* 2010;74:1246–7.

23 Baltruschat SA, Ventura-Campos N, Cruz-Gómez ÁJ, *et al.* Gray matter atrophy is associated with functional connectivity reorganization during the Paced Auditory Serial Addition Test (PASAT) execution in Multiple Sclerosis (MS). *J Neuroradiol* 2015;42:141–9.

24 Cruz-Gómez ÁJ, Ventura-Campos N, Belenguer A, *et al.* The link between resting-state functional connectivity and cognition in MS patients. *Mult Scler* 2014;20:338–48.