Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
0(0) 1–11

DOI: 10.1177/1352458513495584
msj.sagepub.com
SAGE

The link between resting-state functional connectivity and cognition in MS patients

Álvaro J Cruz-Gómez[1], Noelia Ventura-Campos[1], Antonio Belenguer[2], Cesar Ávila[1] and Cristina Forn[1]

Abstract

Background/Objective: The objective of this paper is to explore differences in resting-state functional connectivity between cognitively impaired and preserved multiple sclerosis (MS) patients.

Methods: Sixty MS patients and 18 controls were assessed with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N). A global *Z* score of the BRB-N was obtained and allowed us to classify MS patients as cognitively impaired and cognitively preserved ($n = 30$ per group). Functional connectivity was assessed by independent component analysis of resting-state networks (RSNs) related to cognition: the default mode network, left and right frontoparietal and salience network. Between-group differences were evaluated and a regression analysis was performed to describe relationships among cognitive status, functional connectivity and radiological variables.

Results: Compared to cognitively preserved patients and healthy controls, cognitively impaired patients showed a lesser degree of functional connectivity in all RSNs explored. Cognitively preserved patients presented less connectivity than the control group in the left frontoparietal network. Global *Z* scores were positively and negatively correlated with brain parenchymal fraction and lesion volume, respectively.

Conclusion: Decreased cognitive performance is accompanied by reduced resting state functional connectivity and directly related to brain damage. These results support the use of connectivity as a powerful tool to monitor and predict cognitive impairment in MS patients.

Keywords

Resting state functional connectivity, cognitive impairment, default network, right frontoparietal network, left frontoparietal network

Date received: 14 March 2013; revised: 3 June 2013; accepted: 5 June 2013

Introduction

Multiple sclerosis (MS) is an autoimmune disease that causes demyelination that may alter the dynamic communication within nodes of large-scale brain networks, then contributing to the characteristic deficits observed in MS patients, including neuropsychological impairment.[1]

Functional magnetic resonance imaging (fMRI) has been extensively used to study the cognitive status of MS patients. Many of these studies[2–8] have used fMRI in conjunction with attention or working memory tasks because these cognitive functions recruit frontal and parietal areas that seem to work together, requiring correct interconnection between both cortices.[3] A major finding of these studies is that, at least in early phases of MS when cognitive impairment is not yet detectable, patients activate additional brain areas to compensate for potential functional deficits.[2,6,7] This observation has been supported and expanded on by studies describing enhanced connectivity as a neuroplasticity mechanism that probably compensates for cognitive deficits at early stages of the disease.[3,5,8,9]

Despite this possible convergence among different studies, interpreting brain activity patterns during cognitive

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

Corresponding author:
Cristina Forn, Departament Psicología Bàsica, Clínica i Psicobiología, Campus Riu Sec, Fac. Ciències de la Salut, Universitat Jaume I, E-12071 Castelló, Spain.
Email: forn@psb.uji.es

task performance can present difficulties, particularly when trying to identify compensatory adaptations in neurological populations. First, to conclude that there is functional reorganisation secondary to a possible deficit,[5–7] patients must execute the task with similar accuracy as the control group. Second, differences in brain activation patterns may arise from using different strategies to solve a task, especially if tasks involve complex cognitive operations, thus complicating interpretation of results.[5,10] These drawbacks can be avoided by using fMRI while participants remain motionless with their eyes closed, providing a window into neuronal processes. In this situation, RSNs consume the vast majority of the brain's resources and may prove a richer source of disease-related signal changes in patients with a range of different cognitive profiles regardless of task execution.[11] The few studies describing differences in RSN synchronisation associated with the cognitive status of MS patients had somewhat conflicting results. Some showed evidence of decreased resting-state functional connectivity (rs-FC) in MS patients compared with healthy participants.[12,13] Others found that MS patients with normal cognitive performance and less structural damage showed greater rs-FC than patients with cognitive impairment and greater structural damage.[12,14–16] These authors interpreted enhanced rs-FC as a possible compensatory mechanism that can promote the maintenance of cognitive competence in the initial stages of MS. However, other results seem to contradict this proposal. Faivre et al.[17] evidenced increased rs-FC in MS patients compared with healthy controls (HCs) but found a negative correlation between rs-FC and execution of the Paced Auditory Serial Addition Test assessing cognitive function. Moreover, Hawellek et al.[1] described increased rs-FC as directly related to cognitive impairment, contradicting the hypothesis of adaptive or compensatory effects.

Taking these precedents into account, the present work aims at providing new evidence on the possible use of RSN activity to characterise cognitive deficits of MS patients. For this, we concentrated not only on functional connectivity in the default mode network (DMN) but also in less explored RSNs: the left and right frontoparietal networks (LFPN and RFPN, respectively) and salience network. More specifically, we assessed the functional connectivity of these three RSNs in HCs and two groups of MS patients differing in cognitive status. We sought to find possible functional connectivity alterations underlying the cognitive impairment observed in some MS patients, and to assess the possible existence of compensatory mechanisms in MS patients with preserved cognition.

Methods

Participants

A total of 60 right-handed MS patients (39 women) were recruited from the Hospital General de Castellón and diagnosed with relapsing–remitting MS according to the revised McDonald criteria.[18] Exclusion criteria included alcohol or other drug abuse, and history of psychiatric or any other cerebral diseases. Patients were not enrolled in the study if they received treatment with corticosteroids in the two months prior to the investigation. The disease severity of all patients was measured with the Expanded Disability Status Scale (EDSS) during the week of the scanning procedure.[19] A control group of 18 right-handed HCs (eight women) with no history of medical disability were also included in this study.

Cognitive assessment

All participants were neuropsychologically assessed with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) validated for the Spanish population[20] that includes the Selective Reminding Test (SRT) and 10/36 Spatial Recall Test (SPART), which respectively assess verbal and visuospatial learning. Furthermore, the Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test-3 seconds (PASAT-3) were used as measures of information processing speed and working memory. Finally, the Word List Generation Test (WLGT) was used as an index of executive function.

Following the criteria described by Calabrese et al.,[21] MS participants whose scores were two standard deviations below the corresponding normative mean on at least one test of the BRB-N were considered cognitively impaired (CI; $n = 30$) and the rest were considered cognitively preserved (CP; $n = 30$).

Approval was received from the local ethical standards committee on human experimentation, and written informed consent was obtained from all subjects participating in the study.

MRI data acquisition

FMRI resting-state data were acquired on a 1.5 T scanner (Siemens Avanto, Erlangen, Germany). A total of 270 volumes were recorded over nine minutes using a gradient-echo T2*-weighted echo-planar imaging sequence (repetition time (TR)/echo time (TE) = 2000/30 ms, matrix = 64 × 64 × 30, voxel size = 3.5 × 3.5 × 4.02 mm, flip angle = 90º). During the resting sequence, participants were instructed to stay motionless and relaxed with their eyes closed, to not fall asleep and to think of nothing in particular. Prior to the functional sequences, sagittal high-resolution three-dimensional (3D) MPRAGE T1 images were acquired (TR = 11 ms, TE = 4.9 ms, field of view (FOV) = 24 cm, matrix = 256 × 224 × 176, voxel size = 1 × 1 × 1 mm).

Brain and lesion volume measurements

Using high-resolution 3D images and the segmentation tool of Statistical Parametric Mapping 8 (SPM8; Wellcome

Trust Centre for Neuroimaging, London, UK), the brain parenchymal fraction (BPF) was computed for each participant according to the procedure described by Sanfilipo and colleagues.[22]

After converting sagittal T1 images to axial images, T1-hypointense lesions were visually identified and semi-automatically drawn with Jim software (Version 5.0, Xinapse Systems, Northants, UK; http://www.xinapse.com). We used the T1-acquired images previously described by Ceccarelli et al.[23] to be more precise in detecting the lesions because we acquired 176 images. Lesion masks for each patient were created (transforming the regions of interest into independent images) using the same Jim software and then were binarised using the ImCalc module in SPM8.

RSN analysis

Rs-FC images were preprocessed using SPM8. Preprocessing included slice-timing correction for interleaved acquisitions using sinc-interpolation and resampling with the middle (29th) slice in time as a reference point. Head motion correction, spatial normalisation 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).

Independent component analysis (ICA) was conducted for all participants using the Group ICA of FMRI Toolbox (http://icatb.sourceforge.net/groupica.htm)[24] to find the predefined RSN independent components (ICs). Group-level spatial ICA was applied using the minimum description length criteria to determine the optimal number of ICs, and using the Infomax ICA algorithm[25] to extract 20 ICs. Twenty iterations of ICA were performed using ICASSO software to determine the reliability of the ICA algorithm,[26] and the estimated centrotypes were used as representative ICs. The individual IC maps and time courses were computed using back-reconstruction based on aggregate components of the ICA and the results from the data reduction step.[27] Finally, nine consistent ICs were extracted that are described in the supplementary material and Supplementary Figure 1. Considering the objectives of the present study, three networks related to cognitive processes were selected for further evaluation: (a) the DMN;[28] (b) the frontoparietal network that can be dissociated into the LFPN and RFPN, which represent two lateralised components encompassing frontal, parietal and temporal areas, and the cingulate gyrus;[29] and (c) the salience network that functions to segregate the most relevant stimuli in order to guide behaviour.[30] An analysis of variance (ANOVA), including age and gender as covariates, was calculated to compare rs-FC networks among groups (HC, CI patients and CP patients). Reported results survived family-wise error (FWE) correction for multiple comparisons at the cluster level ($p < 0.05$) determined by Monte Carlo simulations using the AlphaSim utility in REST software (http://www.restfmri.net; $p < 0.005$ voxel-wise threshold, cluster-size criterion of 12 voxels). Next, we conducted different regression analyses to observe the relationship between rs-FC and: (a) global cognitive Z scores computed using all BRB-N tests and according to the criteria developed by Sepulcre et al.;[20] and (b) structural damage in terms of T1-lesion load and the BPF.

Behavioural statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 17.0, Chicago, IL, USA). Demographic, clinical, MRI and cognitive variables were compared among groups using one-way ANOVAs followed by the Scheffé post-hoc test. A regression analysis was used to assess if the rs-FC at the different RSNs (DMN, LFPN, RFPN and salience network) or the radiological variables (T1-lesion load and BPF) considered in this study could predict the cognitive status (global Z score of the BRB-N) of MS patients.

Results

Demographic, clinical, radiological and neuropsychological results for all participants are reported in Table 1. CI patients were older than HCs and presented greater physical disability than CP patients. With regard to MRI parameters, CI patients also presented lower BPFs than HCs and CP patients. The group of CP patients also differed in the measure of the BPF compared with HCs. As expected, MS patients characterised as CI showed poorer performance than CP patients and HCs on all BRB-N tests. More specifically, the numbers of CI patients obtaining scores below normal boundaries were: 22 (SRT), nine (SPART), seven (SDMT), 17 (PASAT-3) and 14 (WLGT).

A linear regression-based analysis confirmed that cognitive performance (global Z scores) of all MS patients could be satisfactorily predicted (overall $R^2 = 0.357$, $p < 0.001$) when using all neuropathological (BPF and lesion load) and neurofunctional parameters assessed in this study as predictive variables. Examination of the standardised regression coefficients revealed that the BPF (beta = 0.597, $p < 0.001$) and connectivity of the DMN (beta = 0.287, $p = 0.051$) were the most relevant variables to estimate the cognitive status of MS patients.

RSN results

Differences among groups in the RSNs are presented in Table 2 and Figure 1. Regarding the DMN, CI patients showed less rs-FC compared with HCs and CP patients, whereas both group of patients (CI and CP) showed less rs-FC at the LFPN compared with HCs. On the other hand,

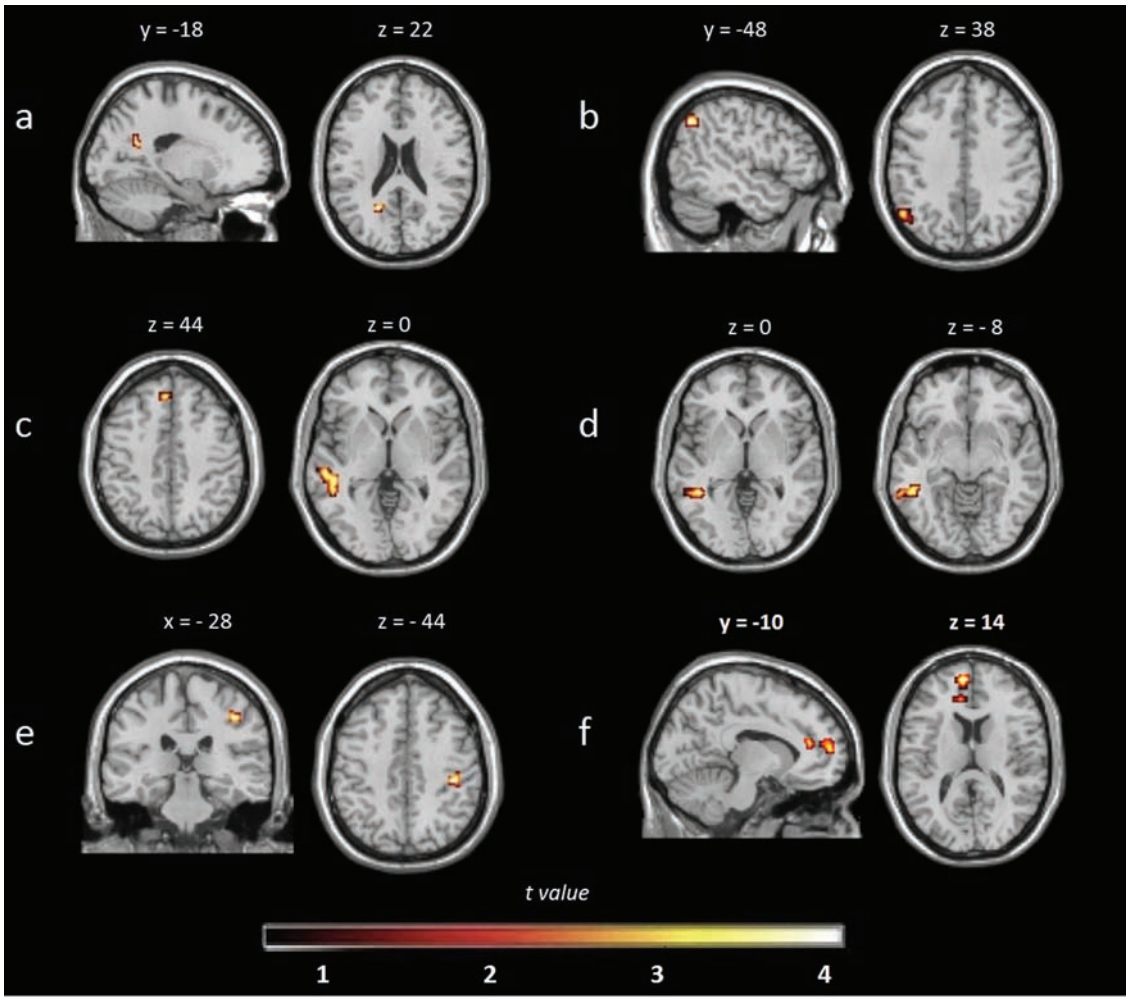

Figure 1. (a) Default mode network (DMN): decreased resting-state functional connectivity (rs-FC) in cognitively impaired (CI) patients compared with healthy controls (HCs); (b) DMN: decreased rs-FC in CI compared with cognitively preserved (CP) patients; (c) left frontoparietal network (LFPN): decreased rs-FC in CI patients compared with HCs; (d) LFPN: decreased rs-FC in CP patients compared with HCs; (e) right frontoparietal network (RFPN): decreased rs-FC in CI compared with CP patients; (f) salience network: decreased rs-FC in CI compared with CP patients. Images are presented in neurological convention and thresholded at $p < 0.005$ (k = 12 voxels), corrected for multiple comparisons using Monte Carlo simulations.

less rs-FC was also observed in the RFPN and salience network in CI patients compared with CP patients.

Relationships found among cognitive status, and radiological and neurofunctional variables of MS patients are presented in Table 3 and Figures 2–4. First, only CP patients showed positive correlations between global cognitive *Z* scores and rs-FC in the RFPN and salience network, predominantly focused on frontal and parietal areas. Furthermore, positive correlations between BPFs and rs-FC at the DMN, LFPN and RFPN, including parietal areas and the anterior cingulate gyrus, were also found in CI and CP patients. Finally, negative correlations among rs-FC in all explored RSNs and T1-lesion load were also found in both patient groups. These negative correlations were observed again at several frontal and parietal areas, including the anterior and posterior cingulate gyri.

Discussion

In the present study, we explored the existence of adaptive functional connectivity changes associated with cognitive function in the DMN, LFPN, RFPN and salience network of MS patients. Our results reveal that CI patients display less rs-FC among different brain areas belonging to these RSNs, thus supporting the notion that RSN alterations may play a significant role in MS cognitive disturbances. On the other hand, CP patients exhibited a degree of connectivity indistinguishable from that of the HC group but stronger in several nodes of the explored RSNs compared with CI patients. These findings might be regarded as providing further support to the previously suggested importance of preserving connectivity within the RSNs to retain normal cognitive competence.

Table 1. Main demographic, clinical, MRI and neuropsychological characteristics of all participants.

	HCs (n =18)	CP patients (n = 30)	CI patients (n = 30)	HC vs CP patients	HC vs CI patients	CP vs CI patients
Mean age (SD) (range)	31.06 (5.67) (22–44)	34.70 (5.48) (23–44)	38.17 (6.08) (20–47)	n.s.	.001	n.s.
Mean years of education (SD)	12.29 (1.99)	11.47 (2.63)	10.50 (2.89)	n.s.	n.s.	n.s.
Mean years of disease evolution (SD) (range)	—	5.50 (4.82) (1–18)	7.90 (5.53) (1–18)	—	—	n.s.
EDSS (range)	—	2.10 (0–6)	3.15 (1–7)	—	—	.009
FSS	—	31.87 (17.48)	40.57 (16.38)	—	—	n.s.
Mean T1 lesion volume (ml)	—	3.38 (5.30)	6.00 (14.05)	—	—	n.s.
Mean BPF (SD)	0.860 (0.015)	0.837 (0.038)	0.812 (0.038)	n.s.	.001	.009
SRT Long-Term Storage (SD)	51.00 (13.03)	48.77 (9.36)	32.70 (13.06)	n.s.	.001	.001
SRT Consistent Long-Term Retrieval (SD)	41.06 (11.37)	38.70 (10.12)	21.80 (12.69)	n.s.	.001	.001
SRT Delayed Recall (SD)	9.61 (1.78)	9.00 (1.85)	6.33 (2.84)	n.s.	.001	.001
10/36 SPART Long-Term Storage (SD)	22.83 (4.34)	22.83 (4.30)	17.27 (5.25)	n.s.	.001	.001
10/36 SPART Delayed Recall (SD)	8.00 (2.19)	7.90 (1.91)	5.70 (2.12)	n.s.	.002	.001
WLGT (SD)	23.11 (4.04)	23.90 (4.09)	16.60 (4.88)	n.s.	.001	.001
SDMT (SD)	57.94 (11.78)	56.60 (7.80)	37.13 (10.03)	n.s.	.001	.001
PASAT-3 s (SD)	46.94 (10.23)	48.13 (7.18)	18.37 (19.84)	n.s.	.001	.001

MRI: magnetic resonance imaging; n.s.: not significant; HC: healthy control; CI: cognitively impaired; CP: cognitively preserved; EDSS: Expanded Disability Status Scale; FSS: Fatigue Severity Scale; BPF: brain parenchymal fraction; SRT: Selective Reminding Test; SPART: Spatial Recall Test; WLGT: Word List Generation Test; SDMT: Symbol Digit Modalities Test; PASAT-3 s: Paced Auditory Serial Addition 3-Second Test.

More specifically, and in close similarity to previous studies,[12,13] we observed that CI patients showed less connectivity in the DMN and LFPN compared with HCs. Interestingly, CP patients exhibited a greater degree of rs-FC than CI patients in the DMN, RFPN and salience network. The abovementioned findings are in agreement with other studies reporting that MS patients with preserved cognitive abilities display normal or enhanced rs-FC in RSNs,[14–16,31] and these results have often been interpreted as adaptive functional changes compensating for cognitive deficits. Following this rationale, we may conclude that in our study, CP patients showed adaptive connectivity changes to compensate for potential cognitive deficits, although alternative explanations must also be considered (see below). The potential association between appropriate rs-FC and the cognitive status of MS patients was further reinforced by the results of our correlational analyses demonstrating that global cognitive Z scores of CP patients were positively correlated with degree of rs-FC in the medial frontal and inferior parietal areas of the salience network and RFPN, respectively. Loitfelder et al.[31] recently reported that MS patients might require high rs-FC in the inferior parietal cortex and the angular gyrus to attain correct performance in attention and working memory tasks. Therefore, our findings are in agreement with accumulating evidence that seem to converge towards a relationship between reduced functional connectivity in the RSNs and cognitive impairment in MS patients.

Most RSN research on MS patients has primarily focused on the DMN.[12,13] However, there are other networks associated with resting processes that may be of special relevance when studying cognitive deficits in MS patients. For example, the LFPN and RFPN are RSNs that are highly consistent among participants and that only recently have started to receive proper attention in the context of MS research.[14,17] The LFPN and RFPN engage areas distant from the frontal and parietal lobes, which may be especially prone to MS pathophysiology. In fact, many recent fMRI studies have explored the engagement of frontoparietal networks associated with performance in attention and working memory tasks under the assumption that disconnection among distal frontoparietal areas may underlie primary cognitive deficits in MS.[3,6,8] Therefore, the LFPN and RFPN may be especially relevant to understanding cognitive impairment in MS patients, which seems to be supported by our results demonstrating clear differences among groups in those networks. In this regard, CP patients did not show a significant increase in LFPN rs-FC but did show greater RFPN rs-FC compared with CI patients, and the magnitude of this increase was correlated with cognitive performance (global Z scores). Combining these results, we may deduce that although CI as well as CP patients showed deficits in the LFPN,

Table 2. Mean (SD) values of z scores of resting state activity within the clusters that show significant differences among HC, CI and CP patients. Results are thresholded at p < 0.005 (k = 12 voxels) corrected for multiple comparisons using Monte Carlo simulations.

	Cluster	MNI space	HC	CP	CI	*p*
DMN						
CI <HC	L parietal lobe	–21 –58 22	2.80 (1.15)	—	1.79 (1.08)	.004
CI<CP	L parietal lobe	–54 –61 37	—	1.98 (0.68)	1.37 (0.72)	.009
LFPN						
CI<HC	L superior temporal lobe	63 –49 –5	1.90 (0.64)	—	1.28 (0.68)	.006
	L medial frontal lobe	–3 35 43	1.33 (0.59)	—	0.79 (0.63)	.017
CP<HC	L temporal lobe	–63 –49 –5	1.92 (0.60)	1.17 (0.72)	—	.000
RFPN						
CI<CP	R postcentral gyrus	42 –25 43	—	1.04 (0.49)	0.62 (0.40)	.003
Salience						
CI<CP	L medial frontal lobe	–6 56 13	—	3.04 (0.71)	1.99 (0.53)	.000
	L anterior cingulate	–12 38 16	—	1.56 (0.55)	0.95 (0.48)	.000

HC: healthy control; CI: cognitively impaired; CP: cognitively preserved; MNI: Montreal Neurological Institute; L: left; R: right; DMN: default mode network; LFPN: left frontoparietal network; RFPN: right frontoparietal network.

Table 3. Correlations among resting-state networks, and cognitive and radiological variables. Thresholded at $p < 0.005$ ($k = 12$ voxels) corrected for multiple comparisons using Monte Carlo simulations

Group	Dependent variable	r	Area	MNI coordinates
Correlations with *Z* global score				
CP patients	RFPN	0.70	R inferior parietal lobe	39 –34 28
		0.70	R parietal lobe	30 –34 40
CP patients	Salience	0.66	R medial frontal gyrus	6 –10 –2
Correlations with BPF				
CI patients	DMN	0.60	L precuneus	–3 –43 46
		0.64	R anterior cingulate gyrus	3 44 13
CP patients	LFPN	0.60	R superior temporal gyrus	57 –25 1
CI patients	RFPN	0.66	R parietal precuneus	6 –37 46
		0.52	R insula	30 –13 16
		0.62	R posterior cingulate	3 –34 22
CP patients	RFPN	0.55	R inferior parietal lobe	42 –46 55
Correlations with T1 LL				
CI	DMN	–0.71	R precentral gyrus	60 –4 14
CP	DMN	–0.65	R supramarginal gyrus	48 –43 31
CI	LFPN	–0.57	L medial temporal gyrus	0 59 22
CP	LFPN	–0.67	L middle frontal gyrus	–42 17 31
		–0.63	L precuneus	–3 –67 37
CI	RFPN	–0.79	R superior frontal gyrus	18 53 37
		–0.65	L medial frontal gyrus	–6 38 40
		–0.73	R posterior cingulate	9 –43 34
CP	RFPN	–0.73	R postcentral gyrus	48 –31 58
CI	Salience	–0.75	B paracentral lobule	0 –43 52
CP	Salience	–0.74	L anterior cingulate gyrus	–3 26 37
		–0.59	R anterior cingulate gyrus	3 20 22

HC: healthy control; CI: cognitively impaired; CP: cognitively preserved; MNI: Montreal Neurological Institute; L: left; R: right; B: bilateral; DMN: default mode network; LFPN: left frontoparietal network; RFPN: right frontoparietal network; BPF: brain parenchymal fraction; T1 LL: T1-lesion load.

only CP patients could retain normal cognitive competence by sustaining proper connectivity among RFPN areas. The notion that increased recruitment of the right side is critical for cognitive performance was previously posed by fMRI studies using tasks that require engagement of the LFPN and RFPN.[2,5,8]

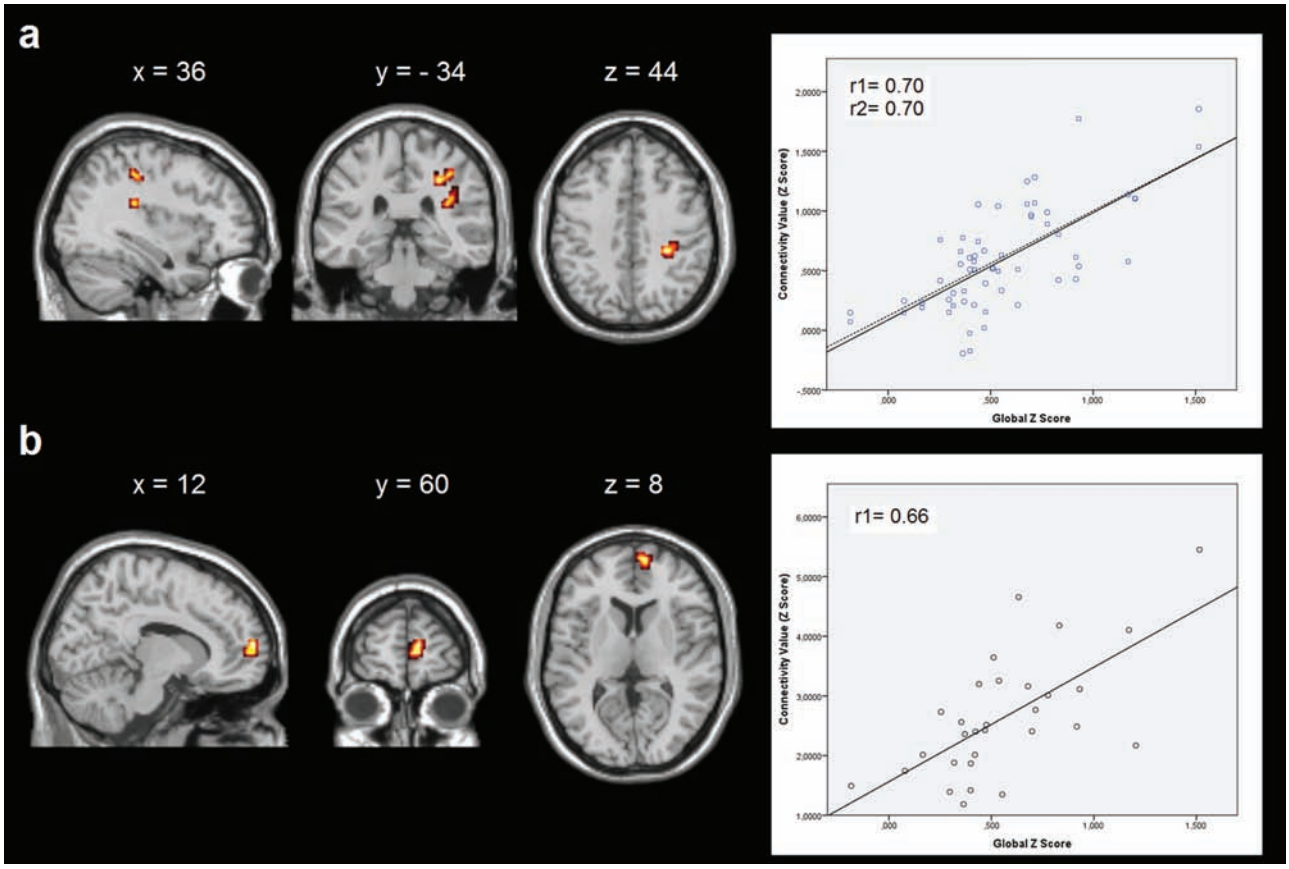

Figure 2. Correlations between resting-state functional connectivity (rs-FC) and global cognitive *Z* scores. (a) Correlation in the right frontoparietal network (RFPN) in cognitively preserved (CP) patients; (b) correlation in the salience network in CP patients. Images are presented in neurological convention and thresholded at $p < 0.005$ (k = 12 voxels), corrected for multiple comparisons using Monte Carlo simulations.

We also studied the salience network associated with behavioural control functions.[30] The relationship between rs-FC in this network and the cognitive status of MS patients had not been previously explored in MS patients, although a recent study described an association between decreased connectivity in this network in relapsing–remitting MS patients and their clinical disability compared with HCs.[32] In our study, CI patients showed reduced rs-FC at the anterior cingulate gyrus in the salience network compared with the CP group. The significance of anterior cingulate activation for cognition in MS is supported by the results of Rocca et al.[12] describing reduced connectivity at the anterior cingulate gyrus in CI patients compared with CP patients.

Cerebral reorganisation is secondary to structural damage.[14,33,34] Previous data suggest that these functional restructuration processes appear when levels of brain damage are low but that these processes can no longer be triggered when damage is more extensive.[33] Following this line of reasoning, we investigated the role of radiological variables in the different connectivity networks. MS patients (either CI or CP) with higher volume of lesions showed less rs-FC in all cognitive networks explored as compared to those patients with less lesion volume, thus suggesting that disease in white matter disrupt the pathways that mediate the transmission of information across brain networks.[35] In this regard, we also observed that BPFs were positively correlated with rs-FC networks in both groups of patients; that is, patients with more brain volume were more cognitively preserved than patients with less brain volume. As expected from previous studies,[35] atrophy was accompanied by alterations in the networks' connectivity and both kinds of alterations probably underlie the reduction of cognitive performance observed in MS patients. This proposal is also supported by the results of the regression analysis performed in the present study, which revealed that the BPF was the best predictor of cognitive performance of MS patients.

In conclusion, this study extends our knowledge about functional alterations of RSNs in MS patients and their possible relationship with cognitive performance. We observed that brain injury was accompanied by reduced functional connectivity at different RSNs, which may probably be responsible for the onset and progression of cognitive

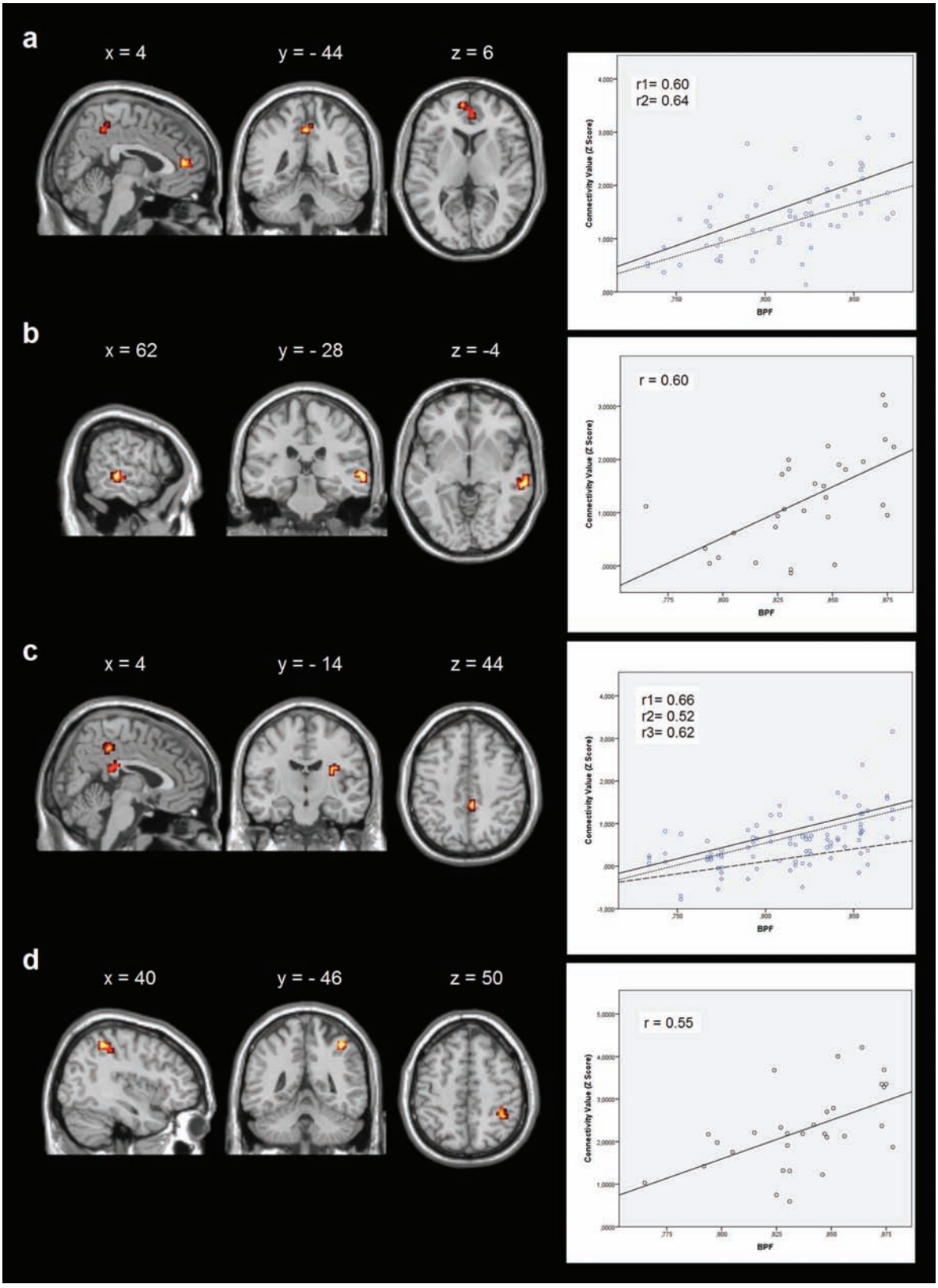

Figure 3. Correlations between resting-state functional connectivity (rs-FC) and brain parenchymal fractions (BPF). (a) Correlation in the default mode network (DMN) in cognitively impaired (CI) patients; (b) correlation in the left frontoparietal network (LFPN) in cognitively preserved (CP) patients; (c) correlation in the right frontoparietal network (RFPN) in CI patients; (d) correlation in the RFPN in CP patients. Images are presented in neurological convention and thresholded at $p < 0.005$ (k = 12 voxels), corrected for multiple comparisons using Monte Carlo simulations.

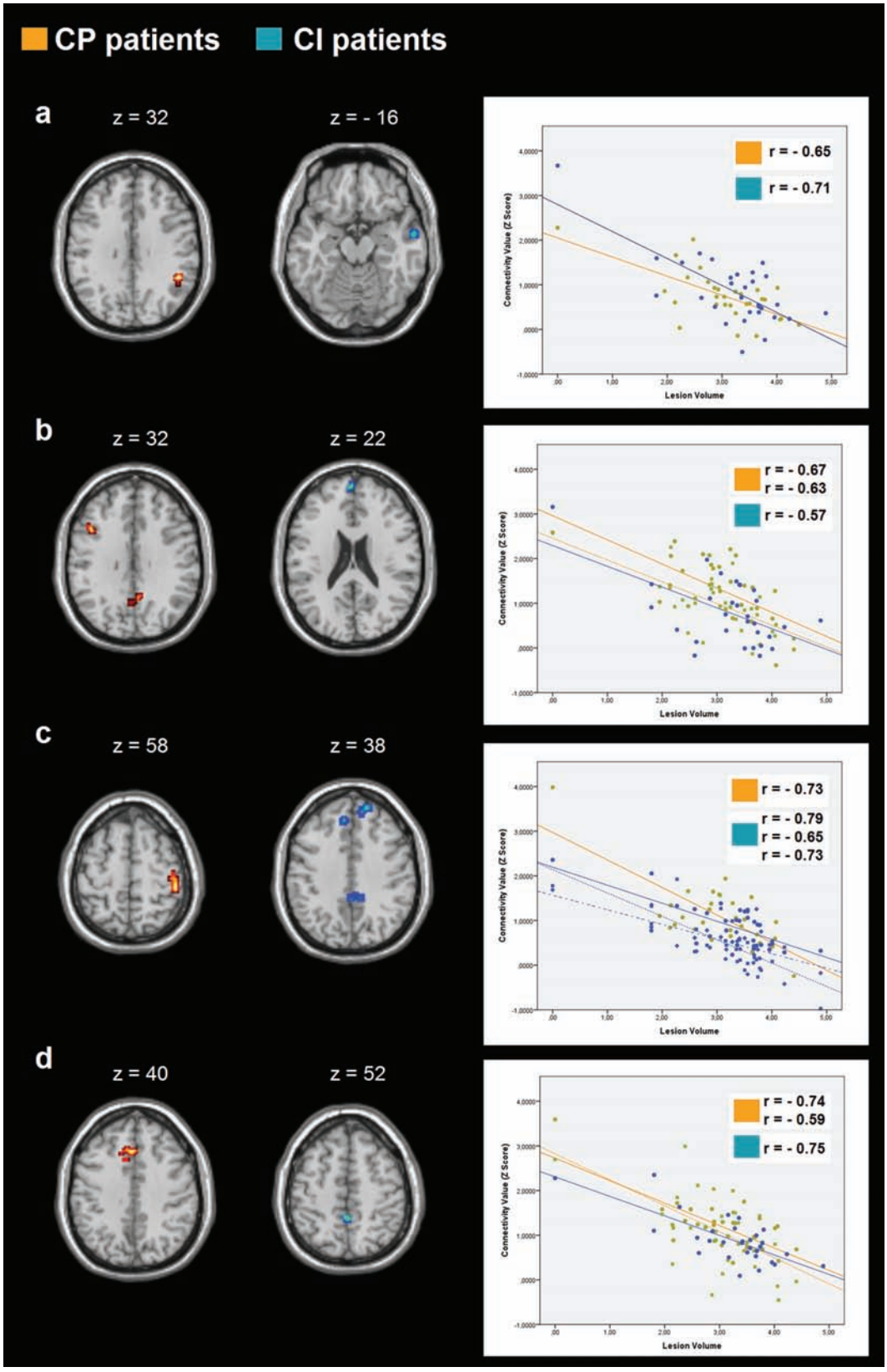

Figure 4. Correlations between resting-state functional connectivity (rs-FC) and T1-lesion load (LL). (a) Correlation in the default mode network (DMN); (b) correlation in the left frontoparietal network (LFPN); (c) correlation in the right frontoparietal network (RFPN); (e) (d) correlation in the salience network. Images are presented in neurological convention and thresholded at $p < 0.005$ (k = 12 voxels), corrected for multiple comparisons using Monte Carlo simulations.

deficits in MS patients. However, and contrary to our initial hypothesis, CP patients did not exhibit a stronger degree of connectivity than HCs in any of the RSNs evaluated. In this regard, it should be noted that the discrepant size of the groups may have led to a reduction in statistical potency of our analysis resulting in false-negative findings. Future studies assessing rs-FC will help to further clarify the use of RSN activity markers to characterise and predict cognitive performance in MS patients and to determine if engaging compensatory neuroplastic mechanisms is required to retain cognitive competence despite disease progression.

Conflict of interest statement

None declared.

Funding

This work was supported by the Brainglot project of the CONSOLIDER-INGENIO 2010 Programme (CSD2007-00012). The project was also supported by grants PSI2010-20168 from MINECO, P1·1B2011-09 from Universitat Jaume I and an educational grant from Biogen Idec.

References

1. Hawellek DJ, Hipp JF, Lewis CM, et al. Increased functional connectivity indicates the severity of cognitive impairment in multiple sclerosis. *Proc Natl Acad Sci U S A* 2011; 108: 19066–19071.
2. Audoin B, Ibarrola D, Ranjeva JP, et al. Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. *Hum Brain Mapp* 2003; 20: 51–58.
3. Au Duong MV, Boulanouar K, Audoin B, et al. Modulation of effective connectivity inside the working memory network in patients at the earliest stage of multiple sclerosis. *Neuroimage* 2005; 24: 533–538.
4. Au Duong MV, Audoin B, Boulanouar K, et al. Altered functional connectivity related to white matter changes inside the working memory network at the very early stage of MS. *J Cereb Blood Flow Metab* 2005; 25: 1245–1253.
5. Cader S, Cifelli A, Abu-Omar Y, et al. Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. *Brain* 2006; 129: 527–537.
6. Forn C, Barros-Loscertales A, Escudero J, et al. Cortical reorganization during PASAT task in MS patients with preserved working memory functions. *Neuroimage* 2006; 31: 686–691.
7. Forn C, Barros-Loscertales A, Escudero J, et al. Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. *Hum Brain Mapp* 2007; 28: 424–430.
8. Forn C, Rocca MA, Valsasina P, et al. Functional magnetic resonance imaging correlates of cognitive performance in patients with a clinically isolated syndrome suggestive of multiple sclerosis at presentation: An activation and connectivity study. *Mult Scler* 2012; 18: 153–163.
9. Bonnet MC, Allard M, Dilharreguy B, et al. Cognitive compensation failure in multiple sclerosis. *Neurology* 2010; 75: 1241–1248.
10. Cifelli A and Matthews PM. Cerebral plasticity in multiple sclerosis: Insights from fMRI. *Mult Scler* 2002; 8: 193–199.
11. Fox MD and Greicius M. Clinical applications of resting state functional connectivity. *Front Syst Neurosci* 2010; 4: 19.
12. Rocca MA, Valsasina P, Absinta M, et al. Default-mode network dysfunction and cognitive impairment in progressive MS. *Neurology* 2010; 74: 1252–1259.
13. Bonavita S, Gallo A, Sacco R, et al. Distributed changes in default-mode resting-state connectivity in multiple sclerosis. *Mult Scler* 2011; 17: 411–422.
14. Roosendaal SD, Schoonheim MM, Hulst HE, et al. Resting state networks change in clinically isolated syndrome. *Brain* 2010; 133: 1612–1621.
15. Hulst HE and Geurts JJ. Gray matter imaging in multiple sclerosis: What have we learned? *BMC Neurol* 2011; 11: 153.
16. Sumowski JF, Wylie GR, Leavitt VM, et al. Default network activity is a sensitive and specific biomarker of memory in multiple sclerosis. *Mult Scler* 2013; 19: 199–208.
17. Faivre A, Rico A, Zaaraoui W, et al. Assessing brain connectivity at rest is clinically relevant in early multiple sclerosis. *Mult Scler* 2012; 18: 1251–1258.
18. 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.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444–1452.
20. 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: 187–195.
21. Calabrese M, Agosta F, Rinaldi F, et al. Cortical lesions and atrophy associated with cognitive impairment in relapsing–remitting multiple sclerosis. *Arch Neurol* 2009; 66: 1144–1150.
22. Sanfilipo MP, Benedict RHB, Zivadinov R, et al. Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: The proportion vs. residual method. *Neuroimage* 2004; 22: 1732–1743.
23. Ceccarelli A, Bakshi R and Neema M. MRI in multiple sclerosis: A review of the current literature. *Curr Opin Neurol* 2012; 25: 402–409.
24. Calhoun VD, Adali T, Pearlson GD, et al. A method for making group inferences from functional MRI data using independent component analysis. *Hum Brain Mapp* 2001; 14: 140–151.
25. Bell AJ and Sejnowski TJ. An information-maximization approach to blind separation and blind deconvolution. *Neural Comput* 1995; 7: 1129–1159.
26. Himberg J, Hyvärinen A and Esposito F. Validating the independent components of neuroimaging time series via clustering and visualization. *Neuroimage* 2004; 22: 1214–1222.
27. Erhardt EB, Rachakonda S, Bedrick EJ, et al. Comparison of multi-subject ICA methods for analysis of fMRI data. *Hum Brain Mapp* 2011; 32: 2075–2095.
28. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. *Proc Natl Acad Sci U S A* 2001; 98: 676–682.
29. Damoiseaux JS, Rombouts SA, Barkhof F, et al. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 2006; 103: 13848–13853.

30. Menon V and Uddin LQ. Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct* 2010; 214: 655–667.
31. Loitfelder M, Filippi M, Rocca M, et al. Abnormalities of resting state functional connectivity are related to sustained attention deficits in MS. *PloS One* 2012; 7: e42862.
32. Rocca MA, Valsasina P, Martinelli V, et al. Large-scale neuronal network dysfunction in relapsing–remitting multiple sclerosis. *Neurology* 2012; 79: 1449–1457.
33. Schoonheim MM, Geurts JJ and Barkhof F. The limits of functional reorganization in multiple sclerosis. *Neurology* 2010; 74: 1246–1247.
34. Rocca MA, Gatti R, Agosta F, et al. Influence of task complexity during coordinated hand and foot movements in MS patients with and without fatigue. A kinematic and functional MRI study. *J Neurol* 2009; 256: 470–482.
35. Filippi M and Rocca MA. MRI and cognition in multiple sclerosis. *Neurol Sci* 2010; 3 (Suppl 2): S231–S234.