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Exploring Neural Efficiency in Multiple Sclerosis Patients during the Symbol Digit Modalities Test: A Functional Magnetic Resonance Imaging Study

María Sol Fittipaldi-Márquez[a] Álvaro Javier Cruz-Gómez[a]
Carla Sanchis-Segura[a] Antonio Belenguer[b] César Ávila[a] Cristina Forn[a]

[a]Departament de Psicología Bàsica, Clínica i Psicobiología, Universitat Jaume I, and [b]Servicio de Neurología, Hospital General de Castellón, Castellón de la Plana, Spain

Keywords
Neurodegenerative disease · Neuropsychology · Multiple sclerosis · Neural efficiency · Neuroimaging

Abstract
Background: Reduced information-processing speed (IPS) is a primary cognitive deficit of multiple sclerosis (MS) patients. The neural efficiency hypothesis describes an inverse relationship between cognitive performance in a task and the amount of cognitive resources devoted to it. Previous studies have shown that the neural efficiency hypothesis provides an appropriate framework to explore cognitive dysfunction in neurological patients. ***Objective:*** The aim of this study was to explore the neural efficiency hypothesis regarding IPS capabilities in cognitively preserved MS patients. ***Methods:*** 16 MS patients and 17 healthy controls (HCs) were enrolled and neuropsychologically assessed. All participants also performed a functional magnetic resonance imaging (fMRI)-adapted version of the Symbol Digit Modalities Test (SDMT) at different interstimulus intervals (ISI: 1.5, 2, and 2.5 s). ***Results:*** MS patients only displayed lower SDMT performance when the ISI was set at 1.5 s. However, MS patients' normal SDMT performance at larger ISIs was achieved at the cost of increased brain activation, hence revealing that they were less cognitively efficient than the HCs. Regression analyses confirmed this conclusion by showing an opposite relationship between SDMT performance and the amount of neural resources recruited in the HC and MS groups. Thus, while a positive relationship between both variables was observed in MS patients, this correlation was negative for the HC group. ***Conclusions:*** MS patients require more cognitive resources than HCs to achieve a normal SDMT performance, then revealing that they are less efficient regarding IPS capabilities.

Introduction

Cognitive impairment is now recognized as one of the most disabling symptoms in multiple sclerosis (MS) patients. Reduced information-processing speed (IPS) seems the central aspect of cognitive decline in MS as it affects about 22–25% of these patients [1], appears in early disease stages, and probably underlies their re-

María Sol Fittipaldi-Márquez and Álvaro Javier Cruz-Gómez contributed equally to this work.

E-Mail karger@karger.com
www.karger.com/ndd

Cristina Forn, PhD
Departament de Psicología Bàsica, Clínica i Psicobiología
Universitat Jaume 1, Avda. Sos Baynat sln.
ES–12071 Castellón de la Plana (Spain)
E-Mail forn@psb.uji.es

duced performance in other intellectual domains, such as working and long-term memory [2]. Therefore, IPS is considered a crucial aspect of neuropsychological evaluations of MS patients [1, 2]. One of the most recommended tests to assess reduced IPS in MS is the oral version of the Symbol Digit Modalities Test (SDMT) [3, 4] which is included in the 2 most widely used batteries in clinical practice to assess cognitive impairment in MS: the Brief Repeatable Battery of Neuropsychological Tests [5] and the Minimal Assessment of Cognitive Function in MS [6]. These batteries include the Paced Auditory Serial Addition Test, which also evaluates IPS. However, it is considered that the SDMT might provide a purer measure of IPS because the Paced Auditory Serial Addition Test is a complex task that requires high levels of working memory resources, while the SDMT is an easier task of visual attention that requires lower levels of working memory [7].

Cognitive decline in MS patients might not always be readily apparent from their neuropsychological test scores. Indeed, a growing number of studies have revealed that MS patients might retain apparently normal cognitive performance by increasing the number of neural resources, at least in early stages of the disease [8–12]. Therefore, these and other studies have advocated the need for coupling neuropsychological assessments with neuroimaging techniques, and for understanding the MS cognitive status as part of the "neural efficiency hypothesis" [13, 14]. This hypothesis states that quick efficient subjects employ fewer resources (reflected as less activation during the task), while less effective or slower subjects require more neural resources (reflected as hyperactivation while doing the task).

As IPS is not a cognitive function per se, rather a trait that underlies other cognitive abilities, the study of its neural underpinnings through neuroimaging procedures might be cumbersome [14]. However, as we previously indicated, the SDMT seems optimal for assessing IPS even in functional magnetic resonance imaging (fMRI)-based settings because it is an easy task whose brain activation pattern mainly depends on IPS capabilities (although a minor component of working memory is also involved), and its variations cannot be attributed to using different cognitive strategies. Indeed in a previous study [14], we used an fMRI-adapted version of the SDMT that allows the interstimulus interval (ISI) to be manipulated, and we observed that: (1) the SDMT is a suitable task for assessing IPS because it requires functional interactions among distant brain areas during task execution; (2) fast, but not slow, SDMT performance requires recruiting the frontal cortex; (3) in accordance with the "neural efficiency hypothesis," higher SDMT scores are associated with the lower activation of several frontal lobe areas.

The present study aimed to test the "neural efficiency hypothesis" in cognitively preserved MS patients by means of the SDMT with different ISI presentations. We expected these patients, compared to healthy controls (HCs), to require a larger number of neural resources while executing the SDMT, especially under experimental conditions with higher IPS demands (e.g., at a shorter ISI). As observed in previous studies [13, 14], we expected the number of neural resources recruited to solve this task to be inversely related to its IPS demands (that is, more neural resources would be required with the shortest ISI). We also hypothesized that MS patients would require a larger number of neural resources while executing the SDMT than HCs, and that these differences would also be related to task difficulty.

Method

Participants

Thirty-three participants were enrolled in this study: 16 MS patients (12 female) and 17 HCs (6 female). Patients were recruited from the Hospital General de Castellón and were diagnosed as relapsing-remitting MS according to the McDonald criteria [15]. In order to be included, they had to be relapse free and steroid free for at least 2 months prior to the study. All the patients underwent neurological examination, for which the Expanded Disability Status Scale was used [16].

All the participants were neuropsychologically assessed with the Brief Repeatable Battery of Neuropsychological Tests validated for the Spanish population [17]. The Vocabulary Subtest of the Wechsler Adult Intelligence Scale III Battery [18] was also used to assess the intelligence quotient. The Fatigue Severity Scale [19] was also administered. None of the participants reported visual problems that would prevent them from correctly performing the fMRI experiment.

The study was approved by the Ethics Standards Committees of the aforementioned Hospital General de Castellón and the Universitat Jaume I, and participants gave informed written consent prior to participating.

Experimental Design

An adapted version of the SDMT, suitable for fMRI studies and described previously by Forn et al. [14], was used in this study. Two tasks were employed, A and B, which were randomly presented as a block design paradigm. Both these tasks contained 12 blocks of 30 s (6 for the control condition and 6 for the activation condition). For both conditions (control and activation), the same upper row was presented on the screen with numbers from 1 to 9, which matched 9 meaningless symbols. For the control condition, participants had to orally report the numbers from 1 to 9 presented

randomly in the center of the screen. The activation condition consisted in presenting one of those symbols in the center of the screen, and participants were instructed to match it with its corresponding number by consulting the upper row and reporting the answer orally. For run A, the conditions with the different ISIs were alternately presented (1.5–2–2.5–1.5–2–2.5 s), while blocks were inversely presented in the SDMT B version (2.5–2–1.5–2.5–2–1.5 s). An important issue was that the upper row with the symbols and matched numbers presented under the control and activation conditions changed every ISI condition in order to prevent participants from memorizing pairs (which avoid working memory functions).

Prior to scanning, participants were provided with an overview of the fMRI task procedure and with a practice task so they could become familiar with it. The visual SDMT series were presented by means of the Presentation software package (Neurobehavioral Systems Inc., Albany, CA, USA) during fMRI acquisition using compatible goggles (VisuaStim, Resonance Technologies Inc.). Foam cushioning was employed to immobilize the participants' heads in the coil to minimize motion artifacts.

MRI Acquisition

All the participants were scanned with a 1.5-T Siemens Avanto (Erlangen, Germany) in the Hospital General def Castellón using a single-shot gradient echo EPI sequence (TR = 3,000 ms; FOV = 250 × 250 mm; matrix = 64 × 64 pixels; TE = 50 ms; number of echoes = 1; slice thickness = 4.5 mm, no gap; flip angle = 90°). Twenty-nine slices were acquired in the axial plane parallel to the anterior-posterior commissural line from bottom to top to provide coverage of the entire brain. A morphological volumetric sagittal 3-dimensional T1-weighted fast-field echo sequence (TR = 11 ms; FOV = 256 × 234 mm; matrix = 256 × 224; voxel size = 1 × 1 x 1 mm; TE = 4.9 ms; number of echoes = 1; flip angle = 15°) was also acquired.

fMRI Analysis

The Statistical Parameter Mapping (SPM8) software (Wellcome Trust Centre for Neuroimaging, London, UK) was used to analyze the fMRI data.

For preprocessing, functional images were reoriented to the anterior-posterior commissural line, realigned and coregistered with the anatomical T1. Then segmentation and normalization were performed using unified segmentation [20] with medium regularization. Finally, functional images were smoothed with a 10-mm gaussian kernel.

The activation task (1.5-s SDMT, 2-s SDMT and 2.5-s SDMT) and control conditions were modeled using the general linear model with a box-car regressor convolved with a canonical hemodynamic response function. The 4 main conditions (1.5-s, 2-s, 2.5-s SDMT and control condition) and head movement factors were also added to the model. The main effects for each condition were calculated after model estimation. The main contrasts of interest were the 3 activation conditions over the control (1.5-s SDMT vs. control, 2-s SDMT vs. control, 2.5-s SDMT vs. control). Each individual contrast was introduced into a second-level random effects analysis by a 1-sample *t* test in order to define the brain areas recruited while executing the SDMT at each ISI by each group separately (MS patients and HCs). An ANCOVA design was run to explore the ISI effects within each group. Two-sample *t* tests were run to address possible differences between the MS patients and HCs in the brain pattern of activation during each ISI of the SDMT. All these analyses were covariated with sex, age and the behavioral execution results of the SDMT in the fMRI. Finally, a regression analysis was performed to investigate possible relationships between the behavioral accuracy (percentage of correct responses) in each ISI of the SDMT fMRI version, with changes in the BOLD signal in the 2 study groups separately. This analysis was covariated with sex and age. All the results were assessed at $p < 0.05$ family-wise error (FWE) cluster-corrected for the multiple comparisons in a combination with a threshold of $p < 0.005$ at the uncorrected voxel level.

MRI Data: Brain Volume and Lesion Volume Measurements

Gray matter fraction (GMF) volume, white matter fraction (WMF), and brain parenchymal fraction (BPF) for all the participants were obtained from the 3-dimensional high-resolution image by following the SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK) segmentation step according to the procedure described by Sanfilipo et al. [21].

In all the patients, T1-weighted hypointense lesions were manually identified and marked on the 3-dimensional sagittal T1-weighted images using the Jim software (version 5.0 Xinapse Systems, UK; http://www.xinapse. com). Subsequently, T1-weighted lesion volume (T1 LV) was quantified by the same software.

fMRI Data and Behavioral Statistical Analyses

Statistical analyses were performed with the Statistical Package for Social Sciences (version 17.0, Chicago, IL, USA). Demographic, clinical and MRI variables were compared between groups by a 2-sample *t* test for unequal group variance. The mean signal intensity values (SPM eigenvalues) of each significant cluster of the 2-sample *t* tests (differences between HCs and the MS patients with different ISI presentations) were extracted and Pearson correlation analyses were made to explore their relationship with the structural variables (T1 LV, GMF, WMF, BPF).

Results

Demographical, Clinical, Radiological, and Neuropsychological Results

No differences in the demographical, clinical, and neuropsychological characteristics of the MS patients and HCs were found, including all the Brief Repeatable Battery of Neuropsychological Test subtests. Although MS patients displayed poorer performance in the fMRI version of the SDMT at the shortest ISI (1.5 s, but not for 2-s and 2.5-s ISIs), SDMT performance was not significantly correlated with any demographical, clinical, or neuropsychological variable considered in this study. Regarding the MRI data, no differences were found in GMF or BPF between the HC and MS patients, although statistical trends of significance were observed in the variable of WMF between patients and HCs ($p = 0.059$); see Table 1 for further details.

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

	MS patients (n = 16)	HCs (n = 17)	p
Demographic and clinical data			
Mean age, years	34.63 (6.07) [22–45]	31.18 (5.87) [22–44]	ns
Mean years of education	11.63 (2.63)	13.35 (2.80)	ns
EDSS	1.78 (0.80) [0–3.5]	–	–
Mean years of disease duration	3.94 (3.59) [1–12]	–	–
FSS	3.33 (2.09)	3.57 (1.15)	ns
Brain and lesion volume			
Mean T1 LV, ml	1,628.63 (644.42)	–	–
GMF	0.419 (0.29)	0.423 (0.25)	ns
WMF	0.433 (0.31)	0.439 (0.18)	ns
BPF	0.852 (0.21)	0.862 (0.15)	ns
Neuropsychological data			
SDMT (correct responses)	52.31 (11.94)	58.47 (11.94)	ns
SDMT (errors)	0.13 (0.34)	0.65 (1.90)	ns
SRT long-term storage	44.13 (11.31)	50.47 (12.45)	ns
SRT consistent long-term retrieval	34.81 (12.32)	40.65 (10.61)	ns
SRT delayed recall	8.44 (2.45)	9.06 (2.56)	ns
10/36 SPART long-term storage	21.81 (5.02)	22.41 (4.65)	ns
10/36 SPART delayed recall	7.75 (1.98)	7.88 (2.15)	ns
Phonetic fluency	14.50 (6.06)	12.71 (3.77)	ns
Semantic fluency (animal naming)	23.06 (6.50)	21.71 (5.00)	ns
PASAT 3	42.63 (17.86)	43.59 (15.22)	ns
Verbal IQ WAIS III (vocabulary)	110.94 (8.99)	116.47 (12.60)	ns
Behavioral data of the SDMT fMRI version			
SDMT 1.5 s, % of correct responses	85.78 (10.85)	93.01 (5.81)	0.022*
SDMT 2 s, % of correct responses	93.23 (5.59)	96.47 (4.64)	ns
SDMT 2.5 s, % of correct responses	98.31 (3.42)	99.26 (1.26)	ns

Standard deviations are given in parentheses, ranges in square brackets. ns, not significant; MRI, magnetic resonance imaging; MS, multiple sclerosis; HCs, healthy controls; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; LV, lesion volume; GMF, gray matter fraction; WMF, white matter fraction; BPF, brain parenchymal fraction; SDMT, Symbol Digit Modalities Test; SRT, Selective Reminding Test; SPART, Spatial Recall Test; PASAT, Paced Auditory Serial Addition Test; IQ, intellectual quotient; WAIS, Wechsler Adult Intelligence Scale. * $p < 0.05$: significant differences between groups.

fMRI Results

Figure 1a shows the brain areas recruited by each group separately (MS patients and HCs) while performing the SDMT at the 3 different ISIs (1.5, 2, and 2.5 s), as revealed by the 1-sample t tests. For all the conditions, both groups exhibited bilateral activations in several posterior areas, including the posterior cingulate cortex, the parietal and occipital lobes and the cerebellum. Activations were also observed in the middle and inferior temporal gyri. As expected for the execution of the SDMT at the 1.5-s ISI, both groups also recruited anterior areas, including the bilateral superior, middle, medial, and inferior frontal gyri. For more specific information, see the results provided in the online supplementary Table 1 (see www.karger.com/doi/10.1159/000460252 for all online suppl. material).

The ANCOVA analyses results are shown in Figure 1b. Significant clusters of activations in the extended bilateral frontal, parietal, temporal, occipital, and cerebellar areas were observed in both study groups for the 1.5-s ISI condition compared to the 2-s and 2.5-s ISI conditions of the SDMT. The reverse contrasts (2-s vs. 1.5-s ISI and 2.5-s vs. 1.5-s ISI) yielded no statistically significant results. More specific information about these results is provided in in the online supplementary Table 2.

As displayed in Figure 2 and Table 2, the 2-sample t test revealed that, compared to the HC group, the MS patients presented more robust activations in the frontal

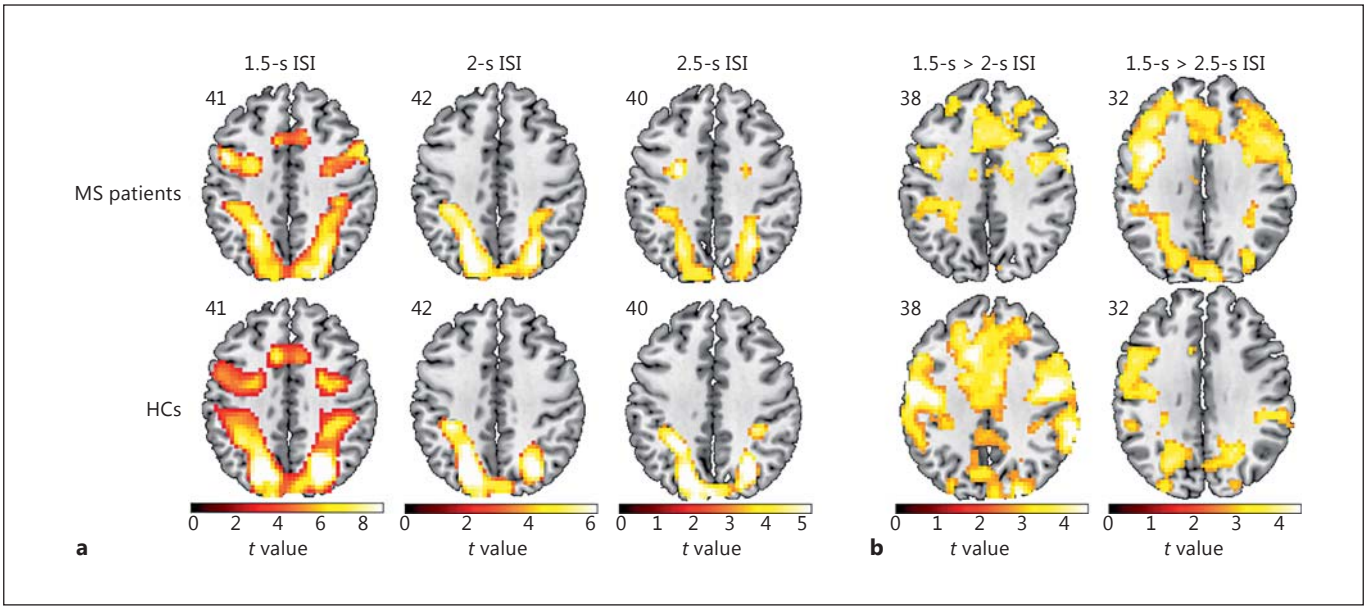


Fig. 1. a Brain areas recruited while executing the fMRI SDMT at each ISI by each group separately (MS patients and HCs), as revealed by the 1-sample *t* tests. **b** Brain areas that showed significantly increased activation for the 1.5-s ISI condition compared to the 2-s and 2.5-s ISI conditions of the fMRI SDMT in each group. All the results are assessed at $p < 0.05$ FWE cluster-corrected, and more specific information is presented in online supplementary Tables 1 and 2.

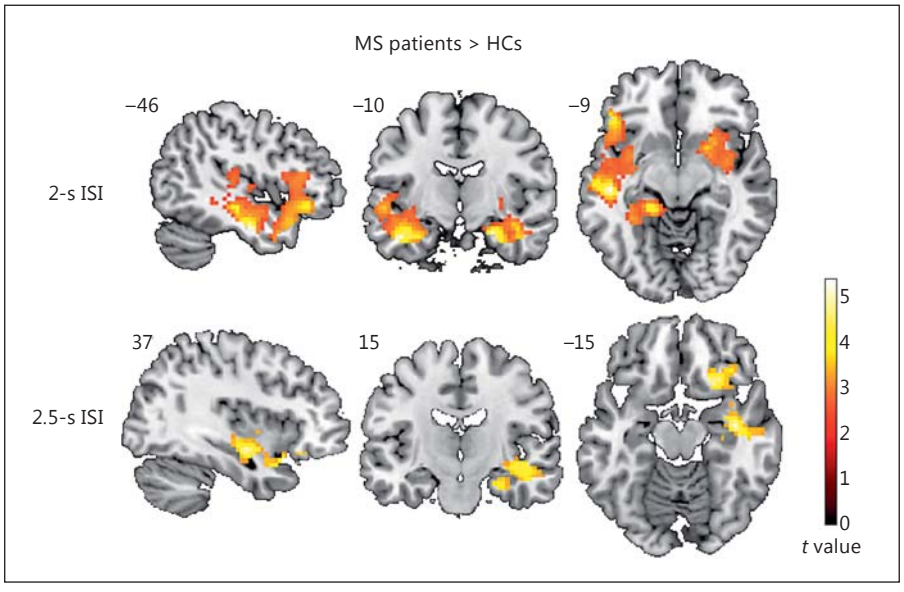


Fig. 2. Brain areas that showed statistically significant increased activation in the MS patients compared to the HCs for the 2-s and 2.5-s ISIs of the fMRI SDMT, as revealed by the 2-sample *t* tests ($p < 0.05$ FWE cluster-corrected). The contents correspond to Table 2.

and temporal areas under the 2-s and 2.5-s ISI SDMT conditions. More specifically under the 2-s ISI condition, the bilateral inferior frontal gyri and the bilateral superior, middle and inferior temporal gyri, as well as the bilateral parahippocampal gyrus, the fusiform gyrus and the hippocampus, were more significantly activated in the MS patients than in the HCs. For the 2.5-s ISI condition, differences were found to be lateralized to the right brain hemisphere. In this case, the right middle and inferior frontal gyri, the right superior, middle and inferior temporal gyri, and the right parahippocampal gyrus, the fusiform gyrus and the hippocampus were significantly more activated in the MS patients than in the HCs. Despite a reduction of SDMT accuracy of MS patients, no

Table 2. Brain areas that showed statistically significantly increased activation in MS patients compared to HCs during the 2-s and 2.5-s ISIs of the fMRI SDMT, revealed by 2-sample *t* tests ($p < 0.05$ FWE cluster-corrected) and displayed in Figure 2

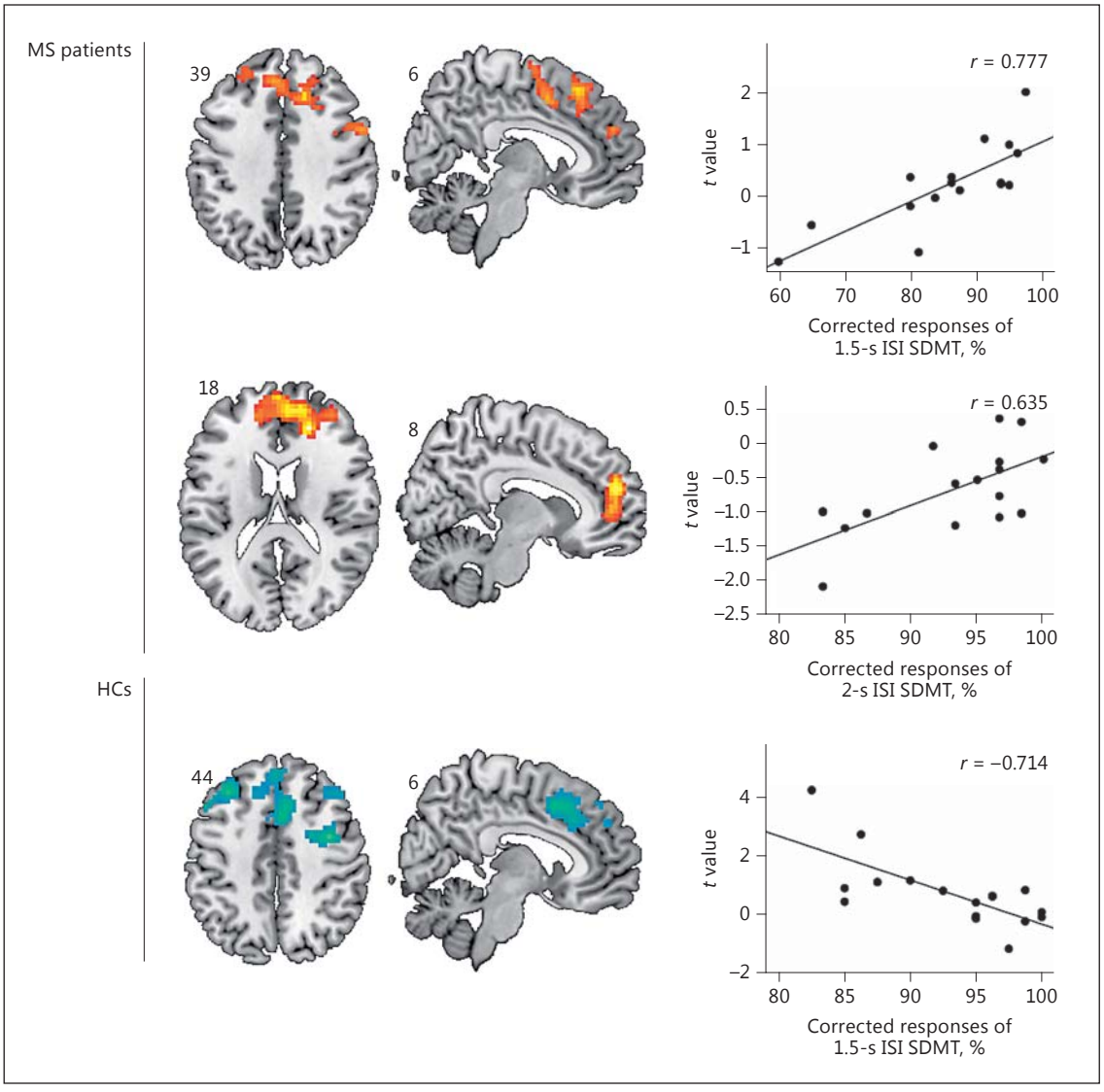
MS patients > HCs	2-s ISI					2.5-s ISI				
	cluster	*t* value	MNI			cluster	*t* value	MNI		
			x	y	z			x	y	z
Left										
Inferior frontal gyrus	1,253	4.16	−51	20	11	319	–	–	–	–
Superior temporal gyrus		3.87	−39	20	−25		–	–	–	–
Middle temporal gyrus		3.22	−60	−13	−10		–	–	–	–
Inferior temporal gyrus		2.95	−57	−13	−19		–	–	–	–
Parahippocampal gyrus		3.59	−33	−43	−10		–	–	–	–
Fusiform gyrus		4.76	−42	−10	−28		–	–	–	–
Hippocampus		3.35	−30	−10	−19		–	–	–	–
Cerebellum anterior lobe		3.45	−15	−37	−16		–	–	–	–
Right										
Middle frontal gyrus	642	–	–	–	–		3.36	21	26	−16
Inferior frontal gyrus		3.56	33	17	−16		4.11	27	26	−19
Insula		–	–	–	–		3.54	42	−15	−7
Putamen		4.43	21	5	−1		2.87	30	−16	−7
Superior temporal gyrus		4.27	36	11	−22		3.59	36	11	−25
Middle temporal gyrus		3.51	55	2	−28		3.40	51	2	−28
Inferior temporal gyrus		3.13	51	−6	−25		3.22	54	−1	−31
Parahippocampal gyrus		3.05	28	−16	−16		3.61	21	−10	−22
Fusiform gyrus		3.26	55	−1	−28		3.36	52	−1	−28
Hippocampus		4.77	28	−13	−19		3.49	27	−13	−22

Table 3. Brain activation areas that showed significant correlations with the behavioral execution (percentage of correct responses) in each ISI condition of the fMRI SDMT in MS patients and HCs ($p < 0.05$ FWE cluster-corrected), corresponding to Figure 3

Anatomical localization	MS patients										HC				
	positive (1.5-s ISI)					positive (2-s ISI)					negative (1.5-s ISI)				
	cluster	*t* value	MNI			cluster	*t* value	MNI			cluster	*t* value	MNI		
			x	y	z			x	y	z			x	y	z
Right inferior frontal gyrus	813	3.96	54	5	38	–	–	–	–	–	–	–	–	–	–
Right superior frontal gyrus		5.69	18	11	62	599	4.00	21	41	38	302	4.96	33	20	53
Right middle frontal gyrus		3.74	21	20	59		3.46	39	50	17		4.95	36	−1	44
Right medial frontal gyrus		4.39	3	5	47		6.14	6	50	20		3.75	9	26	41
Left medial frontal gyrus		3.98	−3	35	41		4.26	−6	50	−4		3.28	−12	29	44
Left middle frontal gyrus		3.12	−27	44	41		–	–	–	–	624	3.77	−48	20	26
Left superior frontal gyrus		4.05	−3	32	53		–	–	–	–		3.59	−15	59	29
Left inferior frontal gyrus		–	–	–	–		–	–	–	–		3.30	−51	20	26
Right anterior cingulate		–	–	–	–		3.27	12	50	−1	–	–	–	–	–
Left anterior cingulate		–	–	–	–		3.30	−3	47	2	–	–	–	–	–

significant activation differences between MS and HC were found at 1.5 s in any brain area. Similarly, no differences were found for the reverse contrasts (HC > MS) under any condition.

The regression analysis of behavioral performance (percentage of correct responses) for each ISI condition of the fMRI version of the SDMT and changes in the BOLD signal yielded several significant results (Fig. 3; Ta-



Color version available online

Fig. 3. Correlations between cerebral responses and behavioral execution for the different conditions of difficulty in the fMRI SDMT in the MS patients and HCs ($p < 0.05$ FWE cluster-corrected). Yellow, positive correlations; blue, negative correlations. See also Table 3.

ble 3). A positive correlation was obtained for the MS patients between the behavioral execution of the SDMT for the 1.5-s and 2-s ISI conditions and activations in the frontal areas ($r = 0.777$, $p = 0.000$, and $r = 0.615$, $p = 0.008$, respectively), including the superior, middle, medial, and inferior frontal gyri (see Table 3 for details). With the HC group, the opposite pattern was observed for task performance at 1.5-s ISI, which correlated negatively with the activity in the frontal areas ($r = -0.714$, $p = 0.001$), including the bilateral superior, middle, and medial frontal gyri, and the left inferior frontal gyrus (Table 3). No significant correlations appeared between the behavioral execution at 2-s and 2.5-s ISI SDMT and the brain activity recorded in the HC group.

Relationship between Brain Activation and MRI Variables

The Pearson index was used to assess whether T1 LV, GMF, WMF or BPF correlated with the activation scores of the anatomical clusters, whose activation in the MS patients statistically differed from that of the HCs (Table 2). None of these correlations yielded statistical significance.

Discussion

This study was designed to compare the brain activation pattern of cognitively preserved MS patients and HCs while they performed an fMRI-adapted version of the SDMT [14]. More specifically, we sought to analyze whether increasing the IPS demands of this task would have a different impact on the cognitive performance and brain activation patterns of the MS patients and HCs, indicative of a differential "neural efficiency" in these 2 groups of participants.

One main finding of this study was that this fMRI-adapted version of the SDMT is a suitable tool for assessing IPS deficits in MS patients. Similarly to what we previously observed in HCs [14], we herein showed that the difficulty of this task can be parametrically adjusted by manipulating the pace (i.e., the ISI) at which stimuli are presented. As the ISIs were reduced, the IPS demands of the SDMT increased, and both groups were forced to deploy more brain resources (e.g., greater activity) to perform it.

Another main finding of this study was that, compared to the HCs, the MS patients showed increased brain activation while they performed the SDMT. This was observed when the IPS requirements of the SDMT were low or moderate (ISIs: 2.5 and 2s), and no performance differences between these groups were observed. More specifically for the 2.5-s ISI condition, the MS patients displayed the same task accuracy as the HCs, but the activity of several of their frontal and temporal brain areas was enhanced. Interestingly, when ISIs were shortened to 2 s, differences between MS and HC became more prominent and were observable in almost the same brain regions, but in both hemispheres (see Fig. 2 and Table 2 for details).

This pattern of results agreed with previous studies and suggests that frontal lobe activation increases in line with task difficulty, and that this brain area is recruited in order to set greater cognitive control [14, 22]. Our findings also agree with those of previous studies, which have described that in early disease stages, MS patients exhibit greater activation or recruit supplementary brain areas. This might be considered a compensatory mechanism to attain normal cognitive performance [8, 9, 23–26]. Accordingly, it is possible to re-interpret all these results as part of the "neural efficiency hypothesis." This hypothesis states that when cognitive operations are performed quickly, brain resource allocation can be minimized, while performance is maximized [13]. More specifically, we propose that MS patients appear to be less efficient subjects (e.g., they are slower and use more brain resources to perform the task properly) than HCs.

In contrast, when ISIs were set at 1.5 s, differences between HCs and the MS patients were not apparent in brain activation, but in the SDMT scores. This pattern of results is apparently due to the increased brain activation observed in the HC group, and also to the impossibility of further increasing the amount of neural resources spent on solving the task in the MS group. As previously proposed [26], since neural resources are limited, compensatory mechanisms might be unable to maintain normal cognitive performance in MS patients under some circumstances (e.g., when brain damage surpasses a certain level or, as in the present study, when performing highly demanding activities).

Interestingly, raising the SDMT IPS demands to a maximal level (ISI: 1.5 s) did not only yield less SDMT accuracy in the MS patients, but also revealed a qualitatively different relationship between task performance and brain resource allocation in each group of participants. An inverse relationship between both variables was found for the HC group; that is, the HCs with higher SDMT scores were faster and required fewer frontal resources to perform the task. Conversely under this stringent experimental condition (but also when ISIs were set at 2 s), SDMT performance in the MS patients correlated directly with the degree of activation of several frontal areas (see Table 3 and Fig. 3 for details); that is, the MS patients with higher SDMT scores were still able to turn on compensatory mechanisms and maintained normal cognitive performance by recruiting more neural resources than those with lower scores. Once again, these results reinforce the conclusion that, as a group, MS patients are less cognitively efficient than HCs. These results also show that when the IPS demands of the SDMT are maximal, individual differences among MS patients emerge. Whereas some of these patients are still able to maintain normal cognitive performance, but deploy more brain resources than HCs, others display reduced frontal lobe activation, which is accompanied by lower SDMT scores. These results are in line with the previously proposed inverted U-shaped relationship between brain activation and cognitive impairment in MS patients [26], and suggest that increasing the IPS demands of the SDMT also enhances its sensitivity to detect early intellectual deficits among MS patients.

In summary, the results of the present study revealed that: (1) the SDMT is a suitable task for measuring IPS in MS patients, and its sensitivity might be parametrically adjusted by varying its ISI; (2) when ISIs were longer or

moderate (2.5 or 2 s), the MS patients displayed an SDMT performance similar to that of the HCs but deployed more cognitive resources (reflected as enhanced brain activity), which reveals reduced neural efficiency; (3) this compensatory mechanism achieved a ceiling effect when ISIs were reduced to 1.5 s and the SDMT execution of the MS patient group worsened; (4) for this stringent experimental condition, HCs and MS patients displayed a qualitatively different relationship between task performance and brain resource allocation, and individual differences within each group of participants became apparent; (5) none of these indices of reduced cognitive performance in MS patients correlated with any of the signs of brain damage observed (probably because all the MS patients were still in the early stages of their disease). Taken together, these results suggest that this version of the SDMT might unravel IPS deficits in early-stage MS patients in 2 ways: first, when neuropsychological assessment is accompanied with fMRI, these deficits in MS patients might be appraised from the larger number of resources they deploy to solve the task (e.g., as reduced cognitive efficiency). Second, when short (i.e., 1.5-s) ISIs are imposed, the IPS deficits of some MS patients are also manifested as low SDMT scores, a finding that might be of special interest for its use in clinical settings.

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Disclosure Statement

The authors declare no conflicts of interest.

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