Neural correlates of episodic future thinking impairment in multiple sclerosis patients

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ABSTRACT

Background. Recent clinical investigations showed impaired episodic future thinking (EFT) abilities in multiple sclerosis (MS) patients. On these bases, the aim of the current study was to explore the structural and functional correlates of EFT impairment in nondepressed MS patients. *Method.* Twenty-one nondepressed MS patients and 20 matched healthy controls were assessed with the adapted Autobiographical Interview (AI), and patients were selected on the bases of an EFT impaired score criterion. The 41 participants underwent a functional magnetic resonance imaging (fMRI) session, distinguishing the construction and elaboration phases of the experimental EFT, and the categorical control tests. Structural images were also acquired. *Results.* During the EFT fMRI task, increased cerebral activations were observed in patients (relative to healthy controls) within the EFT core network. These neural changes were particularly important during the construction phase of future events and involved mostly the prefrontal region. This was accompanied by an increased neural response mostly in anterior, and also posterior, cerebral regions, in association with the amount of detail produced by patients. In parallel, structural measures corroborated a main positive association between the prefrontal regions' volume and EFT performance. However, no association between the hippocampus and EFT performance was observed in patients, at both structural and functional levels. *Conclusion.* We have documented significant overlaps between the structural and functional underpinnings of EFT impairment, with a main role of the prefrontal region in its clinical expression in MS patients.

KEYWORDS*: Episodic future thinking; Multiple sclerosis; Functional magnetic resonance imaging; Cognition; Voxel based morphometry.*

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Autobiographical memory (AM) is defined as the ability to mentally reexperience personal past events. From a theoretical standpoint, it had been proposed that the ability to retrieve past events and the capacity to imagine future events—namely, episodic future thinking (EFT)—were sustained by the same neuro-cognitive platform (Schacter et al., 2012; Tulving, 1985, 2001). Several studies designed to probe this hypothesis were conducted in healthy subjects and confirmed a common core network sustaining AM and EFT, which involves the medial frontal and temporal regions, posterior and retrosplenial cortex, and lateral parietal and temporal regions (Addis, Wong, & Schacter, 2007; Botzung, Denkova, & Manning, 2008). Not surprisingly, some past and future differences have also been described, including greater brain activations during the simulation of future events in the hippocampus and the frontopolar regions (Addis & Schacter, 2008; Addis et al., 2007). Schacter and Addis (2007) suggested the constructive episodic simulation hypothesis to account for the past/ future commonalities and differences. The hypothesis posits that, on the one hand, past and future events rely on similar information stored in episodic memory, which are flexibly recombined into a novel coherent event, and that, on the other hand, higher constructive processes are necessary to preexperience an event. In parallel, a main role of scene construction (Hassabis & Maguire, 2007), personal semantic memory (Irish, Addis, Hodges, & Piguet, 2012a, 2012b), and executive functions (De Vito et al., 2012) have been put forward as potential mechanisms mediating future oriented thought.

From a clinical standpoint, functional benefits of EFT have been described: its role in (a) coping skills for stressful events, with an involvement in emotion regulation and problem solving; (b) goal achievement, for which the act of imagining various scenarios helps to reach the target, and (c) the implementation of intentions (Szpunar, 2010). Furthermore, D'Argembeau, Lardi, and Van der Linden (2012) suggested that EFT, similarly to AM and self-defining EFTs contributes to a person's sense of self and, together with self-defining AMs, gives rise to a strong sense of personal continuity over time. Projecting ourselves into the future has thus a strong adaptive value since it allows us to mentally "try out" different scenarios (D'Argembeau et al., 2010).

Research on EFT conducted in clinical populations has reported the co-occurrence of AM and EFT impairment in single cases (Klein, Loftus, & Kihlstrom, 2002; Tulving, 1985) and group studies of Alzheimer's disease patients (Addis, Sacchetti, Ally, Budson, & Schacter, 2009), schizophrenia (D'Argembeau, Raffard, & Van der Linden, 2008), or frontotemporal dementia (Irish, Hodges, & Piguet, 2013). While the neural substrates of AM impairment have been documented in a few clinical studies, showing increased activations in some specific AM brain regions (Ernst, Noblet, et al., 2014; Maguire, Vargha-Khadem, & Mishkin, 2001; Meulenbroek, Rijpkema, Kessels, Olde Rikkert, & Fernandez, 2010; Poettrich et al., 2009), fewer investigations have explored the neural substrates of EFT impairment. Using voxel-based morphometry (VBM) analysis, previous studies provided some insights into the neural correlates of AM/EFT impairment in patients with Alzheimer's disease, frontotemporal dementia or semantic dementia, showing a relationship between this impairment and brain atrophy, with a specific neural signature depending on the pathology (Irish et al., 2012a; Irish et al., 2013). Regarding functional magnetic resonance imaging (fMRI) studies, to our knowledge, the first study in this domain is the one by Mullally, Hassabis, and Maguire (2012) in a single-case amnesic patient, showing increased activation in the residual hippocampal tissue. However, an important methodological aspect of this work is that the patient was asked to imagine atemporal and fictitious scenes that were not necessarily personally relevant or plausible for the patient. Using a case study approach, Viard et al. (2014) documented in four patients presenting with semantic dementia that the ability to simulate future events mainly depends on the integrity of the medial prefrontal regions and anterior hippocampi, together with the lateral temporal atrophy characteristic of this pathology. In addition, these patients also showed signs of hyperactivations in key nodes of the EFT brain network. In parallel, Hach, Tippett, and Addis (2014) investigated the neural correlates of personal past and future events in depressed persons and reported increased or decreased brain activations, as well as functional connectivity changes within the AM/EFT core network, in comparison with healthy subjects. Overall, it appears that damage in any core regions of the EFT brain network is likely to affect the ability to mentally preexperience future events (Berryhill, Picasso, Arnold, Drowos, & Olson, 2010; Irish et al., 2013).

Recently, AM and EFT have been shown to be impaired in relapsing remitting multiple sclerosis (RR-MS) patients (Ernst, Blanc, et al., 2014). This behavioral study pointed to a main involvement of executive processes at the origin of the deficit. The latter suggestion is supported by our recent findings of increased brain activations mainly located in the prefrontal regions in RR-MS patients during the recollection of personal memories, relative to healthy controls (Ernst, Noblet, et al., 2014). Importantly, in both studies, the patients' other cognitive functions—frequently impaired in MS—such as attention, anterograde memory, or executive functions (Rogers & Panegyres, 2007), were generally preserved. In this context, the investigation of AM and EFT is of importance to broaden the perspectives on cognitive functioning in MS patients, especially considering the complaints associated to this deficit in everyday life functioning, ranging from personal identity, and social or goal achievement difficulties (see Ernst, Blanc, et al., 2014, for MS patients' comments related to this). In addition,

the clinical characteristics of the RR-MS subtype (i.e., an alternation between phases of relapse and partial/complete recovery) and the uncertainty relating to the disease course could particularly impact future thinking and self-identity. In this vein, Moore, MacLeod, Barnes, and Langdon (2006) showed that depressed MS patients anticipated fewer future positive experiences, which were also more centered on the disease, than nondepressed MS patients.

While EFT impairment has been documented at the clinical level in MS patients, to our knowledge, no study to date aimed to explore EFT neural correlates in MS patients. However, previous studies investigating the neural changes associated to cognitive impairment in MS patients reported increased/decreased cerebral activations in brain areas also recruited by healthy controls and/or the recruitment of alternative (frequently contralateral) brain areas (Cader, Cifelli, Abu-Omar, Palace, & Matthews, 2006; Genova, Hillary, Wylie, Rypma, & DeLuca, 2009; Hulst et al., 2012). These findings have been obtained for working memory (Forn et al., 2012; Morgen et al., 2007), information processing speed (Genova et al., 2009), or anterograde memory (Hulst et al., 2012; Mainero et al., 2004; Morgen et al., 2007).

Bearing in mind that AM and EFT share common functional underpinnings (Schacter et al., 2012) and that cerebral activations changes have already been observed during AM performance in MS patients (Ernst, Noblet, et al., 2014), similar results could be expected during the simulation of future events. On these bases, the aim of the present study was to explore the structural and functional neural correlates of EFT impairment in RR-MS patients and to complete previous clinical findings (Ernst, Blanc, et al., 2014). We hypothesized that prefrontal damage would be particularly predictive of EFT impairment. Moreover, we surmised that structural damage would also be associated with cerebral activation changes during EFT performance, relative to healthy controls. Considering on the one hand the main role of the hippocampus in EFT and its particular responsiveness to the quality of future simulations (Addis & Schacter, 2008,2012), and on the other hand the report of frequent hippocampal damage in MS patients (Hulst et al., 2012; Koenig et al., 2014), we also predicted a difference in the neural response to the difficulty of simulation and the amount of detail between MS patients and healthy controls.

METHOD

Participants

Twenty-one RR-MS patients (Polman et al., 2011), who participated in the study of Ernst et al. (Ernst, Blanc, et al., 2014; Ernst, Noblet, et al., 2014) were selected with the following inclusion criteria: an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score $\leq$ 4, an absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (Montgomery & Asberg, 1979), no recent exacerbation of MS symptoms, and right-handedness. Only patients showing impaired EFT performance were selected (see Behavioral Assessment section). Importantly, all these patients also demonstrated AM impairment, which was dealt with in a previous work (Ernst, Noblet, et al., 2014). Twenty right-handed healthy controls (who also took part in the aforementioned studies) were selected to form a matched control group for gender, age, education level, and verbal intellectual quotient. Exclusion criteria for all participants were documented psychiatric illness, neurological disorder (other than MS for the patients), and poor knowledge of French. Demographic and clinical data are summarized in Table 1. The present study was approved by the Committee for Protection of Persons/Centre National de la Recherche Scientifique (CPP/CNRS N° 07023), and we complied with the Declaration of Helsinki.

Behavioral assessment

The behavioral assessment comprised two sessions, which took place before the neuroimaging session. The patients underwent first a comprehensive neuropsychological baseline (see Table 2 for a complete description), similar to that in Ernst et al. (Ernst, Blanc, et al., 2014; Ernst, Noblet, et al., 2014).

EFT performance was then assessed using an adapted version of the Autobiographical Interview (AI; Addis, Pan, Vu, Laiser, & Schacter, 2009; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002), which consists in imagining personal unique events, temporally and contextually specific, occurring over minutes to hours and to generate as much detail as possible about the event. Participants were given cue words to generate five events, which could plausibly occur within the next year (Addis, Pan, et al., 2009). Following Levine et al. (2002), participants spoke about the event without any interruption from the examiner, continuing until it was evident that they had reached a natural ending point. In addition, no time limit was set due to potential decreased cognitive processing speed. The AI session was audio-recorded for later verbatim transcription, and it was scored following the standardized AI scoring procedure (see Levine et al., 2002, for a complete description of the

scoring).

TABLE 1: Demographical and clinical data

Participants	MS patients (n = 21)	Healthy controls (n = 20)	Statistical analysis
Age (in years)	41.52(10.02)	39.15 (8.44)	$t = 0.81$, $p = .41$
Education (in years)	13.00 (1.97)	13.40 (2.35)	$t = -0.59$, $p = .56$
Sex (Ratio female/male)	17/4	17/3	$\chi^2 = 0.11$, $p = .73$
EDSS [range]	2.48 (1.37) [0-4]	—	—
Duration of MS (in years)	11.79 (7.97)	—	—
Number of DMD treatment	1.00 (0.00)	—	—
Verbal intelligence quotient	98.38 (12.71)	97.90 (11.49)	$t = 0.12$, $p = .90$

Note. MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; DMD = disease-modifying drug. Means for the MS patient and the healthy control groups. Standard deviations in parentheses.

TABLE 2 : Neuropsychological baseline examination scores

Tests and scales	MS group score. Mean (SD)
Verbal reasoning	98.38 (12.70)
Verbal IQ-short form (Axelrod, Ryan, & Ward, 2011; Wechsler, 1997)	
Nonverbal reasoning	9.00 (1.73)
PM12 (Raven, 1958)	
Anterograde memory (verbal)	11.84 (1.34)
RAVLT (Rey, 1964)	13.19 (2.01)
Total mean number of words	
Delayed recall	
Anterograde memory (nonverbal)	35.20 (0.92)
ROCF (Rey, 1941; Osterrieth, 1944)	24.88 (6.23)
Copy	24.50 (6.09)
Immediate recall	
Delayed recall	
Language	97.14 (4.21)
Deno 100 (Kremin, 2002)	
Attentional abilities	47.71 (8.90)
Stroop (Stroop, 1935)	45.71 (7.59)
Colours (score T)	45.28 (12.68)
Words (score T)	48.95 (7.72)
Interference (score T)	11.57 (5.17)
Interference score (score T)	
Months back (sc; National Hospital)	
Executive functions	8.42 (1.74)[a]
Tower of London (Shallice, 1982)	18.00 (3.57)
Score	14.76 (5.26)
Time indices	4.19 (2.71)[a]
Brixton (Burgess & Shallice, 1997)	20.55 (4.59)
Cognitive Estimation (Shallice & Evans, 1978)	13.04 (2.87)
Verbal Fluency (National Hospital)	
Categorical	
Phonological	
Information processing speed	53.85 (9.41)
AMIBP subtest (Coughlan & Hollows, 1985)	49.57 (10.50)
Cognitive	2.67 (2.98)
Motor	59.46 (10.84)
Error percentage	
Corrected score	
Visuoperceptual and -spatial abilities	23.28 (4.29)
VOSP (Warrington & James, 1991)	9.61 (0.66)

Silhouettes	
Cubes analyses	
Depression	5.61 (4.49)
MADRS (Montgomery & Asberg, 1979)	
Fatigue	44.50 (14.67)
EMIF-SEP (total; Debouverie, Pittion-Vouyovitch, Louis & Guillemin, 2007)	

Note. MS = multiple sclerosis; AMIPB = Adult Memory and Information Processing Battery; PM12 = Progressive Matrices 12; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure; VOSP = Visual Object and Space Perception; MADRS = Montgomery and Asberg Depression Rating Scale; EMIF-SEP = Echelle de Mesure de l'Impact de la Fatigue. Means for the MS patient group in comparison with the normative data of each test (mean and standard deviation score, 5th percentile or cutoff depending on the test).

[a]Scores under the normal range.

Statistical analyses focused on the internal detail (i.e., strictly episodic detail) generated spontaneously by participants about the future events.

Internal details were averaged across the five events for each participant. External details were not analyzed here but the preserved performance for this type of detail and of personal semantic knowledge in MS patients has already been addressed in previous studies (Ernst, Blanc, De Seze, & Manning, in press; Ernst, et al., 2013).

Since our aim was to explore the functional underpinnings of EFT impairment, MS patients' AI scores were compared to our AI normative database, which includes matched healthy controls (for age, education level, and gender; Ernst et al., 2012). MS patients' EFT performance was deemed to be impaired if the mean number of internal details was $\leq$ 19.

The interrater reliability was verified for 10% of the future events (following Levine et al.'s (2002) recommendations), which were scored by a second scorer blind to group membership. Coefficients for the mean number of internal details showed high interrater reliability (correlation coefficient = .92).

Neuroimaging session

fMRI tasks

As previously mentioned, the current investigation is part of a broader study that explores the neural substrates of AM and EFT impairment in MS patients. Overall, our fMRI paradigm comprises both an AM and an EFT condition, as well as a control condition. Since the neural substrate AM impairment data have already been discussed (Ernst, Noblet, et al., 2014), as mentioned above, only the data addressing the neural substrates on EFT impairment are developed here.

The EFT condition consisted in the evocation of unique personal future events, following the AI's instructions. Thirty-two pairs of arbitrary cue-words were proposed to generate future events (e.g., "family-meal") which could plausibly occur within the next year. Based on Addis et al. (2007), two phases of evocation were distinguished: (a) the construction, corresponding to the search and initial building up of the event, and (b) the elaboration, corresponding to the imagination of detail associated to the event. Participants were instructed to not provide the same events as those previously mentioned during the adapted AI, and this was further verified through the postscan questionnaire (see below). In the case of repetition, the event was excluded from the analysis.

The control task was a categorical task adapted from Addis et al. (2007), which included 32 pairs of words, with which participants had to make a sentence for the construction phase (e.g., "yellow-trousers": "she was wearing yellow trousers"). Then, during the elaboration phase, they had to keep the same sentence structure, replacing the two given cue-words by words of the same semantic category (e.g., "she was wearing a pink dress").

For both tasks, each trial had a fixed duration of 20 s, modulated by the subject's response: The subject had to press on the button 1 of the response box to mark the end of the construction phase. The remaining time, during which a central fixation-cross was presented, corresponded to the elaboration phase.

Prior to scanning, the procedure was explained to participants, and they completed a computerized practice trial for each task in order to be familiar with the experimental design and timing of presentation. Given the time

constraints of the fMRI tasks and the EFT impairment of our patients, particular attention was paid to patients' practice trial to optimize the further completion of the tasks.

The experimental design was organized in four sequences of eight stimuli per condition, beginning systematically with the control task and then alternating between future events and control task conditions. In both tasks, each trial was followed by short periods of fixation of random duration (mean duration = 1.5 s, range = 1 to 2 s). At the beginning of each sequence, the name of the condition was displayed on the screen for 6 s. The presentation order of stimuli within each condition was randomized. The programming and response collection were done with E-Prime 2 software (Psychology Software Tools, Inc.). Words were displayed on a screen in white text with a black background and were viewed using a mirror incorporated in the head-coil.

Immediately following scanning, a postscan questionnaire was completed for the EFT condition in order to verify the adequacy of responses before data analysis. Participants had to indicate the type of event (unique, repetitive, extensive, semantic, or absent), and its spatial and temporal context, and to rate on two 10-cm visual-analog scales the difficulty of imagination and the amount of detail associated with each event. For the spatiotemporal context, participants were asked to write down the most detailed account they were able to about the location of the event and when it will occur. Regarding the type of event, while participants initially determined the specificity of events, a further control of this aspect was carried out by the experimenter (A.E.), based on the spatial-temporal context of events. More precisely, immediately after the completion of the postscan questionnaire, in the absence of a specific spatiotemporal context (necessary to consider an event as unique) or in the case of doubt regarding the classification, participants were asked to provide additional detail about the event to determine its precise nature.

MRI acquisition

MRI examinations were performed on a 3T MRI scanner (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany). Structural images were obtained by means of a 3D T1-weighted SPACE (Sampling Perfection with Application optimized Contrasts using different flip angle Evolution) sequence (time to repetition, TR = 4000 ms; inversion time, TI = 380 ms; echo time, TE = 383 ms; flip angle = 120°; field of view, FOV = 256 mm; matrix = 512 × 512; 176 sagittal slices of 1 mm). 3D T2 Fast Spin Echo images were also acquired with the following parameters: TR = 3200 ms; TE = 409 ms; flip angle = 120°; FOV = 256 mm; matrix = 512 × 512; 176 sagittal slices of 1 mm.

Functional images were acquired with a T2*-weighted echo planar imaging sequence (TR = 2500 ms; TE = 30 ms; matrix = 64 × 64 voxels; FOV = 224 mm; flip angle, FA = 90). The anterior commissure and posterior commissure were identified in the midsagittal slice, and 45 contiguous slices (each 4 mm thick) were prescribed parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

Statistical analyses

Behavioral data

Although patients were selected with impaired EFT performance, between-group comparisons for the AI score were conducted (*t* test) in order to verify that our group of MS patients did show lower EFT scores than the current sample of matched healthy controls included in this study. Between-group comparisons for the postscan variables were also tested by means of *t* test or repeated measures analysis of variance (ANOVA).

Functional neuroimaging analysis

Preprocessing and statistical analyses were conducted using SPM5 software (Statistical Parametric Mapping; Friston et al., 1995). Time-series were realigned to the first volume to correct for motion artefacts, spatially normalized to a standard echo planar imaging (EPI) template based on the Montreal Neurological Institute reference brain in Talairach space (Talairach & Tournoux, 1988) and then spatially smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel.

For the future events and control tasks, evoked hemodynamic response times locked to the onset of the cue presentation (construction phase) were modeled with a canonical hemodynamic response function. Hemodynamic activity related to the elaboration phase was modeled with a boxcar function of 10-s duration that started immediately after the end of the construction phase by button press. The 10-s-duration interval for the elaboration phase was fixed to allow a sufficient time interval to the search of detail, and trials with a construction phase longer than 10 s were excluded. Since a great overlap of the cerebral activations for specific

and repetitive future events has been previously observed (Addis, Cheng, Roberts, & Schacter, 2011), both unique and repetitive events were kept to maximize the number of events included as regressors of interest, especially for patients.

Statistical parametric maps were generated for the comparison between EFT and control conditions, during the construction and elaboration phases, for each subject, in a general linear model. Whole brain between-group comparisons (patients > healthy controls and patients < healthy controls) were conducted by means of two-sample t tests for each contrast image (EFT construction vs. control construction; EFT elaboration vs. control elaboration).

Parametric modulation analyses were performed for the difficulty of imagination and amount of detail, with the creation of a general linear model for the construction and elaboration phases, using the first-order parametric modulation option supplied by SPM5. To that end, to obtain a homogenous distribution of responses, ratings from the two visual analog scales were rescheduled empirically as follow: 0 cm to 5 cm = 1 (low score); 5.1 cm to 7.5 cm = 2 (medium score); and 7.6 cm to 10 cm = 3 (high score). Two sample t tests were then applied to explore the potential between-group differences.

To provide a good balance between controlling the Types I and II error rates, the significance threshold was set at $p = .005$ (uncorrected for multiple comparisons), with a minimum extent threshold of 10 contiguously activated voxels for all the analyses (Lieberman & Cunningham, 2009). Given that the medial temporal lobe structures (parahippocampal gyrus and hippocampus) were of a priori interest and that they are particularly small brain regions, explorative analyses were also conducted with a minimum extent threshold of five contiguously activated voxels.

Structural neuroimaging analysis

Focal gray matter (GM) atrophy was investigated using the VBM framework provided in SPM12b (Friston et al., 1995).

Anatomical MRI images were spatially prepro-cessed in the following way: All T1 structural images were bias corrected and were segmented using an extension of the unified segmentation procedure (Ashburner & Friston, 2005) that includes six classes of tissue. Spatial normalization was then performed using DARTEL algorithm (Ashburner, 2007). First, a study-specific template was created using GM images of all subjects. Second, this template was normalized to Montreal Neurological Institute (MNI) space. Third, the individual deformation field that permits to normalize each GM image to the template was computed and was applied to each GM image and modulated to preserve the total amount of GM volume. A Gaussian kernel (full width at half maximum, FWHM: 8 mm) was then applied to modulated GM images and was entered in the statistical analysis.

Group comparison and statistical correlations between local GM volume and EFT performance were then investigated using the GLM. Similar to previous studies using the AI and exploring the neural correlates of AM and EFT, only the internal details were included in the analysis (Irish et al., 2012a; Irish et al., 2013). Age and total amount of GM were included as nuisance covari-ates in all statistical analyses. A statistical threshold of $p < .001$ without multiple comparison correction and with a cluster spatial extend of 50 voxels was considered in all analyses.

RESULTS

Behavioral results

Similar to our previous studies, neuropsychological baseline scores obtained by patients were in the normal range (i.e., threshold: either z score -1.65 or the 5th percentile, depending on the normative data of each test) for all cognitive functions, with two exceptions: planning and cognitive estimations abilities (Table 2).

Regarding EFT performance, MS patients and healthy controls provided, respectively, a mean number of 8.12 internal details ($SD = 4.65$) versus 20.55 ($SD = 5.70$). As expected, the patients' performance was significantly lower than that of healthy controls for the mean number of internal details ($t = -7.67$, $p < .001$; Figure 1).

Turning to the postscan results (Table 3), there was no group difference in the mean reaction time to generate future events ($t = 0.35$, $p = .73$). A main effect of event type ($F = 88.53$, $p < .001$) was observed, and Tukey HSD post hoc test revealed a greater number of unique events than of the four other event types ($p < .001$ in all the cases). No significant differences were highlighted for the event type between the MS and healthy control

groups, as well as for the difficulty of imagination ($t = -1.19$; $p = .24$). However, a significant difference was observed for the amount of details, with lower scores for patients than for healthy controls ($t = -2.35$, $p = .02$).

Figure 1. *Mean number of internal details provided by multiple sclerosis (MS) patients and healthy controls during the autobiographical interview (AI). *Significant difference.*
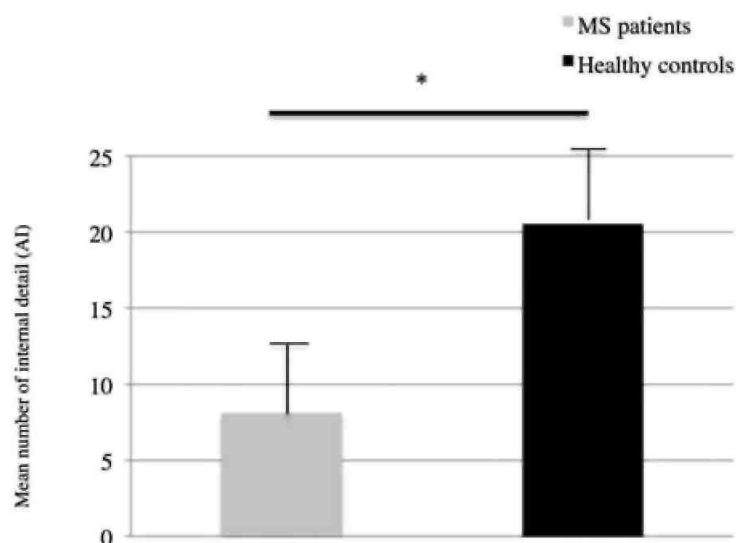

TABLE 3: *Mean for the behavioral measures from the fMRI session for the MS patient and the healthy control groups*

Measures	MS patients	Healthy controls
Construction reaction time (in s)	4.80 (1.06)	4.69 (0.91)
Type of events (number)		
Unique	17.10 (7.76)	19.5 (6.23)
Repetitive	5.29 (5.31)	6.75 (5.86)
Extended	0.52 (1.63)	1.55 (1.82)
Semantic	1.67 (3.55)	0.6 (1.10)
Absent	3.52 (3.49)	1.4 (2.60)
Difficulty of imagination (parametric)	2.33 (0.54)	2.51 (0.42)
Amount of detail (parametric)	1.84 (0.46)	2.16 (0.40)

Note. MS = multiple sclerosis; fMRI = functional magnetic resonance imaging. Standard deviations in parentheses.

Neuroimaging results

EFT construction

Between-group analysis revealed a distributed cerebral network showing significantly greater activations in patients than in healthy controls during the initial generation of future events (Table 4; Figure 2). This enhanced brain network encompassed predominantly the bilateral prefrontal regions (superior, inferior, middle, and medial gyri), the right temporal regions (superior, middle, and fusiform gyri), the bilateral parahippocampal regions, the bilateral, but predominantly right, parietal regions (inferior parietal lobule, postcentral gyrus, and precuneus), the bilateral occipital regions (middle and superior gyri), and the bilateral, but predominantly right, limbic areas (anterior and posterior cingulate).

Regarding the reverse contrast (healthy controls > MS patients), no significant results were observed.

TABLE 4: *Brain regions exhibiting increased activations in MS patients (vs. healthy controls; two-sample f test) during the EFT construction (vs. control construction) and EFT elaboration (vs. control elaboration)*

Brain region	Coordinates (x, y, z)	Z
EFT construction > control construction		
R Middle frontal gyms (BA 6)	(30, -2, 48)	3.83
R Middle frontal gyms (BA 10)	(36, 60, 10)	3.63
R Middle frontal gyms (BA 46)	(48, 50, 8)	3.14
R Superior frontal gyrus (BA 8)	(38, 24, 54)	3.53
R Superior frontal gyrus (BA 6)	(18, -4, 66)	2.64
L Superior frontal gyrus (BA 9)	(-22, 50, 28)	2.98
L Inferior frontal gyrus (BA 47)	(-32, 30, -20)	3.32
R Inferior frontal gyrus (BA 47)	(58, 18, 0)	2.78
R Medial frontal gyrus (BA 9)	(8, 34, 32)	2.90
L Medial frontal gyrus (BA 10)	(-16, 50, 4)	2.99
L Paracentral lobule (BA 31)	(0, -30, 46)	2.73
R Precuneus (BA 7)	(18, -74, 48)	3.33
L Precuneus (BA 7)	(-16, -50, 44)	2.81
R Inferior parietal lobule (BA 40)	(48, -36, 48)	3.39
L Inferior parietal lobule (BA 40)	(-56, -22, 24)	4.15
L Postcentral gyrus (BA 40)	(-56, -30, 18)	4.45
R Postcentral gyrus (BA 7)	(22, -48, 64)	3.05
R Postcentral gyrus (BA 3)	(56, -18, 26)	3.04
R Postcentral gyrus (BA 5)	(4, -44, 64)	2.66
L Postcentral gyrus (BA 7)	(-6, -50, 62)	2.77
R Superior temporal gyrus (BA 22)	(62, -20, 6)	3.25
R Superior temporal gyrus (BA 41)	(46, -32, 12)	3.16
L Sub-gyral (BA 37)	(-44, -42, -10)	4.36
R Middle temporal gyrus (BA 21)	(56, -32, -6)	2.83
R Middle temporal gyrus (BA 37)	(50, -62, 6)	2.89
R Middle temporal gyrus (BA 39)	(52, -68, 20)	2.86
R Fusiform gyrus (BA 37)	(42, -52, -18)	2.90
R Parahippocampal gyrus (BA 36)	(42, -36, -6)	2.86
L Parahippocampal gyrus (BA 30)	(-22, -40, 4)	3.18
L Anterior cingulate (BA 32)	(-12, 30, -10)	3.01
R Posterior cingulate (BA 31)	(28, -58, 14)	3.58
R Posterior cingulate (BA 30)	(26, -66, 12)	3.40
R Anterior cingulate (BA 32)	(8, 18, -10)	3.66
L Anterior cingulate (BA 25)	(4, 0, -2)	3.60
R Middle occipital gyrus (BA 19)	(48, -72, 4)	2.94
L Superior occipital gyrus (BA 19)	(-30, -70, 28)	2.81
R Caudate	(16, 24, -2)	3.16
L Thalamus	(-18, -16, 0)	3.58
R Cerebellum	(26, -50, -24)	3.05
L Cerebellum	(-38, -52, -30)	3.02
L Putamen	(-22, -4, 18)	2.99
R Claustrum	(38, -20, -8)	3.45

EFT elaboration > control elaboration

R Middle frontal gyrus (BA 10)	(44, 44, 22)	3.00
R Superior frontal gyrus (BA 10)	(22, 58, -2)	2.85
L Middle frontal gyrus (BA 46)	(-42, 42, 16)	3.43
L Middle frontal gyrus (BA 9)	(-46, 24, 34)	2.90
R Middle frontal gyrus (BA 9)	(38, 32, 28)	3.00
L Middle temporal gyrus (BA 21)	(-38, 2, -30)	3.27
L Fusiform gyrus(BA 37)	(-44, -62, -12)	3.80
R Cerebellum	(8, -72, -14)	3.46

Note. MS = multiple sclerosis; EFT = episodic future thinking; BA = Brodmann area; L = left; R = right, k = 10 voxels.
$p < .005$.

EFT elaboration

During the elaboration phase, greater cerebral activations, mostly located in the bilateral prefron-tal regions (middle and superior gyri) were highlighted in patients (Table 4; Figure 3). These prefrontal activations were accompanied by activations in the left temporal regions, more precisely in the middle temporal gyrus and the fusiform gyrus.

The reverse contrast showed increased brain activity in healthy controls in posterior cerebral regions, including the left precuneus (Brodmann area, BA 31; xyz = -16 -58 34), the right inferior parietal lobule (BA 40; xyz = 62 -36 24), the right superior (BA 22; xyz = 54 -56 14) and middle (BA 39; xyz = 44 -68 18) temporal gyri, and the left cingulate gyrus (BA 31; xyz = -10 -24 44).

Parametric analyses

Difficulty of access. A differential neural response to the difficulty of access was highlighted between patients and healthy controls. A greater neural response to the difficulty of access was only observed during the construction phase in patients, with increased brain activity in the left parahippocampal gyrus, the right anterior and left posterior cingulate gyri, and left sublobar regions (Table 5; Figure 4).

Regarding healthy controls, an enhanced neural response to the difficulty of access was observed in both phases (Table 6). During the construction phase, significant brain activations were highlighted in the left anterior cingulate and right sublobar regions, while for the elaboration phase, the neural response encompassed the left medial prefrontal regions, the right temporal regions (middle, superior, and fusiform gyri), and the bilateral posterior brain regions (precuneus, cingulate, and middle occipital gyri).

Amount of detail. Concerning the neural response to the amount of detail, increased brain activations were observed in patients (Table 5; Figure 4), while the reverse contrast showed no significant result. More precisely, during the construction phase, our patients showed extensive bilateral prefrontal activations (middle, superior, and inferior gyri), but also activations in the bilateral temporal regions (superior and fusiform gyri), the left supramarginal gyrus, the left cingulate gyrus, the right cerebellum, and bilateral sublobar regions.

Regarding the elaboration phase, the bilateral, but mostly left, prefrontal regions were also recruited (medial, inferior, middle, and superior gyri), as well as parietal regions bilaterally (precu-neus, angular, and supramarginal gyri, superior and inferior parietal lobules), the left temporal regions (middle and superior gyri), and bilaterally, the following structures: parahippocampal gyrus, cuneus, inferior and middle occipital gyrus, anterior and posterior cingulate, cerebellum and sublobar regions.

Figure 2. *Brain regions showing an increased activity in multiple sclerosis (MS) patients (vs. healthy controls) during the episodic future thinking (EFT) construction (vs. control task construction); p = .005, k = 10 voxels, uncorrected. To view this figure in color, please visit the online issue of the Journal.*
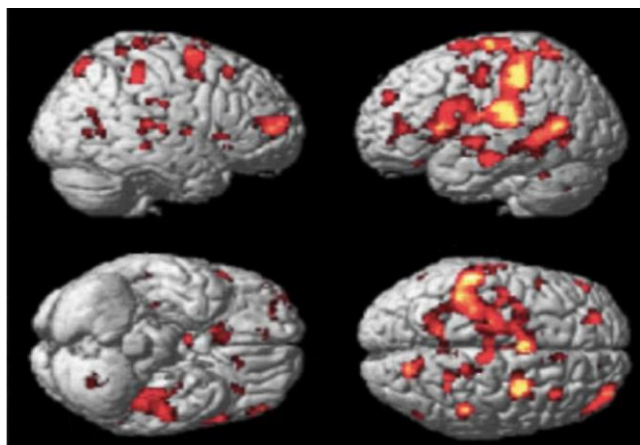

Figure 3. *Brain regions showing an increased activity in multiple sclerosis (MS) patients (vs. healthy controls) during the episodic future thinking (EFT) elaboration (vs. control task elaboration); p = .005, k = 10 voxels, uncorrected. To view this figure in color, please visit the online issue of the Journal.*
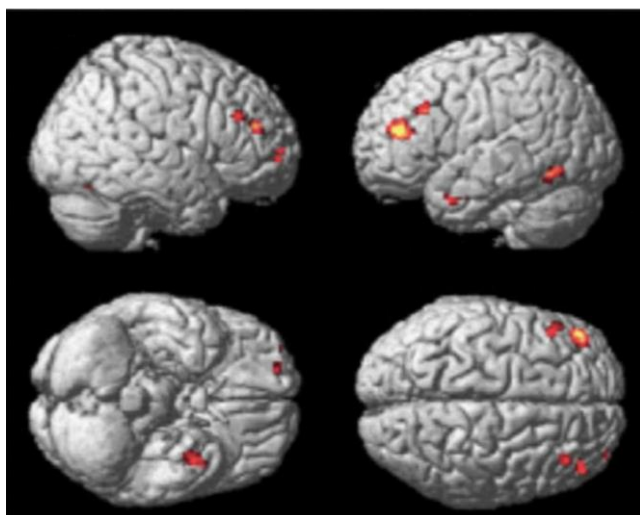

TABLE 5: *Significant brain activations for the parametric response to the difficulty of access and the amount of detail for MS patients (vs. healthy controls; two-sample f test) during the EFT construction and elaboration*

| Brain region	Coordinates (x y, z)	Z
EFT construction: Difficulty of access		
L Parahippocampal gyrus (BA 30)	(-18, -40, 6)	3.29
R Cingulate gyrus (BA 24)	(20, -2, 34)	2.96
L Posterior cingulate (BA 30)	(-14, -50, 16)	3.13
L Thalamus	(-28, -28, 2)	3.32
L Insula (BA 13)	(-28, -26, 26)	2.63
L Lentiform nucleus	(-22, -18, 0)	2.64
EFT construction - Amount of detail		
L Middle frontal gyrus (BA 10)	(-32, 54, 8)	3.08
L Superior frontal gyrus (BA 10)	(-18, 58, 20)	3.42

R Middle frontal gyrus (BA 10)	(36, 52, 10)	3.50
R Superior frontal gyrus (BA 10)	(16, 62, 20)	3.04
L Middle frontal gyrus (BA 47)	(-46, 36, -2)	3.10
R Inferior frontal gyrus (BA 47)	(44, 18, 2)	3.42
L Inferior frontal gyrus (BA 47)	(-34, 26, -10)	2.86
R Precentral gyrus (BA 6)	(40, 0, 34)	3.19
L Middle frontal gyrus (BA 9)	(-42, 26, 26)	3.43
R Superior frontal gyrus (BA 9)	(4, 58, 22)	2.76
R Middle frontal gyrus (BA 6)	(48, 8, 44)	3.15
L Middle frontal gyrus (BA 46)	(-46, 22, 20)	3.34
R Superior frontal gyrus (BA 8)	(18, 36, 56)	3.44
L Middle frontal gyrus (BA 8)	(-26, 12, 34)	2.98
L Inferior frontal gyrus (BA 13)	(-32, 6, -14)	3.30
L Superior temporal gyrus (BA 39)	(-46, -58, 32)	2.86
R Fusiform gyrus (BA 20)	(60, -8, -24)	2.75
R Sub-gyral (BA 20)	(46, -18, -16)	2.81
L Supramarginal gyrus (BA 40)	(-48, -48, 34)	2.77
L Cingulate gyrus (BA 24)	(-6, -8, 32)	2.97
L Thalamus	(-12, -8, 0)	3.74
R Thalamus	(18, -14, 0)	3.46
R Insula (BA 13)	(40, -4, 22)	3.37
L Insula (BA 13)	(-34, 16, 6)	3.04
R Cerebellum	(24, -54, -24)	3.04
L Putamen	(-30, -10, -6)	2.96
R Putamen	(16, 8, -4)	3.04
R Caudate	(10, 8, 6)	2.70
R Claustrum	(34, -20, 4)	3.03
L Claustrum	(-22, 12, -4)	2.70
EFT elaboration: Amount of detail		
L Superior frontal gyrus (BA 8)	(-28, 30, 54)	3.00
R Medial frontal gyrus (BA 9)	(6, 46, 20)	2.93
L Medial frontal gyrus (BA 10)	(-4, 58, 8)	2.97
R Middle frontal gyrus (BA 8)	(30, 42, 46)	3.41
L Middle frontal gyrus (BA 8)	(-54, 16, 40)	2.80
L Middle frontal gyrus (BA 6)	(-44, 14, 54)	2.88
L Superior frontal gyrus (BA 10)	(-24, 64, 18)	2.90
L Inferior frontal gyrus (BA 47)	(-18, 34, -4)	3.48
L Precuneus (BA 7)	(-6, -82, 46)	3.62
R Precuneus (BA 7)	(12, -50, 38)	3.08
R Precuneus (BA 31)	(10, -48, 30)	2.90
L Angular gyrus (BA 39)	(-52, -66, 38)	3.34
L Supramarginal gyrus (BA 40)	(-60, -54, 28)	3.13
R Superior parietal lobule (BA 7)	(42, -68, 52)	2.90
R Inferior parietal lobule (BA 40)	(46, -54, 36)	2.84
L Middle temporal gyrus (BA 21)	(-52, -14, -12)	2.92
L Superior temporal gyrus (BA 39)	(-34, -56, 28)	3.18
L Cuneus (BA 18)	(-8, -82, 18)	3.10
R Cuneus (BA 17)	(20, -80, 10)	2.80
R Cuneus (BA 19)	(2, -80, 40)	3.55
R Cuneus (BA 7)	(2, -66, 30)	2.99
L Inferior occipital gyrus (BA 19)	(-36, -80, -2)	2.88
R Middle occipital gyrus (BA 19)	(36, -86, 18)	2.83
R Parahippocampal gyrus (BA 19)	(42, -48, 2)	2.83
L Parahippocampal gyrus (BA 36)	(-42, -34, -10)	2.91
L Cingulate (BA 31)	(-22, -50, 28)	3.57
R Cingulate (BA 31)	(20, -44, 38)	2.70
L Anterior cingulate (BA 32)	(-2, 34, -10)	3.41
L Insula (BA 13)	(-36, -20, 22)	3.41
R Insula (BA 13)	(30, -20, 24)	2.75
R Thalamus	(2, -12, 16)	3.25

|		
L Cerebellum	(-22, -80, -16)	3.13
R Cerebellum	(12, -82, -12)	2.82
L Caudate	(-20, 16, 20)	3.18
R Caudate	(12, 20, 16)	2.82
R Lentiform nucleus	(12, -4, 0)	3.09

Note. MS = multiple sclerosis; EFT = episodic future thinking; BA = Brodmann area; L = left; R = right, k = 10 voxels. $p < .005$ uncorrected.

Figure 4. Brain regions showing an increased response (A) to the difficulty of access during the episodic future thinking (EFT) construction, and to the amount of details during (B) the EFT construction and (C) the EFT elaboration; $p = .005$, $k = 10$ voxels, uncorrected. To view this figure in color, please visit the online issue of the Journal.
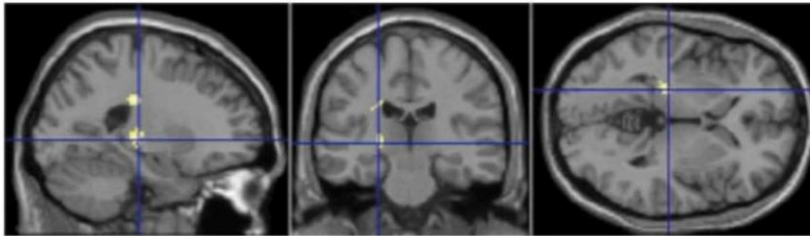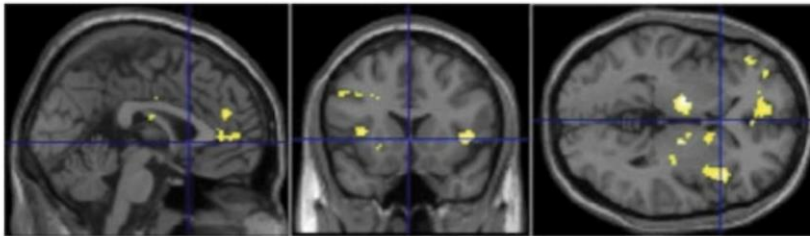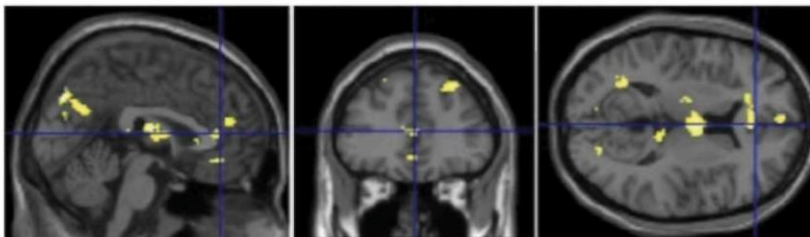

VBM analysis

Compared to healthy controls, patients showed widespread neural atrophy involving the bilateral parahippocampal regions, the right cuneus, the bilateral precentral gyrus, the left postcentral gyrus, the thalamus, and the cerebellum bilaterally (Table 7). The reverse contrast failed to reveal significant clusters.

Regarding the structural correlates of EFT performance in patients, a significant positive correlation was mainly observed between the left prefrontal regions (middle, inferior, medial, and superior frontal gyri), the right superior temporal gyrus, the bilateral inferior parietal lobule, the right precuneus, and the left cuneus volumes and EFT score (Table 8). Conversely, in healthy controls, a significant correlation between EFT score and the volume of several posterior brain regions (cuneus, precuneus, lingual, and postcentral gyri) was highlighted (Table 8).

Moreover, the direct comparison between groups revealed a greater correlation between EFT score and the volume of the middle, inferior, medial, and superior frontal gyri, the middle and superior temporal gyri, and the precuneus in patients than in healthy controls (Table 8). The reverse contrast showed a greater association between EFT performance and the volume of posterior brain regions such as the inferior occipital, the lingual, the superior temporal gyri, and the inferior parietal lobule (Table 8) in healthy controls than in patients.

DISCUSSION

The present study investigated the structural and functional underpinnings of EFT impairment in nondepressed RR-MS patients for the first time, to our knowledge. Interestingly, the EFT deficit has been observed in the context of a relative preservation of general cognitive functioning in our patients and was accompanied by cerebral activation changes in comparison with healthy controls, involving mostly the frontal regions. Similar to Hach et al. (2014) in a study involving depressed patients, these brain activation changes have been observed in patients who were still able to perform adequately the fMRI EFT task. Despite a difference in the amount of details of future events, MS patients and healthy controls had similar reaction times and number of valid trials. This allows us to reasonably interpret the patient's cerebral activation pattern as resulting from pathology, rather than arising from a too poor completion of the task (Cader et al., 2006). Consistent with the literature dealing with the functional changes associated with cognitive impairment in MS patients, we reported both increased and decreased cerebral activations in brain areas pertaining to the EFT brain network normally recruited by healthy controls, but also the recruitment of contralateral brain areas (Cader et al., 2006; Genova et al., 2009; Hulst et al., 2012).

During the EFT construction phase, an enhanced cerebral network was observed, including the anterior, medial, and posterior brain regions, bilaterally. Interestingly, the great majority of the enhanced brain activations in MS patients were located in the EFT core network described in healthy controls (Addis et al., 2007; Botzung et al., 2008). Within these increased brain activations, in agreement with our hypothesis, the bilateral prefrontal regions seemed particularly involved in MS patients. In the context of EFT, these brain areas are related to the executive demands necessary to the extraction and recombination of an infinite assortment of detail into a novel event (Weiler, Suchan, Koch, Schwarz, & Daum, 2011). This increased bilateral prefrontal activation observed during the construction phase is consistent with the retrieval deficit hypothesis suggested by Ernst, Blanc, et al. (2014), which posits that EFT impairment in MS patients is mainly related to executive and, therefore, prefrontal dysfunction. In particular, a disruption of the initial strategic processes required to further extract and recombine episodic details into a novel future event has been suggested. Such suggestion is also supported by the predominant response of the bilateral prefrontal regions to the amount of detail. Additionally, during the elaboration phase, this increased neural response could also reflect the greater cognitive demand for the integration and maintenance of multimodal information, supported by the frontopolar regions (Addis, Pan, et al., 2009), with the increasing amount of detail.

Increased neural activity was also observed in the lateral temporal region, which sustains the reactivation of a "semantic scaffolding" to guide future simulations (Irish et al., 2012a; Irish & Piguet, 2013) and could play a primary role in the recombination process (Schacter et al., 2012).

Structures from the anterior part of the cortical midline (i.e., medial frontal and anterior cingulate) were also highly engaged in MS patients during the construction phase, denoting the well-known self-referential processes, central in EFT (Northoff et al., 2006). The posterior cingulate, the adjacent precuneus, and the bilateral parahippocampal gyrus showed increased activation in our patients (likely associated with visual imagery processes; Greenberg & Rubin, 2003). Regarding the bilateral parahippocampal gyrus, it also plays a pivotal role in the recruitment of the posterior brain regions (Botzung et al., 2008; Viard et al., 2011) to further generate a coherent and detailed mental simulation. All in all, the anterior and posterior portions of the cortical midline that were increasingly activated in our patients relate to findings amply reported in the literature. These observations are useful since they allow us to conclude that MS patients seem to activate areas that are known to be coherent with the task in hand, but more intensely.

Turning to the elaboration phase, an intriguing point was the striking reduction of the extent of brain activations in MS patients in comparison with the EFT construction phase. In the elaboration phase, the brain activations were mainly located in the bilateral prefrontal regions, which differed from the brain network normally engaged in healthy controls, in which less prefrontal recruitment is expected during the elaboration phase. In fact, research has shown that additional details are mainly sustained by the posterior brain regions, in relation to visual imagery processes (Addis et al., 2007). In this perspective, the enhanced activity observed in healthy controls, relative to MS patients, only in the posterior cerebral regions is consistent with Addis et al.'s (2007) findings. This anterior/posterior difference in brain activity between MS and healthy subjects would be

consistent with the above-mentioned suggestion of an initial executive difficulty to extract and recombine episodic details, still present during the elaboration phase. The analysis of patients' neural response to the increase of detail also showed increased cerebral activity in the posterior regions (precuneus, cuneus, occipital, and posterior parietal areas, posterior cingulate gyrus) and in the parahippocampal gyrus. To account for this finding, we suggest that when a certain amount of detail is reached, MS patients' visual imagery processes may be recruited (even if the amount of detail produced by patients remains below that one of healthy controls).

TABLE 6: *Significant brain activations for the parametric response to the difficulty of access for healthy controls (vs. MS patients; two-sample f test) during the EFT construction and elaboration*

Brain region	Coordinates (x, y, z)	Z
EFT construction: Difficulty of access		
L Anterior cingulate (BA 24)	(-4, 38, 8)	2.87
R Insula (BA 13)	(34, 14, -4)	3.07
R Claustmm	(26, 26, 6)	3.08
EFT elaboration: Difficulty of access		
L Medial frontal gyms (BA 25)	(-10, 32, -14)	3.41
R Middle temporal gyms (BA 21)	(62, -6, -12)	2.66
R Fusiform gyrus (BA 20)	(60, -8, -24)	3.36
R Fusiform gyrus (BA 37)	(-40, -46, -8)	3.16
R Superior temporal gyrus (BA 22)	(64, -24, 6)	3.00
R Superior temporal gyrus (BA 41)	(42, -38, 12)	2.92
R Precuneus (BA 31)	(32, -70, 16)	2.95
R Precuneus (BA 7)	(8, -56, 32)	2.72
L Precuneus (BA 31)	(-18, -44, 32)	3.15
L Cingulate gyrus (BA 31)	(-20, -52, 26)	3.00
R Middle occipital gyrus (BA 19)	(36, -70, 6)	3.18

Note. MS = multiple sclerosis; EFT = episodic future thinking; BA = Brodmann area; L = left; R = right, k = 10 voxels. $p < .005$ uncorrected.

TABLE 7: *VBM results showing brain areas with significant gray matter atrophy in MS patients (vs. healthy controls)*

Brain region	Coordinates (x, y, z)	Z	Cluster size
R Parahippocampal gyms (BA 35)	(20, -20, -13)	4.00	115
L Parahippocampal gyms (BA 35)	(-18, -20, -13)	3.35	67
R Cuneus	(15, -95, 2)	3.59	116
R Precentral gyms (BA 4, 6)	(48, -8, 30)	4.94	1629
L Precentral gyms (BA 4, 6)	(-47, -12, 33)	4.93	986
L Postcentral gyms (BA3)	(-32, -29, 48)	3.26	
R Thalamus	(14, -26, 5)	6.52	5795
L Thalamus	(-6, -32, 8)	5.57	
L Cerebellum	(-21, -33, -40)	4.10	83
R Cerebellum	(12, -69, -43)	3.55	394

Note. MS = multiple sclerosis; VBM = voxel-based morpho-metry; BA = Brodmann area; L = left; R = right, k = 50 voxels. $p < .001$ uncorrected.

TABLE 8: *Positive correlations between gray matter volume and EFT performance (AI) in MS patients and healthy controls*

Brain region	Coordinates (x, y, z)	Z	Cluster size
MS patients			
R Middle frontal gyms (BA 8)	(48, 22, 45)	3.72	69
L Superior frontal gyms (BA 10)	(-15, 64, 29)	3.70	71
L Superior frontal gyrus (BA 6)	(-23, 1, 68)	3.66	111
L Medial frontal gyrus (BA 6)	(-17,-11, 45)	3.67	63
L Inferior frontal gyrus (BA 44)	(58, 15, 14)	3.57	218
R Superior temporal gyrus (BA 22)	(62, 6, -1)	4.17	113
R Superior temporal gyrus (BA 38)	(42, 3, -13)	3.88	163
L Inferior parietal lobule (BA 40)	(-44, -51, 51)	3.67	89
R Inferior parietal lobule (BA 40)	(48, -42, 56)	3.63	53
R Precuneus (BA 7)	(26, -75, 41)	3.66	98
L Cuneus (BA 19)	(-17, -84, 35)	3.81	188
R Insula (BA 13)	(40, -12, -3)	3.57	
L Insula (BA 13)	(-42, 7, -6)	3.60	52
Healthy controls			
R Cuneus (BA 19)	(9, -90, 33)	3.82	81
R Lingual gyrus (BA 17)	(8, -89, 5)	3.80	121
R Lingual gyrus (BA 18)	(17, -83, -13)	3.41	58
R Precuneus (BA 19)	(32, -72, 35)	3.77	214
R Precuneus (BA 39)	(38, -66, 36)	3.24	
R Precuneus (BA 7)	(6, -45, 54)	3.38	
R Postcentral gyrus (BA 7)	(2, -51, 68)	3.51	103
MS patients > Healthy controls			
R Superior temporal gyrus (BA 38)	(39, 5, -15)	4.68	483
R Middle temporal gyrus (BA 21)	(62, 6, -12)	3.65	
R Paracentral lobule (BA 6)	(8, -33, 65)	3.58	71
R Middle frontal gyrus (BA 8)	(48, 22, 45)	3.84	71
L Superior frontal gyrus (BA 6)	(-15, 9, 57)	3.72	517
R Inferior frontal gyrus (BA 44)	(52, 15, 14)	3.72	266
R Inferior frontal gyrus (BA 45)	(60, 19, 18)	3.68	
R Medial frontal gyrus (BA 9)	(18, 36, 18)	3.95	119
R Precuneus (BA 19)	(29, -80, 45)	3.58	143
R Precuneus (BA 7)	(23, -75, 39)	3.56	
L Claustrum	(-29, 18, -1)	4.21	339
L Insula (BA 13)	(-41, 12, -3)	3.16	
R Insula (BA 13)	(27, 20, -6)	3.76	104
Healthy controls > MS patients			
L Inferior occipital gyrus (BA 18)	(-36, -89, -6)	3.81	120
L Inferior occipital gyrus (BA 17)	(-24, -98, -10)	3.73	98
R Lingual gyrus (BA 17)	(12, -87, 6)	3.57	59
R Superior temporal gyrus (BA 39)	(45, -50, 17)	3.19	
R Inferior parietal lobule (BA 39)	(39, -65, 39)	3.43	88
L Thalamus	(0,-9, 11)	3.47	55

Note. MS = multiple sclerosis; EFT = episodic future thinking; AI = autobiographical interview; BA = Brodmann area; L = left; R = right, *k* = 50 voxels. *p* < .001 uncorrected.

Regarding healthy controls, an increased neural response was highlighted for the difficulty of imagination during the EFT elaboration, mostly in key brain structures sustaining self-referential processes (medial frontal and posterior cingulate gyri), personal semantics (lateral temporal structures), or visual imagery (precuneus, posterior cingulate, and occipital gyri), all of them being central cognitive processes during EFT elaboration (Addis et al., 2007).

Conversely, contrary to our hypothesis, no functional change was observed in the hippocampus during EFT construction or elaboration, for both healthy controls and MS patients. The hippocampus plays a critical role in the retrieval of details stored in memory, their recombination into a coherent future simulation, and the encoding

of the simulation product in memory, and this brain region is also particularly responsive to the amount of detail (Addis & Schacter, 2008, 2012). In this context, bearing in mind that the amount of detail of future events was self-assessed by patients at a level that turned out to be lower than that of healthy controls, a possibility is that the absence of functional change in the hippocampus reflects this discrepancy in the amount of detail. Alternatively, it remains an option that the significant brain atrophy observed in the adjacent parahippocampal gyrus in patients may have compromised the further involvement of the hippocampus (Hulst et al., 2012). A last alternative is related to the spatiotemporal dynamic of brain activations within the EFT brain network. As previously mentioned, the prefrontal regions sustain the executive component necessary to the extraction/recombination of details (De Vito et al., 2012; Weiler et al., 2011). In the case of MS patients, the absence of a differential hippocampal activity between groups could be related to the early negative impact of the executive component, which might have affected the extraction/recombination of details at the hippocampal level, and the further stream of activations within the neocortex. This is consistent with the reciprocal connections shared between the prefrontal regions and the medial temporal lobe, and the neocortex (Maguire, Kumaran, Hassabis, & Kopelman, 2010). A neuroanatomical corroboration of the latter is the main association found between the volume of prefrontal regions and EFT performance in MS patients, whereas no such association was highlighted for the hippocampus. A significant association was also found between EFT scores and the lateral temporal region, as well as the posterior brain regions.

Our results showed some overlaps with Irish et al. (2013), demonstrating that a discrete set of brain regions could be involved in EFT impairment (similarly to their patients, our patients' prefrontal regions were a contributing structure to EFT deficit). Likewise, similar to Hach et al. (2014) in depressed patients, we found that MS patients recruit brain regions pertaining to the EFT core network, but with signs of up- or down-regulation in comparison with healthy controls.

Overall, consistent with our hypothesis, structural correlates of EFT impairment seemed to converge with the brain areas that showed significant functional changes during EFT performance in MS patients. This finding is consistent with those showing partial overlaps between structural damage (i.e., brain atrophy) and cerebral functional changes during cognitive performance in MS patients (Mainero et al., 2004; Morgen et al., 2007). Our results reinforce the usefulness of the combination of different neuroi-maging techniques to obtain a comprehensive picture of the neural substrates of cognitive impairment in patients. This is especially the case for diffuse brain pathologies like MS, in which some brain damage not sufficient to be detected as significant atrophies could have proximal and distal deleterious impact within the EFT brain network. In this context, a further step would be to introduce a functional connectivity measure that could be particularly relevant considering the spatiotemporal dynamic nature of the EFT brain network (Addis, Pan, et al., 2009). While the current study presents some limitations, like its focus on a group of patients with impaired EFT abilities, it could provide new insights into cognitive impairment in MS patients and complete some recent clinical findings about this topic (Ernst, Blanc, et al., 2014).

CONCLUSIONS

In conclusion, despite significant brain atrophy, we have documented cerebral activation changes in MS patients presenting with EFT impairment, with mainly signs of up-regulation within the EFT network. Overall, these findings supported the notion that disruption in any key nodes of the EFT network would impinge on future simulation, with some specific neural signature depending on the pathology (Berryhill et al., 2010; Irish et al., 2013). While no direct comparison has been made between the functional changes reported here and those documented in the context of a previous study focusing on AM impairment, in a very similar sample of participants (Ernst, Noblet, et al., 2014), it appears that the pre-frontal regions are mainly involved in the occurrence of both AM and EFT impairment in MS patients, but not the hippocampus. This finding supports the strong relationship between AM and EFT deficit documented at the behavioral level (Ernst, Blanc, et al., 2014). On these bases, and from a more clinical standpoint, we hypothesize that EFT functioning could be improved in MS patients by means of a cognitive intervention program for which the efficacy has already been showed in MS patients presenting with AM impairment (Ernst et al., 2013; Ernst et al., 2012). Bearing in mind the negative impact of EFT impairment in MS patients' everyday life (Ernst, Blanc, et al., 2014), future studies addressing this last suggestion would be of clinical value to alleviate impairment in a domain that is at the center of cognition, social relations, and, ultimately, well-being (Schacter et al., 2012; Szpunar, 2010).

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