Published in: Brain & Cognition (2016), vol. 105, pp 34-45
Status: Postprint (author's version)

Functional and structural cerebral changes in key brain regions after a facilitation programme for episodic future thought in relapsing-remitting multiple sclerosis patients

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ABSTRACT

Increasingly studied, episodic future thought (EFT) impairment negatively affects patients' daily life. Along these lines, working with relapsing-remitting multiple sclerosis (RR-MS) patients, we documented the clinical effectiveness of a mental visual imagery (MVI)-based facilitation programme on EFT impairment related to executive function difficulties. We aimed at improving the characterisation of the cognitive and neural underpinnings of RR-MS patients' EFT amelioration, by exploring the structural and functional brain changes following the MVI programme. Seventeen non-depressed RR-MS patients were recruited and randomly assigned in the (i) experimental group (n = 10), who followed the MVI programme or in the control group (n = 7), who followed a verbal control programme. Using an adapted version of the Autobiographical Interview to assess EFT, after facilitation, significant improvement was observed in the experimental group only. This was accompanied by increased activation in the prefrontal region during the generation of future events and was positively correlated with grey matter volume increase in this same brain area. Increased activations in the parahippocampal and the middle temporal gyri were also observed in the experimental group in post-facilitation. Likewise, functional connectivity changes were observed in the posterior brain regions after facilitation. Only minor cerebral changes were observed in the control group, likely reflecting practice effects. Our study showed that EFT improvement following the MVI programme led to functional and structural changes in brain regions sustaining contextual processing, visual imagery, the integration and maintenance of multimodal information. Taken together, these findings suggest that a cognitive intervention focusing on scene construction can be efficient to alleviate EFT impairment related to executive dysfunction. As such, this study opens the way to the development of *tailor-made* rehabilitation programmes using the different cognitive mechanisms involved in EFT.

Keywords: Episodic future thought Cognitive rehabilitation Multiple sclerosis Functional MRI Structural MRI

1. Introduction

The ability to mentally project ourselves into personal episodic future thought (EFT) is ubiquitous in everyday life. It has been estimated that future-oriented thought are experienced, on average, every 16 min during a typical day (D'Argembeau, Renaud, & Van der Linden, 2011). This frequency is related to the adaptive value of EFT, which is thought to play a role in coping with stressful events, goal achievement, emotional regulation, the implementation of actions and the sense of personal continuity over time (Szpunar, 2010; Szpunar, Spreng, & Schacter, 2014). Not surprisingly, in the event of EFT impairment, different aspects of daily life functioning could be affected and the importance of including EFT assessment in clinical settings has recently been stressed (Irish & Piolino, 2015).

In this vein, a growing number of studies reported EFT impairment in clinical conditions such as in Alzheimer's disease (Addis, Sacchetti, Ally, Budson, & Schacter, 2009), semantic dementia (Irish, Addis, Hodges, & Piguet, 2012; Viard et al., 2014), behavioural variant of frontotemporal dementia (Irish, Hodges, & Piguet, 2013), depression (Williams et al., 1996), schizophrenia (D'Argembeau, Raffard, & Van der Linden, 2008) or in relapsing-remitting multiple sclerosis (RR-MS) patients (Ernst et al., 2014). An overview of the literature shows that different cognitive mechanisms seem to be involved in the occurrence of EFT impairment in clinical conditions, including for instance scene construction

(Hassabis & Maguire, 2007), semantic memory (Irish & Piguet, 2013), self-projection (Irish, Piguet, & Hodges, 2012) or executive functions (De Vito et al., 2012; Ernst et al., 2014). In this context, the development of cognitive rehabilitation programmes to ameliorate EFT performance has clinical relevance.

To the best of our knowledge, Ernst, Blanc, de Seze, and Manning (2015) were the first to develop a cognitive rehabilitation programme that aimed at alleviating EFT impairment. This programme was developed to tackle executive function-related EFT impairment in RR-MS patients. Regarding the latter, the origin of EFT impairment in RR-MS patients has been investigated by Ernst et al. (2014), who explored the effect of retrieval support on EFT performance. Specifically, the Autobiographical Interview (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002) enables to identify patients with inefficient retrieval operations, which generally arose from prefrontal lesions, by comparing the number of details provided during a free generation versus a high retrieval support condition. In the case of RR-MS patients, the use of a high retrieval support condition led to a significant EFT improvement, as previously reported in non-amnesic conditions (McKinnon, Black, Miller, Moscovitch, & Levine, 2006; Svoboda et al., 2002). Furthermore, converging evidence were also obtained from neuroimaging findings, showing that EFT impairment in RR-MS patients were mainly associated with increased prefrontal activation changes and with the volume of prefrontal regions (Ernst, Noblet, et al., 2015).

The intervention developed by Ernst, Blanc, et al. (2015) relies on the critical role of mental visual imagery (MVI) in autobiographical memory (AM; i.e. the ability to mentally re-experience personal past events) retrieval and vividness of memories (Greenberg & Rubin, 2003). More specifically, the aim of this programme is to make use of the cueing role of MVI, that is the use of visual details as cues to activate both additional visual information and information related to other sensory modalities (Huijbers, Pennartz, Rubin, & Daselaar, 2011; Rubin, 2005). The latter is illustrated by previous findings showing that MVI abilities are positively related to the representation of contextual information, as well as the amount of visual and other sensory details generated while imagining future events (D'Argembeau & Van der Linden, 2006). While EFT involves a collection of different cognitive processes, visual imagery and executive functions contribute to a large extent to the generation of future events (D'Argembeau, Ortoleva, Jumentier, & Van der Linden, 2010). Based on this, the rationale of the MVI programme is to emphasise on the role and the use of visual imagery in the generation of future events to alleviate the one of executive functions, which is a driving mechanism of EFT impairment in MS patients (Ernst et al., 2014; Ernst, Noblet, et al., 2015). As such, the strategy taught to patients is to use mental visual cues to engage in the construction of future events and flesh them out with details. Although from a different line of research, this idea shares some similarities with the benefit of the episodic specificity induction reported in healthy participants, by influencing the episodic retrieval orientation (i.e. the goal-directed processing strategy) invoked by individuals when remembering or imagining personal events (Madore, Gaesser, & Schacter, 2014).

Clinically, the efficacy of the MVI programme on EFT in MS patients has been shown in the context of a randomised-controlled trial study (Ernst, Blanc, et al., 2015). Following the MVI programme, an increase of the number of internal (episodic) details was observed in these patients when describing personal future events, with an effective transfer of this strategy in daily life and with long-term robustness of treatment effect.

In this perspective, a likely useful question concerns the potential brain changes associated to EFT improvement in RR-MS patients. The issue relates to neuroplasticity, defined as 'the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganising its structure, function, and connections' (Cramer et al., 2011, p. 1592). Several studies conducted in MS patients have shown brain activation and/or functional connectivity changes after cognitive interventions focusing on anterograde memory (Chiaravalloti, Wylie, Leavitt, & DeLuca, 2012; Leavitt, Wylie, Girgis, DeLuca, & Chiaravalloti, 2012), attention (Penner, Kappos, Rausch, Opwis, & Radii, 2006) or in the case of programmes tackling different cognitive functions (Filippi et al., 2012). The inclusion of neuroimaging techniques in cognitive rehabilitation studies is helpful to provide solid evidence of the efficacy of cognitive interventions (Strangman et al., 2005) and also to identify the most effective interventions (Chiaravalloti, Genova, & DeLuca, 2015).

On these bases, we aimed at exploring the neural correlates associated to EFT improvement in RR-MS patients who followed the MVI programme by combining measures of brain changes at the structural, cerebral activation and functional connectivity levels.

The brain network sustaining EFT is well described and encompasses the medial temporal and frontal lobes, the posterior cingulate, the retrosplenial cortex, and the lateral parietal and temporal regions

(Schacter et al., 2012). Amongst these, the hippocampus and the frontopolar region play a critical role in the constructive process of imagining future events (Addis, Wong, & Schacter, 2007). In particular, the hippocampus is involved in the extraction and binding of details associated with future events, but also in the encoding of the simulation product (Addis & Schacter, 2012). As mentioned earlier, in MS patients, significant brain activation changes have been reported within the EFT core network when imagining personal future events, especially increased activations in the bilateral prefrontal regions (Ernst, Noblet, et al., 2015). In this same study, a positive association between the volume of the prefrontal region and the amount of details of future events has also been reported in MS patients. However, no association between the hippocampus and EFT performance was observed in these patients, either at the structural or functional levels.

Based on these findings, we explored in the current study the clinical and cerebral changes associated with EFT improvement in RR-MS patients in a controlled study, comprising also a sham treatment group. We hypothesised that (i) EFT improvement would only be observed following the MVI programme and that this would be expressed both by an increase of the episodic quality of future events and changes experienced by patients in their daily life functioning, (ii) We also hypothesised that this clinical benefit would be mainly accompanied by structural, brain activation, and functional connectivity changes in post-rehabilitation in the prefrontal regions, since they are the key node of EFT impairment in MS patients. Finally, our third hypothesis was related to changes in the posterior brain regions, which would reflect the emphasis made on the role of MVI in EFT. Indeed, since the posterior brain regions sustain visual imagery processes (Greenberg & Rubin, 2003), we suggested that the use of the MVI-based strategy to generate future events in post-facilitation would modulate the involvement of these brain regions in EFT. Complementarily, in the absence of EFT improvement, no brain changes would be observed following the sham intervention.

2. Material and methods

2.1. Patients

Seventeen RR-MS patients (according to the revised McDonald's diagnostic criteria; Polman et al., 2011) were selected from a group of patients involved in a broader study on autobiographical memory and EFT (Ernst, Blanc, et al., 2015; Ernst, Noblet, et al., 2015). The included patients corresponded to the following inclusion criteria: an Expanded Disability Status Scale (EDSS; measure of the functional disability; Kurtzke, 1983) score ≤ 4, no recent exacerbation of MS symptoms, right-handiness, an absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (Montgomery & Asberg, 1979; score ≤ 15), as well as impaired EFT performance in the context of only mild to moderate cognitive impairment in attention and/or executive functions (see Behavioural assessment).

Patients were randomly assigned in two groups: the experimental (n = 10) and the control group (n = 7). Demographic and clinical data are summarised in Table 1. The present study was approved by the 'Committee for Protection of Persons' (CPP/CNRS No 07023) and we complied with the Declaration of Helsinki.

2.2. Behavioural assessment

The 17 participants underwent a comprehensive neuropsycho-logical baseline assessment (see Ernst et al., 2014 for a complete description) to ensure that they did not present severe cognitive impairment that could counteract the good completion of the MVI programme.

To explore EFT, an adapted version of the Autobiographical Interview was carried out (AI; Addis, Sacchetti, et al., 2009; Levine et al., 2002). This test consists in imagining personal unique events, temporally and contextually specific, occurring over minutes to hours, and to give as much detail as possible about the event. Patients were given cue words (i.e. friend, travel) to generate five events, which could plausibly occur within the next year. No time limit was set due to potential decreased cognitive processing speed in MS patients. The AI session was audio-recorded for later transcription and was scored following the standardised AI scoring procedure (see Levine et al., 2002 for a complete description of the scoring).

Since previous studies have documented a strong link between AM and EFT performance (Schacter et al., 2012 for a review), including in MS patients (Ernst et al., 2014), the absence of significant difference between the two patient groups in AM performance was also verified. All the patients underwent the past counterpart of the adapted AI during the same test session (a full description of the

results obtained for the past is provided in Ernst, Blanc, et al., 2015).

All the patients underwent the adapted AI twice, in pre- and post-facilitation. Different cue-words were randomly used across sessions and the absence of events' repetition (i.e. imagining the same personal future event twice) was verified.

Since the aim of the MVI programme was to improve the episodic quality of future events and that personal semantic has been shown to be preserved in RR-MS patients (Ernst, Blanc, et al., 2015), our analysis focused on internal details (i.e. episodic details) spontaneously generated by patients. Internal details were averaged across the five events for each patient. Following Levine et al.'s (2002) procedure, the interrater reliability was verified for 10% of the future events, which were scored by a second scorer, blind of the patient's group allocation and study phase (pre- or post-facilitation). Coefficients for the mean number of internal details showed high interrater reliability (correlation coefficient = 0.92).

At the end of the adapted AI, a semi-structured interview (fully described in Ernst et al., 2014) was carried out in pre- and post-facilitation to characterise the potential impact of EFT difficulties and the perceived benefits of the intervention during the test session and in everyday life. This semi-structured interview tackled four dimensions: the accessibility, the amount of details, the vividness and the emotional intensity of future events.

2.3. Cognitive intervention

Instructions and examples for each intervention are provided as Supplementary Material.

2.3.1. MVI facilitation programme

The MVI programme (created by one of us, LM) is based on the ability to mentally construct scenes and follows a goal-directed approach (Wilson & Gracey, 2009). It encompassed six two-hour sessions (once or twice per week), organised in four steps, with mental visualisation exercises of increasing difficulty, during which the neuropsychologist provides a continuous guidance, (i) The *screening step* aims at probing basic visual imaging abilities and is based on three subtests from the 'Imagery and Perception Battery' (Bourlon et al., 2009). None of the patients showed difficulties to perform these tasks, (ii) The *external visualisation* includes 10 names of objects to be imagined and described, (iii) The *construction phase* consists in figuring out complex scenes, bringing into play several characters. Five verbal items were proposed with for each one, a first training step and a subsequent scene, sharing thematic similarities; (iv) the *self-visualisation* step follows the same procedure, but patients are asked to imagine themselves within a given scenario as they are living the scene.

Table 1: Demographic and clinical data. Mean (and SD) for the MS patient groups.

	MS patient groups		Statistical analysis
	Experimental (n = 10)	Control (n = 7)	
Age in years	38.40 (10.94)	34.71 (8.44)	t = 0.71; p = 0.46
Education in years	13.40 (2.22)	12.57 (1.72)	t = 0.82; p = 0.82
Sex (female/male)	6/4	6/1	χ^2 = 1.31; p = 0.25
EDSS	2.45 (1.73)	1.85 (1.18)	t = 0.78; p = 0.44
Duration of MS (in years)	11.10(11.03)	8.85 (5.27)	t = 0.49; p = 0.63
Number of DMD treatment	1.00 (0.00)	1.00 (0.00)	-

EDSS: Expanded Disability Status Scale; DMD: Disease Modifying Drug.

2.3.2. Verbal control programme

The control programme is based on the role of narrative structure, which provides a scaffold for the evocation of personal events, but which distinctly plays a minor role in mental time travel compared to MVI (Greenberg & Rubin, 2003). This programme has the same functioning and clinical characteristics than the MVI programme.

The main goal is to construct discussions about texts (extracted from websites) with the neuropsychologist's guidance, through steps of increasing difficulty: (i) the *external discussion* comprises 20 texts and aims at identifying influential variables on text understanding (e.g. clarity, vocabulary used, etc.). (ii) The *discussion construction* comprises five items, with for each of them, a training and construction steps. So, the two texts of each item were thematically related to enable the reliance on the first to construct the second text, (iii) The *self-involved discussion* is similar to the

previous step but the exchange is focused on the patient's personal opinion.

2.4. Neuroimaging session

2.4.1. fMRI tasks

The same fMRI paradigm than Ernst, Noblet, et al. (2015) has been used. It encompassed an EFT condition, which consisted in the evocation of unique personal future events following the adapted AI's instructions, and a categorical control task. Based on Addis et al. (2007), we distinguished the construction (i.e. the search and initial building up of the event) and the elaboration (i.e. imagining further details associated to the event) phases.

Immediately prior to scanning, patients completed a computerised practice trial for each task in order to be familiar with the experimental design and timing of presentation of the stimuli. Particular attention was paid to the practice trial to optimise the further completion of the tasks, especially considering the time constraints imposed by the fMRI examination. To ensure that patients understood the distinction between the construction and elaboration phases, they were asked to verbalise their answers during the practice trial. We were watchful to the congruence between the button press and the answer corresponding to the construction phase. Further instructions and practice trials were given when necessary.

Regarding the experimental design, each task (EFT and control tasks) included 32 trials. For the EFT condition, pairs of cue-words were proposed to generate specific future events (e.g. 'family-meal') which could plausibly occur within the next year. The control task was a categorical task adapted from Addis et al. (2007), which included pairs of words with which patients 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: once an event/sentence was generated, patients pressed a button on a four-button response box to mark the end of the construction phase. Then, a central fixation-cross indicated the elaboration phase, which lasted during the remaining time. Patients were instructed to press the button only if an event came to their mind. In the absence of answer, the next trial was automatically presented after the fixed trial duration of 20 s. The experimental design was organised in eight functional runs of 8 stimuli (four functional runs per condition), starting with the control task and then, alternating between the control and the EFT tasks. Each trial was followed by short periods of fixation that were of random duration (mean duration = 1.5 s, range = 1-2 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 randomised. The programming and response collection was done with E-Prime 2 software (Psychology Software Tools, Inc.). Words were displayed on a screen in white text with a black background and viewed using a mirror incorporated in the head-coil.

Importantly, the same procedure was strictly followed for the two fMRI sessions (in pre- and post-facilitation). Each task has been developed in two versions, presented in a counterbalanced order across sessions. Patients were also instructed to not provide the same events as those previously mentioned during the adapted AIs or during the first fMRI session and this absence of events' repetition was also verified based on the post-scan questionnaire.

Immediately following scanning, a post-scan questionnaire was completed in order to verify response accuracy and exclude invalid trials for the EFT task. For each event, patients indicated the type of future events (unique, repetitive, extensive, semantic or absent). The different types of events were defined as follows: (i) unique: specific or particular occurrence of events, within a specific time and space frame, no longer than one day; (ii) repetitive: events that are usual and repeated, and thus lack episodicity; (iii) extended: includes events whose duration is longer than one day (e.g. my week of holidays in New York), without the mention of a specific incident; (iv) semantic: encompasses general, semantic associations with the cue-words not self-relevant (i.e. this winter will be colder than the last year); (v) absent: corresponds to the absence of response in the scanner (i.e. no button press to end the construction phase). Participants were also asked to provide the spatio-temporal context of events, that is, to write down the most detailed account they were able to about the location of the event and when it will occur. Based on this spatio-temporal context, the specificity of events was further controlled by the experimenter (AE). More precisely, immediately after the completion of the post-scan questionnaire, in the absence of a specific spatio-temporal context (necessary to consider an event as unique) or in the case of doubt regarding the classification, patients were asked to provide additional details about the event to determine its precise nature. Patients were also asked to rate on a visual-

analogous scale of 10 cm the amount of details associated to each event (0 = 0 cm, corresponding to a low amount of details and 10 = 10 cm, to a high amount of details).

2.4.2. MR1 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 optimised Contrasts using different flip angle Evolution) sequence (TR = 4000 ms, TI = 380 ms, TE = 383 ms, flip angle = 120°, 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, Voxel size = 3.5 × 3.5 × 3.5 mm^3, Matrix = 64 × 64 × 45 voxels, FOV = 225 × 225 × 157.5 mm, FA = 90). Slices were orientated parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

2.5. *Procedure*

The study procedure followed by the patients is illustrated in Fig. 1. Since the aim of this study was to alleviate EFT impairment, only RR-MS patients presenting with impaired EFT performance at the adapted AI were included (defined as a mean number of internal details ≤ 19, according to the normative database developed by Ernst, Blanc, et al., 2015; Ernst, Noblet, et al., 2015).

Patients were randomly assigned in the experimental or in the control groups and were blind to their allocation. While the neu-ropsychologist was not blind to the patients' allocation, the second AI scorer was blind to this information. Moreover, AI reports were anonymised and not supplied in the chronological order of assessment and were mixed with AIs belonging to healthy subjects, who participated in Ernst et al.'s (2014) study.

2.6. Statistical analyses

2.6.1. Behavioural data

Repeated-measures ANOVA, with the between-factor of Group and the within-factor of Time (pre- and post-facilitation) were run for the AI scores and for the post-scan variables. Statistical analyses were performed using Statistica 10.0 (StatSoft Inc., Tulsa, OK, USA).

2.6.2. Functional neuroimaging analyses

Pre-processing and statistical analyses were conducted using SPM8 software (Statistical Parametric Mapping; Welcome Department of Cognitive Neurology, London, UK). Time-series were realigned to the first volume to correct for motion artefacts, spatially normalised to a standard 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 EFT and control tasks, evoked hemodynamic responses time locked to the onset of the cue presentation (construction phase) were modelled with a canonical hemodynamic response function. Hemodynamic activity related to the elaboration phase was modelled with a boxcar function of 10 s-duration that started immediately after the end of the construction phase indicated by a button press. The 10 s-duration interval for the elaboration phase was fixed to allow a sufficient time interval to the search of details 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 maximise the number of events included as regressors of interest, especially since all the included patients initially showed impaired EFT.

In the context of the general linear model, statistical parametric maps were generated for each subject, in both sessions, for the further contrasts: EFT construction > control task construction and EFT elaboration > control task elaboration. Statistical parametric maps were entered into a second level of analysis for between-group comparisons (two-sample *t*-test), to ensure that the brain network engaged in EFT construction and elaboration by the two groups of patients before facilitation was not significantly different. To explore the brain activation changes following the intervention, within-group comparisons were then conducted between pre- and post-facilitation sessions (paired t-test) for each group (pre- > post-facilitation and post- > pre-facilitation. A statistical threshold of $p < 0.05$ (corrected for multiple comparisons) was set. However, since this study is the first to investigate the neural

correlates of EFT improvement following a cognitive intervention, to have a more informative overview of the results, in the case of no significant result, exploratory analyses were also conducted with a more lenient threshold set at $p < 0.001$ (uncorrected for multiple comparisons), with a minimum extent threshold of five contiguously activated voxels (note however that the latter threshold has been extensively used in the context of previous neuroimaging EFT studies in healthy participants; see for instance Addis et al., 2007; Mullally, Hassabis, & Maguire, 2012; Weiler, Suchan, & Daum, 2010a; 2010b).

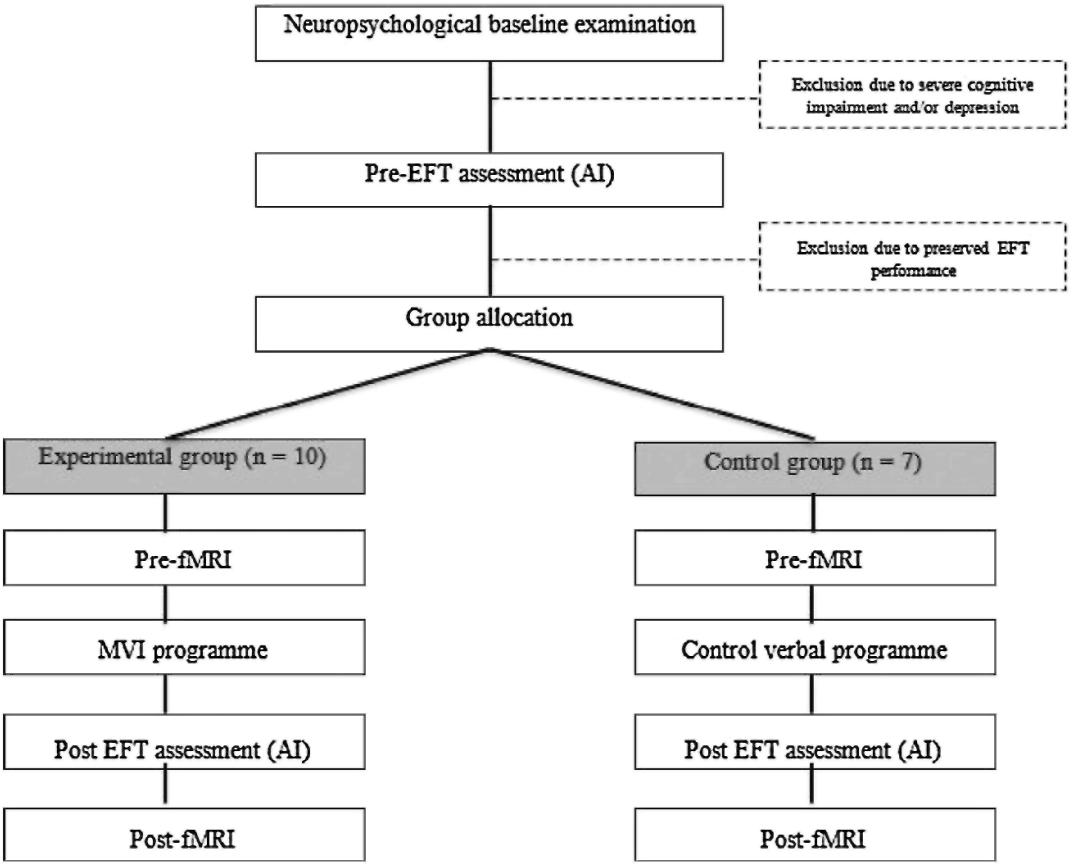
2.6.3. Functional connectivity analysis

Images were pre-processed using SMP8 as follows: images were rigidly realigned to the first scan and corrected for both susceptibility effects and differences in image acquisition time between slices. Images were then registered to a standard space using the Montreal Neurological Institute template and spatially smoothed with a FWHM of the Gaussian kernel of 8 mm.

Then, in each condition, functional connectivity analysed were performed by a group independent component analysis (ICA) with an implementation of the infomax algorithm (Bell & Sejnowski, 1995), as provided by the GIFT v3.0 toolbox (http://mialab.mrn. org). Importantly, construction and elaboration phases were analysed as a whole.

Dimensionality was previously reduced by two principal component analyses, according to the automatic estimator available in GIFT, 70 and 30.7 (±1.5) principal components were retained at the individual level and group level, respectively.

Fig. 1. Study design diagram summarising the group allocation and progression through study phases.



Based on the relationships between mental time travel, self-projection and the default mode network (DMN; Buckner & Carroll, 2007; Spreng & Grady, 2010) and the recent fractionation of DMN

components (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Bado et al., 2014), the anterior and posterior DMN (ADMN and PDMN) were selected as networks of a priori interest. The ADMN encompasses mainly the frontal cluster, as well as anterior and posterior cingulate, precuneus, occipitopari-etal, temporal pole and hippocampal regions, whereas, the PDMN involves mostly the posterior cingulate, the precuneus, the lateral parietal and middle temporal regions, and smaller clusters in the anterior cingulate, and the superior and middle frontal gyri (Damoiseaux, Prater, Miller, & Greicius, 2012).

Each network was manually selected and recorded as Z-score 3D maps. In the case of significant cerebral activation changes highlighted by functional neuroimaging data, a further analysis of potential functional connectivity changes was carried out within each group and for the aforementioned brain networks. To that end, each functional connectivity network was spatially compared by contrasting pre- and post-facilitation sessions with paired t-tests for each group. Statistical analyses were masked by a binarised version of the network, i.e., all the brain areas involved in at least one of the two sessions. Following Leavitt et al. (2012), the statistical threshold was set at $p < 0.05$ (corrected for multiple comparisons) with a minimum extent threshold of five contiguously activated voxels. In the case of no significant results, exploratory analyses were run using an uncorrected threshold for multiple comparisons.

2.6.4. Structural neuroimaging analysis

Focal grey matter (GM) volume was investigated using the VBM framework provided in SPM12b (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/).

Anatomical MR1 images were spatially pre-processed in the following way: all Tl structural images were bias corrected, segmented using an extension of the unified segmentation procedure (Asburner & Friston, 2005) that includes six classes of tissue. Spatial normalisation 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 normalised to Montreal Neurological Institute (MNI) space. Third, the individual deformation field that permits to normalise each GM image to the template was computed and applied to each GM image and modulated to preserve the total amount of GM volume. A Gaussian kernel (FWHM: 8 mm) was then applied to modulated GM images and entered in the statistical analysis.

Correlations between local GM volume and EFT performance were then investigated using the general linear model. Specifically, a repeated measures approach was used to quantify GM volume across the pre- and post-facilitation sessions (GM volume in post- minus GM volume in pre-facilitation). Then, we explored to what extent GM volume change correlated with EFT performance progression, measured by the mean number of internal details provided (EFT score post- minus EFT score pre-facilitation) within each group. Due to MRI acquisition problem, one patient from the experimental group has been excluded from the analysis. The threshold for significance was set at $p < 0.05$ (corrected for multiple comparisons). As for functional analyses and due to the explorative nature of this study, in the case of no significant result, a more lenient statistical threshold of $p < 0.001$ (uncorrected) was applied to provide an informative overview of the results.

3. Results

3.1. Behavioural results

3.1.1. Clinical characteristics

The two patient groups were matched for age, education years, gender, functional disability (EDSS score) and duration of MS (Table 1). With respect to the neuropsychological baseline examination, all the patients showed a preservation of their general cognitive functioning, with only mild impairment in planning and cognitive estimation abilities. No difference in terms of general cognitive functioning was observed between the experimental and the control groups.

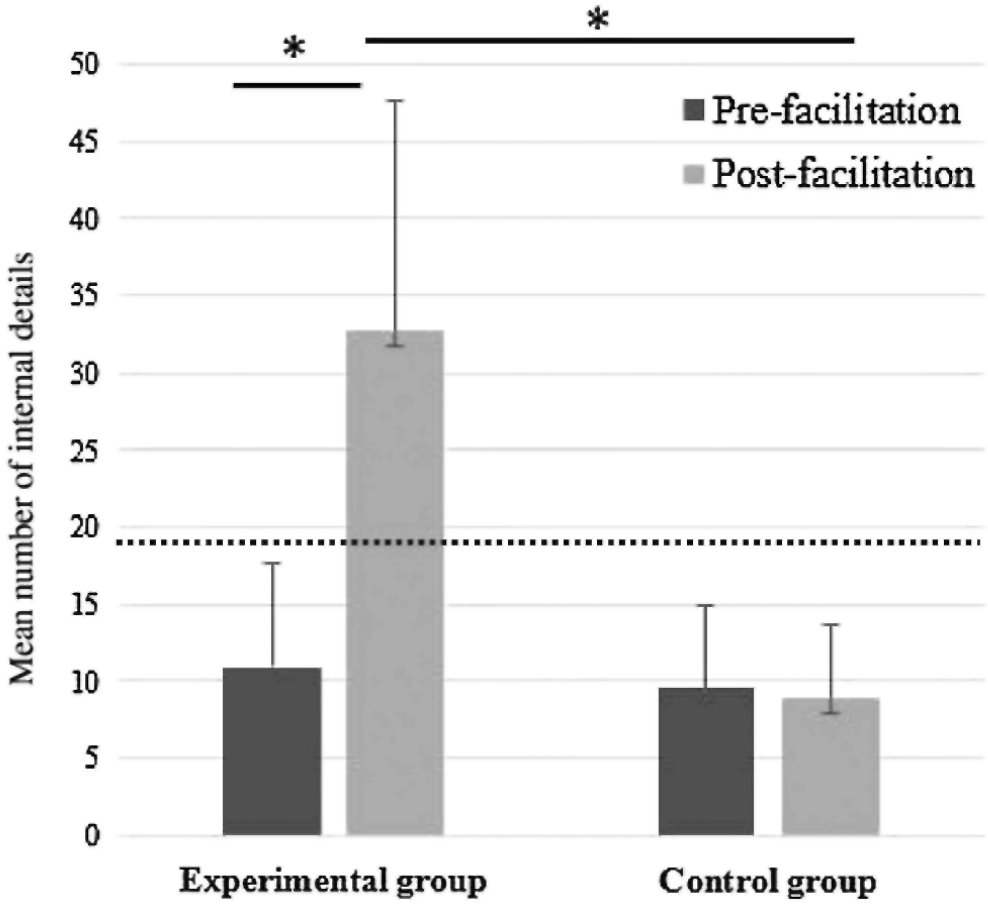
In addition, the two patient groups were matched for AM performance before facilitation and provided a similar number of internal details ($t(15) = -1.14$; $p = 0.26$).

3.1.2. EFT performance in pre- and post-facilitation

Beginning with the EFT assessment, a main effect of Group was observed, $F(1, 15) = 9.86$, $p = 0.006$,

η_p^2 = 0.39, with a greater number of internal details provided by the experimental group. A main effect of Time was also displayed, F(1, 15) = 20.51, $p < 0.001$, η_p^2=0.57, which revealed a general increase of the number of details in post-facilitation. A significant Group × Time interaction was obtained, $F(1, 15) = 22.80$, $p< 0.001$, η_p^2= 0.60, and post-hoc test revealed a significant increase of the number of internal details for the experimental group after facilitation ($p < 0.001$), whereas no such difference was noticed in the control group ($p = 0.99$). Moreover, while an equivalent number of details was observed in the two groups before facilitation ($p = 0.99$), after facilitation, the experimental group showed higher performance than the control group ($p < 0.001$). The mean number of details provided by patients across the assessment sessions is illustrated in Fig. 2. In addition, the experimental group showed a normalisation of the mean number of internal details after facilitation, in comparison with the normative database that initially established the presence of EFT impairment (Ernst, Blanc, et al., 2015; Ernst, Noblet, et al., 2015). Conversely, the mean number of internal details provided by the control group after the verbal programme remained below the normative score.

Fig. 2. Mean number of internal details provided by the two patient groups in pre-and post-facilitation ('significant difference at $p < 0.001$). Dotted line: initial normative score showing EFT impairment (Ernst, Noblet, et al., 2015).



Moreover, patients' comments gathered through our semi-structured interview corroborated the benefits of the MVI programme on the different dimensions explored (accessibility, amount of details, emotional intensity and vividness), with an effective transfer in everyday life functioning. Examples of

patient's comments:

> Patient SE: *'The first time we have done this exercise, it was more like some 'flashes', whereas now, it is more like films'.* Patient AS: *'It's easier to imagine things... To project myself. The first time, before the programme, it was really hard (...). In fact, it's a mechanism that I have learnt, little by little, that I have integrated. And it was not a 'harsh' learning. I had the time to integrate it. It was spontaneous'.*
>
> Patient IB: *'Yes, I think that something is set up, in everyday life, for the future. I have the feeling that, as we went along the sessions, I had the feeling that I was actually living the thing. I'm in. I'm seeing things... Yes, the future events, I feel them. It's no longer stressful for me, I am more self-confident now'.*
>
> Patient MD: 'I *was living hand to mouth, some time ago. (...) It's easier now because I am looking towards my future. And now, I know what I want, so it's easier on that account. I can imagine myself in the near future, with the children, ... the last time, I was saying that I will go to a tea room, etc. and... I was saying that to the children and to D. (her partner). (...) Well, D. says that I will become a filmmaker!'*

3.1.3. Post-scan results

Results obtained by each MS group for all the post-scan variables, before and after facilitation, are summarised in Table 2.

Regarding the mean construction reaction time, no significant main effect of group, F(l,15) = 0.01, p = 0.92, η^2_P = 0.00, and no main effect of time, F(l,15) = 1.83, p = 0.19, η^2_P = 0.10, were highlighted. No significant interaction effect was found, F(1,15) = 0.01, p = 0.91, η^2_P = 0.00.

A similar number of future events was also provided by patients, irrespective of the time of assessment and the type of events, F(1,15) = 1.31, p = 0.26, η^2_P = 0.08. No significant main effect of time was observed, F(1,15) = 0.02, p = 0.86, η^2_P = 0.00. However, the statistical analysis revealed a main effect of event type, F(4,60) = 61.93, p< 0.001, η^2_P = 0.80, with a higher number of unique events in comparison with the four other event categories (p < 0.001 in every case). A comparable number of events pertaining to the four other categories was observed (p value between p = 0.16 and p = 0.98). A significant Time × Event type interaction was displayed, F(4,60) = 2.81, p = 0.03, η^2_P = 0.15. Post-hoc test revealed only a tendency for an increase of the number of unique event after facilitation (p = 0.06). No additional interaction effect was found.

Regarding the amount of details, no significant main effect of time, F(1, 15) = 0.04, p = 0.82, η^2_P = 0.00, nor a main effect of group, F(1, 15) = 1.53, p = 0.23, η^2_P = 0.09, were observed.

3.2. Neuroimaging results

Prior to intervention, no significant between-group differences were observed within the cerebral network sustaining EFT construction and elaboration (see Supplementary Material).

3.2.1. Experimental group

In post-facilitation, following the MVI programme, several brain activation changes were observed in the experimental group (Table 3).

Regarding brain activation changes, no cluster reached statistical significance using a corrected threshold but the following results were observed at p < 0.001, k = 5 voxels. During the construction phase, enhanced cerebral activations were displayed in the bilateral parahippocampal regions, the left middle temporal gyrus (BA 21) and the left superior frontal gyrus (BA 10) in post-facilitation, relatively to pre-facilitation (Fig. 3). The reverse contrast showed no greater activation in pre- than in post-facilitation. During the elaboration, increased activations were observed after facilitation in the left middle frontal gyrus (BA 10) and the right superior frontal gyrus (BA 8) in comparison with the pre-facilitation session (Fig. 3). The reverse contrast (pre- > post-facilitation) showed no significant brain activation.

Regarding functional connectivity measures, significant changes were only observed within the PDMN (p < 0.05, FWE; Table 4; Fig. 4). In post-facilitation, increased functional connectivity was observed in the left lingual gyrus and precuneus (BA 19), the left middle temporal gyrus (BA 39) and the right posterior cingulate (BA 30). Conversely, a higher functional connectivity was showed in the bilateral

precuneus (BA 7/31), the right posterior cingulate (BA 23) and the left angular gyrus (BA 39) in pre- vs. post-facilitation.

Turning to VBM analyses, the following results only reached statistical significance with an uncorrected p value of $p< 0.001$. The AI score progression in post-facilitation was significantly and positively correlated with an increase of GM volume in small clusters in right-sided brain regions after facilitation, including mainly the prefrontal regions (BA 10 and 11; Table 5) (see Fig. 5).

3.2.2. Control group

Within the control group, for both phases of evocation, no brain activation changes were observed in post-facilitation (vs. pre-facilitation).

However, during the construction phase, some brain regions were more activated before than after facilitation (only observable at $p < 0.001$, $k = 5$ voxels), including the left superior frontal gyrus (BA 6; *xyz:* -20, 2, 64; Z-score: 3.51), the left inferior frontal gyrus (BA 9; *xyz:* -58; 6, 26; Z-score: 3.40), the left postcentral gyrus (BA 3; *xyz:* -52, -18, 56; Z-score: 3.53) and the right fusiform gyrus (BA 19; *xyz:* 42, -76, -12; Z-score: 4.45). Regarding the elaboration phase, no significant brain activation changes were observed in pre- vs. post-facilitation.

Likewise, while no functional hyper-connectivity was induced by the verbal programme, the reverse contrast showed a lower functional connectivity within the ADMN after facilitation, especially in the bilateral medial frontal gyrus (BA 10; left: *xyz:* -8, 60, 10; Z-score: 4.72; right: *xyz:* 3, 60, 13; Z-score: 5.18) and the right anterior cingulate (BA 32; *xyz:* 10, 42, 10; Z-score: 4.64).

In parallel, no significant GM volume changes were observed, even at $p < 0.001$ (uncorrected).

Table 2: Post-scan measures: Mean and (SD) for the experimental and control groups.

	Experimental group	Control group	P value
Pre-facilitation			
Construction RT	4.63 (1.10)	4.60 (1.17)	$p = 0.99$
Type of events			
Unique	17.60 (8.65)	21.14 (6.64)	$p = 0.45$
Repetitive	5.50 (5.23)	2.85 (2.54)	$p = 0.89$
Extended	0.60 (1.26)	0.00 (0.00)	$p = 1.00$
Semantic	2.00 (4.13)	1.14 (2.60)	$p = 1.00$
Absent	1.50 (1.90)	3.85 (3.33)	$p = 0.95$
Amount of details	5.60 (1.86)	6.93 (0.72)	$p = 0.57$
Post-facilitation			
Construction RT	4.95 (1.01)	4.87 (1.14)	$p = 0.99$
Type of events			
Unique	21.90 (7.51)	21.85 (7.92)	$p = 1.00$
Repetitive	3.40 (4.42)	2.14 (2.73)	$p = 0.99$
Extended	0.10 (0.31)	0.00 (0.00)	$p = 1.00$
Semantic	0.30 (0.67)	2.42 (3.20)	$p = 0.98$
Absent	1.30 (1.41)	2.42 (3.04)	$p = 0.99$
Amount of details	5.86 (2.28)	6.41 (2.20)	$p = 0.95$

RT: reaction time.

Table 3 : Increased cerebral activations in post-facilitation (vs. pre-facilitation) for the future events construction and elaboration phases in the experimental group ($p < 0.001$ uncorrected).

Brain region	Coordinates *(x, y,* z)	Z-score	Cluster size
Future construction (vs. control task construction)			
L Parahippocampal gyrus (BA 34)	(-24, 0, -12)	3.95	7
R Parahippocampal gyrus	(28, -6, -14)	3.93	17
L Superior frontal gyrus (BA 10)	(-12, 66, 20)	3.47	18
L Middle temporal gyrus (BA 21)	(-40, 2, -20)	3.95	18
Future elaboration (vs. control task elaboration)			
L Middle frontal gyrus (BA 10)	(-24, 62, 20)	3.36	5
R Superior frontal gyrus (BA 8)	(4, 42, 52)	4.09	17

Note: no significant results were obtained using a more conservative threshold of $p < 0.05$ (corrected for multiple comparisons).

Table 4 : Functional connectivity changes before and after facilitation in the experimental group (FWE, $p < 0.05$).

Brain region	Coordinates *(x, y,* z)	Z- score	Cluster size
Post-facilitation > Pre-facilitation			
L Lingual gyrus (BA 19)	(-12, -49, -1)	5.59	5
L Precuneus (BA 19)	(-36, -81, 34)	4.80	17
L Middle temporal gyrus (BA 39)	(-47, -77,31)	4.96	
R Posterior cingulate (BA 30)	(13, -56, 10)	4.97	5
Pre-facilitation > Post-facilitation			
R Precuneus (BA31)	(6, -49, 34)	4.52	38
R Posterior cingulate (BA 23)	(3, -39, 24)	5.33	
R Precuneus (BA 7)	(3, -70, 38)	4.66	11
L Precuneus (BA 7)	(-8, -56, 38)	4.69	5
L Angular gyrus (BA 39)	(-43, -60, 38)	4.61	6

Table 5 : Brain regions showing positive correlations between the AI score progression and GM volume in the experimental group ($p < 0.001$ uncorrected).

Brain region	Coordinates *(x, y,* z)	Z-score	Cluster size
R Middle frontal gyrus (BA 11)	(25, 53, -10)	3.26	31
R Middle frontal gyrus (BA 10)	(28, 48, 9)	3.26	15
R Superior frontal gyrus (BA 10)	(22, 57, 0)	3.15	7
R Putamen	(19, 6, -9)	3.60	90

Note: no significant results were obtained using a more conservative threshold of $p < 0.05$ (corrected for multiple comparisons).

Published in: Brain & Cognition (2016), vol. 105, pp 34-45
Status: Postprint (author's version)

Fig. 3. Brain regions showing increased activations in post-facilitation (vs. pre-facilitation) for the experimental group during the construction and elaboration phases of EFT ($p < 0.001$ uncorrected).

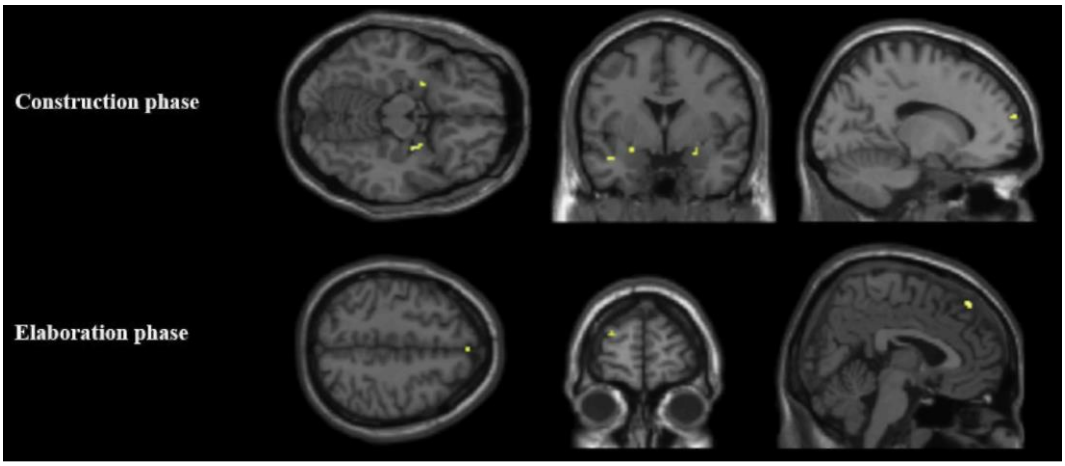


Fig. 4. Brain regions showing increased functional connectivity in post- vs. pre-facilitation (and conversely), in the experimental group (FWE, $p < 0.05$).

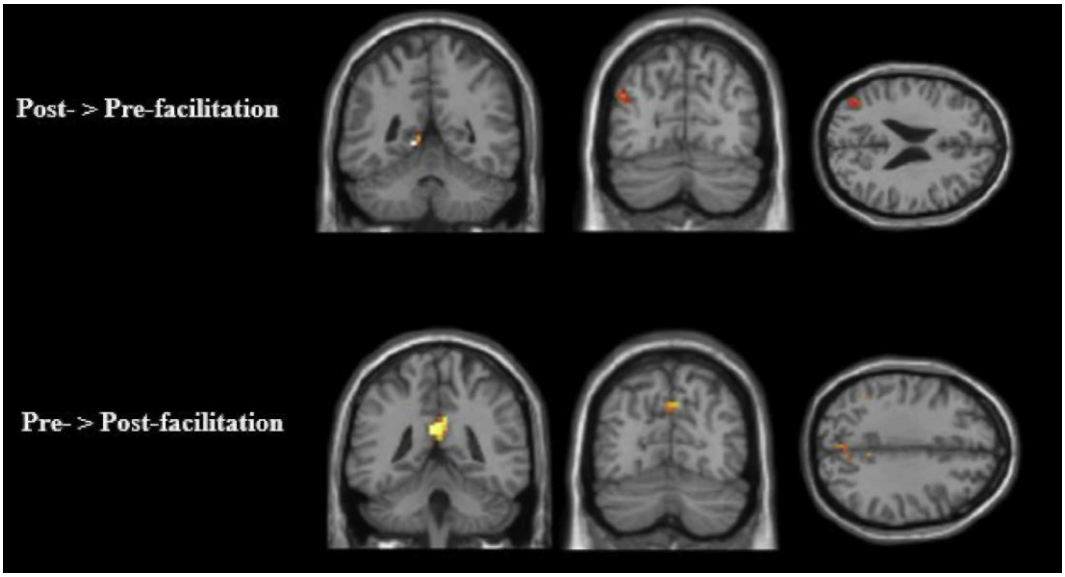
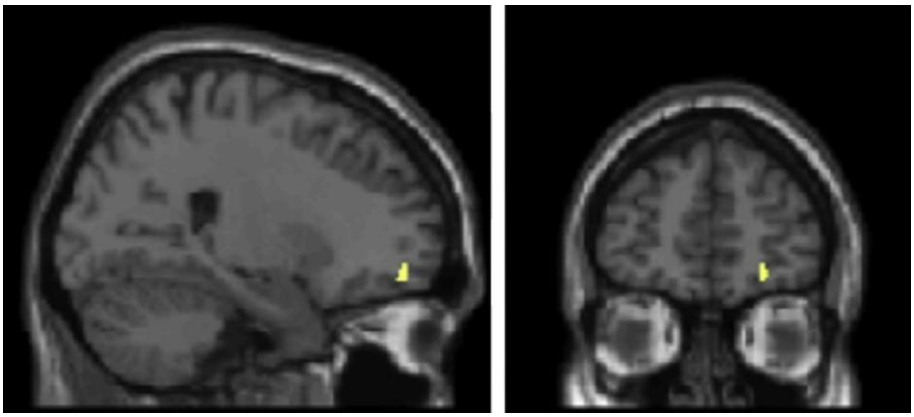


Fig. 5. Brain regions showing a positive correlation between AI score progression (number of internal details) in post-facilitation and GM increase in the experimental group ($p < 0.001$ uncorrected).



4. Discussion

The aim of the present study was to probe the efficacy of a MVI-based facilitation programme on EFT impairment, by testing clinical, functional and structural brain changes in RR-MS patients in the context of a 'placebo'-controlled study.

Prior to facilitation, no group differences were noticed regarding EFT performance (either AI or post-scan measures). Likewise, no differences were observed in the cerebral network sustaining impaired EFT in these patients. Importantly, the good matching between the patient groups was verified in several factors such as the time necessary to construct future events, and the number of both valid trials and details associated with future events. These characteristics formed the bases to interpret the differential brain activations observed between groups after facilitation as likely reflecting the effects of the intervention.

As expected, we reported an increased number of internal (episodic) details provided by the patients from the experimental group after facilitation, which supports the efficacy of the MVI programme on EFT, previously reported by Ernst, Blanc, et al. (2015). In addition, we observed a normalised EFT performance in post-intervention relative to the initial normative database that had shown EFT impairment. These positive outcomes were corroborated by patients' comments, who evoked an effective transfer of benefits in their everyday life functioning - i.e., the core of a 'successful cognitive intervention' (Wilson & Gracey, 2009).

In agreement with our hypotheses and with similar studies in MS patients (Chiaravalloti et al., 2012; Leavitt et al., 2012; Parisi et al., 2012; Penneret al., 2006), we observed signs of neuroplastic-ity associated with cognitive improvement. In the current study, as anticipated, a main involvement of the prefrontal region was observed. In particular, enhanced left frontopolar cerebral activity was reported after facilitation both during EFT construction and elaboration in the experimental group. Signs of up-regulated activity in this brain region, positively related to the amount of details generated, have been previously shown in RR-MS patients in the context of impaired EFT (Ernst, Noblet, et al., 2015). In other words, our findings suggest that the frontopolar region is particularly responsive to the amount of details in RR-MS patients. However, high responsiveness to the amount of details has been associated mainly with the hippocampus in previous studies (see Addis & Schacter, 2012 for a review); a brain region that did not show significant changes after intervention in our RR-MS patients. While the right frontopolar region has initially been described as a key neural signature in EFT (Addis et al., 2007; Okuda et al., 2003), more recently, the role of the frontoporal region has been reconsidered as being involved in the general process of imagining, with a particular role of the left frontal pole in the overall integration and maintenance of multimodal information from diverse systems (Addis, Pan, Vu, Laiser, & Schacter, 2009). In this context, we would like to suggest that the increased left frontopolar activity observed after facilitation in RR-MS patients during both phases could reflect the greater cognitive demand of the integration process since, the richer the episodic details of future events, the more bits of information have to be integrated and held together. Along these lines, it is important to bear in mind the emphasis of the MVI programme on the integration of details from different perceptual modalities in future events. As suggested by Schacter and Addis (2007), the role of the left frontal pole in the integration of multimodal information relies on working memory, and in particular on the episodic buffer (i.e. a system that temporary stores and recombines multimodal information into a unitary episodic representation), which has been suggested to act as the 'stage' on which episodic details are recombined into a hypothetical scenario. As such, several studies have reported a link between working memory and EFT performance, especially regarding the number of details provided (Addis, Wong, & Schacter, 2008; D'Argembeau et al., 2010; Zavagnin, De Beni, Borella, & Carretti, 2016). This idea fits well with the increased left frontopolar activation accompanying EFT improvement in the experimental group, which could reflect the higher cognitive load for the episodic buffer necessary to store and recombine the greater number of episodic details provided by MS patients following the MVI programme. Further studies exploring the relationship between EFT improvement and working memory capacity would be of interest to better understand the underlying cognitive mechanisms of EFT improvement after the MVI programme. Similarly, the greater activation also exhibited in the right superior frontal gyrus in our patients after facilitation could be related to the greater reliance on prefrontal resources in order to bind together richer episodic information during future simulations (Weiler, Suchan, Koch, Schwarz, & Daum, 2011). More generally, this brain region also sustains simulations of self-involved scenarios (Summerfield, Hassabis, & Maguire, 2009). Besides these functional changes, as expected, structural brain changes were also observed in the prefrontal regions in the experimental group. Specifically, an increase of the GM volume in the prefrontal region was positively associated with EFT improvement, which reinforces

the key role of the prefrontal region in EFT in RR-MS patients. However, contrary to our hypothesis, no functional connectivity changes were reported in the prefrontal region following the MVI programme.

After facilitation, increased neural activity was also observed within the experimental group in the left middle temporal gyrus during EFT construction. This brain region has been associated with the reactivation of the semantic scaffold necessary to guide future simulations (Irish & Piguet, 2013). Moreover, while research on EFT mainly focused on its episodic component, converging lines of evidence also highlighted the primary role of semantic knowledge in EFT and its involvement in the recombination process (Schacter et al., 2012). Namely, converging evidence support the role of the semantic memory system in the construction of novel events (Irish et al., 2012). The greater activation of the lateral temporal region accompanying EFT improvement in the present study could be cautiously interpreted in accord to this line of research.

Unexpectedly, we observed increased brain activations in the bilateral parahippocampal region during the EFT construction phase in post-facilitation. Ernst, Nob let, et al. (2015) reported also a greater activity in the bilateral parahippocampal regions in the context of impaired EFT, which was also modulated by the amount of details generated by RR-MS patients. It is established that the parahippocampal region is associated with contextual processing and the generation of complex coherent scenes (St Jacques, Rubin, & Cabeza, 2012). The parahippocampal gyrus plays also a pivotal role in the recruitment of the posterior brain areas supporting MVI (Bar & Aminoff, 2003 ; Botzung, Denkova, Ciuciu, Scheiber, & Manning, 2008; Greenberg & Rubin, 2003; Viard et al., 2011). Importantly, the posterior brain regions are especially involved in imagining future events when the subjects have to generate as many details as possible (Addis et al., 2007). Therefore, considering both the role of the parahippocampal region and that of MVI, in EFT through the facilitation programme, the greater neural activity in these regions could reflect increased reliance on contextual processing and the greater episodic quality of future events after facilitation.

Although no greater brain activations were observed in the posterior cortical areas, we reported functional connectivity changes in the posterior brain regions, confirming partially our hypotheses. These changes were especially observed in the posterior cingulate, a brain region highly implicated in scene construction, that is, the ability of mentally generating, maintaining and manipulating complex and coherent scenes (Hassabis & Maguire, 2007; Irish et al., 2015). Taking into account the role of the posterior brain regions in MVI and their dynamic interactions with the parahippocampal regions, these cerebral changes could be suggested to reflect the emphasis made on the role of MVI in EFT through our programme.

Overall, an intriguing finding is the predominant shift from right- to left-sided functional connectivity changes, whereas increased GM volume following EFT improvement were mainly observed in the right hemisphere. To our knowledge, the only study exploring both GM volume and functional connectivity changes following a cognitive intervention in MS patients failed to report significant structural changes (Filippi et al., 2012). However, a critical issue in our study, compared to Filippi et al.'s findings, is the use of a lenient statistical threshold for an exploratory purpose. As such, the latter GM increase reported here should be interpreted cautiously. Nevertheless, we thought of interest to report these findings in order to encourage further studies to better understand the interactions that are in play between functional and structural changes following a cognitive intervention - a result that remain difficult to interpret for the time being due to the paucity of the literature in this domain and especially, in the absence of similar clinical studies on EFT.

Turning to the control group, the verbal control programme did not result in EFT improvement, as it was hypothesised. Consistent with the clinical findings, no significant structural brain changes were highlighted in this group. However, while no increased cerebral activations were displayed in post-facilitation, we reported signs of down-regulation in several brain regions after facilitation, including the prefrontal, parietal and posterior brain regions. Decreased functional connectivity in the ADMN was also observed. Although statistically non-significant, in the context of anterograde memory rehabilitation, a tendency to decreased neural activity and functional connectivity in several brain regions has been previously reported in an MS control group in post-rehabilitation (Chiaravalloti et al., 2012; Leavitt et al., 2012). While this tendency was observed in the control group, increased cerebral activations were reported in the experimental group. As suggested by Chiaravalloti et al. (2012), decreased brain activations are more likely related to practice effects and habituation to the task completed in the scan.

In summary, to the best of our knowledge, this study is the first to document signs of brain plasticity in a group of brain-damaged patients following improvement of EFT by means of a cognitive intervention.

Although the clinical value of this study has been ascertained by the convergence of clinical findings and of different neuroimaging techniques, a number of limitations should be considered. A first limitation could be seen in small sample size. However, due to the difficulty to constitute relatively homogeneous groups of RR-MS patients in terms of functional disability and cognitive profile, most rehabilitation studies involving clinical and neuroimaging measures include small groups of patients. Moreover, a recent neuroimaging study conducted in MS patients suggests that a large sample size could also lead to misinterpretation of results in the context of cognitive interventions and that small samples or a single-case approach could be relevant in this line or research (Hubacher et al., 2015). In this context, it is worth mentioning that due to the explorative nature of this study, some of our neuroimaging results were based on liberal statistical threshold (although frequently used in previous EFT neuroimaging studies in healthy participants) since the use of corrected p values yield no significant result. As such, our findings should be interpreted with caution. However, we deemed of interest to provide a complete overview of our findings in order to not overlook some neural landmarks (i.e. Type II error) that could be of interest for future investigations in this nascent line of research (see Lieberman & Cunningham, 2009 for a review on Type I and Type II error concerns in fMRI research). As such, we encourage the replication of the current findings in similar clinical settings. On a different issue, while the long-term robustness of benefits from the MVI programme has been ascertained at the clinical level (Ernst, Blanc, et al., 2015), exploring the maintenance of the induced brain plasticity phenomenon reported here would be of value to specify the contribution of these different brain region in EFT improvement.

5. Conclusion

The present study investigated the clinical and brain changes following a successful cognitive intervention tackling EFT impairment in RR-MS patients. In this regard, our findings convey the strong clinical message that EFT impairment could be efficiently alleviated by means of a short cognitive intervention - a message that seems meaningful when considering the growing evidence of the deleterious impact of EFT impairment in patients' daily life (Ernst et al., 2014; Irish & Piolino, 2015). From a more theoretical standpoint, while it has been demonstrated that distinct cognitive mechanisms (e.g. semantic memory, self-projection, scene construction, executive functions) could be involved in the occurrence of EFT impairment in different clinical populations, nothing is known about the possibility to explore those mechanisms to compensate EFT deficit. In this line, our findings support the notion that scene construction, stimulated through the MVI programme, has very likely a key role in alleviating EFT impairment related to executive function difficulties in RR-MS patients.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgments

We are grateful to the patients and their families for their support and involvement in our research. We are also grateful to the 'Fondation pour la Recherche sur la Sclérose en Plaques' (ARSEP; Ile de France; grant to LM) for research funding, and to the Ministry of National Education and Research (AE's PhD grant). AE is now a postdoctoral researcher at the Psychology Department - University of Liege, funded by a Marie Curie COFUND fellowship). We thank B. Journault and C. Vinet-Gasse for their contribution with patients and interrater reliability scoring, A. Botzung and V. Voltzenlogel for their contribution to interrater reliability scoring. We are grateful to the 'Imagerie in vivo' Platform (ICube laboratory) and the CIC of the Strasbourg University Hospitals.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.Org/10.1016/j.bandc.2016.03.007.

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