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Using mental visual imagery to improve autobiographical memory and episodic future thinking in relapsing-remitting multiple sclerosis patients: A randomised-controlled trial study

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Abstract.
Purpose: The co-occurrence of autobiographical memory (AM) and episodic future thinking (EFT) impairment has been documented in relapsing-remitting multiple sclerosis (RR-MS) patients. On these bases, we aimed at probing the efficacy of a mental visual imagery (MVI)-based facilitation programme on AM and EFT functioning in the context of a randomised-controlled trial study in RR-MS patients.
Methods: Using the Autobiographical Interview (AI), 40 patients presenting with an AM/EFT impairment were randomly assigned in three groups: (i) the experimental ($n = 17$), who followed the MVI programme, (ii) the verbal control ($n = 10$), who followed a sham verbal programme, and (iii) the stability groups ($n = 13$), who underwent the AM/EFT test twice, with no intervention in between.
Results: AI's second assessment scores showed a significant improvement of AM and EFT performance only for the experimental group, with a long-term robustness of treatment benefits.
Conclusions: The control and stability groups' results ruled out nursing and test learning effects as explanations of AM/EFT improvement. These benefits were corroborated by the patients' comments, which indicated an effective MVI strategy transfer to daily life. Our results suggest that the MVI programme tackles a common cognitive process of scene construction present in AM and EFT.

Keywords: Autobiographical memory, episodic future thinking, neuropsychological rehabilitation, mental visual imagery, multiple sclerosis

1. Introduction

The experience of brain injury leads to major disruptions in every domain of an individual's life and

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provokes, more often than not, significant changes in how a person interprets his/herself and the world around (Gracey et al., 2008). In this context, clinicians are now aware that neuropsychological interventions need to address cognitive, emotional, psychosocial and behavioural problems resulting from brain injury and that cognitive impairment should not be isolated from other factors (Wilson & Gracey, 2009). In this perspective, the transfer of benefits resulting from neuropsychological interventions to everyday life is considered as the core of "successful cognitive rehabilitation" (Wilson, 1987, 2008).

In the broad spectrum of cognitive dysfunction, memory impairment is one of the most frequent issues following brain injury. Its frequency and the fact that memory disorders compromise patients' ability to participate in daily life activities have probably contributed to the development of several compensatory interventions (Evans, 2009). While the great majority of studies focused on the improvement of anterograde memory, more recently, a growing interest for the development of therapeutic interventions to improve autobiographical memory (AM) has been observed. Briefly stated, AM corresponds to the ability to mentally re-experience personal detailed events, within a specific spatio-temporal context, as they are remembered (Tulving, 2002). Several functions have been attributed to AM, such as its role in the construction of sense of self temporally extended, the development of new social relationships and the nurturing of existing ones, and a directive function where the past serves as a basis to guide present and future behaviours (Rasmussen & Habermas, 2011). Taken together, AM constitutes a central process in any individual's life and, not surprisingly, could be seen as the reason of the endeavour to improve its functioning. To our knowledge, two lines of research have been explored so far to improve AM functioning in patients and have led to positive outcomes: using an external device such as the SenseCam (e.g. Berry et al., 2007; Loveday & Conway, 2011; Pauly-Takacs et al., 2011; Woodberry et al., 2015) and applying training programmes (Raes et al., 2009; Neshat-Doost et al., 2013; Moradi et al., 2014). Overall, it appears that training programmes are applied in psychiatric diseases, whereas external devices are mostly used in neurological conditions presenting with severe AM impairment. In the context of mild-to-moderate AM disorder, Ernst et al. developed a facilitation programme (created by one of us LM; see Ernst et al., 2012, 2013) based on the critical role of mental visual imagery (MVI) in AM retrieval and vividness of memories (Greenberg & Rubin, 2003). The MVI programme was specifically designed to improve AM impairment in relapsing-remitting multiple sclerosis (RR-MS) patients, for which a prefrontal dysfunction origin was suggested. AM impairment in RR-MS patients has been found to be frequent, even in patients presenting with a preservation of their general cognitive functioning, with a deleterious impact of this impairment in patients' daily life (Ernst et al., 2014a). The MVI programme stemmed from this initial clinical observation. This tailor-made facilitation programme was built to alleviate executive function-related AM impairment in RR-MS patients, in the context of, at most, mild cognitive impairment in other cognitive functions, and with the use of an integrated cognitive strategy transferable to daily life functioning. Benefits of this programme on AM functioning were reported, with a high rate of individual improvement and with an effective transfer of treatment benefits in daily life functioning. Nevertheless, beyond the small sample size, some limitations restricted the conclusions drawn from these previous studies, including the absence of a patients' control group or follow-up measures of the robustness of treatment effects.

Recently, based on the theoretical framework of mental time travel (Suddendorf & Corballis, 1997; Tulving, 2001, 2002), Ernst and co-workers extended their findings of AM impairment in RR-MS patients to Episodic Future Thinking (EFT; Ernst et al., 2014a). Similarly to its past counterpart, EFT enables people to mentally simulate personal detailed events within a specific spatio-temporal context. More specific to EFT, it contributes to coping skills, goal achievement, intention's implementation or to the sense of personal continuity overtime (Szpunar, 2010; D'Argembeau et al., 2012). In the case of RR-MS patients, AM and EFT impairment seemed to coexist and deficits in the two temporal directions were highly interrelated. This finding was consistent with the mental time travel literature, which posits that AM and EFT share striking similarities at both cognitive and neural levels (see Schacter et al., 2012 for a review). In both cases, a main role of executive functions was put forward to explain AM and EFT impairment in MS patients, with compromised retrieval strategies, as well as difficulties to extract and recombine details to form personal memories and mental simulations. Importantly, the AM and EFT difficulties were amply corroborated by the patients' reports, who commented on the negative impact of this deficit in their daily life functioning.

Using the same MVI facilitation programme than in previous works (Ernst et al., 2012, 2013), we sought to investigate, in the context of a randomised-controlled trail (RCT) design to what extend AM and EFT could be jointly improved in RR-MS patients. Considering the theoretical (Tulving, 1985; see Schacter et al., 2012 for a review) and empirical (Addis et al., 2009; D'Argembeau et al., 2004, 2008) relationships between AM and EFT, we hypothesised that significant improvement would be observed in both temporal directions. Finally, we hypothesised that any benefits gained thanks to our facilitation programme would show long-term preservation.

2. Material and methods

2.2. Participants

Sixty-two RR-MS patients (following Polman et al.'s, 2011 diagnosis criteria) were recruited, with an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score $\leq$5 and no recent exacerbation of MS symptoms. Only patients presenting with a RR-MS disease course were recruited and the absence of progression between relapses has been verified through clinical follow-up. Patients were seen on a monthly basis at the day-care hospital in the context of their treatment administration (Tysabri®, natalizumab) and on a yearly basis to reassess disease course by means of clinical and MRI examinations.

Only MS patients with impaired AM and EFT performance, in the context of mild to moderate cognitive impairment in attention and/or executive functions and in the absence of major anterograde memory deficit, were included in the present study. Moreover, an absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (Montgomery & Asberg, 1979; score $\leq$15) had to be observed. These additional inclusion criteria were set to control the presence of confounding factors on AM/EFT performance and to guarantee the further good completion of the facilitation programme. After this selection, 40 RR-MS patients were finally included in the study, randomly assigned in three groups: the experimental, the verbal control and the stability groups (see the Procedure section for further details).

Demographic and clinical data are summarised in Table 1. The present study was approved by the 'Committee for Protection of Persons' (CPP/CNRS N° 07023) and we complied with the Declaration of Helsinki.

2.2. Structural neuroimaging data

To obtain descriptive data on the MRI abnormalities presented by the current group of MS patients, brain regions showing significant signs of atrophy have been explored before facilitation.

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 (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.

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

Table 1
Demographic and clinical data: mean (and standard deviation) for the three groups of patients

	MS patient groups			Statistical analysis
	Experimental (n = 17)	Verbal control (n = 10)	Stability (n = 13)	
Age (in years)	42.00 (10.37)	37.40 (8.85)	40.00 (3.85)	$F(2, 37) = 0.95$, $p = 0.39$
Education (in years)	13.29 (2.17)	12.20 (1.55)	13.77 (2.45)	$F(2, 37) = 1.56$, $p = 0.22$
Sex ratio (female/male)	13/4	9/1	9/4	$\chi^2 = 1.41$; $p = 0.49$
EDSS	2.68 (1.58)	2.45 (1.40)	2.77 (1.41)	$F(2, 37) = 0.13$, $p = 0.87$
Duration of MS (in years)	10.97 (9.53)	10.60 (5.66)	11.85 (7.01)	$F(2, 37) = 0.07$, $p = 0.92$
Number of DMD treatment	1.0 (0.0)	1.0 (0.0)	1.0 (0.0)	-

DMD = Disease Modifying Drug.

Anatomical MRI images were spatially pre-processed in the following way: all T1 structural images were bias corrected, segmented using an extension of the unified segmentation procedure (Ashburner & 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 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.

Group comparison on local GM volume was investigated using the General Linear Model and with a group of 18 healthy controls matched for age, gender and education involved in our previous study (Ernst et al., 2014b). Age and total amount of GM were included as nuisance covariates in all statistical analyses. A statistical threshold of $p < 0.001$ without multiple comparison correction and with a cluster spatial extend of $k = 100$ voxels was considered in all analyses.

2.3. Neuropsychological examination

A comprehensive neuropsychological baseline was administered to the MS patients in a first session. General verbal abilities were tested with a short form (Axelrod et al., 2011) of the Verbal IQ of the WAIS-III (Wechsler, 1997) and nonverbal reasoning was assessed using the Advanced Progressive Matrices Set 1 (Raven, 1958). Anterograde memory was examined with the Rey auditory verbal learning test (RAVLT; Rey, 1964), and the Rey-Osterrieth Complex Figure (ROCF; Rey, 1941; Osterrieth, 1944). The executive functions were probed by means of the phonological and categorical fluency tests (National Hospital, London), the Brixton Spatial Anticipation test (Burgess & Shallice, 1997), the Tower of London (Shallice, 1982), and the Cognitive Estimation Task (Shallice & Evans, 1978). The attentional abilities and information processing were assessed using the Information Processing Speed test from the Adult Memory Information Processing Battery (AMIPB; Coughlan & Hollows, 1985), the Stroop test (Stroop, 1935), and the months backwards test (National Hospital, London). Language was tested with the Déno 100 test (Kremin, 2002), and the visuo-perceptual and visuo-spatial abilities with the Silhouettes and Cube Analysis sub-tests from the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991). In addition, the impact of fatigue in everyday life was assessed using the 'Echelle de Mesure de l'Impact de la Fatigue' (EMIF-SEP; Debouverie et al., 2007).

2.4. AM and EFT assessment

In a second session, AM/EFT performance was assessed by means of an adapted version of the Autobiographical Interview (AI; Levine et al., 2002; Addis et al., 2009). MS patients and healthy controls were instructed to retrieve/imagine personal unique events, temporally and contextually specific, occurring over minutes to hours (but no longer than one day) and to freely generate as much details as possible about the event. Regarding the AM condition, three past events per life period were collected [i.e. four or five life periods, depending on the subject's age; 0–11 years, 12–20 years, 21 to (current age −1) or 21–35 years, 36 to (current age −1) and the previous year]. For the EFT component, subjects had to generate five future events that could plausibly occur within the next year. Participants were informed that the cue-words were intended to be used flexibly and no time limit was set to avoid the potential influence of patients' slowed down cognitive processing speed on AM/EFT performance. General probes (e.g. "is there anything else you can tell me?") were used to clarify instructions if necessary and to encourage evocation of additional details.

The AI session was audio-recorded for later transcription and scored following the Levine et al.'s standardised procedure: after the identification of the central episodic event, details were classified as internal details (i.e., an episodic detail related to the central event) or external (i.e., non-episodic information such as semantic details, metacognitive statements, repetitions or episodic details unrelated to the central event). A qualitative assessment of the episodic re-/pre-experiencing was also provided by ratings for episodic richness, time, space, perception and emotion/thought composites for each memory. The free recall and the general probe phases were analysed as a whole, considering the minimal influence of this last one on recall (Levine et al., 2002). For each participant, the number of internal and external details, as well as the mean rating score were averaged across the 12 or 15 past events, and across the five future events for the EFT condition.

Following Levine et al.'s (2002) procedure, the interrater reliability was verified for 10% of the past and 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 all measures showed high interrater reliability (between 0.82 and 0.99).

In order to characterise the potential impact of AM/EFT difficulties and the perceived benefit of the facilitation programme in MS patients' daily life functioning, a semi-structured interview was conducted at the end of each AI session. This semi-structured interview was similar to the one used by Ernst and colleagues (2014a) and encompassed four dimensions: vividness, accessibility, sensory details and emotional intensity of personal past and future events. Considering the broad range of everyday life situations in which AM and EFT abilities are involved, a semi-structured interview was deemed to be better adapted than a questionnaire to explore changes in real life.

2.5. AM and EFT MVI facilitation programme

The MVI programme is based on the ability to mentally construct scenes and to pay close attention to details in the mind's eye. Following a goal directed approach (Wilson & Gracey, 2009), the first step of the programme is to carefully explain its aim, content and how it is supposed to help the memory impairment. This introduction is important to promote its further use in daily life. Along these lines, the neuropsychologist is very attentive to treatment receipt (i.e. the extent to which the patient understands the strategies or techniques taught, and demonstrates the capacity to use them; Hart, 2009).

The MVI programme encompassed six two-hour sessions, once or twice per week (depending on the patient's availability). The programme comprised four steps, with mental visualisation exercises of increasing difficulty, during which the neuropsychologist provided a continuous guidance (as much as necessary), probing the patient from general aspects to more detailed ones, adopting a 'funnel-approach' and learning to work in a sequential manner. (i) The *screening test* was based on three subtests from the 'Imagery and Perception Battery' (Bourlon et al., 2009): the 'mental representation of physical detail', the 'morphological discrimination' and the 'colour comparison' tests. We used a shortened version of each test, with normative data established with a group of 15 healthy controls (unpublished data). These tests were used to probe basic visual imaging abilities, which enabled us to exclude the patients, who presented scores below the normal range for all the three subtests (and therefore incompatible with the implementation of the facilitation programme). (ii) The *external visualisation* included 10 verbal items to imagine and describe in as many details as possible (e.g. shape, colour, size, etc), with the complementary visualisation of an action made with the item (e.g. visualise an onion and visualise it again, once sliced). (iii) The *construction phase* consisted in figuring out complex scenes, bringing into play several characters and various scenarios. Five verbal items were proposed for each part of the exercise: a first training step (e.g. imagine the hotel of your holidays) and a subsequent mental scene construction, sharing thematic similarities (e.g. imagine the house of your dreams), allowing the patient to rely on the training section to construct the next scene. (iv) The *self-visualisation* followed the same procedure but here, patients were asked to visualise themselves within a given scenario, to imagine it as though they were actually living the scene, with the description of all kind of details, sensations or feelings that came to mind. A first training scene was proposed (e.g. imagine you take part in a magic show), followed by a second scene with a similar theme (e.g. imagine you enter in the big cats' cage for a show).

2.5.1. Verbal control programme

Greenberg and Rubin (2003) put forward the role of narrative structure which enables organisation in AM, provides temporal and goal structure, with a kind of scaffold on what has to be included or excluded in a memory. However, narrative structure plays a minor role in comparison with MVI in AM. On theses bases, we developed a narrative-oriented control programme which could plausibly be linked to AM and EFT performance, with the same number and frequency of sessions. Narration was also selected because this cognitive ability is not part of the frequently described cognitive impairment in MS patients. We strictly observed the same clinical characteristics and interactions with patients than the MVI programme. The programme was presented as one focusing on the importance of the information organisation, on the bases of a series of texts extracted and selected from various websites, covering a wide range of news topics. After a first reading of the text, the general goal was to exchange about the topic of the text, introducing

different directions through steps of increasing difficulty. A continuous guidance was provided, with supplementary questions to rekindle the dialogue and patients were encouraged to construct a structured talk. This last point enabled the patient to work in a sequential manner, in parallel with the MVI programme.

Three steps were proposed: (i) *the external discussion* relied on the identification of influent variables on text understanding related to its form (e.g. clarity, vocabulary used) and comprised 20 texts. This step was very brief and corresponded to the MVI programme external visualisation. (ii) The *discussion construction* comprised five items, with a training and a construction step for each item, with two texts thematically related to enable the reliance on the first to construct the second one (e.g. a first text dealing with a trip to South Africa was followed by a text about a trip to Ireland). (iii) The *self-involved discussion* was similar to the previous step, with the addition of questions about his/her own opinion (e.g. a first text about taxing sodas to reduce their consumption was followed by a second text concerning the usefulness of anti-smoking campaigns).

2.6. Procedure

Prior to inclusion, a selection of MS patients was made based on the neuropsychological baseline examination. The aim was to control for the absence of severe cognitive impairment other than AM/EFT deficit. To continue towards the next steps, the patients had to be in the normal range on all tests (threshold: either z-score -1.65 or the 5th percentile, depending on normative data), except for attentional and executive functions, for which mild impairment was accepted (defined in this study as a failure to one attentional test and/or two executive function tests, at the most).

As mentioned above, only MS patients showing AM/EFT impairment were included in this study. The presence of an AM/EFT was based on the AI normative database previously used by Ernst et al. (2012), including the mean number of internal details and the mean total rating obtained during the free recall phase. Indeed, these measures assess the episodic re-/pre-experiencing ability, taking into account the sensitivity of the free recall to detect deficit. Patient's free recall performance were considered to be impaired if the mean score for internal details was ≤ 22 and the mean score for total ratings was ≤ 8 for the AM condition, and if the mean number of internal details was ≤ 18 and the mean total rating was ≤ 7 for the EFT condition.

To obtain a reliable assessment of potential AM/EFT performance change, a strictly similar AI procedure was followed at each session. They only differed in the cue-words, which were set up beforehand and randomly assigned across AI sessions. Importantly, if patients evoked past/future events already provided during a previous AI sessions, or events similar to or based on simulations produced during the MVI programme, patients were asked to find an alternative event.

The final 40 MS patients were randomly assigned in the three following groups: (i) the experimental group, who followed the MVI facilitation programme; (ii) the verbal control group, who underwent the verbal control programme and aimed to verify the absence of a nursing effect; and (iii) the stability group, whose inclusion was thought to control for learning effects due to repeated AM/EFT assessments. Regarding the stability group, the second AI assessment was conducted 6 to 8 weeks after the first AI assessment to homogenise the time interval between the two assessment sessions in every group. Once this step was completed, the 13 patients from the stability group were due to follow the MVI programme. However, owing to personal time constrains from the patient ($n = 2$) or MS relapse ($n = 1$), three patients from the stability group dropped out from the study.

For all MS patients who had followed the MVI programme, a long-term follow up AI assessment was also completed six months after the initial post-facilitation assessment. This additional session aimed at assessing the maintenance of benefits for patients, and to gather their impressions about the use and impact of the MVI strategy in their daily life. A diagram summarising the study design is presented in Fig. 1.

Patients were blind to their allocation group and, importantly, they had never before participated in similar studies. The presentation of the study informed the patients of the constitution of different groups of participants, with two possible interventions, whose efficacy was going to be tested during the study. However, since each patient was followed by the same neuropsychologist (AE for 78% of patients) during his/her participation (from the baseline examination to the long-term follow-up), the neuropsychologist was not blind to the patient's allocation group. Since in the context of a goal directed approach, a blind condition was difficult to set for the neuropsychologist, we designed

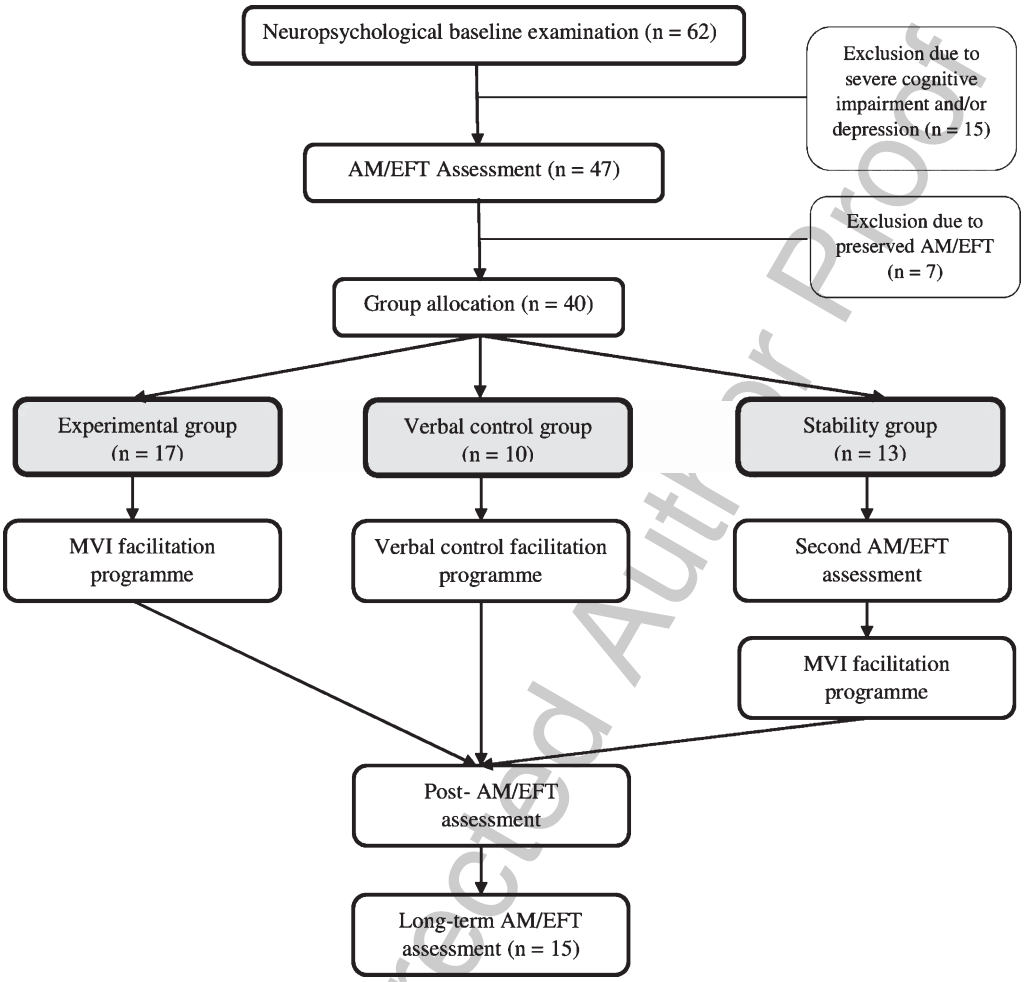

Fig. 1. Study design diagram summarising the group allocation and progression of patients through study phases.

our study in agreement with the recommendations of the Neuropsychological Rehabilitation Consensus Conference (Làdavass et al., 2011). This document acknowledges the potential issues if the investigator is not blind to some aspects of the research. However, to control the potential influence of the investigator's awareness of the patient's group allocation, the second AI scorer was blind to the group membership, in every case. Moreover, AI reports were anonymised, personal past and future events were not supplied for scoring in the chronological order of assessment (i.e., post-facilitation AI from a patient was not systematically given for the second scoring after the pre-facilitation AI) and were mixed with AIs belonging to healthy subjects who participated in the study of Ernst et al. (2014a).

2.7. Statistical analyses

Since the aim of the facilitation process was to improve the episodic richness of past and future events, we paid attention, particularly to the internal details spontaneously provided by patients and the mean total rating scores.

Mixed ANOVA were run with the between factor of Group (experimental, verbal control and stability groups) and the repeated factors of Time (pre- and post-facilitation) and of Detail (internal and external). Analyses were conducted separately for the AM and EFT conditions. Importantly, to obtain comparative data about the effects of the MVI and verbal control programmes versus a potential learning effect on the AI, we used the results obtained on the second

AI assessment (with no in-between intervention) for the stability group. In this context, the facilitation programme and a third AI were presented (after the second AI). Likewise, a second analysis was specifically conducted for the stability group, to explore the benefit of the MVI programme, taking into account their first AI and third AI assessment (corresponding to their pre- and post-facilitation evaluation) by means of *t*-test for dependant samples.

A subsequent statistical analysis was also conducted only for the patients who followed the MVI programme to obtain comparative data about the effectiveness of this programme on AM and EFT performance (internal details), by means of repeated measures ANOVA with the between factors of Temporal direction (AM and EFT) and Time (pre- and post-facilitation).

Finally, the robustness of treatment benefits of the MVI programme was analysed, using the post-facilitation assessment as well as the six-month re-assessment AI scores (internal details and total rating) by means of t-test for dependant samples. For all the comparisons, Tukey HSD *post-hoc* test (for unequal N) was used when appropriate.

3. Results

3.1. Brain atrophy

Structural MRI data revealed signs of neural atrophy in patients in the right parahippocampal gyrus (BA 35; xyz: 20, −20, −13; Z-score: 4.00), the right cuneus

Table 2
Mean (and standard deviation) neuropsychological baseline test scores for the three groups of patients

	Experimental group	Verbal control group	Stability group	Statistical analysis
Verbal IQ	98.29 (14.80)	95.50 (11.90)	98.62 (14.26)	$F(2, 37) = 0.16$, $p = 0.84$
PM12	8.76 (2.08)	8.80 (1.93)	9.08 (2.02)	$F(2, 37) = 0.09$, $p = 0.90$
RAVLT				
-Total mean number of words	11.47 (1.39)	12.30 (1.17)	12.66 (1.44)	$F(2, 37) = 3.04$, $p = 0.06$
-Delayed recall	13.12 (2.06)	13.20 (2.30)	14.15 (1.41)	$F(2, 37) = 1.18$, $p = 0.31$
ROCF				
-Copy	35.21 (1.13)	35.50 (0.85)	35.69 (0.63)	$F(2, 37) = 1.04$, $p = 0.36$
-Immediate recall	25.53 (6.93)	22.05 (4.53)	23.62 (4.38)	$F(2, 37) = 1.24$, $p = 0.29$
-Delayed recall	25.29 (6.24)	21.80 (4.69)	24.12 (3.81)	$F(2, 37) = 1.43$, $p = 0.25$
Deno 100	98.24 (2.56)	95.90 (4.79)	98.50 (1.93)	$F(2, 37) = 0.52$, $p = 0.59$
Stroop				
-Colours (T score)	47.53 (8.06)	47.90 (10.39)	46.15 (7.70)	$F(2, 37) = 0.14$, $p = 0.86$
-Words (T score)	42.00 (12.29)	47.40 (8.85)	47.23 (8.13)	$F(2, 37) = 1.30$, $p = 0.28$
-Interference(T score)	47.76 (9.79)	48.60 (7.47)	50.15 (12.40)	$F(2, 37) = 0.20$, $p = 0.81$
-Interference (T score)	49.35 (7.94)	50.10 (7.05)	53.08 (7.18)	$F(2, 37) = 0.96$, $p = 0.39$
Months back (sec)	12.53 (5.58)	10.40 (2.80)	9.85 (2.79)	$F(2, 37) = 1.67$, $p = 0.20$
Tower of London				
-Score	8.53 (1.84)	8.30 (2.11)	8.58 (1.38)	$F(2, 37) = 0.07$, $p = 0.92$
-Time indices	19.65 (4.23)	17.60 (3.63)	18.00 (2.17)	$F(2, 37) = 1.29$, $p = 0.28$
Brixton (number of errors)	16.00 (5.29)	12.40 (4.25)	13.54 (5.65)	$F(2, 37) = 1.72$, $p = 0.19$
Cognitive Estimation Task	4.71 (3.41)	4.50 (1.96)	4.31 (4.59)	$F(2, 37) = 0.04$, $p = 0.95$
Verbal Fluency				
-Categorical	20.94 (4.22)	20.00 (4.92)	21.23 (5.59)	$F(2, 37) = 1.65$, $p = 0.20$
-Phonological	13.24 (3.17)	12.00 (0.30)	13.54 (3.15)	$F(2, 37) = 2.67$, $p = 0.08$
Information Processing Speed				
-Cognitive	53.71 (10.35)	52.20 (7.00)	54.69 (17.11)	$F(2, 37) = 0.11$, $p = 0.89$
-Motor	45.24 (8.08)	53.50 (10.95)	49.62 (10.06)	$F(2, 37) = 2.02$, $p = 0.14$
-Error percentage	2.34 (3.03)	3.57 (3.73)	3.09 (3.25)	$F(2, 37) = 0.46$, $p = 0.62$
-Corrected score	59.76 (11.95)	57.09 (7.84)	61.33 (20.97)	$F(2, 37) = 0.23$, $p = 0.79$
VOSP				
-Silhouettes	23.00 (3.76)	22.20 (2.66)	23.23 (3.09)	$F(2, 37) = 0.31$, $p = 0.73$
-Cubes Analysis	9.47 (0.80)	9.9 (0.32)	9.92 (0.28)	$F(2, 37) = 1.55$, $p = 0.22$
MADRS	6.59 (5.22)	6.00 (3.89)	6.33 (3.75)	$F(2, 37) = 0.05$, $p = 0.94$
EMIF-SEP (total)	50.14 (16.48)	40.24 (10.16)	50.42 (16.74)	$F(2, 37) = 1.60$, $p = 0.21$

PM12: Progressive Matrices 12; RAVLT: Rey Auditory Verbal Learning Test; ROCF: Rey-OsterriethComplex Figure; VOSP: Visual Object and Space Perception; MADRS: Montgomery and AsbergDepression Rating Scale; EMIF-SEP: Echelle de Mesure de l'Impact de la Fatigue.

(xyz: 15, −95, 2; Z-score: 3.59), the bilateral precentral gyrus (left: xyz: −47, −12, 33; Z-score: 4.93; right: xyz: 48, −8; 30; Z-score: 4.94), the right thalamus (xyz: 14, −26, 5; Z-score: 6.52) and the right cerebellum (xyz: 12, −69, −43; Z-score: 3.55). The reverse contrast, showing brain regions with an inferior GM volume in healthy controls relative to MS patients, failed to reveal any significant clusters.

3.2. Neuropsychological baseline

The patients' neuropsychological (baseline) scores are presented in the Table 2. Equivalent performances between patients' groups were observed for all the cognitive domains explored. In relation to the tests' normative data, our MS patients showed impaired performance only in planning (tower of London test) and cognitive estimation (eponymous task).

3.3. Pre- and post-facilitation AM performance

3.3.1. Mean number of internal and external details

Mean AI scores for the AM and EFT conditions for the three groups of MS patients in pre-facilitation are presented in the Table 3. The mean number of internal details provided for the AM condition in pre- and post-facilitation for each MS group is illustrated in the Fig. 2.

A significant Group × Time × Detail interaction was found, $F(2, 37) = 3.77, p = 0.03, \eta^2_P = 0.16$. *Post hoc* analyses showed equivalent performance for the mean number of internal details in the three groups before facilitation (experimental vs. verbal control group: $p = 0.99$; experimental vs. stability group: $p = 0.99$; verbal control vs. stability group: $p = 1.00$). A similar result was obtained for the external details before facilitation (experimental vs. verbal control group: $p = 1.00$; experimental vs. stability group: $p = 0.90$; verbal control vs. stability group: $p = 0.93$). After facilitation, a greater number of internal details was observed in the experimental group, relative to the stability group ($p = 0.003$) but not to the verbal control group ($p = 0.12$). No significant difference was found between the verbal control and the stability group regarding the mean number of internal details at the second AI assessment ($p = 0.99$). In other words, it appeared that the verbal control group represented an intermediate group between the experimental and the stability groups for the internal detail measure. Concerning the external details, no significant difference was reported between the three groups, showing the same pattern of results than in pre-facilitation (experimental vs. verbal control group: $p = 0.99$; experimental vs. stability group: $p = 0.99$; verbal control vs. stability group: $p = 1.00$).

Table 3
Mean AI scores (and standard deviation) for the AM and EFT conditions for the three groups of MS patients in pre-facilitation

	AM condition		EFT condition	
	Internal details	Ratings	Internal details	Details
Experimental group	13.80 (4.63)	4.04 (1.33)	9.31 (5.69)	2.97 (2.02)
Verbal control group	15.73 (2.65)	4.38 (0.91)	8.58 (4.81)	3.04 (1.81)
Stability group	17.25 (3.18)	5.20 (1.37)	12.12 (5.08)	3.62 (1.85)

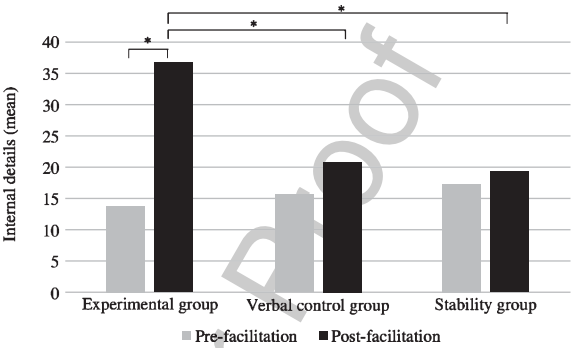

Fig. 2. Mean number of internal details for the AM condition for the three groups of MS patients in pre- and post-facilitation (*significant difference).

The experimental group analysis showed an increase of the mean number of internal details in post-facilitation ($p < 0.001$), together with an increase of the mean number of external details ($p = 0.01$). However, in both pre- and post-facilitation, an equivalent number of internal and external details was observed (pre-facilitation: $p = 0.08$; post-facilitation: $p = 0.20$). In other words, a similar proportion of internal and external details was displayed across time, with a lower number of internal details relative to external details.

With regard to the verbal control group, irrespective of the type of detail considered, no significant changes were reported (internal details, pre- vs. post-facilitation: $p = 0.44$; external details, pre- vs. post-facilitation: $p = 0.83$). In addition, no significant

difference between the mean number of internal vs. external details was displayed for either the pre- ($p = 0.84$) or the post-facilitation ($p = 0.99$) sessions.

Within the stability group, the mean number of internal ($p = 0.99$) and external details ($p = 1.00$) remained stable across time. While a lower number of internal details (vs. external details) was reported in this group before facilitation ($p = 0.01$), this difference disappeared in post-facilitation ($p = 0.15$), showing an equivalent number of internal and external details.

3.3.2. Mean total rating

Performance for the mean total rating over time for the different groups of MS patients are displayed in the Fig. 3.

A significant Group × Time interaction, $F(2, 37) = 26.51$, $p < 0.001$, $\eta^2_P = 0.58$ was shown. Before facilitation, equivalent rating scores were observed between the three groups (experimental vs. verbal control group: $p = 0.99$; experimental vs. stability group: $p = 0.38$; verbal control vs. stability group: $p = 0.83$). Between-group comparisons showed that after facilitation, the experimental group obtained significantly higher mean total rating than the verbal control ($p = 0.001$) and the stability groups ($p < 0.001$). However, no significant difference between the verbal control and the stability groups was evidenced at the second AI assessment ($p = 0.99$). Within group comparisons revealed a significant increase of the mean total rating within the experimental group ($p < 0.001$) and the verbal control group ($p = 0.03$) in post-facilitation, but not in the stability group ($p = 0.30$). In other words, it seemed that the verbal control group exhibited intermediate performance between the experimental and the stability groups after facilitation for the mean total rating measure.

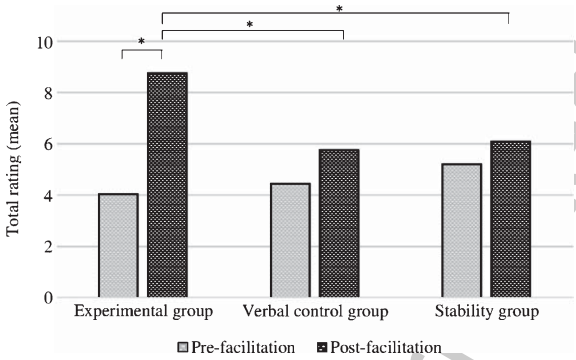

Fig. 3. Mean total rating for the AM condition for the three groups of MS patients in pre- and post-facilitation (*significant difference).

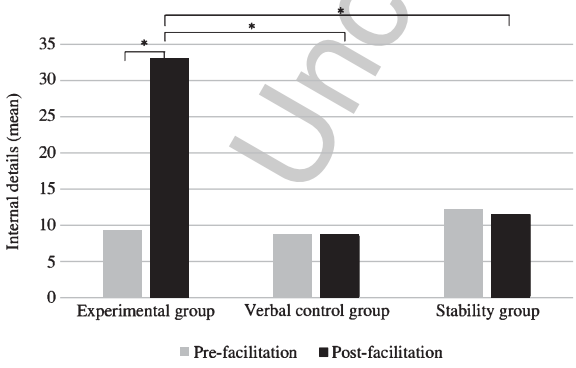

Fig. 4. Mean number of internal details for the EFT condition for the three groups of MS patients in pre- and post-facilitation (* significant difference).

3.4. Pre- and post-facilitation EFT performance

3.4.1. Mean number of internal and external details

Turning to EFT performance, the mean number of internal details provided by each group of patients over time are shown in the Fig. 4.

A significant Group × Time × Detail interaction was observed, $F(2, 37) = 7.27$, $p = 0.002$, $\eta^2_P = 0.28$. Before facilitation, equivalent performance was observed between the three groups for the mean number of internal details (experimental vs. verbal control group: $p = 1.00$; experimental vs. stability group: $p = 0.99$; verbal control vs. stability group: $p = 0.99$) and for the mean number of external details (experimental vs. verbal control group: $p = 0.99$; experimental vs. stability group: $p = 0.56$; verbal control vs. stability group: $p = 0.99$). After facilitation, a greater number of internal details was observed in the experimental group, relative to the verbal control and the stability groups ($p = 0.001$ in both cases). No significant difference was found between the verbal control and the stability group regarding the mean number of internal details at the second AI assessment ($p = 0.99$). Regarding the external details, no significant difference was reported between the three groups, showing the same pattern of results than in pre-facilitation (experimental vs. verbal control group: $p = 1.00$; experimental vs. stability group: $p = 0.99$; verbal control vs. stability group: $p = 0.99$).

Turning to the within group comparisons, a significant increase of the mean number of internal details

was observed in the experimental group in post-facilitation ($p < 0.001$), but no changes were observed for the mean number of external details across time ($p = 0.89$). While an equivalent number of internal and external details was found in the experimental group before facilitation ($p = 0.08$), a greater number of internal (vs. external) details was provided after facilitation ($p = 0.01$). Irrespective of the type of detail considered, no significant change was reported within the verbal control group (internal details, pre- vs. post-facilitation: $p = 1.00$; external details, pre- vs. post-facilitation: $p = 1.00$). Patients from the verbal control group provided a lower number of internal (vs. external) details in both pre- ($p = 0.01$) and post-facilitation ($p = 0.009$) sessions. Within the stability group, the mean number of internal details ($p = 1.00$) and of external details ($p = 0.99$) remained stable across time. Irrespective of the time of assessment, a greater number of external (vs. internal) details was found in the stability group (pre-facilitation: $p < 0.001$; post-facilitation: $p < 0.001$).

3.4.2. Mean total rating

Performance before and after facilitation for each group of patients regarding the mean total rating obtained for the EFT condition are illustrated in the Fig. 5.

Statistical analysis evidenced a main effect of Group, $F(2, 37) = 6.78$, $p = 0.003$, $\eta^2_P = 0.26$, which showed that irrespective of the time of assessment, a higher rating score was observed for the experimental group, relative to the verbal control group ($p = 0.009$). In parallel, the stability group displayed equivalent performance than the experimental group ($p = 0.06$) and the verbal control group ($p = 0.51$).

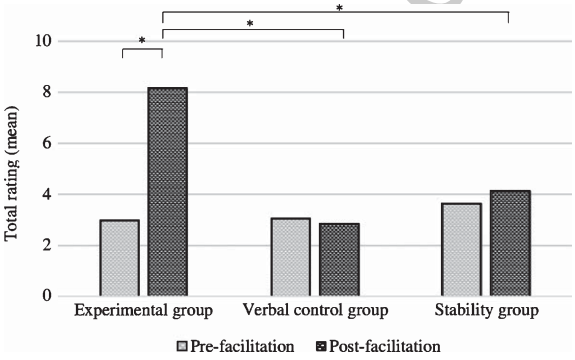

Fig. 5. Mean total rating for the EFT condition for the three groups of MS patients in pre- and post-facilitation (*significant difference).

When the analysis took all patients as one group, a main effect of Time was found, $F(1, 37) = 30.73$, $p < 0.001$, $\eta^2_P = 0.45$, with higher mean total rating obtained at the second EFT assessment. Nevertheless, as evidenced by the significant Group × Time interaction, $F(2, 37) = 29.53$, $p < 0.001$, $\eta^2_P = 0.61$, this result mainly reflects the increase of the total rating score in post-facilitation for the experimental group ($p < 0.001$), since no significant changes between the two sessions of assessment was observed for the verbal control and the stability groups ($p = 0.99$ and $p = 0.94$, respectively). While no significant difference was initially observed between the three groups of patients before facilitation (experimental vs. verbal control group: $p = 1.00$; experimental vs. stability group: $p = 0.97$; verbal control vs. stability group: $p = 0.98$), after facilitation, the experimental group obtained significantly higher mean total rating than the two other groups ($p < 0.001$ in both cases), whereas the verbal control and the stability groups showed equivalent score ($p = 0.76$).

3.5. Post-facilitation results for the stability group

Ten patients from the stability group (from the initial group of 13) underwent the MVI programme after the second AI assessment.

Regarding the AM performance, a higher number of internals details was observed in post-facilitation, relative to pre-facilitation, $t(9) = -6.31$, $p < 0.001$. Similar results were obtained for the mean total rating, with higher scores in post- than in pre-facilitation, $t(9) = -10.03$, $p < 0.001$. A significant increase of the mean number of external details was also observed after facilitation, $t(9) = -2.65$, $p = 0.02$.

Turning to the EFT performance, results showed an increase of the mean number of internal details provided in post-, relative to pre-facilitation, $t(9) = -3.54$, $p = 0.006$. In addition, a higher mean total rating was obtained after facilitation (versus before facilitation), $t(9) = -5.01$, $p < 0.001$. No significant change was observed for the mean number of external details, $t(9) = -0.78$, $p = 0.45$.

3.6. Comparison of AM and EFT performance over time

For the patients who benefited from the MVI programme, this complementary analysis explored the potential different effect of the programme on the

episodic measures of AM and EFT performance. Regarding the mean number of internal details, no main effect of Temporal direction was showed, $F(1, 25) = 2.90$, $p = 0.10$, $\eta^2_P = 0.10$. However, a main effect of Time was displayed, $F(1, 25) = 117.47$, $p < 0.001$, $\eta^2_P = 0.82$, with a higher number of internal details provided in post-facilitation, whatever the temporal direction. No significant Temporal direction x Time was obtained, $F(1, 25) = 0.96$, $p = 0.33$, $\eta^2_P = 0.03$.

Turning to the mean total rating, a higher score was obtained for the past condition than for the future condition, irrespective of the time of assessment, as revealed by a main effect of Temporal direction, $F(1, 25) = 14.35$, $p < 0.001$, $\eta^2_P = 0.36$. A main effect of Time was also obtained, $F(1, 25) = 195.36$, $p < 0.001$, $\eta^2_P = 0.88$, showing an increase of the mean total rating in post-facilitation. The Temporal direction × Time interaction did not reach the statistical threshold, $F(1, 25) = 2.79$, $p = 0.14$, $\eta^2_P = 0.08$.

3.7. Long-term follow up assessment

Descriptive results of the mean AI scores obtained immediately after the facilitation and at the long-term follow up assessments for the AM and EFT conditions are presented in Table 4. The present statistical analyses were conducted on the 15 patients re-assessed to date (on a total of 27 patients who benefited from the MVI programme).

Regarding the AM condition, the analysis of treatment benefit robustness after the MVI programme showed no significant difference between the post-facilitation session and the six months assessment for the mean number of internal details, $t(15) = -0.24$, $p = 0.81$, and the mean total rating, $t(15) = -1.08$, $p = 0.29$.

Turning to the EFT condition, a slight decrease of the mean number of internal details provided by the patients between the post- and the long-term assessment was observed, $t(15) = 2.39$, $p = 0.03$. Nevertheless, a complementary analysis revealed that the mean number of internal details provided at the long term assessment remained significantly higher than in pre-facilitation, $t(15) = -4.16$, $p = 0.001$. Regarding the mean total rating, performance were stable over time, $t(15) = 0.53$, $p = 0.60$.

Moreover, in every case, whatever the temporal direction, the mean number of internal details and the mean total rating remained above the mean scores obtained by the group of healthy controls, which initially determined the presence of an AM/EFT impairment (Ernst et al., 2012).

Table 4
Mean AI scores (and standard deviation) for the AM and EFT condition obtained at T1 (no delay) and T2 (6 month) post-facilitation

	No delay post-facilitation	Six month-follow up
AM condition		
Internal details	38.16 (7.77)	38.85 (11.94)
Rating	9.15 (1.37)	9.67 (2.04)
EFT condition		
Internal details	35.96 (22.65)	28.95 (16.88)
Rating	8.04 (2.36)	7.71 (3.21)

3.8. Individual benefits following the MVI programme

Importantly, beyond the results obtained at the group level, a particular emphasis was also made on the individual benefit of the MVI programme. As the presence of an AM/EFT impairment was initially established based on our normative database, for each MS patient, the mean number of internal details and the mean total rating obtained after facilitation were compared to the normative scores. Twenty-five out of the 27 MS patients (experimental and stability groups), who underwent the MVI programme showed a normalisation of their AM and EFT performance. For the AM condition, one patient from each group showed scores below the threshold, and for the EFT condition, two patients from the stability remained under the normative threshold.

3.9. Semi-structured interview

3.9.1. Pre-facilitation comments

Before the facilitation programme, the great majority of patients expressed difficulties for AM and EFT, which appeared as undifferentiated between the groups of patients.

Regarding their comments about the AI assessment, for the AM condition, patients evoked mainly difficulties to retrieve/select a specific event, with further difficulties to provide details about memories. This was accompanied by low emotional reviviscence and a feeling of "emotional distance" with their memories. Moreover, when assessing the vividness and the mental visual quality of their memories, patients expressed that their memories were like some "flashes"

or "motionless pictures". For their self-assessment in the context of everyday life, their comments largely overlapped with those gathered for the AI performance. The great majority of patients also mentioned concrete life situations, in which they felt uncomfortable due to the fact of forgetting or having difficulties to remember some details or more simply, having doubts about their memories.

Concerning EFT, we obtained similar feedback than for the past events with a particular difficulty to find future events that were not memories. This led the great majority of patients to find the EFT condition harder than the AM condition. Moreover, patients found difficult to focus on a future event and to elaborate on it since a lot of possibilities could be considered. With regard to everyday life, albeit present, less concrete examples of daily life difficulties explicitly related to EFT impairment were provided in comparison with memory problems.

3.9.2. *Post-facilitation comments*

3.9.2.1. MVI facilitation programme. For the patients who underwent the MVI programme (experimental and stability groups), post-facilitation comments unanimously acknowledged a greater easiness of retrieval/imagination, with more detailed memories/projections. A major change was also recounted concerning the vividness of past and future events, which became dynamic "mental films", with reports about motions present in their mental simulations. Furthermore, a greater emotional intensity and feeling of re/pre-living events were mentioned by the patients (also qualitatively noticed by the neuropsychologist during some events' evocation). No differential effect of the programme on AM and EFT was noticed by the patients.

Regarding the benefits in daily life, the same observations than those expressed during the AI testing were reported, and a few patients commented that they needed more time to be sure about of the benefits of the programme in everyday life. In general, an effective treatment receipt seemed to have been obtained since the patients acknowledged an easy use and transfer of this technique in their daily life functioning. Additionally, spontaneous feedback of some patients' relatives also supported the effective transfer and benefits of the MVI programme in daily life.

The long-term follow-up assessment led to the same observations and most of the patients reported that the further use of this technique was easy and now spontaneously carried out. Moreover, at six months, several patients also reported that they had a more general feeling of self-confidence in social and professional situations, with a feeling of internal locus of control and vitality. We provided here illustrations of some patients' comments:

Patient FZ: "It made it possible for me to learn how to visualise things, and by so doing, I am able to control them in a different way, past or future, I can control them. It sounds very positive to me. [. . .] We realise that we knew lots of things, but that we were not aware that we knew them, hidden memories [. . .]. It helps a lot.

Patient CC: "Actually, I had never imagined that I could tell so many things . . . It's as if all these things had been in a box, and the box put aside somewhere. Since I don't need it, I let it where it is. And if I need to remember something, I will search the box, I will open it and start to look inside".

Patient PP: "Yes, there are more details than the last time. Actually, it's as if I am wearing reading glasses now in comparison with the last time. It used to be more or less blurred, but now, it seems more fluent to me, it comes very quickly".

Patient IB: "Before I was panicking, because I knew that I would be unable to remember. I'm not panicking anymore. As we get along the sessions, I have the feeling that I live the thing. I'm in, I live it, and I'm in my thing. I feel less stressed, more self-confident and so, for the birthday, I haven't thought about it before, but now, it is the moment and I will think about it, but serenely".

Patient MM: "I see something, and something else in relation to the first thing comes with it. A memory comes to my mind and I've noticed that I can detail it. I have more memories. If I remember something, I can focus on that, on the memory, and look for details. I'm able to do that. Even for emotional details. I'm positive that from now on, it will help me more and more. [. . .] It's easier to make a decision, whatever it is. I used to hesitate a lot, more than presently. Now, if I don't want something, I know that I don't want it, and I know what I want . . . for me, it's obvious. I wouldn't have dared before. So, all in all, it has restored my self-confidence, that's what I feel . . . It's true, I can feel OK with myself again".

Patient NK: "I think that I found it quicker and it was clearer than the first time we went through these exercises. Even when I remembered a scene, before,

I saw it from far away, while now, the feeling is that I've relived some events at the present time. It's true that sometimes, you realise that the sessions are gaining their own place. It's not every time but sometimes, you've gone a bit of the path, it's done without really realising it. I would never have thought that I could use little tricks like this. It's something that could help me anyway in my life".

Patient DR: "Sometimes, people were surprised because I was able to remember dates, and things like that, but when I became ill, all that was finished, I started having difficulties to keep being myself, I've started... There were things that I had really forgotten. [...] When you came to see me, I thought it providential. Because it was really scaring.... So for me, it's all benefit. I realise that it helped me to be more efficient. I do it more naturally, I ask myself less questions. It's natural, like a mechanism I have by now, a process that I've integrated. And I've noticed that if I don't remember one detail, I go for another, and remembering then three others details, suddenly, something triggers and I can come back to the first point".

Patient VW: "I have the feeling that I'm more the actress of my own life now, whereas before, I was present at some point, but I failed to feel that it was me who was writing the story. I was present, people were talking about something but I had difficulties to take part in, I had difficulties to participate in conversations. Now, I have the feeling that, when a conversation starts, I have something to say, I'm more engaged in the conversation".

3.9.2.2. Verbal control programme. Although no reliable statistical evidence of improvement was noticed in the verbal control group, a general impression that the second AI testing was easier than the first one was reported by the patients. This was explicitly related by the patients to the fact that the exercise was not new for them. However, no obvious changes were mentioned regarding the difficulty to retrieve/imagine specific past and future events, the amount of details, emotional intensity or vividness of the personal episodes during the AI assessment. Concerning their comments on everyday life situations, no clear benefit in relation to memories or future projections was reported. Nonetheless, several patients acknowledged that they felt more ready to pay attention since they had the impression that the programme had helped them to better concentrate when required.

4. Discussion

The aim of the present study was to explore the possibility to jointly improve AM and EFT functioning in RR-MS patients through the use of a MVI-based facilitation programme and in the context of a randomised controlled clinical trial. While previous investigations already demonstrated AM improvement following neuropsychological interventions in various clinical conditions (Berry et al., 2007; Pauly-Takacs et al., 2011; Neshat-Doost et al., 2013; Moradi et al., 2014) and notably in RR-MS patients (Ernst et al., 2012, 2013), this study is the first, to our knowledge, to have extended this finding to EFT abilities.

As expected, our results demonstrate a benefit of the MVI programme on the simulation of personal past and future events, expressed by an enhancement of the amount of episodic details and of their qualitative episodic richness. Overall, no differential improvement was observed for AM and EFT conditions, which seemed to benefit both from the MVI programme. The increased amount of episodic details was accompanied by an increased number of external details for the AM condition, but not for the EFT condition. How to explain the increase of external details in AM? At a clinical level, it is likely that this was due, at least partially, to a side effect, so to speak, of the facilitation programme, which must have encouraged the patients to provide more information about AMs. In the same vein, James et al. (1998) suggested that older adults also tended to provide additional semantic information about their memories to clarify points when facing to a young examiner with different life experiences. Moreover, we observed that after facilitation, our patients shared their impressions, which arose while recollecting. Importantly, they would make spontaneous comments such as 'The last time I have talked about that with X, I didn't remember all these things; I would have never thought I would'. Other comments dealt with the personal significance of the events. After facilitation, patients were also more prone to evoke other memories related to the central event that came to their mind in the flow of recollection (e.g. a patient evoked a car accident as the central event and remembered additional episodic details, belonging to different episodes that were directly related to the accident, such as her appointment with her insurer, or with the mechanic). The latter clarification is doubly important since it shows the effects of the programme and also illustrates a different level of explanation

concerning the increased number of external details. Indeed, as stated above, we follow Levine et al.'s (2002) AI method, including their scoring instructions. As it happens, all the episodic recollections not belonging in the central event are recorded as being "external details", because not directly related to the central episodic even though there are episodic in nature. To account for the difference in the increase of external details in AM and EFT in post-facilitation, we would like to remind that the EFT condition is cognitively considerably more demanding than AM, especially due to executive processes. Moreover, the EFT impairment is more severe than the deficit shown on AM, in our patients (Ernst et al., 2014a). The absence of an increase of external details in the EFT condition is most likely related to the difficulty to make similar comparisons of previous attempts to evoke this particular event in daily life or to mention thematically or causally related future events.

Our findings are also supported by the normalisation of AM and EFT scores, namely the mean number of internal details, in the great majority of our MS patients, relative to our normative database (which initially established the presence of an impairment). An additional main finding is that this performance increase in the context of AM/EFT assessment was also accompanied with a perceived benefit of this technique by patients in their everyday life. Indeed, patients mentioned an easy use and transfer of the MVI strategy in their daily functioning. This last point probably contributed to the general good maintenance of the benefit also observed at the long-term follow up. Nevertheless, regarding the long-term reassessment of EFT performance, the mean number of internal details showed a slight decrease, even if this score remained superior to the normative threshold and to the pre-facilitation performance. Clinically, considering that the last step of the MVI programme focused on the construction of self-involved fictitious scenes, it is possible that immediately after facilitation, following the dynamic established through the programme, an inflated performance could be observed for the EFT condition. This same effect could not be observed for the AM condition, since for the past, contrary to the future events, restrictions regarding the details associated to the event are present to keep a good correspondence with the initial event. However, since no significant change of the qualitative episodic richness of future events was noticed over time, it seems that the general improvement of EFT performance remained present at six months.

Importantly, this enhancement did not seem due to a learning effect on the AM/EFT test, since no significant change was observed when the test was carried out twice, in an equivalent timeframe and with no intervention in-between (the stability group). Furthermore, the AM/EFT improvement was not likely related to a 'nursing effect', since MS patients who followed the sham verbal facilitation programme showed no evidence of enhanced performance in post-facilitation. Moreover, AI scores from the verbal control group remained below those obtained by MS patients after the MVI programme but were equivalent to those obtained by the stability group, at the second AI assessment.

Our results complete those previously obtained by Ernst and colleagues (2012, 2013), by controlling the methodological issues. The present results, and particularly the successful transfer of the benefits to everyday life, were probably helped by the fact that AM and EFT are ubiquitous in our daily life and rely on personal real-life events. The selectivity of the deficit may also have helped the good completion of the facilitation sessions, and the further use and integration of the strategy in daily life (Evans et al., 2003).

Overall, based on our findings, we suggest that early neuropsychological interventions in MS patients seem to lead to positive outcomes for AM and EFT functioning, cognitive functions which seemed both particularly sensitive to MS pathology (Ernst et al., 2014a). As previously mentioned, the programme's origins were clinically grounded observations regarding AM impairment in RR-MS patients and, the extension of this deficit to EFT together with the deleterious impact of these difficulties in daily life, reinforced the importance of the development of this kind of interventions in MS patients. It is possible that the use of early interventions of this kind could be decisive to compensate or delay the expression of cognitive impairment, which have an important negative impact on quality of life in MS patients (Chiaravalloti & DeLuca, 2008).

From a theoretical perspective, the results show that a single cognitive strategy can contribute to AM and EFT improvement, which support the strong relationships between the two temporal directions (see Schacter et al., 2012 for a review). Our findings also contribute to demonstrate that scene construction is a key cognitive process in mental time travel (Hassabis & Maguire, 2007). The latter point is related to the authors' hypothesis that the ability of mentally generating and maintaining a complex and coherent

scene constitutes the main core process of AM and EFT. Scene construction would require the reactivation and retrieval of a range of fragments of information (semantic, contextual, and sensory elements), which are subsequently integrated into a coherent spatial context for their further mental manipulation and visualisation (Hassabis et al., 2007). From a neuroanatomical standpoint, scene construction is supported by a distributed brain network, involving the hippocampus, the parahippocampal gyrus, the retrosplenial cortex, the posterior parietal region and the ventromedial prefrontal cortex (Hassabis et al., 2007). On these bases, whether scene construction is the key cognitive process at the origin of the AM/EFT improvement in our MS patients, the next question would concern the functional underpinnings of this enhancement. Indeed, it could be hypothesised that increased brain activations would be observed within the scene construction core brain network, which in turn would lead to the question regarding the similarities and differences that could be observed between AM and EFT neural networks following their improvement. In fact, while AM and EFT share a common core brain network, several investigations have highlighted discrepancies in the recruitment of some specific brain areas and in their sensitivity to phenomenological properties of past and future events in healthy subjects (see Schacter et al., 2012 for a review). In particular, increased brain activations have been reported in the frontal and medial temporal lobe regions during the imagination of future events. To our knowledge, no study to date has explored the potential similarities and differences between AM and EFT brain networks in the context of brain activation changes induced by an effective neuropsychological intervention in patients. In the case of MS patients, studies on the functional underpinnings of AM impairment remain very scarce, and no study to date has explored the functional changes associated with EFT impairment in these patients. Only one of our previous studies, to our knowledge, explored the functional brain activation changes associated with AM impairment and showed that functional changes were mainly observed in the bilateral prefrontal regions (Ernst et al., 2014b). Investigations along these lines could contribute to the identification and understanding of the brain regions sustaining both impaired and improved AM/EFT performance in MS patients.

In summary, the major finding of this study is that AM and EFT impairment could be efficiently improved by means of a facilitation programme and that the use of a MVI strategy seemed easily integrated and resulted in significant benefits in their daily life functioning. More generally, we hope that this study and its positive outcomes could encourage future investigations in different clinical settings. As mentioned above, the facilitation programme requires to be probed in other MS subtypes or different clinical conditions presenting a similar profile of AM and EFT impairment. The clinical interest would be important bearing in mind the central roles of AM and EFT in everyday life, and more generally in well-being (Szpunar, 2010; Schacter et al., 2012).

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Declaration of interest

The authors report no declaration of interest.

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