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UNIVERSITY OF STRASBOURG

ECOLE DOCTORALE DES SCIENCES DE LA VIE ET DE LA SANTE

Cognitive Neuropsychology and Physiopathology of Schizophrenia (INSERM U 1114)

DOCTORAL DISSERTATION

Prepared by Alexandra ERNST

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Spontaneous and induced cerebral plasticity during autobiographical memory and episodic future thinking performance in relapsing-remitting multiple sclerosis patients

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"There cannot be a philosophy, there cannot even be a decent science, without humanity"

J. Bronowski, *The Ascent of Man*, 1973, p.18

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ABSTRACT

Based on a double approach in clinical neuropsychology and neuroimaging, the aim of the present thesis was twofold: (i) to study relapsing-remitting multiple sclerosis (RR-MS) patients presenting with autobiographical memory (AM) and episodic future thinking (EFT) impairment, and (ii) to improve AM and EFT functioning in the same patients.

To that end, the first corpus of research focused on the study of AM and EFT impairment. A comparable degree of deficit in both temporal directions in RR-MS patients, relatively to healthy controls was shown in the clinical investigation. Moreover, and similarly to the healthy subjects, AM performance remained higher than EFT performance. At the neuroimaging level, impairment was expressed by spontaneous, increased and bilateral brain activity in key brain regions of the AM and EFT networks, for both the construction and elaboration phases of personal events. The enhanced brain activations were particularly apparent during the EFT task and during the construction phase of personal events, again comparatively to healthy controls.

Based on these results, the second set of studies explored the possibilities of rehabilitating AM and EFT accessing processes in these patients. Clinically, the use of a mental visual imagery (MVI)-based facilitation programme led to AM and EFT improvement, with an effective transfer and long-term robustness in our patients' everyday life functioning. AM and EFT seemed to benefit similarly from the MVI programme. Importantly, this positive effect was not attributable to nursing or learning effects. FMRI showed that regarding AM, the clinical benefit was accompanied with increased reliance on brain regions sustaining self-referential process together with decreased reliance of those reflecting an effortful research process. EFT's clinical improvement was expressed by increased reliance on brain regions associated with contextual processing, personal semantics, multimodal integration and binding processes.

Overall, the present work has documented (i) the effectiveness of cognitive facilitation for AM and EFT, which was at the centre of the clinical endeavour of this thesis. (ii) The occurrence of spontaneous and induced brain plasticity changes during AM and EFT performance in RR-MS patients, which were sustained by both common and distinct cerebral mechanisms.

RESUME DETAILLE EN FRANCAIS

1. Introduction et objectifs

La sclérose en plaques (SEP) est une pathologie neurologique caractérisée par une symptomatologie diversifiée et variable selon les patients, incluant notamment des troubles cognitifs pouvant affecter la mémoire antérograde, les fonctions exécutives et attentionnelles, ainsi que la vitesse de traitement de l'information (Chiravalloti et DeLuca, 2008). Un ensemble d'études a par ailleurs montré que ces déficits cognitifs sont fréquemment accompagnés d'un phénomène de plasticité cérébrale spontanée visant à compenser, mais pas toujours de façon efficace, ces troubles cognitifs. Ce phénomène se traduit notamment par des activations cérébrales plus intenses dans des régions normalement sollicitées par des sujets sains et/ou le recrutement de structures cérébrales alternatives, souvent controlatérales (Hulst et al., 2012).

En parallèle, plusieurs études ont également permis le développement de programmes de réhabilitation cognitive visant à compenser ces troubles cognitifs dans la SEP (O'Brien et al., 2008, pour une revue). Néanmoins, la plupart des études à l'heure actuelle se sont focalisées sur la prise en charge des déficits attentionnels ou de la mémoire antérograde, avec des résultats variables selon les études. De plus, cette revue a également mis en évidence la nécessité de méthodologies plus rigoureuses pour évaluer l'efficacité des prises en charge cognitive, incluant en particulier un groupe de patients bénéficiant d'une prise en charge de contrôle (i.e. sans bénéfice clinique attendu), mais aussi un report plus détaillé des caractéristiques des patients inclus et de la prise en charge proposée.

Au-delà des bénéfices sur le plan clinique, certains études ont exploré les corrélats neuro-fonctionnels de ce bénéfice, dans un contexte de plasticité cérébrale induite. Dans le cas de la SEP, des travaux de ce type ont été menés dans le contexte de prise en charge de déficits attentionnels (Penner et al., 2006 ; Ceresa et al., 2013) ou de la mémoire antérograde (Chiaravalloti et al., 2012 ; Leavitt et al., 2012), ainsi que pour des programmes d'interventions non-spécifiques (Sastre-Garriga et al., 2011 ; Parisi et al., 2012 ; Filippi et al., 2012). Malgré le peu d'études menées à ce jour, des données convergentes ont été obtenues,

montrant des changements d'activation cérébrale dans des régions cérébrales spécifiques accompagnant le bénéfice clinique chez ces patients après la réhabilitation.

Plus récemment, une atteinte de la mémoire autobiographique a aussi été décrite dans la SEP (Paul et al., 1997 ; Kenealy et al., 2002 ; Müller et al., 2013), mais peu de consensus émergeait de ces premiers résultats. Dans ce contexte, notre première étude (Ernst et al., 2013) a permis d'établir de façon plus contrôlée la présence d'une atteinte de la mémoire autobiographique chez des patients SEP de forme rémittente (SEP-R) et non-dépressifs, déficit qui serait en lien avec un défaut des stratégies de récupération du souvenir (et non d'une dégradation des traces mnésiques), sous-tendues par les régions préfrontales (Svoboda et al., 2006 ; Botzung et al., 2008). Sur ces bases, un programme de réhabilitation cognitive visant à faciliter l'accès aux souvenirs et à en améliorer la qualité épisodique a été mis en place. Ce programme, basé sur le rôle central de l'imagerie mentale visuelle dans la mémoire autobiographique (Greenberg et Rubin, 2003) et sur les antécédents d'utilisation de l'imagerie mentale visuelle comme méthode de réhabilitation de la mémoire antérograde chez des patients SEP (Chiaravalloti et al., 2005), a donné lieu à des résultats positifs auprès de 10 patients SEP-R lors d'une étude pilote (Ernst et al., 2013).

D'un point de vue théorique, en lien avec le concept de voyage mental dans le temps, la mémoire autobiographique fonctionne de concert avec la capacité de projection dans l'avenir (Suddendorf et Corballis, 2007). Ainsi, la mémoire autobiographique et la projection dans l'avenir impliquent de nombreux processus cognitifs en commun, ce qui se traduit par un chevauchement important entre les patterns d'activations cérébrales observés dans ces deux composantes (Schacter et al., 2012, pour une revue). Il en résulte qu'une atteinte simultanée de la mémoire autobiographique et de la projection dans l'avenir est fréquemment retrouvée dans des populations cliniques (Tulving, 1985 ; Klein et al., 2002 ; D'Argembeau et al., 2008 ; Addis et al., 2009). Toutefois, concernant la SEP, à notre connaissance, aucune étude à ce jour n'a exploré les capacités de projection dans l'avenir de ces patients.

Sur ces bases, les objectifs de la présente étude se sont organisés autour de plusieurs axes :

(i) l'exploration plus approfondie du déficit de mémoire autobiographique, en incluant des données en neuroimagerie

(ii) l'extension du premier objectif à l'étude de la projection dans l'avenir et de ses liens avec la mémoire autobiographique dans la SEP

(iii) l'évaluation de l'efficacité de notre programme de réhabilitation sur la mémoire autobiographique et la projection dans l'avenir, en contrôlant la présence de facteurs confondants tels qu'un effet de « prise en charge » ou d'apprentissage au test évaluant le voyage mental dans le temps

(iv) et d'explorer si ce bénéfice clinique pouvait également se traduire par des changements d'activation cérébrale induits par la prise en charge lors de l'évocation d'évènements passés et futurs.

Ces différents objectifs ont été adressés à travers huit études, dont les résultats principaux seront présentés après une présentation de la méthodologie générale employée.

2. Méthodologie générale

Sur le plan comportemental, la mémoire autobiographique et la projection dans l'avenir ont été évaluées par le biais d'une version adaptée de l'Autobiographical Interview (AI ; Levine et al., 2002), permettant l'évaluation de la composante future et l'utilisation de mots indice (Addis et al., 2008, 2009). L'AI était complétée par un entretien d'auto-évaluation des performances (basé sur Sutin et Robins, 2007 et Shevil et Finlayson, 2006) visant à obtenir des données qualitatives sur le fonctionnement de la mémoire autobiographique et de la projection dans l'avenir, en situation de test et dans la vie quotidienne.

Au niveau de la neuroimagerie, les participants complétaient une tâche de mémoire autobiographique, une tâche de projection dans l'avenir et une tâche sémantique de contrôle. Basé sur Addis et al. (2007), une distinction entre les phases de construction (i.e. récupération/création initiale de l'événement pour la mémoire autobiographique/projection dans l'avenir versus génération mentale d'une phrase pour la tâche de contrôle) et d'élaboration (i.e. recherche/imagination de détails épisodiques pour la mémoire autobiographique/projection dans l'avenir versus répétition mentale de la phrase générée avec inclusion de mots synonymes pour la tâche de contrôle) était effectuée. En parallèle, des images de tenseur de diffusion ont aussi été acquises afin d'obtenir des données structurales (en cours de traitement, non mentionnées dans la section résultats). Chaque tâche a été développée en deux versions pour les sessions pré- et post-facilitation.

Concernant la réhabilitation cognitive, deux programmes ont utilisés lors de cette étude, présentant un fonctionnement général similaire pour garantir les comparaisons :
(i) le *programme expérimental*, basé sur l'imagerie mentale visuelle et dont l'objectif général est pour le patient d'apprendre à construire des scènes mentales détaillées à partir d'items verbaux. Ce programme comportait les étapes de screening (i.e. vérification de l'absence de troubles majeurs de l'imagerie mentale visuelle), de visualisation externe (i.e. visualisation et description d'items isolés), de construction (i.e. scènes impliquant divers personnages) et de visualisation de soi (i.e. scènes dans lesquelles le patient est l'acteur principal).
(ii) le *programme verbal de contrôle*, visant à vérifier l'absence d'un effet « prise en charge » et pour lequel aucune/une moindre amélioration des capacités de voyage mental dans le temps est attendue, en comparaison au programme expérimental. L'objectif général de ce programme était de travailler sur la structuration de l'information à partir de textes proposés au patient. Les différentes étapes de ce programme étaient la discussion externe (i.e. focalisée sur la structure du texte), la construction (i.e. élaboration d'une discussion sur le thème du texte) et la discussion avec implication personnelle (i.e. élaboration d'une discussion en donnant son avis personnel).

Tous les participants recrutés (patients SEP et sujet sains) étaient âgés de 25 à 65 ans, droitiers (pour ceux prenant part aux sessions de neuroimagerie), sans pathologie neurologique (autre que la SEP pour les patients) et psychiatrique. Tous les patients SEP inclus étaient de forme rémittente et avec un score EDSS ≤ 5.
Dans un premier temps, un bilan neuropsychologique de ligne de base était complété par les patients afin d'exclure ceux présentant des troubles cognitifs sévères (autres que de la mémoire autobiographique/projection dans l'avenir) et/ou des signes majeurs de dépression.
Seuls les patients présentant des scores déficitaires à l'AI (en comparaison à une base de données normatives établie par notre équipe auprès de 15 sujets de contrôle) étaient ensuite inclus dans l'étude et répartis de façon aléatoire dans les groupes suivants : (i) le *groupe expérimental* bénéficiant du programme expérimental basé sur l'imagerie mentale visuelle ; (ii) le *groupe « placebo »* bénéficiant du programme verbal de contrôle ; et (iii) le *groupe stabilité* dont l'objectif était de vérifier l'absence d'un effet d'apprentissage à l'AI, avec réalisation de l'AI à deux reprises, sans intervention intermédiaire. A noter que pour des

raisons éthiques, les patients des groupes placebo et stabilité avaient ensuite la possibilité de compléter le programme IMV.

Afin d'évaluer les bénéfices de la réhabilitation, les évaluations comportementales (AI et entretien d'auto-évaluation) et en neuroimagerie étaient donc répétées à la fin du programme de prise en charge pour le groupe expérimental et placebo. De même, une réévaluation à long terme des bénéfices était réalisée à six mois post-réhabilitation pour les patients ayant suivi le programme IMV. Un récapitulatif de la procédure suivie par les patients est illustré par la Figure 1. En parallèle, des sujets sains appariés en âge, sexe, durée de scolarisation et quotient intellectuel verbal ont été recrutés afin de compléter l'AI et une session de neuroimagerie.

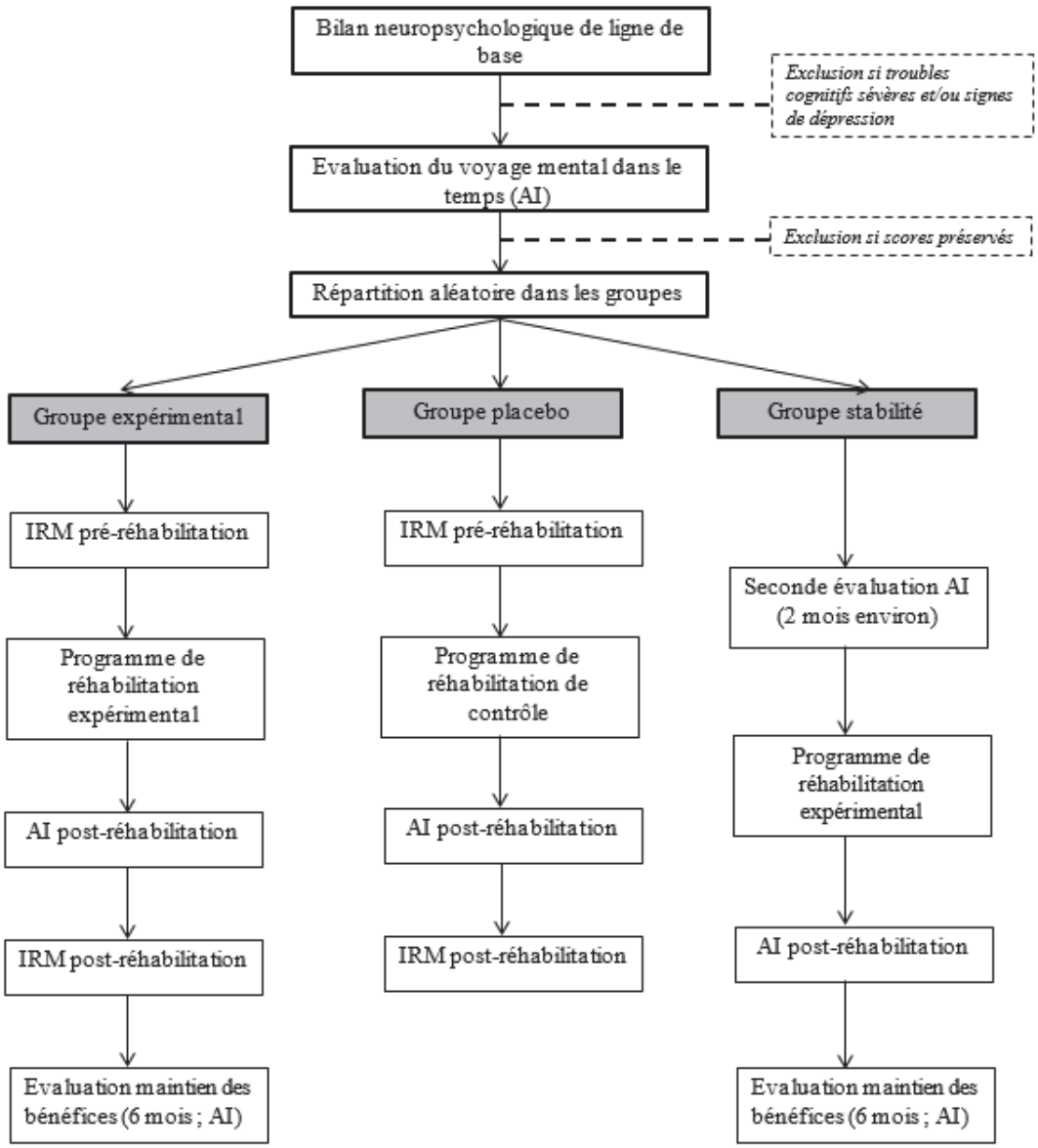

Figure 1. Récapitulatif de la procédure expérimentale

3. Partie expérimentale et résultats

Dans la section suivante, les résultats principaux de l'ensemble des études menées au cours de la thèse seront présentés de façon indépendante.

Etude 1 (*Journal of the Neurological Sciences*, en revision mineure)

L'objectif principal de cette étude était d'évaluer les performances de mémoire autobiographique et de projection dans l'avenir de 39 patients atteints de SEP, en comparaison d'un groupe de 34 sujets de contrôle.

Les résultats obtenus à l'AI ont permis de corroborer la présence d'une atteinte simultanée de la mémoire autobiographique et de la projection dans l'avenir chez les patients atteints de SEP (Figure 2). De la même manière que les sujets de contrôle, les performances obtenues pour la condition passée sont supérieures à celles de la condition future chez les patients atteints de SEP. En outre, une corrélation positive entre les performances de mémoire autobiographique et de projection dans l'avenir a été observée au sein de chacun des deux groupes. De plus, sur la base de l'entretien semi-directif, ces résultats ont été confortés par les plaintes des patients, avec des répercussions négatives dans leur quotidien.

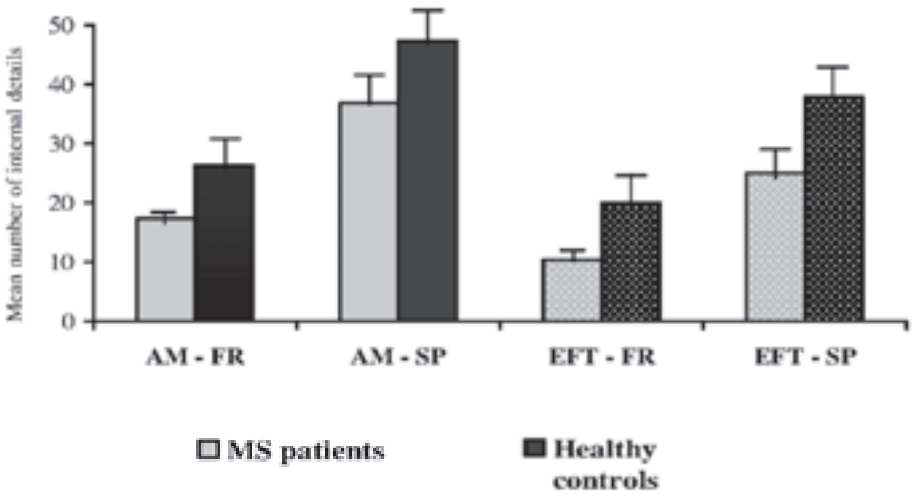

Figure 2. Nombre moyen de détails fournis par les patients SEP et les sujets sains au test de l'AI pour la mémoire autobiographique (AM) et la projection dans l'avenir (EFT) lors de la phase de rappel libre (FR) et indicé (SP)

Etude 2 (soumise)

L'objectif de cette seconde étude était d'explorer les soubassements neuro-fonctionnels du déficit de mémoire autobiographique, préalablement documenté sur le plan clinique chez les patient atteints de SEP. Ainsi, 18 patients présentant un déficit de la mémoire autobiographique et 18 sujets sains ont été recrutés.

Les deux groupes de participants ont présenté des performances équivalentes en termes de nombre d'essais valides et de temps de réaction lors de la tâche d'IRMf.

En revanche, une augmentation de l'activité cérébrale est très nettement observée chez les patients SEP lors des phases de construction et d'élaboration des souvenirs personnels. Plus précisément, lors de la phase initiale de construction, une augmentation de l'activité cérébrale a été observée de façon prédominante dans les régions fronto-pariétales bilatérales (Figure 3).

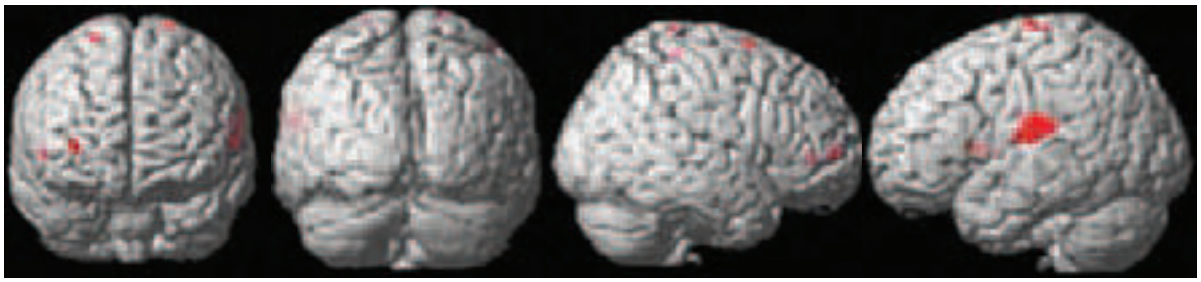

Figure 3. Régions cérébrales montrant une activité cérébrale plus importante chez les patients atteints de SEP (versus les sujets de contrôle) lors de la phase de construction d'événements passés (versus la phase de construction de la tâche de contrôle) ; $p < 0.005$ non corrigée, $k = 10$ voxels

Lors de la phase d'élaboration des souvenirs, une première observation qualitative a mis en évidence une plus faible étendue du pattern d'activation cérébrale recruté par les patients SEP, en comparaison à la phase de construction. Lors de cette phase, des activations cérébrales plus importantes ont été principalement mises en évidence au niveau des régions préfrontales bilatérales, mais aussi de certaines structures cérébrales médianes (Figure 4).

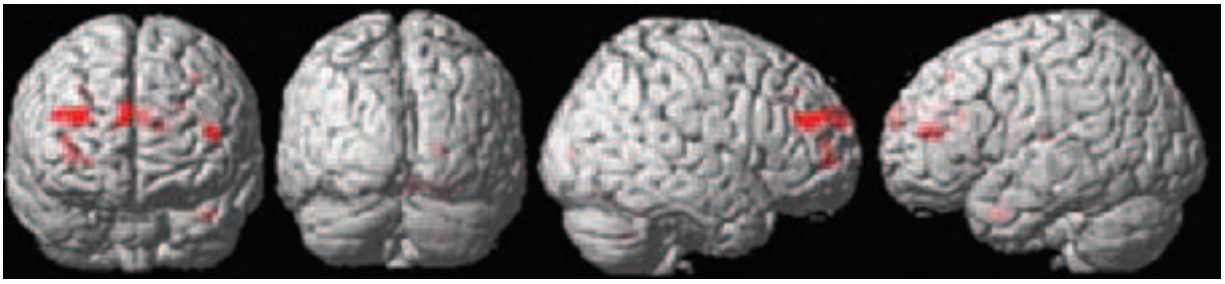

Figure 4. Régions cérébrales montrant une activité cérébrale plus importante chez les patients atteints de SEP (versus les sujets de contrôle) lors de la phase d'élaboration d'événements passés (versus la phase d'élaboration de la tâche de contrôle) ; $p < 0.005$ non corrigée, $k = 10$ voxels

Par ailleurs, la réponse neuronale à la difficulté d'accès aux souvenirs nécessitait des recrutements additionnels chez les patients SEP, en comparaison aux sujets sains, principalement au niveau du gyrus parahippocampique et du gyrus temporal moyen lors de la phase de construction et d'élaboration du souvenir (Figure 5 ; A.1 et B.1). De même, en réponse à l'augmentation de la quantité de détails associés aux souvenirs, les patients atteints de SEP ont montré des activations cérébrales plus importantes que les sujets de contrôle au niveau du gyrus préfrontal médian et de l'uncus lors de la phase de construction, et au niveau du gyri parahippocampique et cingulaire lors de la phase d'élaboration (Figure 5 ; A.2 et B.2).

Concernant le groupe de sujets sains, seules des différences mineures des patterns d'activation cérébrale ont été détectées, en comparaison des patients SEP.

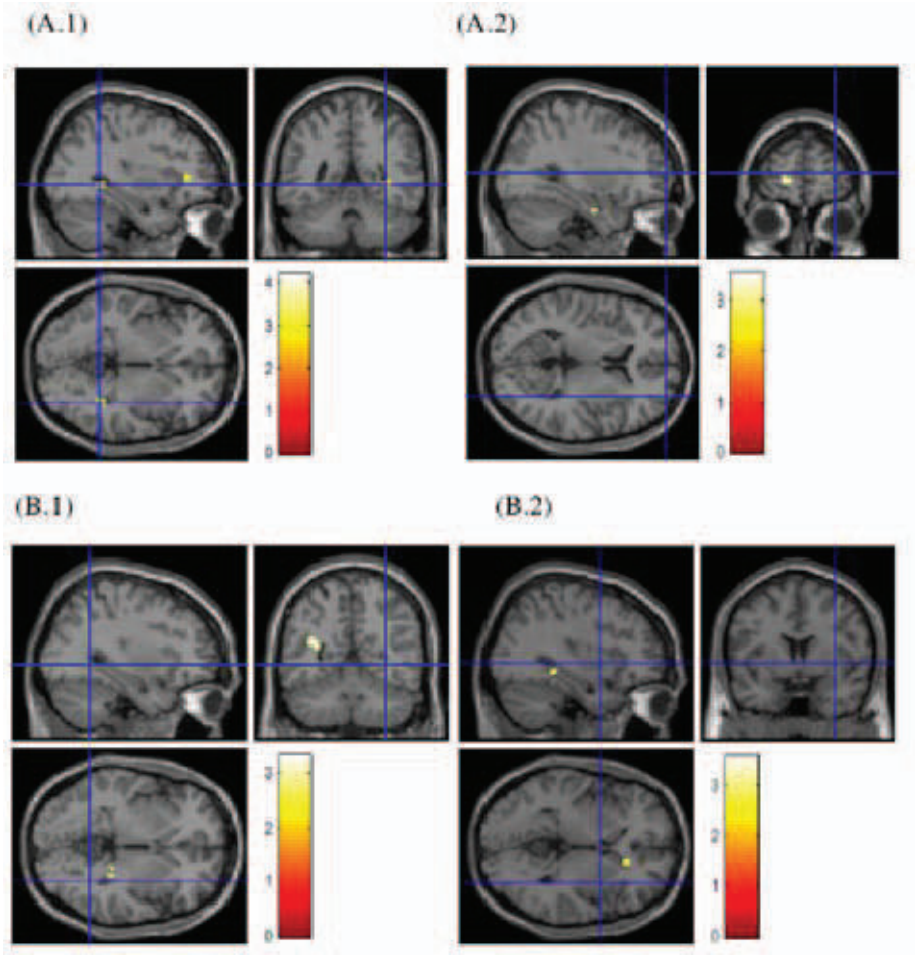

Figure 5. Régions cérébrales montrant une activité cérébrale augmentée chez les patients atteints de SEP (versus les sujets de contrôle) durant les phases de construction (A) et d'élaboration (B) en réponse à la difficulté d'accès (A.1 et B.1) et à la quantité de détails (A.2 et B.2) ; $p < 0.005$ non corrigée, $k = 10$ voxels

Etude 3 (soumission dans un numéro spécial, sur invitation par T. Suddendorf)

En complément de l'étude précédente, cette troisième étude visait à explorer les soubassements cérébraux du déficit de la projection dans l'avenir chez les patients SEP (n = 21), vis-à-vis des sujets de contrôle (n = 20). A nouveau, l'équivalence des deux groupes de participants en termes de nombre d'essais valides et de temps de réaction lors de la tâche d'IRMf a été vérifiée.

Lors de la phase de construction des événements futurs, des activations cérébrales supplémentaires ont été mises en évidence chez les patients au sein d'un réseau cérébral étendu et bilatéralisé, en comparaison des sujets sains. Ce réseau cérébral impliquait les régions préfrontales, temporales externes et médianes, pariéto-occipitales et cingulaires (Figure 6).

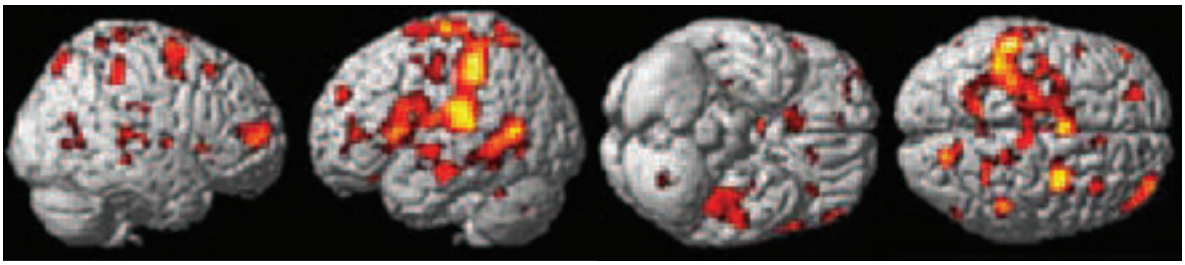

Figure 6. Régions cérébrales montrant une activité cérébrale plus importante chez les patients atteints de SEP (versus les sujets de contrôle) lors de la phase de construction d'événements futurs (versus la phase de construction de la tâche de contrôle) ; $p < 0.005$ non corrigée, $k = 10$ voxels

Toutefois, ces activations cérébrales complémentaires sont apparues comme moins étendues lors de la phase d'élaboration des événements futurs (Figure 7), avec une implication prédominante des régions préfrontales bilatérales chez les patients atteints de SEP.

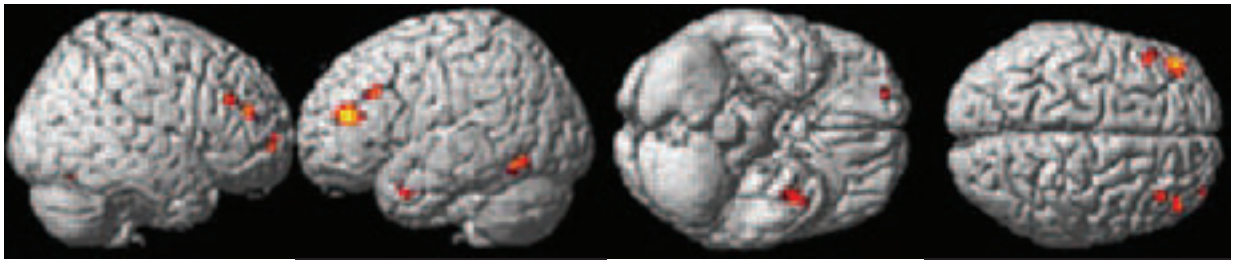

Figure 7. Régions cérébrales montrant une activité cérébrale plus importante chez les patients atteints de SEP (versus les sujets de contrôle) lors de la phase d'élaboration d'événements futurs (versus la phase d'élaboration de la tâche de contrôle) ; $p < 0.005$ non corrigée, $k = 10$ voxels

En comparaison aux sujets de contrôle, les patients ont également montré des activations cérébrales supplémentaires en réponse à la difficulté d'imagination des événements futurs, impliquant les gyri parahippocampique et cingulaire, et ce, uniquement pour la phase de construction (Figure 8, A). En revanche, une réponse neuronale augmentée a été détectée chez

les patients atteints de SEP en fonction de l'augmentation de la quantité de détails lors des deux phases d'évocation des projets. Plus précisément, lors de la phase de construction, cette augmentation de l'activité cérébrale concernait de façon prédominante les régions préfrontales et le gyrus cingulaire (Figure 8, B), alors que pour la phase d'élaboration, un vaste réseau fronto-pariéto-occipital, avec des activations cérébrales complémentaires dans le gyri parahippocampique et cingulaire a été mis en évidence (Figure 8, C).

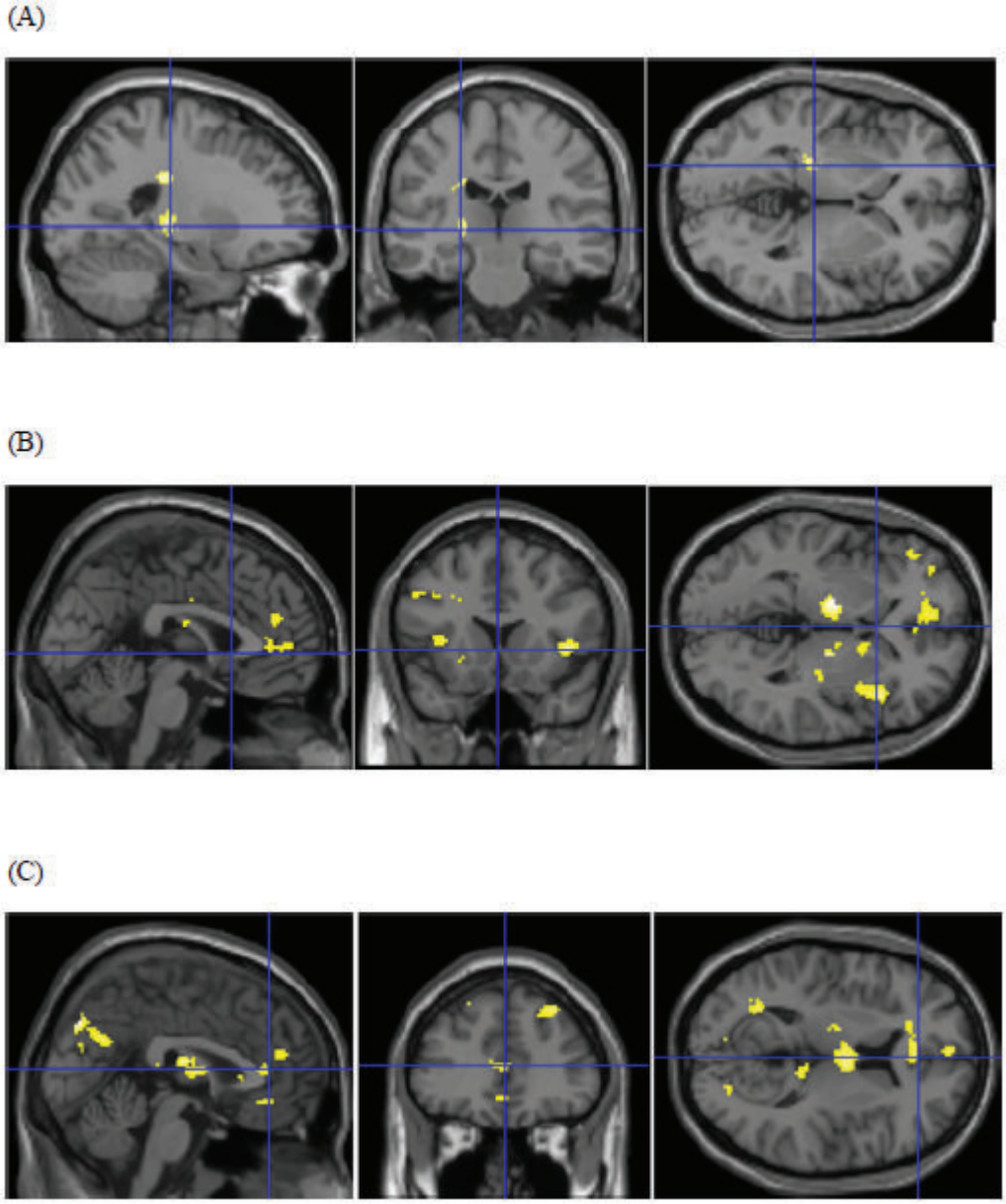

Figure 8. Régions cérébrales montrant des recrutements additionnels chez les patients atteints de SEP (versus les sujets de contrôle) en réponse à la difficulté d'imagination durant la phase de construction (A) et à la quantité de détails durant les phases de construction (B) et d'élaboration (C) ; $p < 0.005$ non corrigé, $k = 10$ voxels

Concernant le groupe de sujets sains, seules des différences mineures des patterns d'activation cérébrale ont été détectées, en comparaison des patients SEP.

Etude 4 (soumise)

La présente étude visait à combiner les données des deux travaux précédents afin d'explorer les différences et similitudes potentielles des soubassements neuro-fonctionnels du déficit de mémoire autobiographique et de la projection dans l'avenir chez les patients atteints de SEP (n = 22), en comparaison d'un groupe de sujets sains (n = 22). Ces analyses ont été réalisées sur un nombre équivalent d'essais valides et avec des temps de réaction similaires pour les deux groupes de participants et conditions temporelles.

Une première analyse a ciblé les régions cérébrales communément recrutées par le voyage mental dans le temps (i.e. événements passés et futurs combinés). A nouveau, des activations cérébrales supplémentaires ont été observées chez les patients, en comparaison des sujets de contrôle (Figure 9, A). Ces recrutements additionnels étaient localisés dans des structures clés du voyage mental dans le temps, incluant les régions fronto-pariétales et temporales, ainsi que des régions cérébrales postérieures et médianes.

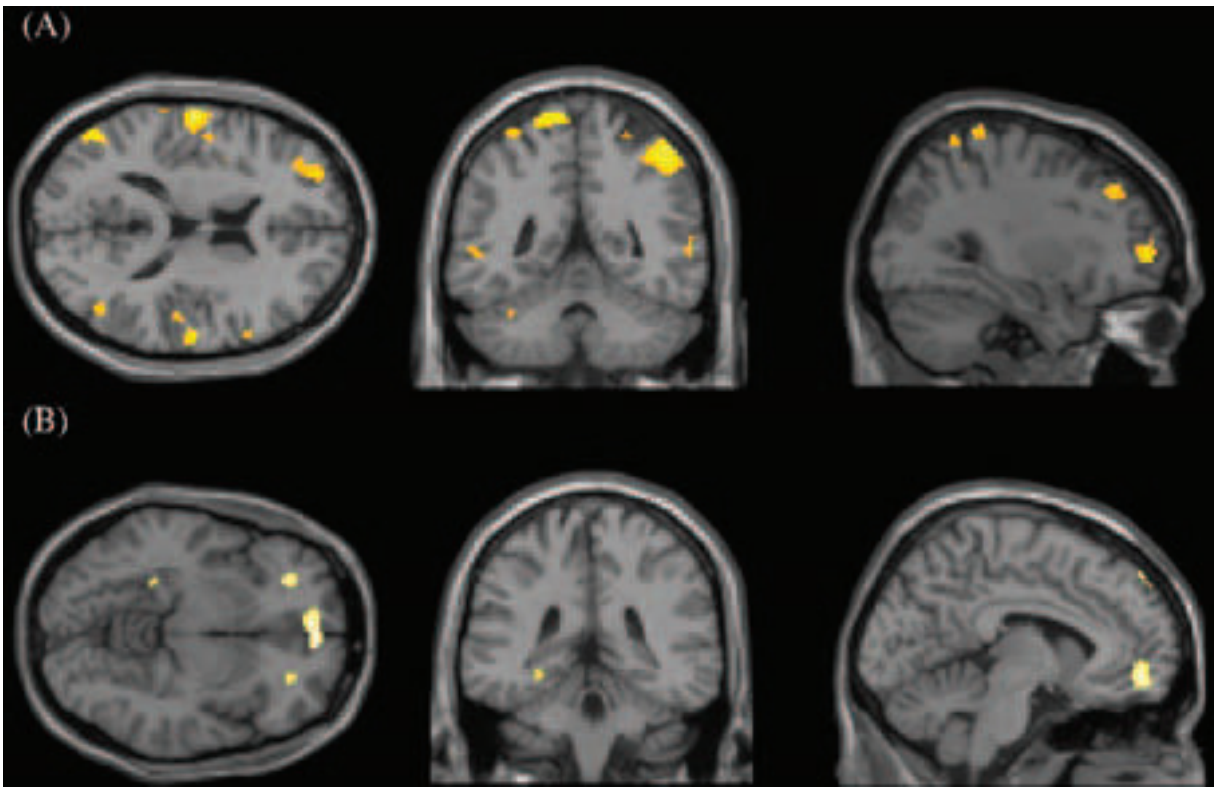

Figure 9. Régions cérébrales sous-tendant le voyage mental dans le temps montrant des recrutements additionnels chez les patients (versus les sujets de contrôles, A) et chez les sujets de contrôle (versus les patients, B) ; FWE, $p < 0.05$.

A l'inverse, des activations plus importantes dans les régions préfrontales médianes ainsi qu'au niveau du gyrus parahippocampique ont été observées chez les sujets sains, vis-à-vis des patients (Figure 9, B).

Une interaction significative a également été mise en évidence entre le groupe et la direction temporelle. Ainsi, pour plusieurs régions cérébrales, une activité cérébrale plus importante a été détectée pour la condition future (versus la condition passée) au sein du groupe de patients, alors que pour le groupe de sujets sains, un niveau d'activité cérébrale équivalent a été observé pour les deux directions temporelles (Figure 10). Ce pattern de résultats concernait plus spécifiquement l'hippocampe droit, les gyri frontaux moyen et supérieur droits, les régions temporales moyennes gauches et supérieures droites, ainsi que le cortex cingulaire postérieur. En parallèle, un pattern d'activation opposé a été observé au sein de l'hippocampe gauche chez les sujets sains, avec une activité plus importante pour la condition passée (versus la condition future).

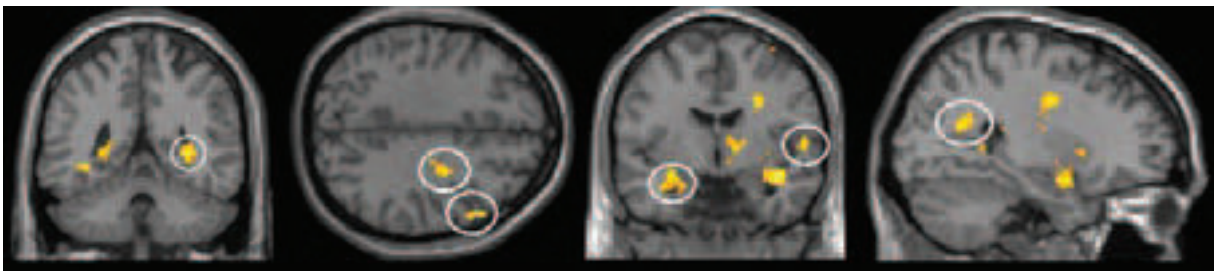

Figure 10. Régions cérébrales montrant une activité cérébrale augmentée pour la condition future (versus passée) chez les patients, mais avec une activité cérébrale similaire pour les deux conditions temporelles chez les sujets sains (Interaction Groupe x Condition temporelle ; $p < 0.001$ non corrigé, $k = 10$ voxels)

Les analyses portant sur l'interaction Groupe x Phase d'évocation ont également donné lieu à des résultats significatifs. En premier lieu, durant la phase de construction, une activité cérébrale plus importante a été détectée chez les patients en comparaison des sujets sains au niveau du gyrus temporal moyen gauche et supérieur droit, ainsi que du lobule pariétal inférieur et supérieur droit (Figure 11, A). Inversement, lors de la phase de construction, les sujets sains activaient de façon plus importante le gyrus préfrontal médian gauche et les régions cérébrales postérieures bilatérales (cuneus et précuneus ; Figure 11, B). Pour ces deux derniers patterns de résultats, les deux groupes de participants montraient en revanche un niveau d'activité cérébrale équivalent lors de la phase d'élaboration. Toutefois, pour le gyrus frontal inférieur gauche et pour le précuneus gauche, l'activité cérébrale de ces deux régions étaient plus importantes pour la phase de construction (versus d'élaboration) chez les patients, alors qu'un degré d'activité cérébrale équivalent a été mis en évidence chez les sujets de contrôle (Figure 11, C).

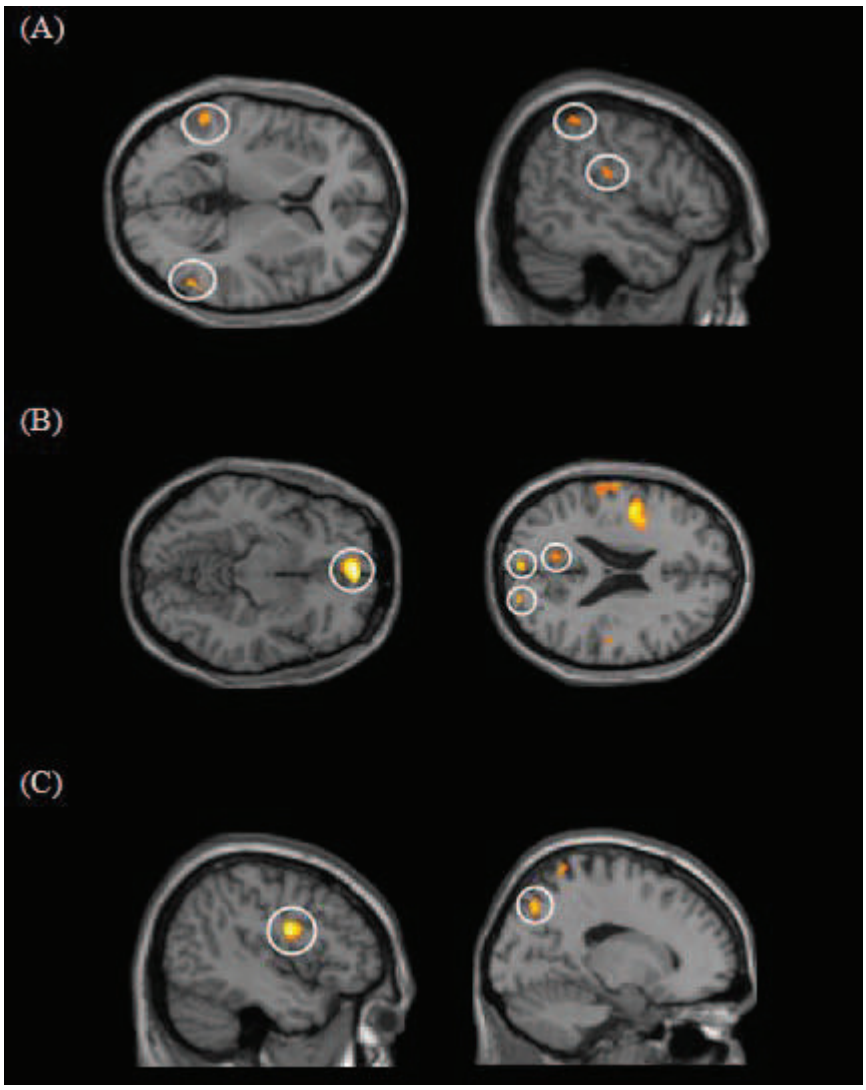

Figure 11. Régions cérébrales montrant un effet d'interaction Groupe x Phase d'évocation significatif ;
(A) Construction patients > construction sujets sains et Elaboration patients = élaboration sujets sains ;
(B) Construction sujets sains > construction patients et Elaboration patients = élaboration sujets sains ;
(C) Construction patients > élaboration patients et Construction sujets sains = élaboration sujets sains ;
($p < 0.001$ non corrigé, $k = 10$ voxels)

Etude 5 (Ernst et al., 2012, *Multiple Sclerosis International*)

Cet article visait à recueillir des données préliminaires sur les effets de notre programme de réhabilitation cognitive basé sur l'imagerie mentale visuelle sur la mémoire autobiographique, au niveau comportemental et en neuroimagerie.

Pour se faire, huit patients ont été recrutés et répartis aléatoirement au sein du groupe expérimental (n = 4) et du groupe stabilité (n = 4). Après réhabilitation, les patients du groupe expérimental ont montré une amélioration significative de leurs performances en mémoire autobiographique. De plus, cette amélioration n'était pas en lien avec un simple effet d'apprentissage au test puisqu'aucune différence significative entre les deux sessions d'évaluation n'a été observée au sein du groupe stabilité.

Au sein du groupe expérimental, ce bénéfice clinique était principalement accompagné d'un recrutement plus important des régions cérébrales postérieures après réhabilitation (Figure 12). En parallèle, une moindre activation des régions cérébrales antérieures a été détectée en post-réhabilitation.

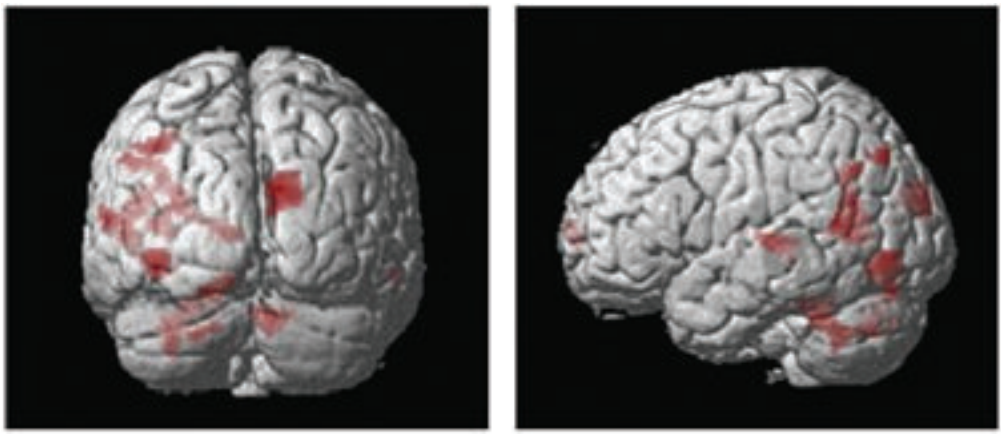

Figure 12. Régions cérébrales montrant des activations supplémentaires après réhabilitation au sein du groupe expérimental ($p < 0.01$, $k = 20$ voxels)

Etude 6 (en préparation)

L'objectif principal de la présente étude était de tester l'efficacité de notre programme de réhabilitation cognitive basé sur l'imagerie mentale visuelle sur la mémoire autobiographique et la projection dans l'avenir, en contrôlant la présence de facteurs confondants tels qu'un effet « prise en charge » ou un effet d'apprentissage au test évaluant le voyage mental dans le temps. De même, le transfert des bénéfices dans le fonctionnement quotidien ainsi que leur maintien à plus long terme ont été explorés.

Ainsi 40 patients atteints de SEP et présentant un déficit des capacités de voyage mental dans le temps ont été recrutés et répartis aléatoirement dans le groupe expérimental (n =17), « placebo » (n = 10) et stabilité (n = 13 ; cf Figure 1).

Avant réhabilitation, les trois groupes de patients présentaient des performances équivalentes tant pour la mémoire autobiographique que pour la projection dans l'avenir. Néanmoins, lors de la seconde évaluation, seuls les patients du groupe expérimental ont montré une amélioration significative de leurs performances en mémoire autobiographique (Figure 13). En outre, les scores de mémoire autobiographique obtenus par le groupe expérimental après la prise en charge sont devenus supérieurs à ceux obtenus par les deux autres groupes lors de la seconde évaluation. Toutefois, après suivi du programme d'imagerie mentale visuelle, les patients du groupe stabilité ont montré eux aussi une amélioration significative de leurs performances en mémoire autobiographique. Sur cette base, il semblerait que les bénéfices à l'issue du programme basé sur l'imagerie mentale visuelle ne soient pas en lien avec un effet de « prise en charge » ou d'apprentissage au test.

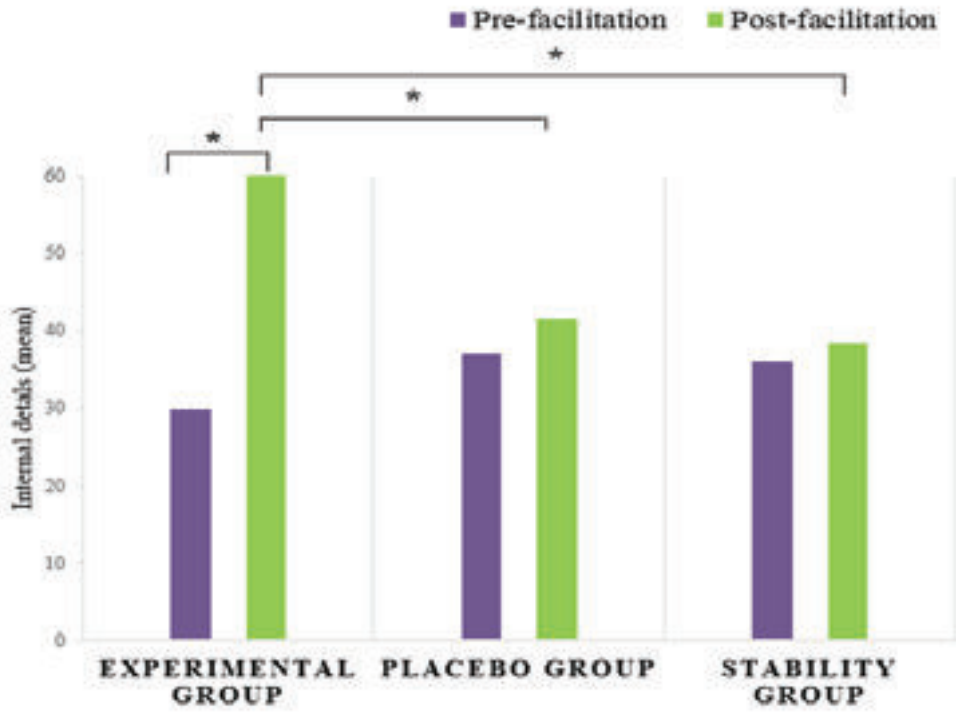

Figure 13. Nombre moyen de détails fournis par les trois groupes de patients en pré- et post-réhabilitation pour la mémoire autobiographique (* $p < 0.001$)

Des résultats similaires ont été observés pour la condition future. En effet, malgré l'absence initiale de différences entre les trois groupes de patients avant la prise en charge, après réhabilitation, le groupe expérimental a montré des scores significativement supérieurs à ceux obtenus par les deux autres groupes de patients (Figure 14). De plus, au sein du groupe expérimental, une nette augmentation du nombre de détails fournis lors de l'évocation d'événements futurs a été mise en évidence. Après suivi du programme d'imagerie mentale visuelle, le groupe stabilité a montré lui aussi une amélioration des performances de projection dans l'avenir. A nouveau, ces résultats semblaient conforter l'absence d'un effet significatif de « prise en charge » ou d'apprentissage au test.

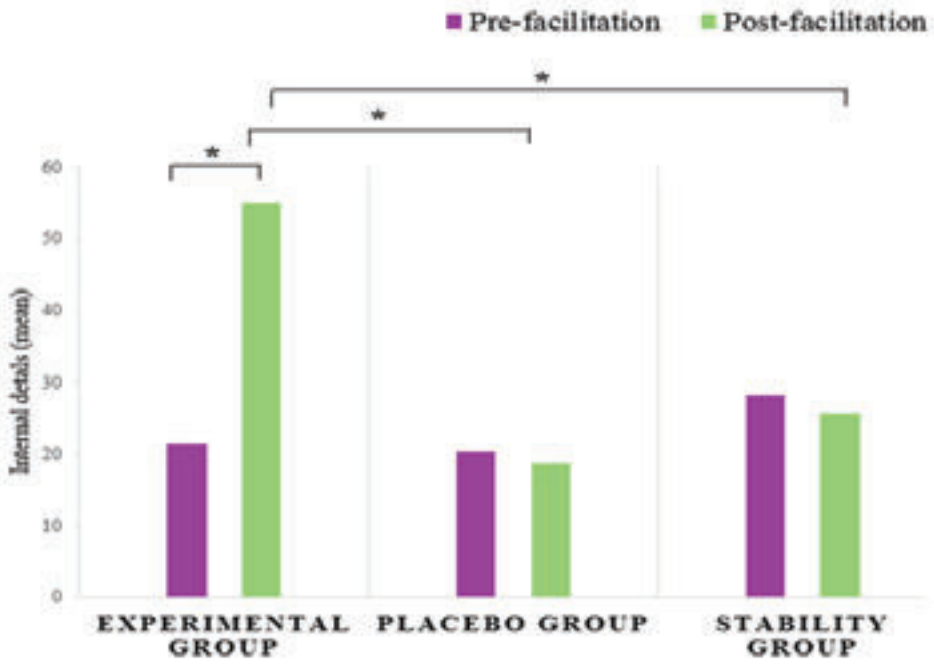

Figure 14. Nombre moyen de détails fournis par les trois groupes de patients en pré- et post-réhabilitation pour la projection dans l'avenir (* $p < 0.001$)

De plus, cette amélioration des capacités de mémoire autobiographique et de projection dans l'avenir suite au programme d'imagerie mentale visuelle s'est traduite par une normalisation des performances du voyage mental dans le temps pour 93% de nos patients et était accompagnée de commentaires positifs des patients, illustrant le transfert efficace de la technique et de ses bénéfices dans le fonctionnement quotidien. Par ailleurs, un maintien à long terme des bénéfices a été mis en évidence chez ces patients.

Etude 7 (en préparation)

Sur la base du bénéfice clinique de notre programme d'imagerie mentale visuelle, l'une des questions complémentaires était de savoir dans quelle mesure cette amélioration pouvait s'accompagner de changements d'activation cérébrale. Cette dernière question a donc fait l'objet de la présente étude, en se focalisant dans un premier temps sur la mémoire autobiographique.

Pour se faire, 10 patients du groupe expérimental et 10 patients du groupe « placebo » issus de l'étude clinique précédente ont été sélectionnés. Les analyses statistiques ont porté sur les données comportementales et de neuroimagerie, avant et après le programme de prise en charge respectif de chaque groupe de patients.

Sur le plan clinique, de façon similaire à l'étude précédente, une amélioration des performances en mémoire autobiographique a été détectée uniquement au sein du groupe expérimental, avec des scores supérieurs à ceux obtenus par le groupe « placebo », en post-réhabilitation.

Concernant les données de neuroimagerie, cette amélioration clinique observée pour le groupe expérimental était accompagnée de changements significatifs des patterns d'activation cérébrale lors de l'évocation de souvenirs autobiographiques. Plus précisément, une augmentation de l'activité cérébrale a été détectée au sein du gyrus préfrontal médian gauche durant la phase de construction du souvenir (Figure 15, A). Lors de la phase d'élaboration, une diminution de l'activité cérébrale à quant à elle été observée au niveau des gyri préfrontaux moyen et inférieur gauche, ainsi que du gyrus fusiforme gauche (Figure 15, B).

Malgré l'absence de changements significatifs sur le plan clinique, des modifications discrètes des patterns d'activation cérébrale ont également été notées pour le groupe « placebo » en post-réhabilitation. En particulier, lors de la phase initiale de construction, une diminution de l'activité du gyrus préfrontal médian gauche a été observée. Cette dernière était suivie d'une augmentation des activations cérébrales au niveau du gyrus préfrontal inférieur gauche durant la phase d'élaboration.

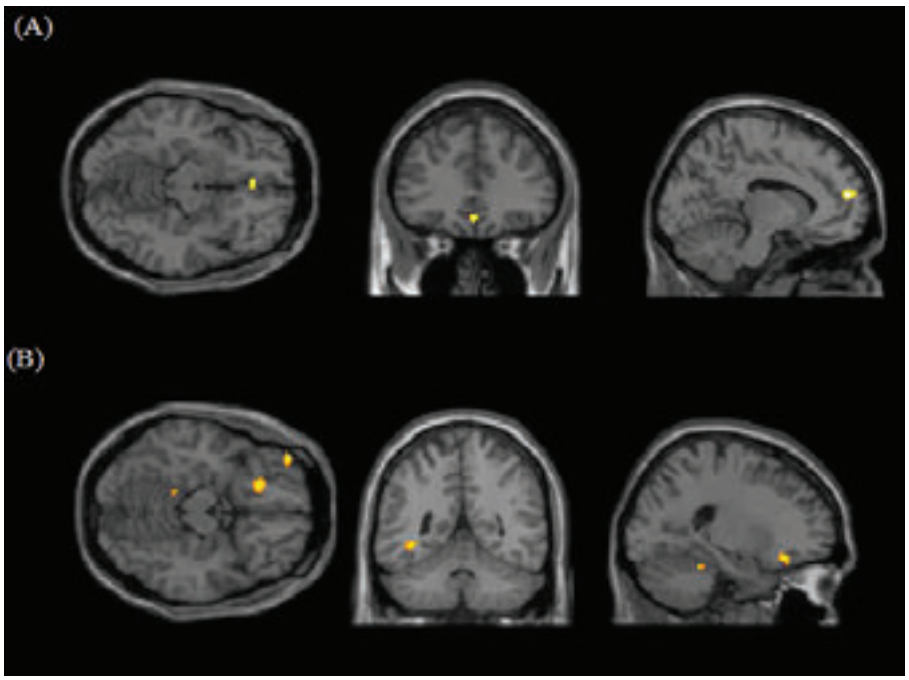

Figure 15. Changements d'activité cérébrale observés au sein du groupe expérimental en post-réhabilitation durant les phases de construction (A) et d'élaboration (B) des souvenirs ; $p < 0.001$; $k = 20$ voxels

Etude 8 (en préparation)

En complément de l'étude précédente, cette dernière étude visait à explorer dans quelle mesure des changements d'activation cérébrale pouvaient également être retrouvés suite à l'amélioration des performances de projection dans l'avenir.

Ainsi, les données comportementales et de neuroimagerie de 10 patients du groupe expérimental et 7 du groupe « placebo » (issus de l'étude clinique précédente) ont été incluses dans les analyses.

De façon consistante avec nos résultats précédents, après réhabilitation, une amélioration des capacités de projection dans l'avenir a été mise en évidence uniquement au sein du groupe expérimental. De plus, les scores des patients de ce dernier groupe étaient supérieurs à ceux du groupe « placebo » à la seconde évaluation.

A nouveau, des changements d'activation cérébrale ont été détectés, accompagnant l'amélioration des performances du groupe expérimental. Ces modifications de l'activité

cérébrale se traduisaient par des activations cérébrales plus importantes après réhabilitation au niveau du gyrus parahippocampique bilatéral, du gyrus temporal moyen gauche et du gyrus frontal supérieur gauche durant la phase de construction des événements futurs (Figure 16, A). De la même manière, durant la phase d'élaboration, une augmentation de l'activité cérébrale a été repérée au sein du gyrus préfrontal moyen gauche et du gyrus préfrontal supérieur droit (Figure 16, B).

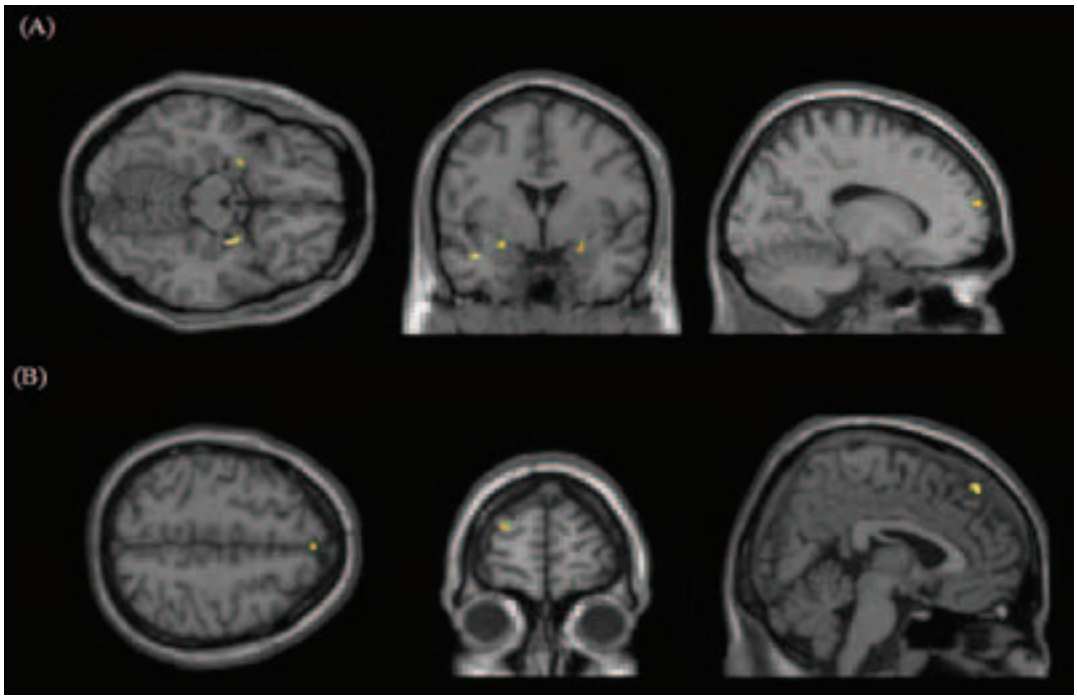

Figure 16. Changements d'activité cérébrale observés au sein du groupe expérimental en post-réhabilitation durant les phases de construction (A) et d'élaboration (B) des événements futurs ; $p < 0.001$; $k = 5$ voxels

Concernant le groupe « placebo », en l'absence de changements cliniques, seule une diminution des activations cérébrales a été notée en post-réhabilitation durant la phase de construction au niveau des gyri préfrontaux inférieur et supérieur gauche, du gyrus postcentral gauche et du gyrus fusiforme droit.

4. Discussion générale et perspectives

Basé sur une double approche en neuropsychologie clinique et en neuroimagerie, cette étude visait à explorer les mécanismes cognitifs et cérébraux sous-tendant le voyage mental dans le temps chez des patients atteints de SEP-R.

Une première série d'études a permis de mettre en évidence une altération conjointe de la mémoire autobiographique et de la projection dans l'avenir chez les patients SEP-R sur le plan comportemental. De la même manière que les sujets sains, de meilleures performances ont été obtenues pour l'évocation de souvenirs passés, vis-à-vis de l'imagination d'événements futurs personnels, reproduisant le pattern de résultats préalablement observés dans d'autres travaux, auprès de sujets sains ou de populations cliniques (D'Argembeau and Van der Linden, 2004; Addis et al., 2008 ; McDonough and Gallo, 2010 ; D'Argembeau et al., 2008 ; Irish et al., 2013 ; Addis et al., 2009). D'un point de vue clinique, ce déficit était corroboré par les patients SEP dans le contexte d'évaluation, mais aussi dans la vie quotidienne. Au regard de la littérature, ces résultats ont permis de conforter la présence d'une atteinte de la mémoire autobiographique chez les patients SEP, en accord avec des travaux antérieurs (Kenealy et al., 2002 ; Ernst et al., 2013) par le biais d'un test d'évaluation sensible. De plus, l'étude actuelle a été la première à notre connaissance à étendre ce résultat à la projection dans l'avenir chez les patients SEP-R.

Comme attendu, ces déficits sur le plan comportemental étaient également traduits par des changements spontanés au niveau des réseaux cérébraux sous-tendant la mémoire autobiographique et la projection dans l'avenir. Plus précisément, des activations cérébrales plus importantes et bilatéralisées au sein de régions clés du réseau cérébral de la mémoire autobiographique et de la projection dans l'avenir ont été observées chez les patients SEP vis-à-vis des sujets de contrôle, incluant les régions préfrontales, temporales et postérieures, avec toutefois un rôle prédominant des régions préfrontales bilatérales. En outre, l'observation de ces modifications spontanées de l'activité cérébrale a pu être faite aussi bien durant la phase de construction que d'élaboration. Ce dernier point était ainsi en accord avec l'observation clinique d'une difficulté des patients à récupérer/imaginer un événement personnel, mais aussi à pouvoir en fournir des détails associés. Par ailleurs, la réponse neuronale à la difficulté d'accès/d'imagination et la quantité de détails a elle aussi montré le recours à des activations

cérébrales supplémentaires par les patients SEP en comparaison des sujets de contrôle. Ces activations étaient elles aussi localisées dans des régions clés du réseau sous-tendant le voyage mental dans le temps, telles que le gyrus parahippocampique, le cortex cingulaire, ainsi que les régions préfrontales et postérieures.

Dans leur ensemble, ces premiers résultats suggèrent que malgré la présence de lésions cérébrales inhérentes à la SEP, des mécanismes de compensation semblent se mettre en place dans le contexte du voyage mental dans le temps, mécanismes toutefois insuffisants pour conduire à une performance normale. Malgré la description de ce type de phénomènes dans le cas de diverses fonctions cognitives chez les patients SEP (Caramia et al., 2010 pour une revue), à notre connaissance, de tels résultats n'avaient jamais été reportés dans le contexte du voyage mental dans le temps. En accord avec les travaux de neuroimagerie antérieurs menés auprès de patients atteints de SEP, ces mécanismes de compensation se traduisaient à la fois par une augmentation de l'activité cérébrale dans des régions également recrutées par les sujets sains, mais aussi par le recrutement de régions cérébrales alternatives, principalement controlatérales (Cader et al., 2006 ; Hulst et al., 2012).

Toutefois, au-delà de ces similitudes et chevauchements des patterns d'activation cérébrale entre la mémoire autobiographique et la projection dans l'avenir, certaines différences semblent à relever dans l'expression des mécanismes de plasticité cérébrale spontanée sous-tendant l'altération de chacune des directions temporelles. En effet, une première observation qualitative portant sur l'étendue des patterns d'activation cérébrale permet de mettre en lumière un recrutement plus important et plus large lors de la phase d'élaboration (versus de construction) de la condition passée, alors que pour la condition future, de plus vaste recrutement ont été observés pour la phase de construction (versus d'élaboration). De la même manière, les activations cérébrales additionnelles mises en évidence chez notre groupe de patients SEP semblent particulièrement importantes lors de l'évocation d'événements futurs, en comparaison au rappel de souvenirs, impliquant l'hippocampe, les régions frontales, temporales externes et cingulaires. De façon générale, une plus forte activité cérébrale a également été observée lors de la phase initiale de construction des événements personnels, sollicitant plus spécifiquement les régions fronto-pariétales, temporales externes et le précuneus. En d'autres termes, la mise en place des mécanismes de compensation reportés chez les patients dans le contexte du voyage mental dans le temps apparait comme d'autant plus importante dans les conditions les plus

« coûteuses » sur le plan cognitif, avec une implication caractéristique des fonctions exécutives (i.e. la projection dans l'avenir et la phase de construction des événements). De façon plus générale, ces éléments apportent également des arguments en faveur de notre hypothèse d'un déficit initial de récupération/génération des événements personnels (Ernst et al., 2013), en lien avec les fonctions exécutives, avec une sollicitation particulière des régions préfrontales bilatérales.

De ce fait, en accord avec la littérature et les données recueillies auprès de sujets sains, nous avons reporté chez les patients atteints de SEP des mécanismes cérébraux communs et distincts entre les deux directions temporelles. Ces résultats suggèrent ainsi que dans le contexte d'une altération des capacités de mémoire autobiographique et de projection dans l'avenir, avec en parallèle des signes de plasticité cérébrale spontanée, certaines caractéristiques typiques du voyage mental dans le temps peuvent être maintenues chez les patients SEP.

En complément à cette première série d'études, un second ensemble de travaux a été dédié à la proposition d'un programme de réhabilitation cognitive visant à améliorer le déficit du voyage mental dans le temps chez les patients atteints de SEP-R. Sur la base de notre étude pilote montrant l'efficacité de notre programme basé sur l'imagerie mentale visuelle sur les performances en mémoire autobiographique (Ernst et al., 2013), notre objectif était de consolider ces résultats dans le contexte d'un essai clinique randomisé et contrôlé, et de les étendre à la projection dans l'avenir. Par ailleurs, notre but était également d'appuyer ces résultats cliniques par des données de neuroimagerie en suivant un design expérimental en pré- et post-réhabilitation.

Sur le plan clinique, malgré des performances initialement équivalentes pour les trois groupes en pré-réhabilitation, seul le groupe expérimental a montré une amélioration significative de ses performances pour la mémoire autobiographique et la projection dans l'avenir en post-réhabilitation, avec des scores devenus significativement supérieurs à ceux des groupes « placebo » et stabilité lors de leur seconde évaluation. A partir de ces données, il semblerait donc que l'amélioration des performances en mémoire autobiographique et de la projection dans l'avenir ne soit pas en lien avec un effet de « prise en charge » ou d'apprentissage au test. De plus, ce bénéfice a été corroboré par les patients du groupe expérimental, avec un taux important de bénéfice individuel et de normalisation des

performances, accompagné par un transfert efficace dans leur fonctionnement quotidien et maintenu lors de la réévaluation à six mois. Concernant ces résultats, il est intéressant de noter qu'un bénéfice équivalent a été observé pour les deux conditions temporelles suite au programme d'imagerie mentale visuelle.

Concernant la traduction de ce bénéfice clinique en termes de plasticité cérébrale induite, des changements d'activation cérébrale dans des régions clés associées au voyage mental dans le temps ont effectivement été mis en évidence suite à la prise en charge au sein du groupe expérimental.

Plus précisément, pour la mémoire autobiographique, ces changements d'activation cérébrale reflétaient une exacerbation du rôle des régions cérébrales sous-tendant les processus de référence à soi et une diminution de l'implication des régions supportant l'effort de récupération du souvenir, par la mise en place de stratégies. En parallèle, pour la projection dans l'avenir, des signes de plasticité cérébrale induite par la prise en charge ont été relevés dans des régions cérébrales impliquées dans les processus contextuels, la sémantique personnelle, ainsi que l'intégration et le maintien d'informations multimodales. A notre connaissance, cette étude est la première à mettre en évidence que l'utilisation d'une stratégie cognitive unique, ici basée sur l'imagerie mentale visuelle, peut donner lieu à des patterns d'activation cérébrale différents accompagnant l'amélioration des performances, en fonction de son contexte d'application, à savoir la mémoire autobiographique ou la projection dans l'avenir. De façon plus générale, ces données supportent aussi la notion de substrats cérébraux ayant des caractéristiques spécifiques à la mémoire autobiographique et à la projection dans l'avenir. Ces derniers résultats mériteraient un examen plus approfondi, avec notamment une comparaison directe entre les deux directions temporelles, afin d'obtenir des informations plus précises quant à la signification fonctionnelle de ces différents changements d'activité cérébrale induits par la prise en charge.

En l'absence d'amélioration clinique des performances du voyage mental dans le temps, seuls des changements mineurs d'activité cérébrale ont été observés au sein de notre groupe « placebo ». Ces modifications mineures ont pu dans certains cas être mis en lien avec une tentative d'utilisation de la stratégie verbale de contrôle ou un effet d'habituation/de répétition de la tâche en IRMf, déjà rapporté pour ce dernier par Chiaravalloti et al. (2012) au sein de leur groupe de patients SEP de contrôle.

Sur la base de considérations théoriques et de nos résultats préliminaires (Ernst et al., 2012), nous avions émis l'hypothèse d'une augmentation prédominante des activations cérébrales dans les régions postérieures par l'intermédiaire du programme basé sur l'imagerie mentale visuelle, processus sous-tendu par ces mêmes régions cérébrales. En effet, ces premiers résultats avaient été interprétés comme reflétant l'accent mis sur le rôle de l'imagerie mentale visuelle, lors de la récupération de souvenirs autobiographiques à travers la prise en charge. Toutefois, ce résultat n'a pas été répliqué sur un plus large échantillon de patients, tant pour la mémoire autobiographique que pour la projection dans l'avenir. Néanmoins, tenant compte du faible échantillon de patients et du seuil statistique peu strict utilisé dans le cadre de cette étude préliminaire, ces résultats doivent être interprétés avec précaution. Cependant, dans la mesure où des changements d'activité cérébrale avaient été observés dans les régions postérieures de façon spontanée chez ces mêmes patients, une question ouverte concerne la possibilité d'observer des changements additionnels induits par la prise en charge dans ces mêmes régions cérébrales. De plus, considérant la dynamique spatio-temporelle des interactions entre les régions cérébrales du réseau sous-tendant le voyage mental dans le temps (Conway et al., 2003 ; Weiler et al., 2011), une autre possibilité reposerait sur la présence de changements qualitatifs et non quantitatifs dans ces régions cérébrales postérieures. Suivant cette hypothèse, des analyses complémentaires de connectivité fonctionnelle vont être introduites dans un futur proche afin d'obtenir une vue plus complète des changements d'activité cérébrale induits par la prise en charge cognitive dans le contexte du voyage mental dans le temps. En outre, ce type d'analyses semble d'autant plus pertinent que des changements de connectivité fonctionnelle ont préalablement été décrits suite à une prise en charge cognitive chez des patients atteints de SEP (Leavitt et al., 2012 ; Parisi et al., 2012). De plus, dans le but d'avoir un panorama complet du phénomène de plasticité cérébrale induite chez les patients SEP, en lien avec les performances du voyage mental dans le temps, des données structurelles (Voxel-based Morphometry et imagerie de tenseur de diffusion) vont également être introduites. De façon indépendante, ces types de mesures structurelles ont montré leur sensibilité aux changements induits par une prise en charge cognitive dans différentes populations cliniques (Eack et al., 2010 ; Nordvik et al., 2012 ; Penades et al., 2013).

Plus globalement, les travaux menés au cours de cette thèse ont permis d'apporter un nouvel éclairage sur les troubles cognitifs observés dans la SEP en s'appuyant à la fois sur des données cliniques et de neuroimagerie fonctionnelle. A travers ces différentes études, nous avons observé que l'altération du voyage mental dans le temps semble très fréquente chez les patients atteints de SEP-R, y compris chez les patients présentant une préservation de leur fonctionnement cognitif général. Bien que nous soyons conscients de l'absence actuelle d'évaluation des capacités de voyage mental dans le temps en évaluation clinique de routine (notamment en lien avec la longueur de son évaluation), nous souhaiterions mettre en avant la nécessité d'accorder plus d'attention à cette capacité dans le travail clinique auprès de patients atteints de SEP. Cette dernière recommandation fait particulièrement sens dans le cas de patients SEP présentant une plainte mnésique, mais pour lesquels aucune altération cognitive n'a été détectée avec les tests neuropsychologiques standards. Cette dernière suggestion se voit également renforcée par la possibilité de compenser ce déficit du voyage mental dans le temps chez ce type de patients, en un court intervalle de temps et avec un maintien à long terme des bénéfices. Dans ce contexte, l'une des suites de ce travail pourrait être d'étendre ces résultats à d'autres sous-types de SEP, mais aussi à d'autres populations cliniques présentant une difficulté de récupération/génération d'événements personnels.

En guise de conclusion, nous souhaiterions mettre l'accent sur l'importance clinique de l'étude de la mémoire autobiographique et de la projection dans l'avenir au sein de populations cliniques, et tout particulièrement dans le but de développer des prises en charge visant à promouvoir leur intégrité. Ce dernier point présente une importante toute particulière en tenant compte du rôle de la mémoire autobiographique et de la projection dans l'avenir dans des domaines tels que la construction et le sentiment de continuité de l'identité personnelle, les relations sociales, l'adaptation/gestion de situations stressantes ou l'atteinte de buts personnels (Rasmussen et Habermas, 2011 ; Szupnar, 2010).

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ABBREVIATIONS LIST

(Listed by alphabetical order)

AM = autobiographical memory

aMCI = amnestic mild cognitive impairment

AI = Autobiographical Interview

EDSS = Expanded Disability Status Scale

EFT = episodic future thinking

fMRI = functional magnetic resonance imaging

DTI = diffusion tensor imagery

MS = multiple sclerosis

MTT = mental time travel

MVI = mental visual imagery

PTSD = post-traumatic stress disorder

RR-MS = Relapsing-remitting multiple sclerosis

RT = reaction time

SD = standard deviation

SMS = Self-memory system

SPI = Serial Parallel Independent

THEORETICAL BACKGROUND

CHAPTER 1

Remembering our past and imagining our future

Human memory is probably one of the most fundamental cognitive functions and has aroused the interest of philosophers and researchers through ages. However, since the 4th century, St. Augustine has posited that human memory is a composite ability and that remembering our own past coexists with the ability to anticipate our own future (see Manning et al., 2013 for a review). Several centuries later, this original point of view was followed and conceptualised with the notion of mental time travel (MTT; Suddendorf and Corballis, 1997; Tulving 2001, 2002), thus contributing to the initiation of a broad body of theoretical and clinical investigations, which will be developed in this chapter after the presentation of some theoretical key issues in memory research.

1. Tulving's SPI memory Model

Following his distinction between semantic and episodic memory in 1972 (Tulving, 1972), Tulving fully integrated these two components into the Serial Parallel Independent (SPI) hierarchical memory model (Tulving, 1985). The SPI model encompasses four components: procedural memory, the perceptive representation system, semantic memory and episodic memory, which were all associated to different levels of consciousness. In fact, the two first components are associated to an anoetic consciousness, whereas semantic memory is defined by a noetic consciousness, with the capacity to remember, without the capacity of reliving the memory. On the contrary, episodic memory is characterised by an autonoetic awareness, which refers to the capacity of reliving the event as it is remembered, with the knowledge that this event pertains to our own past.

Within the semantic and episodic memory systems, a distinction is made between personal and non-personal memory. In this context, *personal semantics* corresponds to factual personal knowledge, e.g. the date of your birth, or general/repetitive personal events, e.g. going to your grandparents every Saturday afternoon (Tulving et al., 1988). Conversely, personal episodic memory, or *autobiographical memory (AM)*, corresponds to the capacity of reliving personal detailed events, within their specific spatio-temporal context, as they are remembered

(Tulving, 1985). Typical AM examples are the day you took your driving test, your 25th Birthday, or your last dinner with friends. According to Tulving (2005), three components are central in AM: the self, the subjective sense of time and the autonoetic consciousness. *Self* refers to the representation of our personal identity and constitutes the 'traveller', who mentally travels into the past and future. Regarding the *subjective sense of time*, it refers to the *autonoetic awareness* that "I am the traveller". In essence, this memory system enables individuals to feel a sense of self-continuity across time, thus resolving the diachronic paradox of the self.

2. Conway's autobiographical memory conception: the Self-memory system

Conway's Self-memory system model (SMS model; Conway, 2005) also relies on the distinction between different memory sub-systems hierarchically organised, which entails the AM conceptual knowledge database and episodic memories. Within the conceptual knowledge database, a hierarchical organisation is also observed, going from (i) *life story schemas or themes*, which represent the most abstract level and correspond to general themes across one's whole life (e.g. relationship or work themes); to (ii) *lifetime periods*, which embrace various knowledge common to a life period (e.g. when I was at the university, when I lived in X); and finally to, (iii) *general events*, which include information about repeated or temporally extended events that occurred over periods of weeks or months (e.g. the staff meetings every Monday, the gymnastic trainings, my week of holiday in Paris). This conceptual database is to distinguish from *episodic memories*, which corresponds to specific personal events containing sensory-perceptual-affective details and are often represented in the form of visual images.

A main component of the SMS model is the self. Two sub-components of the self are distinguished in Conway's model (2005). On the hand, the *conceptual self* encompasses our personal semantic representations (e.g. personal images, personal values). On the other hand, the *working self* is a dynamic system, which contains goal structures that control the encoding and consolidation of new knowledge, and the retrieval of specific memories, with the aim to guarantee their conformity with our personal self-image, goals and values, i.e. coherence, and the potentially contradictory necessity of correspondence to experience.

Importantly, in the SMS model, episodic memory could be recollected either directly or through generative processes. *Direct retrieval* corresponds to involuntary recollection coming from internal or external stimuli, well represented by the famous Proust's madeleine example. In contrast, *generative recall* refers to the effortful processes required for the voluntary recollection of an event, formulated in a three-step iterative process with the initial elaboration of a cue that permits the further search of the memory, with a final assessment of the accessed information. In the context of the SMS model, the generative recall goes through the different hierarchical stages previously described, from lifetime period to associated general events, to the final access to episodic memories, with a particular role of the working self to guide the research. In this perspective, from a neuroanatomical standpoint, the recall of a memory engage firstly the frontal regions (linked to the working self), follow by extensive activations of posterior cerebral regions (associated with the recollection of sensory perceptual details).

By and large, these two models have contributed to the understanding of human memory and have offered strong bases to the conceptualisation and further study of the broader concept of MTT.

3. The concept of mental time travel

As previously mentioned, beyond the ability to remember our own past, episodic memory also enables individuals to project themselves into their future (Tulving 2001, 2002). The notion of MTT, notably developed by Suddendorf and Corballis (1997, 2007), is defined as uniquely human and assumes an adaptive value, where memory does not only enable the accurate report of past episodes, but rather the construction of planned future events. In other words, as mentioned by Suddendorf and Busby (2003), our ability to revisit the past may be a feature of our ability to conceive the future, and past memories provide the 'ingredients' for future simulations.

3.1 Remembering the past and imagining the future are one and the same

Based on this theoretical background, a broad set of studies have highlighted the striking similarities shared by AM and episodic future thinking (EFT; Szpunar, 2010).

Historically, the first line of researches arose from the original observation of single-case amnesic patients, who evidenced difficulties in the evocation of both past and future personal events (Tulving, 1985; Klein et al., 2002). This pattern of results has then been replicated in several group studies with patients from varied aetiologies, including for instance Alzheimer's disease (Addis et al., 2009a), schizophrenia (D'Argembeau et al., 2008), depression (Williams et al., 1996) or medial temporal lobe amnesia (Hassabis et al., 2007). At the behavioural level, several studies conducted in healthy subjects have provided evidence of similar phenomenological properties of past and future events. For example, positive events were associated with an increased subjective re-/pre-experiencing of events, or temporally close events were more detailed and simulated with a greater feeling of re-/pre-experiencing than more distant events (D'Argembeau et al., 2011). The occurrence of involuntary personal simulations for past and future has also been documented (Berntsen and Staerk Jacobsen, 2008).

Likewise, the development of neuroimaging techniques, and notably functional magnetic resonance imaging (fMRI), has widely contributed to the examination of AM and EFT commonalities. Indeed, the examination of the functional underpinnings of AM and EFT in healthy subjects revealed a common cerebral network, which encompasses medial temporal and frontal lobes, posterior cingulate and retrosplenial cortex, and lateral parietal and temporal regions (Addis et al., 2007a; Szpunar et al., 2007; see also Schacter et al., 2012 for a review).

Overall, these investigations established that AM and EFT share common cognitive processes and cerebral underpinnings. In particular, AM and EFT both require self-referential/awareness and mental imagery processes, but also executive functions, working memory, declarative knowledge, recombination and evaluation of the simulation product (Addis et al., 2007a; Weiler et al., 2010a).

Several theoretical proposals have been put forward to explain the relationship between AM and EFT. Currently, three main hypotheses prevail in the literature:

(i) *The self-projection hypothesis* (Buckner and Carroll, 2007), which implies that the ability to project oneself into an alternative simulation, occurring in another time, place or personal perspective than the immediate present, constitutes the core of AM and EFT capacities. Here, a prevailing role of the medial frontal regions sustaining the self-referential process is proposed, conjointly with the medial temporal lobe regions.

(ii) *The scene construction hypothesis* (Hassabis and Maguire, 2007) posits that the ability of mentally generating and maintaining a complex and coherent scene constitutes the main common process of AM and EFT. In other words, imagination seems to be the critical component of past and future simulation, beyond self-involvement and temporal labelling of events. Scene construction would thus 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).

(iii) *The constructive episodic simulation hypothesis* (Schacter and Addis, 2007), which suggests that past and future events rely on similar information stored in episodic memory, that are flexibly recombined into a novel coherent event, and thus involve similar cognitive processes during event construction. In this hypothesis, the hippocampal formation plays a major role for the extraction and recombination of stored episodic details, as well as for the further encoding of the simulation product in memory (Addis and Schacter, 2012).

More generally, several authors have suggested that AM and EFT share also further cognitive and cerebral commonalities with other cognitive functions like navigation or theory of mind, but also with the default network. The latter describes a pattern of activated brain regions with no overt task assignation (Raichle et al., 2001; Raichle and Snyder, 2007; Buckner et al., 2008). It is also related to mind-wandering (Schacter et al., 2007; Hassabis et al., 2007).

3.2. Differential cognitive and functional mechanisms for past and future

Over and above these strong similarities between AM and EFT, a converging line of evidence also support the presence of phenomenological and functional differences between these two cognitive functions.

3.2.1. Behavioural studies

In fact, several studies in healthy subjects have underlined that a greater number of details was provided during the recollection of past events than during the imagination of future events, especially sensory-perceptual details (D'Argembeau and Van der Linden, 2004; Addis et al., 2008; McDonough and Gallo, 2010). This finding has been replicated in clinical populations, particularly in schizophrenia (D'Argembeau et al., 2008), fronto-temporal dementia (Irish et al., 2013), and Alzheimer's disease (Addis et al., 2009a). A few studies have found a dissociation between AM and EFT, showing relatively preserved AM abilities, together with impaired EFT performance in Parkinson's disease (De Vito et al., 2012), semantic dementia (Irish et al., 2012; Duval et al., 2012), and a patient presenting with thalamic lesions (Weiler et al., 2011a).

3.2.2. Neuroimaging studies

Consequently, past/future differences were also noticed in healthy subject's neuroimaging studies. In particular, a greater neural activity has been observed in frontopolar and hippocampal regions during the simulation of future events, relatively to that of past events (Okuda et al., 2003; Addis et al., 2007a). Interestingly, the distinction between the construction phase, i.e. the initial search and building up of the event, and the elaboration phase, which corresponds to the search of additional details associated to the event, provided new insights into AM and EFT differences. In this context, beyond the two aforementioned brain regions, a more extended cerebral network seemed particularly engaged in the future construction (relatively to the past construction), including lateral prefrontal regions, external temporal regions and more posterior brain regions like the precuneus, the fusiform gyrus or the occipital regions (Addis et al., 2007a). However, in this same study, only a greater future-related activation in the external temporal region was noticed during the elaboration phase.
Nevertheless, with a strict procedure enabling the good matching of the phenomenological properties for past and future events (i.e. amount of details, temporal distance and content), Weiler and colleagues (2010a) found slightly different results. Indeed, additional cerebral activations were observed for the past (versus future) during the elaboration phase, which mostly included posterior brain areas (notably the precuneus, lingual gyrus, cuneus, or occipital regions). This increased posterior neural activity for AM was linked to the reactivation of sensory-perceptual details from the original experience. In parallel, this study

also reported greater activations for the future condition in both construction and elaboration phases. However, regarding the hippocampus, contrary to Addis et al. (2007a), Weiler and co-workers have observed an earlier engagement of the posterior hippocampus during the past construction, whereas this region was only engaged during the further elaboration of future events.

Using a different approach, with a spatiotemporal partial least squares analysis and an experimental recombination of event detail paradigm, Addis et al. (2009b) identified within a common core network, two subsystems: the 'remembering core network' and the 'imagining core network'. Originally, the imagining subsystem covered both the imagination of past and future personal events and demonstrated that brain regions like the hippocampus, the medial prefrontal cortex or the inferior frontal gyrus, previously mainly associated to future events, actually support the more general process of self-related imagining rather than strictly prospection. Regarding the remembering subsystem, in addition to the common core network, predominantly posterior visual cortices were involved.

Another body of investigations focused on the differential neural activity elicited by a range of phenomenological qualities of past and future events, especially in the hippocampal region. For instance, the activity of the left anterior hippocampus appeared to be particularly sensitive to the amount of details from future events, whereas the activity of the left posterior hippocampus seemed similarly responsive to the amount of details for both past and future events (Addis and Schacter, 2008). In this same study, the temporal distance of events was also a contributing factor to the hippocampal regions engagement. In fact, the recency of past events modulated the activity of the right parahippocampal gyrus, whereas for the future events, their remoteness was the most influencing factor on the activity of the bilateral hippocampi. Likewise, the probability of occurrence of future events modulated the activity of the right anterior hippocampus (Weiler et al., 2010b).

The 'self-projection' and the 'scene construction' hypotheses put forward no account in relation to the higher cognitive and cerebral functional demands for EFT relatively to AM, to the best of our knowledge. However, in light of the 'constructive episodic simulation' hypothesis, the past/ future discrepancies could reflect the higher constructive processes necessary to pre-experiencing than re-experiencing an event (Schacter and Addis, 2007; Addis et al., 2009b). Specifically related to the hippocampus, its greater recruitment for future

tasks could reflect the extraction and the recombination of details into a coherent novel event, and the additional encoding of the simulation product in memory (Addis and Schacter, 2012). Moreover, the simulation of specific future events also necessitates the formation of new associations between originally disparate event details into a novel scenario, also leading to a greater hippocampal engagement (Addis et al., 2011). In the same way, EFT would also extensively tax executive functions since it requires the extraction and recombination of an infinite assortment of details into a novel scenario, whereas AM consists in the recapitulation of a restricted pool of details (Berntsen and Bohn, 2010).

Overall, the notion of distinct and common mechanisms sustaining AM and EFT is nowadays well established. Beyond the few illustrative, and not comprehensive, studies mentioned in this section, several inconsistencies have been reported within the literature regarding the involvement of some brain structures in MTT. Thus, further investigations are required, taking into account the influence of methodological issues. For instance, a recent meta-analysis from Viard and colleagues (2012) demonstrated that hippocampal involvement in past and future simulations is sensitive to factors like the type of cue proposed to complete the task, the specificity of the retrieved information, the type of task performed (recall vs recognition) or the participants' age.

However, beyond these methodological considerations, in the clinical neuropsychology perspective, studies involving brain-damaged patients could be a solid source of information regarding the role of some brain regions, and on how a cerebral functional network could be modulated/disrupted by disease. In the context of MTT, a couple of investigations have addressed this issue.

4. Visualising the influence of brain insult on the MTT neural basis

Understandably, fMRI studies in clinical conditions remain rare in the domain of MTT. As Maguire et al. noticed in 2001, the dearth of this kind of investigations is probably linked to the fact that "where patients have difficulty with or simply cannot perform a task, then the interpretation of brain activations is difficult because activation differences may be due to disparities in retrieval success or in the presence or absence of memory traces etc. compared with control subjects. However, in situations where patients can still perform tasks

or a subset of the tasks with accuracy and reaction times similar to that of control subjects, then data can be more usefully considered" (p.1157). By controlling these methodological constrains, some studies provided relevant insights.

For instance, Maguire and colleagues (2001) showed increased cerebral activations in key regions of the AM network, predominantly left-lateralised, in medial and lateral regions, with additional recruitment of the contralateral brain areas, in a patient with bilateral hippocampal atrophy. Moreover, despite important structural damage, a greater bilateral hippocampal activation was also highlighted. In parallel, an increased effective connectivity between the retrosplenial cortex and the hippocampus, but also with the medial frontal cortex was observed, with a decreased effective connectivity between the hippocampus and the parahippocampal gyrus, relatively to healthy controls.

Focusing also on medial temporal lobe damage, Addis and colleagues (2007b) examined a group of patients with left temporal lobe epilepsy. These patients, exhibiting mild AM impairment, showed a general reduction of brain activations within the AM network. Contrary to Maguire et al. (2001), no increased activation was observed in comparison with healthy controls, suggesting the absence of compensatory activity supporting AM retrieval. However, as underlined by the authors, one potential issue related to their findings is the absence of a good matching for MRI AM performance between patients and healthy controls. Addis et al.'s results highlighted that damage in the left hippocampal region also had a distal effect on other key nodes from the AM network, as demonstrated by effective connectivity changes in their patients, with an increased role of the left parahippocampal gyrus and an increased connectivity between the left medial parietal and frontal regions.

Interestingly, as reported by Botzung et al. (2007) in a case of psychogenic amnesia, even in the absence of documented structural damage, AM impairment could give rise to functional cerebral changes. Here, the recollection of normally retrieved memories was sustained by a similar brain network than healthy subjects. Conversely, the evocation of scattered memories pertaining to the patient's 'amnesic life period' showed increased brain activity in the bilateral temporo-parieto-occipital regions.

More recently, a growing interest have been observed for the study of AM functional underpinnings in dementia. For instance, in the prodromal stage, namely in patients with amnestic Mild Cognitive Impairment (aMCI), Poettrich et al. (2009) pinpointed a particular dysfunction of the retrosplenial cortex in aMCI individuals, with in parallel greater activations

in the motor and superior temporal areas, relatively to healthy controls. These findings led the authors to suggest a loss of specificity in the neural network supporting AM. Contrary to these results, Matura et al. (2012) showed no significant functional changes during AM recollection between aMCI individuals and matched healthy controls. In Alzheimer's disease, Meulenbroek et al. (2010) reported greater cerebral activity in a network including prefrontal and occipital regions during AM retrieval. Interestingly, enhanced prefrontal activations were negatively correlated with the hippocampal volume of patients, which, according to the authors, could reflect a compensatory mechanism attempt.

In parallel, Maguire and co-workers (2010) conducted a longitudinal fMRI study for three years in a single case with semantic dementia. While preserved at the beginning of the follow-up, clinically, a gradual loss of AM recollections was observed in this patient within this time frame. Parallel neuroimaging results demonstrated an initial reliance on a similar AM brain network than healthy controls, with then, a progressive setting of cerebral functional changes, reflecting potential brain compensatory mechanisms. In fact, greater neural activity was progressively observed in the medial and lateral prefrontal cortex, the external temporal regions and the precuneus. Although the hippocampal region was engaged in AM recollection during the early stage of the disease, its involvement decreased during the follow-up with atrophy progression.

Another recent line of research has extended this kind of investigations to psychiatric conditions. Indeed, in post-traumatic stress disorder (PTSD), St Jacques and colleagues (2011) documented main higher cerebral activations in the amygdala, the hippocampus and the medial prefrontal cortex during the recollection of emotionally intense negative personal memories, in comparison with normal subjects. Moreover, in individuals suffering from PTSD, these enhanced activations were accompanied by a greater functional connectivity between the medial frontal regions and the amygdala for negative intense memories. Turning to schizophrenia, Cuervo-Lombard et al. (2012) showed a predominant recruitment of cerebral regions in schizophrenic patients similar to those engaged in healthy controls during AM retrieval. Nonetheless, slight differences were also noticed, particularly signs of compensatory mechanism in the caudate nucleus, which showed a positive correlation between its activation and better AM performance in these patients. Reduced neural activity was also observed in the anterior cingulate and lateral prefrontal cortices.

Taken together, these investigations evidenced the occurrence of cerebral functional changes in the AM network in various clinical populations, expressed in some cases by increased cerebral activations, and in other cases, by a reduced reliance on AM key brain structures. Functional connectivity changes have also been reported, with again, evidence of increase or decrease connectivity phenomenon.

As introduced in this section, this literature overview illustrates the challenging issue of the adequate completion of MRI AM tasks by patients to obtain satisfying and interpretable results. Another potential limitation noticed in some of these studies is the absence of a stringent clinical AM assessment conducted in parallel of the neuroimaging task. In fact, the AM behavioural data gathered in the context of MRI testing relied frequently on self-assessment, or in measures reflecting the number of valid trials, or timing of responses, which probably provide an incomplete picture of AM functioning in these patients, especially for patients with only mild difficulties.

Surprisingly, this literature overview highlighted that, to the best of our knowledge, no fMRI investigation dealing with the neural basis of EFT in clinical conditions has been conducted to date. Considering the outcomes obtained for the AM component, this kind of research could though be relevant.

Finally, over and above the theoretical contributions of these studies to the understanding of MTT, these kind of investigations are of value for clinicians and could subserve the development of adequate follow-up and ultimately of rehabilitation strategies. These last points seem of particular clinical importance taking into account the central role played by MTT in everyday life.

5. Remembering the past and imagining the future: why do we do it?

Approximately one third of a waking day is devoted to the mental simulation of personal past and future episodes (Szpunar, 2010), conferring to MTT a particular place in our existence. This omnipresence is actually related to the functional roles and benefits that AM and EFT take on in everyday life.

Indeed, theoretical models attribute to AM several main functions (Bluck, 2003; revisited by Rasmussen and Habermas, 2011), including:

(i) a *self*-function, where AM participates in the construction and the sense of continuity of the self, and provides material to the emergence of self-concepts. In this context, AM contributes to self-coherence but also, to self-enhancement, that is, to provide a positive view of the self. However, although identity and AM share a dynamic link, there are not completely overlapping entities (see Prebble et al., 2013 for recent perspectives about this relationship).
(ii) a *social* function, with an involvement of AM in the development of new relationships and the nurturing of existing ones. More precisely, this social function of AM entails aspects like keeping memories about significant others, memories' exchanges to facilitate social bonding, to elicit empathy or intimacy, or simply to inform people about us.
(iii) a *directive* function, where the past, consciously or not, serves as a basis for guiding present and future behaviours, especially for specific past episodes.
At a more general level, AM could be of particular importance in conditions where self-change, self-preservation/enhancement or self-regulation are required (Robinson, 1986; Cohen, 1998; Wilson and Ross, 2003).

Regarding EFT, three main functional benefits have been linked with this MTT component which, based on Szpunar (2010), encompass:
(i) a *coping* function, with a positive influence of the simulation of hypothetical scenario on emotion regulation and problem solving in the context of stressful events. In other words, future simulations enable to anticipate potential obstacles and outcomes, which, when done in a positive manner, contribute to reduce worries about the outcomes and to choose the best scenario. Moreover, the mental generation of a future event could also have a motivational effect to cope with a difficult situation and to work toward the desired goal.
(ii) a *goal achievement* function, for which the imagination of future events allows the setting up of a plan of action, taking into account various approaches and options to reach our goal. Moreover, the sequencing of actions could also promote the initiation of those actions in future.
(iii) an *implementation of intentions* function, which is closely linked to the previous function. Here, the simple act of forming the intention to achieve an action is associated to a greater likelihood of doing that action. Concretely, the formation of an intention contributes to define the 'when', the 'where' and the 'how' of an action.

This brief review of the functional significance of AM and EFT emphasises how central these processes are in human's life and how conjointly AM and EFT contribute to a

person's sense of self and of personal continuity over time. As a consequence, the study of AM and EFT in clinical conditions could be considered to be a priority. Indeed, brain injuries provoke disruptions in all everyday life's realms, from personal identity and self-perception, to social and professional situations, or to emotional issues, to cite a few of them. This last point brings us to the next chapter dealing with the challenging aim of helping brain-injured individuals to cope with and to improve their everyday life functioning by means of neuropsychological interventions.

CHAPTER 2

Neuropsychological rehabilitation: helping patients to cope with cognitive impairment

Historically, the interest for the field of neuropsychological rehabilitation has particularly arisen from the necessity to face the consequences of World War I and World War II in terms of thousands of young brain-injured soldiers (Prigatano, 1986; Johnstone and Stonnington, 2009). To cite a few renowned clinicians, Kurt Goldstein's (1942), Oliver Zangwill's (1947) or Alexander Luria's (1969) major contributions are still present in the modern vision of cognitive rehabilitation.

According to Prigatano (1999), the process of neuropsychological rehabilitation begins with the psychologist's understanding of what are the patient's experiences regarding his or her higher cerebral functions or dysfunction(s). Importantly, thanks to the expansion of neuropsychological rehabilitation in the last decades, 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 the other factors (Wilson and Gracey, 2009).

In a more formal manner, nowadays, cognitive rehabilitation is defined as aiming "to enhance the person's capacity to process and interpret information and to improve the person's ability to function in all aspects of family and community life" (US National Institute of Health Consensus Statement; 1999).

According to the World Health Organisation (2002), two general approaches coexist in cognitive rehabilitation: (i) the *cognitive function retraining*, which aims to improve the underlying cognitive impairment, in the context of a restorative approach. This kind of interventions typically involves the use of training exercises, focusing on a specific cognitive domain. In general, these exercises are hierarchically organised and require a repetitive practice. However, few benefits in everyday life functioning have been reported in the literature, probably related to the fact that these exercises share only slight similarities with real life activities (Sloan and Ponsford, 2013); (ii) The *functional compensation*, whose primary goal is to enhance everyday life functioning by using compensatory strategies. In opposition with the previous approach, here the goal is not to 'restore' but to 'improve'. This approach deals with various issues (i.e. domestic life, employment, self-care, personal

relationships, etc), the aim being in every case, to use the strengths of the patient to compensate cognitive impairment in specific domains that are meaningful and self-relevant for the person. Different means are documented to improve cognitive functioning, including internal strategies (e.g. mnemonic strategies or routines), external strategies (e.g. diary, checklists) or environmental restructuration (e.g. placement of a calendar-block, working in a quiet room). Importantly, whatever the compensatory mechanisms considered, the rehabilitation process encompasses its implementation within day-to-day activities (Sloan and Ponsford, 2013).

Thus, in the last decades, a shift in neuropsychological rehabilitation occurred, moving from an approach focused on drills and exercises to a goal directed approach, where patients, families and rehabilitation staffs work together to define appropriate goals and intervention programmes (Wilson and Gracey, 2009). In this context, cognitive rehabilitation is perceived as an interactive process between several individuals, especially the patient and the therapist(s). Likewise, measures of the functional benefit of rehabilitation in daily life are nowadays mandatory, in addition to more classical measures of assessment (i.e. neuropsychological tests). Although some inconsistent results have been reported following cognitive interventions, Wilson et al. (2003) have identified several reasons for the current success and positive outcomes of behavioural interventions: the availability of many techniques aiming to increase/decrease desirable/problematic behaviours, the specification of the intervention goal at the beginning process (and thus, the definition of the intervention end), the continuous monitoring of behavioural changes, the individualisation of treatment, as well as the current availability of guidelines to design intervention programmes.

In the broad spectrum of cognitive dysfunction, memory impairment is one of the most frequent issues following brain injury since remembering requires the interaction of several cognitive systems like attention or executive functions, but also because memory is sensitive to mood disorders (Evans, 2009). Beyond its frequency, memory disorders clearly disrupt the ability to participate in daily life activities. Thus, it is not surprising that a broad body of rehabilitation researches aimed to alleviate memory impairment.

1. Cognitive rehabilitation of memory disorders

Different strategies have been used in the context of memory interventions, with fluctuating degrees of success (Skeel and Edwards, 2009). However, one strongly consistent finding is the inefficiency of training exercises to enhance memory, whereas the use of compensatory strategies seems to be the most effective approach (Cicerone et al., 2005; Cappa et al., 2005).

Regarding the compensatory interventions, several main internal strategies have been reviewed by Evans (2009), including techniques like (i) *making associations*, in which the material to memorise is linked to meaningful prior knowledge or self-relevant information to promote its subsequent retrieval; (ii) *visual imagery*, which is particularly relevant in the context of verbal memory disorder; (iii) *chunking*, consisting in regrouping information to favour their retrieval; (iv) *mental retracing*, especially useful to remember where something was put, by sequentially retracing our movements, activities or thoughts; (v) *errorless learning*; (vi) *PQRST*, for Preview Question Read State Test technique, which helps in circumstances where a precise material has to be learnt (e.g. chapter from a book, newspapers articles); (vii) *mindmaps*, using multiple modalities by representing the information with verbal, visual and spatial supports put on a paper, with a tree-like organisation, to make the information more memorable.

According to an evidence-based review from Ehlhardt et al. (2008), regarding the management of memory deficit, positive outcomes were favoured by the combination of different strategies tailored to the learning conditions and no single approach has been reported as systematically more effective than another. Nevertheless, several factors could promote the success of learning strategies like a clear definition of the intervention's goal, the training in an ecological context with practice trials distributed over the intervention and with multiple exemplars, as well as the restriction of the error possibility during the rehabilitation process.

Moreover, as mentioned by Glisky (2004) the origin of memory impairment also influences the outcomes of cognitive interventions. In fact, in the context of severe encoding or consolidation deficit, resulting notably from medial temporal lobe damage, whatever the internal strategy proposed, memory enhancement remains difficult to obtain. Thus, for people with more severe memory disorder, the use of external aids should be preferred. On the

contrary, when memory impairment is more related to executive dysfunction, the intervention could focus on the implementation of efficient learning strategy. Besides, another major issue in neuropsychological rehabilitation is self-awareness and insight, whose absence substantially limit the use of compensation strategy (Giacino and Cicerone, 2000).

Overall, while the great majority of studies have focused on anterograde memory rehabilitation, more recently, a growing interest for the development of therapeutic interventions to improve AM functioning has been observed, probably due to its importance in everyday life functioning.

1.1. Managing AM disorders

To the best of our knowledge, the first investigation dealing with AM enhancement is the work by Berry and colleagues (2007) in a patient with limbic encephalitis. Considering the severe AM impairment exhibited by this patient, the therapeutic intervention relied on the use of an external device named SenseCam, which is a wearable camera taking automatically pictures and enabling the further rapid serial visualisations of a large number of pictures, like a movie. Thus, the rehabilitative strategy consisted in the revisualisation of selected important events (chosen by the patient), with the support of her husband. Positive outcomes on AM functioning were observed for this patient, with maintenance of the benefit at the long-term follow up. Moreover, based on the AM results and the patient's comments, the use of the SenseCam seemed more efficient and comfortable than the use of a classical written diary. Later, the SenseCam device has also been used by Brindley and co-workers (2011) in a patient with acquired brain-injury following an assault, who suffered notably from AM difficulties and anxiety disorder. In this single-case study, a particular interest was given to the retrieval of anxiety-provoking personal events for their further use into a broader cognitive-behavioural therapeutic work addressing his anxiety disorder. Again, results showed that the SenseCam efficiently supported memory retrieval, with greater benefit than the use of written diary. In the past few years, the use of the SenseCam device has tremendously grown and results of its positive outcomes on AM have been reported in additional brain-damaged patients with AM impairment (Browne et al., 2011; Hodges et al., 2011; Loveday and Conway, 2011) or even in a child with amnesia (Pauly-Takacs et al., 2011), and more recently in Alzheimer's disease (Woodberry et al., 2014). In parallel, the use of smartphone to support AM functioning in Alzheimer's disease patients has also been tested by De Leo and

colleagues (2011). Their smartphone device was based on the same general principles than the SenseCam and these authors reported a significant AM improvement in this patient, with no feeling of intrusion of the device in daily routines.

Cognitive intervention focusing on AM were also designed for schizophrenic patients. In fact, Blairy and colleagues (2008) developed a group intervention during which patients were trained to recollect specific AMs with the support of a written diary. While the benefit on AM remained modest, an enhancement of AM abilities was found immediately after the intervention, as well as three months later. Using a similar approach combining group sessions and a written diary focusing on specific memories, Ricarte et al. (2012) showed after an event-specific memory training an improvement of the number of retrieved specific memories. This memory improvement was also accompanied with an increase of autonoetic awareness and a decreased of the depressive symptomatology. Recently, Potheegadoo et al. (2014) also documented the effectiveness of a specific cueing procedure based on the AI test on the specificity of AMs, in schizophrenic patients.

Some investigations also examine the benefit of the MEmory Specificity Training (MEST) on AM, which encompasses a series of group sessions and homework tasks aiming to help patients to distinguish specific memories from overgeneral memories and to train them to evoke specific memories. Positive outcomes were obtained with the MEST programme in patients suffering from depression (Raes et al., 2009; Neshat-Doost et al., 2013) with a conjoint improvement of depressive symptomatology, but also more recently in patients with PTSD symptoms, which showed both an increase of memories' specificity and a reduction of PTSD symptoms after intervention (Moradi et al., 2014).

Overall, these studies provided evidence of benefits of cognitive interventions on AM and everyday life functioning of patients. Two lines of research seem to have been explored so far, on the one hand the use of external devices (SenseCam, diaries, smartphone), and on the other hand the application of training programmes to improve AMs' specificity. A further review also highlights that the use of training programme has only been applied in psychiatric diseases, whereas external devices were principally used in neurologic conditions, in the context of relatively severe AM impairment.

However, considering the occurrence of some neurological conditions in young adults, for example MS, resulting sometimes in only mild-to-moderate AM disorder (Ernst et al., 2013),

the need for new cognitive interventions for AM is warranted. A challenging aim would also be to provide the most integrated strategy to optimise its use in the great majority of everyday life situations (i.e. professional, personal, social, etc).

Nevertheless, since cognitive rehabilitation involves certain financial costs, one matter of debate across countries is the clinical and cost-effectiveness of neuropsychological interventions (Wilson, 2009). Some authors like Wood et al. (1999) highlighted that both the direct (i.e. funding necessary to treatment) and the indirect (i.e. payment of time off work, sickness benefit, etc) costs should be considered as parts of the debate. Despite the economic inquiries conducted in different countries, and the growing evidence that cognitive interventions could be economically effective, a certain scepticism remains (Wilson, 2009). As a consequence, the need to provide strong and well-established proofs of the effectiveness of new therapies becomes higher than before. This demand opens up towards neuroimaging techniques to fulfil that purpose.

2. Using neuroimaging to demonstrate the effectiveness of neuropsychological interventions

The application of neuroimaging techniques in the context of neurorehabilitation emerged from the primary demonstration of practice-related cerebral changes in healthy subjects in different cognitive domains, showing in some cases increase, decrease, redistribution or reorganization of cerebral activations with practice (see Kelly et al., 2006 for a review). The rationale being that the understanding of brain mechanisms sustaining practice-induced effects will contribute to detect those involved in repair and recovery of brain-damaged patients. In parallel, the presence of some degree of spontaneous brain plasticity was also documented in clinical conditions several years ago (Chollet and Weiller, 1994; Robertson and Murre, 1999). Beyond the challenge of understanding the underlying brain functional compensatory mechanisms, in the context of cognitive rehabilitation, functional neuroimaging techniques could also represent a useful tool to measure the effectiveness of interventions and, ultimately, a support for patient's selection, or individual adaptation of the intervention (Strangman et al., 2005). However, although a growing number of pre-post rehabilitation fMRI studies are reported, this kind of investigations is in its early days, with a

clear need for further investigations. Some illustrations of these works are provided in the following paragraph.

For instance, in the case of stroke, several studies showed cognitive improvement following rehabilitation, accompanied by cerebral functional changes in the domain of attention (Lincoln et al., 2000), spatial neglect (Langhorne et al., 2011), or working memory (Westerberg et al., 2007). Nevertheless, contradictory findings were also documented with the absence of positive outcomes in post-facilitation, for example for language (De Jong-Hagelstein et al., 2011).

This kind of study design was also applied in the context of traumatic brain injury in patients with acquired reading deficit by Laatsch and Krisky (2006), who demonstrated functional changes at both behavioural and cerebral levels. Focusing on visuospatial attentional abilities in traumatic brain injury patients, Kim et al. (2009) highlighted induced brain activity changes expressed both by a decreased frontal activity and an increased activity in the anterior cingulate gyrus and the precuneus with performance improvement.

Relevant findings have also been obtained in the case of schizophrenia, notably with the work of Wykes and colleagues (2002) dealing with the improvement of working memory functioning. Cognitive improvement was accompanied in this case by enhanced activations in the frontal regions. Enhanced frontal activations following a working-memory cognitive intervention were also reported by Haut and co-workers (2010) in schizophrenic patients. In parallel, after a cognitive intervention, Edwards et al. (2010) showed in schizophrenic patients a normalisation of the brain network sustaining cognitive control, relatively to healthy subjects.

Interestingly, significant functional cerebral changes have been documented following psychotherapy in several conditions, in particular in depression (Collerton, 2013 for a review). During the last years, a growing number of studies focusing on neuropsychological rehabilitation has also been observed in MS, with the conjoint investigation of their functional correlates, and these studies showed promising results. Since MS affects particularly young people, frequently in the most productive period of their life at professional and personal levels, the development and demonstration of the effectiveness of cognitive interventions is particularly important in this disease. Therefore, after a general presentation of MS and its clinical characteristics, a more detailed review of these rehabilitation studies will be done in the next chapter.

CHAPTER 3

Multiple sclerosis: general considerations, cognitive impairment and cognitive rehabilitation

1. Demographical and clinical data

Multiple sclerosis is nowadays the most frequent chronic neurological condition in young adults, with an overall prevalence estimated at least 50/100 000 (Debouverie et al., 2007a). In most of the cases, the diagnosis of MS is established in patients aged between 20 and 40 years and approximately 75% of the cases are women (DeLuca and Nocentini, 2011). An intriguing point is the unequal geographical dispersion of the MS prevalence through the world, with a higher prevalence in the north hemisphere than in the south countries (Rosati, 2001; DeLuca and Nocentini, 2011). Related to this last point, while the exact origin of MS remains unclear, several environmental factors like the aforementioned north-south gradient, but also hygiene and lifestyle, viral or bacterial infections (Ascherio and Munger, 2007a, b), in interaction with genetic factors seem to be involved in the disease.

At the neuroanatomical level, MS is characterised by inflammatory processes, which could appear in the whole central nervous system. This inflammation conducts to demyelination processes in focal areas of the brain or the spinal cord of patients, in which myelin, myelin-forming cells (oligodendrocytes), and axons are destroyed (Trapp and Nave, 2008). In this context, MS is particularly characterised by its multifocal and diffuse nature.

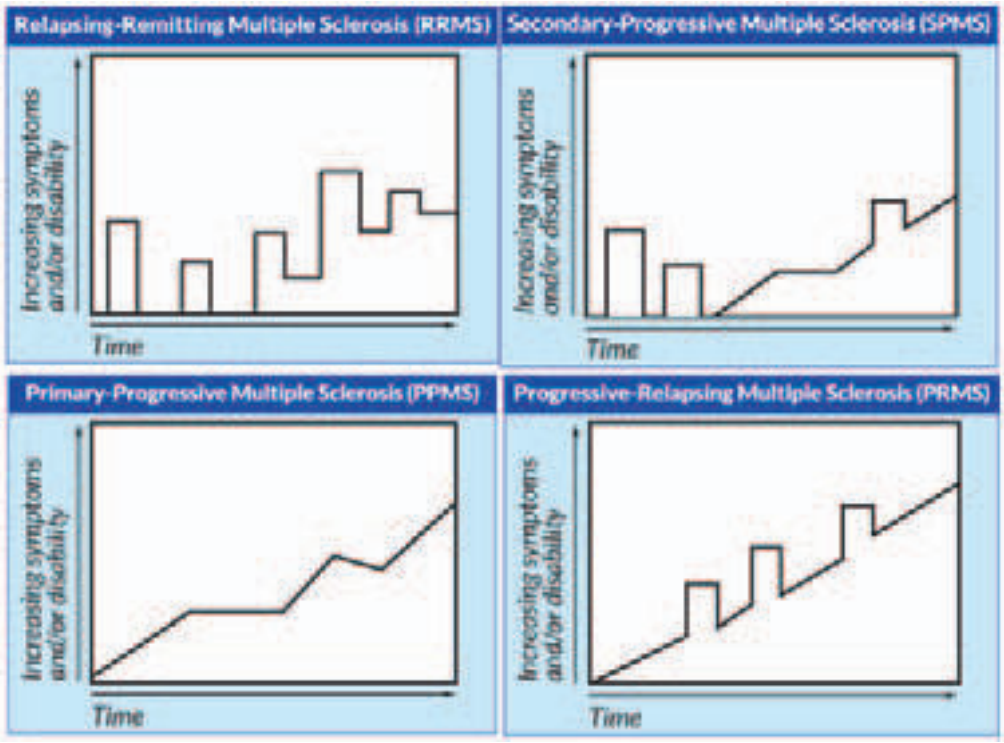
The clinical evolution of MS could take on two kinds of clinical forms: (i) *relapse*, exacerbation or attack, which is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the central nervous system, current or historical, with duration of at least 24 hours, in the absence of fever or infection; (ii) *insidious neurological progression*, which corresponds to one year of disease progression (retrospectively or prospectively determined), with a worsening of neurological symptoms (Polman et al., 2011).

Currently, the diagnosis of MS is established based on the revised criteria of Polman et al. (2011), which include the following points: (i) the presence of at least two attacks with objective clinical evidence; (ii) the dissemination in space, with lesions in at least two regions

of the central nervous system; (iii) and/or the dissemination in time, with lesions observed at different time of the follow-up.

Different disease courses are also distinguished in MS, which are variables across the patients, but also sometimes within the same patient through disease progression. Four main subtypes of MS are distinguished (DeLuca and Nocentini, 2011; Figure 1):

- *Relapsing-remitting MS (RR-MS):* corresponds to almost 85% of the cases at the initial diagnosis. This form is characterised by alternating phases of relapse of symptoms and partial or complete remission, but with no disease progression between relapses.
- *Secondary progressive MS:* follows an initial period of RR-MS, with a conversion to the progressive form as a worsening of neurological functioning, with only minor improvements, is observed.
- *Primary progressive MS:* is characterized by a disease progression since onset, with sometimes stationary phases or mild and transient improvement.
- *Progressive relapsing MS:* is described as a progressive worsening since disease onset, but with additional attacks or exacerbations over time, for which varying degrees of recovery are observed.



(Source: Multiple Sclerosis Association of America website)

Figure 1. Different types of MS disease course

Turning to MS treatment, no curative treatment are nowadays available. However, several pharmacological treatments are proposed to restrain disease progression, with three different lines (Lyon-Caen and Clanet, 1997): (i) the treatment of acute relapse with corticosteroids; (ii) disease modifying treatments (immunosuppressors or immunomodulators), which aim to prevent relapses and to slow disability progression; (iii) symptomatic treatments, which are used to manage MS symptoms (e.g. spasticity, fatigue).

As described earlier, MS has been long-standing and widely described as a white matter disease. However, with the evolution of neuroimaging techniques, it is now well established that MS neuropathological processes could also affect extensively grey matter even at the early stage of the disease, (Chard and Miller, 2009; Filippi and Rocca, 2010), resulting sometimes in detectable brain atrophy (Morgen et al., 2006; Nocentini et al., 2012). Moreover, neuroimaging technical progresses have also allowed the visualisation of lesions in the normal-appearing white and grey matter (Zaaraoui et al., 2010). In parallel, fMRI studies enabled to investigate indirectly the consequence of MS pathology on brain activity, showing cerebral functional changes in MS patients in motor or cognitive tasks (Caramia et al., 2010; Zaaraoui et al., 2010).

As a consequence of this extensive range of neuropathological processes and the potential occurrence of lesions in the whole central nervous system, MS could entail a broad spectrum of symptoms.

2. Symptomatology of MS

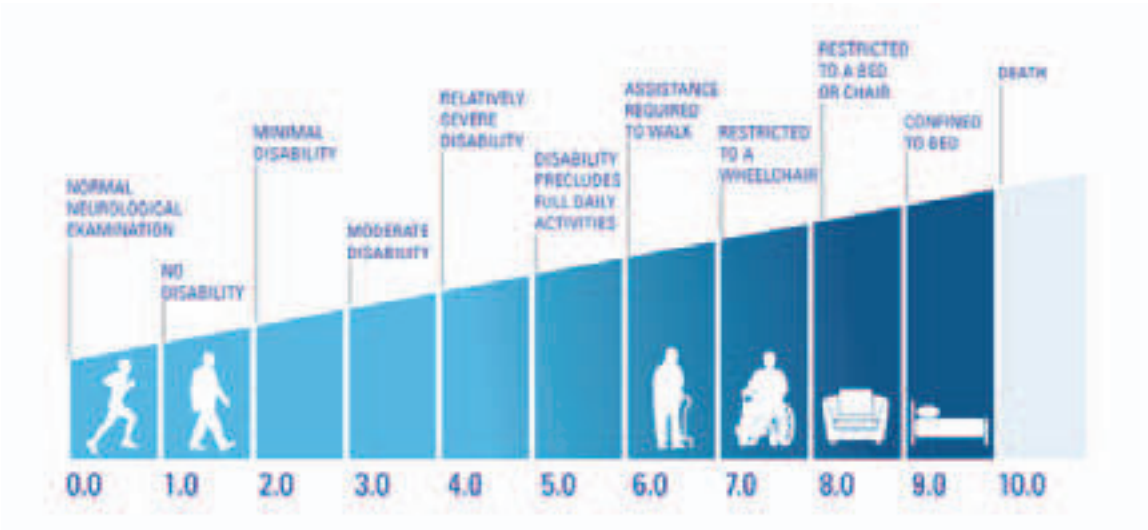
Clinical manifestations of MS covered a wide range of symptoms, with a high variability of the functional alterations and their severity between patients. While the initial presentation of the disease is manifested by an isolated symptom in 45 to 65% of the cases, through disease progression, multiple functional disabilities coexist frequently in the same patient.

2.1. Physical disability

The presence of physical impairment in MS patients is usual and involve sensitive (e.g paraesthesia, anaesthesia), motor (e.g. spasticity, muscular weakness), visual (e.g. optic neuritis, diplopia) symptoms, as well as cerebellar (e.g. tremor) and vestibular signs (e.g.

dizziness), but also bladder dysfunction, bowel problems and sexual dysfunction (Lyon-Caen and Clanet, 1997).

One of the worldwide gold standard to assess physical disability in MS is the EDSS score (Kurtzke, 1983), which is a scale heavily based on neurological exam. The EDSS is a 10-point scale, going from 0 being a normal neurological exam, to 10 corresponding to death due to MS, with intermediate level of disability between these two extremities (Figure 2).



(Source: http://rockvilleroadies.com/multiple-sclerosis/)

Figure 2. Graphical representation of the levels of disability in MS assessed by the EDSS

Regarding treatment for physical symptom in MS, different strategies could be adopted, depending on the symptoms and the patient's needs, including pharmacological, surgical, physiotherapy treatments or occupational therapies (Thompson et al., 2010; Correja de Sa et al., 2011).

2.2. Emotional disturbances and neuropsychiatric syndromes

Feinstein (2007) reported several mood, affective and behavioural disturbances, which could be observed in MS patients, and gathered in six syndromes, *depression* being the most common syndrome, with a lifetime prevalence in MS patients of 50%. In this context, MS patients are also at elevated risk of suicide (5 to 10 times higher in the MS population than in the general population; Siegert and Abernethy, 2005). Facing this high prevalence and the clinical consequences of depression, one challenging question regards the aetiology of

depression. Here, several causes and influent factors have been mentioned, notably brain lesions, psychosocial determinants, fatigue, or potential side effects of disease modifying treatment, all these factors probably also interacting between them (Siegert and Abernethy, 2005; Feinstein, 2007; Thomas et al., 2007).

The five remaining syndromes include (i) *bipolar affective disorder*, with a prevalence of twice than in the general population (Schiffer et al., 1986); (ii) *euphoria*; (iii) *pseudo-bulbar affect* (approximately found in 10% of MS patients); (iv) *psychosis,* which is a more rare condition in MS but seems even though to occur two to three times more frequently in MS patients than in the general population; (v) *personality change*.

Naturally, these six categories are not comprehensive and some other emotional disturbances like *anxiety* (Korostil et Feinstein, 2007), *apathy* (Figved et al., 2005) or *alexithymia* (Chahraoui et al.,2008) have also been described in MS patients.

Nevertheless, an important point in clinical practice is the identification of potential mood and emotional disturbances to offer suitable treatment (pharmacological or psychological therapies) but also to take into account their impact on other MS related symptoms like fatigue and cognitive impairment, and more generally on quality of life. Indeed, while the temporal nature of the relationship between depression and cognitive impairment remains unclear and inconsistent between studies, MS patients experiencing greater global cognitive decline seem to report more depressive symptoms (Barwick and Arnett, 2011). More generally, as depression and other emotional disturbances could lead at their own to cognitive impairment, their great occurrence in MS required a particular attention during clinical routine assessment.

2.3. Fatigue

One of the most common symptoms in MS is obviously fatigue, which is reported in 70 to 90% of patients (Fisk et al. 1994; Freal et al., 1984). Since fatigue is a subjective symptom, obtaining a clear definition of this construct is challenging. However, the MS Council for Clinical Practice Guidelines proposed in 1998 the following definition: “a subjective lack of physical and/or mental energy perceived by the individual or the carer as interfering in daily life activities”. Fatigue in MS could be acute (present for less than six weeks) or chronic (present more than 50% of time for more than six weeks), and affect physical, as well as cognitive dimensions. Importantly, fatigue is neither clearly correlated

with demographical and disease severity variables, nor lesion burden detected by neuroimaging (Béthoux, 2006).

Currently, no strong pathophysiological hypothesis emerged to explain the exact origin of fatigue in MS. Nevertheless, several factors seem to contribute to fatigue in MS, like psychiatric disorders, sleep disturbance, pain, pharmacological treatments, infections, or deconditioning to effort (Béthoux, 2006). Besides, only few treatments are devoted to the improvement of fatigue symptoms, including pharmacological and non-pharmacological approaches, but with variables outcomes (Béthoux, 2006).

In this context, specific questionnaires to assess fatigue in MS have been developed worldwide, notably the Fatigue Impact Scale (Fisk et al., 1994), which has been translated and culturally adapted for use with French MS patients (EMIF-SEP; Debouverie et al., 2007b). EMIF-SEP comprised 40 five-point scale items (21 items in the short form), organised in three dimensions: cognitive, physical and social fatigue. In clinical routine, this self-assessed scale could be useful to obtain an overview of the fatigue experienced by the patient in his/her everyday life in a quick and more objective manner.

As for emotional disturbances, the consideration of fatigue in MS patients is mandatory in clinical practice, owing to its deleterious impact on several dimensions. Notably, during cognitive assessment, fatigue could result in poorer cognitive performance (Andreasen et al., 2010; Claros-Salinas et al., 2010) or in a great variability of responses (Bruce et al., 2010). Thus, as fatigue could be fluctuant between patients, but also within the same patient between and within sessions, particular attention and flexibility during cognitive assessment are essential.

2.4. Cognitive impairment

Since the inaugural work by Rao et al., (1991a), the presence of cognitive impairment in MS patients is well established and occurs in 30 to 70% of the patients. The most common cognitive impairment observed in MS include anterograde memory (verbal and visual modalities), information processing speed, attention, working memory, visuospatial abilities and executive functioning (Zakzanis, 2000; Chiaravalloti and DeLuca, 2008). On the contrary, language and instrumental functions, intellectual efficiency, short term memory and semantic memory seem better preserved (Rao et al., 1991a; Defer et al., 2001; Patti, 2007).

Cognitive impairment can be observed in the early stage of the disease, even in Clinically Isolated Syndrome (Glanz et al., 2007), or in patients with only mild level of functional disability (Ruggieri et al., 2003). Besides, cognitive dysfunctions are more often observed in MS patients with progressive disease course than patients with RR-MS course (Winkelman et al., 2007). However, the relationship between cognitive impairment and physical disability, as well as with the disease duration showed contradictory findings (Rao et al., 1991a; Confavreux and Vukusic, 2006; Nocentini et al., 2006).

2.4.1. Neuroimaging and cognitive impairment in MS

2.4.1.1. Structural neuroimaging

Conventional magnetic resonance imaging techniques, and particularly T2-weighted, T1-weighted, and gadolinium-enhanced T1-weighted sequences, are powerful tools to highlight the presence of focal lesions in MS patients (Zaaraoui et al., 2010). However, regarding the relationship between total lesion load and cognitive impairment, contradictory findings emerge from the literature. Some studies show a correlation between these two variables in whole brain or in particular brain regions (Swirsky-Sacchetti et al., 1992; Foong et al., 1997; Sperling et al., 2001) but other findings highlight the absence of correlations (Fulton et al., 1999; Reuter et al., 2011).

Nevertheless, beyond the macroscopic lesions, microscopic lesions, namely abnormalities in the normal appearing brain tissue, are present in MS. However, this kind of lesions is not efficiently detected with conventional neuroimaging techniques, resulting in an incomplete picture of the lesion load (Filippi et al., 2000). Thus, using notably magnetisation transfer ratio technique, which enables to detect more powerfully both macroscopic and microscopic lesions, some studies shed some light on the relationships between the diffuse brain lesions in MS and disease variables, showing a better correlation between lesion load and cognitive impairment (Filippi et al., 2000; van Buchem et al., 2000; Cox et al., 2004).

In the same vein, the development of DTI has also allowed to better understand MS pathology, with the possibility to discriminate axonal and demyelinating damage. Indeed, DTI enables the visualisation of abnormalities in the normal appearing white and grey matter, but also in lesion tissue (Sbardella et al., 2013) and provides also the basis to explore anatomical connectivity by the technique of tractography (Rocca et al., 2008). The two most commonly used DTI derived measures are (i) the mean diffusivity, which measures overall water

diffusion without any directionality, with higher value reflecting higher diffusivity; (ii) the fractional anisotropy, which is a scalar value ranging from 0 (isotropic diffusion, i.e free water diffusion, as in cerebrospinal fluid) to 1 (anisotropic diffusion, i.e. constrained water diffusion in organised tissues, as in myelinated fibres), and corresponds to the prevalence of diffusivity along one direction (Sbardella et al., 2013). Several studies have shown strong correlations between DTI metrics in whole brain and cognitive impairment (Rovaris et al., 2002; Rovaris et al., 2008; Yu et al., 2012). In parallel, some investigations have adopted a more regional approach, demonstrating notably an association between corpus callosum abnormalities and impaired processing speed, impaired explicit visuomotor sequence learning or general cognitive dysfunction (Lin et al., 2008; Roosendaal et al., 2009; Bonzano et al., 2011; Llufriu et al., 2012; Bodini et al., 2013), but also between fronto-subcortical tracts and executive function deficit (Rocca et al., 2008), as well as between thalamic abnormalities and working memory impairment (Audoin et al., 2007; Tovar-Moll et al., 2009). Focusing on anterograde memory, Fink et al. (2010) also demonstrated a relationship between memory performance and the right uncinate fascicle.

This line of research leads to the suggestion of disconnection at the origin of cognitive dysfunction in MS (Dineen et al., 2009). This phenomenon has been described as the occurrence of disconnection between cortical or subcortical regions sustaining cognitive functions, at the level of interconnecting white matter, or in cortical stages within the association cortex (Catani, 2006). In the context of MS, this hypothesis is coherent with the diffuse and multifocal nature of the neuropathology. Thus, in their study, Dineen et al. (2009) showed significant correlations between working memory, verbal and visual anterograde memory performance and several overlapping, but also distinct, tracts within the whole brain in MS patients. They concluded that mapping the functional anatomic disorganisation of cognitively relevant brain regions could provide new insights into functional connectivity, and spontaneous brain plasticity observed in MS patients during cognitive tasks, and especially how these cerebral mechanisms are functional or disrupted. For instance, Kern and colleagues (2012) have recently demonstrated that structural damage in the fornix was associated with altered neural activity in the hippocampus during the completion of a memory task in MS patients. More precisely, they observed that patients with greater fornix damage showed also less signs of compensatory brain mechanisms, resulting in poorer memory performance.

Finally, at a more general level, some studies aimed to investigate the link between brain atrophy and cognitive impairment in MS. In particular, cortical atrophy has been found to be associated with attentional, executive functions and verbal memory deficits in MS patients (Amato et al., 2004; Morgen et al., 2006). However, stronger correlations between regional brain atrophy measures and cognitive impairment have been displayed, in particular between memory performance and atrophy in temporal and frontal sub-regions (Benedict et al., 2005). In the same manner, Morgen and co-workers (2006) showed a correlation between working memory performance and fronto-parietal atrophy. Besides, it seems that the frontal region is the most prone to brain atrophy and its atrophy is the best predictor of impairment in verbal learning, spatial learning, attention, and conceptual reasoning in MS patients (Benedict et al., 2002). Nevertheless, a recent investigation pinpointed that the negative impact of brain atrophy on cognitive functioning could be attenuated in MS patients with a higher degree of cognitive reserve in the case of information processing efficiency (Sumowski et al., 2009).

This last finding, showing evidence of a modulation effect of the deleterious impact of brain structural damages on cognitive functioning, is actually an important and well-documented question in MS literature. In fact, whatever the structural neuroimaging techniques considered, the magnitude of the correlation between neuroimaging and clinical findings remains suboptimal (Filippi and Rocca, 2009; Caramia et al., 2010). Several contributor factors have been proposed, including the irregular efficacy of reparative and recovery mechanisms following tissue damage (e.g. remyelination, resolution of acute inflammation), but also the presence of spontaneous brain plasticity, or functional compensatory mechanisms (Filippi and Rocca, 2004; 2009). This review opened onto an important and growing body of investigations using functional neuroimaging techniques to refine our understanding of cognitive dysfunction in MS patients.

2.4.1.2. Functional neuroimaging

Currently, cortical adaptive changes are considered as contributors in limiting the clinical expression and consequences of structural damage in MS, although their exact role remains unclear (Filippi and Rocca, 2009).

Penner et al. (2006) posited that the relation between cognitive dysfunction and functional brain changes follows an inverted U-shaped curve, where the ability to compensate impairment is restricted at a certain threshold, from which, once the compensatory

mechanisms are exhausted, the impairment would be manifested. Different expressions of spontaneous brain plasticity have been described, entailing functional enhancement, that is, increased cerebral activation in a brain area also recruited by healthy controls, and/or the recruitment of alternative brain areas, frequently controlateral (Cader et al., 2006; Hulst et al., 2012). At the neurobiological level, brain plasticity could be sustained by "increased axonal expression of sodium channels, synaptic changes, increased recruitment of parallel existing pathways or 'latent' connections, and reorganisation of distant sites" (Filippi and Rocca, 2009, p. 574). Regarding the link between lesion load and the extent of functional reorganisation, inconsistent results have been obtained and thus, this question remains a matter of debate (Filippi and Rocca, 2009).

An overview of the cognitive fMRI investigations conducted in MS highlighted a primary focus on the study of working memory (Staffen, et al., 2002; Wishart et al., 2004; Chiaravalloti et al., 2005a; Morgen et al., 2007; Forn et al., 2012). Taken together, these studies showed increased cerebral activations in MS patients to compensate cognitive impairment, predominantly located in the fronto-parietal areas (see also Kollndorfer et al., 2013 for a review). However, in some of these examinations, more extensive brain activations were displayed, involving supplementary cingulate and precuneus activity (Forn et al., 2012), or cingulate, temporal, and occipital activations (Wishart et al., 2004) or hippocampal/parahippocampal and cingulate activations (Rachbauer et al., 2006). Moreover, Cader and colleagues (2006) demonstrated an adaptive mechanism expressed by an altered inter-hemispheric functional connectivity in prefrontal regions in MS patients during the completion of a working memory task.

To the best of our knowledge, two reports dealt with information processing speed functional underpinnings in MS. In MS patients with slowed RT, Genova et al. (2009) showed a decreased cerebral activity in the bilateral fronto-parietal regions, with a conjoint reliance on the insula, thalamus and anterior cingulate (which differed from the cerebral network engaged by healthy controls), whereas Smith et al. (2012) showed increased neural activity in the prefrontal regions and the right left temporal, with conjoint decrease of the left temporal regions in their MS patients.

Although only a few studies have been conducted on anterograde memory performance, they demonstrated functional changes. Thus, Bobholz et al. (2006) showed predominant cerebral changes during the retrieval phase of the task, located in the fronto-parietal regions. Likewise,

Morgen et al. (2007) demonstrated differential brain activity in the parietal regions during maintenance and recognition of verbal information, while similar cerebral activations were observed during encoding in MS patients and healthy controls. Moreover, an association between the rate of correct memory answers and fronto-parietal activations was observed. Greater fMRI activity has also been reported in MS patients with higher memory performance (in comparison with those with lower performance), particularly in the prefrontal and temporal cortex (Mainero et al., 2004). More recently, Hulst et al. (2012) underlined differential activity in the hippocampus between cognitively preserved patients, showing increase activity in this region, and cognitively impaired patients, which showed less hippocampal activation, during the successful encoding.

Despite the frequent occurrence of dysexecutive impairment in MS, to the best of our knowledge, only two fMRI studies were conducted. The first one focused on planning abilities in MS patients and highlighted similar brain activations in the patients and healthy controls, despite impaired planning performance in the MS patients group (Lazeron et al., 2004). On the contrary, Helekar and co-workers (2010) showed brain compensatory mechanisms in MS patients during the successful completion of a task involving abstraction and cognitive shift. In fact, significant changes in the functional connectivity have been displayed, including a lower number of functional brain networks of smaller sizes and a strengthening of ipsilateral connections in brain sites located in intermediate distances.

However, as underlined by Filippi and Rocca (2009), a major issue, restricting the conclusions that could be drawn from some of these studies, is the difference of task performance between MS patients and healthy controls, mostly present in the aforementioned seminal papers. In fact, in this context, the differences reported in the brain activations could be the consequence of difference of performance or use of discrepant cognitive strategies, and so, could not be interpreted with certainty as the consequences of pathology on the considered cerebral network (Liu et al., 2011).

This review, beyond the methodological recommendations for further studies, also opened onto another set of fMRI investigations in MS focusing on the default brain network. In fact, the use of resting-state sequences, with no overt task to complete during the MRI acquisition, circumvents the aforementioned issue of performance difference between MS patients and healthy controls. Overall, studies based on resting state sequences have shown congruent

results with cognitive task related fMRI paradigms, with increased neural activity in the default brain network of MS patients (Roosendaal et al., 2010; Liu et al., 2011) and functional connectivity changes between key regions from the default-network (see Filippi et al., 2013 for a review).

2.4.2. Improving cognitive impairment in MS patients

Importantly, cognitive impairment in MS patients have an impact on everyday life functioning and quality of life (Chiaravalloti and DeLuca, 2008). Indeed, cognitive deficits largely contribute to unemployment in MS patients (Rao et al., 1991b). More precisely, Benedict et al. (2006) have found that poor cognitive performance, especially for information processing speed, verbal memory, and executive functioning are the best predictors of vocational status in MS patients. Moreover, Rao et al. (1991b) highlighted that MS patients with cognitive impairment have also fewer social activities and have greater difficulties in doing routine household tasks. As the onset of MS often occurs between the ages of 20 and 40 years, which correspond to a particularly active and productive period for individuals in many aspects of their life, the improvement of cognitive impairment in MS patients has been a challenging aim of many researchers in the past decades. Different intervention strategies have been developed to this aim. One of them rely on pharmacological interventions, which entail two approaches: disease-modifying drugs and treatments targeting specifically cognition (Chiaravalloti and DeLuca, 2008; DeLuca and Nocentini, 2011). However, regardless of the approaches, mild, or no effectiveness of pharmacological interventions to reduce cognitive impairment in MS has been demonstrated.

As a consequence, the development of behavioural interventions, like cognitive rehabilitation, has been promoted. In a review, O'Brien et al. (2008) established a picture of cognitive rehabilitation in MS, which highlighted a major focus of these studies on attentional abilities and anterograde memory. Given the fact that executive dysfunctions are frequently observed in MS, surprisingly, few studies have been designed to improve this cognitive domain, with no strong enough evidence to provide clinical guidelines. Similarly, no interventions focusing specifically on processing speed were found, despite the fact that it is one the primary area of cognitive impairment in MS. While interventions for attentional deficits showed mixed results, better outcomes have been obtained for learning and memory. In fact, an overview of these studies showed that the use of learning strategies, like the modified Story Memory

Technique (Chiaravalloti et al., 2005b), self-generated learning (Basso et al., 2006), spaced learning (Goverover et al., 2008), or their combination (Goverover et al.,2011), could particularly lead to significant memory improvement in MS patients. On the contrary, computerised programs have shown mixed or no outcomes on memory (Mendozzi et al., 1998; Solari et al., 2004; Hildebrandt et al., 2007), as it is also the case for group intervention (Carr et al., 2014). A number of non-specific interventions have also been designed, showing again contrasted results (Mendoza et al., 2001; Lincoln et al., 2003).

Overall, in comparison with other clinical populations, particularly traumatic brain injury patients, cognitive rehabilitation in MS has received little attention and remains at its infancy (O'Brien et al., 2008; DeLuca and Nocentini, 2011). Moreover, several methodological weaknesses underlined by O'Brien et al. restrict the conclusions that could be drawn from these studies. Limitations of most of these studies include the absence of disease subtype specification, small sample size, the impact of concurrent ongoing treatment, the absence of precise inclusion criteria about the neuropsychological deficit and the poorly detailed reports of the carried out intervention. In this context, future studies should follow more rigorous methodologies, and particularly placebo-controlled randomised clinical trials, to provide stronger evidence of the effectiveness of cognitive rehabilitation in MS patients.

2.4.2.1. Visualise the effectiveness of cognitive rehabilitation in MS patients

More recently, a growing body of evidence from fMRI studies has contributed to the development of cognitive rehabilitation in MS patients and demonstration of its effectiveness. This set of investigations has emerged from the observation of spontaneous brain reorganisation in MS patients during cognitive tasks (section 2.4.1.2.) and rehabilitation-induced cerebral plasticity after cognitive rehabilitation in other clinical conditions (see Chapter 2, section 2.). Moreover, in parallel, direct demonstrations of induced brain plasticity in MS patients in the motor domain have been reported (Morgen et al., 2004; Rasova et al., 2005).

To the best of our knowledge, the first study examining brain plasticity induced by a cognitive intervention is that from Penner et al. (2006). The authors showed a significant improvement of attentional performance in MS patients with mild to severe attention deficit after training with the AIXTENT software for three to four weeks. This benefit was accompanied with additional activations in a fronto-cingulate-parietal network, which is known as functionally

related to attention processing. Since this original work, Cerasa et al. (2013) obtained convergent results after a computerised cognitive rehabilitation programme in MS patients with predominant attention impairment, with a behavioural improvement associated with increased activity in the posterior cerebellar and superior parietal lobules.

Recently, a second set of studies following a pre-post fMRI design has focused on learning and memory, emerging from the previous work from Chiaravalloti and colleagues (2005b) with the modified Story Memory Technique. In particular, MS patients who benefited from this learning strategy also showed enhanced cerebral activation in frontal, parietal, precuneus, and parahippocampal regions during the completion of a memory task (Chiaravalloti et al., 2012). Importantly, this study involved a 'placebo-control' group of MS patients, for which neither behavioural nor cerebral activations changes were observed at follow-up. In a subset of MS patients enrolled in this study, Leavitt et al. (2012) demonstrated that the benefit of the modified Story Memory Technique could also be expressed by functional connectivity changes. More precisely, they observed changes in the functional connectivity between the left hippocampus and cortical regions involved in memory for visual imagery. Again, no significant difference for the 'placebo-control' group between the pre- and post-rehabilitation measures was found.

Functional neuroimaging proofs of the effectiveness of nonspecific cognitive interventions have been reported by several authors. For instance, Sastre-Garriga and co-workers' (2010) MS patients underwent a cognitive rehabilitation programme dealing with speed of information processing, attention, executive functions, memory and high-level language functions, which entailed both computerised and non-computerised exercises for five weeks. A significant improvement was observed only for attention and a composite score including attentional, processing speed and executive function measures. During the execution of the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977), patients showed enhanced brain activations in the cerebellum and the brainstem. However, no correlations were observed between cognitive improvement and regional increases in brain activation in this study. Likewise, the group of Filippi and colleagues proposed a 12-week cognitive rehabilitation programme to MS patients, based on the RehaCom software (www.schuhfried.at), which focused on attention, information processing, and executive functions. Using resting state sequences, MS patients showed an increased functional connectivity of the anterior cingulate cortex with frontal and parietal regions, which was only

correlated with a significant improvement in the PASAT, while an improvement of executive functioning has also been observed at the behavioural level (Parisi et al., 2012). In contrast, the control group of patients (with no cognitive intervention) included in this work showed at follow-up a decreased functional connectivity of the anterior cingulate cortex with the cerebellum and the right temporal region. Filippi et al. (2012) conducted further neuroimaging analyses on the same MS patients and demonstrated cerebral activity changes in the posterior cingulate cortex, the precuneus and the prefrontal cortex during the completion of the Stroop task in the treatment group. These results were correlated with behavioural cognitive improvement. However, no brain structural modifications (i.e. grey matter volume or normal-appearing white matter) were observed in the patients who benefited from the rehabilitation programme.

Taken together, these investigations provided insights into the mechanisms sustaining the benefits of cognitive rehabilitation in MS patients. Importantly, the results of cerebral activation changes following cognitive interventions promoted their development and paved the way for further works. Nevertheless, while these first reports are important, they have some limitations. First of all, the absence in the great majority of these studies of an appropriate control group of patients following a 'placebo' cognitive programme. Indeed, it is necessary to ensure that the observed cerebral network changes are directly related to the cognitive intervention and not a more general effect (e.g. nursing effect). A further limitation regards the small size of clinical samples.

INTRODUCTION TO THE EXPERIMENTAL SECTION

Autobiographical memory in MS: Assessment and cognitive facilitation

Several lines of investigations dealing respectively with AM and EFT, neuropsychological rehabilitation and MS have been developed in the first sections of the present theoretical background. The literature overview has highlighted the importance of the development of cognitive interventions to improve everyday life functioning of psychiatric and neurological patients, with a particular emphasis on MS patients. In addition, we documented a growing interest in the development of therapeutic interventions to enhance AM functioning, which showed positive outcomes in various clinical conditions. However, to date and to the best of our knowledge, no study focusing on AM improvement in MS patients has been conducted.

On these bases, the last section of this theoretical background aims to put together these three fields of study, namely AM, neuropsychological rehabilitation and MS, and corresponds to a published paper, composing the pilot study of the present thesis' work and therefore, it paves the way for the experimental section of the manuscript.

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Autobiographical memory in multiple sclerosis patients: Assessment and cognitive facilitation

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The multifocal nature of lesions in multiple sclerosis hints at the occurrence of autobiographical memory (AbM) impairment. However, the dearth of studies on AbM in multiple sclerosis is noticeable, notwithstanding the importance of AbM in everyday life. In the first section of this study, 25 multiple sclerosis patients and 35 controls underwent a detailed episodic AbM assessment. Results obtained by means of ANOVA suggested an AbM retrieval deficit in every patient. That pattern of performance paved the way for the second section of the study, in which we followed up 10 out of the 25 patients. Our objective was to assess the effectiveness of a cognitive facilitation programme designed to alleviate AbM retrieval deficits, based on the key role of mental visual imagery on AbM. Statistical group analyses by means of ANOVA and individual analyses using the χ^2 test showed significant differences in AbM test results, in post-facilitation relative to pre-facilitation training, in all 10 patients. Moreover, the patients' comments showed that the positive effects were transferred in their daily life functioning. We would like to suggest that the facilitation programme efficiently enhanced the process of self-centred mental visual imagery, which might have compensated for poor retrieval of personal memories by providing better access to visual details and detailed visual scenes of personal recollections.

Keywords: multiple sclerosis, autobiographical memory, cognitive rehabilitation, mental visual imagery.

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INTRODUCTION

Multiple sclerosis (MS) is an immune inflammatory pathology characterised by the multifocal nature of neurological lesions and the diversity of its neuropathological processes (i.e., demyelination, white and grey matter injuries, atrophy; Trapp & Nave, 2008), which results in a wide variety of symptoms.

With regard to cognition in MS, Rao, Leo, Bernardin, and Unverzagt (1991) demonstrated cognitive impairments in 30 – 70% of MS patients. The cognitive domains that are frequently reported as being affected include attention, information processing speed, executive functions and, particularly, anterograde memory, which seems to be the most frequently impaired function (40 – 60% of MS patients; Calabrese, 2006; Rogers & Pane- gyres, 2007). Although there is no consensus about the memory process that would be predominantly altered in MS, according to several authors, the retrieval process might be more sensitive to MS effects than the encoding or consolidation processes (Calabrese, 2006; Drew, Tippett, Starkey, & Isler, 2008; Rogers & Panegyres, 2007; Sartori & Edan, 2006; Zakzanis, 2000).

More relevant for the present study, is the relationship between remote memory and MS. Two dimensions of personal remote memory seem particularly important in the present context: its influence in everyday life and its neuroanatomical characteristics. We briefly develop these issues before considering personal remote memory in MS patients. Personal remote memory encompasses semantic and episodic components. The former corresponds to factual personal knowledge (personal semantics) with no sense of reliving the event during its recollection (Tulving, Schacter, McLachlan, & Moscovitch, 1988). The second component is typically represented by autobiographical memory (AbM) which refers to the capacity of reliving detailed events, within their specific spatio-temporal context, as they are remembered (Tulving, 1985).

Autobiographical memory is central in everyday normal functioning. Indeed, since it contributes to the construction and continuity of the self, it plays at least two social roles (the nurturing of existing relationships and the development of new ones) and involves a directive function, where the past serves as a basis for guiding present and future behaviours (Rasmussen & Habermas, 2011).

From a neuroanatomical perspective, AbM recruits a widespread cerebral network, predominantly in the left and medial regions, including as core structures the prefrontal cortex, medial and lateral temporal cortices, parieto-occipital regions, temporoparietal junctions and cerebellum (see Svoboda, McKinnon, & Levine, 2006, for a review). As a consequence of this extensive cerebral recruitment, AbM is highly vulnerable to brain damage (Addis, Sacchetti, Ally, Budson, & Schacter, 2009; Matuszewski et al., 2006; Miller et al., 2001; Voltzenlogel et al., 2006). Conversely, personal semantic memory seems more resistant to brain damage (Moscovitch, Rosenbaum, Gilboa, Addis, & Westmacott, 2005) and relies mostly on the lateral temporal cortex (Svoboda et al., 2006). Bearing in mind the neuroanatomical observations in relation to AbM as well as the fact that MS is characterised by multifocal cerebral lesions, we surmised that AbM might be particularly prone to be impaired in MS. This suggestion is supported by the following clinical signs. MS patients happen to mention difficulties in social situations, in which AbM partaking is ubiquitous (Suddendorf & Corballis, 1997). Moreover, in everyday clinical work, it is noticeable that patients experience difficulties in reporting precise personal past events.

However, with regard to the literature on remote memory in MS patients, to the best of

our knowledge, only two studies have investigated this subject: Paul, Blanco, Hames, and Beatty (1997) and Kenealy, Beaumont, Lintern, and Murrel (2002). It appears that several limitations (see the Discussion section) restrict the conclusions that can be drawn from these two studies.

As mentioned above, when considering anterograde memory studies in MS, the memory process that seems to be most impaired in MS is the retrieval process. This observation is relevant also for remote memory since the retrieval process is crucial in AbM and several authors have pointed out the central role of prefrontal regions during the retrieval of personal recollections in healthy subjects (Botzung, Denkova, Ciuciu, Scheiber & Manning, 2008; Manenti, Cotelli, Calabria, Maioli & Minussi, 2010), as well as neurological patients (Matuszewski et al., 2006; Montoya et al., 2006; Smith, Souchay, & Conway, 2009; Zarei, Pourtemad, Bak, & Hodges, 2010). Bearing these results in mind, the greater occurrence of frontal cortex lesions in MS (Arnett, 2003; Bendfeldt et al., 2009; Benedict et al., 2002; Sperling et al., 2001) and the studies that conclude there is frontal lobe dysfunction in MS patients (Drew et al., 2008; Santiago, Guardia, Casado, Carmona, & Arbizu, 2007) suggest a predominant strategy deficit in MS patients, who complain, in everyday clinics, of difficulties in AbM. We have investigated formally this issue, hypothesising that the AbM deficit in MS could rather be due to a failure to access otherwise preserved recollection representations (Rapp & Camarazza, 1993; Warrington & Shallice, 1979). Moreover, given the importance of AbM in everyday life, pending the confirmation of our hypothesis, we endeavoured to develop and implement a tailor-made facilitation programme conceived to back up access to past memories.

Turning presently to cognitive rehabilitation in MS (see O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008, for a review), anterograde memory has been targeted in a number of studies and several rehabilitation methods have been probed that aimed at improving learning abilities in MS patients (Allen, Goldstein, Heyman, & Rondinelli, 1998; Basso, Lowery, Ghormley, Combs, & Johnson, 2006; Chiaravalloti & DeLuca, 2002; Chiaravalloti, Demaree, Gaudino, & DeLuca, 2003; Chiaravalloti, DeLuca, Moore, & Ricker, 2005; Goveover, Hillary, Chiaravalloti, Arango-Lasprilla, & DeLuca, 2009; Hildebrant et al., 2007; Mendozzi et al., 1998; Solari et al., 2004). Among them, the use of mental visual imagery (MVI) techniques lead to positive outcomes in relapsing – remitting MS patients with moderate to severe memory impairment (Chiaravalloti et al., 2005). However, an overview of anterograde memory rehabilitation in MS shows no general agreement either about the comparison of pre- and post-cognitive rehabilitation results or about the transfer of benefits in everyday life. As regards rehabilitation, both measures are important, particularly the latter which is the core of "successful cognitive rehabilitation" (Wilson, 1987, 2008).

MVI – i.e., seeing with the mind's eye – is critical for the retrieval of episodic memories and vividness of remembering (Greenberg & Rubin, 2003; Huijbers, Pennartz, Rubin, & Daselaar, 2011; Moulton & Kosslyn, 2009). More to the point, MVI is involved in the reconstructive process of past events and allows, most particularly, the cueing of visual information, and also information relating to other sensory modalities, about the event (Huijbers et al., 2011; Rubin, 2005).

The importance of MVI in AbM is supported both by case reports of auto- biographical amnesic patients presenting, primarily, an MVI deficit (Green- berg, Eacott, Brechin, & Rubin, 2005; Rubin & Greenberg, 1998), and neuroimaging studies showing that imagination of fictitious scenes and AbM are sustained by overlapping cerebral network activations (Hassabis, Kumaran, & Maguire, 2007; Huijbers et al., 2011). On this basis, the use of MVI in the context of the present study was promising, all the more so that MVI had

already been used as a rehabilitation technique in MS (Chiaravalloti et al., 2005).

In the first part of the present work we report our investigations about AbM impairment in MS using a stringent AbM test. We then analyse the relation- ships between AbM deficits and other cognitive functions to understand the processes underlying the deficit, namely, the associations or otherwise with anterograde memory and executive function performance. In the second section of the study, we present an MVI-based cognitive facilitation programme for MS patients presenting with a selective AbM retrieval deficit. Our aim was to probe the programme under the hypothesis that the number of richly detailed episodic events evoked by the patients could be increased by reinforcing the cueing role of MVI, and by the same token, improve their AbM performance.

METHODS

Subjects

We examined 25 patients with definite MS according to the McDonald criteria (McDonald et al., 2001). Patients were recruited at the Neurology Units of four French hospitals (Strasbourg, Toulouse, Montbéliard, and Besançon). Inclusion criteria were the diagnosis of a relapsing – remitting disease course (RRMS), a mild functional disability corresponding to an Expanded Disability Status Scale (EDSS; Kurtzke, 1983) score ≤ 6, an absence of major signs of depression according to the Beck Depression Inventory – Short form (BDI; score ≤ 13; Beck & Steer, 1993) and absence of anxiety based on the Hamilton Anxiety Scale (HAS; score ≤ 18; Hamilton,1959). A subgroup of 10 patients presenting with selective AbM impairment was drawn. General cognitive functioning (see Neuropsychological baseline examination section) was deemed necessary in order to probe the effects of our programme on AbM with as few confounding factors as possible.

A group of 35 healthy controls matched for gender, age and educational level was also recruited. Ten of them were assessed twice on the AbM test with at least a two month interval between the two sessions.

Exclusion criteria for all the participants included documented psychiatric illness, neurological disorder (other than MS for the patient group) and poor knowledge of French. Demographic and clinical data are summarised in Table 1. All subjects gave prior informed consent; we complied with the APA ethical standards; and the research was approved by the Centre Hospitalier Universitaire de Strasbourg.

Neuropsychological examination

The following baseline tests were presented to the group of 25 patients. Verbal IQ was assessed with the short form (Warrington, James, & Maciejewski, 1986) of the WAIS-R Verbal scale (Wechsler, 1989). Executive functions were assessed using the phonological and categorical fluency tests (National Hospital, London) and the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977). The Information Processing Speed test from the Adult Memory Information Processing Battery (AMIPB; Coughlan & Hollows, 1985) was also administered. Since the experimental test assessing AbM is language-dependent, language was also examined, by means of the Déno 100 test (Kremin, 2002). Visuo-

perceptual and visuo-spatial abilities were tested using the Silhouettes and Cube Analysis sub-tests from the Visual Object and Space Perception Battery (VOSP; Warrington & James, 1991). Anterograde memory was examined using the Selective Reminding Test (SRT; Buschke & Fuld, 1974) or the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) and/or the Recognition Memory Test for Words (RMTW; Warrington, 1984) for the verbal modality. The Complex Figure Test from the AMIPB (Coughlan & Hollows, 1985) was used to assess the visual modality of anterograde memory.

TABLE 1
General data: Mean and standard deviation for the whole group of MS patients and healthy controls assessed for AbM, and for the facilitation subgroup

	MS patients	*Healthy controls*	*Statistical analysis*
AbM assessment group			
N	25	35	-
Age in years	42.96 *SD* 10.94	42.17 *SD* 9.44	$t(58) = -0.30$; $p = .77$
(range)	(28–64)	(24–59)	-
Education in years	13.20 *SD* 2.84	12.71 *SD* 2.82	$t(58) = 0.65$; $p = .52$
(range)	(9–20)	(9–23)	-
Sex (Ratio female/male)	21/4	29/6	$\chi^2 = 0.01$; $p = .91$
EDSS	1.77 *SD* 1.72	-	-
(range)	(0–5.5)		
Duration of MS in years	8.85 *SD* 7.59	-	-
Facilitation subgroup			
N	10	10	-
Age in years	48.6 *SD* 11.46	46.7 *SD* 11.9	$t(18) = 0.33$ ($p = .75$)
Education in years	13.3 *SD* 2.31	14.2 *SD* 3.71	$t(18) = -0.13$ ($p = .9$)
Sex (Ratio female/male)	9/1	9/1	-
EDSS	2.4 *SD* 2.08	-	-
Duration of MS in years	10.6 *SD* 7.23	-	-

EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; *SD*: Standard deviation.

A few methodological disparities in the number of patients who completed the neuropsychological baseline were due to multisite recruitment (see Table 2 for the breakdown of patients who underwent each test). Data for the BDI and HAS were also unavailable for two patients but major signs of depression and/or anxiety were excluded based on clinical examination. The scores of the 10 patients included in the facilitation programme group 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 the AbM score.

TABLE 2

Percentages of patients with deficient scores on neuropsychological baseline tests

Test	N *patients*	*Percentages of patients under normal range*
Verbal IQ	25	0
SRT/RAVLT	15	46.67
RMTW	25	0
AMIPB/Figure recall	25	20
Deno 100	15	4
Silhouettes (VOSP)	25	8
Cube analysis (VOSP)	25	0
Phonological fluency	25	4
Categorical fluency	25	0
PASAT	20	25
AMIPB/Motor speed	25	8
AMIPB/Information processing	25	20
BDI	23	0
HAS	23	0

SRT: Selective Reminding Test; RAVLT: Rey Auditory Verbal Learning Test; RMTW: the Recognition Memory Test for Words; AMIPB: the Adult Memory Information Processing Battery; VOSP: the Visual Object and Space Perception Battery; PASAT: Paced Auditory Serial Addition Test.

Autobiographical memory was assessed, in the 25 patients and 35 control subjects, to probe its two components, episodic and personal semantics, by means of the following tests.

The cue-words Modified Crovitz Test (MCT; Graham & Hodges, 1997; using Manning's 2002 French version). For each cue-word (e.g., letter, friend, film) the participants were asked to produce four recollections, each associated with one of the four different life periods: 0 – 9 years, 10 – 19 years, 20-to-(current age – 1 year), and the past year. The presentation of words and life periods was randomised. No time limit was set to avoid the potential influence of decreased cognitive processing speed on AbM performances, and the participants were encouraged to provide as many details as possible. Memories were subsequently scored on a 5-point scale as follows: 0 = absence of response; 1 = semantic facts related to the target word; 2 = poorly detailed generic events (i.e., overgeneral); 3 = richly detailed generic events (i.e., overgeneral); 4 = poorly detailed specific events (i.e., autobiographical); 5 = richly detailed specific events (i.e., autobiographical). Incomplete responses were probed with general prompts (e.g., "Tell me more"; "Can you think of a specific instance?"). The normality threshold for this test was 74% of the maximum total score (i.e., 88/120; unpublished data from Manning et al.).

The AMI (Kopelman, Wilson, & Baddeley, 1989). This test tackled personal semantics over three lifetime periods – childhood, young adulthood and recent life.

MCT test. As 10 patients were to carry out the MCT a second time, after the facilitation programme, in order to assess its benefits, 10 control subjects were also administered the

MCT a second time, at least 2 months later, with a view to provide evidence of or to rule out a possible learning bias.

Autobiographical memory facilitation programme

The cognitive facilitation programme was constructed to alleviate AbM retrieval difficulties by means of a memory facilitation technique based on MVI. This technique was presented to the patients as a "tool" to use in order to make it easier to access a given recollection and the details associated with it. Therefore, during the MVI training sessions, patients found it increasingly easier to pay close attention to details in the mind's eye, which was used spontaneously when evoking personal recollections. Moreover, they were encouraged to try and use this technique in their everyday life and if needed, to ask the neuropsychologist about the use of this tool. Treatment receipt, i.e., "the extent to which the patient understands the strategies or techniques taught, and demonstrates the capacity to use them" (Bellg et al., 2004) was verified at different times during the training process (by means of direct questions).

The programme consisted of individual sessions lasting two hours once a week for at least six weeks. The patients performed MVI tasks of increasing difficulty, the content of which was divided into four steps. The rate of pro- gression through these steps was flexible and could be adapted to each patient. Completion of the entire programme required at least six sessions but additional sessions were proposed if necessary to complete the pro- gramme at the patient's rhythm of training. Over the duration of the training programme, the role of the neuropsychologist was to teach how to construct visual scenes, and to provide continuous guidance throughout the training sessions.

The screening test. This test was based on 12 size comparisons (De Renzi & Lucchelli, 1994; e.g., "Which object is larger, a knife blade or a saw blade?"). We used this test to probe basic visual imaging abilities and, therefore, be able to exclude patients presenting with severe MVI impairment (incompatible with the realisation of the facilitation programme). Thus, based on unpublished empirical data obtained in a group of normal sub- jects, a minimal score of 9/12 was deemed necessary to continue the programme.

The external visualisation exercise. This included 10 verbal items that the patient had to imagine and describe. (We called this step "external" visualisa- tion because the purpose of the exercise was to imagine an object and not the participant him/herself.) The instruction ran as follows: "I will tell you the name of an object (e.g., an onion), imagine it and describe its colour, shape, size, consistency and every detail that you see." Each item description was checked for accuracy using a list of typical traits. For each item, the patient had to describe static aspects (e.g., colour, shape) and an action carried out with the item (e.g., slicing an onion). The action was imagined to be performed either by him/herself or someone else (no instruction was given as to who was supposed to act, since the patient was asked to concentrate on an object having changed in its physical appearance owing to an action).

The construction exercise. This part of the programme consisted of figur- ing out complex scenes bringing into play several characters. The goal was twofold, i.e., to increase the complexity of the scene by comparison with the previous step and to introduce several

characters performing different complex actions. Five items were proposed with, for each one, a first training step and a subsequent scene construction step. During the training phase, a neuropsychologist guided the patient, starting from a general idea (e.g., "A cook prepares a meal"), to more precise subheadings (e.g., "The cook is in front of a metallic table"). Within subheadings, detailed items were distin- guished (e.g., "On the table, you can see butter, some onions and mushrooms..."). The present step was considered to be external since the par- ticipant was asked to imagine some characters and focus primarily on them, their actions and the context of the scene rather than the patient him/herself. Responses were checked for accuracy in terms of their relation to each sub- heading, but no list of typical or expected responses was used. The number of headings and sub-headings, as well as details produced by the patients was recorded. For the scene construction phase, an item similar to the one used in the training section was proposed (e.g., "Can you imagine the job you would most enjoy and describe it, as we just did with the example of the cook?").

The self-visualisation exercise. This was the training phase that shared the most similarities with AbM since the patients were asked to visualise themselves within a given scenario, to imagine it as though they were actually living the scene and to describe whatever details, sensations or feelings that came to mind. The presentation was similar to that of the previous exercise, comprising a training (e.g., "You are heading towards a hotel reception desk") and a scene construction phase (e.g., "Your room is not ready; picture your- self in the hotel bar"). The difference was that the participant was asked to focus his/her attention on him/herself, i.e., using internal, personal knowledge. As for the previous step, we recorded the number of headings, sub-headings and details produced by the patients.

Statistical analysis

Percentages of MS patients with deficient scores on the neuropsychological baseline examination were calculated for each test, and are presented in Table 2.

Patients' and controls' scores on the MCT were analysed across the different life periods by means of a repeated-measures ANOVA. When appropriate, the ANOVA was followed by Tukey's HSD post-hoc test.

The relationship between AbM performance and, on the one hand, executive function scores, and, on the other hand, the results on anterograde memory tests, were analysed by means of a "frontal lobe function index" (including the PASAT, the phonological and categorical verbal fluency tests) and an "anterograde memory index" (including the SRT/RAVLT, the RMTW and the figure recall test from the AMIPB). For each index, only the patients who had completed the three tests were taken into account for the analysis. Firstly, the performance of each patient was categorised as "preserved" or "deficient" for all these tests. To be classified as "preserved" for the "frontal lobe function index" a patient's score had to be either flawless or to show only one failure. With regard to the "anterograde memory index", "preserved" performance corresponded to at least one score in the normal range on the RMT, plus normal performance on one of the two free recall tests. On this basis, we performed a point-biserial correlation analysis between each index and the MCT global score.

Comparison between MS patients and healthy controls for Personal Semantics (AMI) was performed with the Student t-test.

For statistical analysis involving the cognitive facilitation programme results, we calculated the difference between the MCT global score of MS patients and healthy controls in pre- and post-facilitation by means of a repeated-measure ANOVA, followed by Tukey's HSD post-hoc test. The effect size was then estimated with the partial η^2 value. An individual analysis was also conducted for each patient comparing their global score on the MCT before and after administration of the facilitation programme, using the χ^2 test (see Levaux, Laroi, Offerlin-Meyer, Danion, & Van der Linden, 2011 for statistical analyses for individual comparisons pre-/post-treatment). The same procedure for individual level analysis was used for the healthy controls global score on the MCT.

RESULTS

The percentages of patients who obtained scores under the normal range for the neuropsychological baseline examination are presented in Table 2.

Autobiographical memory assessment

Concerning the comparison of scores on the MCT per life period between the two groups (MS patients and healthy controls), the ANOVA showed a main effect of group, $F(1, 58) = 85.011$, $p < .001$, and a main effect of life period, $F(3, 174) = 17.834$, $p < .001$. However, no significant interaction effect was observed, $F(3, 174) = 1.430$, $p = .235$. Post-hoc analysis revealed that healthy controls had significantly higher scores for each life period relative to patients ($p < .001$ in every case). Within the patient group, significantly lower scores were obtained for the 0 – 9 years and the past year life periods in comparison to the 20-to-(current age – 1 year) life period ($p < .001$ in all cases). No other comparisons reached the statistical significance threshold for the MS group. Within the healthy control group, no significant differences between life periods were observed, excepted for the 0 – 9 years life period for which a lower score was obtained compared to the three remaining life periods ($p < .001$ for the comparison with the 10 – 19 years and the 20-to- (patient's current age – 1 year) life periods and $p < .05$ for the comparison with the past year life period).

Correlation analyses addressing the "frontal lobe function index" were carried out on the scores of 20 patients, while the "anterograde memory index" was calculated on the performance of 15 patients. We found a significant positive correlation between the "frontal lobe function index" and the MCT global score ($r_{pb} = 0.458$, $p < .05$). On the contrary, we found no significant correlation between the "anterograde memory index" and the MCT results ($r_{pb} = 0.284$, $p = .304$).

Personal semantics

Concerning the AMI personal semantics, scores did not differ significantly between MS patients and healthy controls, $t(48) = -.036$, $p = .970$.

Autobiographical memory facilitation programme

It can be seen in Figure 1 that the group analyses showed a significant main group effect on the MCT global score, $F(1, 18) = 21.813$, $p < .001$, with an important effect size, $\eta^2 =$

.55. Post-hoc analyses revealed poorer scores for the patient group ($p < .001$). A significant effect of time of assessment was observed, $F(1, 18) = 108.147$, $p < .001$, with a marked effect size, $\eta^2 = .86$. Post-hoc analyses showed a significant effect only for the comparison of the pre- and post-facilitation scores of MS patients ($p < .001$). A significant interaction effect was also shown between the group and time of assessment factors, $F(1, 18) = 89.663$, $p < .001$, with a large size effect, $\eta^2 = .83$. Post-hoc analysis revealed that the scores achieved by MS patients on the MCT prior to the facilitation programme were significantly lower than that of healthy controls ($p < .001$) but the post-facilitation assessment showed no significant difference between the two groups ($p = .436$).

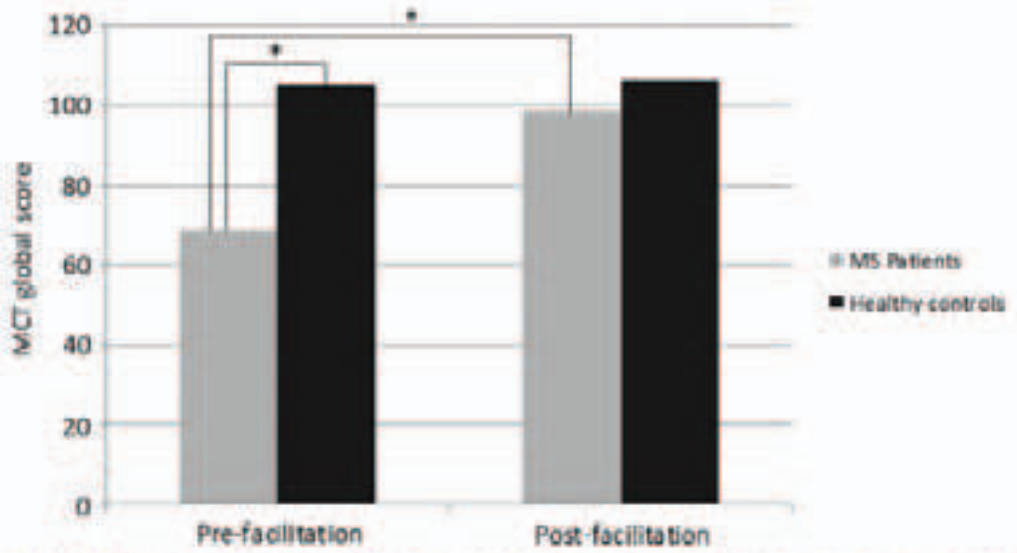

Figure 1. Group analyses of the MCT global score for MS patients pre- and post-facilitation and healthy controls (*$p < .001$).

The individual analyses revealed a significant improvement in the MCT global score for all 10 patients after the rehabilitation sessions (see Table 3). Moreover, seven of them showed scores in the normal interval of their MCT global score (≥ 74% of the maximum total score corresponding to a score of 88/120) after MVI training. For the 10 healthy controls, no significant change in MCT global score was observed between the two assessments (Table 3).

Bearing in mind that our primary goal was to improve everyday life functioning in our patients, we also collected, after the facilitation programme, their comments about the perceived benefits on the second MCT testing and in everyday life (see Appendix 1). Globally, all the patients' comments confirmed the positive effects of the cognitive intervention. Among them, the most frequently evoked benefits were greater ease of retrieval, a greater number of details and better self-visualisation. Positive comments were also conveyed by the patients concerning treatment receipt: they mentioned easy and effective use and transfer of this technique in their daily life functioning.

TABLE 3
Individual analyses of the MCT global score for MS patients pre- and post-facilitation and healthy controls

	MS Patients			*Healthy controls*		
	Pre -	*Post -*	χ^2	*Session 1*	*Session 2*	χ^2
1	40	80	26.67 **	103	105	0.14
2	57	86	14.55 **	97	100	0.25
3	47	93	36.27 **	106	104	0.15
4	66	97	18.38 **	116	113	0.86
5	76	102	14.7 **	102	101	0.03
6	80	117	38.79 **	110	112	0.24
7	87	114	22.32 **	105	107	0.16
8	85	112	20.65 **	105	107	0.16
9	84	101	6.82 *	103	104	0.04
10	68	87	6.58 *	103	111	2.76

*$p < .01$ and **$p < .001$. MCT: Modified Crowitz Test; MS: multiple sclerosis

DISCUSSION

In this study, we have documented AbM impairment concomitant with preserved personal semantics in a group of non-clinically depressed RRMS patients with mild-to-moderate disease severity. One of the interesting findings of the present study, concerning cognitive functioning in MS, is that MS patients, regardless of their scores on different cognitive functions, presented AbM impairment. We would like to suggest that this result is of interest since it reveals, for the first time to our knowledge, that subtle cognitive impairment in MS patients may affect only AbM performance. Moreover, despite the fact that no cognitive profile can be drawn owing to the heterogeneous nature of lesions inherent in this condition, AbM seems to be particularly sensitive to MS neuropathology, which argues for its routine assessment. Our findings are contrary to those obtained by Paul et al. (1997) but in accord with those of Kenealy et al. (2002). However, both Paul et al. and Kenealy et al. used the Autobiographical Memory Interview (AMI; Kopelman et al., 1989). While the personal semantics section in the AMI is very useful and has a good sensitivity, its episodic component is recognised as a short measure of autobiographical assessment, with imprecise temporal resolution and a rather poor sensitivity (McKinnon, Black, Miller, Moscovitch, & Levine, 2006; Piolino, Desgranges, Benali, & Eustache, 2002). Moreover, in those two studies the MS subtypes were not controlled, and the patient populations differed widely in terms of disease severity. By contrast, the use of a more stringent AbM test as well as the selection of a specific subtype of MS patients, whose disease severity was also controlled, could be considered as obvious advantages of the present study, which furthermore sets off the examination of processes that could potentially underlie AbM deficit in MS. Indeed, we investigated the links between AbM, executive functions and anterograde memory patterns of performance in order to confirm or otherwise potential interactions, to try and gain a better understanding of AbM deficit characteristics. We have shown an association between the AbM scores and executive functions but none with anterograde memory performance. This result suggests that AbM deficits could be due to retrieval difficulties

provoked by frontal lobe dysfunction, above and beyond medial temporal lobe dysfunction. This finding is in accord with several studies carried out in various clinical conditions involving the frontal lobe and accounting for AbM impairment in terms of defective retrieval strategies (Della Sala, Laiacona, Spinnler, & Trivelli, 1993; Kopelman, Stanhope, & Kingsley, 1999; Matuszewski et al., 2006; Zarei et al., 2010).

Although AbM impairment in our MS patients covered the whole lifespan, within-group comparisons showed a reversed U-shape profile of scores across the life periods. This pattern of results is very likely due to the higher recall rate of memories from the early adulthood period relative to the other life periods, i.e., the reminiscence bump phenomenon. Privileged access to memories belonging in the reminiscence bump period has been frequently suggested in the literature (see Conway & Rubin, 1993, for a review). We would like to suggest that, although the AbM scores before the facilitation programme were deficient over lifespan, the higher scores observed for the 20-to-(current age – 1 year) life period could be interpreted as a relative preservation of the reminiscence bump. More to the point, this result suggests that easier access to memories from the reminiscence bump reduces the reliance on retrieval strategies.

In the same vein, the effective outcome of our MVI-based facilitation programme corroborates, to a greater degree, the hypothesis of retrieval strategy deficits related to prefrontal cortex dysfunction. Indeed, the MVI training effects would have been different had the encoding or consolidation processes been defective. This is why our programme is best characterised as a "facilitation programme" (Seron & Van der Linden, 2000) as it uses a critical AbM component in an intensified and optimised way. In other words, the facilitation programme may have triggered the use of and reliance on the cueing role of MVI (Huijbers et al., 2011; Rubin, 2005) during both memory retrieval and search for details concerning a unique past event.

The positive outcome does not seem due to a learning effect on the MCT since no changes were observed in the control group's performance. However, we acknowledge the fact that healthy controls had little margin to improve their scores on the second assessment. More compelling evidence can be found in a study involving epileptic patients using the MCT (Voltzen- logel, Despre´s, Vignal, Kehrli, & Manning, 2007), which showed that scores remained unchanged between the two assessment sessions carried out in the study. Moreover, we are currently studying a group of MS patients using a different test, the Autobiographical Interview (AI; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002; kindly communicated by the author, Brian Levine to one of us, LM.). The first results of our on-going study, in which the AI is taken twice with no intervention between the two sessions, show that AbM scores remain stable (Ernst et al., 2012). Taken together, these results seem to indicate that AbM performance, even using different tests, does not seem prone to learning effects.

It is important to note that significantly improved performance on the post- MVI programme MCT was observed in every case, and normalised scores were verified for nearly all patients. We turn now to the important issue of benefit transfer in daily life. This being a central concern in neuropsychological rehabilitation, several studies have dealt with this topic, but failed to show such a transfer (Glisky & Glisky, 2002; Johnstone & Stonnington, 2009). It is therefore of significance that in the present study, we found that improved performance on the AbM test was accompanied by the patients' reports acknowledging easier retrieval of personal memories, a greater number of details and a feeling of being able to "relive the event", not only during the post-facilitation AbM assessment, but also in everyday life. According to our patients' comments, it seems that

they were able to integrate and "automate" the use of MVI as a tool in their daily life. Additionally, spontaneous comments by some patients' relatives further supported the notion of effective transfer of this technique into everyday life. More precisely, they observed changes in the evocation and sharing of memories with the patients, in particular concerning the quantity of details.

Several factors could explain why the transfer of benefits from the facilitation programme operated efficiently in the present study. Firstly, our facilitation programme targeted AbM, which is, in essence, memory of real-life events. Secondly, the patients were taught throughout the facilitation training, how to use a specific strategy, i.e., a mental process that could be applied to real-life situations, and which was abundantly explained to the patients during the facilitation sessions. Relating to the latter point, the use of compensatory strategies has been described as more efficient in terms of transfer in everyday life, especially concerning memory rehabilitation, than the use of training methods which aim at restoring a damaged function (Glisky & Glisky, 2002). Finally, according to the study of Evans, Wilson, Needham, and Brentnall (2003), the main predictors of the good use of compensation strategies in everyday life are: younger age, mild severity of impairment, deficit specificity, and premorbid use of strategies. In the present study, this facilitation programme was proposed to relatively young patients with a selective AbM deficit. Moreover, the strategy we taught must have been spontaneously used before the illness since it is based on a critical component necessarily required for AbM. From a neuroanatomical point of view, although we yet have to obtain neuroanatomical data, we would like to suggest that emphasis put on the role of MVI in AbM and, by the same token, on the posterior cerebral regions (Hassabis et al., 2007), could have compensated for the weakness of the retrieval strategy processes supported by the prefrontal cortex (Botzung et al., 2008; Manenti et al., 2010), which is more affected in MS in comparison to posterior brain regions (Arnett, 2003; Bendfeldt et al., 2009; Benedict et al., 2002; Sperling et al., 2001).

One of the limitations of the present work is due above all to the small size of the group that underwent the facilitation programme. However, despite the latter, we obtained statistical evidence of AbM improvement, which indicates the clinical interest of the study. To overcome the above-mentioned limitation and to confirm our hypotheses concerning the initial retrieval strategy deficit, a neuroimaging study involving a larger group of MS patients has been initiated (for preliminary results, see Ernst et al., 2012). A further limitation of the work concerns the fact that the post-facilitation AbM assessment did not follow a blind-investigator study design and, for the time being, the presence of a "nursing effect" cannot be altogether ruled out. Finally, long-term follow-up measures are required to examine the robustness of the treatment effects.

On the positive side, the present work is, to the best of our knowledge, the first study focusing on AbM cognitive rehabilitation in MS, and our findings seem to be promising and encourage future investigations. Moreover, the development of this kind of intervention appears as a priority considering the absence, or at least the suboptimal effectiveness, of current pharmacological treatments for cognitive impairment in MS (Krupp et al., 2011; Lovera et al., 2010; Thompson, Toosy, & Ciccarelli, 2010), especially considering the well-known deleterious impact of cognitive deficits on MS patients' everyday lives.

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APPENDIX 1

GG: “Last time it was more elusive. I could come up with more details, today, if I had the very same words, I’d tell much more things. My feeling is that there’s a difference, concerning the details, above all, but also in terms of giving more meanings to words; I’ve found that. All in all, it’s there, more easily. My people are aware of it. I happen to talk about things that I wouldn’t before. It often happens with my parents as my mother talks about me when I was a kid and I didn’t remember those things, but now I do.”

MH: “I’m much more aware of details now... Any recollection I remember, opens up, so to say, several other memories with you and at home as well.”

SR: “It was easier this time. The first time I found it really hard; it’s the same exercise, though. Last time I couldn’t find things in my memory. Today, they just pop out. I realise I can look for in my memory, a word I mean, I’m able to look for it. I say it’ll be there and it’s there. I have the feeling that I don’t need to look for it as much as before. It’s not mixed up in my head, I have a thing, I deal with that and little by little things come out. Before the sessions, I used to feel paralysed and nothing would come out. Lots of small recollections are there now. Something appears and other things arrive on the top of that and it grows up.”

MS: “I feel it’s different now, there is this idea of being in the context. I’m really re-living the thing. I remember the first session and no, it’s not the same thing. I carry out the exercise more carefully. I re-live the scene; I’m able to see I’m in. I’m good at re-visualising the situation. Before the sessions, I was not very good; it was much more difficult to remember; now recollections arrive easily. I really realise how different it is. I can see that in my everyday life as well.”

OBJECTIVES

Throughout the theoretical background, we documented the presence of AM impairment in non-depressed RR-MS patients. Based on behavioural data, we suggested that AM impairment in these patients was very likely due to a retrieval-strategy deficit, and thus, associated with executive abilities. Nonetheless, no direct investigation of the functional underpinnings of AM impairment had been conducted yet to verify this hypothesis. Furthermore, in relation to the concept of MTT and the clinical studies showing the presence of a simultaneous AM and EFT impairment in several clinical conditions, an open question concerns the status of EFT in RR-MS patients.

In parallel, although we reported some evidence of the benefits of a MVI-based cognitive facilitation programme on AM functioning, it was preliminary and incomplete. Indeed, further investigations were required to probe the effectiveness of the MVI facilitation programme. Additionally, the literature overview highlighted the growing interest in and requirement of fMRI evidence to support the effectiveness of cognitive interventions. Should EFT be impaired in RR-MS patients, the likelihood to improve it by using the same MVI facilitation programme was also an open question.

On theses bases, the present thesis' objectives are as follows:

(i) To provide a more in-depth investigation of AM impairment in RR-MS patients with the support of neuroimaging techniques;

(ii) To extend the investigation to EFT in RR-MS patients;

(iii) To explore the common and distinct cognitive and cerebral mechanisms sustaining AM and EFT functioning in RR-MS patients;

(iv) To probe the effectiveness of the MVI facilitation programme on AM and EFT functioning by controlling different potential confounding and testing both the clinical and cerebral network changes induced by this cognitive intervention.

Based on the theoretical background and our clinical experience, we hypothesised that both AM and EFT would be compromised in RR-MS patients and that this impairment would be accompanied by cerebral functional alterations of the AM and EFT cerebral networks, relatively to healthy subjects. Furthermore, since AM and EFT show common and different phenomenological and cerebral functional characteristics in normal functioning, we suggested

that AM and EFT commonalities/differences would be found in the context of impaired performance in RR-MS patients, at both clinical and neuroimaging levels.

Regarding the cognitive facilitation work, we expected that the MVI programme would be used as a new learned strategy or "mental tool" not only in the context of AM/EFT assessment of cognitive facilitation, but also in everyday life functioning. We hypothesised that for that to occur, it was necessary that the benefits were derived from the programme effectiveness rather than nursing or learning effects. Moreover, we also expected that the use of this MVI programme and the ensuing AM and EFT improvement would induce cerebral activation changes in the brain networks sustaining AM and EFT in RR-MS patients.

EXPERIMENTAL SECTION

PRELIMINARY WORK

1. Assessment of AM and EFT

The Modified Crovitz test (Graham and Hodges, 1997) was used in our preliminary study (Ernst et al., 2013). However, an overview of the current literature showed an increasing use of the AI (cited 376 from 2002 to 2014, Google Scholar database) developed by B. Levine and colleagues (2002).

The AI provides several advantages for AM assessment, particularly the simultaneous examination of the episodic and semantic components of AM, the distinction of two recall phases (i.e. the free recall and the specific probe phases) and the use of a stringent scoring procedure, including quantitative and qualitative measures. In the light of our preliminary study and our previous clinical observations, the use of the AI with MS patients, in the context of AM rehabilitation, appeared to be appropriate on different issues. The AI's specific probe phase seems particularly useful in the context of our retrieval-deficit hypothesis. Likewise, given the fact that we observed a mild to moderate degree of AM impairment in MS patients, a more stringent scoring procedure than the Modified Crovitz test would also be more sensitive to AM impairment, and by the same token to AM improvement after the facilitation intervention. The use of the AI in the present work was preceded by the following adaptation procedures.

1.1. French translation, adaptation and training to the scoring procedure of the AI

1.1.1. Translation

As no French version of the AI was available, the first step after the reception of the material, kindly communicated by B. Levine to L. Manning, was the translation of the test, which was, as far as possible, faithfully transposed. However, some cultural and language adjustments were required at this step. For example, in the specific probe phase, 'place' information contain originally questions regarding the 'state' or 'province', which make sense in the United States and Canada, but were not appropriate when applied in France and so, suppressed at the translation. The final specific probes are presented in the Table 1.

Table 1. Adapted specific probing from the AI

TEMPORAL
- Year?
- Season?
- Month?
- Time of the month?
- Date?
- Day of the week?
- Time of day?
PLACE
- City?
- Quarter or district?
- Building?
- Room? Part of the building/room?
PERCEPTUAL INFORMATION
- People/object/visual images?
- Position/location in relation to others/objects?
- Colours?
- Sounds?
- Tastes/smells?
- Physical sensations?
- Weather?
- Body position: Sitting? Standing? (Or else)
- Event duration
- Clothes? Colours of clothes?
EMOTION/FEELING
- Feelings? Emotions?
- Thoughts?
- Expressed emotions?

As we chose to conduct a more general self-assessment of performances at the end of the AI (see the semi-structured interview section below), we also suppressed all the scales dealing with the clarity of visualisation, the change of emotional state regarding this event, the personal importance and the rehearsal. For the qualitative ratings, only the rating included in the total rating score (i.e. place, time, perceptual, emotional and episodic richness) were considered in this study. Therefore, the AMI and the time integration ratings were excluded.

The initial instructions were shortened to be better adapted to clinical populations, but all supplementary information was provided if necessary. Instructions were summarised in four points: (i) the personal involvement in the event, with the recollection of being personally involved; (ii) the evocation of unique event, from a specific time and place; (iii) events

occurring over minutes or hours, but not more than one day; (iv) the importance of providing as many details as possible about the event. Some parts of the initial instructions concerning the use of an audio-recorder, the confidentiality and the guarantee that the chosen events would not be interpreted in terms of reason of this choice, personality, etc were presented before the AI instructions with an information note.

1.1.2. Adaptation

In the context of the present study, the use of the AI departed from the standard procedure for several considerations.

Firstly, as the AI was originally developed to assess the memory evocation, in relation to the concept of MTT (Suddendorf and Corballis, 1997; 2007), we introduced the assessment of EFT (Szpunar, 2010; see Schacter et al., 2012 for a review). The use of the same testing procedure for the AM and the EFT assessments was of importance to guarantee valid comparisons between the two conditions. Here, we based our adaptation on the previous studies from Addis et al., (2008; 2009a), which investigated the EFT abilities in healthy old subjects and mild Alzheimer's disease patients. The instructions followed those for the past events (see Translation section), with some additional explanations concerning the characteristics of unique future events to ensure the good understanding of the task. The participants were informed that it was important not to use past events or parts of memories to imagine a future event, but to create something new, that never happened before, or at least, not in the same way or context. In the studies from Addis et al., the time interval considered for the EFT projection was 'the next few weeks' and 'the next few years'. Considering the need to provide a sufficient time interval to elicit several future projections (especially as the same time interval would be considered for the fMRI task, see below), we chose a time interval of the next year. Nevertheless, the participants were instructed that "if a closer episodic future event comes to mind, you may talk about it, even if the event is to happen in the next days". Our clinical experience with MS patients guided also the choice of this time interval and its flexibility. Indeed, regarding the uncertainty surrounding MS evolution, and particularly for RR-MS, the engagement in future projections could be influenced by some psychological factors, such as a conscious decision of the patient not to engage in future projects. It is likely that, the more distant the future event, the more important the potential negative impact on the future projection.

Based on Addis et al., (2008; 2009a), we also introduced the use of cue-words for the AM and EFT conditions. A list of cue-words was then established (Table 2), most of them belonging to the Crovitz test, and they were randomly chosen across participants and assessment sessions. The participants were informed that the cue-words were provided to encourage mental simulation of past and future personal events, and so, that they were intended to be used flexibly.

Table 2. List of cue words provided for the AM and the EFT conditions

AM condition	EFT condition
Car	Shop
Train	Garage
Bike	Market
Dog	Family
Cat	Friend
Bird	Encounter
Church	Rdv
Castle	Lunch
Restaurant	Trip
School	Week end
Ruin	Hobby
Broken	Relaxation
Repair	Home
Surprise	Garden
Disappointment	Park
Smile	Street
Anger	Visit
Flower	Invitation
Bootle	Mountains
Friend	Help

Regarding the AM testing, we also modified the number of events to be retrieved from one (in the standard Levine et al.'s version) to three past events per life period explored. This choice has been supported by our previous clinical experience with the Modified Crovitz Test and by the AM impairment profile of MS patients. The aim of testing a greater number of past recollections was to assess more comprehensively the retrieval process and to avoid the likelihood of the patients providing only the most accessible detailed recollections. Indeed, with the Modified Crovitz Test, we qualitatively observed that some memories (generally the

most accessible, emotional, or striking past events) could be well detailed by MS patients. However, these memories could coexist, in the same patient, with very poor detailed memories when a large number of recollections was requested for each life period. This clinical observation was confirmed by the study of Leyhe et al. (2009), and Barnabe et al. (2012), recommending to increase the number of past events tested by the AI, for the same reasons mentioned above. Moreover, we were also concerned by the sensitivity of our AM test to detect the potential improvement AM in post-facilitation. Therefore, we obtained a total of 12 or 15 memories per subject (depending on the number of life periods completed). With regard to the EFT testing, following Addis et al. (2009a), we instructed the participants to generate five events.

Beside these adjustments, we introduced a more important modification related to the completion of the specific probe phase directly after the free recall of each event. Originally, Levine et al. (2002) recommended performing the specific probes only at the end of all the free recall evocations, to prevent contamination of the subsequent events by the probing. However, the application of this procedure raised several issues in the context of our study. Firstly, to avoid confusion between the past and future events, since the assessment of the AM and the EFT was carried out during the same testing session. Secondly, a better management of fatigue during the AI and the possibility to carry out multiple AI testing sessions. This issue is also important since all the patients completed at least the AI three times, in pre- and post-facilitation, and at the long-term follow up. Thus, the completion of the task in the same conditions for all the testing sessions towards the specific probe phase was methodologically required.

1.1.3. Scoring procedure and training

One of the AI's strength is the use of a strict and stringent scoring procedure. To accurately follow this procedure, a 'two-steps' training material was kindly communicated to L. Manning by B. Levine and was completed as required.

The AI scoring consists in the first identification of the main episodic event. Each memory is segmented into information bits or details, which correspond to a unique occurrence, observation, fact, or though (typically expressed as a grammatical clause). All additional information in a clause are considered as a supplementary detail. Then, all details are classified in different categories and subcategories of details (see Table 3) through the free

recall and the specific probe phases. The main categorical distinction is internal or external details. Internal details entail information which pertain directly to the main episodic event, whereas external details are not part of the main event or correspond to factual information not specific to the central event. In parallel, several qualitative ratings (Table 3) were also attributed for each memory and recall phases.

Table 3. Description of the categories and subcategories of details and ratings of the Autobiographical Interview scoring

Category	Description
Internal details	
Event	Happenings, individuals present, weather conditions, physical/emotional actions, or reactions in others
Place	Year, season, month, day of week, time of day
Time	Localisation of an event including the city, street, building, room, part of room
Perceptual	Auditory, olfactory, tactile, taste, visual and visual details, body position, duration
Thought/emotion	Emotional state, thoughts, implications
External details	
Event	Specific details from other incidents (from all of the above categories) external to the main event recalled
Semantic	General knowledge or facts, on-going events, extended states of being
Repetition	Unsolicited repetition of details
Other	Metacognitive statements, editorializing
Ratings	
Episodic richness	Qualitative estimate of re-experiencing (0 to 6 points)
Place	Qualitative estimate of the localisation of a specific location (0 to 3 points)
Time	Qualitative estimate of the localisation of the event within a specific time frame (0 to 3 points)
Perceptual	Qualitative estimate of the perceptual re-experiencing in the aforementioned modalities (0 to 3 points)
Thought/emotion	Qualitative estimate of the emotional re-experiencing (0 to 3 points)

Adapted from Levine et al., 2002

1.2. Constitution of a normative database for the AI

Since the presence of an AM/EFT impairment was an inclusion criteria for the MS patients, we obtained norms from a group of 15 healthy controls, representative of the 'standard' demographical data of MS population (mean age between 20 and 40 years, with approximately 75% of women; DeLuca and Nocentini, 2011). Educational level and cultural origin of the participants (although only fluent French speakers were included), were diversified. Thus, we recruited 11 women and 4 men (73.33% of women), with a mean age of 36.13 years (SD: 14.72) and a mean years of education of 15.00 (SD: 2.90). Each subject underwent the AI assessment in one session. The order of presentation between AM and EFT conditions was counterbalanced, as were the order of the cue-words and the past life periods. All the AI sessions were audio-recorded for later transcription and scoring following the standardised Levine et al.'s procedure (previously described in the 'Training to scoring procedure' section). For each participant, the number of internal details and the composite ratings were averaged across all the past events for the AM condition and across all the future events for the EFT condition, for each recall phase. Following Levine et al.'s procedure, the specific probe phase scores were analysed cumulatively with the free recall phase scores. The interrater reliability was verified for 10% of the past and future events, which were scored by a second scorer. Coefficients for all measures showed high interrater reliability (between 0.82 and 0.99).

Finally, the normative data were established on a total of 174 past events and 75 future events. All the mean scores are summarised in the Table 4 for the AM condition and the Table 5 for the EFT condition. All scores were rounded up to the nearest superior unit.

Table 4. Mean score for the AI measures during the two recall phases for the AM condition

FREE RECALL			**FREE RECALL + SPECIFIC PROBE**		
Internal details	External details	Total ratings	Internal details	External details	Total ratings
22	13	8	40	21	12

Table 5. Mean score for the AI measures during the two recall phases for the EFT condition

FREE RECALL			**FREE RECALL + SPECIFIC PROBE**		
Internal details	External details	Total ratings	Internal details	External details	Total ratings
18	10	7	34	17	10

Thus, the presence of an AM/EFT impairment for MS patients was determined using (i) the scores for the free recall phase, owing to the free recall sensitivity to detect AM/EFT retrieval deficit and (ii) the mean number of internal details and total ratings, since these two measures assess the episodic re-experiencing ability and are, consequently, the most sensitive to detect AM/EFT impairment. As the purpose of the present study was to alleviate AM/EFT difficulties, and since our pilot study (Ernst et al., 2013) showed the efficacy of our MVI programme even for mild AM difficulties, we established strict inclusion criteria. So, to be sensitive to mild impairment, MS patients were included if they obtained AI scores below those of the normative mean scores for the free recall phase.

1.3. Creation of the semi-structured interview for the self-assessment of AM/EFT performances

In our pilot study (Ernst et al., 2013), we gathered clinical information about the patients' perception of their AM difficulties and benefits following the AM facilitation programme. Based on these observations, we adapted the Memory Experiences Questionnaire (Sutin and Robins, 2007) from which we selected four dimensions: vividness, accessibility, quantity of details and emotional intensity. This semi structured interview (see Table 6) was applied to characterise more precisely the patient's AM/EFT difficulties, as well as the potential effects of those difficulties in real life, and to evaluate the benefits of the facilitation programme. The choice of the four dimensions was based on our previous experience of the potential impaired and improved dimensions mentioned by the patients. For each dimension, the patient had to give his/her impressions for the AM and for the EFT conditions, with a distinction between the AI testing session and their perception in daily life.

The interview followed directly the AI assessment and was audio-recorded for further transcription. A preliminary testing of the interview was conducted with the 15 healthy controls. If necessary, additional information or questions were provided to finally obtain a representative overview of the patient's impressions.

Table 6. Semi-structured interview for the self-assessment of AM/EFT performance

	AM		**EFT**	
	AI assessment	*Everyday life*	*AI assessment*	*Everyday life*
Accessibility In general, how would you describe the degree of difficulty with which you retrieve/imagine a unique event?				
Details In general, how do you find, the quantity of details in your memories/projects? Well detailed, on average, or rather poorly detailed?				
Emotional intensity In general, do you feel an emotional (re)living when you evoke memories/projects? If yes, how would you describe its intensity?				
Vividness In general, how you describe the vividness of your memories/projects? How would you assess the quality of your 'mental movies'?				

2. Neuroimaging session

To investigate the functional underpinnings of AM and EFT in MS, we developed an event-related fMRI paradigm based on those created by Addis et al. (2007a). One of the strength of Addis et al.'s work relies on the distinction between (i) the construction phase, which corresponds to the search and reconstruction of a past event or the creation of a future event, and (ii) the elaboration phase, which is the retrieval or the imagination of supplementary details about the event. In the context of MS, considering both the previously observed retrieval deficit accompanied with a qualitative impoverishment of their memories (resulting in a poor number of episodic details) and their general improvement after facilitation (Ernst et al., 2013), the separate analysis of these two recall phases could provide a more extensive overview of potential spontaneous and induced brain plasticity phenomenon.
To avoid the potential effect of re-encoding the AM and EFT episodes, based on Addis et al., the fMRI tasks of the present work consisted in lists of arbitrary cue-words, which were similar for all the participants.

2.1. Creation of the fMRI tasks

We adapted Addis et al.'s design (2007a), initially conceived to test normal subjects. Thus, to guarantee an optimal completion by MS patients, we increased the number of trials per condition and modified the timeframe of the events to cover the same life periods as presented in the AI. The instructions for the past and the future tasks were the same as for the AI, and followed those from Addis et al.'s: participants were instructed to generate unique personal events, temporally and contextually specific, occurring over minutes or hours, but no more than one day. Explicit mention to the similarity of the event's characteristics with the AI was reminded and examples were provided.

Addis and colleagues (2007a) presented a cue-word to elicit the recollection/imagination of past and future events. We presented two cue-words to adapt the task to MS patients, bearing in mind that the fMRI tasks require time-constrains (see below the experimental design). Thus, two lists, each of 32 pair of words per condition, were constructed. For the past events task, the pair of words were distributed in the different life periods based on the probability of occurrence of the event in the subject's life (e.g. 'Driving – Licence' proposed for the period from 12 to 20 years, or 'First – Job' for the period from 21 to 35 years).

Concerning the control task, using two cue-words, we constructed a categorical control task inspired by those of Addis et al., during which the patient had initially to construct a sentence including these words (e.g. with 'cake-chocolate': 'The pastry chef's speciality is the chocolate cake'). Then, for 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. 'The pastry chef's speciality is the apple pie'). We did not include the visual control task since the emphasis of our experimental facilitation programme is precisely on MVI, and that enhanced brain activations in relation to MVI were expected in post-facilitation, this could lead to some potential confounding factors.

The pertinence of the pair of words to elicit past/future events and to complete the control task was then verified (see the Preliminary testing – Behavioural testing section).

During fMRI sessions, we used a four-response button box. To indicate the end of the construction phase (for all the tasks), participants had to press on the button 1. The additional buttons were used to complete two four-point rating scales at the end of the elaboration phase. Indeed, for past and future events tasks, each trial was followed by two four-point rating scales dealing with the degree of vividness (1 = very poor vividness to 4 = very high

vividness) and of emotional intensity felt during the remembering phase (1 = very poor emotional intensity to 4 = very high emotional intensity). For the control task, the participants had to assess the degree of difficulty (1 = very few difficulty to 4 = very high difficulty) and the degree of pleasantness (1 = very poor pleasantness to 4 = very high pleasantness).

With regard to the experimental design, as in the original procedure, 20 sec per trial were allocated to the construction and elaboration phases for all the tasks. Concerning the rating scales, 4 sec were allocated per scale. To allow a sufficient time interval, especially to the search of details during the elaboration phase of past/future events, trials with a construction phase longer than 10 sec will be excluded for the further analyses. The initial experimental design of Addis and colleagues comprised six runs of 16 trials, with four trials from each condition. Since MS patients with mild attentional and/or executive functioning deficit could be included, to minimise the attentional and flexibility burden and so, the risk of a poor completion of the tasks, we slightly modified the experimental design to avoid too much alternations between the tasks. The fMRI data were acquired during one acquisition session, divided in 12 sequences (four per condition) including each eight trials (Figure 3). The presentation order of stimuli within each condition was randomised. Before each sequence, the name of the condition appeared for 6 sec. In all the tasks, each trial was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s).

The programming and response collection was done with E-Prime 2 software (Psychology Software Tools, Inc.) and words were displayed on a screen in white text with a black background.

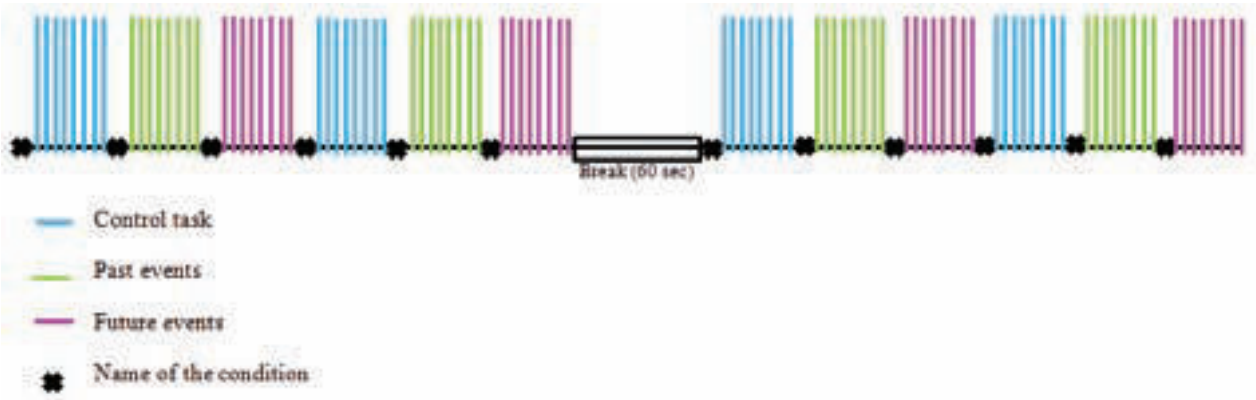

Figure 3. Schematic illustration of the fMRI experimental design. The different tasks are presented alternately and stimuli are randomly presented within each task.

2.2. Construction of the post-scan questionnaire

A post-scan questionnaire was developed based on Addis et al. (2007a) to verify the adequacy of the responses, but also to collect additional information about the phenomenological properties of the past and future events recollected/imagined during the fMRI session. The questionnaire has been designed for self-assessment, immediately after the scanning. Thus, the first dimension explored the categorisation of the type of event with five options: (i) unique: specific or particular occurrence of events, within a specific time and space frame, no longer than one day; (ii) repetitive: composed of events memories, which are usual and repeated, and thus lack temporal specificity; (iii) extended: includes events longer than one day (e.g. my week of holidays in Rome), without the mention of a specific incident; (iv) semantic: encompasses general, semantic associations with the cue-words not self-relevant; (v) absent: corresponds the absence of response in the scanner (i.e. no button press to end the construction phase). The spatio-temporal context of the event was also briefly stated to enable the further verification of its actual presence and so, the adequate categorisation of the event as unique. Data concerning the emotional valence of the events were also gathered, and participants had to indicate if the event is positive, neutral or negative, as well as the visual perspective (field, observer or both). Three visual-analog scales of 10 cm were presented, assessing respectively the difficulty of access/imagination (very easy to very difficult) to the amount of details (very poorly detailed to very detailed) and the personal significance of the event (insignificant, did not change my life to personally significant, life-changing event).

The post-scan questionnaire was subdivided in two sections, entailing respectively the past and the future events, in which all the pairs of cue-words associated to their life period were listed in the order of apparition in the scanner.

2.3. Preliminary testing of the fMRI tasks

2.3.1. Behavioural testing

To test the items to be used in the fMRI, the timing and visual presentation of the task, six healthy subjects (five women) with a mean age of 39.83 years (SD = 15.79) carried out the two versions of the fMRI tasks on a screen computer in two separated sessions. Responses were given on the numeric keyboard and recorded with E-Prime 2 software. Immediately after the completion of the task, the post-scan questionnaire was proposed to the subject. At the end of the second session, an informal interview was conducted with the subject to obtain their impressions and comments on the tasks. Descriptive results of the preliminary fMRI tasks obtained in the Table 7.

Table 7. Mean (and standard deviations) scores obtained for the post-scan questionnaire variables by the subjects during the behavioural pre-testing (cumulatively for the two versions)

	Past events	**Future events**
Type of events		
Unique	80.07 % (9.60)	76.08 % (14.66)
Repetitive	11.27 % (7.85)	15.97 % (13.32)
Extended	1.86 % (3.75)	1.06 % (2.79)
Semantic	0.78 % (2.71)	0.78 % (2.71)
Absent	6.02 % (6.04)	6.11 % (7.91)
Emotional valence		
Positive	57.64 % (16.96)	51.61 % (20.72)
Neutral	22.26 (20.06)	34.51 % (24.60)
Negative	20.10 % (7.93)	13.88 % (9.13)
Visual perspective		
Actor	28.25 % (39.62)	17.96 % (38.44)
Observer	49.36 % (43.09)	50.61 % (49.63)
Both perspectives	22.39 % (30.56)	31.43 % (44.89)
Access	7.27 (1.09)	7.37 (1.03)
Details	6.94 (1.25)	6.14 (1.85)
Personal significance	6.24 (1.73)	5.74 (2.29)

Potential differences between the two versions of the programme were also tested to ensure their equivalence for the type of events, by means of Wilcoxon pairs test. For the past events condition, no significant difference was observed between the two versions. Regarding the future events conditions, a smaller number of unique events ($Z = 2.02$; $p = 0.04$) and a greater number of repetitive events ($Z = 2.02$; $p = 0.04$) were highlighted in the programme 2. Based on the raw data, we identified and modified three non-pertinent pairs of words. Visual perspective and personal significance measures were finally discarded to avoid a too time consuming questionnaire. Thus, only minimal modifications have to been introduced.

2.3.2. Neuroimaging testing

The fMRI tasks were also pretested in the fMRI environment with a group of four healthy subjects (3 women) with a mean age of 36.50 years (SD = 11.17) . All the participants underwent two fMRI sessions to complete the two versions of the task. Pre-testing results showed a mean number of valid trials of 27.13 (SD = 3.23) for the past events, of 26.25 (SD = 6.75) for the future events and of 28.50 (SD = 5.45) for the categorical task. These results were consistent with those obtained by healthy subjects in the initial study of Addis et al. (2007a). Mild-to-high ratings scores were obtained for the past and future events for the vividness, respectively 2.60 (SD = 0.53) and 2.59 (SD = 0.82), and for the emotional intensity, respectively 2.58 (SD = 0.34) and 2.18 (SD = 0.43). Regarding the control task, the participants' mean scores for the difficulty scale was 2.02 (SD = 0.34) and 2.50 (SD = 0.38) for the pleasantness scale. An important point concerned also the construction RT and results showed a mean RT for the construction phase of 5.09 s (SD = 1.62) for the past events, of 4.59 s (SD = 1.46) for the future event and of 4.86 s (SD = 1.62) for the categorical task. Here too, our data were in agreement with previous studies in healthy subjects (Addis et al., 2007a) and notably with the study of Conway et al., (2003), which determined electro-physiologically that the average time taken to retrieve an event is approximately 5 sec. The mean RT for the rating scales presented during scanning showed that the time interval of 4 sec allocated for each rating was sufficient, as highlighted by the following mean RT results: respectively for past and future events: RT vividness = 1.52 sec (SD = 0.43) and 1.53 sec (SD = 0.34); RT emotion = 1.17 sec (SD = 0.34) and 1.18 sec (SD = 0.50); and for the control task: RT difficulty = 1.87 sec (SD = 0.38) and RT pleasantness = 1.39 sec (SD = 0.30).

Based on these preliminary data, the past events and the future events tasks seemed to result in comparable performance for all the variables.

The final verification of the appropriateness of our fMRI tasks was the examination of its functional underpinnings. Qualitatively, the cerebral activations were consistent with the existing literature on the cerebral core network sustaining AM and EFT (Svoboda et al., 2006; Hassabis et al., 2007; Addis et al., 2007a; Botzung et al., 2008). Qualitative within-subject comparisons showed an overlap between the past and future conditions, as reported in previous studies (Botzung et al., 2008). However, as previously observed in healthy subjects (Addis et al., 2007a; Schacter et al., 2012), the future condition seemed to require more extended brain activations than the past condition.

3. Elaboration of the control verbal facilitation programme

Since of our pilot study (Ernst et al., 2013) did not involve a patients control group, the presence of a potential nursing effect on the benefit observed in post-facilitation cannot be ruled out. Thus, a 'placebo' group of patients was introduced in the present study.

Several clinical 'ingredients' from our MVI programme were pinpointed: (i) the use of goal-directed approach; (ii) a constant exchange with the patient; (iii) a progression of the patient through the sessions and steps of increasing difficulty; (iv) the absence of failure or errors; (v) positive feedbacks; (vi) a self-focused final step in the programme; (vii) related to all the previous points, an improvement of self-esteem and self-confidence (qualitative observations). Thus, we developed a placebo programme, which complied with all these points, following the same general presentation, number, frequency and duration of sessions from our MVI programme.

Beyond the main role of MVI in AM, 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 schema on what has to be included or excluded in a memory. However, narrative structure distinctly plays a more minor role than MVI in AM. On theses bases, we chose to develop a narrative-oriented control programme, which could so be plausibly linked to AM and EFT performance. Importantly, narration was also selected because this cognitive ability is not part of the frequently described cognitive impairment in MS patients. Besides,

even if a narrative impairment would have been present in our patients, the comprehensive neuropsychological examination and the AI assessment would permit to identify it.

The programme was presented as focusing on the importance of the structuration of the information. As we based this programme on the verbal modality, a series of texts extracted from internet was selected from various websites, covering a wide range of news topics. After a first reading of the text, the general goal was to construct an exchange, a discussion about the topic of the text, but with different direction through the steps of increasing difficulty. Of course, the patient was informed that he/she has the possibility to refer and re-read the text all along the discussion, as it is not a memory exercise. No equivalent screening test, as in the MVI programme, was developed since this ability was indirectly and qualitatively already assessed during the baseline and AM/EFT examination. Thus, the programme entails three steps, which were as followed:

1) The *external discussion*, which comprised 20 texts and consisted in discussions about the text form (e.g. its clarity, its potential origin, the vocabulary used, etc). Here, the aim was to identify variables which influence the understanding of a text. This step was very brief and corresponded to the external visualisation from the MVI programme.

2) The *discussion construction* included five items, with for each one a first training text and then, a construction text. This organisation has been made to follow the same as the corresponding construction step of the MVI programme. So, the two texts of each item were thematically related to enable the reliance on the first to construct the second one. For example, a first text dealing with a trip in South Africa was proposed, and then a second text about a trip in Ireland.

3) The *self-involved discussion* had the same functioning as the previous step, with five items comprising two texts. For instance, a first text about taxing sodas to reduce their consumption was provided, with then a second concerning the usefulness of anti-smoking campaigns. However, here, the emphasis was made on the personal opinion of the patient about this subject.

As during the MVI programme, the neuropsychologist provided a continuous guidance during the discussion elaboration, with supplementary questions to rekindle the exchange. A general guidance was also made to encourage the patient to construct a structured talk, by developing one point before starting another, organised if possible in sub-sections. This last point enabled to teach to the patient to work in a sequential manner, as for the MVI programme during

scene construction. More generally, a particular attention was paid to include all the aforementioned clinical 'ingredients' from the MVI programme during the placebo programme sessions.

In conclusion, the present preliminary work allowed us to obtain the prerequisite to our different study's objectives at both the behavioural and functional neuroimaging levels. Eight studies have been carried out in the present work and the remaining of the thesis encompasses their presentation.

STUDY 1

Ernst A, Blanc F, De Seze J, Sellal F, Chauvin B and Manning L. Impaired mental simulation of specific past and future personal events in non-depressed multiple sclerosis patients. (*Journal of the Neurological Sciences*, in minor revision)

Abstract

The aims of the present study were (i) to explore autobiographical memory and episodic future thought in multiple sclerosis (MS), using Levine's Autobiographical Interview. (ii) To investigate the influence of the Interview's high retrieval support condition (the specific probe phase) on MS patients' past and future simulation. (iii) To obtain the patients' estimations of their own difficulties, during the test, and in everyday life.

To that end, we examined 39 non-depressed relapsing-remitting MS patients and 34 healthy subjects matched for gender, age and education level. The 73 participants underwent an adapted version of the Autobiographical Interview in two conditions: remembering and imagining personal events. The group of patients also underwent an extended neuropsychological baseline, including particularly, anterograde memory and executive functions.

The results showed that the MS patients' scores on the baseline were mildly or not impaired. On the contrary, the Autobiographical Interview measure, i.e., the mean number of internal details, for each of the two phases of the test -free recall and specific probe- was significantly lower in simulated past and future events in comparison with the healthy controls. Within each group, autobiographical memory performance was superior to episodic future thought performance. A strong positive correlation was observed between past and future mental simulation scores in both groups.

In conclusion, our results showed, for the first time, the co-occurrence of deficit of remembering the past and imagining the future in MS patients. They also showed more difficulty in imagining future events than remembering past events for both patients and normal controls. MS being a neurological condition very frequent in the young adult population, the clinical considerations of our study might be of interest. Indeed, they give rise to new insights on MS patients' daily life difficulties related to impaired mental simulation of personal events despite general abilities, including anterograde memory, only mildly or not impaired.

Keywords: Multiple sclerosis, Cognition, Autobiographical memory, Episodic future thought, Neuropsychology, retrieval conditions

1. Introduction

The occurrence of cognitive impairment in multiple sclerosis (MS) has been established for the past 20 years (Brassington & Marsh, 1998; Rao et al., 1991), covering a wide range of cognitive functions such as anterograde memory, executive functions, attentional processes, information processing speed, among others (Rogers & Panegyres, 2007).

More recently, the investigation of autobiographical memory (AM) in MS patients has attracted some attention. Briefly stated, AM is the capacity of reliving detailed events, within their specific spatio-temporal context, as they are remembered (Tulving, 1985). An overview of AM studies in MS (Paul et al., 1997; Kenealy et al., 2002; Muller et al., 2013; Ernst et al., 2013; Ernst et al., 2012) shows some conflicting results, which seem to rely mainly on some methodological discrepancies, particularly, the sensitivity of the test used to assess AM in MS. The call for a stringent AM test is also motivated by the fact that notwithstanding the variability of AM test performance, MS patients' complaints are frequent. These clinical observations together with neuroanatomical and conceptual considerations (see below), led to the suggestion that AM impairment in MS patients is likely caused by a deficit of retrieval strategies rather than loss of personal recollections (Ernst et al., 2013; Ernst et al., 2012). The deficit would be then attributed to dysfunctional prefrontal regions (Botzung et al., 2008; Manenti et al., 2010).

From a neuroanatomical standpoint, MS patients' difficulties in remembering past events are coherent with both the multifocal nature of MS lesions and the widespread cerebral network recruited during AM tasks (Svoboda et al., 2006). This cerebral network encompasses predominantly the left and medial cerebral regions, namely, the prefrontal cortex, medial and lateral temporal cortices, parieto-occipital regions, temporoparietal junctions and cerebellum. Consistent with these findings, the preliminary fMRI results obtained by Ernst et al., (2012) showed enhanced bilateral prefrontal region activations during the initial retrieval phase of past events, which seemed to corroborate the retrieval-deficit hypothesis. Moreover, the enhanced prefrontal activation having been observed bilaterally, the suggestion was one of a compensation mechanism attempt, although insufficient to result in normal AM performance (Ernst et al., 2012).

Recent neuroimaging and clinical studies have examined the ability to mentally simulate hypothetical scenarios not only from past recollections but also those that may potentially occur in the future, i.e., the relationships between remembering the past and imagining the

future. Imagining future personal events or episodic future thought (EFT; Szpunar, 2010; see Schacter et al., 2012 for a review), is the ability to mentally pre-experience a personal event that may happen in the future. The relation between AM and EFT, sometimes referred to as "mental time travel" (Suddendorf & Corballis, 1997; 2007), has been extensively studied in the healthy subject (e.g. Addis, Wong & Schacter, 2007; Botzung, Denkova & Manning, 2008; Szpunar, 2007), revealing a common cerebral network assumed to reflect the engagement of similar cognitive processes. Indeed, AM and EFT not only involve self-referential processes, but also the retrieval and binding of details into a coherent event representation, which includes conceptual and sensory information, with a strong reliance on visual imagery processes (Addis, Wong & Schacter, 2007).

Subsequently, in clinical studies, it was surmised that EFT would also be deficient whenever AM impairment had been observed. Investigations carried out in several clinical conditions such as Alzheimer Disease (e.g. Addis et al., 2009), amnesic Mild Cognitive Impairment (e.g. Gamboz et al., 2010), schizophrenia (e.g. D'Argembeau, Raffard & Van Der Linden, 2008), depression (e.g. Williams et al., 1996), or medial temporal lobe amnesia (e.g. Hassabis et al., 2007; Race, Keane & Verfaellie, 2011) confirmed the co-occurrence of deficit in the simulation of past and future personal events.

To our knowledge, EFT has never before been explored in MS patients despite the characteristically onset of the illness occurring during young adulthood and despite the clinical value of the central role of mental time travel in everyday life. Indeed, AM contributes to the construction and the continuity of the personal identity and it plays at least two social roles, the development of new relationships and the nurturing of existing ones, and involves also a directive function, where the past serves as a basis for guiding present and future behaviours (Rasmussen & Habermas, 2011; Bluck, 2003). With regard to EFT, three main functional benefits have also been described (Szpunar, 2010) comprising a role in (i) coping skills for stressful events, with an implication in emotion regulation and problem solving; (ii) goal achievement, for which the act of imagining various scenarios helps to reach the desired goal and finally, (iii) the implementation of intentions, for which a higher likelihood of completing an action is observed when there is an intention to implement this action. Furthermore, D'Argembeau, Lardi & Van der Linden (2012) suggested that EFT, similarly to AM and, particularly, self-defining EFTs contribute to a person's sense of self

and, together with self-defining AMs, give rise to a strong sense of personal continuity over time.

On the bases of both the above mentioned works on the interdependence between AM and EFT in terms of common cognitive processes, and previous reports on AM in MS patients, the aims of the present study were (i) to explore autobiographical memory and episodic future thought non-depressed relapsing-remitting MS patients, (ii) to investigate the influence of a high retrieval support condition on MS patients' past and future simulation, and (iii) to obtain the patients' reports about their difficulties during the test, and in everyday life. To that end, we probed the ability to MS patients to generate future episodic events, as well as to remember recent past events and remote past events from across the lifespan. The rationale for exploring remote past events relied on the importance of having a comprehensive view of MS patients' AM performance. Effectively, taking into account the suggestion of an AM *retrieval*-deficit hypothesis in MS patients, exploring only recent past events, which are generally more accessible memories, could result in an underestimation of the AM impairment. A similar pattern of impairment was expected between future events and both time intervals, recent and remote past events in MS patients. Complementarily, a correlation between AM and EFT scores in our patients was also expected.

As the AM test sensitivity is a main concern to explore AM functioning, we carried out the research with the Autobiographical Interview (AI; kindly communicated by Brian Levine to one of us, LM), based on its sensitivity to detect AM and EFT deficits in different clinical populations (e.g. Addis et al., 2009; Gamboz et al., 2010; De Vito et al., 2012). Moreover, as the AI includes both a free recall and a high retrieval support condition (i.e. the specific probe phase), a further aim was to investigate the influence of this last condition on AM and EFT performance in MS patients. Finally, we also aimed at obtaining the patients' self-reports on their difficulties during the mental simulation testing, but also more generally in their everyday life.

2. Methods

2.1 Participants

Thirty-nine patients with definite MS according to the Polman et al.'s criteria (Polman et al., 2011) were recruited at the Neurology Units of two French hospitals (Strasbourg and Colmar). Inclusion criteria were as follows: RR-MS disease course, Expanded Disability

Status Scale (EDSS; Kurtzke, 1983) score ≤5, absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979: significant clinical threshold score ≥ 15), and no recent exacerbation of MS symptoms. Thirty-four healthy controls matched for gender, age and education level were also recruited. Exclusion criteria for all the participants included documented psychiatric illness, neurological disorder (other than MS for the patient group) and poor knowledge of French. 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 APA ethical standards.

Table 1. Demographic and clinical data: Mean and (standard deviation) for the MS patient and the healthy control groups

	MS patients	Healthy controls	Statistical analysis
N =	39	34	–
Age in years	39.77 (SD 7.88)	37.85 (SD 11.64)	t = 0.83; p = 0.41
Education in years	13.38 (SD 2.15)	14.21 (SD 2.71)	t = -1.44; p = 0.15
Sex (Ratio female/male)	33/6	26/8	χ^2 = 0.77; p = 0.37
EDSS [range]	2.54 (1.38) [0-5]	n.a	–
Duration of MS in years	12.07 (7.56)	n.a	–
Number of DMD treatment	1.0 (SD 0.0)	n.a	–

EDSS: the Expanded Disability Status Scale; SD: Standard deviation; n.a: not applicable

2.2 Neuropsychological baseline examination

The patients completed a comprehensive baseline examination in order to verify their cognitive status allowing us to control any potential confounding variables on the AM and EFT performance. It comprised the following functions, *general verbal abilities*, tested with the Verbal IQ, short form (Axelrod, Ryan & Ward, 2011) of the WAIS-III (Wechsler, 1997), *nonverbal reasoning* 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 National Hospital's, London, phonological and categorical fluency tests, 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 (the 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). Additionally, the effects of fatigue in everyday life were assessed using the "Echelle de Mesure de l'Impact de la Fatigue," (EMIF-SEP; Debouverie et al., 2007).

Finally, in the interest of obtaining qualitative information about MS patients' perception of potential AM/EFT difficulties during the assessment, but also in everyday life, we proposed a semi-structured interview (described in Ernst et al. 2013) at the end of the AI session.

2.3 Assessment of mental simulation of past and future events

The assessment of AM and EFT was based on the AI described in Levine et al. (2002). It consists in retrieving/imagining personal unique events, temporally and contextually specific, occurring over minutes to hours and to generate freely as many details as possible about the event. We used the adapted version of the AI (Addis, Wong & Schacter, 2008; Addis et al., 2009), introducing cue-words, which allowed us carried out comparable examinations of AM and EFT. Additionally, based on previous studies (Barnabe et al., 2012; Ernst et al., 2012; Leyhe et al., 2009), we modified the number of events to be retrieved from one (in the standard version) to three past events per life period explored [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]. The aim of testing a greater number of past recollections was to assess more comprehensively the retrieval process and to avoid the likelihood of the patients providing only the most accessible detailed recollections (Barnabe et al., 2012; Leyhe et al., 2009). With regard to the EFT testing, following Addis et al. (2009), we instructed the participants to generate five events, which could plausibly occur during the coming weeks or months or any interval during the next year. These instructions attempted to

minimise any potential conscious avoidance of EFT in the patients due to the uncertainty surrounding disease progression.

The order of presentation between AM and EFT tasks was counterbalanced as were the order of the cue-words and the past life periods. To encourage mental simulation of past and future personal events, participants were informed that the cue-words were intended to be used flexibly (e.g. the cue-word "train" could result in a personal recollection of a journey by any other means of transport). No time limit was set to avoid the potential influence of decreased cognitive processing speed on AM/EFT performance for MS patients.

General probes (e.g. 'is there anything else you can tell me?') were used to clarify instructions if necessary and to encourage evocation of supplementary details. It was followed by the specific probe phase, which is a structured interview to elicit additional details.

The AI session was audio-recorded for later transcription and scoring following the standardised Levine et al.'s (2002) procedure. Two phases of recall were analysed, the free recall and the specific probe phases. However, for the subsequent statistical analyses, the specific probe phase scores were analysed cumulatively with the free recall phase scores.

After the identification of the central 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 else episodic details unrelated to the central event). For each participant, the number of internal details was averaged across the 12 or 15 past events for the AM, or the three past events for the previous year, and across the five future events for the EFT conditions for each recall phase. Since Ernst et al., (2013) highlighted an impairment of the episodic component of AM, whereas the personal semantics was preserved, only the mean number of internal details was considered for the following statistical analyses.

The interrater reliability was verified for 10% of the past and future events, which were scored by a second scorer, following Levine et al.'s (2002) procedure. Coefficients for all measures showed high interrater reliability (between 0.82 and 0.99).

2.4 Statistical Analyses

Mean scores obtained by the MS patients for each neuropsychological baseline test were calculated.

Differences between the MS patients and healthy controls in AM/EFT were analysed for the mean number of internal details by running mixed ANOVAs to explore main effects of group (MS vs healthy controls), temporal direction (past vs future) and recall phase (free vs specific probe phases), as well as relevant interactions.

A similar complementary analysis including only the previous year for the AM condition vs the EFT condition was also conducted by means of a mixed ANOVA to obtain a comparison of the performance (mean number of internal details) with a matched temporal interval.

Pearson coefficient correlations between AM (remote and recent memories) and EFT performance within the two groups were calculated for the mean number of internal details across the two phases of recall.

3. Results

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

Table 2. Neuropsychological baseline examination scores: Mean (and SD) for the MS patient group

	MS group scores
Verbal IQ	98.46 (12.73)
PM12	9.23 (1.74)
RAVLT	
- Total mean number of words	12.36 (1.34)
- Delayed recall	13.74 (1.72)
ROCF	
- Copy	35.67 (0.72)
- Immediate recall	24.73 (4.60)
- Delayed recall	24.71 (4.62)
Deno 100	97.53 (3.51)
Stroop	
- Colours (score T)	46.0 (8.03)
- Words (score T)	44.64 (7.56)
- Interference (score T)	47.71 (10.55)
- Interference score (score T)	51.71 (7.82)
Months back (sec)	10.79 (3.35)
Tower of London	
- Score	8.15 (1.69) **
- Time indice	18.10 (3.60)
Brixton (number of errors)	14.74 (6.19)
Cognitive Estimation Task	4.28 (3.20) **
Verbal Fluency	
- Categorical	20.07 (4.81)
- Phonological	13.18 (3.22)
Information Processing Speed	
- Cognitive	55.72 (13.07)
- Motor	48.77 (9.35)
- Error percentage	2.80 (3.16)
- Corrected score	62.43 (15.45)
VOSP	
- Silhouettes	23.51 (3.65)
- Cubes Analysis	9.79 (0.52)
MADRS	6.05 (4.10)
EMIF-SEP (total)	48.35 (14.94)

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

** Scores under the normal range

3.1 Remote past events vs future events

Regarding the mean number of internal details (Figure 1), mixed ANOVA revealed a main effect of group $F(1, 142) = 42.29$, $p < 0.001$, $\eta^2_P = 0.23$, which reflected that, irrespective of the temporal direction or the recall phase, MS patients' scores were significantly lower than those of the healthy controls. A main effect of the temporal direction was also highlighted $F(1, 142) = 28.48$, $p < 0.001$, $\eta^2_P = 0.17$, showing that the mean number of internal details provided in the AM condition was higher than for the EFT condition, whatever the group or the recall phase. No significant Group x Temporal direction interaction was evident ($p = 0.66$).

A main effect of the recall phase was also observed, $F(1, 142) = 982.06$, $p < 0.001$, $\eta^2_P = 0.87$, with a greater number of internal details provided during the specific probe than during the free recall phase. The specific probe phase enabled a greater increase of the mean number of internal details for the healthy controls (vs the MS patients), irrespective of the temporal direction, as revealed by the significant Recall Phase x Group interaction, $F(1, 142) = 4.44$, $p = 0.03$, $\eta^2_P = 0.03$. Moreover, a differential effect of the specific probe phase on AM and EFT was displayed, with a significant Recall Phase x Temporal direction interaction $F(1, 142) = 12.53$, $p < 0.001$, $\eta^2_P = 0.08$, showing a lower increase of the mean number of internal details during the specific probe phase for the EFT condition. No significant 3-way interaction was obtained.

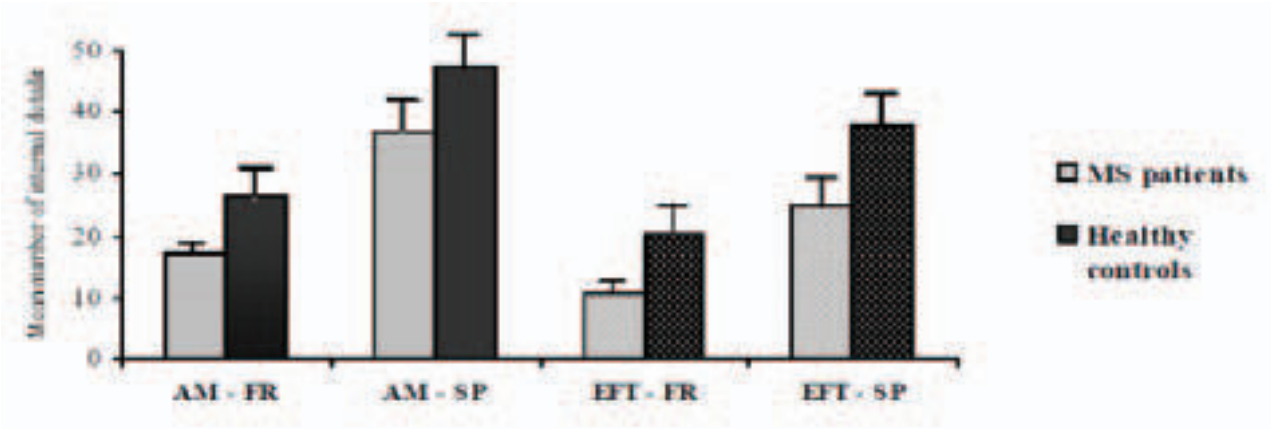

Figure 1. Mean number of internal details produced by the MS patients and the healthy controls for the AM (all life periods) and the EFT conditions during the free recall (FR) and the specific probe (SP) phases.

3.2 Recent past events vs future events

Considering only the previous past year (AM condition) and the EFT condition, analyses for the mean number of internal details showed a main effect of group, $F(1, 142) = 29.62$, $p < 0.001$, $\eta^2_P = 0.17$, with lower scores for the MS patients in both conditions (Figure 2). A main effect of temporal direction was replicated, with AM scores superior than EFT scores, $F(1, 142) = 65.99$, $p < 0.001$, $\eta^2_P = 0.32$, in both group. No significant Group x Temporal direction was observed ($p = 0.65$).

Irrespective of the group and the temporal direction, the mean number of internal details provided by the subjects after the specific probe phase was significantly higher than those of the free recall phase, as evidenced by a main effect of the recall phase, $F(1, 142) = 773.54$, $p < 0.001$, $\eta^2_P = 0.84$. A significant Recall phase x Temporal direction has been shown, $F(1, 142) = 46.49$, $p < 0.001$, $\eta^2_P = 0.24$, with a greater benefit of the specific probe phase on past recall than on future simulation. No other interaction effect was significant.

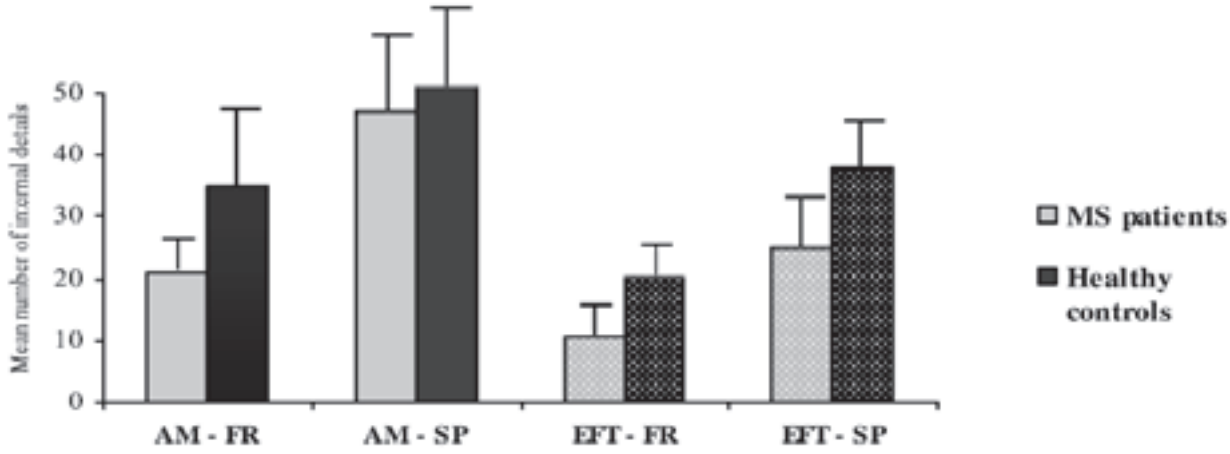

Figure 2. Comparison of the mean number of internal details produced by the MS patients and the healthy controls for the previous year (AM condition) and the next year (EFT condition) during the free recall (FR) and the specific probe (SP) phases.

3.3 Correlations between AM and EFT performance

Finally, the correlations between the AM and EFT scores within each group were carried out. For the MS patients, the mean number of internal details correlated positively with the EFT results during the free recall ($r = 0.59$, $p < 0.001$) and the specific probe phases ($r = 0.60$, $p < 0.001$). Comparable results were observed when the correlation analyses were run between

the previous and the next year for the mean number of internal details ($r = 0.54$, $p < 0.001$) during the free recall phase, as well as during the specific probe phase (mean number of internal details: $r = 0.41$, $p = 0.01$).

The same pattern of results was obtained for the healthy controls for the free recall (mean number of internal details: $r = 0.77$, $p < 0.001$) and the specific probe phases (mean number of internal details: $r = 0.74$, $p < 0.001$). Regarding the relationship between EFT and the previous year AM performance, strong correlations were obtained during both the free recall phase for the mean number of internal details ($r = 0.75$, $p < 0.001$) and the specific probe phase ($r = 0.75$, $p < 0.001$).

3.4 Qualitative self-assessment of AM and EFT performance

With regard to the semi-structured interview, the qualitative results gathered in the form of patients' comments (see the Appendix for extracts from patients' interviews), corroborated the aforementioned quantitative results. Generally, MS patients verbalized difficulties for the retrieval/imagination of a specific event, but also an impoverishment of details, conducting to low vividness and emotional intensity throughout the evocation of an event during the testing session, and also in some real life situations. Additionally, most of our patients' comments also stated that the EFT task was experienced as being harder than the AM task.

4. Discussion

We have documented the mental simulation of past and future personal events in non-depressed RR-MS patients. The results showed a mildly impaired neuropsychological baseline performance together with significantly poorer scores, compared with controls, in the mental simulation of past and future personal events. These findings are in accord with our previous work (Ernst et al., 2013) on AM in MS, using the Crovitz Test in a relatively small sample. The present results support the notion that AM and EFT, in the light of the relatively well preserved neuropsychological baseline, could be particularly sensitive to MS neuropathology. Our results might modify the often absent assessment of AM and EFT in clinical routine, since they suggest new insights into how MS patients' everyday life is affected by impaired mental time travel capacity (see below).

Turning to the AM and EFT performance, compared with healthy subjects, the patients generated significantly fewer episodic details in both remembering past events and imagining

future episodes, with a comparable degree of impairment for both temporal directions. In every case, taking into account remote or recent past events, lower scores were observed for the simulation of future events.

This AM/EFT deficit was observed for the two retrieval conditions (i.e free recall and specific probe phases). Although a high retrieval support with specific cues led the patient group to a relative performance improvement, it turned out to be insufficient since the scores remained under the healthy controls' results. In other words, it seemed that the healthy controls benefited in a greater extend of the specific cueing than the MS patients, irrespective of the temporal direction of the mental simulation. However, the greater benefit of the specific cueing for healthy controls was observed only when all the AM life periods were taken into account (it disappeared in the one year past/future condition). This finding suggests that a high retrieval support could be particularly effective for MS patients for the more recent past events, which are also, in general, more easily detailed (D'Argembeau & Van der Linden, 2004). Differential results between the two recall phases on AM scores, showing an improvement after the specific cueing, have been described in different clinical populations, especially patients presenting with prefrontal cortex lesions, in a context of retrieval strategy impairment, relying mostly on the prefrontal regions (Levine et al., 2002; Svoboda et al., 2002; McKinnon et al., 2006). In contrast, in the context of amnesic patients presenting with medial temporal lobe or diencephalic damage, the effect from a higher retrieval support is inefficient or modest,at best (Moscovitch et al., 2000; Levine et al., 2002).

The smaller number of details produced during the EFT condition compared with the AM condition was observed in both groups. This result is in accord with previous investigations, showing that past events are more detailed than future events in healthy subjects (Addis, Wong & Schacter, 2008; D'Argembeau & Van der Linden, 2004), and also in patients presenting with an AM/EFT impairment (e.g. Addis et al., 2009). Addis and her colleagues interpreted their findings in terms of a more important cognitive demand in pre-experiencing an event compared with remembering an event. The increased cognitive demand would tax above all executive functions because EFT requires the extraction and recombination of an infinite assortment of details into a novel event, whereas AM consists in the recapitulation of a more limited pool of details (Berntsen & Bohn, 2010). This notion is in accord with De Vito et al.'s (2012) study, showing impaired EFT performance with preserved AM scores in Parkinson disease patients, who present with a characteristic dysexecutive syndrome. De Vito

et al.'s aim was to assess EFT performance in patients, who, besides their dysexecutive condition, were non amnesic and therefore, different from our autobiographical amnesic MS patients. Despite this difference both studies have documented impaired EFT, which suggests the particularly vulnerable quality of the ability to simulate personal future events.

The effect of specific cueing on the simulation of future events was lower compared with cueing either recent or remote past events, in both groups. This finding could reflect the fact that the specific cueing is more effective when the number of possibilities is limited. For example, when imagining a future dinner with friends, the issue about the menu would give rise to countless possibilities. On the contrary, when remembering a dinner with friends, virtually any remembered detail as a response to the specific probe (e.g. X tasted for the first time sushi; we were with N, who loves pasta) may restrict the possibilities of the menu.

Taken together, the two mentioned findings, i.e., the benefit of a high retrieval support during the AI specific probe phase on the mental simulation tasks, and the poorer performance for EFT relative to AM condition could be seen as an additional argument for the retrieval deficit hypothesis in MS patients.

Despite the results being coherent with the non MS literature, the investigation of EFT in MS patients raises an important issue owing to the clinical presentation of the disease, and especially for RR-MS patients. Namely, because of the uncertainty surrounding MS evolution, one could argue that the EFT deficit, found in the present study, could reflect psychological factors such as a conscious decision of the patient not to engage in future projects despite the absence of depressive symptoms. However, the positive correlation observed between AM and EFT deficit in the patient group suggests that the EFT performance reflected a cognitive deficit. We are aware that a psychological influence cannot be ruled out, but practically all the patients reported cognitive difficulties, particularly so in relation to the EFT. We observed no examples of psychological inhibition or conscious avoidance of EFT during the semi-structured interview, which was probably due to the relatively short interval in which the patients were asked to mentally simulate potential scenarios (see the Appendix section).

Bearing in mind the essential role of AM and EFT in everyday life (D'Argembeau, Renaud & Van der Linden, 2011; Rasmussen & Habermas, 2011; Szpunar, 2010), the present findings suggest some clinical issues. In the first place, besides our MS patients' occasional complaints, the semi-structured interview showed that they were well (and accurately) aware

of their difficulties and able to verbally articulate them to convey a clear message. Given the fact that the quantitative results endorsed the qualitative assessment, and that the patients alluded to real life not infrequently, it could be useful to introduce the same type of questions at the end of the AI and similar tests, in routine clinical practice. Moreover, in previous studies (Ernst et al., 2013; Ernst et al., 2012), a cognitive facilitation programme has been proposed to improve AM in MS patients, which resulted in normalised AM performance, and whose benefits were efficiently transferred to daily-life functioning. Whether those positive AM results would be also observed in the EFT mental simulation is again an issue of clinical interest. Indeed, bearing in mind the role of EFT in coping for stressful events and goal achievement, improving the EFT ability could be particularly useful vis-à-vis some particular requirements in the course of the disease.

To conclude, the present findings showed that RR-MS patients had cognitive difficulties in the mental simulation of past and future personal events similar to other clinical conditions, and a cognitive profile suggesting that in MS, these difficulties can be more taxed than several other cognitive functions that were also explored. They showed too that qualitative evaluation of AM/EFT difficulties has clinical value.

Our results encourage further investigation, namely, trying to understand how simulated future events that are known to be important in real life are modulated by the course of the disease. Any research along these lines would be closely related to current investigations centred in understanding why simulated future events *are* important in real life (Szpunar et al., 2013). On a more matter-of-fact level, this study also encourages the replication of the results with a larger sample of MS patients and the introduction of functional neuroimaging data. In relation to the latter, one remaining question concerns the possibility of a compensation mechanism attempt during an EFT task (although insufficient to result in normal performance), as previously observed for AM performance in MS patients (Ernst et al., 2012). If that were the case, a potentially interesting investigation would be to explore the similarities and differences between AM and EFT in the setting up of cerebral compensation mechanisms.

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Declaration of interest

The authors report no declaration of interest.

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Appendix

Excerpts of patients' comments during the semi-structured interview presented at the end of the Autobiographical Interview

Autobiographical Memory

IB: I'm forever hesitating when I recollect, I always hesitates. That's very…, it's horrible, because I have lots of memories somewhere, but they are snippets of memories (…). The only thing that could, eventually, help me is to talk with the people who were there… also to reconstruct myself, to remember or to go back to people, whose … to things that I have already forgotten, actually. It doesn't always come back and that, that is very upsetting. I have this feeling that my memories disappear and it pains me.

MFW: It's difficult because it's terrible not be able to remember … if someone tells you anything, I don't know, asks you "where were you?" that kind of questions… I mean, sometimes they can keep asking you endlessly. It's the same with things that I should absolutely know, but I don't. It's very hard sometimes because deep inside I tell myself "you look like an idiot and yet you know that stuff", but I know no longer, not easy really, it's hard.

NK: I'd say that for some memories, I've given you quite a lot of details, but for other memories I gave you a general idea, one important thing, and I just couldn't get the details as I should have, of course I should have (…) There are many things that I can't any longer remember (…) What really gets on my nerves is to have these flashes and I can't say when it was, who it was…

VW: I can't get it, can't get back to the film. No, no, no. Sometimes there are some things that… the event is … as if I had erased it, as if I had never been there, as if … My friend remembers "Come on! There was this and that, we went to…" And I say "Really? But I was not there". "Yes you were" And I really feel like I have nothing to do with the event.

Episodic Future Thought

NG: Not OK, also because I have some difficulties to project myself into the future, difficult to imagine a scenario that could happen… it's always quite complex because when dealing with quite specific things you never know how people will react in that situation. That's why it's always a little bit blurred.

CL: I'd say that, well it's not clear for me because I've really tried to get it, really tried to find the … no, there were no details. Let's say that I've just taken bits of what I've lived at some moments and put them in the project.

VF: It's no longer flashes or images I have; I think it's something in between. It's more static, if there is a little bit of movement it doesn't last long (…). Yes, I was saying things that have already happened; I know I had to dissociate them…

IN: I had to look for longer, anyway, to think more…There is this stuff that comes more or less spontaneously, but for other things I really need to look for…

CE: Imagine myself in a scenario, seeing all that surrounds me is not easy compared to an experienced situation. To find the moments, let's say, it's not that hard, but after that, to describe all the things that go with it, people, context of the room, the place…

IJ: It's somewhat like the past, it remains blurred.

MFW: It's clear that I'm unable to project myself…I just can't, well, it's near future, if I try to think… I'll only be able to tell you one… but no, no details for me. No, no details, well I'd say it's less than a flash, it's an act, if you know what I mean (…) But otherwise, it's for sure I can't project myself, I just can't.

STUDY 2

Ernst A, Denkova E, Blanc F, De Seze J, Gounot D and Manning L. Spontaneous brain plasticity in multiple sclerosis patients during an autobiographical memory test. (submitted)

Abstract

Our aim was to investigate whether the increased neural effort phenomenon due to structural damage, observed in multiple sclerosis (MS) in anterograde memory deficit was also present in impaired autobiographical memory (AM). Eighteen patients and 18 controls underwent the Autobiographical Interview (AI). The 36 participants underwent an fMRI session designed to assess the construction and elaboration of AMs. A categorical control task was also presented. Patients were trained in the fMRI procedure to optimise the practical aspects accompanying the task itself. The AI showed significantly poorer scores ($P< 0.001$) for the patients, but behavioural results on the fMRI AM task were similar for the two groups. Compared with controls, the patients showed increased and bilateral cerebral activations ($P< .005$) during the construction and elaboration phases. The prefrontal, temporal and posterior cerebral region activations were located within the core network sustaining AM. The bilateral prefrontal activations were particularly important. The parametric neural responses to the difficulty of access and amount of details of memories were significantly different for the two groups. There was an increased recruitment of the right hippocampal region ($P< 0.005$). The findings suggested the presence of spontaneous brain plasticity during AM and corroborated our retrieval-deficit hypothesis in MS patients.

Keywords: spontaneous brain plasticity, multiple sclerosis, autobiographical memory, autobiographical inventory, functional MRI

1. Introduction

The occurrence of spontaneous cerebral plasticity in neurological patients has been established (Chen, Epstein, & Stern, 2010) and described in different conditions such as multiple sclerosis (Filippi & Rocca, 2004), Alzheimer's disease (Bookheimer et al., 2000), stroke (Johansson, 2000) or traumatic brain injury (Levin, 2003). Regarding multiple sclerosis (MS), previous fMRI studies have reported cerebral activation changes, entailing increased activation in brain areas also recruited by controls, and/or the recruitment of alternative brain areas (Hulst et al., 2012). These phenomena have been interpreted as the manifestation of an increased neural effort due to structural damage (Hawellek, Hipp, Lewis, Corbetta, & Engel, 2011) in impaired cognition in MS (Rogers & Panegyres, 2007) such as attention and working memory (Kollndorfer et al., 2012), anterograde memory (Mainero et al., 2004; Morgen et al., 2006; Hulst et al., 2012) or executive functions (Lazeron, Rombouts, Scheltens, Polman, & Barkhof, 2004). However, the neural underpinnings of spontaneous brain plasticity were not investigated in the case of autobiographical memory (AM), which by its ultimate links to the self plays a major role in daily life functioning and its impairment can lead to debilitating consequences. Therefore, the aim of the present paper was to investigate the issue of brain plasticity linked to AM in case of MS.

AM, the ability to mentally re-experience personal past events (Tulving, 2002), has been shown to be impaired in MS (Kenealy, Beaumont, Lintern, & Murrell, 2002; Ernst et al., 2012; Ernst et al., 2013; Müller et al., 2013). The multifocal nature of MS cerebral lesions (e.g. Trapp & Nave, 2008), together with the widespread neural network sustaining AM, have been suggested to account for AM impairment in MS patients. More precisely, on the one hand, AM processes have been primarily associated with a network including the medial prefrontal cortex, the medial and lateral temporal cortices, the parieto-occipital regions and the temporo-parietal junction (Svoboda, McKinnon, & Levine, 2006). On the other hand, several studies carried out in MS patients have demonstrated that structures such as the frontal cortex (Benedict et al., 2002; Bendfledt et al., 2009) and the hippocampus (Sicotte et al., 2008; Hulst et al., 2012), which are essential in the AM core network, are frequently damaged.

Despite evidence of AM deficit in MS, only one preliminary study (Ernst et al., 2012), to our knowledge, has investigated the neural underpinnings associated with impaired performance

in personal episodic memory tests. Among others, these preliminary results showed that beyond the initial difficulty to retrieve a specific memory, the access to details associated with the event was also compromised. Building on these initial observations, the aim of the present study was to investigate whether the increased neural effort phenomenon due to structural damage, observed in anterograde memory deficit in MS was also present in impaired AM. To this end, we study (i) the functional cerebral substrates sustaining both the access and further elaboration of personal recollections and (ii) the influence of recollective qualities of memories on cerebral activations in MS. By contributing to understand the impaired AM process in MS, we could improve, eventually, the patients' follow-up. We hypothesised that functional changes would be predominantly observed in prefrontal regions during retrieval and elaboration of memories. Moreover, considering the evidence of hippocampal damage in MS (Sicotte et al., 2008; Hulst et al., 2012), the role of the hippocampus in AM, and evidence suggesting that the hippocampal activity is modulated by the recollective qualities of memory (Addis, Moscovitch, Crawley, & McAndrews, 2004; Addis & Schacter, 2008), we also expected functional changes in the hippocampal region in the MS patients relatively to controls.

2. Materials and Methods

2.1 Subjects

Eighteen patients with definite MS according to the Polman et al.'s criteria (Polman et al., 2011) were recruited at the Neurology Units of two French hospitals (Strasbourg and Colmar). Inclusion criteria were the diagnosis of a relapsing-remitting disease course, EDSS (Kurtzke, 1983) score ≤5, absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (Montgomery & Asberg, 1979; clinical threshold score ≥ 15) no recent exacerbation of MS symptoms and AM impairment (see below).

Eighteen healthy controls matched for gender, age, education level and verbal Intellectual Quotient were recruited. Exclusion criteria for all the subjects were documented psychiatric illness, neurological disorder (other than multiple sclerosis for the patients) and poor knowledge of French. 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.

Table 1.Demographical and clinical data. Mean (and standard deviation) for the multiple sclerosis patient and the healthy control groups

	MS patients	Healthy controls	Statistical analysis: Test and p values
N =	18	18	–
Age in years	41.11 (SD 10.22)	39.72 (SD 8.61)	t = 0.44; *p* = 0.66
Education in years	13.22 (SD 2.05)	13.44 (SD 2.45)	t = -0.29; *p* = 0.80
Sex (Ratio female/male)	15/3	15/3	$\chi^2 = 0.0$; *p* = 1.0
EDSS [range]	2.50 (1.37) [0-5]	–	–
Duration of MS in years	12.53 (8.68)	–	–
Number of DMD treatment	1.0 (SD 0.0)	–	–
Verbal Intellectual Quotient	99.78 (SD 11.94)	98.06 (SD 12.10)	t = 0.43; *p* = 0.67

SD = Standard deviation

2.2 Behavioural assessment

All the patients underwent a neuropsychological baseline examination (results are not shown; see Ernst et al., 2012 for a complete description of the baseline). The AM assessment was carried out using the Autobiographical Interview (AI), kindly communicated by B. Levine to LM; Levine et al., 2002) for the patients and the healthy controls. The AI consists in retrieving personal unique events, temporally and contextually specific, occurring over minutes to hours and to generate freely as many details as possible about the event. We used an adapted version of the AI, allowing the introduction of cue-words (Addis, Wong, & Schacter, 2008; Addis, Sacchetti, Ally, Budson, & Schacter, 2009) and the possibility to probe a greater number of past recollections to assess more comprehensively the retrieval process (Barnabe, Whitehead, Pilon, Arsenault-Lapierre, & Chertkow, 2012; Leyhe, Muller, Milian, Eschweiler, & Saur, 2009). Thus, 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]. 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 the patients' slowed down cognitive processing speed on AM performance. The present work focuses on the free recall phase deficit specifically.

The AI session was audio-recorded for later transcription and scoring following the standardised procedure Levine et al., 2002). We included patients, whose AM scores were

below the mean of the normative data, which was provided for the French version of the AI by Ernst et al. (2012).

2.3 Neuroimaging data

2.3.1 fMRI tasks

Two fMRI tasks were proposed during scanning. The *experimental task* (i.e. past events condition) consisted in the evocation of unique personal past events, contextually specific, occurring over minutes or hours, but no more than one day. Examples were provided and the similarity to the event's characteristics of the AI was reminded. We proposed 32 pairs of words to elicit memories (e.g. 'store-crowd'), covering the same life periods mentioned above. The participants were instructed about the fact that the cue-words were meant to generate a past event in a flexible way. Based on Addis, Wong, & Schacter (2007), we distinguished two phases in the evocation of the event: (i) the construction phase corresponding to the search and initial building up of the event, and (ii) the elaboration phase corresponding to the retrieval of details associated with the event. Each trial had a fixed duration of 20 sec modulated by the subject's response: once a memory was retrieved, the subject had to press button 1 on the response box to mark the end of the construction phase. The remaining time, during which a central fixation cross was presented, was devoted to the elaboration phase.

The *control task* was a categorical task that included 32 pairs of words, with which participants had to construct a sentence for the construction phase (e.g. with 'cake-chocolate': 'The pastry chef's speciality is the chocolate cake'). Once the sentence was constructed, they had to press button 1 to pursue with the elaboration phase during which the participants had to keep the same sentence structure, replacing the two given cue-words by words of the same semantic category (e.g. 'The pastry chef's speciality is the apple pie'). The fixed duration for each trial was also 20 sec.

Prior to scanning, the procedure was explained to the participants and we asked them to complete a computerised practice trial for each task in order to be familiar with the experimental design and timing of presentation of the stimuli. Given the fact that the fMRI examination imposes time constraints, particular attention was paid to the patients' practice trials to optimise the further completion of the task during the scanning session. Additionally, a more specific practice trial for the control task was carried out to instruct the participants to

avoid any self-implication in the sentence construction (no sentences with 'I '), since this process was of interest in the experimental condition.

The experimental design was organised in four sequences of 8 stimuli, per condition, beginning systematically with the control task and then alternating between past events and control task conditions. In both tasks, each trial was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s).At the beginning of each sequence, the name of the condition was displayed on the screen for 6 s. The presentation order of stimuli within each condition was 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.

Immediately following scanning, a post-scan questionnaire was completed for the past events condition, in order to verify the adequacy of the responses and to exclude potential non-episodic memories before the data analysis. Thus, for each past event, participants had to indicate the type of memory (unique, repetitive, extensive, semantic or absent), the spatial and temporal context of the event, the emotional valence and rate, on two visual-analogue scales of 10 cm, the difficulty of access and the quantity of details.

2.3.2 fMRI acquisition

Images were acquired using a 3T MRI scanner (Siemens Verio). The image sequence was a T2*-weighted echo planar imaging sequence (TR=2500 ms, TE=30 ms, Matrix=64x64 voxels, FOV=224 mm, FA=90). The anterior commissure and posterior commissure were identified in the midsagittal slice, and 45 contiguous slices (each 4mm thick) were prescribed parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

2.4 Statistical analyses

2.4.1 Behavioural data

Although AM impairment was an inclusion criteria for patients (based on normative data), between group comparisons for the AI scores with the control group recruited for the present study were conducted (*t*-test). Between group comparisons for the variables of the post-scan questionnaire were tested also by means of *t*-test or repeated measures ANOVA.

2.4.2 Neuroimaging data

Pre-processing and statistical analyses were conducted using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK, Friston et al., 1995). 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 and Tournoux, 1988), and then spatially smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel.

For both conditions, 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 sec-duration that started immediately after the end of the construction phase by button press. The 10 sec-duration interval for the elaboration phase was fixed to allow a sufficient time interval to detail search and the trials with a construction phase longer than 10 sec were excluded.

To obtain a sufficient number of valid trials for the past condition (particularly given the patients' AM impairment), we chose to keep both unique and repetitive events as regressors of interest, especially as a great overlap of the cerebral activations was previously observed for these two types of memories (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Addis, Moscovitch, Crawley, & McAndrews, 2004). Correct control trials were also included as regressors of interest.

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

Parametric modulation analyses were performed for the difficulty of access and quantity of details, with the creation of a general linear model for the construction and elaboration phases, using the first-order parametric modulation option supplied by SMP5. To this end, to obtain a homogenous distribution of the responses, ratings from the two visual analogue-scales were rescheduled empirically as follows: 0 cm to 5 cm = 1 (low score); 5.1 cm to 7.5 cm = 2

(medium score) and 7.6 cm to 10 cm = 3 (high score).Two sample *t*-tests were then applied to explore the potential between group differences.

To provide a good balance between controlling the Type I and II error rates, the significance threshold was set at $p = 0.005$ (uncorrected for multiple comparisons), with a minimum extent threshold of ten contiguously activated voxels for all the analyses (Lieberman & Cunningham, 2009). Given that the medial temporal lobe structures (parahippocampal gyrus and hippocampus) were of a priori interest and that they are particularly small brain regions, explorative analyses were also conducted with a minimum extent threshold of five contiguously activated voxels ($p = 0.005$ uncorrected) similarly to previous AM studies (Holland, Addis, & Kensinger, 2011).

3. Results

3.1 Behavioural results

With regard to the AI performance, the MS patients and the healthy control group provided respectively, on average, 14.71 internal details (SD = 3.56) vs 29.11 (SD = 7.56), with a mean total ratings of 4.12 (SD = 1.11) vs 7.71 (SD = 1.63) during the free recall phase. As expected, the patients performance was significantly lower than that of the healthy controls for the mean number of internal details ($t = -7.31$; $p < 0.001$) and the mean total ratings ($t = -7.74$; $p < 0.001$).

Turning to the neuroimaging results (Table 2), there was no group difference in the mean reaction time to retrieve a memory ($t = 0.87$; $p = 0.39$). Post-scan results highlighted a main effect of the event type ($F = 123.30$; $p < 0.001$), and Tukey HSD post-hoc test revealed a higher number of unique events in comparison with the four other event types ($p < 0.001$ in all the cases). Nevertheless, a comparable mean number of unique ($p = 0.58$) repetitive ($p = 1.0$), extended ($p = 0.99$), semantic ($p = 0.99$) and absent ($p = 0.88$) memories between the two groups was found. A main effect of the emotional valence was observed ($F = 63.67$; $p < 0.001$), and the Tukey HSD post-hoc test revealed a higher number of positive past events in comparison with neutral and negative events ($p < 0.001$ in all the cases). However, a similar distribution between positive ($p = 0.81$), neutral ($p = 0.48$), and negative past events ($p = 0.99$) was observed in the two groups. The mean rating for the difficulty of access ($t = 0.99$; $p = 0.33$) and for the quantity of details ($t = -0.57$; $p = 0.57$) did not differ between the two groups.

Table 2. Mean (and standard deviation) for the behavioural measures from the fMRI session for the multiple sclerosis patient and the healthy control groups

	MS patients	Healthy controls
Construction reaction time (in sec)	5.40 (0.93)	5.07 (1.28)
Type of events		
Unique	17.39 (5.48)	19.83 (6.00)
Repetitive	4.22 (4.05)	4.00 (3.54)
Extended	0.61 (0.91)	1.27 (1.84)
Semantic	1.22 (2.82)	0.50 (1.10)
Absent	4.61 (4.38)	2.77 (1.83)
Emotional valence		
Positive	12.83 (5.04)	14.28 (3.00)
Neutral	3.22 (3.87)	5.27 (2.65)
Negative	5.94 (2.75)	5.50 (2.77)
Difficulty of access (parametric)	2.45 (0.38)	2.34 (0.30)
Quantity of details (parametric)	1.99 (0.41)	2.06 (0.36)

3.2 Neuroimaging results

3.2.1 Past events construction

During the initial construction phase, between group analysis revealed significantly greater activations in MS patients than in healthy controls in several brain areas (Table 3; Fig. 1). These increased cerebral activations were predominantly located in the frontal regions, including the right inferior frontal gyrus (BA 46), the right middle frontal gyrus (BA 10), the right superior frontal gyrus (BA 6) and the left precentral gyrus (BA 6/43/44), and also in the left transverse temporal gyrus (BA 42), the left postcentral gyrus (BA 40), the right postcentral gyrus (BA 2) and the left insula (BA 13).

The reverse contrast (healthy controls vs MS patients) showed significantly greater brain activation only in the right superior temporal gyrus (BA 13; $x = 46$, $y = 0$, $z = -8$, $Z = 2.79$).

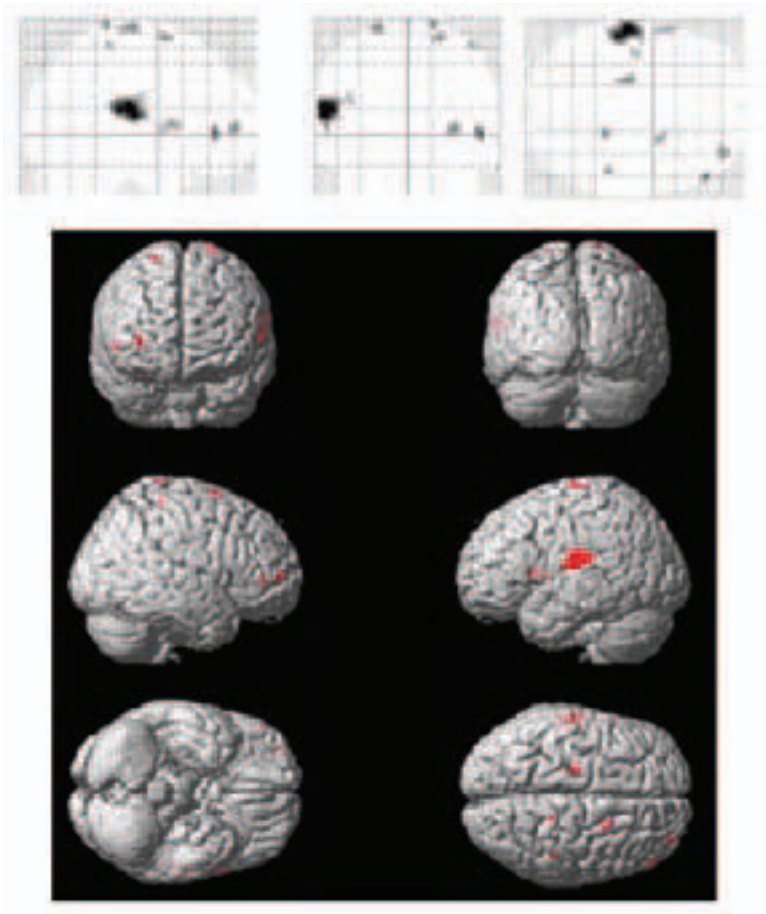

Figure 1. Brain regions showing an increased activity for MS patients (vs healthy controls) during the past events construction (vs control task construction); uncorrected *p* value *p*.005, *k* = 10 voxels

Table 3. Brain regions exhibiting significant activations for MS patients (vs healthy controls; two sample *t*-test) during the past event construction (vs control construction) and the past event elaboration (vs control elaboration)

Brain Region	Coordinates (x, y, z)	Z-score
Past event construction > control construction		
L Precentral gyrus (BA 43)	(-54, -8, 12)	2.85
L Precentral gyrus (BA 44)	(-60, 10, 8)	2.95
L Precentral gyrus (BA 6)	(-58, 0, 6)	2.74
R Inferior frontal gyrus (BA 46)	(52, 42, 2)	3.15
R Middle frontal gyrus (BA 10)	(34, 56, 6)	2.98
R Superior frontal gyrus (BA 6)	(24, 6, 70)	2.96
L Transverse temporal gyrus (BA 42)	(-60, -18, 14)	3.58
L Postcentral gyrus (BA 40)	(-56, -26, 20)	3.48
R Postcentral gyrus (BA 2)	(48, -36, 64)	2.95
L Insula (BA 13)	(-42, 14, 24)	2.78
Past event elaboration > control elaboration		
R Middle frontal gyrus (BA 10)	(30, 40, 22)	3.30
L Superior frontal gyrus (BA 10)	(-2, 66, 24)	3.30
R Inferior frontal gyrus (BA 47)	(16, 10, -14)	2.92
R Middle frontal gyrus (BA 8)	(22, 24, 38)	2.85
L Middle frontal gyrus (BA 8)	(-32, 34, 48)	3.0
R Middle frontal gyrus (BA 9)	(40, 46, 26)	3.58
R Superior frontal gyrus (BA 9)	(8, 54, 28)	3.56
L Medial frontal gyrus (BA 9)	(-6, 44, 26)	3.07
L Middle frontal gyrus (BA 46)	(-42, 40, 14)	3.24
L Superior frontal gyrus (BA 9)	(-24, 38, 30)	3.05
R Medial frontal gyrus (BA 9)	(12, 26, 30)	2.82
R Middle occipital gyrus (BA 18)	(22, -92, 4)	3.62
L Middle temporal gyrus (BA 21)	(-34, 4, -30)	3.67
L Superior temporal gyrus (BA 42)	(-60, -20, 12)	2.70
L Thalamus	(-18, -12, 16)	3.21
R Thalamus	(2, -4, 2)	3.08
L Anterior cingulate (BA 25)	(-6, 14, -8)	2.72
R Anterior cingulate (BA 32)	(10, 20, -8)	3.47
R Cingulate gyrus (BA 24)	(10, -8, 32)	2.79
L Cingulate gyrus (BA 32)	(0, 24, 34)	2.75
R Posterior cingulate (BA 23)	(6, -38, 26)	3.21
R Cuneus (BA 17)	(16, -84, 6)	2.67
L Precuneus (BA 7)	(-8, -50, 60)	3.00
R Cerebellum anterior lobe	(24, -52, -24)	3.51
R Cerebellum posterior lobe	(24, -60, -46)	3.45
R Caudate nucleus	(18, 12, 8)	2.89
L Caudate nucleus	(-20, 2, 22)	3.67
L Putamen	(-20, 10, 14)	3.23

3.2.2 Past events elaboration

Differential activations between MS patients and healthy controls were also observed during the elaboration on additional details from past events (Table 3; Fig. 2). MS patients recruited more extensively the frontal regions, with significant activations in the right middle frontal gyrus (BA 8/9/10), the left middle frontal gyrus (BA 8/46), the right inferior frontal gyrus (BA 47), the right superior frontal gyrus (BA 9), the left superior frontal gyrus (BA 9/10), the bilateral medial frontal gyrus (BA 9). Increased activations were also observed in the left middle (BA 21) and superior (BA 42) temporal gyrus, the right middle occipital gyrus (BA 18), the left cingulate gyrus (BA 25/32), the right cingulate gyrus (BA 23/24/32), the right cuneus (BA 17), the left precuneus (BA 7), the right cerebellum and in basal nuclei (bilateral thalamus, bilateral caudate nuclei, left putamen).

The healthy controls did not show significantly more activation than the patients in any brain regions.

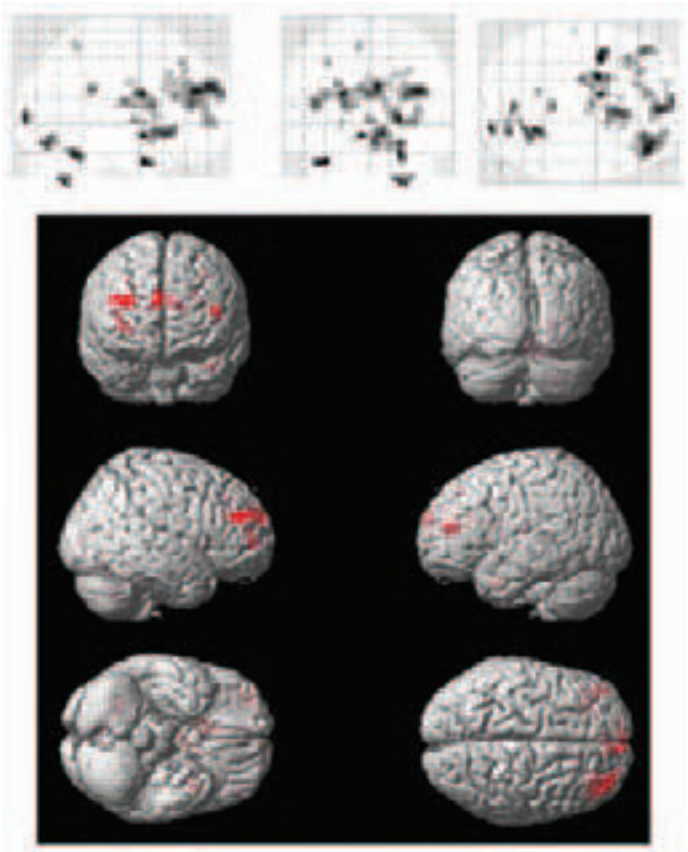

Figure 2. Brain regions showing an increased activity for MS patients (vs healthy controls) during the past events elaboration (vs control task elaboration); uncorrected *p* value *p*.005, *k* = 10 voxels

3.2.3 Parametric modulation of brain activity during past events construction

Differential neural responses to the difficulty of access and quantity of details were highlighted between MS patients and healthy controls during retrieval of past events (Tables 4 and 5; Fig. 3 A.1 and A.2).

Table 4. Significant brain activations for the parametric modulation of the difficulty of access and quantity of details for MS patients (vs healthy controls; two sample t-test) during the past event construction and elaboration

Brain Region	Coordinates (x, y, z)	Z-score
Past event construction – Difficulty of access		
R Parahippocampal gyrus (BA 19)	(34, -48, -2)	2.93
Past event construction – Quantity of details		
L Medial frontal gyrus	(-16, 58, 2)	3.22
R Uncus (BA 28)	(28, -10, -26)	2.87
Past event elaboration – Difficulty of access		
L Middle temporal gyrus (BA 22)	(-36, -54, 18)	3.07
L Parahippocampal gyrus (BA 30)	(-30, -48, 8)	2.97
R Parahippocampal gyrus (BA 27)	(22, -34, 0)	2.86
Past event elaboration – Quantity of details		
R Parahippocampal gyrus (BA 37)	(32, -38, -10)	3.29
R Fusiform gyrus (BA 37)	(44, -42, -12)	2.89
R Cingulate gyrus (BA 31)	(24, -28, 40)	3.00

Indeed, for the patients, the response to the difficulty of access entailed a greater activity only in the right parahippocampal gyrus (BA 19) in comparison with the healthy controls. The reverse contrast showed increased activations for the healthy controls in the bilateral postcentral gyrus (BA 7), the right superior parietal lobule (BA 7), the left middle frontal gyrus (BA 6), the right middle temporal gyrus (BA 21), the left lingual gyrus (BA 19) and the left cerebellum in response to the difficulty of access.

Concerning the quantity of details, the between group analysis showed a significantly greater modulation effect for the patients in the left medial frontal gyrus and the right uncus (BA 28), whereas the healthy controls recruited more the left superior temporal gyrus (BA 13) in response to the quantity of details.

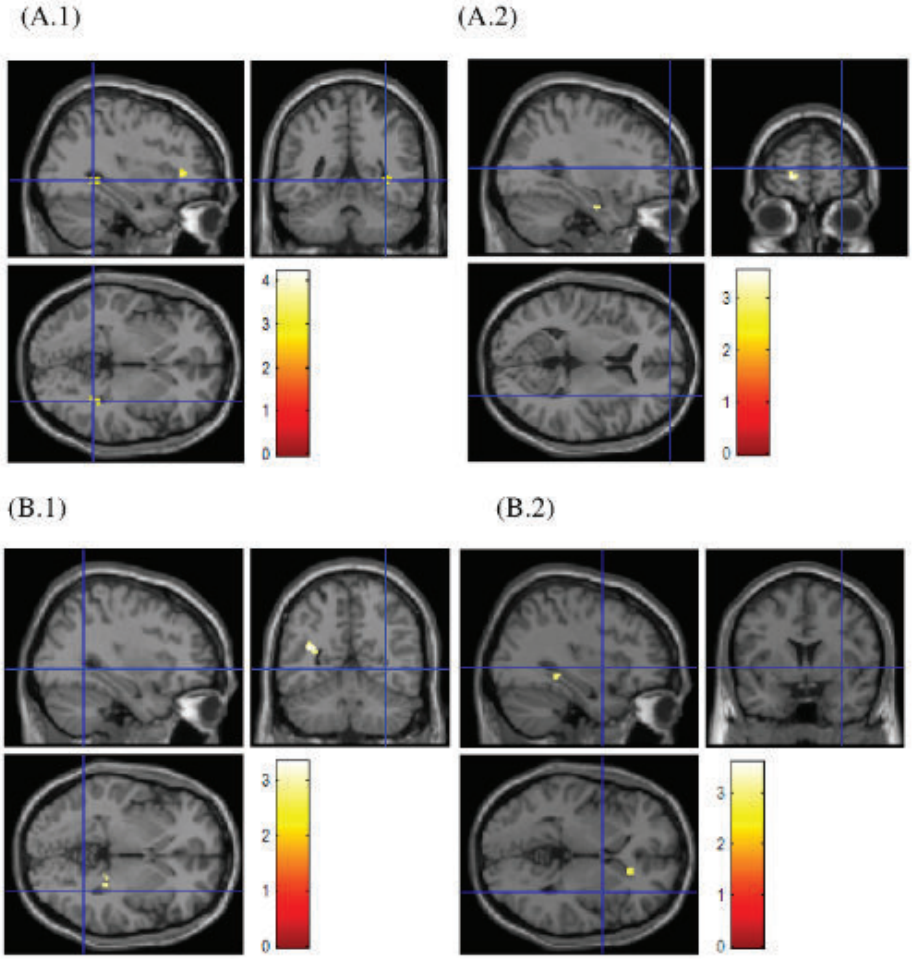

Figure 3. Brain regions showing an increased response to parametric modulation for MS patients (vs healthy controls) during the construction (A) and the elaboration (B) phases for the difficulty of access (A.1 and B.1) and the quantity of details (A.2 and B2)); uncorrected p value p.005, k = 10 voxels

3.2.4 Parametric modulation of brain activity during past events elaboration

During the elaboration phase, the parametric response for the difficulty of access and quantity of details involved different brain regions in the two groups (Tables 4 and 5; Fig. 3 B.1 and B.2).

MS patients showed a greater response to the difficulty of access in the left parahippocampal gyrus (BA 30), the right parahippocampal gyrus (BA 27), and in the left middle temporal gyrus (BA 22) in comparison with the healthy controls. Analysis with k = 5 highlighted also a significant activation in the right hippocampus. Conversely, compared with patients, controls'

neural responses to the difficulty of access led to greater left-lateralised activations in the lingual gyrus (BA 19), the middle temporal gyrus (BA 19) and the cuneus (BA 17).

Regarding the neural responses to the quantity of details, the patients recruited more intensively than the controls right-sided brain regions, with significant activations in the parahippocampal gyrus (BA 37), the fusiform gyrus (BA 37) and the cingulate gyrus (BA 31). Again, analysis with k = 5 revealed a significant activation in the right hippocampus. The reverse contrast showed a significantly greater activation of the right middle temporal gyrus (BA 39) for the healthy controls in response to the quantity of details.

Table 5. Significant brain activations for the parametric modulation of the difficulty of access and quantity of details for healthy controls (vs MS patients; two sample t-test) during the past event construction and elaboration

Brain Region	Coordinates (x, y, z)	Z-score
Past event construction – Difficulty of access		
L Postcentral gyrus (BA 7)	(-22, -48, 72)	3.55
R Superior parietal lobule (BA 7)	(36, -72, 52)	3.19
R Postcentral gyrus (BA 7)	(6, -52, 72)	3.12
L Middle frontal gyrus (BA 6)	(-36, 2, 64)	3.29
R Middle temporal gyrus (BA 21)	(56, 0, -18)	3.09
L Lingual gyrus (BA 19)	(-18, -66, 0)	3.09
L Cerebellum posterior lobe	(-20, -74, -16)	3.00
Past event construction – Quantity of details		
L Superior temporal gyrus (BA 13)	(-52, -44, 16)	3.49
Past event elaboration – Difficulty of access		
L Lingual gyrus (BA 19)	(-20, -66, -2)	3.34
L Middle temporal gyrus (BA 19)	(-38, -82, 20)	3.09
L Cuneus (BA 17)	(-12, -80, 6)	2.83
Past event elaboration – Quantity of details		
R Middle temporal gyrus (BA 39)	(46, -72, 26)	2.97

4. Discussion

In the present study, we have shown that AM impairment observed at the clinical level in MS patients was accompanied by cerebral activation changes during the fMRI task. Importantly, this latter task was performed at a comparable level to that of the control group. We interpret

the MS patients' brain activation changes in terms of indicators of likely spontaneous compensatory cortical mechanisms during AM processing.

In the present section, we start by considering some factors in relation to the preserved AM task performance during the fMRI examination, we then discuss spontaneous cerebral plasticity in MS in both the construction and elaboration phases of the AM test, the neural responses to the difficulty of access and amount of details, and we conclude with some implications of our findings.

We observed no significant differences between patients and controls for the post-scan interview variables. This result could seem counterintuitive, especially for the type of events, difficulty of access and amount of details. However, since one criterion for patients' inclusion was impaired score on the AI, we paid particular attention to the practice trials preceding the fMRI session to optimise the procedural aspects accompanying the task itself. In addition to careful training, two-cue-words were provided during the fMRI task, instead of a single cue-word given during the AI, to guide memory recollection. The effects of these measures were reflected, besides the absence of significant differences on the AM task during scanning between the two groups, qualitatively in the fact that nearly all the patients reported that the fMRI AM task was easier than the AI. Therefore, the observed cerebral activation changes are interpreted as resulting from pathology, and not from performance differences, use of discrepant cognitive strategies, or a too poor completion of the task by the patient group (see Cader, Cifelli, Abu-Omar, Palace, & Matthews, 2006; Liu et al., 2011 for issues related to the interpretation of cerebral functional changes in cognitive task-related fMRI studies in MS).

However, some other variables could also explain the non-significantly different results between groups in the post-scan questionnaire. Considering the issue of the AM test sensitivity, it is possible that the simple categorisation of the type of events and the two visual-analogue scales were not sensitive enough to detect deficits similar to that observed in the patients' AI. Moreover, it should be noted that the post-scan measures relied on self-assessment, which could imply the influence of different decision criteria within the participants, whereas the AI is an objective measure of the number of episodic details provided by the subjects. In relation to this point, the patients mentioned that given the short time window devoted to the search of details, their perceived ability to find details until the end of the elaboration phase gave them the impression that they had more detailed memories during the fMRI than during the AI session.

While spontaneous brain plasticity in MS patients has been previously reported in different cognitive domains (e.g. Morgen et al., 2006; Hulst et al., 2012; Kollndorfer et al., 2012), the present study is the first, to our knowledge, to provide evidence of spontaneous brain plasticity during recollection of AMs, which are of particular importance given their major roles in normal daily life functioning. Specifically, the spontaneous plasticity in our patients was manifested by both functional enhancement of brain areas also recruited by healthy controls and recruitment of alternative, mostly contralateral, brain areas. The recruitment of the contralateral brain areas is a well-described adaptive mechanism in MS patients in the context of cognitive and motor tasks (Cader et al., 2006). A further finding in the present study was that the neural response to the recollective qualities of memories seemed also to be modulated differently in the patient group compared with the control group and to involve some key AM regions, as for instance, the hippocampus.

Taking together, the brain activation changes could reflect an increased neural effort due to structural damage (Hawellek et al., 2011) in the AM core network, particularly the prefrontal regions and the hippocampus.

Brain activation changes in the bilateral prefrontal regions, notably observed in the present work, is in accord with previous studies (Ernst et al., 2012; 2013). This result could be accounted for by the significant role of the frontal system in AM retrieval (Svoboda et al., 2006) and the comparatively more frequent occurrence of frontal lesions in MS (Benedict et al., 2002; 2009). Activations in these frontal regions extended towards the parietal regions, to form a frontoparietal network engaged in memory retrieval.

Regarding the *construction phase* of AM, the patients exhibited predominantly functional changes in the bilateral frontal regions. The right-lateralised activations are particularly significant since the AM core network is predominantly left-lateralised (Maguire, 2001; Addis et al., 2007b; Botzung, Denkova, Ciuciu, Scheiber, & Manning, 2008). The frontal region activations were accompanied by increased bilateral parietal activations. The greater activity of this bilateral frontoparietal network is of interest considering that, besides the well-known role of frontal regions in AM retrieval (Svoboda et al., 2006; Cabeza & St Jacques, 2007) involvement of parietal regions in the early phase of AM has also been described (Berryhill, Phuong, Picasso, Cabeza, Olso, 2007; Addis et al., 2007b).

St Jacques, Kragel, & Rubin (2011) introduced the notion of the left “frontoparietal network” and, given that this network is related to both executive control processes (Vincent, Kahn,

Snyder, Raichle, Buckner, 2008; Niendam et al., 2012) and the Attention to Memory model (Cabeza, 2008), it has been suggested that its role is linked to the important demand of top-down attentional control processes during the construction of memories. The frontoparietal network could be especially involved in memory retrieval "when judgements are uncertain and that further analysis of the stimulus in relation to mnemonic representations is required" (Vincent et al., 2008; p. 3338). We suggest that, taking into account the relationships between AM deficit and executive functioning in MS patients, the enhanced recruitment of the bilateral frontoparietal regions reflect the higher cognitive demand and need of top-down attentional processes during the construction phase in MS patients.

Addis et al. (2007b) reported early posterior cerebral activations during the construction phase, which is consistent with the role of visual imagery in the retrieval and vividness of episodic memories (Greenberg and Rubin, 2003). The increased recruitment of these regions was observed during the elaboration phase in our patients, suggesting that the primary focus on executive demand during the construction phase, "delayed" the visual imagery processes.

In relation to the *elaboration phase* of AM, our patients exhibited cerebral activation changes also located mostly in the prefrontal regions. Addis et al. (2007b) underscored the implication of predominantly left prefrontal regions during the elaboration phase. These brain structures are also involved in further retrieval, verification and selection of information (Svoboda et al., 2006) required during the elaboration of memories and the left medial prefrontal region is particularly engaged in self-referential process (Maguire, 2001; Gilboa, 2004; Cabeza & St Jacques, 2007; Buckner, Andrews-Hanna, & Schacter, 2008). Our patients recruited the middle and superior frontal gyri and medial frontal regions, but more intensely than the controls and accompanied by right frontal activations.

Summerfield, Hassabis, & Maguire (2009) for their part have proposed that the right posterior cingulate cortex activity is modulated by the realness and self-implication during memory recollection and Northoff et al. (2006) have suggested that the anterior cingulate cortex is associated with the recall of self-events and may mediate the interaction between the emotional significance and the self-relevance of stimuli (Moran, Macrae, Heatherton, Wyland, & Kelley, 2006; Sharot, Riccardi, Raio, & Phelps, 2007). These brain regions are particularly activated during the elaboration phase of memories (Addis et al., 2007b). Our patients recruited these structures more intensely than the controls. Moreover, we observed a bilateralised activation of the anterior cingulate cortex, and activation of the right posterior

cingulate cortex. These findings suggest a neural spontaneous response to compensate difficulties in self-implication and self-relevance processes during the elaboration phase.

Regarding the temporal regions, we observed an enhanced activity in the left middle temporal gyrus (BA 21) associated with AM semantic knowledge (Svoboda et al., 2006) but no contralateral recruitment. Based on the relative preservation of personal semantics in MS (Ernst et al., 2013) we suggest with caution that personal semantic representations could play a role in compensating AM recollection difficulties, manifested by the enhanced activity in this region, but that no supplementary effort (bilateral activation) was necessary to access efficiently AM semantic information.

Considering the posterior cerebral regions, sustaining visual imagery, our patients showed a remarkably enhanced activity in the right middle occipital gyrus, the right cuneus and the left precuneus, which could reflect the effortful process necessary to achieve a detailed mental image of the memory.

Based on previous reports showing hippocampal damage in MS (Sicotte et al., 2008; Hulst et al., 2012) and the central role of the hippocampus in AM (Addis et al., 2004a; 2004b) functional changes in hippocampal region were hypothesised in the present study. Surprisingly, no significantly differential hippocampal activations between groups were found. However, a differential hippocampal/parahippocampal activity was observed between the two groups when *parametric modulation measures* were introduced. (i) The patients' difficulty of access was associated with enhanced cerebral activations in the right parahippocampal gyrus during memory construction and in the right hippocampus and the bilateral parahippocampal gyrus during elaboration. (ii) Right hippocampus/parahippocampal gyrus and right uncus activations were associated with the patients' amount of details during the construction and elaboration phases, respectively. This result is consistent with previous reports showing that the number of details modulates the engagement of the left hippocampus in healthy subjects (Addis et al., 2004b; Addis & Schacter, 2008). On these bases, we suggest that our patients' right-lateralised activations reflect a more effortful access and binding of details together with the potential impact of hippocampal damage on these functions.

Activity in the middle temporal gyrus (BA 22) was also significantly modulated by access difficulty during the elaboration phase for the patient group. Taking into account that this region is implicated in AM semantic knowledge (Svoboda et al., 2006), its enhanced activity

could indicate greater involvement of AM semantic information secondary to an increased access difficulty.

A further finding related to the number of details was the implication of the left medial frontal region and right posterior cingulate gyrus. As mentioned above these brain structures support self-implication and realness of memories (Buckner et al., 2008; Summerfield et al., 2009), which are central components of episodic re-experiencing. In this context, the enhanced activation in MS patients could reflect improved re-experiencing with the increase of details.

With regard to the *control subjects*, the neural response to the difficulty of access and amount of details seemed to involve mostly the core regions of the AM network during the event construction, including anterior, temporal and posterior cerebral regions. These increased brain activations (in comparison with the patient group) were predominantly observed in the left hemisphere. The same applies to the elaboration phase, during which predominantly left posterior brain regions from the AM core network seemed particularly responsive.

5. Conclusions

In conclusion, we would like to suggest that the phenomena of bilateralisation and enhancement of cerebral activations observed in the present study in our patient group reflect spontaneous compensation mechanisms, sufficient enough to obtain similar performance in the context of our trained fMRI task, but insufficient to result in normal AM performance in a more stringent test and in the context of everyday life functioning. Related to this last point, it is important to note that, clinically, patients' AM complaints are frequent and consistent with AI impaired scores.

The present findings encourage the use of neuroimaging studies to better understand AM impairment in MS and construct cognitive rehabilitation programmes on those bases. The interest of these issues derives from observations of the deleterious impact of AM deficit in patients' everyday life. Among the reasons of such an impact is the fact that AM is ubiquitous and plays major roles in daily life functioning (Rasmussen and Habermas, 2011).

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The authors declare no competing financial interests.

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STUDY 3

Ernst A, Blanc F, De Seze J, Gounot D and Manning L. Spontaneous brain plasticity in multiple sclerosis patients during episodic future thought: a clinical and functional neuroimaging study. (To be submitted in a special invited issue)

ABSTRACT

Objective. Autobiographical memory (AM) and episodic future thinking (EFT) are ubiquitous in daily life, share the same neurocognitive platform and allow us to mentally travelling in time. Because it has been found that AM is impaired in multiple sclerosis (MS), the expected following question, in the mental time travel perspective, regards the status of EFT in the same clinical population. Our aim is, consequently, to investigate EFT in MS.

Method. To that end, EFT performance in 21 non-depressed MS patients and 20 matched controls was assessed using the Autobiographical Interview (AI). Once the testing was completed, all the participants underwent a functional MRI session, comprising an EFT and a categorical control tests. Both tasks included two phases, construction and elaboration. *Results.* They showed (i) MS patients' significantly lower AI scores than controls. (ii) Increased and bilateral cerebral activations in the core EFT network in the patient group relative to controls. These neural changes were particularly important during the construction phase of the EFT. (iii) An increased neural response mostly in anterior, but also in posterior cerebral regions in association with the amount of details produced by the patients. A further hypothesis regarding increased hippocampal activation in the patient group was not confirmed by the results.

Conclusions. EFT's status in MS patients was shown to be impaired despite the presence of spontaneous bilateral prefrontal region plasticity, likely supporting the effort to compensate the deficit. Clinically, this study provided new insights, considering EFT's central role in everyday life and wellbeing.

Keywords: Cognition, Anticipation psychological, Neuropsychological tests, Nervous system disease, Demyelinating disease, Imagery.

INTRODUCTION

Episodic autobiographical memory (AM) is defined as the capacity to mentally re-experience personal past events. Its study has included theoretical contributions (Tulving, 2001), establishing links between the ability to simulate past events and the capacity to imagine potential future events or episodic future thought (EFT). Moreover, it has been claimed that AM primary function evolved to provide bases to EFT (Suddendorf & Corballis, 1997). From a more applied point of view, three main functional benefits have also been described comprising a role in (i) coping skills for stressful events, with an implication in emotion regulation and problem solving; (ii) goal achievement, for which the act of imagining various scenarios helps to reach the desired goal and finally, (iii) the implementation of intentions, for which a higher likelihood of completing an action is observed when there is an intention to implement this action (Szpunar, 2010). Furthermore, D'Argembeau et al. (2012) suggested that EFT, similarly to AM and, particularly, self-defining EFTs contribute to a person's sense of self and, together with self defining AMs, give rise to a strong sense of personal continuity over time. Finally, in relation to everyday life, it has been reported that we spend approximately one third of a waking day mentally simulating personal episodes, particularly, future events (Szpunar, 2010).

Theoretical models have been matched by advances in normal subjects' fMRI research (Addis et al., 2007; Botzung et al., 2008; Szupnar et al., 2007), revealing, on the one hand, an overlapping brain activation pattern for AM and EFT in the medial frontal and temporal regions, posterior and retrosplenial cortex, lateral parietal and temporal regions. On the other hand, AM has been specified as a source of details to be combined and form new mentally pre-experienced episodes. The cognitive effort involved in this ability appears to be supported by increased hippocampal engagement during future simulation (Addis & Schacter, 2008). In clinical research, theoretical contributions have been implemented in a few neuropsychological case studies (Klein et al., 2002; Tulving, 1985) and only a handful of group studies, namely, Alzheimer's disease (Addis et al., 2009), schizophrenia (D'Argembeau et al., 2008), and medial temporal lobe amnesia (Hassabis et al., 2007).

On these bases, investigating EFT's status in a group of patients, presenting with impaired AM, seems a consistent clinical research extension. More precisely, AM impairment having been observed in multiple sclerosis (MS) patients (Ernst et al., 2012; 2013), our aim was to

obtain a more comprehensive picture of the mental time travel (MTT; Sudendorf & Corballis, 2007; Tulving, 2001) in this clinical condition, using both neuropsychological and neuroimaging data. Importantly, the relapsing-remitting MS patients reported in these studies, showed simultaneously, AM deficit and mild or no impaired performance on cognitive domains frequently impaired in MS such as attention, anterograde memory or executive functions (Rogers & Panegyres, 2007).

These results were supported by preliminary neuroimaging data showing the presence of spontaneous brain plasticity in the bilateral prefrontal regions during an AM task, although insufficient to result in normal AM performance (Ernst et al., 2012). This finding was both consistent with the suggestion of a prefrontal-based retrieval process deficit in MS (Botzung et al., 2008; Ernst et al., 2012; 2013) and the greater occurrence of prefrontal lesions in MS (Bendfeldt et al. 2009).

Our hypotheses were (i) that spontaneous brain plasticity associated with future simulation deficit would be observed in the bilateral prefrontal regions, relatively to healthy controls. We based this hypothesis on both the reports showing spontaneous cerebral reorganisation in MS during various cognitive tasks (Kollndorfer et al., 2013; Lazeron et al., 2004; Morgen et al., 2007) and the preliminary results relating cerebral activation changes to impaired AM performance in MS. (ii) We expected functional changes to occur at the hippocampal level associated with two qualitative measures, the difficulty of simulating EFT and the amount of details generated during that task. This suggestion was motivated both by the particular responsiveness of the hippocampus to the quality of simulation (Addis & Schacter, 2008; Weiler et al., 2010) and previous evidences of hippocampal damage in MS (Hulst et al., 2012).

MATERIAL AND METHODS

Subjects

Twenty-one relapsing-remitting MS patients (Polman et al., 2011) with the following inclusion criteria were recruited: an EDSS (Kurtzke, 1983) score ≤4, an absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (Montgomery & Asberg, 1979) and no recent exacerbation of MS symptoms.

Twenty healthy controls matched for gender, age, education level and verbal Intellectual Quotient were recruited. Exclusion criteria for all the subjects were documented psychiatric

illness, neurological disorder (other than MS for the patients) and poor knowledge of French. 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.

Table 1. Demographical and clinical data. Mean (and standard deviation) for the multiple sclerosis patient and the healthy control groups

	MS patients	**Healthy controls**	**Statistical analysis**
N =	21	20	_
Age in years	41.52 (10.02)	39.15 (8.44)	$t = 0.81$; $p = 0.41$
Education in years	13.00 (1.97)	13.40 (2.35)	$t = -0.59$; $p = 0.56$
Sex (Ratio female/male)	17/4	17/3	$\chi^2 = 0.11$; $p = 0.73$
EDSS [range]	2.48 (1.37) [0-4]	–	–
Duration of MS in years	11.79 (7.97)	_	_
Number of DMD treatment	1.00 (0.00)	_	_
Verbal Intellectual Quotient	98.38 (12.71)	97.90 (11.49)	$t = 0.12$; $p = 0.90$

Behavioural assessment

In a first step, the patients underwent a neuropsychological baseline covering the following functions: general verbal abilities, tested with the Verbal IQ, short form (Axelrod et al., 2011) of the WAIS-III (Wechsler, 1997), nonverbal reasoning assessed using the Advanced Progressive Matrices Set 1 (Raven, 1958). Anterograde memory was examined with the Rey auditory verbal learning test (Rey, 1964), and the Rey-Osterrieth Complex Figure (Rey, 1941; Osterrieth, 1944). The executive functions were probed by means of the National Hospital's, London, phonological and categorical fluency tests, 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 (Coughlan & Hollows, 1985), the Stroop test (Stroop, 1935), and the months backwards test (the 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). Additionally, the effects of fatigue in everyday life were assessed using the "Echelle de Mesure de l'Impact de la Fatigue," (Debouverie et al., 2007).

Then, the EFT was assessed using an adapted version of the Autobiographical Interview (AI; Addis et al., 2009; Levine et al., 2002) which consists in imagining personal unique events, temporally and contextually specific, occurring over minutes to hours and to generate freely as many details as possible about the event -. Participants were given cue words to be used flexibly to generate five events, which could plausibly occur during the next weeks or months (Addis et al., 2009). No time limit was set due to eventual decreased cognitive processing speed. The AI session was audio-recorded for later transcription and scored following the standardised procedure (Levine et al., 2002): 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 else episodic details unrelated to the central event). For each participant, the number of internal details was averaged across the five future events for the EFT conditions for each recall phase. Since Ernst et al.'s (2013) previous study highlighted an impairment of the episodic component of AM, whereas the personal semantics was preserved, only the mean number of internal details was considered for the following statistical analyses.

The interrater reliability was verified for 10% of the future events, which were scored by a second scorer, following Levine et al.'s procedure. Coefficients for all measures showed high interrater reliability (between 0.82 and 0.99).

fMRI tasks

Two fMRI tasks were run. The experimental task (i.e. EFT condition) consisted in the evocation of unique personal future events following the AI's instructions. Thirty-two pairs of words were proposed to generate future events (e.g. 'family-meal'), which could plausibly occur during the next weeks or months. Based on Addis et al. (2007), we distinguished two phases in the evocation of the event: (i) the construction, corresponding to the search and initial building up of the event, and (ii) the elaboration, corresponding to the imagination of details associated with the event.

The control task, a categorical task, included 32 pairs of words, with which participants had to construct a sentence for the construction phase (e.g. with 'yellow-trousers': 'she was wearing yellow trousers'). During the elaboration phase, the participants 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 task, each trial had a fixed duration of 20 sec, modulated by the subject's response: the subject had to press button 1 on the response box to mark the end of the construction phase. The remaining time, during which a central fixation cross was presented, was devoted to the elaboration phase.

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

The experimental design was organised in eight sequences of 8 stimuli, beginning systematically with the control task and then alternating between future events and control task conditions. In both tasks, each trial was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s).At the beginning of each sequence, the name of the condition was displayed on the screen for 6 s. The presentation order of stimuli within each condition was 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.

Immediately following scanning, a post-scan questionnaire was completed for the EFT condition, in order to verify the adequacy of the responses before the data analysis. Thus, participants had to indicate the type of event (unique, repetitive, extensive, semantic or absent), its spatial and temporal context, its emotional valence and to rate on two 10 cm visual-analogue scales the difficulty of imagination and the amount of details.

fMRI acquisition

Images were acquired using a 3T MRI scanner (Siemens Verio). The image sequence was a T2*-weighted echo planar imaging sequence (TR=2500 ms, TE=30 ms, Matrix=64x64 voxels, FOV=224 mm, FA=90). The anterior commissure and posterior commissure were

identified in the midsagittal slice, and 45 contiguous slices (each 4 mm thick) were prescribed parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

Statistical analyses

Concerning behavioural data, between group comparisons were conducted for the AI score (*t*-test) and for the variables of the post-scan questionnaire (*t*-test or repeated measures ANOVA).

Regarding neuroimaging data, pre-processing and statistical analyses were conducted using SPM5 software (Friston et al., 1995). 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 both conditions, 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 sec-duration that started immediately after the end of the construction phase by button press. The 10 sec-duration interval for the elaboration phase was fixed to allow a sufficient time interval to detail search and the trials with a construction phase longer than 10 sec were excluded.

Since a great overlap of the cerebral activations for specific and repetitive future events was previously observed (Addis et al., 2011) both unique and repetitive events were included as regressors of interest.

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

Parametric modulation analyses were performed for the difficulty of imagination and amount of details, with the creation of a general linear model for the construction and elaboration phases, using the first-order parametric modulation option supplied by SMP5. To this end, to obtain a homogenous distribution of the responses, ratings from the two visual analogue-scales were rescheduled empirically as follows: 0 cm to 5 cm = 1 (low score); 5.1 cm to 7.5

cm = 2 (medium score) and 7.6 cm to 10 cm = 3 (high score).Two sample *t*-tests were then applied to explore the potential between group differences.

To provide a good balance between controlling the Types I and II error rates, the significance threshold was set at $p = 0.005$ (uncorrected for multiple comparisons), with a minimum extent threshold of ten contiguously activated voxels for all the analyses (Lieberman & Cunningham, 2009). Given that the medial temporal lobe structures (parahippocampal gyrus and hippocampus) were of a priori interest and that they are particularly small brain regions, explorative analyses were also conducted with a minimum extent threshold of five contiguously activated voxels ($p = 0.005$ uncorrected).

RESULTS

Behavioural results

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

Table 2. Neuropsychological baseline examination scores: Mean (and SD) for the MS patient group

	MS group scores
Verbal IQ	98.38 (12.70)
PM12	9.00 (1.73)
RAVLT	
- Total mean number of words	11.84 (1.34)
- Delayed recall	13.19 (2.01)
ROCF	
- Copy	35.50 (0.92)
- Immediate recall	24.88 (6.23)
- Delayed recall	24.50 (6.09)
Deno 100	97.14 (4.21)
Stroop	
- Colours (score T)	47.71 (8.90)
- Words (score T)	45.71 (7.59)
- Interference (score T)	45.28 (12.68)
- Interference score (score T)	48.95 (7.72)
Months back (sec)	11.57 (5.17)
Tower of London	
- Score	8.42 (1.74) **
- Time indice	18.00 (3.57)
Brixton (number of errors)	14.76 (5.26)
Cognitive Estimation Task	4.19 (2.71) **
Verbal Fluency	
- Categorical	20.55 (4.59)
- Phonological	13.04 (2.87)
Information Processing Speed	
- Cognitive	53.85 (9.41)
- Motor	49.57 (10.50)
- Error percentage	2.67 (2.98)
- Corrected score	59.46 (10.84)
VOSP	
- Silhouettes	23.28 (4.29)
- Cubes Analysis	9.61 (0.66)
MADRS	5.61 (4.49)
EMIF-SEP (total)	44.50 (14.67)

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

** Scores under the normal range

With regard to the AI performance, the MS patients and the healthy control group provided respectively, on average, 8.12 episodic details (SD = 4.65) vs 20.55 (SD = 5.70). As expected,

the patients performance was significantly lower than that of the healthy controls for the mean number of episodic details (t = -7.67; p< 0.001).

Turning to the post-scan results (Table 3), there was no group difference in the mean reaction time to generate future events (t = 0.35; p = 0.73). A main effect of the event type (F = 88.53; p< 0.001) was observed, and Tukey HSD post-hoc test revealed a higher number of unique events in comparison with the four other event types (p< 0.001 in all the cases). A main effect of the emotional valence was also showed (F = 59.43; p< 0.001), with a higher number of positive future events in comparison with neutral and negative events (Tukey HSD test: p< 0.001 in all the cases).No significant differences were highlighted for the event types or for the emotional valence between the MS and the healthy control groups, as well as for the difficulty of imagination (t = -1.19; p = 0.24).However, a significant difference was observed for the amount of details, with lower scores for MS patients than for healthy controls (t = -2.35; p = 0.02).

Table 3. Mean (and standard deviation) for the behavioural measures from the fMRI session for the multiple sclerosis patient and the healthy control groups

	MS patients	Healthy controls
Construction reaction time (in sec)	4.80 (1.06)	4.69 (0.91)
Type of events		
Unique	17.10 (7.76)	19.5 (6.23)
Repetitive	5.29 (5.31)	6.75 (5.86)
Extended	0.52 (1.63)	1.55 (1.82)
Semantic	1.67 (3.55)	0.6 (1.10)
Absent	3.52 (3.49)	1.4 (2.60)
Emotional valence		
Positive	14.10 (6.55)	16.2 (4.60)
Neutral	5.48 (5.21)	7.2 (5.38)
Negative	2.76 (2.02)	3.35 (2.32)
Difficulty of imagination (parametric)	2.33 (0.54)	2.51 (0.42)
Quantity of details (parametric)	1.84 (0.46)	2.16 (0.40)

Neuroimaging results

EFT Construction

Between group analysis revealed an extended cerebral network showing significantly greater activations for MS patients in comparison with healthy controls during the initial generation of future events (Table 4; Figure 1). This enhanced brain network encompassed predominantly the bilateral prefrontal regions (superior, inferior, middle and medial gyri), the right temporal regions (superior, middle and fusiform gyri), the bilateral parahippocampal regions, the bilateral, but predominantly right, parietal regions (inferior parietal lobule, postcentral gyrus and precuneus), the bilateral occipital regions (middle and superior gyri), and the bilateral, but predominantly right, limbic areas (anterior and posterior cingulate).

However, the reverse contrast (healthy controls > MS patients) showed no significant result.

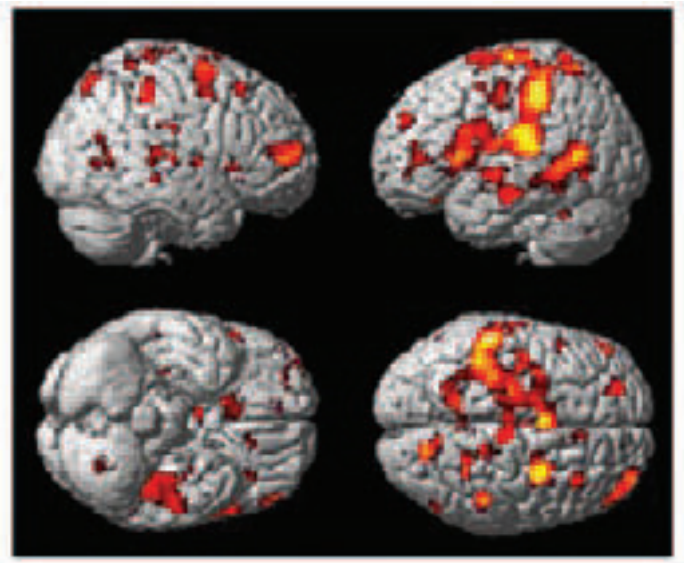

Figure 1. Brain regions showing an increased activity for MS patients (vs healthy controls) during the EFT construction (vs control task construction); uncorrected *p* value p.005, k = 10 voxels

Table 4. Brain regions exhibiting significant activations for MS patients (vs healthy controls; two sample *t*-test) during the EFT construction (vs control construction) and the EFT elaboration (vs control elaboration)

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

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

EFT Elaboration

During the further research of details, greater cerebral activations, mostly located in the bilateral prefrontal regions (middle and superior gyri) were highlighted for MS patients (Table 4; Figure 2). These prefrontal activations were accompanied with activations in the left temporal regions, more precisely in the middle temporal gyrus and the fusiform gyrus.

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

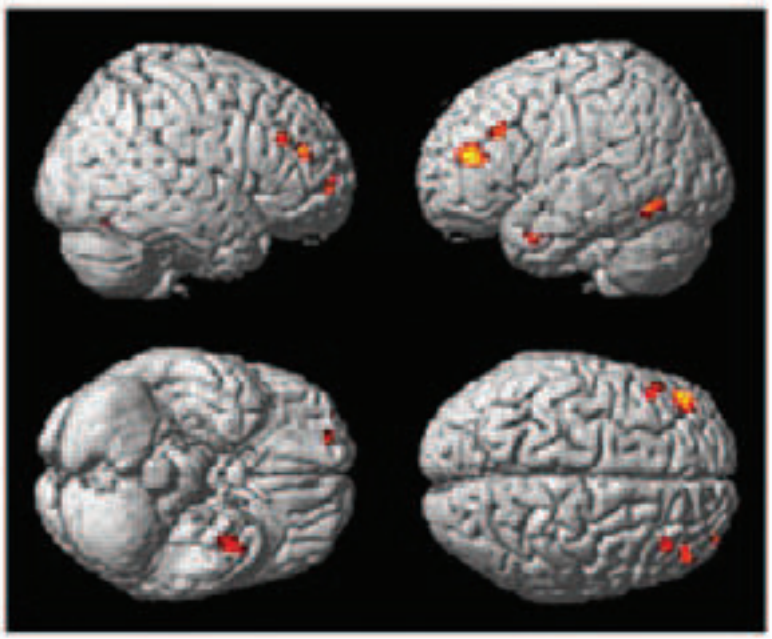

Figure 2. Brain regions showing an increased activity for MS patients (vs healthy controls) during the EFT elaboration (vs control task elaboration); uncorrected p value p.005, k = 10 voxels

Parametric Analyses

Difficulty of access

A differential neural response to the difficulty of access was highlighted between MS patients and healthy controls.

A greater neural response to the difficulty of access was only observed during the construction phase for MS patients, with predominantly increased brain activity in the left parahippocampal gyrus, the right anterior and left posterior cingulate gyri and left sub-lobar regions (Table 6; Figure 3).

Regarding the healthy controls, an enhanced neural response to the difficulty of access was observed in both phases (Table 5). During the construction, significant brain activations were highlighted in the left anterior cingulate and right sub-lobar regions, while for the elaboration phase, the neural response encompassed the left medial prefrontal regions, the right temporal regions (middle, superior and fusiform gyri) and bilateral posterior brain regions (precuneus, cingulate and middle occipital gyri).

Table 5. Significant brain activations for the parametric modulation of the difficulty of access and quantity of details for healthy controls (vs MS patients; two sample t-test) during the EFT construction and elaboration

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

Amount of details

Concerning the neural response to the amount of details, only a significantly higher brain activity was observed for the MS patients (Table 6; Figure 3), while the reverse contrast (healthy controls > MS patients) showed no significant result during either phases.

Table 6. Significant brain activations for the parametric modulation of the difficulty of access and amount of details for MS patients (vs healthy controls; two sample t-test) during the EFT construction and elaboration

Brain Region	Coordinates (x, y, z)	Z-score
EFT construction – Difficulty of access		
L Parahippocampalgyrus (BA 30)	(-18, -40, 6)	3.29
R Cingulate gyrus (BA 24)	(20, -2, 34)	2.96
L Posterior cingulate (BA 30)	(-14, -50, 16)	3.13
L Thalamus	(-28, -28, 2)	3.32
L Insula (BA 13)	(-28, -26, 26)	2.63
L Lentiform nucleus	(-22, -18, 0)	2.64
EFT construction – Amount of details		
L Middle frontal gyrus (BA 10)	(-32, 54, 8)	3.08
L Superior frontal gyrus (BA 10)	(-18, 58, 20)	3.42
R Middle frontal gyrus (BA 10)	(36, 52, 10)	3.50
R Superior frontal gyrus (BA 10)	(16, 62, 20)	3.04
L Middle frontal gyrus (BA 47)	(-46, 36, -2)	3.10
R Inferior frontal gyrus (BA 47)	(44, 18, 2)	3.42
L Inferior frontal gyrus (BA 47)	(-34, 26, -10)	2.86
R Precentral gyrus (BA 6)	(40, 0, 34)	3.19
L Middle frontal gyrus (BA 9)	(-42, 26, 26)	3.43
R Superior frontal gyrus (BA 9)	(4, 58, 22)	2.76
R Middle frontal gyrus (BA 6)	(48, 8, 44)	3.15
L Middle frontal gyrus (BA 46)	(-46, 22, 20)	3.34
R Superior frontal gyrus (BA 8)	(18, 36, 56)	3.44
L Middle frontal gyrus (BA 8)	(-26, 12, 34)	2.98
L Inferior frontal gyrus (BA 13)	(-32, 6, -14)	3.30
L Superior temporal gyrus (BA 39)	(-46, -58, 32)	2.86
R Fusiform gyrus (BA 20)	(60, -8, -24)	2.75
R Sub-gyral (BA 20)	(46, -18, -16)	2.81
L Supramarginal gyrus (BA 40)	(-48, -48, 34)	2.77
L Cingulate gyrus (BA 24)	(-6, -8, 32)	2.97
L Thalamus	(-12, -8, 0)	3.74
R Thalamus	(18, -14, 0)	3.46
R Insula (BA 13)	(40, -4, 22)	3.37
L Insula (BA 13)	(-34, 16, 6)	3.04
R Cerebellum	(24, -54, -24)	3.04
L Putamen	(-30, -10, -6)	2.96
R Putamen	(16, 8, -4)	3.04

R Caudate	(10, 8, 6)	2.70
R Claustrum	(34, -20, 4)	3.03
L Claustrum	(-22, 12, -4)	2.70
EFT elaboration – Amount of details		
L Superior frontal gyrus (BA 8)	(-28, 30, 54)	3.00
R Medial frontal gyrus (BA 9)	(6, 46, 20)	2.93
L Medial frontal gyrus (BA 10)	(-4, 58, 8)	2.97
R Middle frontal gyrus (BA 8)	(30, 42, 46)	3.41
L Middle frontal gyrus (BA 8)	(-54, 16, 40)	2.80
L Middle frontal gyrus (BA 6)	(-44, 14, 54)	2.88
L Superior frontal gyrus (BA 10)	(-24, 64, 18)	2.90
L Inferior frontal gyrus (BA 47)	(-18, 34, -4)	3.48
L Precuneus (BA 7)	(-6, -82, 46)	3.62
R Precuneus (BA 7)	(12, -50, 38)	3.08
R Precuneus (BA 31)	(10, -48, 30)	2.90
L Angular gyrus (BA 39)	(-52, -66, 38)	3.34
L Supramarginal gyrus (BA 40)	(-60, -54, 28)	3.13
R Superior parietal lobule (BA 7)	(42, -68, 52)	2.90
R Inferior parietal lobule (BA 40)	(46, -54, 36)	2.84
L Middle temporal gyrus (BA 21)	(-52, -14, -12)	2.92
L Superior temporal gyrus (BA 39)	(-34, -56, 28)	3.18
L Cuneus (BA 18)	(-8, -82, 18)	3.10
R Cuneus (BA 17)	(20, -80, 10)	2.80
R Cuneus (BA 19)	(2, -80, 40)	3.55
R Cuneus (BA 7)	(2, -66, 30)	2.99
L Inferior occipital gyrus (BA 19)	(-36, -80, -2)	2.88
R Middle occipital gyrus (BA 19)	(36, -86, 18)	2.83
R Parahippocampal gyrus (BA 19)	(42, -48, 2)	2.83
L Parahippocampal gyrus (BA 36)	(-42, -34, -10)	2.91
L Cingulate (BA 31)	(-22, -50, 28)	3.57
R Cingulate (BA 31)	(20, -44, 38)	2.70
L Anterior cingulate (BA 32)	(-2, 34, -10)	3.41
L Insula (BA 13)	(-36, -20, 22)	3.41
R Insula (BA 13)	(30, -20, 24)	2.75
R Thalamus	(2, -12, 16)	3.25
L Cerebellum	(-22, -80, -16)	3.13
R Cerebellum	(12, -82, -12)	2.82
L Caudate	(-20, 16, 20)	3.18
R Caudate	(12, 20, 16)	2.82
R Lentiform nucleus	(12, -4, 0)	3.09

More precisely, during the construction phase, MS patients showed extensive bilateral prefrontal activations (middle, superior and inferior gyri), but also activations in the bilateral temporal regions (superior and fusiform gyri), the left supramarginal gyrus, the left cingulate gyrus, the right cerebellum and bilateral sub-lobar regions.

Regarding the elaboration, the bilateral, but mostly left, prefrontal regions were also recruited (medial, inferior, middle and superior gyri), as well as the bilateral parietal regions (precuneus, angular and supramarginal gyri, superior and inferior parietal lobules), the left temporal regions (middle and superior gyri), the bilateral parahippocampal gyrus, the bilateral occipital regions (cuneus, inferior and middle occipital gyrus), the bilateral anterior and posterior cingulate, the bilateral cerebellum and bilateral sub-lobar regions.

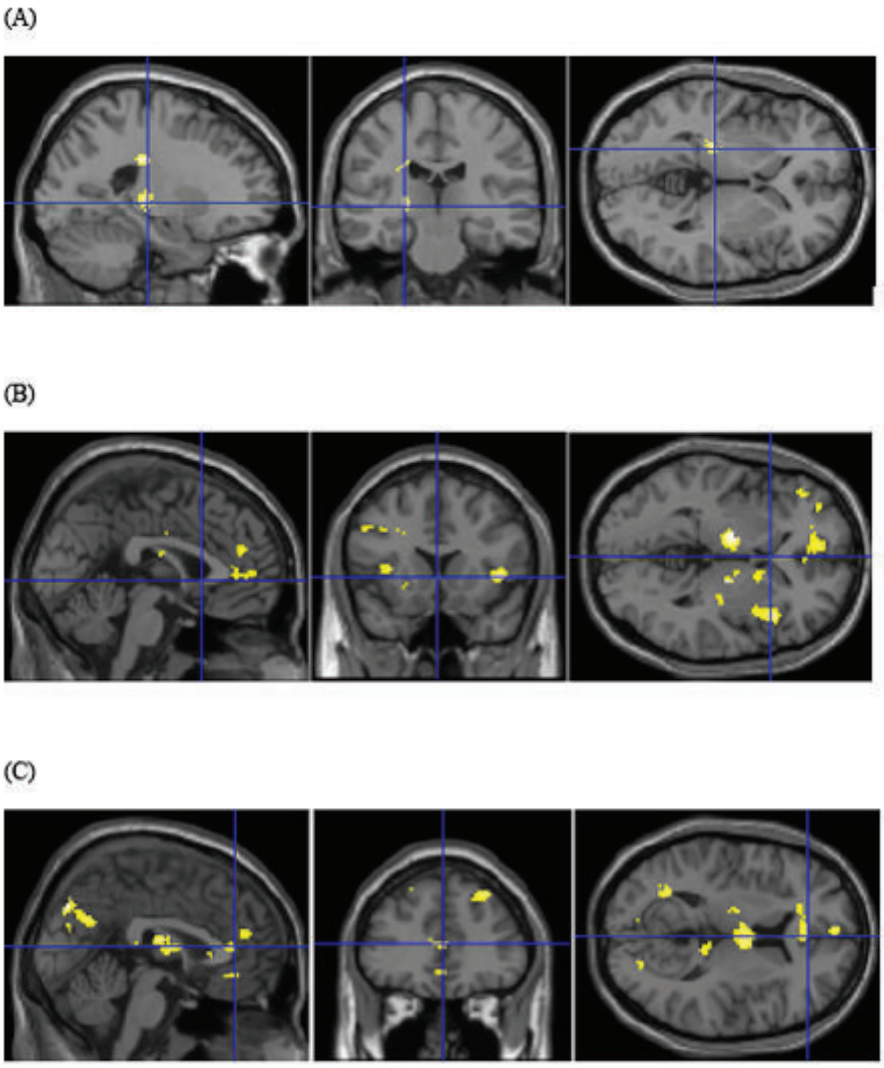

Figure 3. Brain regions showing an increased response to the difficulty of access during the EFT construction (A) and to the amount of details during the EFT construction (B) and the EFT elaboration (C); uncorrected p value p.005, k = 10 voxels

DISCUSSION

The present study directly investigated the functional underpinnings of EFT impairment in non-depressed relapsing-remitting MS patients, for the first time, to our knowledge. Interestingly, this EFT deficit has been observed in the context of a relative preservation of general cognitive functioning in our patients. The EFT deficit was accompanied by cerebral activation changes relatively to healthy controls. This finding is consistent with the AM deficit previously described in MS patients (Ernst et al., 2012; 2013) and the literature showing the co-occurrence of AM and EFT impairment in various clinical populations (Addis et al., 2009; D'Argembeau et al., 2008; Hassabis et al., 2007; Klein et al., 2002; Tulving, 1985).

During the EFT construction phase, a predominantly enhanced bilateral cerebral network was observed, including anterior, medial and posterior brain regions. Interestingly, the great majority of the enhanced brain activations in MS patients were located in the core EFT brain network described in healthy controls, which engaged right, but mostly left-lateralised brain regions (Addis et al., 2007; Botzung et al., 2008). This observation together with the recruitment of alternative, particularly contralateral, brain regions are consistent with the most frequently brain plasticity processes observed in MS (Hulst et al., 2012). In general, these phenomena have been interpreted as the expression of an increased neural effort due to structural damage (Hawellek et al. 2011).

The notion of increased neural effort is consistent with the high cognitive demand required by the extraction and recombination of an infinite assortment of details into a novel event, taxing, particularly, executive functions sustained by prefrontal regions (Weiler et al., 2011). In relation to the AM retrieval deficit in MS patients (Ernst et al., 2012; 2013) bearing in mind that we observed a lower number of future episodic details, we suggest that this initial step of extraction/recombination could be compromised and reflected in the increased bilateral prefrontal activations observed during the construction phase. This suggestion is corroborated by the predominant response of the same cerebral region to increase in the amount of details.

Besides the above mentioned prefrontal recruitment, during the construction phase, the great majority of the enhanced brain activations in MS patients were observed in some key nodes of the EFT network. This was the case for the right lateral temporal region, which sustains the reactivation of acquired personal semantic information to guide future simulations (Viard et

al., 2011). Since a relative preservation of personal semantics has been observed in MS (Ernst et al., 2013), the enhanced recruitment of the lateral temporal region could reflect the greater reliance on semantic process to guide EFT construction. Structures from the anterior part of the cortical midline (i.e. medial frontal and anterior cingulate) were also highly engaged bilaterally by MS patients during the construction phase. Importantly, these brain regions are involved in self-referential processes central in EFT (Northoff et al., 2006). This was also the case for further structures increasingly activated in our patients, such as the posterior portions of the midline structures, namely the posterior cingulate and the adjacent precuneus, also involved in visual imagery processes together with the occipital regions (Greenberg & Rubin, 2003). Regarding visual imagery, the bilateral parahippocampal gyrus, also increasingly activated in our patients, plays a pivotal role in the recruitment of the posterior brain regions (Botzung et al., 2008; Viard et al., 2011) to further generate coherent detailed mental simulation. Nevertheless, since these brain regions are normally more involved during the EFT elaboration phase (Addis et al., 2007), we suggest, cautiously, that the parahippocampal, anterior and posterior cingulate gyri enhanced neural responses to the difficulty during EFT construction, could reflect reliance on self-referential processes to further prompt mental simulation.

Turning to the elaboration phase, an intriguing point was the striking reduction of the extent of the increased brain network in MS patients in comparison with the EFT construction. Here, the brain activations were mainly concentrated in the bilateral prefrontal regions and thus, diverged from the network normally engaged by healthy controls, in which less prefrontal recruitment was observed during the elaboration phase. It has been observed that the mental operation of trying to find additional details is notably sustained by visual imagery processes that rely on more posterior brain regions (Addis et al., 2007). In this perspective, relatively to MS patients, the enhanced activity observed in our healthy controls only in the posterior cerebral regions is consistent with this observation. On these bases, the anterior/posterior difference in brain activity between MS and healthy subjects could be consistent with the above mentioned suggestion of an initial difficulty during the effortful extraction/recombination of details still present during the elaboration phase.

In contrast, the analysis of the neural response to the increase of details showed besides the prefrontal activations, an increased cerebral activity predominantly observed in more posterior regions (i.e. precuneus, cuneus, occipital and posterior parietal areas, posterior cingulate

gyrus) and in the parahippocampal gyrus. It is likely that these cerebral activations in MS patients reflected greater involvement of brain regions sustaining visual imagery as the amount of details increased.

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

Surprisingly, and contrary to our hypothesis, no functional changes in the hippocampus were observed in MS patients, neither during EFT construction nor elaboration (even though this structure plays a critical role in the retrieval of details stored in memory, their recombination into a coherent future simulation and the encoding of the simulation product in memory, and is particularly responsive to the amount of details; Addis & Schacter, 2008; 2012). The absence of a significant differential hippocampal activity between groups could be accounted for by the fact that the effortful process of detail extraction/recombination is also sustained by the prefrontal regions (Weiler et al., 2011). We suggest that a deleterious impact of the executive component might have affected the further steps of extraction/recombination at the hippocampal level. This could be supported by the predominant higher activity in these regions observed in our patients.

In conclusion, we have documented EFT impairment in non-depressed MS patients as evidenced by poorly detailed simulated future events compared with controls. EFT impairment was also detected at the neuro-functional level, showing MS characteristic spontaneous compensatory mechanisms in bilateral prefrontal regions. This is coherent with reports in the MS literature on fMRI-related cognitive tasks (Hulst et al., 2012), but no study before has reported results in future simulation. It is worth noting that despite the difference in the richness of details, MS patients and healthy controls had similar reaction time and number of valid trials, allowing us to reasonably interpret the patient's cerebral activation pattern as resulting from pathology, rather than arising from fMRI-related difficulties or a too poor task performance (Cader et al., 2006).

While further investigation is needed to better understand EFT impairment in MS patients, this study could provide new insights into cognitive impairment in MS, bearing in mind the

important role that future projection plays in coping skills, goal attainment and implementation of intentions, among other. It also encourages the use of neuroimaging studies with the more general purpose of developing cognitive rehabilitation programmes to alleviate impairment in a domain that is at the centre of cognition, social relations, and ultimately, wellbeing (Schacter et al., 2012; Szpunar, 2010).

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STUDY 4

Ernst A, Noblet V, Denkova E, Blanc F, De Seze J, Gounot D and Manning L. Distinct and common mechanisms of spontaneous brain plasticity during mental time travel in relapsing-remitting multiple sclerosis patients. (Submitted)

Abstract

Mental time travel (MTT) entails the ability to mentally project into the past autobiographical memory (AM), and the episodic future thinking (EFT). While, AM and EFT share common phenomenological and cerebral functional properties, distinctive characteristics have been documented in healthy and clinical populations. However, no study investigated the functional underpinnings of MTT impairment in brain-damaged patients. We therefore set out to fill this absence by studying 22 relapsing-remitting multiple sclerosis (MS) patients and 22 matched controls. The participants underwent an AM/EFT assessment by means of the Autobiographical Interview, followed by a functional MRI session. The fMRI examination consisted in AM and EFT tasks, with a distinction between the construction and elaboration phases of events. Clinically, the results showed impaired performance for both AM and EFT in MS patients, which was accompanied, on the fMRI side, by increased cerebral activations mostly located in frontal regions extended to parietal, external temporal and posterior regions, during both AM/EFT tasks, relatively to healthy controls. However, enhanced brain activations in MS patients were particularly apparent during the EFT task, involving the hippocampus, frontal, external temporal and cingulate regions. Similarly, personal events' construction required greater fronto-parieto-temporal activations in MS patients than in healthy controls, and relatively to the elaboration phase. Taking together, our results suggested the occurrence of brain plasticity mechanisms in the context of MTT in MS patients, manifested by both distinct and common mechanisms for AM and EFT. Clinically, this study provided new insights, considering AM/EFT's central role in everyday life of patients.

Introduction

Episodic memory allows not only to remember the past, but also to project oneself in the future (Tulving, 2001; Tulving, 2005). This notion, referred as mental time travel (MTT; Suddendorf & Corballis, 2007; Tulving, 2001), entails the autobiographical memory (AM) and the episodic future thinking (EFT) components, and has been investigated during the past two decades by means of case and group clinical studies, and more recently using the neuroimaging approach in the intact brain. The single-case studies demonstrated concurrent difficulties for past and future personal events (Tulving, 1985; Klein, Loftus & Kihlstrom 2002). These original findings have been confirmed by several group studies showing the simultaneous occurrence of AM/EFT impairment in various clinical conditions, particularly, in Alzheimer's disease (Addis, Sacchetti, Ally, Budson, & Schacter, 2009), schizophrenia (D'Argembeau, Raffard, & Van Der Linden, 2008), depression (Williams et al., 1996) or medial temporal lobe amnesia (Hassabis, Kumaran, Vann & Maguire, 2007). With regard to the neuroimaging studies in healthy subjects, a striking overlap between the functional underpinnings of remembering the past and imagining the future has been observed. The brain regions involved in these studies include among others, the medial frontal and temporal regions, posterior and retrosplenial cortex, lateral parietal and temporal regions, predominantly left-lateralised (Addis, Wong & Schacter, 2007a; Szupnar, Watson & McDermott, 2007; Botzung, Denkova & Manning, 2008). Taking together, these studies established that AM and EFT share common cognitive processes and cerebral network**s**.

One of the best known hypotheses suggested to account for these findings is the "constructive episodic simulation hypothesis" (Schacter & Addis, 2007). The authors posit that the construction of novel events relies on the extraction and the recombination of stored event details, and that both past and future projections require the involvement of cognitive processes such as self-referential processing and mental imagery.

Despite these similarities, some differences between AM and EFT have been documented. In particular, a greater neural activity has been observed in frontopolar and hippocampal regions during the simulation of future events, relatively to that of past events, especially during the initial construction of the event (Okuda et al., 2003; Addis et al., 2007a). In light of the 'constructive episodic simulation' hypothesis, this differential neural activity between past and future could reflect the higher cognitive demand necessary to pre-experiencing than re-experiencing an event (Addis et al., 2009). Indeed, EFT would especially tax executive

functions, because it requires the extraction and recombination of an infinite assortment of details into a novel event, whereas AM consists in the recapitulation of a more restricted pool of details (Berntsen & Bohn, 2010). Similarly, the greater hippocampal recruitment for future tasks could mirror the extraction and the recombination of details into a coherent novel event, and the additional encoding of the simulation product in memory (Addis & Schacter, 2012). As a consequence, several behavioural studies showed a higher number of episodic details provided for past than for future events in healthy subjects (Addis, Wong & Schacter, 2008; D'Argembeau & Van der Linden, 2004), as well as in clinical conditions (D'Argembeau et al., 2008; Addis et al., 2009). Moreover, in two further clinical conditions, Parkinson disease (De Vito et al., 2012) and thalamic lesion (Weiler, Suchan, Koch, Schwarz, & Daum, 2011), EFT impairment was demonstrated, in the context of relatively preserved AM abilities.

Furthermore, in relation to neural mechanisms implemented to respond to brain insult, a few studies have shown brain activation changes during AM recollection (in comparison with healthy subjects) in an hippocampal-damaged patient (Maguire, Vargha-Khadem, & Mishkin, 2001), or in temporal lobe epilepsy (Addis, Moscovitch & McAndrews, 2007b), Alzheimer's disease (Meulenbroek, Rijpkema, Kessels, Olde Rikkert & Fernandez, 2010) and post-traumatic stress disorder (St Jacques, Botzung, Miles & Rubin 2011a). The changes in the patient's brain network observed during AM tasks was interpreted at least in one study (Maguire et al., 2001) as resulting from spontaneous brain plasticity. However, to our knowledge, no clinical study has investigated functional neural changes within an experimental design that allows to compare cerebral network activations between AM and EFT.

Studies in different clinical populations such as traumatic brain injury (Levin, 2003), stroke (Johansson, 2000), or multiple sclerosis (MS; Filippi & Rocca, 2004) have demonstrated the occurrence of cerebral changes, associated with a variety of cognitive function, but neither AM nor EFT. Regarding MS patients, a converging line of investigations has shown the presence of functional cerebral changes during the completion of anterograde memory (Mainero et al., 2004; Morgen et al., 2007; Hulst et al., 2012), executive functions (Lazeron, Rombouts, Scheltens, Polman & Barkhof, 2004) or attention/working memory (see Kollndorfer et al., 2013 for a review) tasks. These cerebral activation changes entailed increased activations in brain areas also recruited by healthy controls, and/or the recruitment of alternative brain areas (Hulst et al., 2012). Therefore, they have been interpreted as the

manifestation of an increased neural effort due to structural damage (Hawellek, Hipp, Lewis, Corbetta & Engel, 2011).

Recently, AM impairment has been described in MS patients (Ernst et al., 2012; 2013; Müller et al., 2013). Ernst and colleagues posited a prefrontal cortex-based retrieval strategy deficit at the origin of AM impairment due to its role in retrieval processes of memories (Svoboda McKinnon & Levine, 2006; Cabeza & St Jacques, 2007), and the fact that this is a frequently damaged region in MS patients (Benedict et al., 2002; Bendfeldt et al., 2009). The retrieval deficit hypothesis was corroborated by the enhanced bilateral prefrontal activation observed during AM recollection in MS patients, which has been interpreted as a compensation mechanism attempt, although insufficient to result in normal AM performance (Ernst et al., 2012). Moreover, at the behavioural level, beyond the initial difficulty to retrieve a specific memory, the access to details associated with the event seemed also compromised in MS patients (Ernst et al., 2012, 2013).

In parallel, the hippocampus, which plays a major role in AM and EFT (Addis, Moscovitch, Crawley & McAndrews, 2004a; Addis et al., 2007a) could also be damaged in MS patients and be accompanied by cerebral functional changes during the completion of an anterograde memory task (Sicotte et al., 2008; Hulst et al., 2012). In this context, considering the aforementioned role of the hippocampus in the extraction/recombination processes of personal events, a conjoint influence of hippocampal damage could be observed in the case of MS patients.

On these bases, the aim of the present study was twofold: (i) to explore the status of AM and EFT at the behavioural level in MS patients, and (ii) to investigate their cerebral underpinnings in the same patients. Clinically, we hypothesised that MS patients would generate a lower number of episodic details in comparison with healthy subjects, resulting in impaired performance for both AM and EFT. We also expected significantly lower performance for EFT than for AM in both groups. Regarding the neural mechanisms, functional changes were expected in the frontal regions and the hippocampus in the patient group. Finally, we hypothesised that functional changes would be more important during the simulation of future events in MS patients.

Methods

Participants

We recruited 22 relapsing-remitting MS patients (Polman et al., 2011) with the following inclusion criteria: an EDSS (Kurtzke, 1983) score ≤4, an absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (Montgomery & Asberg, 1979) and no recent exacerbation of MS symptoms.

Twenty-two healthy controls matched for gender, age, education level and verbal Intellectual Quotient were recruited. Exclusion criteria for all the subjects were documented psychiatric illness, neurological disorder (other than MS for the patients) and poor knowledge of French. 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.

Table 1. Demographical and clinical data. Mean (and standard deviation) for the multiple sclerosis patient and the healthy control groups

	MS patients	Healthy controls	Statistical analysis
N =	22	22	_
Age in years	40.31 (10.08)	39.63 (8.68)	$t = 0.24$; $p = 0.81$
Education in years	13.13 (2.14)	13.22 (2.30)	$t = -0.13$; $p = 0.89$
Sex (Ratio female/male)	17/5	19/3	$\chi^2 = 0.61$; $p = 0.43$
EDSS	2.45 (1.37)	_	_
Duration of MS in years	11.38 (8.24)	_	_
Number of DMD treatment	1.0 (0.0)	_	_
Verbal Intellectual Quotient	98.13 (14.06)	97.27 (11.62)	$t = 0.22$; $p = 0.82$

Neuropsychological assessment

The MS patients underwent a comprehensive neuropsychological baseline examination in the first session (see Ernst et al., 2012 for a complete description). The aim was to verify the patients' general cognitive status, which was shown to be normal with the exception of a mild executive deficit.

A second session was devoted to AM/EFT assessment by means of the Autobiographical Interview (AI; Levine, Svoboda, Hay, Winocur & Moscovitch, 2002), adapted for the assessment of the EFT component and the use of cue-words (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 and to generate freely as many 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, which could plausibly occur in 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 the patients' slowed down cognitive processing speed on AM/EFT performance.

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 else episodic details unrelated to the central event). For each participant, the number of internal details was averaged across the 12 or 15 past events, and across the five future events for the EFT conditions for each recall phase. A complementary analysis was also conducted, taking into account only the previous year for the AM condition and the EFT scores. The rationale for this additional analysis was to ensure that a similar pattern of results would be observed with a matched temporal interval in both conditions, and thus guarantee the further comparisons for the fMRI tasks (see below).

Since Ernst et al.'s (2013) previous study highlighted an impairment of the episodic component of AM, whereas the personal semantics was preserved, only the mean number of internal details was considered for the statistical analyses. Likewise, only the free recall phase condition (combined with the general probe condition) was considered in the statistical analyses.

The interrater reliability was verified for 10% of the past and future events, which were scored by a second scorer. Coefficients for all measures showed high interrater reliability (between 0.82 and 0.99).

Neuroimaging session

fMRI tasks

The fMRI session comprised two experimental tasks: the past events and the future events conditions. The participants were reminded about the similarity with the event's characteristics of the AI's and that the tasks consisted in the evocation of unique personal past/future events, contextually specific, occurring over minutes or hours, but no more than one day. In both tasks, 32 pairs of words were proposed to elicit personal events (e.g. for the past condition: 'sand-sun'; for the future condition: 'meal-family'), covering the same life periods mentioned above. The participants were instructed about the fact that the cue-words were meant to generate a past or future events in a flexible way.

Based on Addis et al. (2007a), two phases were distinguished in the evocation of the event: (i) the construction phase corresponding to the search and initial building up of the event, and (ii) the elaboration phase corresponding to the retrieval/imagination of details associated with the event. Each trial had a fixed duration of 20 sec modulated by the subject's response: once an event was retrieved/imagined, the subject had to press button 1 on the 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.

Prior to scanning, after an initial explanation of the procedure, the participants completed a computerised practice trial for each task in order to be familiar with the experimental design and timing of presentation of the stimuli. A particular attention was paid to the patients' practice trials to optimise the further completion of the tasks during the scanning session, especially as the fMRI examination imposes time constraints.

The experimental design was organised in four sequences of 8 stimuli, per condition, alternating between past events and future events conditions. In both tasks, each trial was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s). At the beginning of each sequence, the name of the condition was displayed on the screen for 6 s. The presentation order of stimuli within each condition was 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.

Immediately following scanning, a post-scan questionnaire was completed, in order to ensure responses accuracy and exclude invalid trials before the data analysis. For each past or future

event, participants had to indicate the type of events (unique, repetitive, extensive, semantic or absent), the spatial and temporal context of the event, the emotional valence and rate, on two visual-analogue scales of 10 cm, the difficulty of access/imagination and the quantity of details.

Acquisition of fMRI data

Images were acquired using a 3T MRI scanner (Siemens Verio). The image sequence was a T2*-weighted echo planar imaging sequence (TR=2500 ms, TE=30 ms, Matrix=64x64 voxels, FOV=224 mm, FA=90). The anterior commissure and posterior commissure were identified in the midsagittal slice, and 45 contiguous slices (each 4mm thick) were prescribed parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

Statistical analyses

Behavioural analyses

Regarding the AI scores, differences between the MS patients and healthy controls in AM/EFT were analysed for the mean number of internal details by repeated-measures ANOVA to explore main effects of group (MS versus healthy controls) and of temporal direction (past versus future), as well as relevant interactions.

Repeated-measures ANOVAs were also used to investigate potential differences between the MS patients and the healthy controls for the type of events and the emotional valence from the post-scan questionnaire, with one between-subjects factor (group: MS patients and healthy controls) and two within-subjects factors (Temporal direction: past and future, five levels for the type of events and three levels for the emotional valence). In the same manner, repeated-measures ANOVAs were applied to investigate the potential influence of the group and of the temporal direction on the construction reaction time, the difficulty of access/imagination and the amount of details. Analyses were followed by Tukey HSD post-hoc test when appropriate.

MR image preprocessing and statistical analysis

Functional images 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 both conditions, 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 sec-duration that started immediately after the end of the construction phase by button press. The 10 sec-duration interval for the elaboration phase was fixed to allow a sufficient time interval to detail search and the trials with a construction phase longer than 10 sec were excluded.

Since a great overlap of the cerebral activations for unique and repetitive events has been observed for past as well as for future events (Addis et al., 2004a; Addis, McIntosh, Moscovitch, Crawley & McAndrews, 2004b; Addis, Cheng, Roberts & Schacter, 2011), both type of events were included as regressors of interest, especially to obtain a sufficient number of valid trials for patients.

Statistical analyses were conducted using SPM8 software (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/). For each participant, contrasts (past events versus an implicit baseline and future events versus an implicit baseline) were entered into a second level of analysis, by employing a 2 (Group: MS, healthy controls) x 2 (Task: past events, future events) x 2 (Phase: construction, elaboration) ANOVA. Statistical analyses were thresholded by using correction for multiple comparisons (FWE, $p < 0.05$). However, since no previous study has been conducted in mental time travel in brain-damaged patients, in order to have more informative overview of the results, in the case of no significant result, exploratory analyses were also conducted with a more lenient threshold of $p < 0.001$ uncorrected and a minimum extent threshold of ten contiguously activated voxels.

Results

Behavioural results

At the behavioural level, AI scores showed a significant main effect of group $F(1, 42) = 73.80$, $p < 0.001$, with MS patients exhibiting poorer performance than healthy controls, irrespective of the temporal direction. A main effect of temporal direction was also highlighted, $F(1, 42) = 55.65$, $p < 0.001$, demonstrating a lower mean number of internal details for the future than for the past condition, irrespective of the group of subjects. A similar pattern of results was exhibited when taking into account only the previous year for the AM condition versus the EFT score, with lower performance for the MS patients than for

the healthy controls, $F(1, 42) = 38.98$, $p < 0.001$, and lower performance for the EFT than for the AM condition, $F(1, 42) = 55.35$, $p < 0.001$. No interaction effect reached the threshold of statistical significance.

Turning to the post-scan results (Table 2), no significant differences were observed for the mean construction reaction time between the two groups, $F(1, 42) = 1.46$, $p = 0.23$, or the two temporal directions, $F(1, 42) = 2.81$, $p = 0.10$.

Table 2. Mean (and standard deviation) for the behavioural measures from the fMRI session for the multiple sclerosis patient and the healthy control groups

	MS patients		**Healthy controls**	
	Past	**Future**	**Past**	**Future**
Construction RT (in sec)	5.29 (1.01)	4.81 (0.96)	4.93 (1.24)	4.63 (0.89)
Type of events				
Unique	17.77 (5.19)	17.81 (7.43)	20.72 (6.08)	18.86 (6.31)
Repetitive	4.45 (3.97)	4.63 (4.57)	3.72 (3.36)	7.22 (5.91)
Extended	0.68 (0.99)	0.54 (1.59)	1.22 (1.74)	1.50 (1.76)
Semantic	1.50 (2.80)	1.95 (3.36)	0.54 (1.14)	0.54 (1.05)
Absent	3.63 (3.84)	3.40 (3.45)	2.50 (1.99)	1.63 (2.87)
Emotional valence				
% Positive	57.55 (15.73)	64.27 (19.87)	55.05 (10.62)	61.45 (17.36)
% Neutral	14.90 (13.18)	22.06 (17.96)	22.45 (11.39)	26.12 (17.97)
% Negative	27.53 (10.68)	13.66 (10.18)	22.48 (9.52)	12.42 (8.12)
Difficulty of access/ imagination	7.01 (1.65)	7.20 (1.73)	7.22 (1.23)	7.65 (1.28)
Amount of details	5.76 (1.34)	5.66 (1.43)	6.43 (1.37)	6.67 (1.37)

Similarly, for the type of event, neither a main effect of group, $F(1, 42) = 1.92$, $p = 0.17$, nor of temporal direction, $F(1, 42) = 1.61$, $p = 0.21$, were obtained. However, a main effect of the type of event has been revealed, $F(4, 168) = 174.77$, $p < 0.001$, with a higher number of unique event in comparison with the four other types ($p < 0.001$ in all the cases). Post-hoc comparisons showed also a higher number of repetitive events in comparison with extended ($p < 0.001$), semantic ($p < 0.001$) and absent ($p = 0.04$) events. However, an equivalent

number of extended, semantic and absent events was shown (statistical threshold between p = 0.15 and p = 0.99).

Regarding the emotional valence, no significant main effect of group, $F(1, 42) = 1.45$, p = 0.23, or temporal direction, $F(1, 42) = 0.05$, $p = 0.81$, were observed. However, a significant main effect of emotional valence was shown, $F(2, 84) = 105.95$, $p < 0.001$, with a higher rate of positive events in comparison of neutral ($p < 0.001$) and negative events ($p < 0.001$), irrespective of the temporal direction. The mean rates of the neutral and negative events were equivalent (p = 0.73). A Temporal direction x Valence interaction was obtained, $F(2, 84)$ = 14.38, $p < 0.001$, showing a lower rate of negative events for the future than for the past events condition ($p < 0.001$), whereas positive and neutral events showed similar scores across the two temporal directions (respectively $p = 0.17$ and $p = 0.36$).

Results from the two-visual analog scales showed no significant difference for the difficulty of access/imagination between the groups, $F(1, 42) = 0.65$, $p = 0.42$, or between the two temporal direction, $F(1, 42) = 2.46$, $p = 0.12$. However, a main effect of group has been obtained for the amount of details, $F(1, 42) = 4.85$, $p = 0.03$, with a lower self-assessed amount of details for the MS patients than for the healthy controls, irrespective of the temporal direction.

Neuroimaging results

Brain regions differently engaged by MS patients and healthy controls

Statistical analyses revealed a significant main effect of group (Table 3), with extensive additional brain activations for the MS patients in comparison with the healthy controls during the execution of the past and future tasks, irrespective of the recall phase (Figure 1.A). These increased cerebral activations were mainly observed in the bilateral frontal regions (inferior, middle, superior and medial gyri, as well as the supplementary motor area) and extended to the bilateral parietal regions (in their inferior, superior gyri and the somatosensory cortex) and the bilateral temporal structures (inferior, middle and superior parts). More posterior cerebral activations were also exhibited in the bilateral precuneus, as well as in the anterior regions of the cortical midline, namely the bilateral cingulate gyrus. Bilateral insular cortex and left cerebellum activations were also reported.

Table 3. Brain regions differentially engaged in mental time travel in MS patients and healthy controls (Main effect of group; FWE $p < 0.05$)

Brain region	Coordinates (x, y, z)	Z-score
MS > Healthy controls		
R Superior frontal gyrus (BA 6)	(24, -2, 66)	4.57
R Middle frontal gyrus (BA 8)	(26, 36, 38)	6.20
L Inferior frontal gyrus	(-48, 46, 0)	5.88
L Precentral gyrus (BA 6)	(-36, -12, 34)	5.75
R Middle frontal gyrus (BA 10)	(32, 56, 4)	5.71
R Medial frontal gyrus (BA 8)	(2, 44, 42)	5.68
R Inferior frontal gyrus (BA 44)	(60, 16, 10)	5.41
R Inferior frontal gyrus (BA 45)	(52, 14, 22)	5.24
L Superior frontal gyrus (BA 9)	(-18, 52, 34)	5.43
L Middle frontal gyrus (BA 10)	(-26, 54, 20)	5.42
R Superior frontal gyrus (BA 8)	(36, 26, 54)	5.23
L Precentral gyrus (BA 44)	(-58, 12, 6)	5.11
L Inferior frontal gyrus (BA 47)	(56, 18, -6)	4.87
R Middle frontal gyrus (BA 6)	(50, 8, 44)	4.85
R Inferior frontal gyrus (BA 46)	(50, 44, 10)	4.72
L Superior frontal gyrus (BA 6)	(-4, 26, 60)	4.70
R Middle frontal gyrus (BA 46)	(48, 32, 18)	4.59
R Inferior frontal gyrus (BA 47)	(52, 36, -6)	4.58
R Superior frontal gyrus (BA 10)	(20, 52, 20)	4.57
L Cingulate gyrus (BA 32)	(-4, 12, 36)	5.37
R Cingulate gyrus (BA 32)	(4, 16, 38)	4.51
L Postcentral gyrus (BA 2)	(-60, -26, 46)	Inf
L Postcentral gyrus (BA 43)	(-62, -14, 20)	6.83
L Inferior parietal lobule (BA 40)	(-64, -24,26)	6.67
R Inferior parietal lobule (BA 40)	(48, -44, 56)	7.24
R Postcentral gyrus (BA 2)	(52, -30, 54)	6.51
R Superior parietal lobule (BA 7)	(46, -60, 50)	5.68
L Postcentral gyrus (BA 7)	(-18, -52, 72)	6.64
L Postcentral gyrus (BA 5)	(-36, -44, 66)	5.52
L Precuneus (BA 7)	(-14, -74, 46)	5.95
R Postcentral gyrus (BA 43)	(64, -14, 14)	5.92
R Precuneus (BA 7)	(16, -72, 48)	5.17
R Superior temporal gyrus (BA 22)	(60, -54, 8)	6.77
R Middle temporal gyrus (BA 37)	(44, -64, 8)	5.59
R Middle temporal gyrus (BA 21)	(62, -26, -8)	6.10
L Middle temporal gyrus (BA 39)	(-50, -68, 12)	6.03
R Middle temporal gyrus (BA 22)	(50, -36, 8)	5.50
L Inferior temporal gyrus (BA 20)	(-60, -16, -22)	5.16

L Middle temporal gyrus (BA 22)	(-54, -50, 2)	4.89
L Middle temporal gyrus (BA 21)	(-50, 2, -10)	4.50
R Insula (BA 13)	(52, -22, 20)	5.25
L Insula (BA 13)	(-34, 4, 18)	4.81
L Cerebellum	(-36, -60, -24)	5.23
Healthy controls > MS		
R Medial frontal gyrus (BA 11)	(2, 56, -12)	5.87
L Medial frontal gyrus (BA 10)	(-4, 52, -4)	5.51
L Middle frontal gyrus (BA 11)	(-28, 38, -4)	5.81
R Middle frontal gyrus (BA 11)	(26, 40, -10)	5.15
L Superior frontal gyrus (BA 8)	(-16, 44, 52)	5.56
L Parahippocampal gyrus (BA 37)	(-30, -38, -10)	5.09
R Uncus (BA 20)	(34, -6, -28)	4.76
L Cerebellum	(-4, -46, -38)	4.73

The reverse contrast displayed distinct brain regions which were more activated in healthy controls than in MS patients (Figure 1. B). These brain regions encompassed on the one hand the medial, superior and middle portions of the prefrontal cortex, bilaterally and on the other hand, the left parahippocampal gyrus (BA 37) and the right uncus (BA 20).

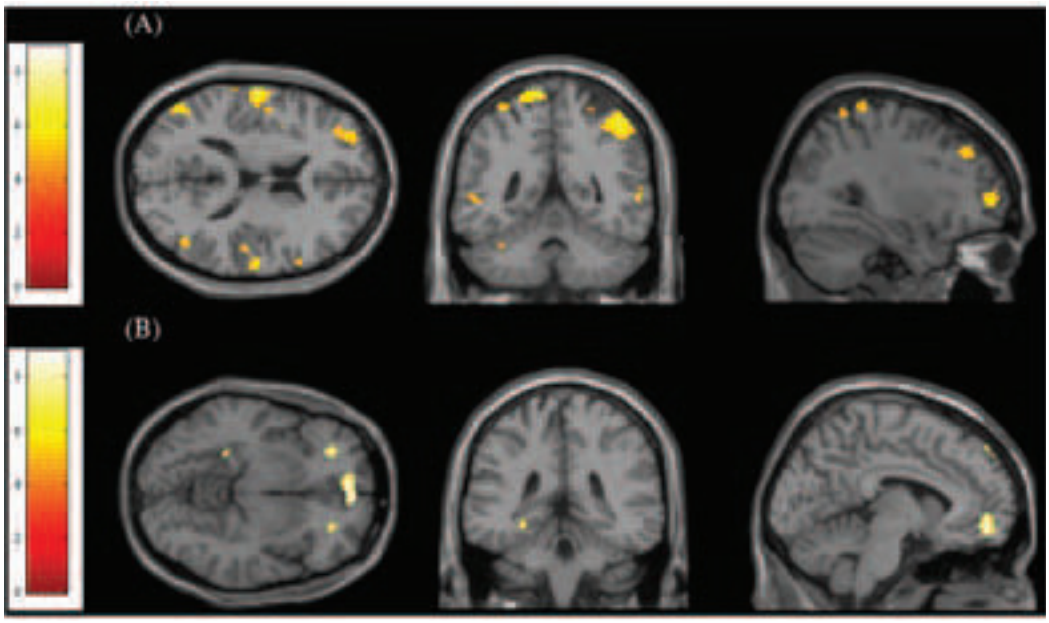

Figure 1. Brain regions showing increased activity during mental time travel in MS patients (A) and healthy controls (B; FWE, $p < 0.05$)

Differential brain activations for past and future events

Analyses focusing on the brain activations differences for the past and future tasks (Table 4), irrespective of the group or the recall phase, demonstrated a main effect of task, but with no greater recruitment for the past in comparison with the future. On the contrary, several additional cerebral activations were highlighted for the future task, notably in the frontal regions (medial and supplementary motor area) and the parietal regions (supramarginal gyrus and somatosensory areas), all right-lateralised.

Table 4. Differential cerebral activations for past and future events (Main effect of temporal direction; FWE, $p < 0.05$)

Brain region	**Coordinates (x, y, z)**	**Z-score**
Past > Future		
No significant activation		
Future > Past		
R Medial frontal gyrus (BA 6)	(10, -4, 58)	5.24
R Precentral gyrus (BA 6)	(60, -2, 28)	5.06
R Postcentral gyrus (BA 2)	(50, -24, 34)	4.89
R Supramarginal gyrus (BA 40)	(56, -46, 22)	4.56
R Insula (BA 13)	(44, -22, 24)	5.84

Differential brain activations for the construction and elaboration of personal events

A main effect of the recall phase has been obtained (Table 5). In particular, several brain regions showed an enhanced recruitment during the construction phase, encompassing predominantly the bilateral frontal areas (inferior, middle, medial and motor regions), but also the right middle temporal gyrus (BA 21), and left posterior brain regions (middle occipital, lingual and fusiform gyri, extending in BA 18 and 19). The reverse contrast also highlighted some cerebral regions with enhanced activations during the elaboration phase, including predominantly the right frontal regions (middle and superior gyri), the left parietal lobe (inferior parietal lobule and somatosensory cortex), the left anterior cingulate (BA 24) and the left transverse temporal gyrus (BA 41). In addition, bilateral activations of the insular cortex and the left claustrum were observed.

Table 5. Brain regions differentially engaged in the construction and the elaboration phase of past and future events (Main effect of recall phase; FWE $p < 0.05$)

Brain region	Coordinates (x, y, z)	Z-score
Construction > Elaboration		
L Middle frontal gyrus (BA 9)	(-44, 14, 26)	Inf
L Middle frontal gyrus (BA 46)	(-54, 30, 18)	Inf
L Medial frontal gyrus (BA 11)	(-4, 42, -14)	Inf
L Medial frontal gyrus (BA 10)	(-2, 48, -8)	Inf
R Inferior frontal gyrus (BA 9)	(36, 10, 26)	7.82
R Precentral gyrus (BA 4)	(38, -20, 62)	7.49
R Middle frontal gyrus (BA 46)	(42, 28, 18)	7.38
R Middle frontal gyrus (BA 8)	(22, 28, 40)	6.95
R Middle temporal gyrus (BA 21)	(56, -6, -16)	Inf
L Middle occipital gyrus (BA 18)	(-24, -86, 20)	Inf
L Lingual gyrus (BA 18)	(-24, -70, -12)	Inf
L Fusiform gyrus (BA 19)	(-34, -70, -12)	Inf
R Cerebellum	(30, -66, -24)	4.83
Elaboration > Construction		
R Inferior parietal lobule (BA 40)	(62, -36, 42)	Inf
L Postcentral gyrus (BA 40)	(-54, -28, 20)	7.15
L Postcentral gyrus (BA 3)	(-42, -28, 66)	7.13
L Postcentral gyrus (BA 2)	(-52, -26, 58)	6.63
R Precentral gyrus (BA 44)	(52, 12, 6)	Inf
L Superior frontal gyrus (BA 9)	(-30, 48, 30)	6.22
R Middle frontal gyrus (BA 46)	(44, 44, 4)	5.55
R Middle frontal gyrus (BA 10)	(38, 48, 14)	4.74
R Superior frontal gyrus (BA 9)	(18, 52, 28)	5.02
L Anterior cingulate (BA 24)	(0, 24, 24)	4.93
L Transverse temporal gyrus (BA 41)	(-40, -30, 12)	4.55
L Insula (BA 13)	(-40, 6, -6)	Inf
R Insula (BA 13)	(42, 8, -4)	6.90
L Claustrum	(-36, -14, -4)	5.88

Distinct influence of the group on the past and future tasks

A significant Group x Task interaction was obtained (only evident at $p < 0.001$; $k = 10$ voxels), which revealed differential cerebral mechanisms between the two groups during the completion of the past and future tasks (Table 6). Overall, several brain regions showed an enhanced recruitment in the MS patients during the future task, while these same cerebral structures were similarly engaged for the past and future conditions in the healthy controls

(Figure 2). This enhanced brain network for future simulation in the MS patients involved the right middle (BA 9) and superior frontal gyri (BA 6), the left middle temporal gyrus (BA 21), the right superior (BA 22) and transverse temporal (BA 41) gyri, but also the right sub-gyral temporal region (BA 20). Significant activations were also observed in the right anterior (BA 24) and posterior (BA 31) portions of the cingulate cortex, as well as in the left amygdala, the bilateral insular cortex, the bilateral thalamus, the bilateral basal ganglia and the right cerebellum. Increased activations in MS patients were also displayed in the right hippocampus and parahippocampal gyrus during the future task. Moreover, the patients also showed greater activation in the left hippocampus for future than for past events, contrasting with the healthy controls, who demonstrated the opposite result.

Table 6. Distinct influence of the group on the brain activations for the past and future tasks (Group x Task interaction; $p < 0.001$; $k = 10$)

Brain region	**Coordinates (x, y, z)**	**Z-score**
MS: future > past and HC: past = future		
R Middle frontal gyrus (BA 9)	(56, 18, 36)	4.14
R Superior frontal gyrus (BA 6)	(36, -2, 68)	3.75
R Parahippocampal gyrus (BA 34)	(30, 2, -14)	3.94
R Hippocampus	(32, -46, 4)	3.92
L Amygdala	(-28, -8, -14)	4.01
L Middle temporal gyrus (BA 21)	(-34, -4, -24)	3.59
R Superior temporal gyrus (BA 22)	(58, -6, 6)	3.67
R Transverse temporal gyrus (BA 41)	(38, -28, 8)	3.96
R Insula (BA 13)	(42, -16, -6)	4.47
L Insula (BA 13)	(-38, -24, 2)	4.24
R Sub-gyral (BA 20)	(40, -8, -16)	4.24
R Cingulate (BA 31)	(24, -28, 44)	3.36
R Cingulate gyrus (BA 24)	(20, -16, 38)	3.57
R Posterior cingulate (BA 31)	(28, -58, 20)	3.99
L Thalamus	(-2, -18, 12)	4.40
R Thalamus	(8, -12, 8)	4.32
L Caudate	(-30, -26, -2)	4.21
R Putamen	(26, 12, 2)	3.37
R Cerebellum	(2, -66, -20)	3.77
MS: future > past and HC: past > future		
L Hippocampus	(-28, -32, -8)	4.18

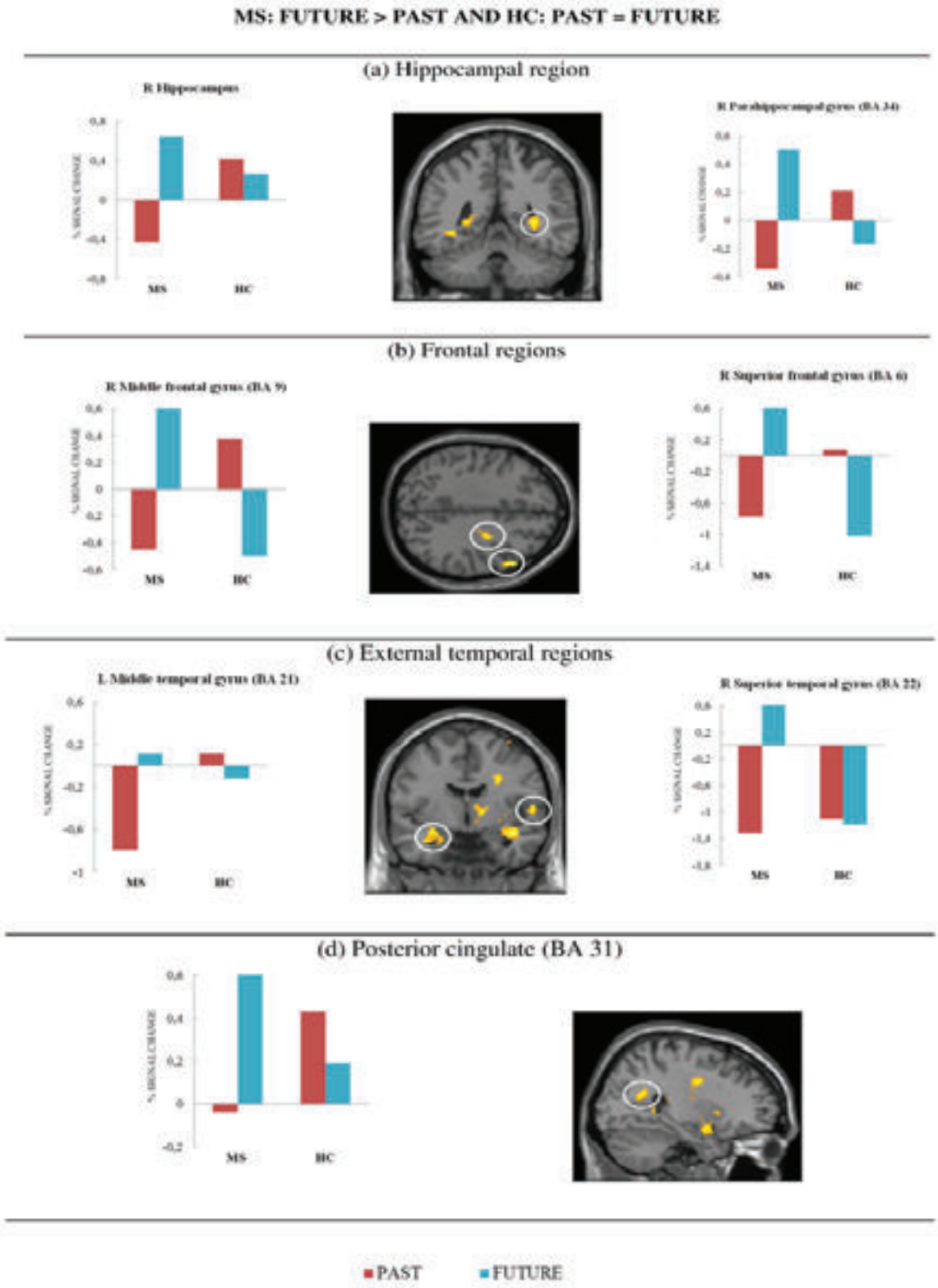

Figure 2. Brain regions showing a greater neural activity for the future events (versus the past) in MS patients but a similar neural activity for both tasks in healthy controls (Group x Task interaction; $p < 0.001$ unc; $k = 10$ voxels).

Influence of the recall phase on cerebral activations for the MS patients and healthy controls

Statistical analyses evidenced a significant Group x Task interaction (Table 7; again only evident at $p < 0.001$; $k = 10$ voxels). A first set of results showed that, while equivalent cerebral activations were observed during the elaboration phase in both groups, distinct brain regions were preferentially recruited by the MS patients and the healthy controls during the construction phase. In fact, during the construction phase, the healthy subjects recruited in a greater extent than MS patients primarily left-lateralised regions, including the medial frontal gyrus (BA 10), the cuneus (BA 18/19) and the precuneus (BA 31). For the MS patients, increased brain activations in response to the construction phase have been highlighted in the right superior and left middle temporal gyrus (BA 22), the right inferior parietal lobule (BA 40) and the right superior parietal lobule (BA 7; Figure 3).

Table 7. Distinct influence of the recall phase in MS patients and healthy controls during the evocation of past and future events (Group x Recall phase interaction; $p < 0.001$; $k = 10$)

Brain region	**Coordinates (x, y, z)**	**Z-score**
HC construction > MS construction and HC elaboration = MS elaboration		
L Medial frontal gyrus (BA 10)	(0, 54, -10)	4.94
L Cuneus (BA 18)	(-2, -88, 22)	4.10
R Cuneus (BA 19)	(22, -88, 22)	3.58
L Precuneus (BA 31)	(-10, -60, 22)	3.45
MS construction > HC construction and MS elaboration = HC elaboration		
R Superior temporal gyrus (BA 22)	(60, -54, 8)	4.08
L Middle temporal gyrus (BA 22)	(-56, -48, 2)	3.99
R Inferior parietal lobule (BA 40)	(48, -44, 56)	3.40
R Superior parietal lobule (BA 7)	(26, -68, 54)	3.26
MS: construction > elaboration and HC: construction = elaboration		
L Inferior frontal gyrus (BA 9)	(-44, -2, 24)	4.82
L Precuneus (BA 7)	(-16, -72, 44)	3.49
L Insula (BA 13)	(-34, 4, 18)	3.99
HC: elaboration > construction and MS: construction = elaboration		
L Postcentral gyrus (BA 2)	(-62, -30, 42)	4.21
L inferior parietal lobule (BA 40)	(-64, -24, 26)	3.77
L Postcentral gyrus (BA 7)	(-16, -52, 72)	3.49
R Insula (BA 13)	(52, -22, 24)	3.35
L Postcentral gyrus (BA 1)	(-64, -16, 22)	3.70

Secondly, the MS patients showed greater left-lateralised activations during the construction phase (versus the elaboration phase) in the inferior frontal gyrus (BA 9), the precuneus (BA 7) and the insula (BA 13), whereas these brain regions were similarly engaged in both recall phases by the healthy subjects.

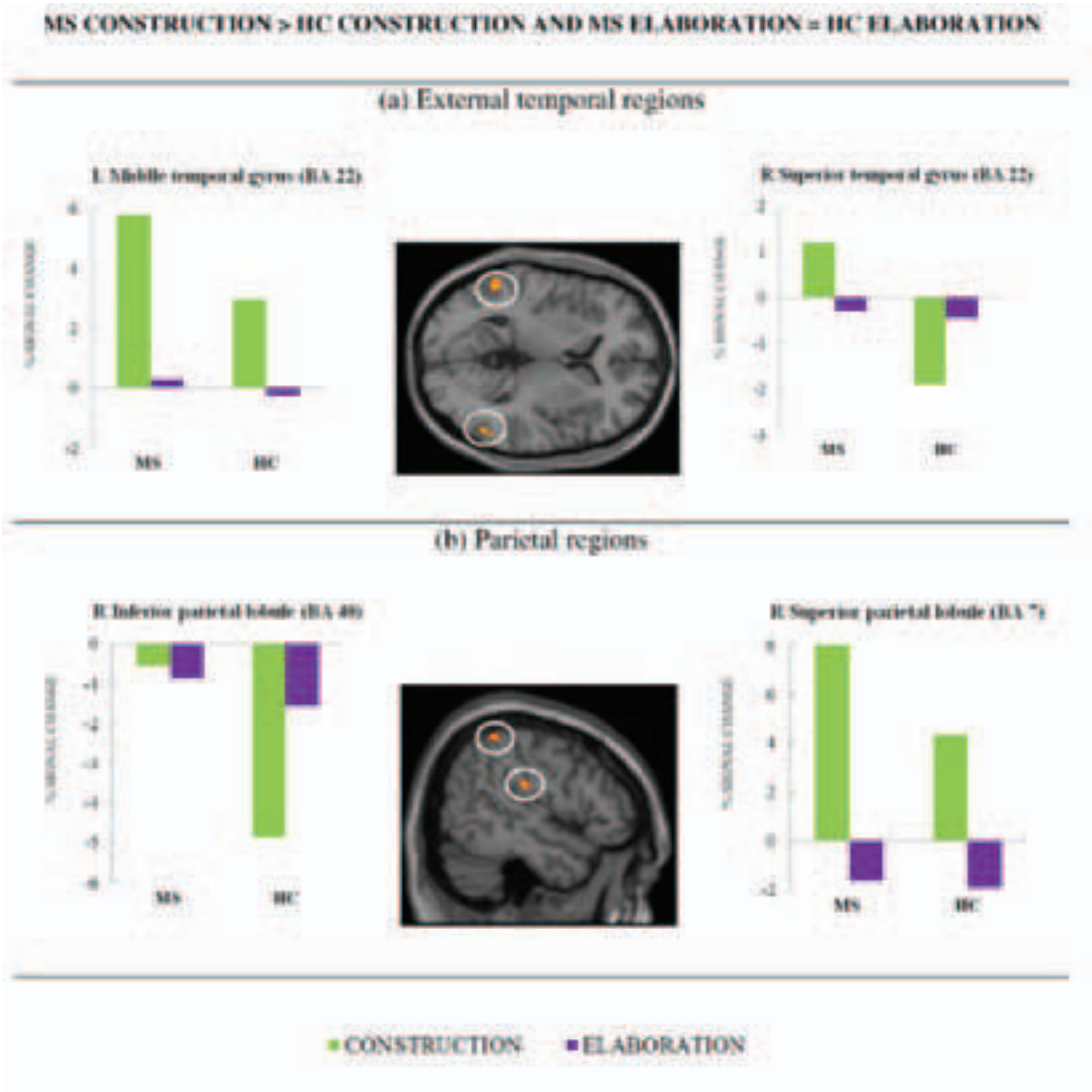

Figure 3. Brain regions exhibiting enhanced cerebral activations in MS patients (versus healthy controls) during the construction phase but with no significant group difference during the further elaboration phase (Group x Phase interaction; $p < 0.001$ unc; $k = 10$ voxels).

Finally, the elaboration phase required additional brain activations in the healthy subjects group in comparison with the construction phase, which were mainly located in the left parietal lobe, namely the postcentral gyrus (BA 1/2/7) and the inferior parietal lobule (BA 40), but also in the right insular cortex. These latter cerebral activations were nonetheless similarly engaged by the MS patients during both recall phases.
No significant Task x Phase interaction was shown.

Discussion

The aim of the present study was to investigate, for the first time to our knowledge, the simulation of past and future personal events in relapsing-remitting MS patients, with a double approach in clinical neuropsychology and functional neuroimaging.
Clinically, as expected, the MS patients showed impaired performance in both AM and EFT, expressed by a lower number of episodic details in comparison with the healthy controls. In agreement with our hypotheses, better performances were observed for the AM than for the EFT condition in both groups, replicating the results from previous studies (D'Argembeau & Van der Linden, 2004; Addis et al., 2008; D'Argembeau et al., 2008; Addis et al., 2009). Importantly, the same pattern of scores has been obtained when comparing EFT performance with AM performance both across lifespan and for the most recent life period alone.
There were no significant differences for the post-scan questionnaire variables between the two groups (with the exception of the amount of details, showing a lower score for the MS patients). The absence of significant differences could be explained by the fact that a particular emphasis had been made on the practice trial preceding the scan to optimise the procedural aspects accompanying the tasks. In the same vein, the presence of two-cue-words during the fMRI tasks (instead of a single cue-word during the AI) was also set to optimise the further good completion of the tasks by the patients. Additionally, it is important to note that the post-scan measures relied on self-assessment, with constrained categories and measures of responses, whereas the AI scores involved a strict scoring procedure based on the absolute production of the participants. Considering the issue of the AM test sensitivity previously reported in MS patients (Ernst et al., 2012, 2013), it is possible that the simple categorisation of the type of events was not sensitive enough to detect deficits similar to those observed in the AI. The same is true for the absence of significant difference between the past and future events for the post-scan questionnaire measures, versus the significant difference

observed during the AI. However, the absence of significant differences between the two temporal directions, and the two groups, guarantee the interpretation of the patients' cerebral activation changes as resulting from pathology, and not from a too poor completion of the tasks due, for example, to inadequate cognitive strategies (see Lazeron et al., 2004; Cader, Cifelli, Abu-Omar, Palace & Matthews, 2006; Liu et al., 2011 for issues related to the interpretation of cerebral functional changes in cognitive task-related fMRI studies in MS).

Turning to neuroimaging results, using an fMRI paradigm based on Addis et al. (2007a), we obtained several similar results. For instance, no brain region showed a greater activity for the past than for the future condition. On the contrary, additional cerebral activations have been noticed for the future condition in frontal and parietal regions, which are in agreement with those previously documented in the literature (Addis et al., 2007a; Szpunar et al., 2007). The same is true for the comparison between the two recall phases, showing, in agreement with Addis et al. (2007a), two sets of brain regions differentially engaged for the construction and the elaboration phases. Owing to the inclusion of patients in our study, some variations in the brain networks were naturally present relatively to the published data on healthy subjects, while they were in accord with reports of cerebral functional changes during AM recollection in other clinical populations (Maguire et al., 2001; Addis et al., 2007b; Meulenbroek et al., 2010; St Jacques et al., 2011). Along these lines, we observed neural changes signalling spontaneous brain plasticity during mental time travel in the patient group.

Consistent with the retrieval deficit hypothesis in MS (Ernst et al. ,2012, 2013), increased brain activations in the bilateral frontal regions together with enhanced bilateral parietal activations, notably in the inferior parietal lobule have been largely displayed during the evocation of personal past and future events, relatively to healthy controls. Recently, St Jacques, Kragel and Rubin (2011b) introduced the notion of the "frontoparietal network", which is related to executive control processes, and therefore, especially involved in the initial construction of memories. Thus, the enhanced activity in this frontoparietal network could reflect the actual higher cognitive demand required during the generation of events in our MS patients. Supporting this view, in our MS patients, frontal and parietal activations were particularly exhibited during the construction phase and during the evocation of future events, which highly required executive control processes.

Regions from the bilateral temporal lobes (in particular the BA 20/21/22) were also more widely recruited by our patients. These regions pertain typically to the AM/EFT core network

and sustain personal semantic knowledge. This cognitive process has a primary role during the event generation, where general personal knowledge serve as a basis for the research of more specific episodes, but is also involved during the further research of details, in relation to semantic representations of the recollected details (Svoboda et al., 2006). Since personal semantics appeared to be preserved in our patients (Ernst et al., 2013), these greater brain activations could reflect, on the one hand, an effective compensation mechanism, resulting in normal personal semantic performance, and, on the other hand, it could be interpreted as indicating a greater reliance on personal semantic processes during the simulation of personal events to compensate episodic difficulties. Favouring the latter suggestion is the observation of greater recruitment of these temporal regions in the patient group, especially during the construction phase and the EFT task that particularly require personal semantics (Svoboda et al., 2006; Viard et al., 2011). Additionally, these temporal region activations were accompanied by greater fronto-parietal activations, likely reflecting the fact that the construction phase and the future condition are particularly demanding in executive control processes.

In parallel, no greater recruitment of the hippocampal region was demonstrated in our patients when past and future events were analysed together. Interestingly though, the bilateral hippocampus and the right parahippocampal gyrus showed a higher activity for future versus past events in the patient group. The higher hippocampal region activity, for the future condition, followed the fronto-parietal and external temporal region enhanced activations. This pattern of cerebral increased activations was triggered by the increased cognitive demands reflecting, very likely, brain compensation mechanism. Regarding the healthy controls, while the right hippocampus and the parahippocampal gyrus showed no different neural activity between the two temporal directions, the opposite pattern was highlighted for the left hippocampus, i.e., an increased activity for the past versus the future condition. While this latter observation is in agreement with previous reports (Abraham, Schubotz & von Cramon, 2008; Botzung et al., 2008; Weiler, Suchan & Daum 2010), it is not in accord with Addis et al., (2007a), who showed greater hippocampal activation for the future than for the past, particularly observed during the initial construction of the event. Likewise, distinct time course of the hippocampal engagement has also been highlighted across the evocation phases for past and future conditions (Weiler et al., 2010). In this context, the greater hippocampal

engagement for the past condition found in the present study could have been influenced also by the united analysis of the construction and elaboration phases.

Regarding more posterior brain regions, and particularly those of the cortical midline and its adjacent structures (i.e. the posterior cingulate gyrus and the precuneus), they were associated with mental visual imagery processes (Greenberg & Rubin, 2003; Szupnar et al., 2007; Summerfield, Hassabis & Maguire, 2009) and contribute to the number of details retrieved/imagined and the subjective sense of remembering/imagining. The anterior portion of the cortical midline, including the anterior cingulate gyrus and the medial frontal gyrus, are involved in self-referential processes (Northoff et al., 2006). In the case of our patients, increased brain activations were observed in the bilateral precuneus and anterior cingulate gyrus during mental time travel. Moreover, both anterior and posterior cingulate gyri were particularly engaged during future simulation in the patient group, reflecting likely the current setting up of visual imagery and self-referential processes. However, this spontaneous cerebral mechanism remained insufficient since the patients did not produce recollections as rich in details as the controls'.

Conversely, only a few supplementary cerebral activations have been reported in the healthy controls, located in key nodes of the AM/EFT cerebral network. In particular, they showed a greater neural activity in the medial frontal regions, but also in the middle and superior frontal gyri, the parahippocampal gyrus and the adjacent uncus during the simulation of past and future events. Moreover, the medial frontal gyrus and posterior brain regions (i.e. the precuneus and the cuneus) showed an increased early engagement during the construction phase in the healthy controls, while these same activations seemed delayed to the elaboration phase in the MS patients. Increased activations in the healthy controls were also observed in the somatosensory regions during the elaboration phase (versus the construction phase), while a similar level of activity was observed in the patient group across the evocation periods. In the AM literature, the somatosensory cortex is closely linked to the retrieval of somatosensory representations related to the event, the emotional intensity, and it is also especially engaged during the further elaboration of events (Daselaar et al., 2008; Botzung, Rubin, Miles, Cabeza & LaBar, 2010).

In summary, these findings show that spontaneous compensatory brain mechanisms known in other cognitive functions in MS, also take place in mental time travel, and that, similarly to other cognitive abilities, they seem to be insufficient to result in normal performance at the

clinical level (Mainero et al., 2004; Penner, Opwis & Kappos, 2007). Interestingly, distinct and common mechanisms of spontaneous cerebral plasticity seemed to be observed in MS patients during the simulation of personal past and future events. Since particular brain activation changes were above all observed during the most executive demanding conditions, our results provided also supportive arguments to the retrieval-deficit hypothesis suggested by Ernst et al. (2012, 2013).

Regarding the central role of AM and EFT in everyday life functioning, for instance in identity, social situations, coping skills or goal attainment, but also more generally in well-being (Szpunar, 2010; Rasmussen & Habermas, 2011), this study promotes further investigations to better understand AM/EFT impairment in MS. Moreover, as suggested by Pelletier, Audoin, Reuter and Ranjeva (2009), an ultimate follow-up of this kind of neuroimaging studies would be to use the present findings to develop tailor-made cognitive rehabilitation in MS patients to improve their everyday life functioning.

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STUDY 5

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Research Article

Induced Brain Plasticity after a Facilitation Programme for Autobiographical Memory in Multiple Sclerosis: A Preliminary Study

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This preliminary study tackles the assessment and treatment of autobiographical memory (AbM) in relapsing-remitting multiple sclerosis (RR-MS) patients. Our aim was to investigate cerebral activation changes, following clinical improvement of AbM due to a cognitive training based on mental visual imagery (MVI). We assessed AbM using the Autobiographical Interview (AI) in eight patients and 15 controls. The latter subjects established normative data. The eight patients showed selective defective performance on the AI. Four patients were trained cognitively and underwent pre- and post-AI and fMRI. The remaining four patients took a second AI, at the same interval, but with no intervention in between. Results showed a significant improvement of AbM performance after the facilitation programme that could not be explained by learning effects since the AI scores remained stable between the two assessments in the second group of patients. As expected, AbM improvement was accompanied by an increased cerebral activity in posterior cerebral regions in post-facilitation fMRI examination. We interpret this activation changes in terms of reflecting the emphasis made on the role of MVI in memory retrieval through the facilitation programme. These preliminary significant clinical and neuroimaging changes suggest the beneficial effects of this technique to alleviate AbM retrieval deficit in MS patients.

1. Introduction

Multiple sclerosis (MS) is a neurological disease characterised by the multifocal nature of neurological lesions in the central nervous system, which results in demyelination, white and grey matter injuries and/or atrophy [1]. As a consequence of the cooccurrence of lesions, a wide range of symptoms can be observed in MS, including cognitive impairment [2]. Deficits on cognitive domains as anterograde memory, executive functions, attentional processes, or information processing speed have been described [3] and a number of clinical studies have also developed different cognitive rehabilitation programmes for MS patients [4].

However, very few studies have been carried out in MS to investigate autobiographical memory (AbM). Briefly stated, AbM is the capacity to relive detailed events, evoking the spatiotemporal context, in which they were encountered, as they are remembered [5]. AbM deficit in MS has been debated in the literature despite the comparatively modest number of works on the topic. Paul et al. [6] found personal semantics impairment in MS patients, while Kenealy et al. [7] observed episodic personal memory deficits, but these studies did not control for the illness subtypes. More recently, Müller et al. [8] reported impaired AbM in MS patients in secondary progressive MS patients and no deficit in relapsing-remitting multiple sclerosis patients (RR-MS),

while Ernst et al. [9] demonstrated AbM deficit in RR-MS patients. Although, no "direct" comparison can be drawn between these two recent studies (Müller et al. and Ernst et al.), due to several methodological discrepancies, the contradictory findings are probably only apparent (see the Discussion section). Our previous clinical study [9] has shown that AbM impairment in RR-MS patients was very likely caused by a deficit of retrieval strategies, and that AbM deficit in MS could be alleviated with a cognitive facilitation programme. This programme was based on the cueing role of mental visual imagery (MVI) in AbM, which is involved in the reconstructive process of past events and allows to cue visual and other sensory modality information about the event [10, 11].

The clinical conclusions of our previous work led us to consider the cerebral substrates of the documented improvement of AbM functioning following the facilitation programme.

Several fMRI studies in MS have been reported, demonstrating cerebral activations during different cognitive tasks, particularly attentional processes and working memory tasks [12–14]. Those studies have highlighted the presence of a spontaneous cerebral plasticity in MS. Nevertheless, only a few studies have explored the possibility of an induced cerebral plasticity in MS patients following cognitive rehabilitation. These investigations on training-induced brain plasticity in MS have effectively shown cerebral activations changes after cognitive rehabilitation for attentional deficit, [15] attentional, dysexecutive and information processing impairments [16], or anterograde memory impairment [17]. No such study has been realised on AbM in MS patients, to our knowledge.

Therefore, the aim of the present preliminary study is to better document the mechanisms sustaining the efficacy of our MVI-based facilitation programme on AbM retrieval. To this end, we test both clinical and cerebral network changes before and after facilitation. Two sets of studies on neurocognitive relationships are relevant in the present work. In the first place, the studies showing that the AbM cerebral network is widespread and recruits predominantly the left and medial cerebral regions. Among those regions, the "core" structures are the prefrontal cortex, medial and lateral temporal cortices, parieto-occipital regions, temponoparietal junctions, and cerebellum [18]. Concerning prefrontal regions, several authors have pointed out their central role in the retrieval process [19, 20]. The further group of relevant studies in the present work are those reporting that MVI relies mostly on posterior cerebral regions [18] and that MVI implication in AbM is also supported by the partial overlapping of cerebral activations observed during AbM and MVI tasks [21]. On those bases, we hypothesised that the patients showing an improvement of AbM performance documented by clinical changes measured after cognitive training, would also show cerebral activation changes during the remembering processes of personal past events. More specifically, we expected an increased activation of posterior cerebral regions in the postfacilitation fMRI session given that our programme was constructed to enhance and optimise the role of MVI in AbM.

2. Materials and Methods

2.1. Participants. Eight patients with definite MS according to the Mac Donald criteria [22] were recruited at the Neurology Units of two French hospitals (Strasbourg and Colmar). Inclusion criteria were the diagnosis of a relapsing-remitting disease course, a mild functional disability corresponding to an Expanded Disability Status Scale (EDSS) [23] score ≤ 4, an absence of major signs of depression according to the Montgomery and Asberg Depression Rating Scale (MADRS, significant clinical threshold score ≥ 15), [24] no recent exacerbation of MS symptoms and right-handedness for patients who underwent fMRI sessions.

Fifteen healthy controls were also recruited to constitute a normative database for the AbM test. Exclusion criteria for all the participants included documented psychiatric illness, neurological disorder (other than MS for the patient group), and poor knowledge of French. Demographic and clinical data for the groups of MS patients are summarized in Table 1. All subjects signed prior informed consent, we complied with the APA ethical standards, and the research was approved by the "Committee for Protection of Persons" (CPP/CNRS N° 07023).

2.2. Neuropsychological Baseline Examination. The following baseline tests were presented to the MS patients. *Verbal IQ* was assessed with the short form [25] of the WAIS-III Verbal scale [26] and *nonverbal reasoning* with the Advanced Progressive Matrices Set I [27]. *Anterograde memory* was examined using the Rey auditory verbal learning test (RAVLT) [28] for the verbal modality and the Rey-Osterrieth Complex Figure (ROCF) [29, 30] was used to assess the visual modality. *Executive functions* were assessed using the phonological and categorical fluency tests (National Hospital, London), the Brixton Spatial Anticipation test [31], the Tower of London [32] and the Cognitive Estimation Task [33]. Concerning attentional and information processing, the *Information Processing Speed* test from the Adult Memory Information Processing Battery (AMIPB), [34] the Stroop test [35] and the months back test (National Hospital, London) were also administered. Since the experimental test assessing AbM is language-dependent, *language* was also examined, by means of the Dêno 100 test [36]. The *visuoperceptual and visuospatial abilities* were tested using the Silhouettes and Cube Analysis subtests from the Visual Object and Space Perception Battery (VOSP) [37]. Finally, the short version of the "Echelle de Mesure de l'Impact de la Fatigue" (EMIF-SEP) [38] was proposed to evaluate the *impact of fatigue* in daily life.

2.3. Autobiographical Memory Assessment. The autobiographical interview [39] (AI; kindly communicated by the author, Brian Levine to one of us, LM.) was translated into French and adapted following Addis and colleagues [40]. Three cue-words were presented to the participants to probe past events for each of the four or five life periods depending on 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. We therefore obtained either 12 or 15 past events per

Table 1: Demographical and clinical data (mean and standard deviation) for the two groups of MS patients.

	Experimental fMRI group	Control group	Statistical analysis
$N =$	4	4	—
Age in years	37.25 SD 5.50	39.75 SD 5.06	$U = 6.50$; $P = 0.66$
Education in years	12.75 SD 1.50	11.75 SD 0.50	$U = 4.50$; $P = 0.31$
Sex (ratio female/male)	3/1	2/2	$\chi^2 = 0.53$; $P = 0.465$
Laterality (ratio right-/left-handed)	4/0	1/3	$\chi^2 = 4.8$; $P = 0.028^*$
EDSS (median score)	1.50	2.50	$U = 7.50$; $P = 0.88$
(range)	[0–4]	[0–4]	
Duration of MS in years	15.00 SD 9.31	13.5 SD 7.23	$U = 6.50$; $P = 0.66$
Number of DMD treatment	1.00 SD 0.00	1.00 SD 0.00	$U = 8.00$; $P = 1.00$

EDSS: the expanded disability status scale; SD: standard deviation; DMDs: disease modifying drugs. *<0.05.

participant, which differs from the usual AI procedure in which only one memory per life period is required. However, if only one single event per period was to be found, the participant was more likely to provide the most accessible detailed recollection [41, 42]. Consequently, we departed from the standard procedure to test a greater number of recollections in order both to probe more comprehensively the retrieval process and assess the benefits of our facilitation programme. The order of presentation of the cue-words and time periods was counterbalanced. Participants were asked to retrieve unique past events temporally and contextually specific, having occurred over minutes or hours (but not more than one day) and to generate freely as much details as possible about this event. They were informed that the cue-words, as stimuli triggering personal recollections, were intended to be used flexibly rather than literally. No time limit was set to avoid the potential influence of decreased cognitive processing speed on AbM performance. General probes were used to clarify instructions if necessary and to encourage the recall of additional details. The next step consisted in administering the specific probe phase, that is, a structured interview to test further details about a given event.

The assessment session was audio-recorded for later transcription and scoring. We carried out the latter using the AI standardised scoring procedure. Only two phases of recall were distinguished, that is, the free recall and specific probe phases, since the free recall and the general probe phases were analysed as a whole considering the minimal effect of general probes on recall [39]. However, scores were analysed cumulatively across the two levels of recall (i.e., free recall and specific probes). The first step of scoring was the identification of the main event, this permitting to classify each detail as internal (i.e., an episodic detail related to the main event) or external (i.e., nonepisodic information as semantic detail, repetition, metacognitive statement or episodic details but not related to the main event). A qualitative assessment of the episodic re-experiencing was also provided by ratings for episodic richness, time, space, perception and emotion/thought composites for each memory.

After an extensive training in the scoring method (also supplied by Brian Levine to one of us, L. Manning), scoring for all the participants was done by one scorer (A. Ernst) and 10% of the memories were analysed by a trained second scorer (five trained students), following Levine et al.'s instructions [39]. Coefficients for all measures showed a high interrater reliability (between 0.82 and 0.99).

We used a semistructured interview to obtain a qualitative evaluation by the patients of their AbM performance. The aim of this interview was twofold to characterise more precisely the patient's AbM difficulties as well as the potential effects of those difficulties in real life and to evaluate the benefits of the facilitation programme. This interview was adapted from the Memory Experiences Questionnaire, [43] from which we selected four dimensions (vividness, accessibility, sensory details and emotional intensity) based on our previous study [9]. A semi-structured interview was deemed to be better adapted than a questionnaire to explore everyday life.

2.4. Autobiographical Memory Facilitation Programme. The cognitive facilitation programme was constructed to alleviate AbM retrieval difficulties by means of a memory facilitation technique based on MVI. This technique was presented to the patients as a "tool" to facilitate access to a given recollection and the details associated to it. Therefore, during the MVI training sessions, patients found it increasingly easier to pay close attention to details in the mind's eye, which was used spontaneously when evoking personal recollections. Moreover, they were encouraged to try and use this technique in their everyday life and if needed, to ask questions to the neuropsychologist about the use of this tool. Treatment receipt, that is, "the extent to which the patient understands the strategies or techniques taught, and demonstrates the capacity to use them" (p. 836) [44] was verified at different times during the training process, by means of direct questions.

The programme consisted in 2-hour individual sessions once a week for at least six weeks. The patients performed MVI tasks of increasing difficulty, the content of which was divided into four steps. The rate of progression through these steps was flexible and could be adapted to each patient. Completion of the entire programme required at least six sessions but additional sessions were proposed if necessary to complete the programme at the patient's rhythm of training. All over the duration of the training programme, the role of

the neuropsychologist was to teach how to construct visual scenes, and to provide continuous guidance throughout the training sessions.

(1) The *screening test* was based on three sub-tests of the imagery and perception battery [45]: the mental representation of physical detail test, the morphological discrimination test, and the colour comparison test. We used a shortened version of each test with normative data established with a group of 15 healthy controls (different from the healthy control group who participated in the present study; unpublished data). We used these tests to probe basic visual imaging abilities, which enabled us to exclude patients presenting with severe MVI impairment (incompatible with the realisation of the facilitation programme). Thus, patients who presented scores below the normal range for all the three sub-tests were excluded.

(2) The *external visualization* exercise included 10 verbal items that the patient had to imagine and describe. (We called this step "external" visualisation because the purpose of the exercise was to imagine an object and not the participant him/herself). The instruction ran as follows: "I will tell you the name of something (e.g., an onion), imagine it and describe its colour, shape, size, consistency and every detail that you see." Each item description was checked for accuracy using a list of typical traits. For each item, the patient had to describe static aspects (e.g., colour, shape) and an action carried out with the item (e.g., slicing an onion). The action was imagined to be performed either by him/herself or someone else (no instruction was given as to who was supposed to act, since the patient was asked to concentrate on an object having changed in its physical appearance owing to an action).

(3) The *construction* exercise of the programme consisted in figuring out complex scenes bringing into play several characters. The goal was twofold: to increase the complexity of the scene by comparison with the previous step and to introduce several characters performing different complex actions. Five items were proposed with, for each one, a first training step and a subsequent scene construction step. During the training phase, a neuropsychologist guided the patient, starting from a general idea (e.g., "a cook prepares a meal"), to more precise subheadings (e.g., "the cook is in front of a metallic table"). Within subheadings, detailed items were distinguished (e.g., "on the table, you can see butter, some onions and mushrooms . . . "). The present step was considered to be external since the participant was asked to imagine some characters and focus primarily on them, their actions and the context of the scene rather than the patient him/herself. Responses were checked for accuracy in terms of their relation to each subheading, but no list of typical or expected responses was used. The number of headings and subheadings, as well as details produced by the patients was recorded. For the scene construction phase, an item similar to the one used in the training section was proposed (e.g., "can you imagine the job you would most enjoy? Will you describe it, as we just did with the example of the cook?").

(4) The *self-visualisation* exercise was the training phase that shared the most similarities with AbM since the patients were asked to visualise themselves within a given scenario, to imagine it as though they were actually living the scene and to describe whatever details, sensations or feelings came to mind. The presentation was similar to that of the previous exercise, comprising a training phase (e.g., "you are heading towards a hotel reception desk") and a scene construction phase (e.g., "your room is not ready: imagine yourself in the hotel bar"). The difference was that the participant was asked to focus his/her attention on him/herself, that is, using internal, personal knowledge. As for the previous step, we recorded the number of headings, sub-headings and details produced by the patients.

3. Imaging

Images were acquired using a 3T MRI scanner (Siemens Verio). The image sequence was a T2* -weighted echo planar imaging (EPI) sequence (TR = 2500 ms, TE = 30 ms, Matrix = 64 × 64 voxels, FOV = 224 mm, FA = 90). The anterior commissure (AC) and posterior commissure (PC) were identified in the midsagittal slice, and 45 contiguous slices (each 4 mm thick) were prescribed parallel to the AC-PC plane to cover the whole brain.

Concerning fMRI tasks, each of them was developed in two versions, randomly allocated for each patient to before and after facilitation sessions. The *experimental task* (i.e., past events condition) consisted in the evocation of unique personal past events temporally and contextually specific, occurring over minutes or hours, but no more than one day. Thirty-two pairs of words were proposed to elicit memories (e.g., purchase-car; country-walk), covering the same life periods than previously mentioned in the AI. Based on Addis et al., [46] two phases were distinguished in the evocation of the event: (i) the construction phase, which is the search and initial building up of the event, and (ii) the elaboration phase, which corresponds to the retrieval of details associated to the event. Each trial had a fixed duration of 20 s but the duration of the two phases, respectively, were determined by the patient's response: once a memory was retrieved, the patient had to press on the button 1 and this ended the construction phase. The remaining time, during which a central fixation cross was presented, was devoted to the elaboration phase. This was followed by a rating phase with two 4-point scales per event, each presented for 4 s, for which the patient had to rate the degree of vividness (1 = very poor vividness to 4 = very high vividness) and of emotional intensity felt during the remembering phase (1 = very poor emotional intensity to 4 = very high emotional intensity).

The *control task* was a categorical task that included 32 pairs of words, with which patients had to construct a sentence for the construction phase (e.g., with leather–boots: "In the shop, there are a lot of different leather boots"). Once the sentence was constructed, they had to press on the button 1 to pursue with the elaboration phase during which patients had to repeat the same sentence and to replace only the two initial words by words of the same semantic category (e.g., with the previous sentence: "In the shop, there are a lot of different cloth sneakers"; "In the shop, there are a lot of different plastic sandals"; etc). The fixed duration for each trial was also 20 s. Two 4-point scales, each for 4 s, followed each trial and patients had to assess the degree of difficulty (1 = very few difficulty to 4 = very high difficulty) and the degree of pleasantness (1 = very poor pleasantness to 4 = very high pleasantness). In both tasks the last rating was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s).

It is to note that in the context of this preliminary study we focused our subsequent analyses on the construction phase of AbMs, since it reflects the access to AbMs, which according to our main hypothesis is defective in MS patients. Also, due to the small number of participants, we did not use vividness and emotional ratings for further analyses.

The experimental design was organised in four sequences of eight stimuli, beginning systematically with the control task and then alternating between past events and control task conditions. 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 responses collection was done with E-Prime 2 software (Psychology Software Tools, Inc.) and responses were given on a MR-compatible four-button response box. Words were displayed on a screen in white text with a black background and viewed using a mirror incorporated in the head-coil.

Prior to scanning, the tasks were explained to patients and they underwent a computerised practice trial for each task in order to be familiar to the experimental design and to the rhythm of presentation of the stimuli. They also received a more specific practice trial for the control task during which they were instructed to avoid self-implication in the sentences that they had to construct (e.g., no sentences with "I ...") and to try and minimise mental visual associations with the words, since these two processes were of interest for the experimental task.

Immediately following scanning, a postscan interview was realised for the past events condition in order to verify the adequacy of the responses and to exclude potential nonepisodic memories before the data analysis. Thus, for each past event, patients had to indicate the type of memory (unique, repetitive, extensive, semantic, or absent) and briefly, the spatial and temporal context of the event.

4. Procedure

The first section of the present study aimed at providing normative data for the AI. Consequently, the healthy control group underwent a single AI assessment session. The good matching between the group of healthy controls and MS patients was verified for age ($U = 42.00$; $P = 0.24$) and gender distribution ($\chi^2 = 0.28$; $P = 0.59$). Mean scores of the number of internal details and total ratings were calculated for each recall phase and used to determine the normative data. The presence of an AbM impairment for our MS patients was determined using two measures. (i) The scores for the free recall phase owing to the free recall sensitivity to detect AbM retrieval deficit, which seems to be the memory process most involved in AbM impairment in MS patients. (ii) The mean number of internal details, which was 22.12 and total ratings, which was 8.38. These two measures assess the episodic reexperiencing ability and consequently, our MS patients' AbM performance was considered to be impaired if the mean score for internal details was ≤ 22.12 and the mean score for total ratings was ≤ 8.38 for the free recall phase.

Prior to inclusion, MS patients underwent a two-part screening tests. (i) The neuropsychological baseline examination (described above) to control for the absence of severe cognitive impairment other than AbM deficit. To pursue with the second part, 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. (ii) The AbM assessment session was carried out. To be included in the study, patients had to show AbM scores below the healthy controls' mean scores as mentioned above for internal details and total ratings for the free recall phase.

The patients included in the study were allocated in two groups: the experimental fMRI group and the control group. The allocation was not entirely randomised due to three patients, who were left-handed and could not be included in the experimental fMRI group. Patients in the experimental fMRI group underwent the MVI facilitation programme described above with two fMRI sessions following a before/after facilitation design. The effects of the facilitation programme on the behavioural measure were also assessed with the AI at the end of the programme. The control group was included to investigate potential learning effects on the second AI assessment session. Therefore, this group carried out the AI twice, with no intervention between the two sessions. However, for ethical reasons, the MVI facilitation programme was proposed to all the patients from the control group following the second assessment (results not shown here). A diagram summarising the study design and progression trough the study phases is presented in Figure 1.

The blind allocation of the patients' group could not be done since the baseline examination, the AbM assessments and the facilitation programme were conducted by the same neuropsychologist (A. Ernst). Nevertheless, to control a potential influence of the investigator awareness of the patients' group allocation, the second AI scorer was blind of the group membership, in every case. Moreover, AI reports were anonymised and memories were not supplied for scoring in the chronological order of assessment (i.e., after facilitation AI from a patient was not systematically given for scoring after the before facilitation AI).

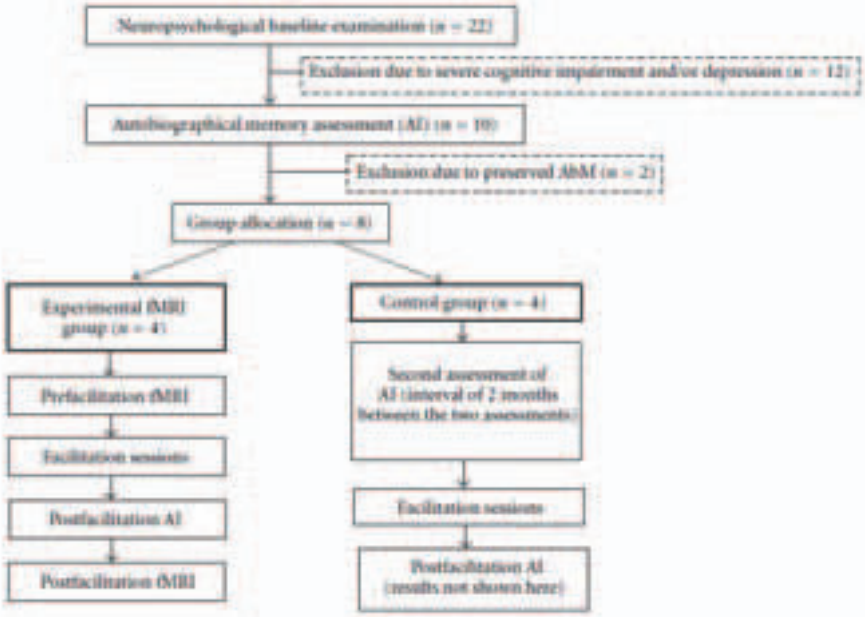


Figure 1: Diagram of the study design and progression trough study phases.

5. Statistical Analyses

5.1. Behavioural Data. Potential differences between the two groups of MS patients for all tests of the neuropsychological baseline assessment were analysed with the Mann-Whitney test. Concerning the AI data, the Mann-Whitney test was used to detect between-group differences for each measure (i.e., mean number of internal details and the mean total ratings) for the free recall and specific probe phases. These comparisons were carried out for the two assessment sessions. Moreover, for each measure and recall phases mentioned above, a descriptive comparison between the patients' mean scores and the normative data from the healthy controls was carried out for the two AI assessments. A within-group analysis was also realised, by means of the Wilcoxon matched pairs test, to measure the degree of AbM improvement/stability between the two assessment sessions for the experimental fMRI and the control group. This procedure was used for the number of internal details and the total ratings for the free recall and specific probe phases.

5.2. Neuroimaging Data. Preprocessing and statistical analyses were conducted using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK) [47]. 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 (MNI) reference brain in Talairach space, [48] and then spatially smoothed using an 8 mm full-width at half-maximum isotropic Gaussian kernel. For both conditions and fMRI sessions, evoked hemodynamic responses time locked to the onset of the cue presentation (construction phase) were modelled with a canonical hemodynamic response function, and hemodynamic activity related to elaboration was modelled with a boxcar function of 10 sec-duration. Although all trials were modelled, only memory trials corresponding to unique past events (based on participants' responses during scanning and post-scan interviews) and correct control trials were included in regressors of interest. The ratings were modelled as a variable of no interest. Statistical parametric maps were generated for the comparison between the construction phase of past and control conditions (past versus control), for each subject, in the context of the general linear model. The two sets of contrast images (before and after facilitation) were then subjected to a second level of analysis to perform a within-subject comparison between before and after facilitation data (paired t-test). For all these analyses, due to the small sample of patients, the significance threshold was set at $P = 0.01$, uncorrected for multiple comparisons, with a minimum extent threshold of 20 contiguously activated voxels.

6. Results

6.1. Behavioural Results. No significant difference was observed between the two groups of patients for the neuropsychological baseline examination, except for the MADRS, for which a higher mean score was observed for the control group (Table 2). However, the MADRS mean score for the two groups remained noticeably under the significant clinical threshold (score $\geq$ 15 to consider the presence of mild depression), consequently, this difference between the two

Table 2: Scores (mean and SD) for all MS patients by group for the neuropsychological baseline examination.

	Experimental fMRI group	Control group	Statistical analysis
Verbal IQ	94.00 SD 13.04	93.25 SD 11.44	$U = 7.00$; $P = 0.77$
PM12	10.25 SD 0.96	8.25 SD 3.20	$U = 6.00$; $P = 0.56$
RAVLT			
Total mean number of words	12.40 SD 1.10	12.80 SD 1.42	$U = 6.00$; $P = 0.56$
Delayed recall	14.25 SD 0.96	14.25 SD 0.96	$U = 8.00$; $P = 1.00$
ROCF			
Copy	35.50 SD 1.00	35.75 SD 0.50	$U = 7.50$; $P = 0.88$
Immediate recall	27.25 SD 4.99	22.50 SD 1.22	$U = 2.50$; $P = 0.11$
Delayed recall	27.25 SD 4.19	24.38 SD 2.14	$U = 4.50$; $P = 0.31$
Deno 100	97.25 SD 3.77	98.25 SD 2.06	$U = 7.50$; $P = 0.88$
Stroop			
Colours (score T)	43.00 SD 10.49	43.75 SD 10.43	$U = 7.00$; $P = 0.77$
Words (score T)	44.50 SD 4.12	48.75 SD 5.85	$U = 4.00$; $P = 0.25$
Interference (score T)	45.50 SD 15.72	48.00 SD 12.57	$U = 8.00$; $P = 1.00$
Interference score (score T)	47.25 SD 12.04	51.50 SD 5.80	$U = 6.50$; $P = 0.66$
Months back (sec)	10.75 SD 4.50	11.75 SD 2.75	$U = 6.00$; $P = 0.56$
Tower of London			
Score	7.50 SD 1.73	9.00 SD 0.82	$U = 3.00$; $P = 0.14$
Time indice	21.25 SD 6.50	18.50 SD 1.29	$U = 7.50$; $P = 0.88$
Brixton (number of errors)	16.50 SD 3.11	13.50 SD 6.56	$U = 6.00$; $P = 0.56$
Cognitive estimation task	3.50 SD 3.11	4.25 SD 4.03	$U = 7.50$; $P = 0.88$
Verbal fluency			
Categorical	19.50 SD 3.87	19.00 SD 8.12	$U = 5.00$; $P = 0.38$
Phonological	11.25 SD 3.86	14.00 SD 4.69	$U = 6.50$; $P = 0.66$
Information processing speed			
Cognitive	52.75 SD 11.32	50.50 SD 10.15	$U = 7.00$; $P = 0.77$
Motor	40.25 SD 10.53	51.75 SD 10.44	$U = 2.00$; $P = 0.08$
Error percentage	3.29 SD 3.79	1.76 SD 1.36	$U = 6.50$; $P = 0.66$
Corrected score	39.96 SD 13.71	55.29 SD 11.90	$U = 6.00$; $P = 0.56$
VOSP			
Silhouettes	20.25 SD 2.63	21.75 SD 3.30	$U = 5.50$; $P = 0.47$
Cubes analysis	9.75 SD 0.50	9.75 SD 0.50	$U = 8.00$; $P = 1.00$
MADRS	2.50 SD 3.00	7.75 SD 2.87	$U = 1.00$; $P = 0.04^*$
EMIF-SEP (total)	39.57 SD 8.12	42.56 SD 15.74	$U = 4.50$; $P = 0.31$

PM12: Progressive matrices 12; RAVLT: Rey auditory verbal learning test; ROCF: Rey-Osterrieth Complex Figure; VOSP: visual object and space perception; MADRS: Montgomery and Asberg depression rating scale; EMIF-SEP: Echelle de mesure de l'impact de la fatigue. $^*\alpha = 0.05$.

groups was not taken into account in further analyses. Neuropsychological baseline's results showed impaired performances in only one attentional test for one patient in each group and low-average scores for one or two tests exploring executive functions for 3 patients of the experimental fMRI group and 2 patients of the control group.

Turning to AbM performances, for the first AI assessment, the mean number of internal details and the mean total ratings obtained during the free recall phase were 18.07 and 5.58, respectively, for the experimental fMRI group and 19.22 and 5.72, respectively, for the control group. For both groups, the scores were below the mean scores established with the healthy controls (see above). In regard to the *first* AI assessment, no significant difference for the mean number of internal details ($U = 8.00$; $P = 1.00$) nor the mean total ratings ($U = 5.00$; $P = 0.38$) during the free recall phase were observed between the two groups of patients. The same results were obtained for the specific probe phase (mean number of internal details: $U = 7.00$; $P = 0.77$ and mean total ratings: $U = 6.00$; $P = 0.56$). Likewise, the patients' mean scores for the specific probe phase (39.33 internal details for the experimental fMRI group and 39.00 internal details for the control group, with a mean total ratings of 11.12 for the experimental fMRI group and 10.58 for the control group), were below those obtained by the healthy controls (40.2 for the mean number of internal details and 12.47 for the mean total ratings).

In contrast, the scores on the second AI assessment showed significant differences between the experimental fMRI and the control groups for the free recall phase (mean

number of internal details: $U = 0.00$; $P = 0.02$ and mean total ratings: $U = 0.00$; $P = 0.02$) and for the specific probe phase (mean number of internal details: $U = 0.00$; $P = 0.02$ and mean total ratings: $U = 0.00$; $P = 0.02$). In every case, patients included in the experimental fMRI group performed significantly better than those in the control group during the second AI assessment, which corresponded to the post-facilitation examination for the experimental fMRI group.

With regard to the experimental fMRI group, the within-group analysis for before and after facilitation AI assessment highlighted a significant improvement of the patients' scores on the AI for all the measures of the free recall phase (number of internal details: $T = 104.50$; $P = 0.00$ and total ratings: $T = 95.00$; $P = 0.00$) and of the specific probe phase (number of internal details: $T = 81.00$; $P = 0.00$ and total ratings: $T = 155.50$; $P = 0.00$). Improvement of AI scores for the experimental fMRI group after facilitation condition was supported by the comparisons with those of the healthy controls. Indeed, the patient group showed a normalisation of their mean score for all the free recall phase measures (mean number of internal details = 36,9 versus 22.12 and mean total ratings = 9.39 versus 8.38) and for the specific probe phase (patients' mean number of internal details = 68.85 versus 40.2 and mean total ratings = 14.79 versus 12.47). Conversely, the comparison of the two sessions of AI assessment for the control group showed no significant differences during the free recall phase for the number of internal details ($T = 622.50$; $P = 0.70$) nor the total ratings ($T = 557.00$; $P = 0.94$). Also during the specific probe phase, no significant differences were observed for the number of internal details ($T = 571.50$; $P = 0.39$) nor the total ratings ($T = 545.00$; $P = 0.65$). For the second AI assessment of the control group, the results of the comparisons with the healthy controls' mean scores were parallel to their first AI examination, including mean scores below those of the healthy controls for the free recall phase (mean number of internal details = 20.6 versus 22.12 and mean total ratings = 5.83 versus 8.38). For the specific probe phase, an "apparent normalisation" was observed for the mean number of internal details (patients, 42.12 versus 40.2). Qualitative analysis revealed a punctual variation that resulted in an increased score (namely, one recollection). This observation together with the absence of a significant difference for the mean number of internal details between the two AI assessments for the control group, led us to rule out a normalisation process in this case. Moreover, no improvement was observed for the mean total ratings relative to normal controls (11.08 versus 12.47).

Based on the semi-structured interview, the patients' comments confirmed the positive effects of the facilitation programme during the second AI testing as well as in everyday life. The perceived benefits concerned a greater easiness of retrieval, a greater amount of details and better vividness during memory evocation. However, no change was mentioned concerning the emotional intensity. An effective treatment receipt seemed to be obtained since the patients acknowledged an easy use and transfer of this technique in their daily life functioning. Additionally, we also had the opportunity to get spontaneous comments by some patients' relatives who confirmed the benefits of the facilitation programme.

7. Neuroimaging Results

7.1. After versus before Facilitation Data. The paired t-test comparison we performed, for the contrast between past and control conditions, revealed that brain regions exhibiting a greater difference in activity between after and before facilitation fMRI sessions were primarily located in posterior regions. More precisely, after the facilitation programme, our patients elicited greater recruitment of the right cuneus (BA 19), the left inferior and superior occipital gyri (BA 18, 19), the left precuneus (BA 19) as well as of parts of the lateral temporal cortex, primarily on the left (BA 22, 38, 39) (see Table 3 and Figure 2).

7.2. Before versus after Facilitation Data. The reverse comparison indicated that regions showing a greater difference in activity before the facilitation programme were exclusively located in anterior parts of the brain: the two larger clusters of differential activity were indeed located in the prefrontal cortex (PFC), the first encompassing both dorsolateral and medial aspects of the PFC, the second corresponding to the dorsolateral PFC (BA 45, 9) (see Table 4 and Figure 3).

8. Discussion

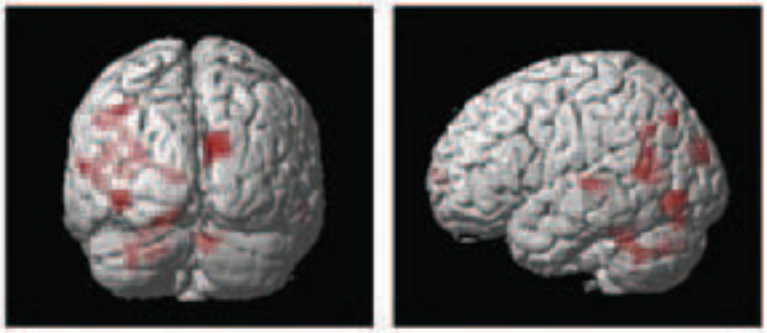
In the present preliminary study, we reported AbM performance improvement following a facilitation programme in four RR-MS patients and provided evidence of changes at the neural level. The clinical improvement was verified on the AI [39], which entailed obtaining French normative data. Importantly, our results are comparable to those reported by Levine et al. [39]. Based on these normative data, we showed a normalisation of patients' AbM free recall performances following the facilitation programme, which suggested a compensation of the initial retrieval deficit. We controlled for the potential learning effects of the AbM test by means of comparisons between an experimental fMRI group and a control group comprising also four RR-MS patients, who received no cognitive intervention but underwent the AI test twice.

Besides our previous study, [9] only three further works, to our knowledge, have tackled AbM assessment in MS. Our findings are in accord with Kenealy et al. [7] and they are contrary to those obtained by Paul et al. [6] and Müller et al. [8]. These two latter studies concluded that episodic personal memory was preserved in their MS patients either with no specification of the illness subtypes [6] or in defined RR-MS subtype [8]. The test used in these two works was the autobiographical memory interview (AMI), [49] which has been said to have a good sensitivity for the personal semantics section, but a poor sensitivity for the episodic incident section [50, 51]. Interestingly, Müller et al. [8] also found that patients with secondary progressive MS exhibited graded loss of personal incident memory on the AMI. However, the absence of such AbM deficit for RR-MS in Müller et al.'s [8] study could suggest that the

Table 3: Brain regions exhibiting a greater difference in activity during the after versus before rehabilitation fMRI session in the comparison between past and control conditions.

Brain Region	Coordinates (x, y, z)	Z-score	Cluster size
R Cuneus (BA 19)	(12, −94, 24)	4.62	179
L Inferior/Middle Occipital Gyrus (BA 18, 19)	(−36, −74, −4)	3.84	115
L Precuneus (BA 19)	(−36, −76, 44)	2.82	39
L Superior Temporal Gyrus/Middle Temporal Gyrus/Posterior Cingulate (BA 22, 39, 31)	(−60, −54, 12)	3.91	240
L Superior Temporal Gyrus (BA 41)	(−48, −22, 6)	3.59	66
R Middle Temporal Gyrus (BA 21)	(58, −2, −12)	3.31	21
R Superior Temporal Gyrus (BA 38)	(52, 18, −34)	3.25	22
R Superior Frontal Gyrus (BA 10)	(28, 64, 4)	3.31	47
R Thalamus	(12, −14, 12)	4.43	75
L Caudate/Thalamus	(−34, −32, 0)	3.05	29
L Cerebellum	(−34, −52, −32)	3.94	118
R Cerebellum	(8, −72, −28)	3.73	61
L Cerebellum	(−16, −68, −34)	3.63	25
L Cerebellum	(−16, −78, −20)	3.27	40

Talairach Coordinates Reported. BA: Brodmann's area; L: left hemisphere; R: right hemisphere.



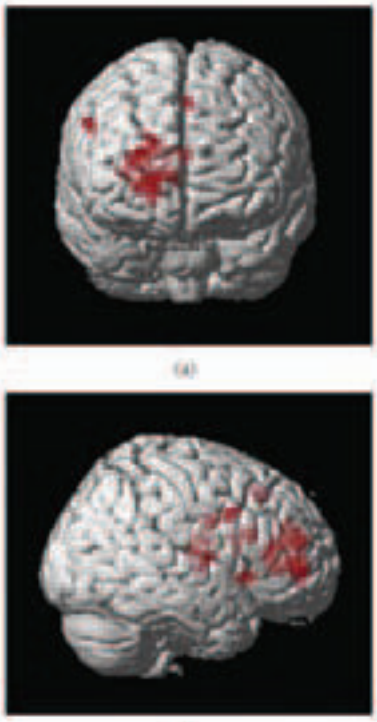
(a) (b)

Figure 2: Posterior (top) and right lateral (bottom) views of the group activation map showing increased differential activity after the facilitation programme, for the contrast between past and control conditions ($P = 0.01$, $k > 20$).

Table 4: Brain regions exhibiting a greater difference in activity during the before versus after rehabilitation fMRI session in the comparison between past and control conditions.

Brain Region	Coordinates (x, y, z)	Z-score	Cluster size
R Medial/Superior Frontal Gyrus (BA 10)	(16, 46, 8)	4.14	192
R Inferior/Superior Frontal Gyrus (BA 45, 9)	(34, 28, 10)	3.96	163
R Inferior Frontal Gyrus (BA 9)	(52, 4, 32)	3.37	23
R Anterior Cingulate (BA 33)	(2, 20, 18)	3.36	27
L Superior Frontal Gyrus (BA 8)	(−2, 26, 48)	3.04	29
R Insula (BA 13)	(40, −10, 2)	3.86	80
R Putamen	(20, 20, −4)	3.51	41
R Caudate/Cingulate Gyrus (BA 32)	(10, 10, 16)	3.39	54

Talairach Coordinates Reported. BA: Brodmann's area; L: left hemisphere; R: right hemisphere.



(a)

(b)

Figure 3: Anterior (top) and left lateral (bottom) views of the group activation map showing increased differential activity *before* the facilitation programme, for the contrast between past and control conditions ($P = 0.01$, $k > 20$).

AbM impairment in RR-MS is moderate and subtle and consequently, not readily detected by the AMI. These results and what they suggest are coherent with our results using a more stringent AbM test in RR-MS patients, which show mild to moderate AbM deficit. Although this is the first study, to our knowledge, to use the AI in MS, it has already been used in different neurological conditions like temporal lobe epilepsy [52], Alzheimer disease [53] or semantic dementia [50], showing the effectiveness of this autobiographical test in clinical settings.

Moreover, our preliminary fMRI findings are coherent with our retrieval-deficit hypotheses, involving a frontal lobe dysfunction [19, 20], in the AbM deficit in MS. Indeed, the enhanced cerebral activation during the construction phase of past recollections was observed in the bilateral prefrontal regions, only during the before facilitation session. This observation suggests a bi-lateralisation of cerebral activations since the AbM core cerebral network involves predominantly left cerebral regions [18]. Furthermore, it could reflect a compensation mechanism attempt, although insufficient to result in normal AbM performance. This suggestion is supported by studies exploring spontaneous functional reorganisation in MS, which show compensation mechanisms during cognitive task, but which are not always powerful enough to result in a complete preservation of cognitive functioning and consequently give rise to mild cognitive impairment [13, 54].

With regard to our fMRI results following the facilitation programme, they are coherent with the published reports dealing with the effects of various cognitive rehabilitation programmes on neural substrates in MS patients, that is, the presence of cerebral activation changes after cognitive intervention [15–17].

The present fMRI findings are coherent with our hypothesis since they showed that the improved AbM performance was accompanied by cerebral activation changes during the construction processes of personal past recollections. Importantly, changes in activation were observed in posterior cerebral regions, which are known to be associated with the mental processes we trained in our MS patients, that is, MVI [18]. Moreover, these changes were observed during the construction phase, which indicates the effective use of MVI to retrieve memories. This latter finding is consistent, not only with the global improvement of AbM scores after the facilitation programme but also, and above all, with the normalisation of AbM scores for all the patients during the free recall phase, which is a sensitive indicator of retrieval deficit. The posterior cerebral regions showing activation changes were, probably, under activated secondary to an insufficient PFC activation (see above). This suggestion is based on research using hemodynamic response function (HRF) analyses during AbM construction processes. Indeed, an earlier peak in the PFC relative to peaks reached in more posterior regions has been shown [19]. In cases in which the initial PFC HRF is subnormal, the HRF curve of the following (more posterior) regions could be affected and present under activation. This would also imply a possibility of "return to normal" either by a normalised initial HRF peak or by compensation mechanisms induced by cognitive training.

Beside these quantitative changes, the differences between the before and after facilitation semi structured interviews of patients showed positive effects in terms of a greater easiness of retrieval, a greater amount of details, a better vividness and an effective use of this technique in their daily life functioning. In addition, some patients' relatives confirmed the benefits of the facilitation programme in daily life. These last points are of importance considering that the primary goal of cognitive rehabilitation is to improve everyday life functioning in patients [55, 56].

While these preliminary findings are of interest, we are aware of some methodological limitations that restrict the conclusions that can be drawn from this study. Despite the statistical evidence obtained for behavioural and fMRI data, our sample of patients is small and replication of these results with a larger sample would be required. Additionally, a larger sample could also give the opportunity to explore more precisely the link between the changes observed for clinical and fMRI measures. With regard to the facilitation programme, the presence of a "nursing effect" cannot be ruled out until a "placebo" group of patients is included. Furthermore, long-term follow-up measures would be valuable to examine the robustness of the treatment effects.

Notwithstanding these limitations, our preliminary findings seem to be promising and encourage further investigations, all the more so that our results are in agreement with findings from previous studies which have explored the effect of cognitive rehabilitation on behavioural and neuroimaging measures in MS in diverse cognitive functions (attention, [15] executive functions and information processing [16] or anterograde memory [17]).

Finally, this preliminary study is, to the best of our knowledge, the first neuroimaging study focusing on AbM cognitive facilitation in MS patients. Expanding this type of intervention for MS patients seems necessary due to the deleterious impact of cognitive deficit in everyday life. This is particularly the case with AbM, considering its importance in everyday life functioning [57, 58].

Conflict of Interests

The authors report that they have no conflict of interests.

Acknowledgments

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STUDY 6

Ernst A, Blanc F, De Seze J and Manning L. Using mental visual imagery to improve autobiographical memory and episodic future thinking in relapsing-remitting multiple sclerosis patients: a randomised-controlled cognitive rehabilitation study. (In preparation)

MATERIAL AND METHODS

1. Participants

Sixty-two relapsing-remitting MS patients (following Polman et al.'s, 2011 diagnosis criteria) were initially recruited with an EDSS (Kurtzke, 1983) score ≤ 4 and no recent exacerbation of MS symptoms. 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 ≤ 15) had to be observed. These additional inclusion criteria was set to guarantee the further good completion of the facilitation programme and allowed the final inclusion of 40 MS patients, randomly assigned in three groups: (i) the experimental group, who aimed to probe the efficacy of our MVI facilitation programme; (ii) the placebo group, designed to verify the absence of a nursing effect; (iii) the stability group, who aimed to verify the absence of a learning effect in the AM/EFT assessment (see section 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.

Table 1. Demographical and clinical data. Mean (and standard deviation) for the three MS patients groups and the healthy controls

	MS patients groups			**Statistical analysis**
	Experimental (n = 17)	**Placebo (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 (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

2. Neuropsychological examination

A comprehensive neuropsychological baseline was administered in all MS patients during a first session, including the assessment of anterograde memory, executive functions, attentional abilities, language, information processing speed, visuoperceptual and visuospatial abilities, as well as the impact of fatigue on daily life activities (see Table 2 from the Results section and Ernst et al., 2012 for a complete description of the baseline tests).

In a second session, AM/EFT performance were assessed by means of the Autobiographical Interview (AI; Levine et al., 2002), adapted for the assessment of the EFT component and the use of cue-words (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 and to generate freely as many 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, which could plausibly occur in 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 the 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. It was followed by the specific probe phase, which is a structured interview to elicit 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 else episodic details unrelated to the central event). A qualitative assessment of the episodic re-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). In the same vein, the free recall and specific probe phases were analysed cumulatively across the phases. Then, for each participant, the number of internal and external

details, as well as the mean rating were averaged across the 12 or 15 past events, and across the five future events for the EFT conditions, for each recall phase.

The interrater reliability was verified for 10% of the past and future events, which were scored by a second scorer, following Levine et al.'s (2002) procedure. Coefficients for all measures showed high interrater reliability (between 0.82 and 0.99).

To characterise the potential impact of AM/EFT difficulties in MS patient's daily life functioning, but also to obtain information about the perceived benefit of facilitation, a semi-structured interview was conducted at the end of the AI in pre- and post-facilitation. This interview was adapted from the Memory Experiences Questionnaire (Sutin and Robins, 2007) and took on four main dimensions: vividness, accessibility, sensory details and emotional intensity of personal past and future events.

3. AM and EFT facilitation programmes

3.1. MVI facilitation programme

The MVI programme is a *tailor-made* (created by one of us, LM) and goal directed cognitive facilitation initially designed to improve AM retrieval deficit in MS patients. This programme is based on the ability to mentally construct scenes and to pay close attention to details in the mind's eye, which was used spontaneously when evoking personal recollections. In the context of the present study, the use of this programme was also extended to EFT.

The first step of the programme is to present its aim, content and functioning to the patient, which is of importance to promote its further use in daily life. In this perspective, a particular attention was paid 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; p. 836), which was verified at different times during the training process.

The MVI programme encompassed six two-hour sessions, once or twice per week (depending on the patient's availability), which were conducted, for the great majority of our patients, at their home. The rationale for this possibility was to make easier the sessions' following for the patients.

The programme comprised four steps, with mental visualisation exercises of increasing difficulties, during which the neuropsychologist provided guidance as much as necessary: (i) the *screening test* was based on three subtests from the "Imagery and Perception Battery" (Bourlon et al., 2009) and aimed to probe basic visual imaging abilities. (ii) The *external*

visualisation, included 10 verbal items to imagine and describe in as many details as possible (shape, colour, size, etc), with then the complementary visualisation of an action made with the item. (iii) The *construction phase* consisted in figuring out complex scenes bringing into play several characters and various scenario. Five items were proposed with, for each one, a first training step and a subsequent scene construction step sharing thematic similarities, allowing the patient to rely on the training to construct the further scene. (iv) The *self-visualisation* followed the same functioning as the previous step, but here, patients were asked to visualise themselves within a given scenario, to imagine it as though they were actually living the scene (see Ernst et al., 2012; 2013 for more a detailed description of the programme).

3.2. Verbal control programme

A narrative-oriented control programme was developed to present a match functioning with the MVI programme in terms of number/frequency of sessions and clinical 'ingredients', but with no a priori influence on AM and EFT. Based on texts, the general goal was to construct a discussion about the topic of the text, with different direction, through steps of increasing difficulty and with constant guidance from the neuropsychologist. Three steps were proposed: (i) the *external discussion* relied on the identification of influent variables on the understanding of a text (e.g. clarity, vocabulary used, etc) and comprised 20 texts. (ii) The *discussion construction* comprised five items, with for each one a 'training text' and a 'construction text', thematically related and about which an exchange was generated. (iii) The *self-involved discussion* has the same functioning as the previous step, but here, the discussion about the text was made by asking the patient to give his/her own opinion.

Here too, the great majority of the patients opted for at home sessions.

4. Procedure

Prior to inclusion, a first selection of MS patients was made based on the neuropsychological baseline examination (described above). The aim was to control for the absence of severe cognitive impairment other than AM/EFT deficit. To pursue, 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.

Besides, as mentioned above, only MS patients showing AM/EFT impairment were included in this study. The presence of an AM/EFT was determined based on the AI normative database previously used by Ernst et al. (2012), using the mean number of internal details and the mean total rating obtained during the free recall phase. Indeed, these measures assess the episodic re-experiencing ability, taking into account the sensitivity of the free recall to detect retrieval deficit. Thus, 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.

The final 40 MS patients were randomly assigned in the following three groups: (i) the *experimental MS group*, which aimed to assess the efficacy of the MVI facilitation programme; (ii) the *placebo MS group*, designed to verify the absence of a nursing effect and which followed the verbal control programme. For ethical reasons, all the patients from this group had the possibility to complete the MVI programme after the end of their participation; (iii) the *stability MS group* was set to verify the absence of a potential learning effect in the AM and EFT test. Thus, these patients underwent a second AI assessment after an interval of approximately two months (which corresponds to the average time between the two AI assessments for the others groups), with no intervention in between. Then, the MVI facilitation programme was proposed to all the patients from this last group. However, after the second AI assessment, due 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 to evaluate the maintenance of the benefit for the patients, but also to gather their impressions about the use and impact of the facilitation MVI strategy in their daily life. A diagram summarising the study design is presented in Figure 1.

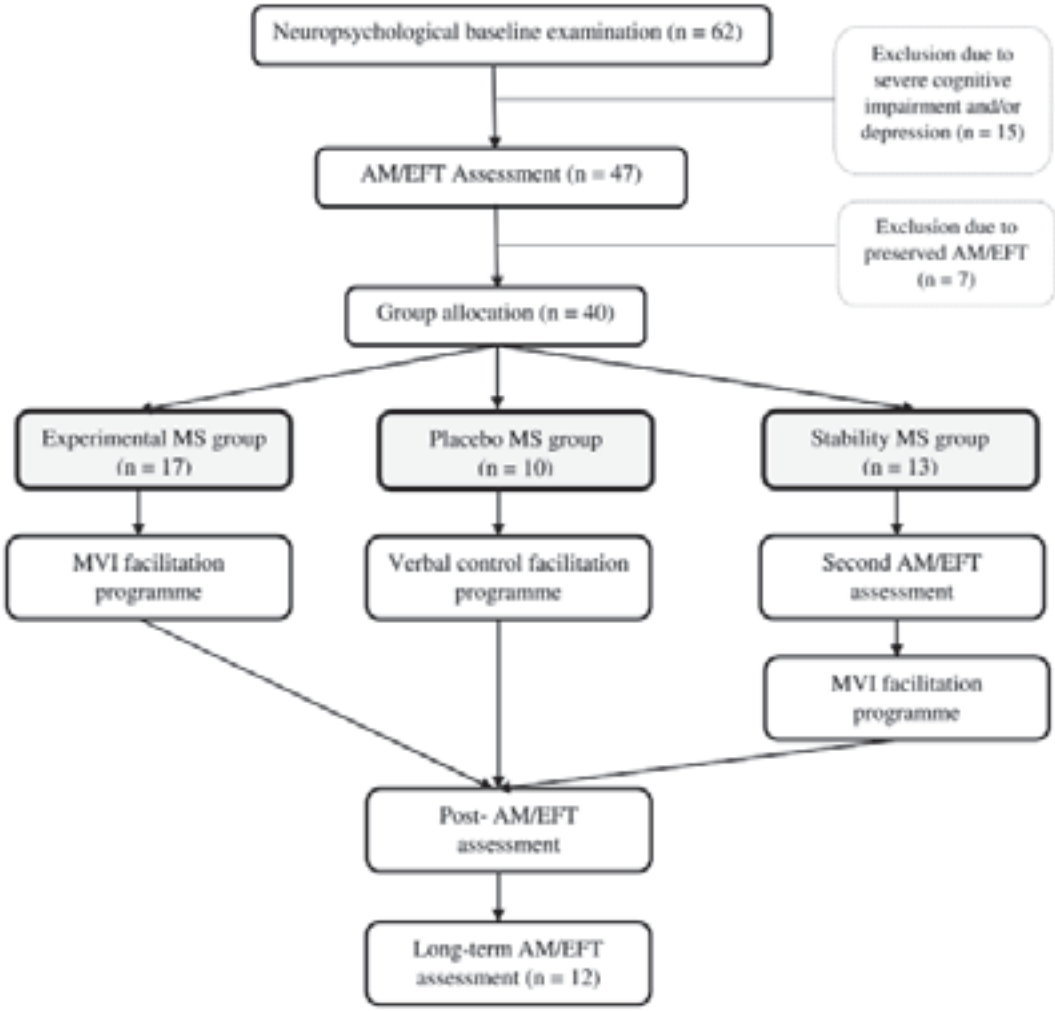

Figure 1. Study design diagram summarising the group allocation and progression through study phases

All the patients were blind to their allocation group. The original information about the study informed the patients of the constitution of different groups of participants, with two possible interventions, of which the efficacy was tested during the study. However, since each patient was followed by the same neuropsychologist (AE for 78% of patients) during his/her entire participation (from the baseline examination to the long-term follow-up), the neuropsychologist was not blind to the patient's allocation group. Nevertheless, to control the potential influence of the investigator awareness of the patients' group allocation, the second AI scorer was blind of the group membership, in every case. Moreover, AI reports were anonymised and 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).

5. Statistical analyses

In a first step, comparisons of the AI performance between the three groups of patients were conducted for the AM and the EFT condition in pre-facilitation to ensure that no statistical difference was evident at this stage. Repeated measures ANOVAs were run for: (i) the mean number of internal and external details with one between factor of Group (experimental, placebo, stability MS groups) and the two within factors of Details (internal, external) and of Phase (free recall, specific probe phases); (ii) the mean total rating, with the between factor of Group and the within factor of Phase.

A second set of analyses focused on the differential post-facilitation outcomes across the three groups. As the primary aim of the facilitation was to improve the episodic quality of past and future events, the post-facilitation analyses only focused on the internal details and the mean total rating. A repeated measures ANOVAs were thus applied with the between factor of Group, the within factor of Phase, and the additional within factor of Time (pre-, post-facilitation). Importantly, to obtain comparative data about the effect of the MVI and verbal programmes versus a potential learning effect in the AI, for the stability group, the results obtained at their second AI assessment (with no intermediate intervention) were here token into account. A subsequent analysis was then specifically conducted for the stability group to explore the benefit of the MVI programme completed by this group, thus taking into account their pre- and *actual* post-facilitation AI scores, by means of *t*-test for dependant samples, corrected for multiple comparisons ($p = 0.01$).

Finally, persistence of the benefit of the MVI programme was analysed, using the post-facilitation and six months re-assessment AI scores (internal details and total rating) by means of *t*-test for dependant samples, corrected for multiple comparisons ($p = 0.01$).

For all the comparisons, Tukey HSD post-hoc test (for unequal N) was used when appropriate.

RESULTS

Results from the neuropsychological baseline examination obtained by the patients from each group are presented in the Table 2. Equivalent performances between the groups of patients

were observed for all the cognitive domains explored. In relation to the clinical normative data from these tests, our MS patients showed impaired performance only in planning (tower of London) and cognitive estimation (eponymous task).

Table 2. Scores (mean and SD) for all MS patients by group for the neuropsychological baseline examination

	Experimental MS group	Placebo MS group	Stability MS 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 (.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-Osterrieth Complex Figure; VOSP: Visual Object and Space Perception; MADRS: Montgomery and Asberg Depression Rating Scale; EMIF-SEP: Echelle de Mesure de l'Impact de la Fatigue

1. Pre-facilitation performances in AM and EFT

1.1. AM condition: comparison of the three groups of MS patients

Regarding performance for the AM condition (Table 3), in pre-facilitation, no significant difference was observed between the three groups, irrespective of the type of details or the recall phase, $F(2, 37) = 1.81$, $p = 0.17$, $\eta^2_P = 0.08$. A main effect of Details was found, $F(1, 37) = 316.05$, $p < 0.001$, $\eta^2_P = 0.89$, revealing a higher number of external than internal details provided by the patients, whatever the recall phase ($p < 0.001$). A main effect of Recall phase was also observed, $F(1, 37) = 12.17$, $p = 0.001$, $\eta^2_P = 0.24$, showing that irrespective of the group or the type of details, higher scores were obtained for the specific probe phase in comparison with the free recall ($p < 0.001$). Neither Group x Details, nor Group x Recall phase, nor Details x Phase interaction were obtained.

Similar results were displayed for the mean total rating, with no significant difference between the groups of patients within both recall phases, $F(2, 37) = 1.67$, $p = 0.20$, $\eta^2_P = 0.08$. A main effect of Recall phase was showed, which highlighted a higher mean total rating after specific probing across the MS groups, $F(1, 37) = 508.01$, $p < 0.001$, $\eta^2_P = 0.93$. No Group x Phase interaction was found.

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

	FREE RECALL			FREE RECALL + SPECIFIC PROBE		
	Internal	External	Ratings	Internal	External	Ratings
Experimental MS group	13.80 (4.63)	21.27 (10.94)	4.04 (1.33)	29.96 (9.53)	38.38 (19.52)	8.77 (2.51)
Placebo MS group	15.73 (2.65)	20.83 (5.86)	4.38 (0.91)	37.01 (8.95)	(38.29 (14.89)	9.63 (1.73)
Stability MS group	17.25 (3.18)	27.60 (11.74)	5.20 (1.37)	36.05 (6.31)	46.93 (19.13)	9.72 (1.58)

1.2. EFT condition: comparison of the three groups of MS patients

Turning to the EFT performance (Table 4), taking into account the mean number of details (internal and external), although a main effect of Group reached initially the significance threshold, $F(2, 37) = 3.33$, $p = 0.05$, $\eta^2_P = 0.15$, post-hoc comparisons revealed no significant difference, neither between the experimental and the placebo groups ($p = 0.94$), nor between the experimental and the stability groups ($p = 0.07$), or the placebo and the

stability groups (p = 0.20), irrespective of the recall phase. A main effect of Details was observed, $F(1, 37) = 191.06$, $p < 0.001$, $\eta^2_P = 0.83$, with a greater amount of external than internal details provided by the patients across the recall phases ($p < 0.001$). A main effect of Recall phase was also observed, $F(1, 37) = 32.25$, $p < 0.001$, $\eta^2_P = 0.46$, showing an increase of the number of details (internal and external) during the specific probe, irrespective of the group ($p < 0.001$). No Group x Detail or Group x Phase interactions were significant.

Regarding the mean total rating, no significant main effect of Group was exhibited, $F(1, 37) = 0.59$, $p = 0.56$, $\eta^2_P = 0.03$, whatever the recall phase. However, a main effect of Recall phase was displayed, $F(1, 37) = 174.68$, $p < 0.001$, $\eta^2_P = 0.82$, with lower mean total rating for the free recall than for the specific probe phase ($p < 0.001$). The Group x Phase interaction did not reach the statistical threshold.

Table 4. Mean AI scores (and standard deviation) for the EFT condition for the three groups of MS patients in pre-facilitation

	FREE RECALL			**FREE RECALL + SPECIFIC PROBE**		
	Internal	External	Rating	Internal	External	Rating
Experimental MS group	9.31 (5.69)	18.04 (11.88)	2.97 (2.02)	21.53 (11.39)	36.00 (24.21)	7.00 (3.61)
Placebo MS group	8.58 (4.81)	22.56 (12.65)	3.04 (1.81)	20.28 (11.82)	38.96 (19.80)	6.48 (3.15)
Stability MS group	12.12 (5.08)	28.27 (11.85)	3.62 (1.85)	28.21 10.66)	52.12 (19.98)	7.94 (2.40)

2. Post-facilitation performance in AM and EFT

2.1. AM condition

2.1.1. Mean number of internal details

Regarding the post-facilitation AM assessment, mean number of internal details provided by each MS group over time are presented in the Figure 2.

Results highlighted in a first instance a main effect of Group, $F(2, 37) = 4.83$, $p = 0.01$, $\eta^2_P = 0.21$, and post-hoc test showed that, irrespective of the time of assessment and the recall phase, a higher performance was observed for the experimental group than for the stability group ($p = 0.02$), but similar results were obtained between the experimental and the placebo groups ($p = 0.15$) and between the placebo and the stability groups ($p = 0.86$).

A main effect of Time was displayed, $F(1, 37) = 72.87$, $p < 0.001$, $\eta^2_P = 0.66$, which revealed better performance in post-facilitation, whatever the group or the recall phase. A greater mean number of internal details was also noticed during the specific probe phase, irrespective of the group or the assessment time, as highlighted by a main effect of Recall phase, $F(1, 37) = 476.97$, $p < 0.001$, $\eta^2_P = 0.92$.

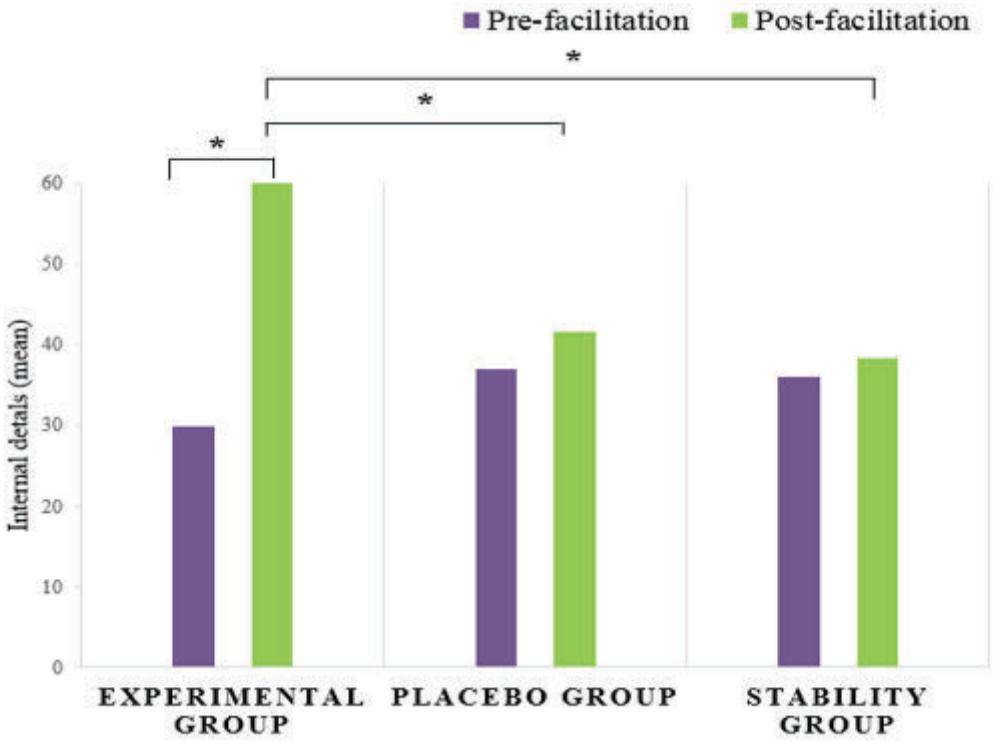

Figure 2. Mean number of internal details for the AM condition for the three groups of MS patients in pre- and post-facilitation (Group x Time interaction; * significant difference)

In parallel, a Group x Time interaction was found, $F(2, 37) = 37.41$, $p < 0.001$, $\eta^2_P = 0.67$. Post-hoc test revealed that, when taking into account the effect of time within each group, in the experimental group, a significant improvement of the mean number of internal details was observed in post-facilitation ($p < 0.001$), whereas no significant change was noticed in pre- and post-facilitation in the placebo ($p = 0.25$) or in the stability ($p = 0.93$) groups. Besides, focusing on the group differences across the pre- and post-facilitation sessions, the experimental group exhibited a greater number of internal details in post-facilitation than the placebo ($p < 0.001$) and the stability ($p < 0.001$) groups. However, no significant difference

was reported between the placebo and the stability group in post-facilitation regarding the number of internal details ($p = 0.93$).

Moreover, a Group x Time x Phase significant interaction was also obtained, $F(2, 37) = 10.92$, $p < 0.001$, $\eta^2_P = 0.37$. Post-hoc test revealed that within the experimental group, a higher number of internal details after facilitation was evident during the free recall ($p < 0.001$) and during the specific probe phase ($p < 0.001$). A similar result was evident in the placebo group, showing in post-facilitation an increase of the number of internal details during the free recall ($p < 0.001$) and the specific probe ($p = 0.04$) phases. Regarding the stability group, no significant change of the number of internal details was noticed during the free recall ($p = 0.84$) or the specific probe ($p = 0.68$) phases between the two AI sessions. Furthermore, the between group comparisons in post-facilitation across the recall phases showed similar results between the experimental and placebo groups during free recall ($p = 0.11$), but higher performance for the experimental group during the specific probe phase ($p = 0.007$). After facilitation, the experimental group also displayed a greater number of internal details than the stability group, for both free recall ($p = 0.003$) and specific probe ($p < 0.001$) phases. Finally, in post-facilitation, no significant difference was evidenced between the placebo and the stability groups for the number of internal details provided during the free recall ($p = 0.99$) and the specific probe phases ($p = 0.99$).

However, while no significant change between the two AI sessions was initially observed in the placebo group when considering both free recall and specific probe phases, but since differential results were highlighted for this group within the two recall phases relatively to the two others groups, raw data were more deeply analysed. This analysis revealed an inflated number of internal details in post-facilitation for one patient in the placebo group (mean number of internal details during the free recall: 40.75 versus 20.79 on average for the rest of the group). This patient evoked in post-facilitation three vivid memories of serious accidents, strongly meaningful for her, provoking this inflated score. Considering this last Group x Time x Phase interaction, with the exclusion of this patient, a significantly higher number of internal details remained evident after facilitation in the placebo group during the free recall phase ($p = 0.01$), but not during the specific probe phase ($p = 0.80$). However, in comparison with the experimental group, the placebo group displayed a lower number of internal details in the free recall ($p = 0.03$) and the specific probe phase ($p < 0.001$) in post-facilitation. Results of the comparison between the placebo and the stability groups remained unchanged.

2.1.2. Mean total rating

Performance for the mean total rating over time for the different groups of MS patients are displayed in the Figure 3, cumulatively for the free recall and the specific probe phases.

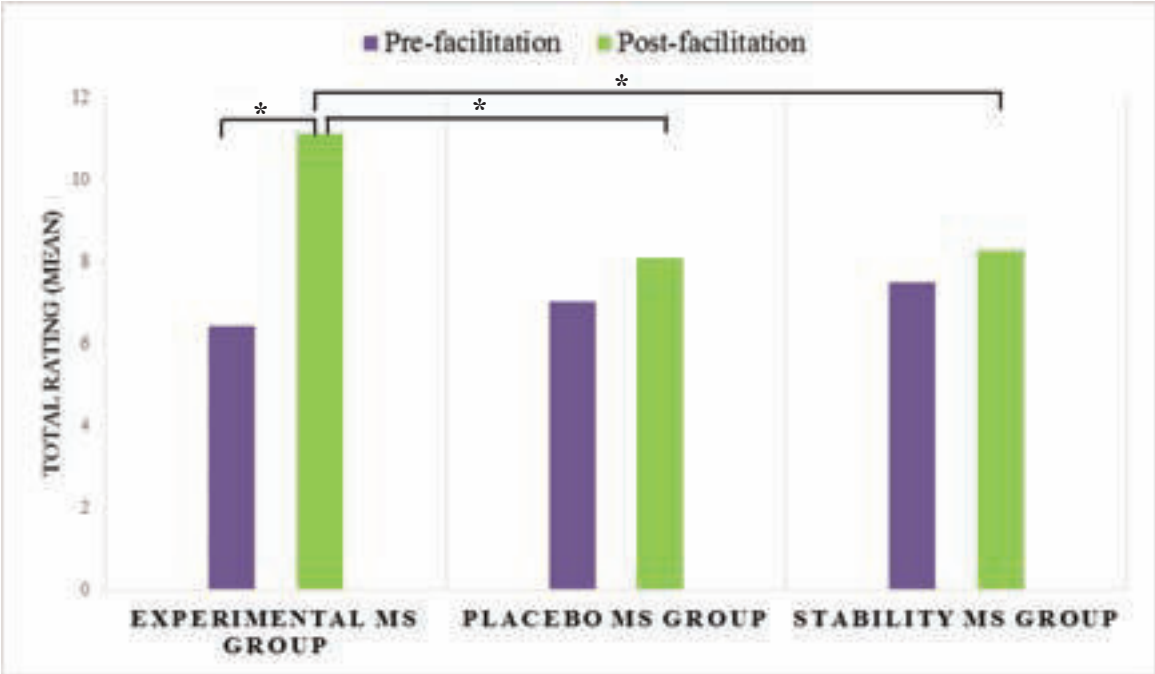

Figure 3. Mean total rating for the AM condition for the three groups of MS patients in pre- and post-facilitation (Group x Time interaction; * significant difference)

Irrespective of the time or the recall phase, no significant main effect of Group was found, $F(2, 37) = 2.51$, $p = 0.09$, $\eta^2_P = 0.11$. A main effect of Recall phase was observed, $F(1, 37) = 718.39$, $p < 0.001$, $\eta^2_P = 0.95$, with significantly greater total rating during the specific probe phase than during the free recall, for all the groups and time of assessment.

Differential results were obtained in pre- and post-facilitation, as evidenced by a main effect of Time, $F(1, 37) = 64.86$, $p < 0.001$, $\eta^2_P = 0.63$, with higher total rating after facilitation, whatever the group or the recall phases.

In addition, a significant Group x Time interaction, $F(2, 37) = 24.92$, $p < 0.001$, $\eta^2_P = 0.57$ was showed. Post-hoc test revealed that a significant increase of the mean total ratings was present after facilitation within the experimental group ($p < 0.001$). The same within group comparison showed no significant difference in pre- and post-facilitation for the placebo

group (p = 0.34) and for the stability group (p = 0.54) for the mean total rating. Between group comparisons showed that after facilitation, the experimental group obtained significantly higher mean total rating than the placebo (p = 0.002) and the stability groups (p = 0.001). However, no significant difference between the placebo and the stability groups was evidenced at the second AI assessment (p = 0.99).

No other statistical comparison reached the significance threshold.

2.2. EFT condition

2.2.1. Mean number of internal details

Turning to the influence of facilitation on EFT, the mean number of internal details provided by the patients over time are shown in the Figure 4.

A main effect of Group was obtained, $F(2, 37) = 11.92$, $p < 0.001$, $\eta^2_P = 0.39$, showing a higher number of internal details in the experimental group, relatively to the placebo ($p < 0.001$) and the stability (p = 0.10) groups, irrespective of the time or the recall phase. In opposition, the placebo and the stability groups showed equivalent performance (p = 0.35). The number of internal details was also subjected to a main effect of Recall Phase, $F(1, 37) = 233.54$, $p < 0.001$, $\eta^2_P = 0.86$, with higher performance during the specific probe phase, whatever the group and the time of assessment. An increase of the number of internal details was also demonstrated in post-facilitation, as highlighted by a main effect of Time, $F(1, 37) = 29.46$, $p < 0.001$, $\eta^2_P = 0.44$, irrespective of the group or the recall phase.

A significant Group x Time interaction was found, $F(2, 37) = 43.99$, $p < 0.001$, $\eta^2_P = 0.70$. Post-hoc test revealed that within the experimental group, a greater number of internal details was provided after facilitation ($p < 0.001$), but also relatively to the placebo and stability groups ($p < 0.001$ in both cases) at the same time of assessment. Regarding the placebo and the stability groups, neither a between group (p = 0.87), nor within group differences were observed in post-facilitation (p = 0.99 for both groups) for the mean number of internal details.

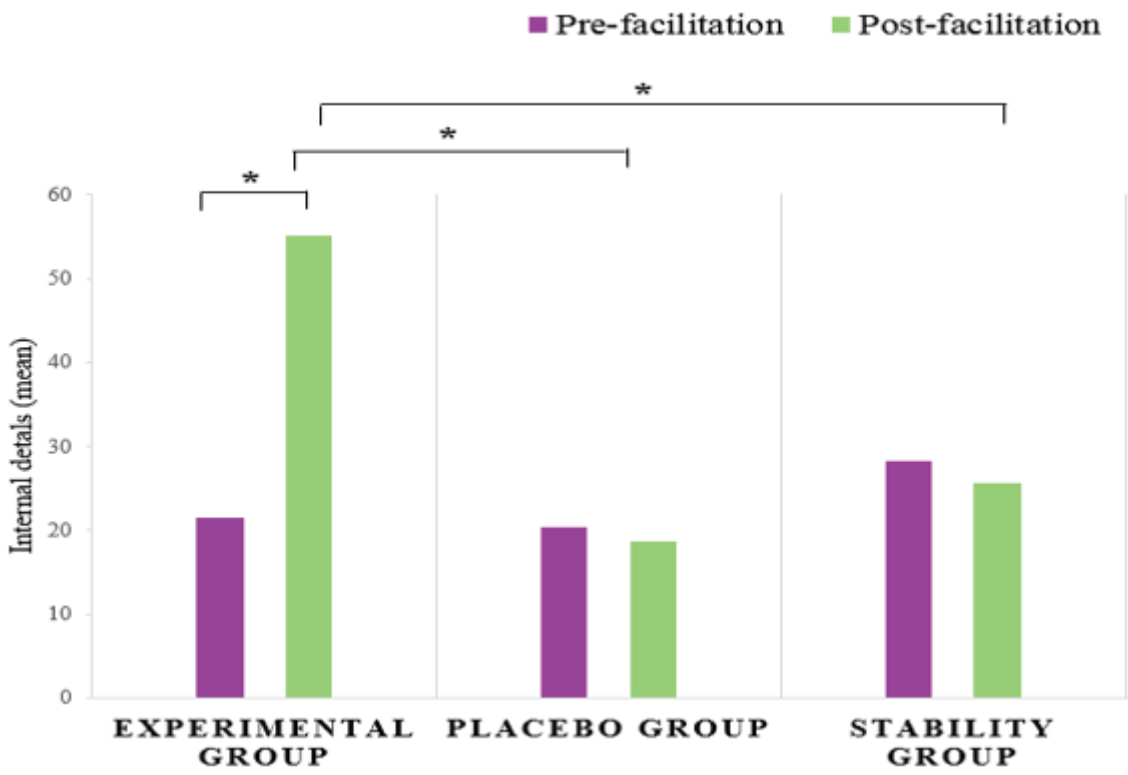

Figure 4. Mean number of internal details for the EFT condition for the three groups of MS patients in pre- and post-facilitation (Group x Time interaction; * significant difference)

A Group x Recall phase interaction reached the statistical threshold, $F(2, 37) = 3.66$, $p = 0.03$, $\eta^2_P = 0.16$. As highlighted by post-hoc test, while an increase of the number of internal details during the specific probe phase was displayed in each group ($p < 0.001$ in all cases), during the specific probe phase, the experimental group provided more internal details than the placebo ($p < 0.001$) and the stability ($p = 0.02$) groups, irrespective of the time of assessment. However, an equivalent number of details was observed between the placebo and the stability group across the recall phases ($p = 0.44$).

Finally, a three-way interaction Group x Time x Recall phase was found, $F(2, 37) = 13.91$, $p < 0.001$, $\eta^2_P = 0.43$. For the experimental group, post-facilitation performance were higher than in pre-facilitation for both the free recall ($p < 0.001$) and the specific probe phases ($p < 0.001$). No such difference between pre- and post-facilitation was replicated in the placebo group during the free recall ($p = 1.00$) or the specific probe phase ($p = 0.99$), or in the stability group, for the free recall ($p = 0.99$) and the specific probe phase ($p = 0.77$). Besides, in post-facilitation, the experimental group showed a greater number of internal details relatively to

the two other groups during the free recall ($p = 0.003$ for both groups) and during the specific probe phase ($p < 0.001$ for both groups). Conversely, no significant difference was exhibited between the placebo and the stability groups during the free recall ($p = 0.99$) and the specific probe phase ($p = 0.97$).

2.2.2. 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 Figure 5.

Statistical analysis evidenced a main effect of Group, $F(2, 37) = 7.47$, $p = 0.001$, $\eta^2_P = 0.28$, which showed that, irrespective of the time of assessment and the recall phase, a higher rating score was observed for the experimental group relatively to the placebo group ($p = 0.005$). In parallel, the stability group displayed equivalent performance than the experimental group ($p = 0.07$) and the placebo group ($p = 0.38$). A main effect of the Recall phase was also demonstrated, $F(1, 37) = 295.27$, $p < 0.001$, $\eta^2_P = 0.88$, showing an increase of the total rating during the specific probe phase, whatever the groups or the time of assessment.

Without considering the group affiliation or the recall phase, a main effect of Time was found, $F(1, 37) = 22.34$, $p < 0.001$, $\eta^2_P = 0.37$, with higher mean total rating attributed for the second EFT assessment. Nevertheless, as evidenced by the significant Group x Time interaction, $F(2, 37) = 30.04$, $p < 0.001$, $\eta^2_P = 0.61$, this result mainly reflects the increase of the total rating score in post-facilitation for the experimental group ($p < 0.001$), since no significant change between the two sessions of assessment was observed for the placebo and the stability groups ($p = 0.99$ in both cases). Furthermore, after facilitation, the experimental group obtained significantly higher mean total rating than the two other groups ($p < 0.001$ in both cases), whereas the placebo and the stability groups showed equivalent score ($p = 0.90$).

No other statistical comparison reached the significance threshold.

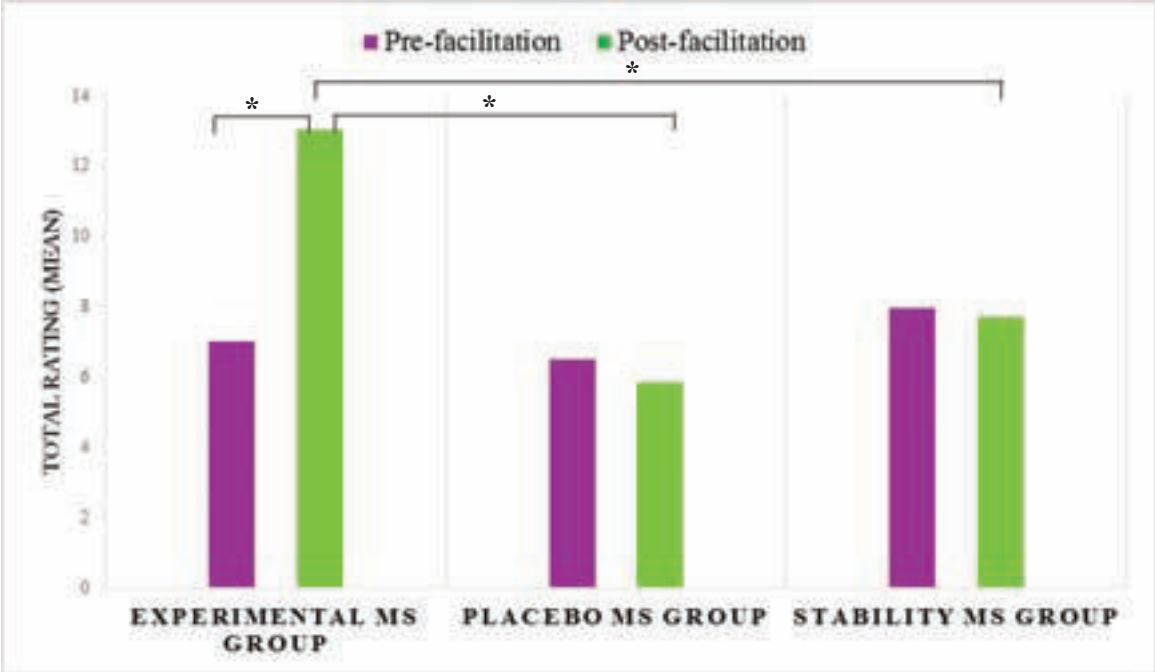

Figure 5. Mean total rating for the EFT condition for the three groups of MS patients in pre- and post-facilitation (Group x Time interaction; * significant difference)

2.3. Comparison of AM and EFT performance over time

The aim of this complementary statistical analysis was to examine potential difference between the evolution of scores before and after facilitation for the AM and the EFT conditions, within and between each group.

Regarding the mean number of internal details, no significant Condition (AM, EFT) x Group x Time interaction was found, $F(2, 37) = 2.37$, $p = 0.10$, $\eta^2_P = 0.11$. Similarly, the Condition x Group x Time x Phase interaction did not reach the statistical threshold, $F(2, 37) = 1.61$, $p = 0.21$, $\eta^2_P = 0.08$.

However, for the mean total rating, a significant Condition x Group x Time interaction was evidenced, $F(2, 37) = 3.70$, $p = 0.03$, $\eta^2_P = 0.16$. Post-hoc test showed that, within the experimental group, while in pre-facilitation higher rating was attributed for the AM than for the EFT condition ($p = 0.04$), no such difference remained in post-facilitation ($p = 0.97$). In opposition, within the placebo group, the total rating score for the AM condition was significantly higher than for the EFT condition in both pre- ($p = 0.005$) and post-facilitation ($p < 0.001$). The same was true for the stability group, which displayed greater total rating for the AM than for the EFT condition before ($p = 0.03$) and after facilitation ($p < 0.001$).

No significant Condition x Group x Time x Phase interaction was obtained, $F(2, 37) = 2.36$, $p = 0.10$, $\eta^2_P = 0.11$.

2.4. Post-facilitation results for the stability MS 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, relatively to pre-facilitation during the free recall phase, $t(9) = -6.31$, $p < 0.001$, as well as during the specific probe phase, $t(9) = -4.40$, $p < 0.001$. Similar results were obtained for the mean total rating, with higher scores in post- than in pre-facilitation for the free recall phase, $t(9) = -10.03$, $p < 0.001$, and the specific probe phase, $t(9) = -5.36$, $p < 0.001$.

Turning to the EFT performance, results showed an increase of the mean number of internal details provided in post-, relatively to pre-facilitation during both the free recall, $t(9) = -3.54$, $p = 0.006$, and the specific probe phases, , $t(9) = -3.69$, $p = 0.004$. In addition, higher mean total rating were obtained after facilitation (versus before facilitation) during the free recall phase, $t(9) = -5.01$, $p < 0.001$, and during the specific probe phase, $t(9) = -4.06$, $p = 0.002$.

2.5. Long-term follow up assessment

Descriptive results of the mean AI scores obtained immediately after the facilitation and at the long-term follow up for the AM and EFT conditions were presented in Table 5.

The analysis of the robustness of benefits after the MVI programme over time showed that, regarding the AM condition, no significant difference was observed between the mean number of internal details during provided during the free recall phase, $t(11) = 0.04$, $p = 0.96$, or during the specific probe phase, $t(11) = 0.19$, $p = 0.84$. In the same manner, the comparison of the mean total rating obtained immediately after the facilitation and six months later showed no significant difference between the measures during the free recall, $t(11) = -0.84$, $p = 0.41$, or the specific probe phase, $t(11) = 0.57$, $p = 0.57$.

Turning to the EFT condition, a good maintenance of the mean number of internal details between the post- and the long-term assessment was observed for the free recall phase, $t(11) = 2.17$, $p = 0.06$, whereas for the specific probe phase, a significant decrease was noticed at six months, $t(11) = 3.98$, $p = 0.002$. Regarding the mean total rating, similar results were obtained

between the post- and the six months assessment during the free recall phase, $t(11) = 0.53$, $p = 0.60$, and the specific probe phase, $t(11) = 2.83$, $p = 0.02$.

Moreover, in every case, whatever the temporal direction, the mean number of internal details and the mean total rating remained above the normative data threshold during the free recall and the specific probe phases.

Table 5. Mean AI scores (and standard deviation) for the AM and EFT condition obtained immediately in post-facilitation and at the six months long-term follow-up

	POST-FACILITATION		**FOLLOW UP**	
	Free recall	Free recall + SP	Free recall	Free recall + SP
AM condition				
Internal details	38.12 (8.11)	63.73 (12.51)	37.97 (12.03)	62.76 (16.91)
Rating	9.15 (1.43)	13.72 (1.54)	9.59 (2.11)	13.49 (1.49)
EFT condition				
Internal details	34.28 (22.79)	56.96 (21.70)	27.38 (16.61)	45.95 (21.34)
Rating	7.88 (2.39)	12.83 (2.02)	7.51 (3.27)	11.30 (2.53)

2.6. 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 during the free recall phase were compared to the normative scores. On the 27 MS patients (experimental and stability groups) which underwent the MVI programme, 25 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. Semi-structured interview

3.1. Pre-facilitation comments

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

Regarding their comments about the AI assessment, for the AM condition, patients mainly evoked a difficulty to retrieve/select a specific event, with further difficulties to provide details about memories. This was accompanied with little emotional reviviscence and an impression of 'emotional distance' with their memories. Moreover, when assessing the vividness and the mental visual quality of their memories, patients mainly evoked 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 because of forgetting, or difficulty to remember some precise details, or simply doubts about their memories.

Concerning EFT, similar feedbacks than for the past events were generally obtained about the testing session, with a particular difficulty to find future events standing out from memories. This conducted 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. In regard to everyday life, contrary to memories, very few patients provided concrete examples of daily life difficulties explicitly related to EFT. Most of them did not have the impression to really project themselves (at least in a voluntary and conscious manner) into elaborated future scenarios.

3.2. Post-facilitation comments

3.2.1 MVI facilitation programme

For the MS patients which underwent the MVI programme (experimental and stability groups), comments in post-facilitation 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 clear and dynamic 'mental films', with reports about motions present in their mental simulations. Furthermore, a greater emotional intensity and re/pre-living were mentioned by the patients (also qualitatively noticed by the neuropsychologist during event's evocation). No differential effect of the programme on AM and EFT was observed by the patients, but a similar degree of difficulty was here underlined between AM and EFT conditions.

Regarding the benefit in daily life, the same observations than during the AI testing were recounted. However, a few patients admitted that they needed more time, to take a more

global overview of the benefit in day to day life. An effective treatment receipt seemed to be obtained since the patients acknowledged an easy use and transfer of this technique in their daily life functioning. Additionally, spontaneous feedbacks of some patient's 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 mindless for them. Beyond that, at six months, several patients also reported that they had a more general feeling of self-confidence in social and professional situations, with a kind a new 'dynamic' and ownership regarding their life. Illustrations of some patients' comments are provided in the Appendix 1.

3.2.2. Verbal control programme

Although no statistical evidence of performance improvement was noticed in the placebo group, a general feeling that the second AI testing was easier than the first one was reported by these patients. This last point 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 were reported. Nonetheless, several patients acknowledged that they felt more vigilant and that the programme helped them to better focus their attention when required.

DISCUSSION

Cognitive impairment have a clear impact in everyday life functioning of MS patients, appealing for the development of new cognitive rehabilitation techniques (Chiaravalloti and DeLuca, 2008). Beyond the common cognitive impairment described in MS (see DeLuca and Nocentini, 2011 for a review), an AM impairment related to a retrieval deficit has been documented in relapsing-remitting MS patients (Ernst et al., 2012; 2013). Moreover, in these pilot studies, Ernst and co-workers showed that this AM impairment could be alleviated with a MVI based facilitation programme. Considering both the strong relationships between AM and EFT (see Schacter et al., 2012 for a review) and the evidence of a conjoint AM and EFT deficit in MS (see Study 1), one remaining question concerned the possibility to improve both AM and EFT functioning in MS patients.

Thus, the aim of the present study was to probe the efficacy of the MVI facilitation programme on both AM and EFT in the context of a randomised controlled clinical trial. As expected, our results demonstrated 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. No differential improvement was observed for AM and EFT, which seemed to benefit from the MVI programme in a similar manner. Besides, the great majority of our MS patients showed a normalisation of their AM and EFT scores, relatively 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 observed at the long-term follow up. However, regarding the long-term reassessment, while EFT scores remained stable during the free recall, the mean number of internal details provided during the specific probe phase showed a decrease, even if this score remained superior to the normative threshold. However, no significant change of the qualitative EFT episodic richness was noticed during this same phase at six months. Regarding this result, it seems that the general improvement of EFT performance remained present, but that specific cueing had less influence on the number of episodic details imagined at six months. Clinically, considering that the last step of the MVI programme focused on the construction of self-involved fictitious scenes, with a guidance of the neuropsychologist during scene construction through questions, it is possible that immediately after facilitation, following the dynamic established through the programme, an inflated performance could be observed for the specific probe phase of EFT. This same effect could not be observed for AM condition, since for the past, contrary to the future events, restrictions regarding the details associated to the event are present to correspond accurately to the initial event.

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 undergone twice in an equivalent timeframe, with no intervention in between. Importantly, the cognitive intervention was then offered to the patients from this last group and it seemed that the waiting period between the two AI assessments had no deleterious impact on the way these patients benefited from the MVI programme.

Furthermore, this AM/EFT improvement was not likely related to a simple 'nursing effect', since MS patients who followed a sham verbal facilitation programme showed no clear evidence of enhanced performance in post-facilitation. Moreover, AI scores from the placebo group remained below those obtained by MS patients after the MVI programme, but equivalent to those obtained by the stability group.

To the best our knowledge, this study is the first to focus on both AM and EFT cognitive rehabilitation in a clinical population. Our conclusive results obtained with MS patients, and especially the successful transfer of the benefits in everyday life, were probably favoured by several points. First of all, AM and EFT are by essence omnipresent in our life and rely on personal real-life events. Secondly, while selecting MS patients with only mild cognitive impairment other than AM/EFT deficit could appear restrictive, this selectivity of the deficit promotes on the contrary the good completion of the facilitation sessions, but also the further good use and integration of strategy (Evans et al., 2003). It does not mean that the MVI programme could not be used at all in MS patients presenting initially with different and more extensive cognitive impairment, but rather than, in the context of a rehabilitation process, the enhancement of other cognitive abilities (e.g. attentional abilities) should be addressed before and only then, the use of the MVI programme should eventually be reconsidered.

More generally, we hope that this study and the evidence of a possible enhancement of AM/EFT functioning within a short-time programme could encourage future investigations in different clinical settings. This could be of particular clinical interest considering the central roles of AM and EFT in everyday life, and more generally in well-being (Schacter et al., 2012).

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Appendix 1. Post-facilitation comments from patients following the MVI facilitation programme

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.

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".

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".

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".

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 detailed 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. Before I wouldn't dare. So, all in all, it has restored my self-confidence, that's what I feel… It's true, I can assert myself again".

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”.

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”.

STUDY 7

Ernst A, Blanc F, Gounot D, De Seze J, and Manning L. Benefits from an autobiographical memory facilitation programme in relapsing-remitting multiple sclerosis patients: a clinical and functional neuroimaging study. (In preparation)

MATERIAL AND METHODS

1. Participants

Twenty relapsing-remitting MS patients (following Polman et al.'s, 2011 diagnosis classification) corresponding to the following inclusion criteria were recruited: an EDSS (Kurtzke, 1983) score ≤ 4, no recent exacerbation of MS symptoms, right-handedness, 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 AM performance in the context of only potential mild to moderate cognitive impairment in attention and/or executive functions (see Behavioural assessment section). All these MS patients participated to a larger study (described in Study 6) dealing with autobiographical memory (AM) and episodic future thinking (EFT) facilitation and were randomly allocated in two groups (see below). 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.

Table 1. Demographical and clinical data. Mean (and standard deviation) for the MS patients groups

	MS patients groups		**Statistical analysis**
	Experimental (n = 10)	**Placebo (n = 10)**	
Age in years	38.40 (10.94)	37.40 (8.84)	$t = 0.22$; $p = 0.82$
Education in years	13.40 (2.22)	12.20 (1.55)	$t = 1.40$; $p = 0.17$
Sex (female/male)	6/4	9/1	$\chi^2 = 2.40$; $p = 0.12$
EDSS	2.45 (1.73)	2.45 (1.40)	$t = 0.00$; $p = 1.00$
Duration of MS (in years)	11.10 (11.03)	10.60 (5.66)	$t = 0.12$; $p = 0.90$
Number of DMD treatment	1.00 (0.00)	1.00 (0.00)	_
Verbal Intellectual Quotient	98.70 (16.98)	97.00 (11.21)	$t = 0.26$; $p = 0.79$

DMD = Disease Modifying Drug

2. Clinical data and procedure [1]

All the MS patients underwent first a complete neuropsychological baseline examination, followed by the AM assessment by means of the AI (Levine et al., 2002). The same AI

[1] The present section is generally dealt with, since it has been described in the 'Material and Method' section of Study 6 (p. 213-218)

normative database (Ernst et al., 2012) and procedure were used to determine the presence of AM impairment and thus, the inclusion of a given patient.

Two groups of MS patients were constituted: (i) the *experimental MS group*, which followed the MVI facilitation programme, and (ii) the *placebo MS group*, which underwent the verbal control programme (see Study 6 for the description of the programmes).

The same study design as in the Study 6 was followed, with the exception of the introduction of neuroimaging sessions. For both groups of patients, a pre-facilitation fMRI session was conducted immediately after the pre-facilitation AI assessment. This fMRI session was followed by the implementation of the facilitation programme and then, with the subsequent post-facilitation second AI assessment. The post-facilitation fMRI session was then carried out within the two weeks following the post-AI.

3. Neuroimaging data

3.1. fMRI tasks

Two fMRI tasks were proposed during scanning, each of them comprising two versions for the pre- and post-facilitation sessions. The presentation of these two versions was counterbalanced between the two sessions.

The *experimental task* (i.e. past events condition) consisted in the evocation of unique personal past events, contextually specific, occurring over minutes or hours, but no more than one day. Importantly, the similarity to the event's characteristics of the AI was reminded to promote the good understanding of the task by the patient and examples were provided. Thirty-two pairs of words were proposed to elicit memories (e.g. 'countryside-sun'), covering the same life periods proposed in the AI. The participants were instructed about the fact that the cue-words were meant to generate a past event in a flexible way. Based on Addis et al. (2007) we distinguished two phases in the evocation of memories: (i) the construction phase corresponding to the search and initial building up of the event, and (ii) the elaboration phase corresponding to the retrieval of details associated with the event. Each trial had a fixed duration of 20 sec modulated by the subject's response: once a memory was retrieved, the subject had to press button 1 on the response box to mark the end of the construction phase. The remaining time was devoted to the elaboration phase, during which a central fixation cross was presented.

The *control task* was a categorical task that included 32 pairs of words, with which participants had to construct a sentence for the construction phase (e.g. with 'cap-green': 'The boy in the street wears a green cap'). Once the sentence was constructed, they had to press button 1 to pursue with the elaboration phase during which the participants had to keep the same sentence structure, replacing the two given cue-words by words of the same semantic category (e.g. 'The boy in the street wears a red beret'). The fixed duration for each trial was also 20 sec.

Prior to scanning, the procedure was explained to the patients and we asked them to complete a computerised practice trial for each task in order to be familiar with the experimental design and timing of presentation of the stimuli. Taking into account the time constraints imposed by fMRI, a particular attention was paid to this practice trial to optimise the further completion of the task by the patients during the scanning session. Thus, the practice was repeated as much as necessary before entering the scan and complementary explanations were provided if necessary. Additionally, a more specific practice trial for the control task was carried out to instruct the participants to avoid any self-involvement in the sentence construction (no sentences with 'I '), since this process was of interest in the experimental condition. This instruction and training procedure was followed for both fMRI sessions, even if the session functioning was familiar to the patient in the post-facilitation.

The experimental design was organised in four sequences of 8 stimuli, per condition, beginning systematically with the control task and then alternating between past events and control task conditions. In both tasks, each trial was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s). At the beginning of each sequence, the name of the condition was displayed on the screen for 6 s. The presentation order of stimuli within each condition was 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.

Immediately following scanning, a post-scan questionnaire was completed for the past events condition, in order to verify the adequacy of the responses and to exclude invalid trials before data analysis. Thus, for each past event, participants had to indicate the type of memory (unique, repetitive, extensive, semantic or absent), the spatial and temporal context of the

event, the emotional valence and rate, on two visual-analogue scales of 10 cm, the difficulty of access and the amount of details.

fMRI acquisition

Images were acquired using a 3T MRI scanner (Siemens Verio). The image sequence was a T2*-weighted echo planar imaging sequence (TR=2500 ms, TE=30 ms, Matrix=64x64 voxels, FOV=224 mm, FA=90). The anterior commissure and posterior commissure were identified in the mid-sagittal slice, and 45 contiguous slices (each 4mm thick) were prescribed parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

4. Statistical analyses

4.1. Behavioural data

The good matching between the two groups of patients was verified for all the neuropsychological baseline measures by means of *t*-tests.

Regarding the AM performance, as the present study focused on the influence of cognitive facilitation in episodic AM re-experiencing, only the mean number of internal (i.e. strictly episodic) and the mean total rating obtained during the free recall phase of the AI were considered in the further statistical analyses. Repeated-measures ANOVA were run to explore potential differences in the AI scores between the groups (Group factor) of patients in pre- and post-facilitation (Time factor).

Post-scan variables were also compared between the groups of patients in pre- and post-facilitation by means of repeated-measures ANOVA. All the analyses were followed by Tukey HSD post-hoc test when necessary.

4.2. Neuroimaging analyses

Regarding neuroimaging data, pre-processing and statistical analyses were conducted using SPM5 software (Friston et al., 1995). 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 both conditions, 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 sec-duration that started immediately after the end of the construction phase by button press. The 10 sec-duration interval for the elaboration phase was fixed to allow a sufficient time interval to detail search and the trials with a construction phase longer than 10 sec were excluded.

Since a great overlap of the cerebral activations for specific and repetitive past events was previously observed (Addis et al., 2004) both unique and repetitive events were included as regressors of interest.

In the context of the general linear model, statistical parametric maps were generated for each subject in both sessions (pre- and post-facilitation) for the further contrasts: past construction > control task construction and past elaboration > control task elaboration. These statistical parametric maps were then entered into a second level of analysis for the comparison between the two groups of patients (two-sample *t*-test) and within the sessions, before and after the facilitation, in each group (paired *t*-test). The significance threshold was set at $p = 0.001$ (uncorrected for multiple comparisons), with a minimum extent threshold of 20 contiguously activated voxels for all the analyses.

RESULTS

1. Behavioural results

Equivalent performance for all the neuropsychological baseline tests were observed for the two groups of patients (Table 2), with the exception of the delayed recall of the ROCF for which a lower performance was obtained by the placebo group. Nevertheless, as their mean score remained in the normal interval provided by normative data of the test (Fasteneau et al., 1999), this difference was not further taken into account. In comparison with the normative data provided for each test, impairment in planning and cognitive estimation abilities were shown in our MS patients.

Table 2. Scores (mean and SD) for all MS patients by group for the neuropsychological baseline examination

	Experimental MS group	Placebo MS group	Statistical analysis
Verbal IQ	98.70 (16.98)	97.00 (11.21)	$t = 0.26$; $p = 0.79$
PM12	9.70 (1.15)	8.80 (1.93)	$t = 1.26$; $p = 0.22$
RAVLT			
-Total mean number of words	11.96 (1.17)	12.30 (1.17)	$t = -0.64$; $p = 0.52$
-Delayed recall	13.90 (1.10)	13.20 (2.30)	$t = 0.86$; $p = 0.39$
ROCF			
-Copy	35.20 (1.13)	35.50 (0.85)	$t = -0.66$; $p = 0.51$
-Immediate recall	27.50 (7.27)	22.05 (4.53)	$t = 2.01$; $p = 0.06$
-Delayed recall	27.45 (6.37)	21.80 (4.69)	$t = 2.25$; $p = 0.03$*
Deno 100	97.60 (3.02)	95.90 (4.79)	$t = 0.94$; $p = 0.35$
Stroop			
-Colours (T score)	44.90 (8.76)	47.90 (10.39)	$t = -0.69$; $p = 0.49$
-Words (T score)	45.20 (5.80)	47.40 (8.85)	$t = -0.65$; $p = 0.51$
-Interference(T score)	47.90 (11.58)	48.60 (7.47)	$t = -0.16$; $p = 0.87$
-Interference (T score)	50.10 (8.87)	50.10 (7.05)	$t = -0.00$; $p = 1.00$
Months back (sec)	13.20 (6.92)	10.40 (2.80)	$t = 1.18$; $p = 0.25$
Tower of London			
-Score	8.90 (1.85)	8.30 (2.11)	$t = 0.67$; $p = 0.50$
-Time indices	20.60 (4.06)	17.60 (3.63)	$t = 1.74$; $p = 0.09$
Brixton (number of errors)	15.30 (5.37)	12.40 (4.25)	$t = 1.33$; $p = 0.19$
Cognitive Estimation Task	4.70 (3.71)	4.50 (1.96)	$t = 0.15$; $p = 0.88$
Verbal Fluency			
-Categorical	20.70 (4.90)	20.00 (4.92)	$t = 0.31$; $p = 0.75$
-Phonological	12.30 (3.16)	12.00 (.30)	$t = 0.20$; $p = 0.83$
Information Processing Speed			
-Cognitive	50.00 (10.18)	52.20 (7.00)	$t = -0.56$; $p = 0.58$
-Motor	42.40 (8.42)	53.50 (10.95)	$t = -1.25$; $p = 0.22$
-Error percentage	1.31 (2.77)	3.57 (3.73)	$t = -1.53$; $p = 0.14$
-Corrected score	55.66 (11.87)	57.09 (7.84)	$t = -0.31$; $p = 0.75$
VOSP			
-Silhouettes	22.80 (4.10)	22.80 (2.66)	$t = -0.00$; $p = 1.00$
-Cubes Analysis	9.80 (0.42)	9.9. (0.32)	$t = -0.60$; $p = 0.55$
MADRS	6.00 (5.63)	6.00 (3.89)	$t = -0.00$; $p = 1.00$
EMIF-SEP (total)	47.49 (18.09)	40.24 (10.16)	$t = 1.10$; $p = 0.28$

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

* Significant difference

1.1. AM performance

Regarding the mean number of internal details provided during the free recall phase of the AI, repeated-measures ANOVA evidenced a main effect of Group, $F(1, 18) = 5.78$, $p = 0.02$, showing a higher score for the experimental group. A main effect of Time was also obtained, $F(1, 18) = 74.60$, $p < 0.001$, with a greater number of internal details provided in the post-facilitation AI assessment. However, as highlighted by the significant Group x Time interaction, $F(1, 18) = 21.11$, $p < 0.001$, these effects mainly reflected the greater AI score obtained by the experimental group's patients in post-facilitation ($p < 0.001$), which was also significantly higher than those obtained by the patients from the placebo group after facilitation ($p = 0.03$). Importantly, no significant difference between the two groups was present before facilitation ($p = 0.92$). A greater number of internal details was observed in post-facilitation for the placebo group ($p = 0.04$), relatively to the pre-facilitation session. However, analysis of the raw data put forward a particularly inflated score for one patient from this group, who provided three very striking and meaningful memories in post-facilitation, explaining this inflated score.[2] When conducting the same analysis by excluding this patient, no significant change of the mean number of internal details was observed after facilitation in the placebo group ($p = 0.14$). An illustration of number of details' changes across the sessions for each group of patient is provided in the Figure 1.

A similar pattern of results was obtained with the mean total rating, with a main effect of Group, $F(1, 18) = 7.38$, $p = 0.01$, with higher total rating for the experimental group. A main effect of Time was also replicated, $F(1, 18) = 81.60$, $p < 0.001$, revealing an increase of the mean total rating in post-facilitation. A significant Group x Time interaction was found, $F(1, 18) = 23.56$, $p < 0.001$, revealing significantly higher total rating in post-facilitation for the experimental group ($p < 0.001$), but also higher total rating than the placebo group after facilitation ($p < 0.001$). Importantly, equivalent total rating was observed between the two groups in pre-facilitation ($p = 0.97$). Again, for the placebo group, a significant increase of the mean total rating was observed in a first instance ($p = 0.03$), but when conducting the same analysis without the aforementioned patient with inflated scores, this difference between the two sessions of assessment did not remain significant ($p = 0.10$).

[2] Corresponding to the same patient already mentioned in the Study 6

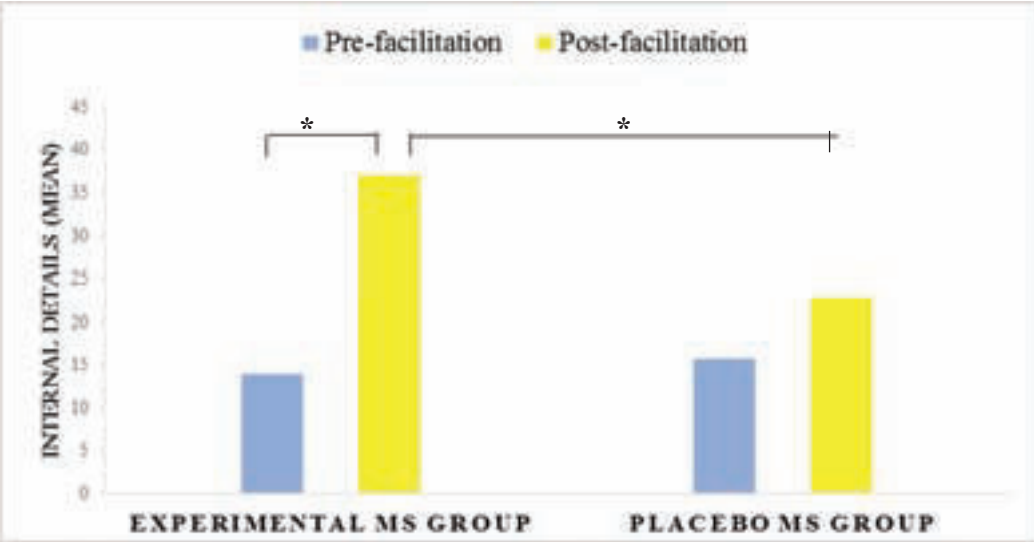

Figure 1. Mean number of internal details provided by the two groups of patients in pre- and post-facilitation sessions during the free recall phase (* significant difference)

1.2. Post-scan results

Results obtained for each MS group for all the post-scan variables, before and after facilitation, are summarised in the Table 3.

Direct comparison of the mean construction reaction time showed no significant main effect of group, $F(1, 18) = 0.04$, $p = 0.83$, and no main effect of time, $F(1, 18) = 1.17$, $p = 0.29$, as well as no significant Group x Time interaction, $F(1, 18) = 3.44$, $p = 0.08$.

Regarding the type of events provided during scanning, no main effect of group was observed, $F(1, 18) = 2.84$, $p = 0.10$. However, a significant main effect of time was highlighted, $F(1, 18) = 6.00$, $p = 0.02$, showing a higher number of responses for the post-facilitation session. The type of events was also subjected to a main effect, $F(4, 72) = 109.51$, $p < 0.001$, with Tukey post-hoc HSD test revealing a greater number of unique events in comparison with the four other types ($p < 0.001$ in all the cases). An equivalent number of repetitive, extended, semantic and absent event was found (significance threshold between $p = 0.06$ and $p = 99$). A significant Time x Event type interaction was displayed, $F(4, 72) = 13.77$, $p < 0.001$, which revealed an increased number of unique events in post-facilitation ($p < 0.001$), while the number of events from the four other categories remained stable between the two sessions (repetitive: $p = 0.25$; extended: $p = 0.99$; semantic: $p = 0.99$; absent: $p = 0.99$). Neither a significant Group x Time nor a Group x Event type interactions were obtained.

Table 3. Post-scan measures: Mean and (SD) for the experimental and placebo MS patient groups

	Experimental group		**Placebo group**	
	PRE	POST	PRE	POST
Construction RT	4.83 (1.31)	5.50 (1.13)	5.16 (0.77)	4.98 (1.18)
Type of events				
Unique	17.20 (7.22)	23.80 (5.26)	17.00 (6.34)	22.90 (4.22)
Repetitive	4.20 (1.93)	2.70 (4.59)	5.50 (5.35)	2.40 (2.41)
Extended	1.10 (1.37)	0.40 (1.26)	0.90 (1.85)	0.40 (1.26)
Semantic	1.20 (2.14)	0.30 (0.67)	1.80 (3.29)	1.30 (2.49)
Absent	2.90 (3.95)	1.80 (1.98)	2.90 (2.88)	3.10 (3.34)
Emotional valence				
Positive (%)	62.24 (13.73)	57.04 (15.05)	53.99 (16.51)	51.99 (15.57)
Neutral (%)	15.42 (14.94)	21.63 (14.01)	24.28 (16.06)	23.95 (19.16)
Negative (%)	22.33 (9.36)	21.36 (7.17)	21.72 (11.29)	23.65 (6.85)
Difficulty of access	6.92 (1.96)	6.87 (2.22)	7.51 (1.16)	7.07 (1.25)
Amount of details	5.11 (1.73)	5.95 (2.08)	6.64 (0.76)	6.26 (1.72)

RT = reaction time; PRE / POST: pre-facilitation / post-facilitation

A significant main effect of emotional valence was also noticed, $F(2, 36) = 35.2$, $p < 0.001$, with a higher rate of positive events in comparison with neutral and negative events ($p < 0.001$ in both cases), while an equivalent number of neutral and negative events were observed ($p = 0.97$). No other significant difference regarding the emotional valence was exhibited.

Concerning the two visual analog-scales, for the difficulty of access, no main effect of group, $F(1, 18) = 0.33$, $p = 0.57$, or main effect of time, $F(1, 18) = 0.56$, $p = 0.46$, reached the significance statistical threshold. The same is true for the amount of details scale, with no significant main effect of group, $F(1, 18) = 1.88$, $p = 0.18$, as well as no significant main effect of time, $F(1, 18) = 0.56$, $p = 0.46$. No significant interaction effect was observed.

2. Neuroimaging results

Prior to intervention, no significant difference was observed in the cerebral activity during the past event construction and elaboration (versus the respective control task phase) between the experimental and placebo patient groups.

2.1. Experimental group: influence of the MVI facilitation programme on AM cerebral network

Focusing on the experimental group, increased cerebral activations were displayed in post- versus pre-facilitation during the construction phase of past events (Table 4; Figure 1). In particular, enhanced neural activity was observed in the left medial frontal gyrus (BA 10/11) as well as in the right thalamus. The reverse contrast (pre- versus post-facilitation) showed no significant brain activation.

Table 4. Enhanced cerebral activations in post-facilitation (versus pre-facilitation) for the past events construction (versus control task construction) in the experimental group

Brain region	**Coordinates (x, y, z)**	***Z*-score**
Past construction (vs control construction)		
L Medial frontal gyrus (BA 10)	(-10, 56, 16)	4.08
L Medial frontal gyrus (BA 11)	(0, 36, -12)	3.72
R Thalamus	(8, -16, 8)	3.63

Talairach Coordinates Reported; $p < 0.001$ uncorrected; k = 20 voxels

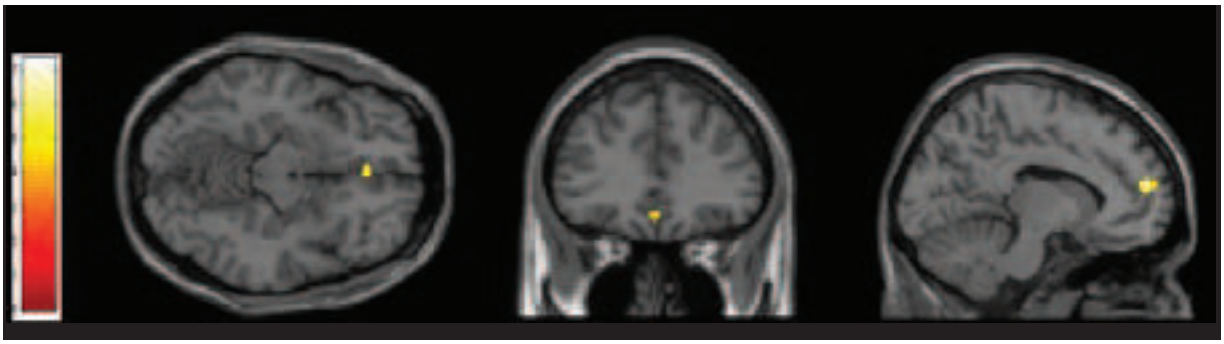

Figure 1. Increased brain activations in post-facilitation (versus pre-facilitation) for the experimental group during the construction phase of past events ($p < 0.001$ unc; $k = 20$ voxels)

Regarding the elaboration phase of past events, no significant activated voxels survived to the statistical threshold in post-facilitation, in comparison with pre-facilitation. In contrast, the examination of brain regions more activated in the pre- versus the post-facilitation revealed greater activations in the left middle (BA 11) and inferior (BA 47) frontal gyrus, but also in the left fusiform (BA 37) and the left cerebellum (Table 5; Figure 2).

Table 5. Differential cerebral activations in pre-facilitation (versus post-facilitation) for the past events elaboration (versus control task elaboration) in the experimental group

Brain region	**Coordinates (x, y, z)**	***Z*-score**
Past elaboration (vs control elaboration)		
L Middle frontal gyrus (BA 11)	(-42, 52, -14)	4.22
L Inferior frontal gyrus (BA 47)	(-16, 28, -16)	4.14
L Fusiform gyrus (BA 37)	(-38, -48, -8)	4.02
L Cerebellum	(-12, -38, -24)	4.58

Talairach Coordinates Reported; $p < 0.001$ uncorrected; k = 20 voxels

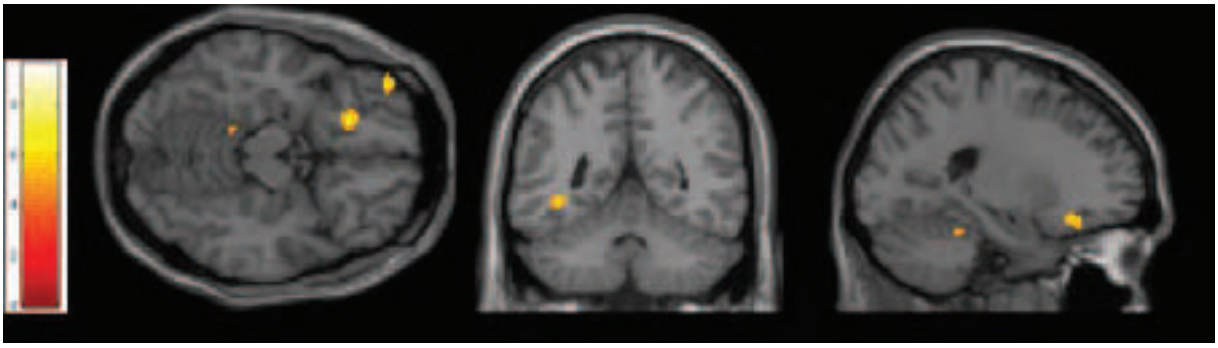

Figure 2. Cerebral regions showing greater activations in pre-facilitation (versus post-facilitation) in the experimental group during the elaboration phase of past events ($p < 0.001$ unc; $k = 20$ voxels)

2.2. Placebo group: influence of the verbal facilitation programme on AM cerebral network

Turning to the placebo group, no greater brain activation was exhibited during the past events construction phase in post-facilitation, relatively to pre-facilitation. On the contrary, the

reverse contrast pre- versus post-facilitation showed a cluster of activation in the left medial frontal gyrus (BA 10; *xyz*: -10, 60, 4; *Z*-score: 3.55).

During the elaboration phase, this group of patients showed enhanced cerebral activation in the left superior frontal gyrus (BA 6; *xyz*: -8, 38, 60; *Z*-score: 3.86) after facilitation. No greater activation was observed for the pre-facilitation in relation to the post-facilitation session.

DISCUSSION

The aim of the present randomised placebo controlled study was to examine the effectiveness of a MVI-based cognitive facilitation programme on AM, by exploring both clinical and cerebral functional changes in relapsing-remitting MS patients.

Importantly, only MS patients presenting initially with AM deficits were included in this study. Prior to intervention, the two groups of patients were well matched, in terms of demographical, neuropsychological baseline scores, AM performance, post-scan measures, and for the cerebral network sustaining impaired AM. Moreover, after facilitation, since equivalent behavioural performance were obtained by the two groups during scanning, differential brain activations observed after facilitation would more likely reflect the effect of facilitation, rather than a difference of performance per se between the patient groups.

At the clinical level, the patients who underwent the MVI programme showed a significant AM improvement in terms of increased number of episodic details provided spontaneously after facilitation during the second AI. This finding is in agreement with our previous studies using the same MVI programme (Ernst et al., 2012; 2013; see also Study 6). In contrast, the completion of our sham verbal control programme did not result in AM improvement. This result excludes potential nursing effect.

As expected, the benefit of the MVI programme was also present at the neural level as indicated by the cerebral activation changes following the facilitation intervention. In particular, the enhanced brain activations observed in the left medial frontal regions corresponded to the construction phase of memories. Indeed, this brain region, pertaining to the anterior portion of the cortical midline, is strongly involved in AM since it sustains self-referential process (Northoff et al., 2006). Based on the concept of subjective sense of remembering (Greenberg and Rubin, 2003), we suggest that the MVI programme, by

improving detail retrieval, and hence, the episodic quality of memories and their reviviscence, led to a greater sense of self-involvement and reliving memories in our MS patients.

Surprisingly, following the MVI programme, no greater brain activations were noticed during the further elaboration phase of past events. This finding could seem counterintuitive at first glance, since at the clinical level, a greater number of episodic details was clearly observed. Nonetheless, any attempt of interpretation should take into account cerebral regions which showed a greater activity in the pre-facilitation, in that they mainly included left lateral frontal regions and the fusiform gyrus. These brain regions have been reported during spontaneous functional changes during AM recollection in MS patients (see Study 2). Likewise, we showed in the same work that the activity of the fusiform gyrus was modulated by the amount of episodic details, showing increased neural activity associated with the growing amount of details. These enhanced activations were interpreted as a compensatory mechanism attempt, i.e., neural effort to compensate brain damage (Hawellek et al., 2011), insufficient though to result in normal AM performance. These considerations lead us to interpret the post-facilitation decreased activations as indicating a diminished effortful process necessary to the retrieval of further details associated to memories.

However, contrary to our main hypothesis and the results of our preliminary study (Ernst et al., 2012), no greater recruitment of the posterior brain regions following the MVI programme was observed. Indeed, as the aim of our facilitation programme was to emphasise the role of MVI in AM, we hypothesised that the brain regions sustaining MVI, namely the posterior brain regions (Greenberg and Rubin, 2003) would, as a consequence, show increased neural activity after facilitation. Since signs of spontaneous brain plasticity were already displayed before facilitation, with enhanced activations in the posterior brain regions in MS patients (see Study 2), one open question concerns the possibility to "add up" supplementary compensation mechanisms in these same brain regions in terms of cerebral activity further increase. Nevertheless, since the enhanced posterior brain activations before facilitation were insufficient to achieve normal AM performance, it is likely that our MVI programme impinges on 'qualitative' rather than 'quantitative' changes. If this were the case, the necessary brain support would take place in the form of functional connectivity changes in the posterior brain regions after facilitation. This suggestion is based on previous investigations conducted in MS patients that demonstrated the presence of functional connectivity changes induced by cognitive rehabilitation (Leavitt et al., 2012; Parisi et al., 2012). In this context,

further investigations, including the examination of functional connectivity changes, will be carried out to have a more in-depth understanding of the functional and cerebral changes induced by the MVI programme.

Regarding our placebo group, as aforementioned, clinically, our verbal control programme did not result in an AM improvement. However, cerebral activation changes were noticed in pre- and post-facilitation, particularly during the elaboration phase, in which a locus of enhanced activation was observed in the lateral frontal region after facilitation. It is well established that the frontal lobe plays a role in the organisation of information (Lezak et al., 2004). Thus, taking into account that our verbal sham programme put the emphasis on the structuration and the organisation of information, this increased frontal activation could reflect the actual attempt to use the strategy taught through the sham programme, but with no obvious clinical benefit on AM. Although unexpected, this result could be of importance since it likely reflects the good compliance to the placebo condition. In parallel, decreased activity was shown in the medial frontal region in post-, relatively to the pre-facilitation in our placebo patients during the initial generation of memories. However, presently, this last finding remained difficult to interpret and further investigations would be required.

Despite these clinically relevant findings, there are some methodological limitations like the small sample size. This issue is of particular importance, owning to the heterogeneity between MS patients, particularly regarding the neuropathological processes involved in MS, the lesion burden and the localisation of brain lesions. Despite the fact that we set stringent inclusion criteria at the behavioural level to constitute strictly homogeneous groups, and that the experimental group patients showed individually a benefit of the MVI programme, subtle cerebral changes are bound to have occurred, but difficult to be detected. Issues like the presence of undetected changes and/or the likelihood of induced brain plasticity being slightly differently manifested from one patient to another are most challenging. Furthermore, another limitation of our study is the absence of a fMRI long term follow-up of these cerebral functional changes.

To conclude, to the best of our knowledge, with the exception of our preliminary investigation (Ernst et al., 2012), this study is the first demonstrating the occurrence of an induced brain plasticity in the context of AM in MS patients, but also more generally in a clinical population. Since this study highlighted a behavioural improvement of AM functioning, accompanied with changes at the neural level, in a short time period of six cognitive

facilitation sessions, we hope that these positive results could promote further and wider studies aiming to the development of new therapeutic interventions to enhance everyday life functioning of patients.

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STUDY 8

Ernst A, Blanc F, De Seze J, Gounot D, and Manning L. Increased activations in key brain regions after a facilitation programme for episodic future thinking in relapsing-remitting MS patients. (In preparation)

MATERIAL AND METHODS

1. Participants

Seventeen relapsing-remitting MS patients (following Polman et al.'s, 2011 diagnosis classification) were selected from a group of MS patients involved in a broader study on autobiographical memory and episodic future thinking facilitation (see Study 6). Selected patients corresponded to the following inclusion criteria: an EDSS (Kurtzke, 1983) score ≤ 4, no recent exacerbation of MS symptoms, right-handedness, 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 potential mild to moderate cognitive impairment in attention and/or executive functions (see the Neuropsychological assessment section).

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.

Table 1. Demographical and clinical data. Mean (and standard deviation) for the MS patients groups

	MS patients groups		**Statistical analysis**
	Experimental (n = 10)	**Placebo (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	$\chi^2 = 1.31$; $p = 0.25$
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)	_

DMD = Disease Modifying Drug

2. Clinical data and procedure [3]

In a first session, a comprehensive neuropsychological baseline examination was completed by all the MS patients. Then, in a second session, EFT assessment was conducted by means of the AI (Levine et al., 2002), in an adapted version allowing the assessment of EFT (Addis et al., 2009). To determine the presence of an EFT impairment, the mean number of internal

[3] See 'Material and Methods' of the Study 6 (p. 213-218) for a complete description of the EFT task, procedure and content of cognitive facilitation programmes

details and mean total ratings supplied during the free recall phase by the MS patients were compared to our AI normative database.

Following the inclusion, MS patients were randomly assigned in two groups: (i) the *experimental MS group*, which followed the MVI facilitation programme, and (ii) the *placebo MS group*, which underwent the verbal control programme.

In addition to the study design described in the Study 6, two functional neuroimaging sessions were introduced: the first one before the beginning of the facilitation programme (immediately after the pre-facilitation AI assessment) and the second one after the facilitation programme (in the days or weeks following the post-facilitation AI examination).

3. Neuroimaging session

3.1. fMRI tasks

Since the patients underwent the fMRI session twice, in pre- and post-facilitation, the fMRI tasks were developed in two versions, and presented in counterbalanced order within the patients.

The *experimental task* (i.e. future events condition) consisted in the evocation of unique personal and plausible future events, contextually specific, occurring over minutes or hours, but no more than one day. To promote the good completion of the task by the patients, the similarity to the event's characteristics of the AI was reminded and examples were provided. A particular emphasis was also made on the importance to create a novel future event and to avoid the direct use of memories or parts of them to simulate future events. Thirty-two pairs of words were proposed to generate future events (e.g. 'friend-meeting') that could possibly occur within the next year. The participants were instructed about the fact that the cue-words were meant to generate a past event in a flexible way. Based on Addis et al. (2007) we distinguished two phases in the simulation of future events: (i) the construction phase corresponding to the search and initial imagination of a given event, and (ii) the elaboration phase corresponding to the imagination of details associated with the event. Each trial had a fixed duration of 20 sec modulated by the subject's response: once a memory was created, the subject had to press button 1 on the response box to mark the end of the construction phase. The remaining time was devoted to the elaboration phase, during which a central fixation cross was presented.

The *control task* was a categorical task that included 32 pairs of words, with which participants had to construct a sentence for the construction phase (e.g. with 'ring-diamond': 'The woman wears a ring with a big diamond'). Once the sentence was constructed, they had to press button 1 to pursue with the elaboration phase during which the participants had to keep the same sentence structure, replacing the two given cue-words by words of the same semantic category (e.g. 'The woman wears a necklace with a big emerald'). The fixed duration for each trial was also 20 sec.

Prior to scanning, instructions were followed by a computerised practice trial for each task that was completed by the patient as many times as necessary to get familiarised with the experimental design and timing of presentation of the stimuli, notwithstanding which, complementary explanations were provided if necessary. Additionally, a more specific practice trial for the control task was carried out to instruct the participants to avoid any self-implication in the sentence construction (no sentences with 'I '), since this process was of interest in the experimental condition. Importantly, these instructions and procedure were similarly conducted for both fMRI sessions, even if the session functioning was familiar to the patient in the post-facilitation.

The experimental design was organised in four sequences of 8 stimuli, per condition, beginning systematically with the control task and then alternating between future events and control task conditions. In both tasks, each trial was followed by short periods of fixation that were of jittered duration (mean duration = 1.5 s, range = 1 to 2 s). At the beginning of each sequence, the name of the condition was displayed on the screen for 6 s. The presentation order of stimuli within each condition was 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.

Following scanning, a questionnaire was completed for the future events condition, in order to verify the adequacy of the responses and to exclude invalid trials before data analysis. Thus, for each past event, participants had to indicate the type of event (unique, repetitive, extensive, semantic or absent), its spatio-temporal context, the emotional valence and rate, on two visual-analogue scales of 10 cm, the difficulty of imagination and the amount of details.

fMRI acquisition

Images were acquired using a 3T MRI scanner (Siemens Verio). The image sequence was a T2*-weighted echo planar imaging sequence (TR=2500 ms, TE=30 ms, Matrix=64x64 voxels, FOV=224 mm, FA=90). The anterior commissure and posterior commissure were identified in the mid-sagittal slice, and 45 contiguous slices (each 4mm thick) were prescribed parallel to the anterior commissure and posterior commissure plane to cover the whole brain.

4. Statistical analyses

4.1. Behavioural data

A first set of analyses focused on the neuropsychological baseline scores to verify the good matching between the two groups of patients by means of *t*-tests.

A second set dealt with the EFT performance, with a focus on its episodic component, which was assessed by the mean number of internal details (i.e. strictly episodic) and the mean total rating. Moreover, only the scores obtained during the free recall phase were taken into account for this analysis. Repeated-measures ANOVA were run to explore potential differences in the AI scores between the groups of patients before and after facilitation.

Post-scan variables were also compared between the groups of patients, in pre- and post-facilitation, by means of repeated-measures ANOVA.

When appropriate, all the analyses were followed by Tukey HSD post-hoc test (for unequal N).

4.2. Neuroimaging analyses

Regarding neuroimaging data, pre-processing and statistical analyses were conducted using SPM5 software (Friston et al., 1995). 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 both conditions, 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 sec-duration that started immediately after the end of the construction phase by button press. The 10 sec-duration interval for the elaboration phase was fixed to allow a

sufficient time interval to detail imagination. Thus, the trials with a construction phase longer than 10 sec were excluded.

Since a great overlap of the cerebral activations for specific and repetitive future events was previously observed (Addis et al., 2011) both unique and repetitive events were included as regressors of interest.

In the context of the general linear model, statistical parametric maps were generated for each subject in both sessions for the further contrasts: future construction > control task construction and future elaboration > control task elaboration. These statistical parametric maps were then entered into a second level of analysis for the comparison between the two groups of patients (two-sample *t*-test) and within the sessions, before and after the facilitation, in each group (paired *t*-test). The significance threshold was set at $p = 0.001$ (uncorrected for multiple comparisons), with a minimum extent threshold of five contiguously activated voxels for all the analyses.

RESULTS

1. Behavioural results

Regarding the neuropsychological baseline examination, our MS patients showed preserved general cognitive abilities, with the exception of impaired performance in planning and cognitive estimation. A single difference was noticed between the two groups of patients for the motor speed, patients from the experimental group being slower. However, the score obtained by this last group remained in the normal range and this difference was thus not considered in the further analysis.

Table 2. Neuropsychological baseline examination: Mean and (SD) for the two groups of MS patients

	Experimental MS group	Placebo MS group	Statistical analysis
Verbal IQ	98.70 (16.98)	99.14 (12.56)	t = -0.05; p = 0.95
PM12	9.70 (1.15)	9.00 (2.00)	t = 0.91; p = 0.37
RAVLT			
-Total mean number of words	11.96 (1.17)	12.17 (1.34)	t = -0.34; p = 0.73
-Delayed recall	13.90 (1.10)	13.14 (2.67)	t = 0.81; p = 0.42
ROCF			
-Copy	35.20 (1.13)	35.57 (0.78)	t = -0.74; p = 0.46
-Immediate recall	27.50 (7.27)	23.64 (4.22)	t = 1.25; p = 0.22
-Delayed recall	27.45 (6.37)	23.00 (5.17)	t = 1.52; p = 0.14
Deno 100	97.60 (3.02)	95.42 (5.79)	t = 1.01; p = 0.32
Stroop			
-Colours (T score)	44.90 (8.76)	48.00 (11.25)	t = -0.63; p = 0.53
-Words (T score)	45.20 (5.80)	46.71 (7.56)	t = -0.46; p = 0.64
-Interference(T score)	47.90 (11.58)	48.71 (8.88)	t = -0.15; p = 0.87
-Interference (T score)	50.10 (8.87)	50.57 (7.39)	t = -0.11; p = 0.90
Months back (sec)	13.20 (6.92)	9.57 (2.07)	t = 1.33; p = 0.20
Tower of London			
-Score	8.90 (1.85)	8.71 (2.42)	t = 0.17; p = 0.86
-Time indices	20.60 (4.06)	16.85 (4.09)	t = 1.86; p = 0.08
Brixton (number of errors)	15.30 (5.37)	12.71 (4.60)	t = 1.03; p = 0.31
Cognitive Estimation Task	4.70 (3.71)	4.57 (2.22)	t = 0.08; p = 0.93
Verbal Fluency			
-Categorical	20.70 (4.90)	18.71 (5.05)	t = 0.81; p = 0.42
-Phonological	12.30 (3.16)	11.71 (3.25)	t = 0.37; p = 0.71
Information Processing Speed			
-Cognitive	50.00 (10.18)	53.42 (8.14)	t = -0.73; p = 0.47
-Motor	42.40 (8.42)	53.85 (10.82)	t = -2.45; p = 0.02*
-Error percentage	1.31 (2.77)	3.00 (3.16)	t = -1.16; p = 0.26
-Corrected score	55.66 (11.87)	58.55 (9.13)	t = -0.54; p = 0.59
VOSP			
-Silhouettes	22.80 (4.10)	22.85 (1.77)	t = -0.03; p = 0.97
-Cubes Analysis	9.80 (0.42)	10.00 (0.42)	t = -1.24; p = 0.23
MADRS	6.00 (5.63)	6.14 (4.74)	t = -0.05; p = 0.95
EMIF-SEP (total)	47.49 (18.09)	38.94 (9.71)	t = 1.33; p = 0.27

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

* Significant difference

1.1. EFT performance

Turning to EFT assessment, statistical analyses focusing on the mean number of internal details highlighted in a first instance a main effect of Group, $F(1, 15) = 9.86$, $p = 0.006$, with a greater number of episodic details provided by the experimental group, irrespective of the time of assessment. A main effect of Time was also displayed, $F(1, 15) = 20.51$, $p < 0.001$, which revealed a general increase of the number of details in post-facilitation, whatever the group considered. However, as showed by the significant Group x Time interaction, $F(1, 15) = 22.80$, $p < 0.001$, and the post-hoc test, this previous result was mainly explained by the significant increase of the number of internal details exhibited by the experimental group after facilitation ($p < 0.001$), whereas no such difference was noticed in the placebo 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 placebo group ($p < 0.001$). The mean number of details provided by the patients across the assessment sessions is illustrated in the Figure 1.

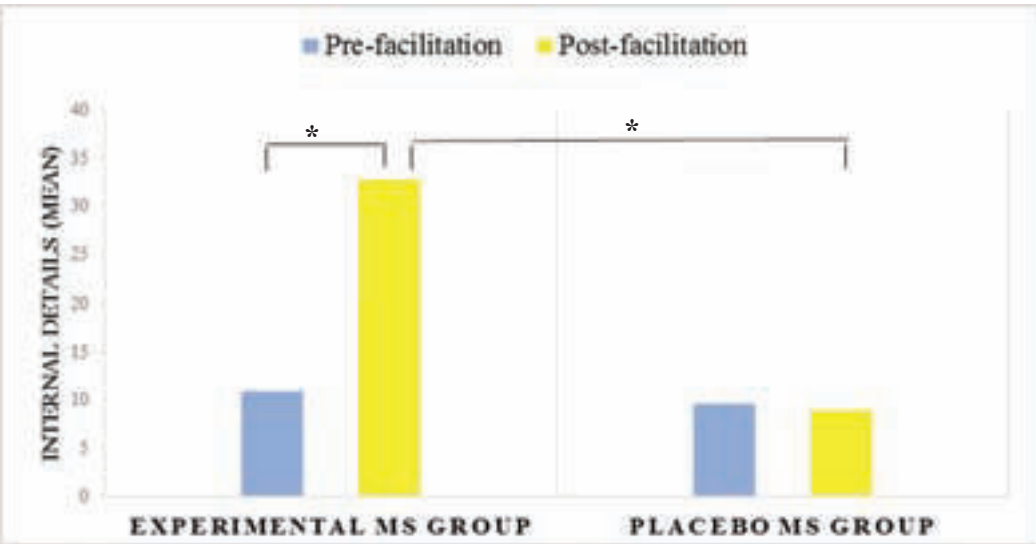

Figure 1. Mean number of internal details provided by the two patients groups in pre- and post-facilitation conditions during the free recall phase (* significant difference)

These findings were replicated when using the measure of the mean total rating, with a main effect of Group, $F(1, 15) = 8.40$, $p = 0.01$, and a main effect of Time, $F(1, 15) = 24.47$, $p < 0.001$, showing respectively better performance for the experimental than for the placebo group and higher rating in post- than in pre-facilitation. In addition, a significant Group x

Time interaction was displayed, $F(1, 15) = 33.98$, $p < 0.001$. Post-hoc test revealed that, while equivalent mean total rating was attributed to the two groups of patients in pre-facilitation ($p = 0.98$), significantly higher rating was observed for the experimental group after facilitation in comparison with the placebo group ($p = 0.001$). Moreover, within group analysis demonstrated that a significant improvement of the mean total rating was noticed in the experimental group in post- relatively to pre-facilitation ($p < 0.001$), but that such a difference was not observed in the placebo group ($p = 0.93$).

1.2. Post-scan results

Results obtained for each MS group for all the post-scan variables, before and after facilitation, are summarised in the Table 3.

Table 3. Post-scan measures: Mean and (SD) for the experimental and placebo patient groups

	Experimental group		**Placebo group**	
	PRE	POST	PRE	POST
Construction RT	4.63 (1.10)	4.95 (1.01)	4.60 (1.17)	4.87 (1.14)
Type of events				
Unique	17.60 (8.65)	21.90 (7.51)	21.14 (6.64)	21.85 (7.92)
Repetitive	5.50 (5.23)	3.40 (4.42)	2.85 (2.54)	2.14 (2.73)
Extended	0.60 (1.26)	0.10 (0.31)	0.00 (0.00)	0.00 (0.00)
Semantic	2.00 (4.13)	0.30 (0.67)	1.14 (2.60)	2.42 (3.20)
Absent	1.50 (1.90)	1.30 (1.41)	3.85 (3.33)	2.42 (3.04)
Emotional valence				
Positive (%)	60.28 (17.01)	70.26 (14.41)	72.19 (21.40)	68.89 (21.36)
Neutral (%)	26.61 (17.86)	18.84 (11.32)	18.78 (13.99)	23.16 (17.81)
Negative (%)	13.19 (9.45)	10.88 (8.25)	9.02 (10.90)	7.94 (5.91)
Difficulty of imagination	7.03 (1.81)	6.95 (2.23)	8.26 (0.82)	7.83 (1.15)
Amount of details	5.60 (1.86)	5.86 (2.28)	6.93 (0.72)	6.41 (2.20)

RT = reaction time; PRE / POST: pre-facilitation / post-facilitation

Regarding the mean construction reaction time, no significant main effect of group, $F(1, 15) = 0.01$, $p = 0.92$, and no main effect of time, $F(1, 15) = 1.83$, $p = 0.19$, were highlighted. No interaction effect was found.

An equal number of events was also provided by the patients, irrespective of the time of assessment and the type of events, $F(1, 15) = 1.31$, $p = 0.26$. No significant main effect of time was observed, $F(1, 15) = 0.02$, $p = 0.86$. However, the statistical analysis revealed a main effect of event type, $F(4, 60) = 61.93$, $p < 0.001$, 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 (threshold between $p = 0.16$ and $p = 0.98$). A significant Time x Event type was displayed, $F(4, 60) = 2.81$, $p = 0.03$. Nevertheless, post-hoc test only revealed a tendency for an increase of the number of unique event after facilitation ($p = 0.06$), while the number of events from the other categories remained stable (repetitive: $p = 0.77$; extended: $p = 0.99$; semantic: $p = 0.99$; absent: $p = 0.99$). No additional interaction effect was found.

Turning to emotional valence, within all the analyses on this variable, only a main effect of valence reached the significant statistical threshold, $F(2, 30) = 57$, $p < 0.001$. A higher rate of positive events was exhibited, relatively to neutral and negative events ($p < 0.001$ in both cases), while an equivalent rate was observed between neutral and negative events ($p = 0.12$).

The self-assessed difficulty of access showed no significant change between the two sessions, $F(1, 15) = 0.26$, $p = 0.61$, and no significant difference between the two groups of patients, $F(1, 15) = 2.46$, $p = 0.13$. The same is true for the scale dealing with the amount of details, with no significant main effect of time, $F(1, 15) = 0.04$, $p = 0.82$, and no significant main effect of group, $F(1, 15) = 1.53$, $p = 0.23$. For both scales, no significant interaction was found.

2. Neuroimaging results

Prior to intervention, no significant difference was observed in the cerebral networks sustaining the future event construction and elaboration (versus the control task's respective phases) in the experimental and placebo groups.

2.1. Experimental group: differential brain activations in pre- and post-facilitation

In post-facilitation, following the MVI programme, several brain activation changes were observed in the experimental group (Table 4).

Table 4. Increased cerebral activations in post-facilitation (versus pre-facilitation) for the future events construction and elaboration phases in the experimental group

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

Talairach Coordinates Reported; $p < 0.001$ uncorrected; $k = 5$ voxels

For 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 the post-facilitation session, relatively to the pre-facilitation session (Figure 2). The reverse contrast showed no greater activation in pre- than post-facilitation.

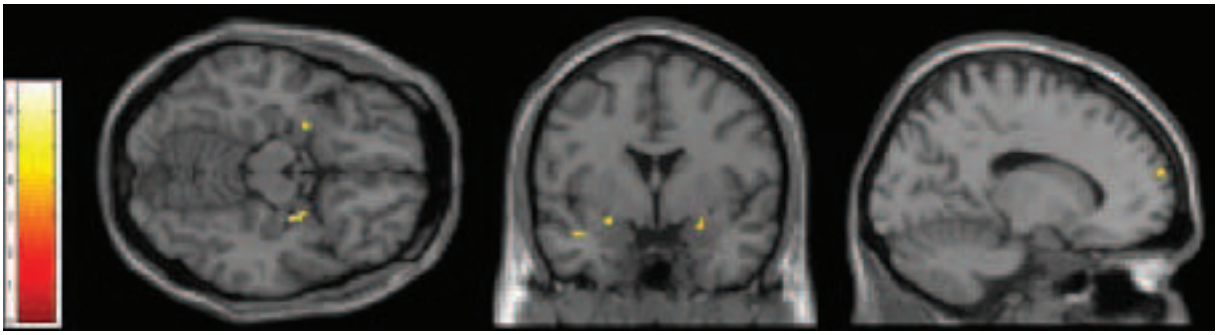

Figure 2. Enhanced brain activations in post-facilitation (versus pre-facilitation) for the experimental group during the construction phase of future events ($p < 0.001$ unc; $k = 5$ voxels)

Regarding the further elaboration of future events, increased activations were observed after the facilitation programme in the left middle frontal gyrus (BA 10) and the right superior frontal gyrus (BA 8) in comparison with the pre-facilitation session (Figure 3). The reverse contrast (pre > post-facilitation) showed no significant brain activation.

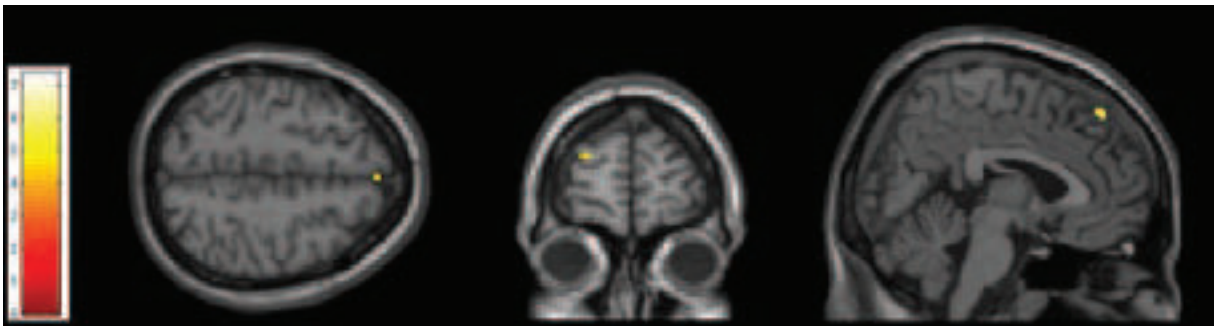

Figure 3. Brain regions showing an increased activity in post-facilitation (versus pre-facilitation) for the experimental group during the elaboration phase of future events (p < 0.001 unc; k = 5 voxels)

2.2. Placebo group: comparison of cerebral activations before and after the verbal control programme

In the placebo group, for both construction and elaboration phases of future events, no brain activations changes were observed in post-facilitation, relatively to pre-facilitation.

However, during the construction phase, the reverse contrast, showing brain regions more activated before than after the facilitation, revealed significant activations in a brain network extending from 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) to the right fusiform gyrus (BA 19; *xyz*: 42, -76, -12; *Z*-score: 4.45). Regarding the elaboration phase, no significant brain activation change was observed in pre- versus post-facilitation.

DISCUSSION

Projecting ourselves into future scenarios is a ubiquitous mental activity in everyday life and since EFT is involved in coping with stressful events, goal achievement and implementation of actions, it has an important adaptive value (Szpunar, 2010). In the event of EFT

impairment everyday life functioning is consequently affected as it has been demonstrated in relapsing-remitting MS patients (Study 1). In parallel, it is well established that AM and EFT share common cognitive and cerebral mechanisms (see Schacter et al., 2012 for a review). Based on these commonalities between AM and EFT, as well as on the demonstration of improved AM performance in MS patients by means of an MVI-based facilitation programme (Ernst et al., 2012; 2013), the aim of the present study was to extend this finding to EFT, by testing both clinical and cerebral network changes induced by facilitation.

Thus, we designed a randomised controlled clinical trial, in which only MS patients presenting initially with impaired EFT performance were included, and then allocated into two groups: patients, who underwent our MVI programme (the experimental group), and patients, who followed a placebo verbal programme (the placebo group). Prior to facilitation, no group differences were noticed regarding the neuropsychological baseline scores, as well as for the EFT performance in both AI assessment and post-scan measures, and for the cerebral network sustaining impaired EFT in these patients. Besides, a good matching between the two groups of patients was obtained in terms of mean reaction time, number of valid trials and phenomenological properties of future events, thus guarantying that the differential brain activations observed after facilitation in the two groups would more likely reflect the effect of facilitation, rather than a difference of performance per se.

Regarding the experimental group, our results supported the clinical benefit of the MVI programme on EFT performance. This clinical improvement was both manifested by an increased number of episodic details provided spontaneously by the patients after facilitation, as well as an improvement of the episodic quality of future events. As expected, improvement was also expressed at the cerebral network level.

In particular, after facilitation, increased brain activations were observed in the bilateral parahippocampal regions during the construction of future events. Interestingly, we previously reported a spontaneous greater activity of the bilateral parahippocampal regions during EFT, which was also positively modulated by the amount of details generated by MS patients, relatively to the healthy controls (Study 3). It has been established that the parahippocampal regions play are associated with contextual processing, and they play a pivotal role in the recruitment of posterior brain areas supporting MVI (Bar and Aminoff, 2003; Greenberg and Rubin, 2003; Botzung et al., 2008; Viard et al., 2011). Importantly, these brain regions are especially involved when the subjects have to generate as many details

as possible (Addis et al., 2007). Therefore, considering both the role of the parahippocampal regions and that of MVI in EFT, through the facilitation programme, the greater neural activity in these regions could reflect an increase reliance of contextual processing after facilitation. Furthermore, although no greater recruitment of the posterior cortical areas per se was observed, taking into account their dynamic interactions with the parahippocampal regions and their support of MVI processes, potential functional connectivity changes between these two regions could be present in the post-facilitation conditions. This suggestion begs for further analysis since its implementation is feasible and its interest warranted. Increased neural activity was also observed in the left middle temporal gyrus (BA 21) during the construction of future events after facilitation in the experimental group. In the context of EFT, this brain region has been associated with the reactivation of personal semantic information to guide future simulations (Viard et al., 2011). Moreover, while researches 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). Thus, in our patients, the greater activation of the external temporal region accompanying EFT improvement was not unexpected.

Enhanced left frontopolar cerebral activity (BA 10) was also reported after facilitation both during EFT construction and elaboration in the experimental group. As for the parahippocampal areas, signs of spontaneous changes were also previously showed in MS patients during EFT, positively related to the amount of future details that was generated (Study 3). In the literature, the frontopolar region has been described as a key neural signature of EFT, especially during the construction phase (Okuda et al., 2003; Addis et al., 2007). More recently, the role of the frontoporal region has been reconsidered as being involved in the general process of imagining, with a particular role in the overall integration and maintenance of multimodal information from diverse systems (Addis et al., 2009b). In this context, we would like to suggest that the increased frontopolar activity observed after facilitation in MS patients during both phases could reflect the greater cognitive demand of this integration process since, with the improvement of the episodic richness of future events, more information have to be integrated and held together. Similarly, the greater activation also exhibited by these patients in post-facilitation in the right superior frontal gyrus (BA 8) could also be related to the greater need of prefrontal resources required to bind together more rich episodic and semantic information during future simulations (Weiler et al., 2011).

Moreover, this same brain region seems also particularly involved in the simulation of self-involved scenario (Summerfield et al., 2009).

Turning to the placebo group, as expected, clinically, our sham verbal programme did not lead to an improvement of EFT performance, with unchanged results across the sessions. In line with these clinical findings, no cerebral activation changes were displayed in post-, relatively to the pre-facilitation fMRI session. However, some cerebral activations were observed to be decreased in post-, relatively to pre-facilitation, including prefrontal, parietal and posterior brain regions. Although statistically non-significant, in the context of a recognition anterograde memory task, a tendency of decreased neural activity in several brain regions was also noticed in the MS placebo group at the second fMRI assessment by Chiaravalotti and colleagues (2012). In both studies, this tendency was observed only in the placebo group, whereas only increased cerebral activations were reported in the experimental group. As suggested by Chiaravalotti et al. decrease of neural activity could be attributed 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 brain plasticity changes following the clinical improvement of EFT abilities by means of cognitive intervention. Although the clinical value of this study has been ascertained by means of the clinical-neuroimaging convergent evidence, replication of results with a larger sample of patients is required. Furthermore, as the long-term robustness of the facilitation benefit was reported at the behavioural level (Study 6), an intriguing question concerns the cerebral underpinnings of the benefits' maintenance. One could hypothesise that in the absence of clinical changes, stable pattern of cerebral activations would be observed. However, alternative and opposite options could also make sense: with the use of the taught strategy during several months, and thus with a greater practice of it, would we observed a decrease of the cerebral activations reported immediately after facilitation? Or conversely, with the greater practice of this strategy and the potential greater efficiency in its use, would we observed a further increase of the activity in the brain regions sensitive to change in post-facilitation? As far as we know, to date, no investigation has yet dealt with this question.

Beyond the scientific enthusiasm aroused by brain plasticity investigations following cognitive interventions, at a more matter-of-fact level, this kind of studies also provide solid evidence of the effectiveness of neuropsychological rehabilitation in brain-damaged patients and thus, promote their use and extensive development.

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GENERAL DISCUSSION AND PERSPECTIVES

The general aim of the present thesis was to explore MTT abilities in non-depressed RR-MS patients, using a double approach, clinical neuropsychology and neuroimaging. In this context, our investigation aimed to contribute to a better understanding of both cognitive functioning and its underlying cerebral mechanisms in MS patients with direct relevance and implications for clinical practice.

Thus, a first section of this work tackles the clinical and cerebral functional characteristics of MTT impairment in MS patients. Indeed, while AM deficit in MS patients have already been reported at the clinical level (Kenealy et al., 2002; Müller et al., 2013; Ernst et al., 2013), the present work is the first to our knowledge to document the presence of EFT impairment in MS patients. Furthermore, relatively to healthy controls, MS patients showed a similar degree of impairment for the AM and EFT components, which suggested that both MTT subcomponents were equally affected by MS pathology with, in addition, a strong association between AM and EFT performance.

A major finding is that MTT impairment was accompanied by spontaneous cerebral activations changes during the evocation of personal past and future events in MS patients, in comparison with the cerebral networks engaged by healthy controls. Since these brain activity changes were observed during both the construction and the elaboration phases of personal events, these data seemed to confirm our clinical observations of patients' difficulties in the initial retrieval/generation of personal events, but also in the remembering/imagining of details associated with them. Interestingly, for both AM and EFT components, MS patients showed, most particularly, increased and bilateral cerebral activations in key brain regions from the MTT network, including prefrontal, temporal and posterior cerebral regions. Within these brain areas, a predominant role of the prefrontal regions -widely recruited in both temporal directions- has been highlighted. Moreover, we documented that several core MTT brain regions, like the parahippocampal and the cingulate gyri, or frontal and posterior brain regions were particularly responsive to the difficulty of access/imagining and to the amount of details generated by MS patients. Taken together, despite MS brain lesions, cerebral compensatory mechanisms seem to occur in the context of MTT, although insufficient to result in normal performance. While observations akin to this conclusion have been made in MS patients in relation to various cognitive functions (see Caramia et al., 2010 for a review), they had never before been reported for the MTT ability, to the best of our knowledge. In

agreement with the fMRI MS literature, we observed cerebral activation changes, which entailed increased activations in brain areas also recruited by controls, and/or the recruitment of alternative brain areas, mostly contralateral.

Beyond the striking similarities in the spontaneous brain activation changes observed for AM and EFT cerebral networks, some differences in the 'brain response' to impairment were also noticed between the two temporal directions in MS patients. In fact, regarding the number of brain regions exhibiting an increased activity relatively to healthy controls, a first qualitative observation was that more brain regions seemed engaged in the elaboration phase of past events in comparison with the construction phase, whereas for future events, a larger brain network was recruited for the construction, relatively to the elaboration phase. More extensive brain recruitments were also observed for the future than for the past events in response to the difficulty of the task and to the amount of episodic details, with a particular engagement of the prefrontal regions. A more in-depth investigation of these AM/EFT cerebral networks' discrepancies confirmed that additional brain recruitments were evident in MS patients during the EFT task, involving the hippocampus, frontal, external temporal and cingulate regions.

Overall, common and distinct spontaneous brain plasticity mechanisms seemed to be observed in the context of clinical AM and EFT impairment in MS patients. Regarding the literature, common and differential brain mechanisms also sustain AM and EFT in normal functioning with, in general, a greater neural activity for EFT (see Schacter et al., 2012 for a review).Thus, our findings suggest that, in the case of diffuse brain pathology like MS, the normal global pattern of MTT brain activity would be observed showing, however, some changes in brain activations, resulting from modulations to compensate the damaged normal circuits. A supporting evidence of this hypothesis is that a greater neural activity, in MS patients, was highlighted for the EFT condition only, within the brain regions reported by Addis et al. (2007a), in healthy participants.

In parallel, a greater cerebral activity in fronto-parieto-temporal regions was also reported in our MS patients during the construction phase of past and future events, relatively to the elaboration phase, and in comparison with the healthy subjects. Since the EFT condition and the construction phase of personal events are the most effortful from a cognitive standpoint, and tax especially the executive functions, the particular greater neural effort showed in these conditions by MS patients are not unexpected. On the contrary, these neuroimaging findings provide supportive arguments to our retrieval-deficit hypothesis, associated with executive

functions abilities, to explain AM and EFT impairment in MS patients, together with the general increased neural activity in the frontal regions observed in our patients.

Complementary to this first part, the second section of this thesis was dedicated to the proposition of a cognitive intervention to alleviate MTT impairment in MS patients.

Based on our pilot study showing the effectiveness of a MVI-based facilitation programme on AM functioning in MS patients (Ernst et al., 2013), we further probed its efficacy on AM in the context of a placebo randomised clinical trial and extended by the same way its use to EFT. Furthermore, to support the expected clinical benefits on MTT, we introduced fMRI sessions in a pre-/post-facilitation study design.

Clinically, the MVI facilitation programme seemed efficient to improve both AM and EFT functioning, with no differential benefit between the two temporal directions. An additional important point is that, beyond improvement, the great majority of the MS patients showed a normalisation of their performance after the facilitation intervention, with a long term robustness of its positive effect. Furthermore, since the primary aim of neuropsychological rehabilitation is to improve everyday life functioning, the perceived benefits by patients of the facilitation are also an important indicator of therapeutics' efficacy. In our investigation, comments from patients and their relatives clearly supported the benefits of the MVI programme and its effective transfer to real life situations. Importantly, we also demonstrated that these positive outcomes were not related to nursing or to learning effects.

Regarding the cerebral expression of the cognitive benefit, induced brain activation changes were observed for both AM and EFT in key brain regions of the MTT network, with the following characteristics. First of all, the two temporal directions relied on distinct cerebral mechanisms in our patients. In relation to AM, cerebral activation changes reflecting both an increase reliance on brain regions sustaining self-referential process and a decrease of those reflecting an effortful research process were displayed after the MVI programme. In parallel, induced brain activity changes in the context of EFT involved most particularly, cerebral regions sustaining contextual processing and personal semantics, as well as those sustaining the integration and maintenance of multimodal information from various systems. To the best of our knowledge, this study is the first to document that the use of a cognitive strategy based on visual imagery alone could result in differential brain activities, depending on the context of its application, with an equivalent degree of behavioural effectiveness. Thus, these results

also suggest that AM and EFT showed clear distinctive brain characteristics, beyond their similarities. Importantly, neural differences characterising AM and EFT have been reported in healthy subjects (Schacter et al., 2012) and, in the present work, in AM/EFT abilities in MS patients in both pre- and post-facilitation intervention. Needless to say, further investigations in MS but also in other clinical populations, are required to interpret the exact functional significance of these differential induced brain activation changes between AM and EFT, with the introduction of direct comparisons of AM and EFT brain networks.

Turning to a different issue, irrespective of the temporal direction, we did not replicate our preliminary finding of a main increased activity in posterior brain regions through the MVI programme that we initially reported in the context of AM. Indeed, based on theoretical considerations and this preliminary report, our hypothesis was that the emphasis made on the role of MVI in MTT through the cognitive intervention would result in a greater recruitment of posterior brain regions. However, considering the very small sample size of patients and the lenient statistical threshold applied to fMRI data in the context of this pilot study, these results called for a cautious interpretation. Nevertheless, considering both the presence of increased brain activity reported in those regions before facilitation and the spatio-temporal dynamic nature of the interactions between the brain regions within the MTT cerebral network (Conway et al., 2003; Weiler et al., 2011b), one remaining possibility is the occurrence of more 'qualitative' than 'quantitative' activation changes. Thus, in a near future, further analyses with the introduction of functional connectivity measures will be conducted to obtain a more comprehensive picture of the potential cerebral changes induced by the MVI programme for both AM and EFT components. Analyses of this kind might be particularly relevant since induced functional connectivity changes following a cognitive intervention have already been reported in MS patients (Leavitt et al., 2012; Parisi et al., 2012). Besides, since T1 and T2-weighted images, as well as DTI sequences were also acquired during both the pre- and post-facilitation MRI sessions in our protocol, a further investigation would also tackle potential induced structural brain changes following the MVI programme. Rarer than fMRI studies, a few papers reported the influence of cognitive interventions on cerebral structural measures in clinical populations other than MS (Eack et al., 2010; Nordvik et al., 2012; Penades et al., 2013). Ultimately, if some structural modifications could be highlighted in our research, the crossing over and overlapping of the functional and structural data could provide additional data about the actual and potential cerebral effects of the MVI programme.

Overall, the present work could contribute to provide new insights into cognitive functioning in RR-MS patients by supplying both behavioural and cerebral functional data of MTT impairment. Along the different studies in the present work, we have observed that MTT impairment is very frequent in the RR-MS population, even in the context of a general preservation of cognitive functioning. While we are aware that AM and EFT are not assessed in clinical routine assessment, particularly because of its time consuming examination, we would like to suggest that more attention should be paid to AM/EFT in MS clinics, especially for patients presenting with memory complains in everyday life, but with no signs of cognitive deficit with the more standard neuropsychological tests. This suggestion is especially reinforced by the results showing improved performance and maintenance in the long run after a comparatively rapid and simple cognitive intervention. An important open question remains concerning the possibility to extend our findings to the other MS subtypes, or even to other clinical conditions showing retrieval-deficit characteristics at the origin of MTT impairment. The present thesis could help to promote investigations along these lines.

By way of conclusion, we would like to emphasise once again the clinical importance of studying AM/EFT in brain-damaged patients. Indeed, the experience of acquired brain injury provoke major disruptions in every domain of an individual's life and provokes more often than not, significant changes in how he/she interpret his/herself and the world around (Gracey et al., 2008). In the context of AM/EFT impairment, brain-injured individuals would be partially or totally unable to remember how they used to be or what they used to do, and therefore, it will be difficult or even impossible for them to create/adjust their self and personal identity by integrating at least part of the changes triggered by the brain injury (Kovarsky et al., 2007; Coetzer, 2008). The latter issues underline the importance of developing therapeutic interventions to promote AM/EFT integrity, all the more so that in different clinical conditions such as traumatic brain injury or MS, the consequences of cerebral damage occur in young adults, who are in the most active and determinant period of their life in terms of identity construction (Conway and Pleydell-Pearce, 2000). As a consequence, AM/EFT improvement would help to promote patients' well-being, as expressed by VW, one of our patient, '*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'*.

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Spontaneous and induced cerebral plasticity during autobiographical memory and episodic future thinking performance in relapsing-remitting multiple sclerosis patients

Résumé

Basée sur une approche en neuropsychologie et neuroimagerie, cette étude visait à (i) caractériser le déficit du voyage mental dans le temps (VMT : mémoire autobiographique et projection future) chez des patients atteints de sclérose en plaques de forme rémittente et (ii) à améliorer leur performance.
Nous avons montré que le déficit du VMT s'accompagne de changements d'activations cérébrales spontanés dans des régions clés du réseau cérébral du VMT, en comparaison de sujets sains. Par ailleurs, l'utilisation d'un programme de facilitation cognitive a permis une amélioration significative des fonctions étudiées, non attribuable à un effet « placebo » ou d'apprentissage. Le bénéfice clinique s'est traduit par une augmentation de l'activité cérébrale dans des régions cérébrales clés du réseau, mais distinctes selon la direction temporelle.
Les huit expériences ont ainsi démontré que le déficit du VMT entraîne une plasticité cérébrale spontanée et que intervention cognitive est efficace et sous-tendue par des processus cérébraux détectables.

Mots clés : mémoire autobiographique, projection dans l'avenir, sclérose en plaques, réhabilitation cognitive, IRM fonctionnelle

Résumé en anglais

Based on a double approach in clinical neuropsychology and neuroimaging, the aim of the present thesis was twofold: (i) to study relapsing-remitting multiple sclerosis (RR-MS) patients presenting with autobiographical memory (AM) and episodic future thinking (EFT) impairment, and (ii) to improve AM and EFT functioning in the same patients.
Thus, we showed a deficit in both AM and EFT in RR-MS patients, which was expressed by spontaneous brain activity changes in key brain regions of the AM and EFT networks, relatively to healthy controls. Then, we documented that the use of a mental visual imagery (MVI)-based facilitation programme led to AM and EFT improvement, which was not attributable to nursing or learning effects. This clinical benefit was accompanied with an increased reliance on distinct key brain regions of the core AM and EFT network.
Overall, we documented the effectiveness of cognitive facilitation for AM and EFT, and the occurrence of spontaneous and induced brain plasticity changes during AM and EFT performance in RR-MS patients, which were sustained by both common and distinct cerebral mechanisms.

Keywords: autobiographical memory, episodic future thinking, multiple sclerosis, cognitive rehabilitation, functional MRI