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Autobiographical memory and future thinking impairments in multiple sclerosis: cognitive and neural mechanisms, functional impact and rehabilitation

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Abstract

Learning and memory impairments are common in individuals with multiple sclerosis (MS) and have pervasive effects on everyday life functioning. Hence, memory and learning have received particular attention in the cognitive rehabilitation literature in MS. The effectiveness of memory rehabilitation on memory performance is supported by several studies, but the generalisability of the benefits to daily life and memory for real-life events has rarely been examined. Recently, a new line of research focusing on memory for personal life events (i.e., autobiographical memory) has emerged in the MS literature. This approach is complementary to classical learning and memory paradigms and also allows for approaching memory in a broader context, one that considers memory as the ability to remember past episodes and imagine events that may occur in one's personal future (i.e., future thinking). This review provides an overview of the findings in this line of work. The first part summarises current evidence regarding the cognitive and neural mechanisms underlying autobiographical

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memory and future thinking impairments in MS. It points out that these domains are frequently and early impaired in individuals with MS because of an executive/frontal-related deficit. Individuals with MS are generally aware of these deficits and their negative impact on everyday life, so the development of strategies to alleviate such deficits seems of paramount importance. Thus, in the second part, I present the main outcomes of a cognitive intervention developed by our research group, which has been specifically designed to alleviate autobiographical memory and future thinking impairments in individuals with MS. The implications of these findings for neuropsychological care and well-being of individuals with MS are discussed in the final section, with an emphasis on the functional role of autobiographical memory and future thinking in various domains, including personal identity.

Keywords: autobiographical memory; future thinking; cognitive rehabilitation; visual imagery; self; multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurological condition of the central nervous system. Because of the distributed and multifocal nature of lesions in MS, the clinical profile of these patients is highly variable and heterogeneous and could include a broad range of symptoms such as sensory, motor, visual, or cognitive impairments [1]. Cognitive impairment is frequent in MS, even in the early stage of the disease, and its prevalence ranges from 30% to 70% [2]. Most commonly observed are impairments in verbal and visual episodic memory, information processing speed, attention, working memory, and executive functions [2]. Cognitive disorders have deleterious consequences on multiple aspects of daily life (e.g., employment, social activities, routine household tasks) and on quality of life [3,4].

A growing number of neuropsychological interventions have been developed to alleviate cognitive impairments and improve the functional status of individuals with MS [for reviews see 5,6]. In this field, researchers working on cognitive rehabilitation for learning and memory deficits have been particularly prolific in the last 2 decades, owing to increasing attention given to memory problems and complaints in individuals with MS but also because of the negative impact of memory disorders on everyday life [7]. Positive post-intervention results have generally been reported on memory performance, but to date, only one intervention [8] has met the methodological requirements to provide practice standards [5,6]. Furthermore, few studies have examined the effectiveness of these interventions on everyday memory and memory for real-life events, although these dimensions are central to the concerns of individuals with MS [see however 8-11].

In this context, our research group has recently begun to address this issue by examining autobiographical memory in individuals with MS. Autobiographical memory is by essence memory for real-life situations and is at the heart of what defines an individual as a person in society [12]. Autobiographical memories are important for social functioning (e.g., keeping memories about significant others, informing people about us) and serve as a basis for guiding present behaviours based on solutions and experiences from the past [13]. Furthermore, it is now well established that autobiographical memory not only supports the recall of past episodes but also allows people to mentally project themselves into the future and anticipate events that might happen to them [14]. This ability ─ generally called future thinking ─ has numerous functional implications, including intention implementation, coping with stressful events, emotional regulation, goal-directed behaviours, or decision making [15,16]. Thus, autobiographical memory and future thinking deficits could have disruptive and pervasive effects in many different aspects of daily functioning.

In a series of studies [17-19], we have shown that autobiographical memory and future thinking are frequently and early impaired in individuals with MS but that these deficits could be alleviated by means of a cognitive facilitation programme. This paper attempts to provide an overview of the findings in this line of work. The first section tackles the cognitive and neural mechanisms involved in autobiographical memory and future thinking impairments in individuals with MS. In the second section, I present the main outcomes of our cognitive intervention study in people with MS, before concluding with future directions in the field, especially on the functional consequences of impaired autobiographical memory and future thinking on personal identity and well-being.

Cognitive and neural mechanisms underlying autobiographical memory and future thinking impairments in MS

Definitions

Autobiographical memory and future thinking[1] correspond, respectively, to the ability to mentally re-experience or pre-experience personal events as they are remembered or imagined (e.g., remembering your 18th birthday or imagining your next dinner with friends). At a theoretical level, autobiographical memory and future thinking consist of different types of representations that are organised in a hierarchical structure (i.e., Conway's Self Memory System [20]; see [21] for the extension of this model to future thinking): on one extreme lies

[1] Although the notion of episodic future thinking is conceptually related to other forms of future-oriented thoughts such as prospective memory, they are not synonymous. Prospective memory corresponds to the ability to remember to carry out intended activities in the future (e.g., pick up milk on the way home from work). Contrary to episodic future thinking, the formation and accomplishment of such intentions do not necessarily require the mental simulation of specific future episodes [15].

specific and unique episodes containing perceptual, affective, sensory, place, or time-related details (i.e., episodic representations) and on the other more abstract and conceptual knowledge about oneself (i.e., semantic representations).

An important feature of episodic autobiographical memory and future thinking is that they are the product of (re)constructive processes; that is, they are based on information and details stored in memory that are extracted and flexibly (re)combined into a (novel) coherent event. Cognitive and neuroimaging studies have shown a tight overlap between autobiographical memory and future thinking. For instance, the (re)construction of both past and future episodes requires the orchestration of a number of cognitive functions and mechanisms such as episodic memory, executive functions, scene construction, or self-referential processes [14]. In parallel, neuroimaging studies have shown that autobiographical memory and future thinking rely on a largely similar brain network, including medial temporal and frontal lobes, posterior cingulate and retrosplenial cortex, and lateral parietal and temporal areas [14]. With the reliance on such an extensive network of brain regions, autobiographical memory and future thinking are highly vulnerable to brain damage. According to Irish and Piguet [22], disruption to any key nodes of this brain network might impinge on the ability to mentally travel into the past or the future. Therefore, the diffuse and multifocal nature of brain lesions in MS represents a propitious ground for the development of autobiographical memory and future thinking impairments.

Behavioural assessment

Various methodologies have been developed to assess autobiographical memory and future thinking, with parallel versions for the past and future. They mainly consist of semi-structured interviews and questionnaires (e.g., the modified Crovitz cueing procedure [23,24], adapted Autobiographical Interview [25], or Temporally Extended-TEMPau [26]). Typically,

participants are asked to provide specific past or future events that happened or will happen to them in particular time frames, in response to cue-words (e.g., car) or themes (e.g., relationship). The specificity and episodic richness of past and future events are then rated on ordinal scales (from the absence of event, semantic representations to episodic events) or by quantifying the number of episodic details provided in event descriptions.

Surprisingly, studies examining autobiographical memory in individuals with MS remain relatively sparse and provided inconsistent results, which were likely due to sample selection and test sensitivity issues [27-29]. In controlling for these aspects, we examined autobiographical memory and future thinking in people with non-depressed relapsing-remitting MS (RRMS) (see Table for clinical and demographic data), who showed low to mild levels of functional disability (i.e., Expanded Disability Status Scale score ≤5, [30]) and cognitive impairment (according to a comprehensive neuropsychological examination including tests for learning and memory, executive functions, language, processing speed, visuo-perceptual and visuo-spatial abilities)[2]. Using a stringent assessment method (i.e., the modified Crovitz cueing procedure [23]), we documented an autobiographical memory deficit that covered the whole lifespan, but which specifically affected episodic representations in individuals with MS [17]. This impairment was significantly correlated with executive function scores but not anterograde memory performance (i.e., the ability to learn new information). This deficit in retrieval of episodic autobiographical memories led us to the proposal that episodic future thinking would also be significantly compromised.

[2] These clinical characteristics apply to all our studies described in this paper. In addition, because depression reduces the specificity of autobiographical memory and future thinking [31], patients showing signs of clinical depression were excluded from these studies to control for this potential confounding effect.

In a follow-up study [18] using the Autobiographical Interview [25], we confirmed that this impairment extended to future thinking, with a similar magnitude of the deficit across temporal directions. Indeed, for both temporal conditions, past and future events contained significantly fewer episodic details when described by individuals with RRMS versus matched healthy controls. The positive correlation observed between past and future performance suggested the involvement of (at least in part) common cognitive mechanisms. Importantly, the use of specific probes to support remembering or imagining bolstered the number of episodic details provided by people with MS (although their performance remained under the normal range), which further supported the idea of a dysexecutive origin of these deficits. Multiple executive control processes are involved at different stages of the (re)construction of personal past and future events [32-34]: the strategic search for details stored in memory, their evaluation and potential rejection if they cannot be unified into a coherent mental representation. In addition, executive control processes are necessary to link together bits of multimodal information and hold the retrieved details in working memory while constantly updating the content of the constructed representation to fit with the situational demands. Because future thinking requires the extraction and recombination of an infinite assortment of details into a novel event, whereas autobiographical memory consists of the recapitulation of a more restricted pool of details, future thinking more extensively taxes executive functions [35].

Neuroimaging assessment

At this stage, neuroimaging techniques have been found useful to delve deeper into the cognitive and neural bases of autobiographical memory and future thinking deficits in individuals with RRMS. To do so, we used an adapted version of the functional MRI paradigm developed by Addis and colleagues [24], which allows for distinguishing the

construction (i.e., initial access and building up of the event) and elaboration (i.e., retrieval/imagining of associated details) of past and future events. In short, participants had to evoke specific past and future events (32 trials per condition) in response to pairs of cue-words (e.g., family-meal).

In 2 studies involving individuals with RRMS presenting impaired autobiographical memory [36] and future thinking [37] (see Table for clinical and demographic data), we found greater brain activations mainly in the bilateral prefrontal regions for these individuals as compared with matched healthy controls (whole-brain between-group analysis; statistical threshold set at $p < 0.005$ uncorrected, with k = 10 voxels, based on Lieberman and Cunningham [38]). This result suggested a predominant executive/frontal-related deficit, which impeded both the initial access and detailed elaboration of past and future events. These brain activation changes likely reflected unsuccessful brain compensatory mechanisms that were insufficient to compensate for autobiographical memory and future thinking deficits.

In a follow-up study [39], we also found a significant Group × Condition interaction ($p < 0.001$, uncorrected) showing that as compared with matched healthy controls, individuals with RRMS (clinical and demographic data presented in Table) showed greater activations for the future in the prefrontal and hippocampal regions relative to the past. Future thinking impairment in individuals with RRMS was better explained by the combination of a difficulty to initiate a strategic extraction of details (depending on the prefrontal regions) and impaired constructive processes that compromise the integration and binding of details into a coherent scene (depending on the hippocampus).

Qualitative assessment

Across these studies, we also gathered information on the functional impact of autobiographical memory and future thinking impairments in individuals with RRMS. To do so, autobiographical memory and future thinking assessment was systematically accompanied by a semi-structured interview, which aimed at collecting individuals' impressions of their perceived difficulties. The analysis of these interviews indicated that individuals with RRMS were generally aware of their autobiographical memory and future thinking problems, which mostly consisted of difficulties in retrieving/imagining specific events. They also described that their memories/future projections generally contained few details and were associated with low degrees of vividness and emotional intensity. As illustrated by the following excerpts of patients' comments, these observations applied to not only the past and future events provided during the testing session but also to real-life situations [18]:

> MFW: "*It's difficult because it's terrible not being able to remember… If someone tells you something, I don't know, asks you "where were you?", that kind of question… 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.*"
>
> 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 have erased it, as if I have never been there, as if … My partner 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."*
>
> 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."*

From a clinical perspective, this series of studies has contributed to expanding the scope of knowledge on the cognitive disorders experienced by people with RRMS in their everyday life, by showing that autobiographical memory and future thinking are frequently and early impaired in these patients. Furthermore, it is worth emphasising that individuals with RRMS were generally aware of their difficulties and the impact of these deficits on their daily life functioning. Hence, these clinical observations have motivated the development of a tailor-made cognitive intervention specifically designed to alleviate autobiographical memory and future thinking deficits in individuals with RRMS.

Using mental visual imagery to rehabilitate autobiographical memory and future thinking in individuals with RRMS

As developed in the previous section, our behavioural and neuroimaging findings have converged on the idea that impaired executive/prefrontal functions adversely affect the (re)construction and elaboration of past and future events in individuals with RRMS. To handle these difficulties, we developed a cognitive intervention that targets cognitive processes involved in different stages of the (re)construction of events, which all tax executive resources: the strategic selection, extraction and evaluation of multimodal details, and their integration and maintenance into a coherent mental representation. In addition, because MS frequently occurs in young adults, who are in a very active period of their life, we also intended to provide a compensatory strategy that could be easily used in everyday life. On these bases, we built up a cognitive intervention aiming at boosting mental visual imagery (MVI) abilities to alleviate the specific autobiographical memory and future thinking deficits presented by people with RRMS. The rationale for basing the intervention on MVI was threefold: 1) robust evidence in favour of the critical role of MVI in autobiographical memory

and future thinking [14,40]; 2) an intuitive relationship between autobiographical memory/future thinking and MVI, the latter enabling the construction of "mental films" of past and future events; and 3) previous rehabilitation studies showing that MVI is an efficient technique to improve learning and memory in individuals with MS [8, 41].

The MVI programme[3] consists of six 2-hour sessions performed once or twice per week (depending on the person's availability). Following a goal-directed approach [42], the first step of the programme is to explain its aim, content and functioning to promote its further use in daily life. Along these lines, the neuropsychologist is also particularly attentive to treatment receipt (i.e., the extent to which the person understands the strategies or techniques taught and demonstrates the capacity to use them [43]). The programme is organised in 4 steps, with mental visualisation exercises of increasing difficulty, during which the neuropsychologist provides continuous guidance and probes the person from general to detailed aspects. 1) The *screening step* is adapted from 3 subtests from the Imagery and Perception Battery [44]: the "mental representation of physical detail" (e.g., "*Does a wolf have round or pointed ears?"*), the "morphological discrimination" (e.g., "*What is the main visual distinctive feature between a nail and a screw?"*) and the "colour comparison" tests (e.g., "*Which item has the lightest colour: corn or butter?"*). This step aims to exercise basic MVI abilities and ensure the absence of severe impairment in this domain (which would be incompatible with the accomplishment of the programme). 2) The *external visualisation* includes 10 verbal items to imagine and describe in as much detail as possible (e.g., shape, colour, size), with the complementary imagination of an action made with the item (e.g., visualising an onion and then, visualising it being sliced). 3) The *construction phase* consists of the imagination of complex mental scenarios, bringing into play several characters performing multiple actions in various contexts. This part includes 5 verbal items, divided

[3] The full MVI programme is available on request.

into 2 steps: a first training step (e.g., "*Imagine the hotel for your holidays"*) and a subsequent thematically close scenario (e.g., *"Imagine the house of your dreams"*). This allows the person to rely on the scaffolding of the first scenario to construct the second one. 4) The *self-visualisation* follows the same procedure but here, the individual becomes the main character of imagined scenarios. Thus, the person is encouraged to imagine the scenario as she/he is actually experiencing it at present and to describe everything that comes to her/his mind while imagining the scenario (environment/setting, images, sounds, emotions, sensations, tastes, odours). It starts with a first training scene (e.g., *"Imagine you take part in a magic show"*), followed by a second thematically close scenario (e.g., *"Imagine you enter in the big cats' cage for a show"*).

The effectiveness of the MVI programme has been tested in a randomised controlled study involving individuals with RRMS (see Table for clinical and demographic data), who presented autobiographical memory and future thinking impairments (measured by the mean number of episodic details provided for past and future events) [19]. Individuals were randomly assigned to the experimental (i.e., the MVI programme), verbal control or stability groups, and were blinded to their allocation group. The verbal control group underwent a narrative-oriented sham intervention that followed the same structure and principles as the MVI programme but with lower (or no) expected benefits on autobiographical memory and future thinking, considering the more secondary role of narrative structure in these cognitive domains as compared with MVI [40]. The stability group was set up to control for potential learning effects due to repeated autobiographical memory and future thinking assessments; thus, participants in this group underwent the assessment twice but with no intervention in between. Although a similar performance was observed across the 3 groups before the intervention, only the experimental group showed a significant autobiographical memory and future thinking improvement after the intervention (Figure). In this group, the magnitude of

the improvement in post-intervention was not significantly different between past and future events. “Placebo” and test–retest effects were ruled out by the 2 control groups, who showed no significant changes in level of performance across testing sessions. Importantly, at the individual level, most individuals showed a normalisation of their performance after the MVI programme, with a long-term maintenance of the treatment effect at 6 months after the end of the intervention.

In addition to these objective cognitive measures, we were also interested in the perceived benefits of the MVI programme. Results from the semi-structured interviews suggested good treatment receipt and an easy use and transfer of this compensatory strategy in everyday life functioning. Examples of comments are provided here:

> MM: “*I see something, and something else in relation with the first thing comes with it. A memory comes to my mind and I’ve noticed that I can detail it. I have more memories. If I remember something, I can focus on that, on the memory, and look for details. I’m able to do that. Even for emotional details. I’m positive that, from now on, it will help me more and more.* […] *It’s easier to make a decision, whatever it is. I used to hesitate a lot, more than presently. Now, if I don’t want something, I know that I don’t want it, and I know what I want . . . for me, it’s obvious. I wouldn’t have dared before. So, all in all, it has restored my self-confidence, that’s what I feel… It’s true, I can feel OK with myself again”.*
>
> 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 scary... So for me, it’s all benefits. 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 by remembering then 3 other details, suddenly, it triggers something and I can come back to the first point".

AS: "*It's easier to imagine things … To project myself. The first time, before the programme, it was really hard* […]. *In fact, it's a mechanism that I have learnt, little by little, that I have integrated. And it was not a hard learning. I had the time to integrate it. It was spontaneous*."

IB: "*Yes, I think that something is set up, in everyday life, for the future. I have the feeling that, as we went along the sessions, I had the feeling that I was actually living things. I'm in. I'm seeing things. … Yes, the future events, I feel them*."

Interestingly, although the MVI programme showed a similar efficacy for autobiographical memory and future thinking at the behavioural level, the cognitive and neural mechanisms sustaining these improvements were partly distinct [45,46] (see Table for demographic and clinical characteristics of our RRMS patient groups). Whole-brain within-group comparisons (paired *t*-tests) between pre- and post-facilitation sessions showed that individuals who benefited from the MVI programme displayed significant brain activation changes for the past and the future in the prefrontal areas ($p < 0.001$, uncorrected), which reflected changes in processes sustaining the effortful research, extraction and maintenance of multimodal information [32,33]. In addition, for both the past and future, functional connectivity changes were also found in the posterior brain regions ($p < 0.05$, corrected), which support visual imagery processes [47]. However, increased activation in the medial prefrontal region, supporting a self-referential process ($p < 0.001$, uncorrected) [48], was observed for only the past. Conversely, future thinking improvement was specifically

characterised by increased activation in the parahippocampal and middle temporal gyri (p < 0.001, uncorrected), which are associated with contextual and semantic processing [22,49]. Moreover, correlations between performance improvement and grey-matter volume increase also showed distinct patterns, with significant changes in the parahippocampal gyrus for the past and in the prefrontal region for the future (p < 0.001, uncorrected). Thus, these neuroimaging studies completed our behavioural findings by providing a fine-grained view of the role of visual imagery in the dynamic orchestration of the different cognitive processes involved in constructing past and future personal events, which underlies the benefits of the MVI programme. Furthermore, our findings suggest that structural brain changes are not necessarily concomitant with functional changes or they can follow slightly different trajectories: for instance, in the parahippocampal gyrus, we detected changes at the structural level for the past and functional changes for the future. Although these findings raise intriguing questions about the mechanisms of neuroplasticity, because of the paucity of cognitive rehabilitation studies using multimodal neuroimagery and the absence of other studies examining the influence of autobiographical memory and future thinking improvement on their underlying brain networks, these findings are difficult to interpret at this stage. Further studies are warranted to uncover the complex nature of rehabilitation-induced brain plasticity.

Conclusion and future directions

Autobiographical memory and future thinking impairments have been an overlooked feature of the cognitive phenotype of MS and yet, they have pervasive effects in many aspects of individuals' life. Time constraints and the lack of reliable assessment instruments with acceptable psychometric standards probably contribute to hinder the inclusion of autobiographical memory and future thinking assessment in clinical settings. Nevertheless,

our work suggests that more attention should be paid to autobiographical memory and future thinking in the MS clinic, especially in cases where memory/prospection complaints are not objectified with standard neuropsychological tests. This suggestion is reinforced by the fact that individuals with RRMS included in our studies were generally aware of their difficulties (however, this characteristic may not apply to individuals with MS in general because anosognosia could be observed even in the early stages of the disease) and that autobiographical memory and future thinking impairments could be efficiently compensated in the long run by a relatively short and easy-to-use intervention, such as the MVI programme. However, in practice, we point out that the effectiveness and generalisability of the MVI programme in subtypes other than RRMS remain to be tested.

From a clinical perspective, the mean age of MS onset coincides with a critical life period (20-40 years) in terms of identity construction and key life choices and decisions [50]. Autobiographical memory and future thinking provide the building blocks of identity construction and maintenance, so their preservation is essential to maintain self-continuity and coherence despite illness. Along these lines, Voltzenlogel and colleagues [51] showed that about two thirds of individuals with RRMS (in a group of 25) recalled at least one illness-related memory when asked to provide the 5 most personally significant memories defining themselves (i.e., self-defining memories [52]). Moreover, these illness-related memories were more integrated to the self and were judged as particularly central to one's life as compared with other self-defining memories. The integration of the illness into the self has been associated with lower psychological distress in individuals with MS [53]. Because MS also raises important concerns and uncertainties about the future [54], understanding how illness becomes (or not) a part of one's future identity is of paramount importance. To my knowledge, no study to date has examined this issue in individuals with MS and yet, it may

have important implications for the development of psychotherapeutic interventions aiming at promoting coping and psychological adjustment.

In addition to personal identity, the myriad other functional domains related to autobiographical memory and future thinking [13,15] further advocate for their consideration within the clinical arena. Future studies investigating the influence of autobiographical memory and future thinking deficits on other functions that are frequently impaired in individuals with MS such as decision-making, emotion regulation, or social participation [55-58], represent promising avenues of research. Future research along these lines may help elucidate the cognitive underpinnings of everyday difficulties experienced by people with MS and ultimately support the development of innovative rehabilitation techniques.

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Conflict of interest. None declared.

Legend

Figure. Mean number of episodic details produced for (A) past and (B) future events by individuals with relapse-remitting multiple sclerosis from the experimental, verbal control and stability groups before and after the mental visual imagery intervention.

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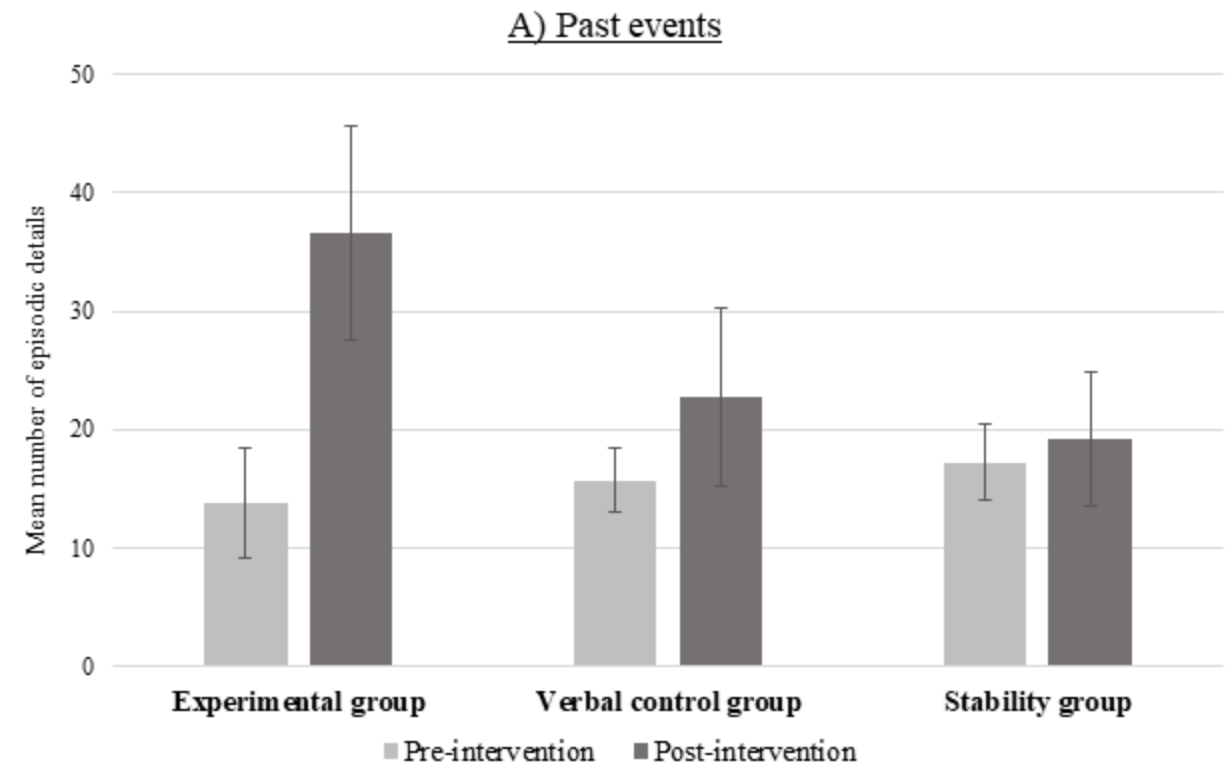
A) Past events
Mean number of episodic details
50
40
30
20
10
0
Experimental group
Verbal control group
Stability group
Pre-intervention
Post-intervention

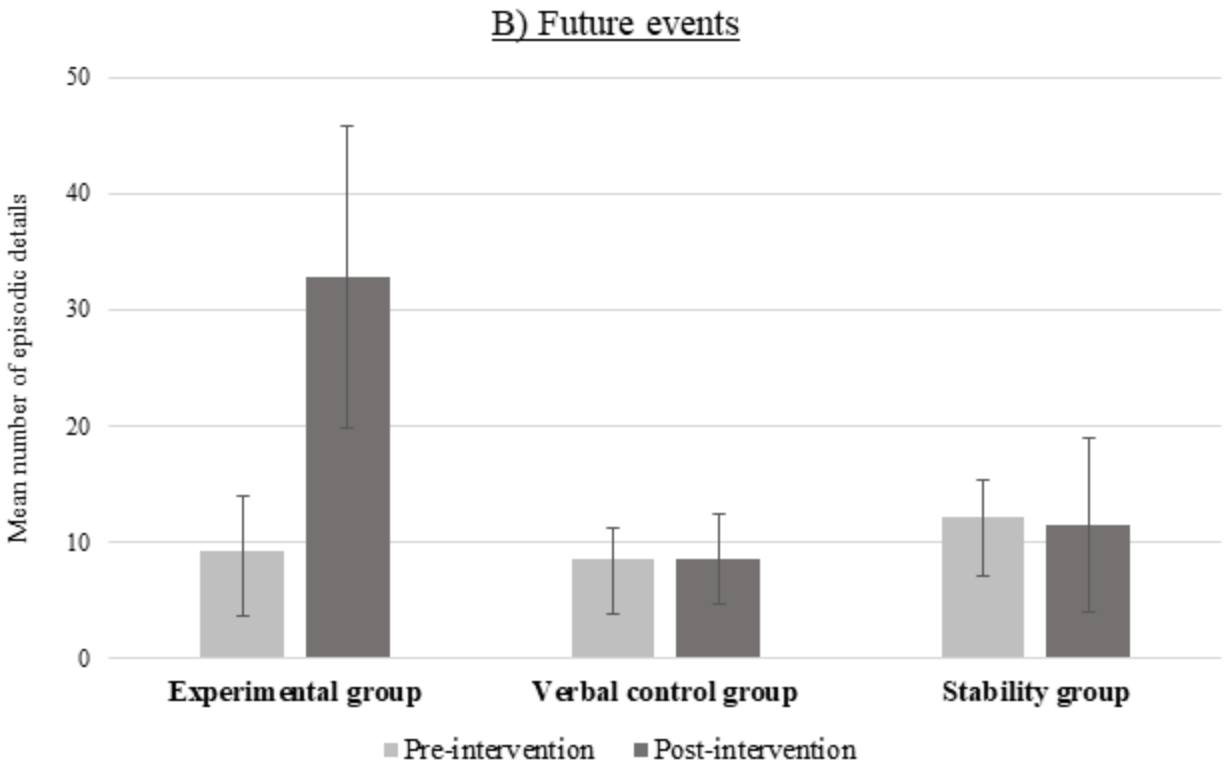
B) Future events
Mean number of episodic details
50
40
30
20
10
0
Experimental group
Verbal control group
Stability group
Pre-intervention
Post-intervention

Table 1. Demographic and clinical characteristics of individuals with relapsing-remitting multiple sclerosis (RRMS) and matched healthy controls included in the reviewed studies.

Study	RRMS	Healthy controls
Ernst et al. 2013 [17]	n = 25; 21 women Age: 42.96 (10.94) Years of education: 13.20 (2.84) EDSS score: 1.77 (1.72) Disease duration: 8.85 (7.59) years	n = 35; 29 women Age: 42.17 (9.44) Years of education: 12.71 (2.82) — —
Ernst et al. 2014 [18]	n = 39; 33 women Age: 39.77 (7.88) Years of education: 13.38 (2.15) EDSS score: 2.54 (1.38) Disease duration: 12.07 (7.56) years	n = 34; 26 women Age: 37.85 (11.64) Years of education: 14.21 (2.71) — —
Ernst et al. 2015 [36]	n = 18; 15 women Age: 41.11 (10.22) Years of education: 13.22 (2.05) EDSS score: 2.50 (1.37) Disease duration: 12.53 (8.68) years	n = 18; 15 women Age: 39.72 (8.61) Years of education: 13.44 (2.45) — —
Ernst et al. 2015 [37]	n = 21; 17 women Age: 41.52 (10.02) Years of education: 13.00 (1.97) EDSS score: 2.48 (1.37)	n = 20; 17 women Age: 39.15 (8.44) Years of education: 13.40 (2.35) —

	Disease duration: 11.79 (7.97) years	—
Ernst et al. 2016 [39]	n = 22; 17 women Age: 40.31 (10.08) Years of education: 13.13 (2.14) EDSS score: 2.45 (1.37) Disease duration: 11.38 (8.24) years	n = 22; 19 women Age: 39.63 (8.68) Years of education: 13.22 (2.30) — —
Ernst et al. 2015 [19]	*Experimental group* n = 17; 13 women Age: 42.00 (10.37) Years of education: 13.29 (2.17) EDSS score: 2.68 (1.58) Disease duration: 10.97 (9.53) years *Verbal control group* n = 10; 9 women Age: 37.40 (8.85) Years of education: 12.20 (1.55) EDSS score: 2.45 (1.40) Disease duration: 10.60 (5.66) years *Stability group* n = 13; 9 women	None

	Age: 40.00 (3.85) Years of education: 13.77 (2.45) EDSS score: 2.77 (1.41) Disease duration: 11.85 (7.01) years	
Ernst et al. 2018 [45]	*Experimental group* n = 10; 6 women Age: 38.40 (10.94) Years of education: 13.40 (2.22) EDSS score: 2.45 (1.73) Disease duration: 11.10 (11.03) years *Verbal control group* n = 10; 9 women Age: 37.40 (8.84) Years of education: 12.20 (1.55) EDSS score: 2.45 (1.40) Disease duration: 10.60 (5.66) years	None
Ernst et al. 2016 [46]	*Experimental group* n = 10; 6 women Age: 38.40 (10.94 Years of education: 13.40 (2.22) EDSS score: 2.45 (1.73)	None

	Disease duration: 11.10 (11.03) years *Verbal control group* n = 7; 6 women Age: 34.71 (8.44) Years of education: 12.57 (1.72) EDSS score: 1.85 (1.18) Disease duration: 8.85 (5.27) years	

Data are mean (SD).

EDSS, Expanded Disability Status Scale