Neurofeedback therapy for the management of multiple sclerosis symptoms: current knowledge and future perspectives

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Perspective

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) that constitutes the second most common cause of disability in young adults [1]. Demyelination, neurodegeneration and synaptopathy characterize the pathophysiology of this disease and could clinically manifest as sensory, motor, cerebellar, cognitive, affective and behavioral symptoms [2].

Fatigue is a frequent and debilitating symptom in patients with multiple sclerosis (MS). Affective manifestations are also of high prevalence in this population and can drastically impact the patients’ functioning. A considerable proportion of patients with MS suffer from cognitive deficits affecting general and social cognitive domains. In addition, pain in MS is commonly observed in neurology wards, could be of different types, and may result from or be exacerbated by other MS comorbidities. These complaints tend to cluster together in some patients and seem to have a complex pathophysiology and a challenging management. Exploring the effects of new interventions could improve these outcomes and ameliorate the patients’ quality of life. Neurofeedback (NFB) might have its place in this context by enhancing or reducing the activity of some regions in specific electroencephalographic bands (i.e., theta, alpha, beta, sensorimotor rhythm). This work briefly revisits the principles of NFB and its application. The published data are scarce and heterogeneous yet suggest preliminary evidence on the potential utility of NFB in patients with MS (i.e., depression, fatigue, cognitive deficits and pain). NFB is simple to adapt and easy to coach, and its place in the management of MS symptoms merits further investigations. Comparing different NFB protocols (i.e., cortical target, specific rhythm, session duration and number) and performing a comprehensive evaluation could help developing and optimizing interventions targeting specific symptoms. These aspects could also open the way for the association of this technique with other approaches (i.e., brain stimulation, cognitive rehabilitation, exercise training, psychotherapies) that have proved their worth in some MS domains.

Keywords
Multiple sclerosis, Fatigue, Cognition, Anxiety, Depression, Neurofeedback

1. Introduction

To start, 75–90% of patients with MS (PwMS) suffer from fatigue [3–7]. Despite the early description of MS fatigue by Freal and colleagues in 1980s [8], elucidating its pathophysiological mechanisms and finding efficient treatment options are still challenging tasks for researchers in this field. Regarding the underlying mechanisms of MS fatigue, immunological studies suggest an association between its occurrence and proinflammatory cytokines (e.g., Interleukin-6, Tumor Necrosis Factor-α, and Interferon-γ) [2]. In addition, neuroimaging studies hint towards functional or structural abnormalities affecting a large cortico-striato-thalamo-cortical loop at the basis of this symptom. This loop was found to include the striatum, thalami, fronto-parietal regions, and to a lesser extent temporal and occipital areas [3, 4]. Moreover, few neurophysiological works (i.e., electroencephalography (EEG) and evoked potentials) have proposed a correlation between this complaint and abnormalities involving the cortico-cortical connectivity in beta and theta bands, the sensorimotor network activity of the left dominant hemisphere in the beta band, and the amplitudes or latencies of event-related potentials [9–12]. In addition, EEG protocols that included motor tasks have suggested an association between fatigue and cortical hyperactivity during the movement, as well as inhibitory failure at the end of the movement [13]. Here, there was an interest to explore the relationship between MS fatigue and the decrease in EEG power prior to movement as well as the increase in EEG power after the movement (i.e., event-related desynchronization (ERD) and synchronization (ERS), respectively [14, 15]). In these studies, fatigued patients were found to have higher ERD and ERS over frontocentral areas relative to nonfatigued patients and healthy counterparts [13]; they also exhibited an anterior widespread of ERD. Both parameters were associated with fatigue severity. Other studies found a relationship between the interhemispheric imbalance in the activity of sensorimotor homologous areas (at rest and during movement) and MS fatigue [16]. This correlation seems driven by a decreased EEG power in the right sensorimotor cortex.
in fatigued PwMS, compared to healthy controls (HC) and PwMS without fatigue [16]. Furthermore, fatigued PwMS were found to have high alpha and low beta small-worldness (SW), a measure of regional functional connectivity) in the sensory network of left hemisphere, of which low beta SW was associated with fatigue severity [12]. In this context, using noninvasive brain stimulation technique such as transcranial direct current stimulation (tDCS), might help restoring the balancing in the activity of homologous areas—which appeared to improve MS fatigue—or targeting the left dominant areas [17]. The asymmetrical role of the dominant side in the altered connectivity is another argument supporting the association between MS fatigue and the multiple disconnection syndrome [18].

Besides fatigue, PwMS frequently complain of affective symptoms. Anxiety and depression symptoms occur in around 41% and 50% of patients respectively, could coexist with fatigue, are associated with difficulties in emotion regulation, and constitute an important source of impairment [19–21]. Some studies have suggested the involvement of parietal, temporal and limbic dysfunctions in depression, septo-fornical damage in anxiety, and abnormalities in frontal regions and/or their connections in both manifestations [19]. Additionally, a correlation has been found between neuroinflammation and these symptoms, particularly the levels of Interleukin-2 with anxiety, and Tumor Necrosis Factor-α and Interleukin-1β with depression [22]. Apart from anxiety and depression, PwMS have difficulties in identifying and describing their own emotions, and exhibit an externally oriented thinking and an impoverished fantasy life, all of which characterize the multicomponent construct known as alexithymia [23]. The latter is found in up to 53% or patients and seems to be related to gray matter (thalamus and basal ganglia) and white matter atrophy (corpus callosum and deep white matter) [23, 24].

Similar to the affective sphere, the cognitive sphere is altered during the course of the disease in up to 65% of PwMS [25]. This concerns the general (i.e., attention/information processing speed, memory, and executive functions) and social cognitive domains (i.e., emotion recognition, theory of mind, empathy) [25–27]. Some neuroimaging studies proposed associations between these deficits and structural and functional abnormalities of the whole brain (i.e., lesion load, diffuse cortical atrophy, microstructural pathologies involving the normally appearing white matter) or specific regions and their connections (regional atrophy, regional hypo/hyperactivation pattern, abnormal functional connectivity at rest or during the performance of cognitive tasks) [25–27]. Some reports suggest specific neural substrates according to deficient domains, such as for information processing speed with, thalamus and cerebellar abnormalities, memory deficits with precuneus, frontal and hippocampal pathologies, executive functions and dysfunctions of prefrontal regions, precuneus, basal ganglia, cerebellum, and insular and cingulate cortices, or social cognition with frontal, parietal and temporal regions lesions, amygdala, and/or their connecting tracts [25–27]. Moreover, neurophysiological works using EEG, magnetoencephalography (MEG), or event-related potentials found an association between cognitive deficits and cerebral activities disturbance. For instance, increased frontal theta/beta waves ratio is associated with attentional/information processing deficits, increased alpha power is associated with overall deficits, information processing speed as well as memory impairment, and increased theta power in parietal and temporal regions tend to be associated with overall cognition and memory deficits [28–30]. There are also evidences that a widespread slowing in deep gray matter [29] and abnormalities in event-related potentials [31] are associated with cognitive deficits.

Furthermore, up to 75–86% of PwMS experience chronic pain, which could be of several types, with central neuropathic extremity pain being the most common one [32, 33]. The latter mainly manifests as lower limb dyesthesias defined as a chronic, continuous, and burning sensation that worsens at night or with physical activity [33]. Lesions impairing the integrity of the spinothalamic nociceptive pathways and the subsequent loss of GABAergic interneurons involved in the ‘cold inhibition’ of pain were proposed at the basis of this pain type [33]. In addition, recent functional magnetic resonance imaging (fMRI) and MEG studies found that painful PwMS exhibit abnormalities in cross-network functional coupling within the pain connectome [34–36]. Such abnormalities involved the links between the salience network and each of the default mode network, the ascending nociceptive pathway, and the descending anti-nociceptive pathway [34–36]. In resting-state MEG or EEG studies, PwMS with chronic pain were found to have a slowing of peak power frequency in the alpha band [35], an increased power in the alpha band, or a decreased power in the beta band in regions that belong to the pain matrices with a correlation with pain intensity [35, 37]. Compared to PwMS without central neuropathic pain (CNP), those suffering from CNP had higher absolute and relative power spectral density (PSD) in the beta band and higher absolute PSD in the theta and beta bands in most of the studied areas [37].

Neurophysiological findings are summarized in Table 1 (Ref. [9–13, 16, 28–30, 35, 37, 38]).

Interestingly, the above-described manifestations might coexist in some PwMS, they could interact with each other’s, and have sometimes been proposed altogether as a specific symptoms cluster that occurs in this clinical population [19, 39–41]. From a therapeutic point of view, there are several limitations in the management of these symptoms. Most benefits and several side-effects have been attributed to the available pharmacological options [3, 32, 33, 42, 43]. For these reasons, there are still therapeutic gaps and unmet needs in this domain and new strategies are highly required. Facing this reality, there is a growing interest in exploring the effects of alternative interventions such as neuromodulation, cognitive rehabilitation, psychotherapies, and exercise ther-
apy which have yielded promising results in some of these symptoms [3, 4, 41–45].

Besides these choices, EEG-based Neurofeedback (EEG-NFB) has emerged as an innovative procedure that seems to be beneficial in several neuropsychiatric diseases, namely attention deficit and hyperactivity disorder (ADHD), other cognitive deficits, anxiety and depression, pain, and fatigue to cite a few [46–49]. In addition, several studies have highlighted the role of NFB in optimizing performance of healthy individuals in diverse fields, such as dancing, artistry, and medical studies [50, 51]. Therefore, EEG-NFB could be helpful for PwMS and might have a place in the fatigue management armamentarium.

EEG-NFB is a type of biofeedback that is based on the recording of raw EEG activity, its online analysis and the extraction of its various components. The latter are then fed to subjects in the form of an auditory, visual or combined feedback. For instance, EEG rhythms are displayed on a screen in the form of colored bars and, by using this information, individuals try to change their cerebral activity in order to improve their performance [52]. Description of various EEG rhythms and the main EEG-NFB types will be discussed in the following sections. When the recorded EEG signal is used to control external objects (computers, machines, prostheses…) and not to modulate brain activities by feedback, the technique is called Brain Computer Interface (BCI).

2. Brain waves, and neurofeedback types and applications

Cerebral activity could be recorded by placing electrodes on the scalp, an ancient technique that goes back to 1930 where a German psychiatrist, Hens Berger, documented the electrical nature of human brain functioning [53]. Nowadays, recent technological advances have allowed the development of methods that aim to optimize the acquisition and analysis of EEG data in various environments (e.g., MATLAB); they also highlighted the potential application of EEG in experimental and clinical settings (e.g., source localization methods, studying the functional connectivity, EEG-NFB, BCI) [54–56].

Thanks to this neurophysiological method, it is now widely admitted that neuronal activity varies among brain regions, and diverse patterns of brain waves have been categorized. Each pattern reflects a specific function and has a particular frequency and amplitude. Hence, five types of brain waves could be distinguished: delta (<4 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–100 Hz). Delta waves are observed during deep sleep, theta waves are recorded during sleepiness or light sleep, alpha rhythm is the hallmark of calm wakefulness, beta rhythm is the signature of alertness and gamma waves are seen when the person is trying to solve a problem [52]. In addition, some subtypes of brain rhythms have been described in certain brain regions. For instance, the sensorimotor rhythm (SMR) has been defined in the central (rolandic) cortical areas; it varies between 13 and 15 Hz and is also known as low beta. Moreover, two or three subtypes of alpha activities have been differentiated, each of them being related to a specific behavior [57]. This concerns low-alpha and high-alpha which have been found to be linked to a distinct brain function [58, 59]. Indeed, it has been suggested that EEG activities in the low-alpha band are predominantly associated with attentional processes, whereas EEG activities in the high-alpha band are primarily involved in semantic memory [60, 61].

There are two different directions in EEG-NFB training. It either focuses on low frequencies (alpha/theta protocol) to decrease tension and anxiety and ameliorate concentration [46], or it emphasizes on high frequencies (low beta or SMR) to reinforce attention and inhibit distractibility [62]. While the former strategy is done with eyes closed condition and

### Table 1. Association between electroencephalographic data and common multiple sclerosis symptoms.

| Symptom         | Association with EEG data                                                                                                                                 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cognitive deficits | Correlation between increased alpha power (global) and overall deficits as well as attention/IPS and memory deficits [28–30]            |
|                 | Trend toward a correlation between increased theta power (i.e., parietotemporal regions) and global as well as memory deficits [29]           |
|                 | Correlation between increased frontal theta/beta waves ratio and attentional/IPS deficits [28, 38]                                                      |
|                 | Correlation between fatigue and abnormalities involving the cortico-cortical connectivity in beta/theta bands and the sensorimotor network activity of the left dominant hemisphere in the beta band [9–12] |
| Fatigue         | Correlation between fatigue and increased beta temporo-parietal FCR and increased beta and theta fronto-frontal FCR [12]                       |
|                 | Increased alpha and decreased beta SW in the left hemisphere among fatigued patients; correlation between beta SW and fatigue [12]           |
|                 | Increased ERD and ERS in frontocentral regions among fatigued patients [13]; correlation between ERD/ERS and fatigue                              |
|                 | Correlation between asymmetry of right and left sensorimotor cortices EEG power and fatigue [16]                                                     |
|                 | Increased interhemispheric connectivity among fatigued patients; correlation between the interhemispheric coherence index and fatigue during a right-hand movement [16] |
| Pain            | Slowing of alpha peak power, increase of the alpha power and decrease of the beta-band power in regions belonging to the pain matrix          |
|                 | in patients with MS suffering from chronic pain; correlation between such abnormalities and pain intensity [35]                                 |
|                 | Increased absolute and relative PSD in the beta bands as well as absolute PSD in beta and theta bands among patients with MS suffering from central neuropathic pain [37] |

FCR, Functional connectivity at rest; HC, Healthy controls; EEG, Electroencephalography; ERD, Event-related desynchronization; ERS, Event-related synchronization; IPS, information processing speed; MS, Multiple sclerosis; PSD, Power spectral density; SW, Small-worldness.
aims to induce a relaxation state, the latter requires high vigilance level, and thus eyes are kept open throughout the whole session. For instance, beta waves reflect important focus, good concentration, and high mental performance. Given these data, beta training has been usually applied to improve attention [46], ameliorate school performance and reading ability [63], among others.

On the one hand, alpha waves are good indicators of alert relaxation, calmness and a pleasant state of mind. Therefore, NFB targeting alpha frequencies have been used to decrease anxiety and stress [64], alleviate pain and permit muscle relaxation and enhancement of cognitive performance [65]. Moreover, alpha/theta training is one of the most popular training for stress reduction [50]. This protocol uses an auditory feedback and aims at increasing the ratio of theta-to-alpha activities during a wakeful eyes-closed condition. Thus, it induces a deep relaxation state, given the association between theta activity and meditative states [66], as well as the wakefulness-to-sleep transition [67]. This protocol has been found to improve the performance of professional dancers and medical students, increase creativity and ameliorate microsurgical skills of ophthalmologic surgeons [50, 62].

On the other hand, beta waves reflect important focus, good concentration, and high mental performance. Given these data, beta training was applied to improve attention [46], ameliorate school performance and reading ability [63], among others. In addition, the antiepileptic effects of enhancing low-beta (SMR) activities in the rolandic region with or without a synchronous decrease of theta activities was assessed by several research teams. The impact of SMR training on seizure frequency was first documented, in 1969 in a cat model [68], and then replicated few years later in humans [69]. Apart from epilepsy, this strategy has been found to be efficacious in children with ADHD, allowing a decrease of their hyperactivity status.

3. Neurofeedback across multiple sclerosis studies

The effectiveness of EEG-NFB in reducing MS symptoms has been rarely evaluated. Very few studies have been performed in this context. In the first study targeting depression and fatigue, 24 PwMS (relapsing-remitting form) had significant improvement in these symptoms following the application of 16 sessions of EEG-NFB aiming to decrease alpha/theta power and increase beta power in the left prefrontal area (electrode over F3 of the 10–20 international system for electrode positioning) [70]. The beneficial effects lasted at least two months following the intervention and could be attributed to the choice of the cortical target and the type of EEG-NFB training. On the one hand, prefrontal regions are incriminated in the symptomatology of fatigue and depression in PwMS [19]. On the other hand, it is now widely accepted that frontal alpha asymmetry plays a key role in the generation of depression (for review, please refer to [71, 72]). In other words, increased alpha activity in left frontal regions compared to right frontal areas, reflects a reduced functioning of the left ones which are known to be involved in positive emotions. Following this logic, decreasing alpha/theta power along with an enhancement of the beta waves of the left frontal regions would ameliorate depression as observed in psychiatric samples [71, 72], and could alleviate depression and associated fatigue as seen in PwMS [70].

Taking into consideration what has been tried in other neurological and/or psychiatric diseases, EEG-NFB protocols adopted in ADHD children might be interesting to understand the mechanisms underlying the clinical improvement and develop protocols that are adapted for PwMS [73–78]. One of the most applied ADHD protocols—the theta/beta NFB training—consists of reducing theta activity and/or enhancing beta activity in the central and/or frontal regions. It is based on neurophysiological studies that documented high theta power, low beta power, or high theta/beta ratio in patients with ADHD [75]. Theta/beta protocol resulted in an improvement of the attention capacities and a reduction of hyperactivity of ADHD children. Another pertinent protocol applied in this population is the ‘SMR training’, which consists of increasing SMR activities in the central region of the right hemisphere. SMR training results in satisfactory outcomes regarding attention and hyperactivity disorders. Such results seem to be related to the implication of SMR in behavioral inhibition, vigilance stabilization and sleep quality [79].

Based on this background, two studies have addressed the effects of NFB on cognitive deficits in PwMS. The first one applied a five-session training program that aimed at decreasing the theta/beta ratio in the frontal cortical region (Fz) in 56 PwMS having different disease subtypes (mixed cohort) [38]. Compared to patients with normal information processing speed, impaired patients had a higher frontal theta/beta ratio; the latter transiently decreased during EEG-NFB sessions compared to baseline, which supports its promising role as a potential marker of processing speed in PwMS.

Conversely, another study aimed at increasing the theta/beta ratio in the central region (Cz) (i.e., ‘SMR training’) using 10 home-based sessions in 17 PwMS (mixed cohort) [80]. Half of the patients were responders to EEG-NFB, with an improvement in long-term memory and executive functions, associated with an enhancement of SMR power [80]. Therefore, theta/beta modulation and SMR training merit to be explored in upcoming EEG-NFB trials in order to assess their potential clinical implication for managing cognitive deficits in PwMS. In addition, given that an alteration of attentional networks, mainly alertness circuits, has been proposed to be incriminated in the pathophysiology of fatigue in PwMS [81], one can assume that enhancing attentional capacities of these patients could also alleviate fatigue and ameliorate patients quality of life, warranting a further exploration of this hypothesis in future.

Finally, Jensen and colleagues assessed the utility of EEG-NFB in enhancing the response to hypnosis in PwMS suffer-
| Study          | Study design               | Population | NFB setting | NFB intervention | Outcomes | Results                                                                 |
|---------------|----------------------------|------------|-------------|------------------|----------|-------------------------------------------------------------------------|
| Choobforoushzadeh et al. [70] | Randomized controlled parallel study | 24 PwMS | Active: F3  | NFB training (16 sessions) | Depression: HADS depression subscale | Improvement in fatigue and depression scores after the intervention and lasting 2 months |
|               |                            |            |             |                  |          | **Active arm:** 12 RR, 6 males                                            |
|               |                            |            |             |                  |          | Decrease theta (4–8 Hz) and alpha (8–12 Hz) activity during reinforcement of 15–18 Hz beta for the first 20 min then reinforcing 12–15 Hz for the final 10 min |
|               |                            | DD: 6.91 ± 4.52 years, EDSS: 3.8 ± 1.5 | Visual game and audio | **Fatigue:** FSS | **Treatment as usual** |
| Jensen et al. [82] | Pilot study                | 32 PwMS with | Active: AFz | NFB training: 6 sessions (2 per week) over CPAQ, 3 weeks followed by 1 hypnosis session, then 4 NFB training sessions preceding 4 self-hypnosis sessions | Improvement in outcomes following either or both treatment interventions compared to control (pain intensity) |
|               |                            |            |             |                  |          | **Randomized chronic pain and/or fatigue**                              |
|               |                            |            |             |                  |          | **Active arm:** 10 PwMS                                                 |
|               |                            |            |             |                  |          | Increase theta (3–7 Hz), low-beta (12–15 Hz), high-beta (22–30 Hz), and gamma (45–60 Hz) activity |
|               |                            |            |             |                  |          | **Control arm:** 9 PwMS                                                 |
|               |                            |            |             |                  |          | Feedback using NeXus-4 amplifier                                           |
|               |                            |            |             |                  |          | **Similar effects of both interventions in terms of fatigue**            |
| Study                  | Study design          | Population | NFB setting                      | NFB intervention | Outcomes                                                                 | Results                                                                 |
|-----------------------|-----------------------|------------|----------------------------------|------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------|
| 17RR, 6SP, 3PP, 6UT   | Keune et al. [38]      | 10 PwMS:   | Active electrode Training        | NFB training: 5 sessions (over 2 weeks) | Theta/beta ratio stable across sessions                                 | Reduction in the theta/beta ratio within sessions driven by a reduction of theta power |
|                       |                       | 6 RR, 3SP, 1PP, | Feedback                        |                  |                                                                           |                                                                        |
| 8 males               | Cross-sectional study | 8 males    | Active electrode Training        | Mindfulness      | Fatigue: FSS                                                             | Greater longer-term analgesic effects obtained following NFB compared to mindfulness training |
|                       |                       | DD: 20.09 ± 10.00 | Feedback                        |                  |                                                                           |                                                                        |
| 17RR, 6SP, 3PP, 6UT   | Active electrode Training | NFB training: 5 sessions (over 2 weeks) | Mindfulness      | Fatigue: FSS                                                             | Greater longer-term analgesic effects obtained following NFB compared to mindfulness training |
|                       |                       | 8 males    | Feedback                        |                  |                                                                           |                                                                        |
|                       | Cross-sectional study | 8 males    | Audio feedback                   |                  |                                                                           |                                                                        |
|                       | Cross-sectional study | 8 males    | Audio feedback                   |                  |                                                                           |                                                                        |

**Table 2. Continued.**

- Theta reduction following both interventions
- Theta, beta and gamma activity increase following the NFB training arm
- Beta and gamma activity decrease following the mindfulness arm
### Table 2. Continued.

| Study                  | Study design         | Population | NFB setting | NFB intervention | Outcomes | Results |
|------------------------|----------------------|------------|-------------|------------------|----------|---------|
|                        |                      |            | Active electrode | Training Feedback |          |         |
|                        |                      |            |            |                  |          |         |
|                        |                      |            |              |                  |          |         |
| 3 males                | Reduce theta/beta ratio | No control intervention | DD: 9.45 ± 6.05 years, EDSS 4.0 [2.5–7] Visual feedback | Cognitively impaired patients (SDMT) | Kober et al. [80] Pilot study | 14 PwMS | Active: Cz NFB training group (10 sessions) Cognition: BRB-N Long-term memory and executive functions improvement in 7/14 patients who were able to regulate their brain activity during NFB training |
|                        |                      |            |              |                  |          |         |
| 13 RR, 1 SP            | Increase sensorimotor rhythm (12–15 Hz) | No control intervention | Other measures: No significant effects of NFB over the other variables in neither group | DD: 9.0 ± 1.9 years, EDSS: 2.3 [3.5] Visual feedback | Classed as responders vs. non-responders |
| 7 males                |                      |            |              |                  |          |         |

Data are presented as mean ± SD/SE or median [IQR or range]. BPI, Brief Pain Interference; BRB-N, Brief Repeatable Battery of Neuropsychological Tests; CPAQ, Chronic Pain Acceptance Questionnaire; DD, Disease duration; EDSS, Expanded Disability Status Scale; HADS, Hospital Anxiety and Depression Scale; FSS, Fatigue Severity Scale; MAAS, Mindful Attention Awareness Scale; MSQOL-54, Multiple Sclerosis Quality of Life-54; NFB, Neurofeedback; NRS, Numerical Rating Scale; N/A, Not applicable; PCDS, Pain Catastrophizing Scale; PHQ, Patient Health Questionnaire; PP, Primary progressive; PROMIS, Patient Reported Outcomes Measurement System; RR, Relapsing remitting; SDMT, Symbol Digit Modalities Test; SP, Secondary progressive; UT, Unidentified type.

4. Conclusions

This report provides a brief reappraisal of EEG-NFB principles and its application in MS. Facing the debilitating nature of MS symptoms and unsatisfactory outcomes of pharmacological options, EEG-NFB might have its place in the management of PwMS. However, the available data are scarce and heterogeneous. Preliminary evidence suggests the potential of using EEG-NFB to enhance frontal beta rhythm in the context of depression and fatigue, reduce theta/beta ratio or increase SMR for targeting cognitive deficits, and augment theta rhythm to prime the hypnotic response and relieve pain. Nevertheless, taking into consideration the newly proposed “symptoms cluster” (i.e., a cluster associating fatigue, affective and cognitive symptoms), acting on one of its components may also lead to improvement of the other components. In addition, anxiety, social cognitive deficits and alexithymia constitute other important domains that were not yet targeted by EEG-NFB. Various EEG-NFB protocols for targeting anxiety are already available and might be applicable in PwMS [71, 72], while other protocols could be considered for addressing social cognition and alexithymia [84]. EEG-NFB is obviously still at its infancy in this clinical population. Future trials would benefit from including a comprehensive evaluation, as well as comparing different types of EEG-NFB (i.e., cortical target, specific rhythm, session duration and number) to determine the optimal protocols in

...ing from chronic pain [82, 83]. Since hypnotic response is characterized by slower brain oscillations, the authors aimed at increasing theta power in midline frontal cortical areas [82] or left anterior regions [83] prior to hypnosis in the aim of improving its effectiveness. Compared to a control intervention (i.e., hypnotis alone), NFB enhanced the response to hypnosis in PwMS, supporting its potential role as a priming strategy [82, 83]. Future works should assess the impact of NFB on pain in MS when applied as a monotherapy.

The above-mentioned EEG-NFB protocols are summarized in Table 2 (Ref. [38, 70, 80, 82, 83]).
this context. EEG-NFB is simple to adapt and easy to coach. These aspects would open the way for the association of this technique with other approaches (i.e., brain stimulation, cognitive rehabilitation, exercise training, psychotherapies) that have proved their worth in some MS domains.

Abbreviations
ADHD, attention deficit and hyperactivity disorder; BCI: brain computer interface; CNP, central neuropathic pain; CNS, central nervous system; EEG, electroencephalography; ERD, event-related desynchronization; ERS, event-related synchronization; HC, healthy controls; MEG, magnetoencephalography; MRI, magnetic resonance imaging; MS, multiple sclerosis; NFB, neurofeedback; PwMS, patients with MS; PSD, power spectral density; SMR, sensorimotor rhythm; SW, small-worldness; tDCS, transcranial direct current stimulation.

Author contributions
Conceptualization, methodology, writing—review and editing, SSA, BB, JPL and MAC.

Ethics approval and consent to participate
Not applicable.

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