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Neuromuscular electrical stimulation reduces spinal excitability in Multiple Sclerosis patients with spasticity symptoms

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ABSTRACT

Background: The use of neuromuscular electrical stimulation (NMES) has been recently proposed in patients with neurological diseases, such as spinal cord injuries and stroke, to improve symptoms of spasticity, resulting in both increased control of voluntary movements and improved functional ability in daily activities. Despite several authors suggest that these results could be related to a reduced spinal excitability, which is known to be higher in spastic patients, no previous studies investigated the neurophysiological mechanisms underlying the effect of NMES in reducing spasticity. In addition, there are no studies in the literature adopting NMES to improve spasticity in patients with Multiple Sclerosis (MS). Therefore, this study aims at comparing acute responses in spinal excitability, as measured by H-reflex, between MS patients with and without spasticity, following three experimental conditions: 1) isometric voluntary contraction (ISO) of the ankle plantar flexor muscles; 2) NMES passively applied (pNMES) to the ankle plantar flexor muscles; and 3) NMES superimposed onto isometric voluntary contraction (NMES+) of the same muscles.

Methods: 15 MS patients with spasticity (MS+) and 15 MS patients without spasticity (MS-) took part in a single experimental session, which consisted in the application of NMES to the ankle plantar-flexor muscles in the most spastic and compromised leg. Following the assessment of maximum voluntary isometric contraction (MVIC), participants were asked to perform 15 repetitions of 6 s at 20 % of MVIC, with 6 s of recovery between repetitions, during the three experimental conditions (ISO, pNMES, NMES+). Before and after each condition, soleus (SOL) H-reflex amplitudes were recorded by using surface electromyography (sEMG).

Results: In MS+, H-reflex amplitude significantly decreased after both pNMES ($p = 0.007$) and NMES+ ($p = 0.003$), while it was unaltered after ISO ($p = 0.829$). In MS-, H-reflex amplitude did not change under any experimental condition (ISO: $p = 0.383$; pNMES: $p = 0.328$; NMES+: $p = 0.087$).

Conclusion: The reduction of H-reflex after pNMES and NMES+ can be attributed to a reduced spinal excitability in spastic MS patients, which may be attributed to presynaptic inhibition, recurrent inhibition, gamma-aminobutyric acid activity and persistent inward current. These results are highly relevant from both neurophysiological and clinical point of views, suggesting new approaches to manage spasticity symptoms in neurological patients.

1. Introduction

Multiple Sclerosis (MS) is a common autoimmune inflammatory disease (Lane et al., 2022), characterised by demyelination and axon damage throughout the central nervous system (Bjartmar and Trapp, 2001; Hemmer et al., 2006), leading to several heterogenous and unpredictable symptoms. Among these symptoms, spasticity is one of the most common (Burke, 1988; ; Pandyan et al., 2005). Lance (1980) described spasticity as a velocity-dependent increase in tonic stretch reflexes and exaggerated tendon jerks, which stem from stretch reflex

Abbreviation: NMES, Neuromuscular electrical stimulation; MVIC, Maximal voluntary isometric contraction; sEMG, Surface electromyography; PSI, Presynaptic inhibition; PIC, Persistent inward current; RI, Recurrent inhibition.

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hyperexcitability. Neurophysiological aspects of spasticity are usually assessed by the Hoffmann reflex (H-reflex) technique (Alibiglou et al., 2008; Decq et al., 2004; Rougier et al., 2007; Voerman et al., 2005). The H-reflex represents a low threshold spinal reflex that can be used to study some pathways that are responsible for spasticity (Leocani et al., 2015; León et al., 2023; Morita et al., 2001; Squintani et al., 2016), such as presynaptic inhibition (PSI), post-activation depression, recurrent inhibition (RI), and reciprocal inhibition (Morita et al., 2001; Sinkjaer et al., 1995). In people with MS (pwMS) and spasticity, it has been shown that the control of these inhibitory mechanisms is altered to a varying degree (Morita et al., 2001), inducing a reduced H-reflex latency and an increased H-reflex amplitude (Sehgal and McGuire, 1998; Traversa et al., 2000) during different tasks (Morita et al., 2001; Motl and Dishman, 2003; Sinkjaer et al., 1995; Sosnoff and Motl, 2010). These changes in latency and amplitude are associated with increased spinal excitability, which is a hallmark of spasticity (Levin and Hui-Chan, 1993).

The hyperactivity of spinal reflex arc leads to several consequences involving muscle spasms and clonus, pain, feelings of stiffness, bladder dysfunction, sleep disturbances, fatigue, and restricted mobility, which compromise the ability to perform daily activities (Boorman et al., 1992; Hugos and Cameron, 2019; Thompson and Wolpaw, 2021). In recent years, non-pharmacological approaches, such as neuromuscular electrical stimulation (NMES), have been proposed to improve spasticity in people with a number of neurological diseases, such as stroke and spinal cord injury (Motta-Oishi et al., 2013; Popović et al., 2009). NMES is a Food and Drug Administration–approved treatment for reducing muscle pain and spasms (Wahls et al., 2010), which induces visible muscle contractions through electrical stimuli transcutaneously applied to superficial skeletal muscles (Botter et al., 2011; Maffiuletti, 2010). Current studies indicate that NMES combined with other interventions was associated with decreased upper limb spasticity and increased range of joint movement in patients with stroke (Stein et al., 2015) and spinal cord injury (Bochkezanian et al., 2018). Nevertheless, to the best of our knowledge, no previous studies investigated the effect of NMES intervention on spasticity in pwMS.

Despite these promising results, the use of NMES is not fully accepted as a routine practice in rehabilitation. This could be attributable to a scarce understanding of the neurophysiological mechanisms underlying NMES-related improvements in neurological patients. Some of these mechanisms have been investigated in healthy individuals, either young or older. In young individuals, previous studies showed that NMES acts at the level of spinal reflexes, modifying spinal excitability (Borzuola et al., 2020; Scalia et al., 2023). Particularly, when NMES is superimposed to isometric voluntary contraction, it induces an acute potentiation of the soleus H-reflex amplitude immediately after exercise (Borzuola et al., 2023, 2020; Lagerquist et al., 2012; Scalia et al., 2023). In contrast, when NMES in passively administered, it induces a considerable attenuation of the H-reflex (Borzuola et al., 2020; Grosprêtre et al., 2018; Gueugneau et al., 2017; Milosevic et al., 2019; Scalia et al., 2023; Wegrzyk et al., 2015). Interestingly, only in one study by Scalia et al. (2024), who investigated the effect of NMES on spinal excitability in pwMS, no significant changes in the H-reflex amplitude were observed after both passive and superimposed NMES (Scalia et al., 2024). However, in this study, all MS patients did not have any symptoms of spasticity.

Therefore, the aim of this study was to compare the acute modulation of spinal excitability, as measured by H-reflex of the Soleus (SOL) muscle, between MS patients with spasticity and MS patients without spasticity, following a single intervention consisting of three experimental conditions: 1) NMES superimposed onto voluntary contraction (NMES+) of the plantar-flexor muscles of the ankle; 2) passive NMES (pNMES) applied to the plantar-flexor muscles of the ankle; 3) voluntary isometric contractions (ISO) of the plantar-flexor muscles of the ankle. Based on the results reported from previous studies that have applied this protocol on healthy individuals and MS patients without spasticity (Borzuola et al., 2020; Scalia et al., 2023, 2024), the first hypothesis is that the H-reflex would increase after NMES+, decrease after pNMES, and remain unchanged after ISO in MS patients with spasticity. The second hypothesis is that the H-reflex would remain unchanged after all three experimental conditions in MS patients without spasticity.

2. Material and methods

2.1. Participants

A total of thirty patients with MS were recruited for participation from October 2022 and October 2023. MS participants had been previously diagnosed with MS by a consultant neurologist and were recruited from the Multiple Sclerosis Centres of Santa Maria Goretti Hospital (Latina, Italy) and San Pietro 'Fatebenefratelli' Hospital (Rome, Italy). Potentially eligible patients with relapse-remitting, as well as primary and secondary progressive MS, were provided with information about the study by their neurologists, who also sent them an informative letter. A screening process was then conducted by the study team to establish eligibility to participate in the study among subjects interested in being enrolled. MS patients aged 20 to 65 with a disease duration of 5 to 25 years, stable medical status in the past 3 months, an Expanded Disability Status Scale score (EDSS) of <6.5, and the ability to walk independently at household distances were included in the study (Almuklass et al., 2018; Hoque et al., 2019). Patients receiving ongoing pharmacological treatment for spasticity were included in the study only if their anti-spastic medication had been stable for a minimum of three months as well as if they confirmed their willingness to not to take medications to manage spasticity symptoms during the test day, as this could influence spinal excitability. MS participants were excluded if they met one of the following exclusion criteria (Almuklass et al., 2018; Hoque et al., 2019): MS relapse in the past 3 months; comorbidity with other cardiovascular, lung and/or orthopaedic disorders; history of seizures or/and epilepsy; contraindications to electrical stimulation (implanted pacemaker or other biomedical devices, metal, allergies to surface electrode gel); and ongoing pregnancy. None of the participants had experience with NMES exercise before performing the experimental session.

Moreover, in all patients, a neurologist clinically tested the level of pain with the Visual Analog Scale (VAS); and the presence or absence of spasticity with the Modified Ashworth Scale (MAS). Based on the MAS results, MS participants were dived into two groups: thus, 15 participants were part of the 'MS-' group, involving MS patients without spasticity (MAS $= 0$); and 15 participants were included in the 'MS+' group, involving MS participants with spasticity in at least one leg (MAS ≥ 1).

Participants who met the inclusion/exclusion criteria were asked to sign an informed consent approved by the Institutional Ethics Review Board of the University of Rome "Foro Italico" (CAR 120/2022) before participating.

The sample size was determined a priori based on a statistical power analysis (G*Power software v.3.1.9.4) for a mixed-model ANOVA (within-between factors) ($\alpha=0.05$, statistical power $= 0.95$, effect size $=$ 0.31), as described by Cohen (1992) (Cohen, 1992). Effect size was estimated based on previous studies investigating modulation of spinal excitability in response to acute exercise (Borzuola et al., 2020; Scalia et al., 2023, 2024).

2.2. Experimental procedure

All measurements were conducted in the laboratory of "Bioengineering and Neuromechanics of Movement" at the University of Rome "Foro Italico". The experimental procedures, including both the instrumentation and the experimental protocol, have been extensively described in some previous studied by the authors (Borzuola et al., 2024; Scalia et al., 2023, 2024). The details of the procedures are illustrated in

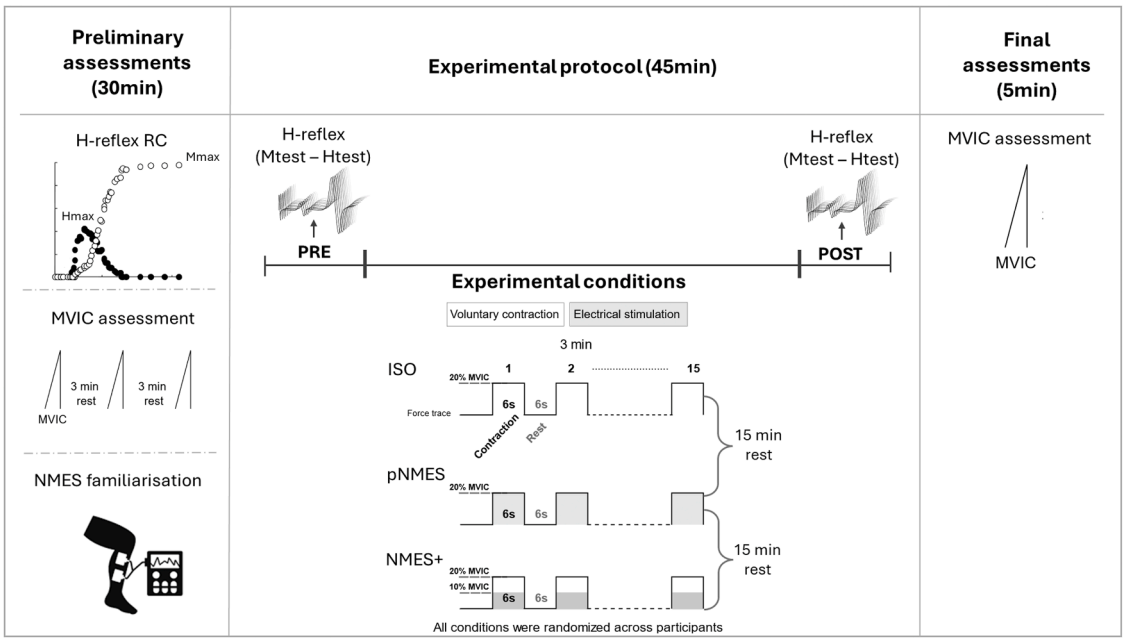

Fig. 1. Experimental procedure. Description of the experimental procedure, which involved a preliminary assessment phase, the three experimental conditions (ISO, pNMES, and NMES+), and a final assessment phase.

Fig. 1.

In summary, participants took part in a single experimental session during which they performed three experimental conditions: ISO, pNMES and NMES+. Each condition consisted of 6 s of contraction and 6 s of recovery, for a total of 15 repetitions. The conditions were randomly assigned and interspersed with 15 min of recovery. Before and after each experimental conditions, twenty H-reflex measures (i.e. peak-to-peak amplitudes) were carried out using surface electromyography (sEMG) (Fig. 2a). As illustrated in Fig. 3, the stimulus intensity was selected to evoke a H-reflex (Htest) on the ascending part of the recruitment curve with an amplitude corresponding to 80–85 % of Hmax. Throughout the experiment, a small M-wave corresponding to Htest (Mtest) was chosen and monitored to ensure consistency and reliability of the H-reflex assessment. A H-reflex measure was accepted if the amplitude of the M-wave was within ± 5 % of the selected Mtest. The amplitudes of all H-reflexes and M-waves were normalized to Mmax and averaged within each trial.

Before starting the experimental conditions, the maximal voluntary isometric contraction (MVIC) of the ankle plantar flexor muscles was measured (Fig. 2b) to set the target force of 20 % of the MVIC during the experimental conditions. This intensity was selected since it has been shown to affect spinal excitability without tiring muscles (Borzuola et al., 2023; Grosprêtre et al., 2018; Gueugneau et al., 2017; Scalia et al., 2023, 2024), and to avoid pain or discomfort during NMES (Wiest et al. 2017). In ISO, participants voluntarily contracted their plantar flexor muscles to achieve 20 % MVIC. In pNMES, the plantar flexor muscles

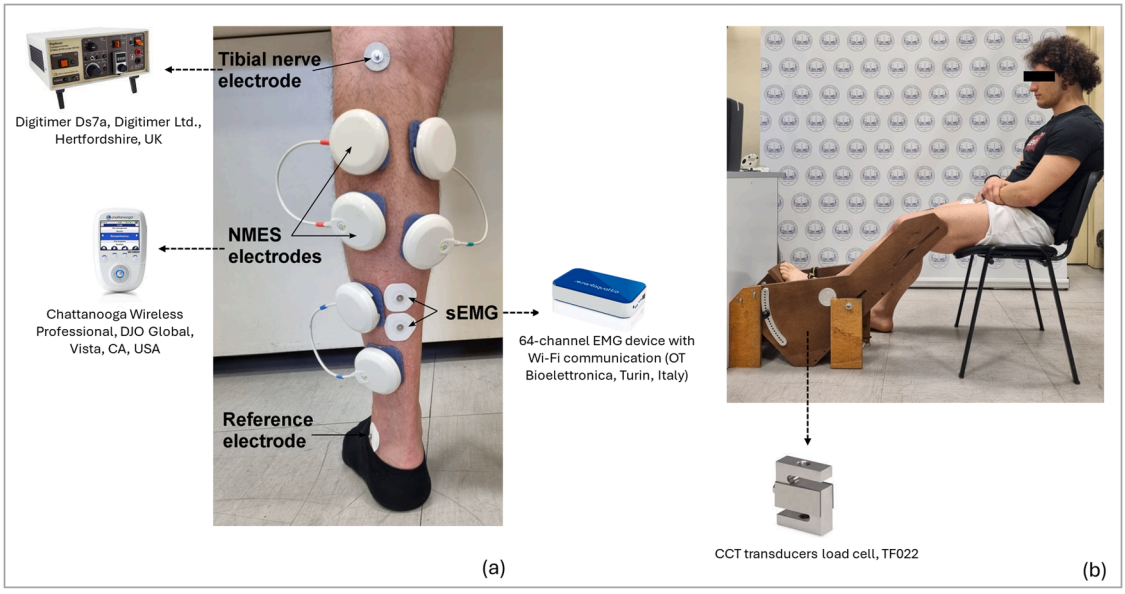

Fig. 2. Experimental set up. a) Position of sEMG and stimulation (NMES and H-reflex) electrodes. b) Patient's position on the dynamometer chair during the MVIC, the H-reflex recruitment curve (RC) and the three experimental conditions (pNMES, NMES+, ISO), with hips at 90° (0° = neutral hip position), knees at 60° (0° = full knee extension) and ankles at 0° (0° = foot orthogonal to the shank axis).

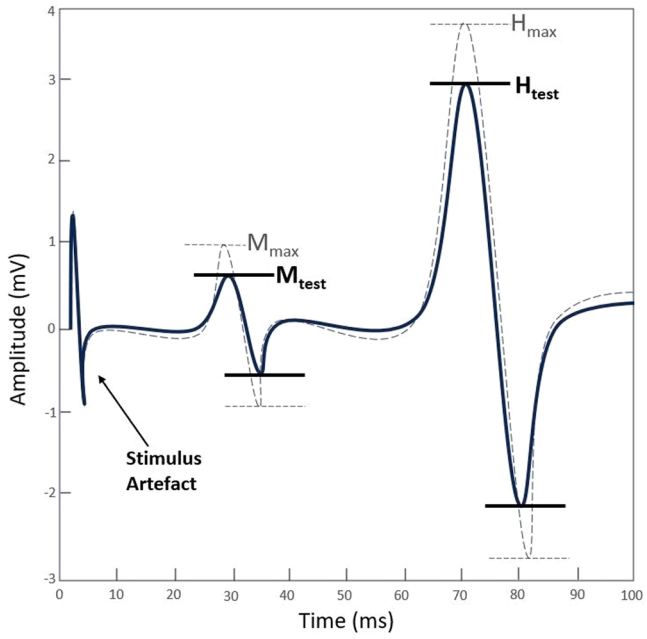

Fig. 3. Procedure for selection of *H*−reflex and *M*−wave. The grey dashed line represents the maximum *H*−reflex (Hmax) and the corresponding *M*−wave (Mmax). The black solid line represents the *H*−reflex test (Htest) (80−85 % of Hmax) and the corresponding *M*−wave test (Mtest) (5 % of Mmax). Figure from Scalia et al. (2024), with permission.

were passively stimulated to achieve the 20 % of MVIC; the current pulse intensity was progressively increased (average NMES intensity: MS+ = 18.5 mA, range 8.2–28.6 mA; MS- = 18.8, range 8.5–29.3 mA) to reach the target force. In NMES+, the current pulse intensity was set (average NMES intensity: MS+ = 13.8 mA, range 6.9–24.4 mA; MS- = 13.5, range 7.1–24 mA) to produce half of the target force (10 % of MVIC), while participants voluntarily contracted their plantar flexor muscles at 10 % of MVIC to reach the full target force of 20 % MVIC. The MVIC was measured again at the end of the three experimental conditions to confirm that muscle fatigue had not occurred.

In order to electrically stimulate ankle plantar flexors, a muscle stimulator (Chattanooga Wireless Professional, DJO Global, Vista, CA, USA) that produces rectangular, balanced biphasic pulses was used. According to the electrical stimulator user's manual, three self-adhesive electrodes (diameter 50 × 50 mm, Compex Dura-Stick® Plus a Snap, DJO Global, Vista, CA, USA) with positive polarity were applied to the motor points of the gastrocnemius lateralis, gastrocnemius medialis, and soleus muscles. The motor points of the three muscles were determined using a hand-held cathode ball electrode. Hence, an electrode with negative polarity was placed about 3 cm above each positive electrode (Fig. 2). A pulse frequency of 20 to 50 Hz and a pulse duration of 400 μs were selected to administer NMES. These NMES parameters were intended to reduce discomfort (Maffiuletti, 2010).

For MS-, all procedures were performed on the participant's weaker or more affected leg (based on self-report) (Almuklass et al., 2018); for MS+, all procedures were performed on the patient's spastic leg, based on clinical screening (MAS score).

2.3. Data analysis

All data were analysed using a custom Matlab code (Matlab 2015b, Mathworks Inc., Natick, MA, USA). For each stimulation, possible pre-activation of SOL muscle occurring before the reflex assessment was checked in the sEMG recordings. sEMG traces that showed pre-activation, and the corresponding H-reflex measure were removed from data analysis.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS 24.0 (IBM Corp., Armonk, NY, USA). A two-way mixed ANOVA was used to investigate statistical differences in H-reflex and M-wave measures between the two groups, the three experimental conditions, and over time. "Condition" and "Time" represented the two within-subjects factors with "Condition" having three levels (ISO, pNMES and NMES+), and "Time" having two levels (PRE and POST). 'Group' represented the between-subjects factor, with 'MS+' referred to MS patients with spasticity, and 'MS-' referred to MS patients without spasticity. When a significant main effect or interaction was found, paired t tests were used for post hoc analyses. In addition, a t-test was performed to compare MVIC values at the beginning (Pre-test) and at the end (Post-test) of the entire experimental protocol in both MS- and MS+. Moreover, a *t*-test was carried out on the levels of current intensity used during pNMES and NMES+ in both groups. The alpha level for statistical significance was set to $p < 0.05$, with a Bonferroni correction for multiple post hoc comparisons. Normality and sphericity of the data were checked using the Shapiro–Wilk Test and the Mauchly Test, respectively. Data are reported as group mean ± standard deviation (SD).

3. Results

3.1. Demographics and clinical characteristics

Table 1 shows age, gender, anthropometric characteristics, type of MS, duration of illness, presence of spinal cord lesion, scores of MAS, EDSS and VAS in both groups of participants.

3.2. Neurophysiological and MVIC measurement

All recorded data showed a normal distribution and the Mauchly test confirmed that the assumption of sphericity was not violated for any of the variables.

The ANOVA on the normalized H-reflex amplitude showed no significant effects of 'Condition' ($F = 1.306$, $\eta p2 = 0.271$, $p = 0279$) and 'Group' ($p = 0404$); however, there was a significant effect of Time ($F = 16.638$, $\eta p2 = 0.058$, $p = 0.001$) and 'Condition*Time*Group' interaction ($F = 3.684$, $\eta p2 = 0.007$, $p = 0.031$). Post-hoc analysis showed a significant decrease in the H-reflex amplitude following both pNMES (−13.6 %; $p = 0.007$) and NMES+ (−11.8 %; $p = 0.003$), but no significant differences following ISO ($p = 0.498$), in MS+. Conversely, H-reflex amplitude did not significantly change following all three experimental conditions (ISO: $p = 0.383$; pNMES: $p = 0.328$; NMES+: $p = 0.087$) in MS-.

Moreover, post hoc analysis showed no significant differences in PRE H-reflex amplitude between all three experimental conditions (ISO,

Table 1
Patient's data. Participant descriptive characteristics.

	MS- (15)		MS+ (15)	
Characteristics	mean	SD	mean	SD
Age	44	12	49	9
Sex (n female, %)	6 (40)		6 (40)	
Height [m]	1,74	0,77	1,71	0,74
Body Mass [kg]	71,87	11,93	69,93	13,78
Body Mass Index (BMI)	23,74		23,9	
Type of MS				
Relapse-Remittent (n, %)	15 (100)		5 (33)	
Primary-Progressive (n, %)	0 (0)		5 (33)	
Secondary-Progressive (n, %)	0 (0)		5 (33)	
Spinal lesion (n yes (%))	8 (53)		7 (47)	
Duration of disease (year)	15	8	17	6
MAS	-	–	2,3	1,1
EDSS	1,3	0,4	5,2	1,3
VAS	1,2	1,1	4,6	2,0

pNMES, NMES+), in both groups, confirming consistency and reliability of the H-reflex assessment. In addition, although the H-reflex amplitude appears to be higher in the MS+ group than the MS- group at baseline, statistical analysis did not show a significant difference between the two groups (ISO: MS+ vs MS-, $p = 0390$; pNMES: MS+ vs MS-, $p = 0333$; NMES+: MS+ vs MS-, $p = 0353$). PRE and POST values of all conditions are reported in Table 2 (a, b).

Fig. 4 (a, b) describes a typical example of SOL H-reflex and M-wave sEMG response to a series of 20 electrical stimuli that were averaged within the same trial before (PRE) and after (POST) each experimental condition (ISO, NMES, NMES+) in one MS participants of the MS+ group (Fig. 4a) and in one MS participant of the MS- group (Fig. 4b). Fig. 5 (a, b) reports the mean values of SOL H-reflex amplitude and associated M-waves that were both normalized to Mmax before (PRE) and after (POST) the three experimental conditions (ISO, pNMES, NMES+) in MS+ (Fig. 5a) and in MS- (Fig. 5b).

The *t*-test analysis on the Pre-test and Post-test MVIC values showed no significant differences in both MS+ ($p = 0.742$; Pre-test: 26.1 ± 18.9 vs Post-test: 25.5 ± 15.4) and MS- ($p = 0.356$; Pre-test: 39.9 ± 18.4 vs Post-test: 37.7 ± 18.2) groups, as illustrated in Table 3, thus showing that no fatigue occurred.

Finally, the t-test analysis on the current intensity level used during pNMES and NMES+ showed no significant differences between MS+ and MS- (pNMES, MS+ vs MS-: $p = 0.87$; NMES+, MS+ vs MS-: $p = 0.62$), thus showing that the current intensity did not influence the results.

4. Discussion

The main result of this study was the different H-reflex response between MS patients with spasticity (MS+) and those without spasticity (MS-) following a single NMES session. In MS+, the amplitude of H-reflex decreased after both pNMES and NMES+, and did not change after ISO, confirming that both passive and superimposed NMES modulate spinal excitability in these patients while voluntary contraction does not. This was partially in agreement with our hypothesis as we expected an increased H-reflex amplitude only after NMES+. On the other hand, in MS- there were no significant differences in H-reflex amplitude following all three experimental conditions (pNMES, NMES+, ISO). This result is in accordance with our hypothesis and suggests that both passive and superimposed NMES have the same effect as voluntary isometric exercise and do not affect spinal excitability in MS patients without spasticity.

Table 2
PRE and POST H-reflex values. (a) The amplitudes of the H-reflex before (PRE) and after (POST) all three experimental conditions (ISO, pNMES, NMES+) in both groups (MS+, MS-) are reported as a mean ± standard deviation. (b) PRE values of H-reflex amplitudes in MS- and MS+. The corresponding p-values of each condition are illustrated in the table. *Significantly different from PRE.

(a)

		PRE	POST	Δ (%)	p value
ISO	MS+	0.58 ± 0.33	0.58 ± 0.33	−1 %	0.498
	MS-	0.47 ± 0.4	0.44 ± 0.34	−5 %	0.383
pNMES	MS+	0.59 ± 0.32	0.51 ± 0.33	−13.6 %	0.007*
	MS-	0.46 ± 0.4	0.45 ± 0.4	−3 %	0.328
NMES+	MS+	0.59 ± 0.33	0.52 ± 0.33	−11.8 %	0.003*
	MS-	0.46 ± 0.41	0.43 ± 0.39	−6 %	0.087

(b)

	MS- p-value	**MS+** p-value
PRE ISO vs PRE pNMES	0.667	0.582
PRE ISO vs PRE NMES+	0.753	0.499
PRE pNMES Vs PRE NMES+	0.99	0.754

In our study, the acute attenuation of SOL H-reflex amplitude after pNMES is consistent with previous studies, which reported that pNMES reduces spinal excitability in healthy individuals (Borzuola et al., 2020; Grosprêtre et al., 2018; Gueugneau et al., 2017; Milosevic et al., 2019; Scalia et al., 2023, 2024 ; Wegrzyk et al., 2015). These results suggest that pNMES might directly act on some spinal mechanisms that are mainly involved in the H-reflex modulation, even in spastic patients. Specifically, it has been demonstrated that electrical stimulation increases the concentration of gamma-aminobutyric acid (GABA) within the spinal cord. GABA is one of the major inhibitory neurotransmitters involved in presynaptic inhibition (PSI) mechanisms, which play a key role in spasticity as spastic patients usually show a reduction in PSI level, resulting in enhanced spinal excitability (Morita et al., 2001; Sinkjaer et al., 1995). Moreover, electrophysiological studies performed in animal models showed that increased GABA activity after electrical stimulation may influence spinal excitability by reducing the persistent inward current (PIC) (Donnelly et al., 2021). PIC is an intrinsic property of the neuronal membrane which consists of a lasting, depolarising inward current that increases motor neurons excitability (Heckman et al., 2008; Schwindt and Crill, 1980). In spastic patients, the absence of descending control of PIC activation causes long-lasting reflexes and muscle spasms (Bennett et al., 2004). Therefore, in the context of spasticity, the application of pNMES could be of fundamental importance for reducing spinal excitability, possibly by increasing the inhibitory action of GABA in the spinal cord, leading to increased PSI and inhibited PIC generation. Our results may explain, at least in part, the positive effect of pNMES intervention on reducing spasticity symptoms, which has been reported by previous clinical studies (Bochkezanian et al., 2018; Motta-Oishi et al., 2013; Popović et al., 2009; Stein et al., 2015).

Spastic MS patients reported a decrease in H-reflex even after NMES+. To explain our results, which are in contrast with current evidence on healthy individuals that revealed enhanced spinal excitability after an intervention with NMES+ (Borzuola et al., 2020; Lagerquist et al., 2012; Scalia et al., 2023, 2024), it is important to consider that spasticity depends on a set of different factors that lead to a reduction not only in PSI but also in other presynaptic mechanisms, such recurrent inhibition (RI). RI reduces the number and the rate at which motoneurons fire, resulting in a smaller stimulus response and a decrease in current flow (Katz and Pierrot-Deseilligny, 1982). This phenomenon is mediated by specific inhibitory interneurons, called Renshaw's cells. Usually, when muscles or nerves are electrically stimulated, the efferent pathways are activated both orthodromically and antidromically (Bergquist et al., 2011; Milosevic et al., 2019). Particularly, the antidromic volley, which conducts the electrical stimulus toward the cell body into the spinal cord, may activate Renshaw cell interneurons, increasing RI and, therefore, reducing spinal excitability (Barbeau et al., 2000; Iles and Roberts, 1987; Mazzocchio et al., 1994; Pierrot-Deseilligny and Burke, 2005). In addition, some authors reported that low-intensity muscle contractions may enhance RI compared to high-intensity muscle contractions (Hultborn and Pierrot-Deseilligny, 1979). In our study, participants were asked to reach 20 % of MVIC during each experimental condition. Particularly, in the NMES+ condition, the voluntary effort was around 10 %, which indicates a very low muscle contraction intensity. Thus, it is plausible that the combination of electrical stimulation and low-intensity muscle contractions could have reduced the H-reflex amplitude in MS patients with spasticity by increasing RI.

When considering MS patients without spasticity, we found no significant changes in H-reflex amplitude following pNMES and NMES+

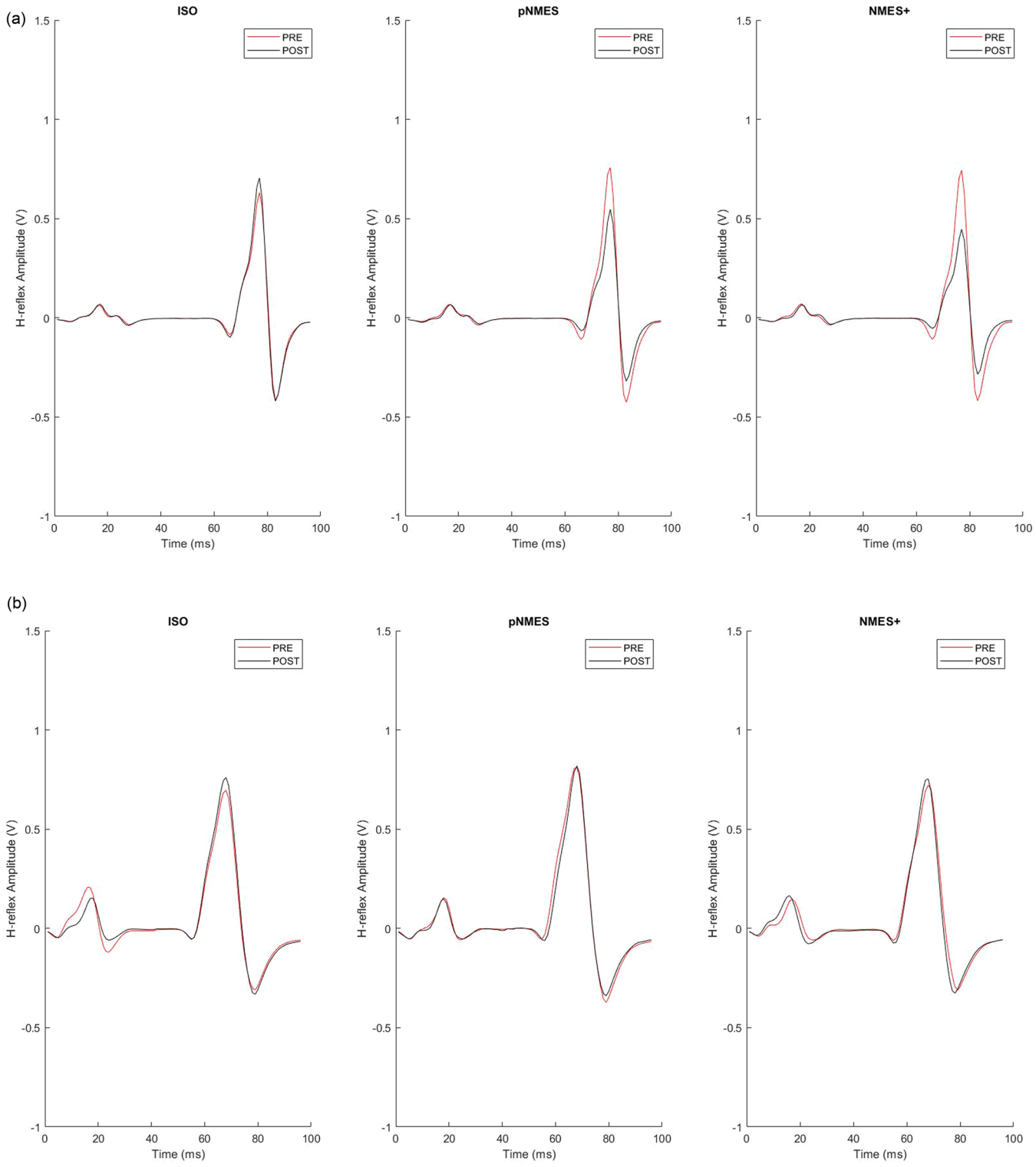

Fig. 4. (a, b) H-reflex and M-wave before and after the three experimental conditions. The figure shows an example of the difference in the mean of H-reflex responses following 20 electrical stimulations of the posterior tibial nerve, before (PRE) and after (POST) each experimental condition (ISO, pNMES, NMES+) in a patient of the MS+ group (**a**) and in a patient of the MS- group (**b**). The red line represents the mean PRE; the black line represents the mean POST.

compared to baseline values. This result is consistent with our previous study (Scalia et al., 2024) and could be explained by an alteration in the balance between inhibitory (mediated by GABA) and excitatory (mediated by glutamate) neurotransmission due to the neuroinflammation. Therefore, the results of the present study point out that the damage to the spinal reflex pathway due to spasticity may have impaired these inhibitory/excitatory mechanisms in spastic MS patients to a greater extent than in MS patients without spasticity. The difference in acute H-reflex responses to NMES suggests that alterations in PICs as well as reductions in PSI and other inhibitory mechanisms levels are largely affected in spastic MS patients compared to MS patients without spasticity. Thus, in MS patient without spasticity, NMES seems to have less consistent effect on these mechanisms, not inducing a modulation in H-reflex amplitude, hence spinal excitability. However, further

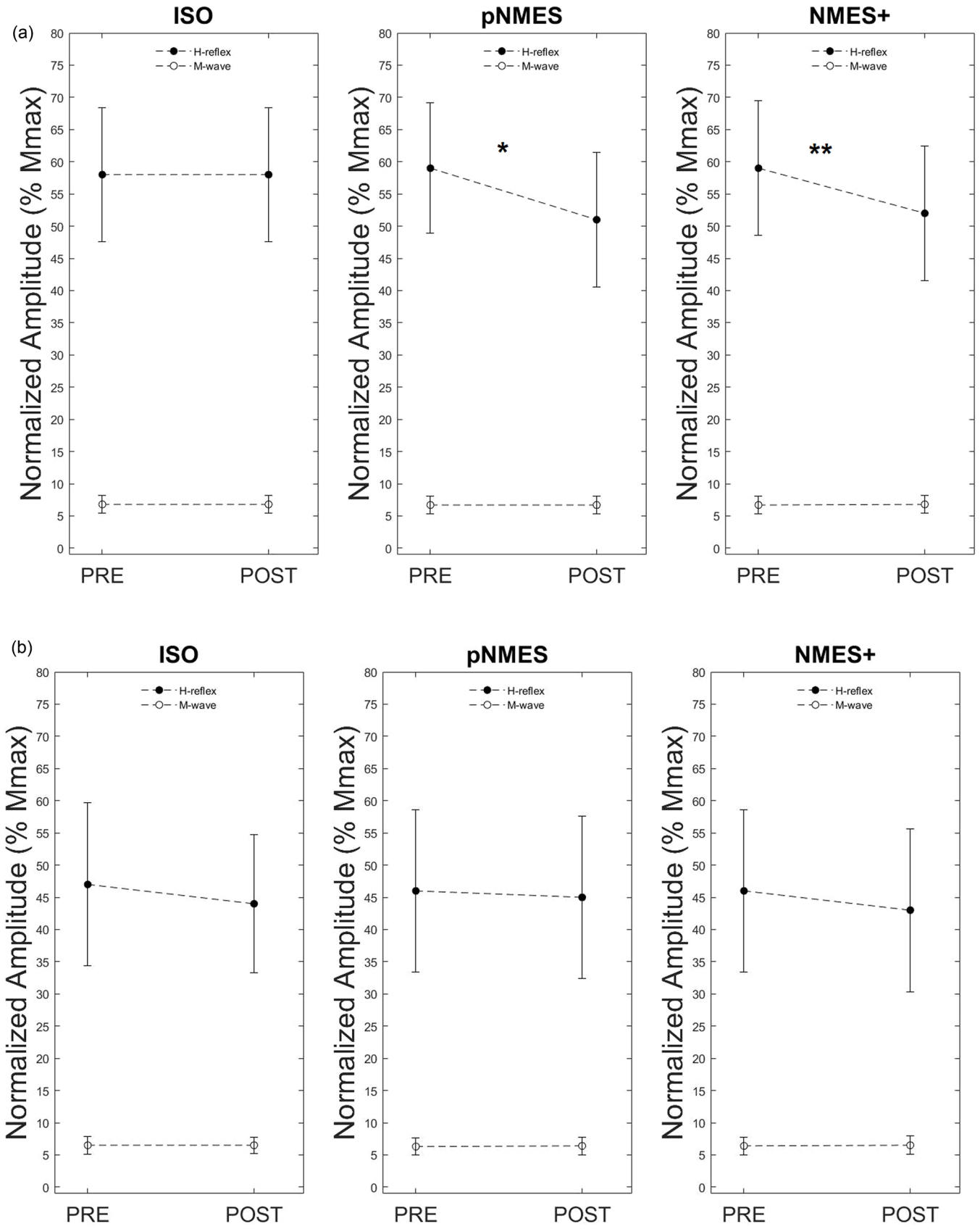

Fig. 5. (a, b) H-reflex and M-wave normalised by M_{max}. (a) Amplitude of soleus H-reflexes and corresponding M-waves normalised to M_{max} before (PRE) and after (POST) the three experimental conditions (ISO, pNMES and NMES+), in MS+. Data are reported as group means ± standard deviation (* $p = 0.010$; ** $p < 0.000$). (b) Amplitude of soleus H-reflexes and corresponding M-waves normalised to M_{max} before (PRE) and after (POST) the three experimental conditions (ISO, pNMES and NMES+) in MS-. The H-reflex and M-wave amplitudes averages did not change in ISO, pNMES or NMES+. Data are reported as group means ± standard deviation.

investigation is required to elucidate how NMES alters synaptic neurotransmission in pwMS.

Finally, MS patients with and without spasticity showed no significant changes in H-reflex responses after ISO condition. This result is in accordance with previous studies (Borzuola et al., 2020, 2023; Scalia et al., 2023), suggesting that our protocol may not be long enough to induce significant acute modulation of spinal circuitry in MS patients. A longer training protocol may be necessary to observe changes in H-reflex amplitude after isometric contraction. However, when implementing a longer intervention protocol, it is important to consider muscle fatigue since it reduces Ia-afferent excitation and increases excitability thresholds (Borzuola et al., 2020; Grosprêtre et al., 2018; Sosnoff and Motl, 2010). In this regard, the baseline MVIC values did not decrease in MS patients of both groups after the three experimental conditions, indicating that fatigue did not occur at the end of the entire protocol.

Limitations of our study are related to the absence of direct measurements of GABA, PSI, PIC and RI, even though these mechanisms may be primarily responsible for changes in spinal excitability in spastic patients. Having more information about the potential implications of these neurophysiological mechanisms' activity may explain why, in the present study, MS patients with and without spasticity had different responses after the NMES intervention. In addition, although the statistical power analysis showed that the estimation of sample size was adequately addressed, further studies should be designed in a larger cohort of participants to consolidate these findings. Another limitation could be related to the different types of MS represented in the two groups. In the MS+, patients were diagnosed as PP, SP and RR and presented higher EDSS and VAS score, while in MS- all patients were diagnosed as RR (Table 1). Thus, it could be argued that spinal reflex responses might vary based on patients' characteristics. However, although spasticity may be present in RR patients with minimal disability, there is a much higher incidence of spasticity in PP or SP patients (Patejdl et al., 2017; Goicochea Briceño et al., 2023), which also experience higher levels of disability and pain. Furthermore, in a previous study (Scalia et al. 2024), the authors reported that in a MS group without spasticity there were no significant differences in the H-reflex responses following both pNMES and NMES+, similar to the findings of the present study. Therefore, it is reasonable to conclude that the decrease of H-reflex amplitudes after pNMES and NMES+ in the MS+ group can be largely attributed to the presence of spasticity. Moreover, the clinical aspects of spasticity were not evaluated during the experimental protocol of this study. Although the results of this study may be relevant for understanding some of the neurophysiological mechanisms underlying the effect of NMES on spinal excitability in MS patients, the lack of clinical measures does not allow to confirm a clinical relevance of these results. We believe that a clinical assessment, such as MAS, that could have been carried out before and immediately after each of the three experimental conditions (ISO, pNMES and NMES+), could have added clinical value to the neurophysiological results of this study. From a neurophysiological perspective, these findings provide a foundation for future longitudinal studies on the long-term effects of NMES interventions on spinal excitability in clinical settings. In fact, in our study, the effects of NMES on spinal excitability lasted <15 min, as shown by the H-reflex values at rest (Table 2). The 'short-time' effect could be explained by the fact that participants were asked to perform only 15 low-intensity isometric muscle contractions with NMES, passive or superimposed. In this case, the protocol duration and the number of repetitions were not sufficient to create 'long-term' adaptations, but only short-term adjustments which disappeared after 15 min. In addition, in this study, NMES was applied only locally, on a group of three planta flexors muscles. Therefore, to test the long-term effects (over 15 min) of NMES, it would be necessary to increase the number of series and repetitions per muscle group or apply a total body electrical stimulation.

5. Conclusion

The present study is the first to unveil some of the neurophysiological mechanisms that could be associated with the reduction in spasticity that was observed in pwMS following NMES. In MS patients with spasticity, NMES decreases spinal excitability likely by acting on some inhibitory mechanisms which are mainly involved in spinal excitability, such as PSI, RI, PIC and GABA activity. In contrast, in patients with MS without spasticity, NMES did not affect H-reflex responses, and it had the same effects on spinal excitability as voluntary isometric contractions. These results are highly relevant from a neurophysiological point of view as they demonstrated that NMES affects short-term spinal excitability in spastic MS patients. Moreover, pivotal studies are critical to discover physiological mechanisms. From a clinical point of view, these results are crucial to setting up longitudinal studies with clinical relevance, which should involve both neurophysiological and clinical evaluations. Long-term protocols are essential in order to introduce NMES in rehabilitation protocols. Furthermore, it could be interesting to investigate the effects of NMES on cortical activation and motor unit recruitment in pwMS with spasticity symptoms.

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CRediT authorship contribution statement

Martina Scalia: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Riccardo Borzuola:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Martina Parrella:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Giovanna Borriello:** Writing – review & editing, Resources, Methodology, Investigation. **Francesco Sica:** Writing – review & editing, Resources, Methodology, Investigation. **Fabrizia Monteleone:** Writing – review & editing, Resources, Methodology, Investigation. **Andrea Macaluso:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

None.

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