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Long-Term TENS Treatment Improves Tactile Sensitivity in MS Patients

Koen Cuypers, MSc,[1,2] Oron Levin, PhD,[2] Herbert Thijs, PhD,[1] Stephan P. Swinnen, PhD,[3] and Raf L. J. Meesen, PhD[1-3]

Abstract

Background. Transcutaneous electrical nerve stimulation (TENS) is commonly used in neurorehabilitation for the treatment of pain and spasticity. *Objective*. The long-term effects of sensory stimulation by means of TENS on hand sensitivity were investigated in patients with multiple sclerosis (MS). *Methods*. TENS was applied for 3 weeks (1 hour per day) on the median nerve region of the dominant hand. Sensitivity was assessed by the Semmes–Weinstein monofilaments before and 12 hours following the last intervention as well as 3 weeks later. *Results*. Long-lasting increases in tactile sensitivity were achieved by repetitive stimulation of sensory afferents with TENS in MS patients but not in healthy subjects. This increased sensitivity was not only restricted to the median nerve area but also expanded to the ulnar nerve area. Remarkably, MS patients reached the same level of sensitivity as healthy subjects immediately after the intervention, and long-term effects were reported 3 weeks later. *Conclusions*. The findings of this study demonstrated lasting improvements in tactile sensitivity of the fingers as a result of a long-term TENS intervention in MS patients, who ultimately reached a level comparable with that of healthy subjects.

Keywords

transcutaneous electrical nerve stimulation (TENS), sensitivity, multiple sclerosis (MS), Semmes–Weinstein monofilaments

Introduction

Transcutaneous electrical nerve stimulation (TENS) involves application of electrical currents to the skin at varying frequencies, pulse durations, and intensities. This results in recruitment of large-diameter sensory nerve fibers and/or mechanoreceptors without creating significant muscle contraction.[1] It is commonly used in neurorehabilitation for easing symptoms such as pain and spasticity. Nonetheless, only few studies have evaluated the clinical effect of TENS on multiple sclerosis (MS). For example, significant reduction in spasticity in the plantar flexor muscles of the ankle after 4 weeks of TENS treatment was reported in MS patients by Armutlu et al,[2] whereas Sluka et al[1] found that a majority of patients reported TENS to result in a reduction of pain, spasticity, and joint stiffness. However, studies exploring the effect of peripheral sensory stimulation on recovery of sensory functions in MS are limited.

Approximately 25% of patients with MS may have a reduced tactile sensitivity attributed to a pure sensory attack at disease onset,[2] whereas in approximately 40% of onset cases, paresthesias are present.[3] For example, Sanders and Arts[3] reported diminished sensation of at least 1 of the 3 sensation modalities (being touched, pain, and vibration) during a clinical examination in 70% of MS patients.

There is evidence that increased afferent input following peripheral sensory stimulation can lead to changes in excitatory and inhibitory interactions within the adult mammalian cortex.[4,5] Previous studies have demonstrated that sustained alterations in sensory input affect map representations in the somatosensory cortex[6,7] associated with recovery of sensorimotor deficits.[8,9] In contrast to MS, recovery of somatosensory modalities in stroke has been well documented.[10] Nevertheless, functional neuroplastic reorganization is not only reported in stroke[11] but also in MS.[12,13] In this respect, brain plasticity may play a crucial role in limiting the clinical consequences of MS-related damage during the early stages of the disease in clinically stable patients.[14] Recent evidence has shown that peripheral stimulation can modulate sensitivity in MS. For example, Mima et al[15] found that a short-term intervention with TENS applied over hand muscles increased sensory thresholds during and

[1]Hasselt University, Diepenbeek, Belgium
[2]PHL University College, Hasselt, Belgium
[3]Katholieke Universiteit Leuven, Leuven, Belgium

Corresponding Author:
Raf Meesen, REVAL Research Group, Department of Health Care, PHL University College, Guffenslaan 39, 3500 Hasselt, Belgium
Email: koen.cuypers@phl.be

immediately after intervention. However, the effects of repetitive peripheral stimulation have not yet been documented in MS, particularly in view of inducing long-term aftereffects. This is the principal goal of the present study, wherein we will focus on the long-term effects of TENS on tactile sensitivity in MS patients. We hypothesize that long-term sensory stimulation by means of TENS will induce long-term sensory aftereffects.

Methods

Subjects

Twenty-six patients with MS (7 men and 19 women) aged 25 to 67 years (mean 47.70 ± 9.29 years) and 30 healthy subjects (13 men and 17 women) aged 22 to 74 years (mean 47.63 ± 13.40 years) were included in this study. All subjects gave their written informed consent to participate in the study. Patient characteristics are shown in Table 1. All patients exhibited stable MS, showing no relapse for 6 months prior to the intervention. Patients with other pathologies associated with peripheral and/or central sensory dysfunction or under psychotropic or antiepileptic medication were excluded. Expanded Disability Status Scale (EDSS) scores ranged between 3 and 6.5 (mean 4.52 ± 0.96). Initially, the number of patients was 29. Three patients were excluded, 2 suffered from acute relapse and 1 did not show up for testing.

Healthy subjects were also screened for pathologies associated with peripheral and/or central sensory dysfunction and medication intake. There was no dropout.

Procedure

Each group (both MS patients and healthy subjects) was subdivided into an intervention group and a control group (Figure 1). Groups were balanced for age, gender, and handedness (all *P*s > .05). The intervention group received TENS on the dominant hand, whereas the control group received no additional intervention. In both groups, sensitivity of the dominant and nondominant hands was examined at the onset of the study (baseline), as well as 3 (postintervention) and 6 (follow-up) weeks later. To rule out short-term effects in excitability, postintervention measurements were taken 12 hours following the intervention. The dominant hand undergoing the intervention was called the target hand. Handedness was assessed according to the Edinburgh Handedness Inventory.[16] A laterality quotient (LQ) of +100 represented extreme right hand preference, whereas an LQ of −100 represented extreme left hand preference. Twenty-four patients were right-handed (mean LQ = 79.91 ± 18.23) and 2 were left-handed (mean LQ = −60.00 ± 14.14), whereas 28 healthy subjects were right-handed (mean LQ = 93.85 ± 10.71) and 2 were left-handed (mean LQ = −78.66 ± 14.01). Experimental procedures conformed to the Declaration of Helsinki and were approved by the local ethics committee of the University of Hasselt.

Intervention

TENS (Intelect Digitens, Chattanooga Group, Hixson, TN) was applied on the median nerve region (more specifically, the thenar eminence) of the dominant hand, using self-adhesive electrodes (Dura-stick II, 1.5 × 4 cm). A biphasic alternating current with a frequency of 100 Hz, and pulse width of 250 μs was automatically modulated to prevent habituation. More specifically, during the beginning of the 0.5-second period, the width was decreased to 50% of its original setting, and during the next 0.5-second period, the frequency was decreased to 50% of its original setting. This pattern was repeated every second for 1 hour. This was done to prevent nerve accommodation, such that no intensity changes were required for long and effective treatment. Stimulation intensity was below the motor threshold and produced a tingling sensation in the stimulated area without muscle twitch or pain. Intensity was first increased above motor threshold and was subsequently decreased until visual and tactile muscle contraction disappeared. For both intervention groups, the timing of stimulation was fixed and occurred more specifically between 6 PM and 8 PM. This protocol was applied for 3 weeks for 1 hour per day.

Sensitivity

Semmes–Weinstein monofilaments (Smith & Nephew, Inc, Germantown, WI) were used to determine finger sensitivity. This test is known for its validity, reliability, reproducibility, and responsiveness and is widely used in research as well as in clinical settings.[17,18] Participants were seated in front of the examiner with both hands relaxed in supination. The examiner was blind to the intervention. Five different monofilament diameters (2.83, 3.61, 4.31, 4.56, and 6.65 expressed as the log of force in milligrams; the corresponding forces in grams are, respectively, 0.07, 0.4, 2, 4, and 447) were used, corresponding, respectively, with the following clinical classification: normal, diminished light touch, diminished protective sensation, loss of protective sensation, and untestable. The monofilaments were randomly presented in a descending or ascending order to the thumb, index finger, and fifth finger. Each filament was pressed against the skin until it was buckled for approximately 1.5 seconds. The participants were instructed to give a verbal response when they felt a touch. All filaments were tested 3 times with randomization in order and finger before switching to the next monofilament. The

Table 1. Patient Characteristics

							Functional System Scores								
ID	Group	Age	Sex	First Symptom	Diagnosis	MS Type	Visual	Brainstem	Pyramidal	Cerebellar	Sensory	Bladder/ Bowel	Mental	EDSS	Medication
1	Treatment	44	Female	2005	2005	RR	3	1	3	1	3	0	1	4	Avonex
2	Treatment	56	Female	1969	1982	PP	2	2	4	3	3	1	3	6	—
3	Treatment	46	Male	1984	1984	RR	1	2	3	2	2	1	2	4	—
4	Treatment	59	Female	1994	1999	PP	2	1	4	3	3	2	2	6	—
5	Treatment	25	Female	2001	2003	RR	2	2	4	2	3	4	2	6	—
6	Treatment	41	Female	1984	2002	RR	2	1	0	1	3	0	1	4	Copaxone
7	Treatment	47	Male	1999	2001	SP	1	0	4	5	2	2	2	7	—
8	Treatment	44	Male	1999	1999	SP	1	0	3	2	1	0	1	4	Rebif
9	Treatment	42	Male	1990	1990	RR	1	2	3	2	2	0	1	4	Copaxone
10	Treatment	63	Female	2007	2007	SP	1	2	3	3	3	1	0	6	Betaferon
11	Treatment	54	Female	?	1993	SP	5	2	2	1	0	1	1	4	Rebif
12	Treatment	40	Female	1991	1991	PP	0	0	3	0	0	0	0	6	Copaxone
13	Treatment	60	Male	1996	2001	PP	1	1	3	3	2	1	2	5	Biofenac
14	Treatment	42	Female	1996	1998	PP	0	0	3	3	2	2	2	6	Betaferon
15	Treatment	46	Female	1979	1985	RR	0	1	3	2	2	1	1	4	—
16	Control	48	Female	1985	1985	RR	1	2	3	2	3	2	1	4	Betaferon
17	Control	48	Female	1990	1992	SP	3	0	3	1	2	3	3	4	Copaxone
18	Control	50	Male	1999	2000	PP	2	2	2	0	1	2	2	3	Rebif
19	Control	46	Female	1979	1983	SP	0	2	3	4	3	2	2	5	—
20	Control	49	Female	1978	1996	RR	0	2	3	1	1	0	2	4	Copaxone
21	Control	57	Female	1975	2000	SP	2	0	3	3	1	1	0	6	Betaferon
22	Control	50	Female	1981	1981	PP	3	2	3	2	1	1	2	4	Copaxone
23	Control	67	Female	1985	1985	PP	1	0	4	2	0	1	0	6	Rebif
24	Control	48	Female	2000	2000	RR	1	0	3	2	2	3	1	5	—
25	Control	49	Male	1997	1997	SP	3	1	2	1	2	2	1	3	—
26	Control	37	Male	1991	2002	RR	2	2	2	2	2	0	2	4	Copaxone

Abbreviations: MS, multiple sclerosis; RR, relapsing-remitting; PP, primary-progressive; SP, secondary-progressive; EDSS, Expanded Disability Status Scale.

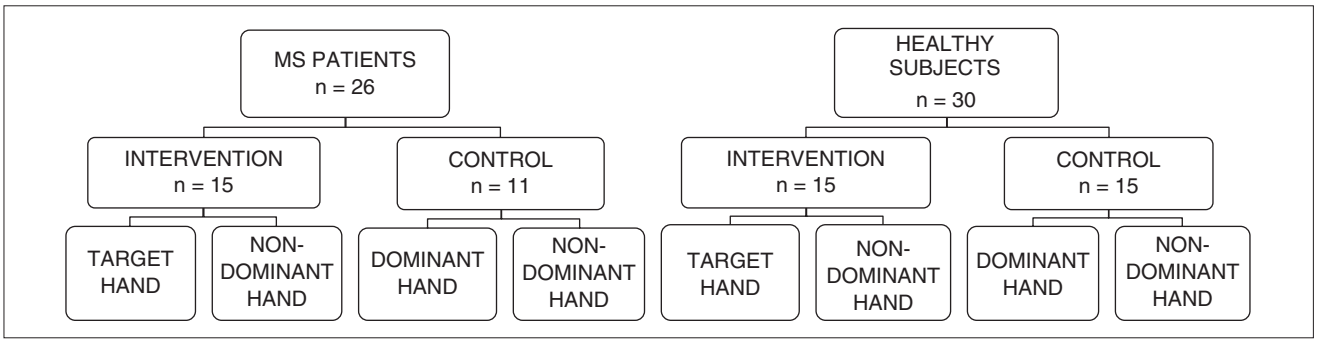

Figure 1. Overview of subject groups and subdivisions

filament with the lowest pressure score, which was felt 3/3 times on the fingertip, was recorded as the score for this fingertip.

Data Analysis

Advanced linear applications (SPSS 16.0) were used. Dominant and nondominant hands were analyzed separately to fulfill the assumption of independence. Differences in finger sensitivity between independent groups were analyzed using the Mann–Whitney *U* test. Effects over time were analyzed within groups using Friedman's repeated-measures analysis of variance (ANOVA). In addition, the Wilcoxon signed rank test was used for repeated measurements on a single sample. The level of significance was set at $P < .05$.

Results

Overall, as shown in Table 2, tactile sensitivity in MS patients was more impaired when compared with healthy subjects for all fingers at baseline (all *P*s < .05). More specifically, most patients showed either diminished light touch (35.26%) or diminished protective sensation (40.38%), whereas healthy subjects showed mainly normal sensitivity (38.89%) or diminished light touch (53.33%). In addition, no significant differences in sensitivity between intervention and control subjects were observed within groups (both healthy and MS) at baseline (all *P*s > .05).

MS Patients

Intervention group versus control group. The Mann–Whitney *U* test for postintervention versus baseline revealed a significant group effect for the thumb ($P = .002$), index finger ($P = .004$), and fifth finger ($P = .027$) of the dominant (target) hand, indicating a significant increase in sensitivity immediately after the intervention. For the index finger of the target hand this effect remained significant ($P = .047$) when the follow-up session was compared with baseline, indicating a long-lasting increase in sensitivity. For the nondominant hand no significant effects were found (all *P*s > .05).

Intervention group. Friedman's repeated-measures ANOVA revealed significant effects of TENS on sensitivity over time in the thumb ($P = .000$), index finger ($P = .000$), and the fifth finger ($P = .002$) of the target hand. Wilcoxon matched pairs signed rank tests showed that sensitivity of the thumb ($P = .000$), index finger ($P = .000$), and fifth finger ($P = .004$) increased significantly when comparing postintervention with baseline measures (Figure 2). At follow-up, sensitivity was still significantly higher in comparison with the baseline for thumb ($P = .031$) and index finger ($P = .016$) but not in the fifth finger ($P = .500$). For the nondominant hand (Figure 3), no significant effects were reported (all *P*s > .05).

Control group. Friedman's repeated-measures ANOVA revealed no significant changes in sensitivity over time (all *P*s > .05). As shown in Figures 2 and 3, Wilcoxon matched pairs signed rank tests revealed no significant changes in sensitivity at postintervention or follow-up when compared with baseline (all *P*s > .05).

Healthy Subjects

Intervention group versus control group. The Mann–Whitney *U* tests showed no significant group effects for differences in finger sensitivity over time between the intervention and control groups (all *P*s > .05), indicating that the level of sensitivity was similar in both groups.

Intervention group. Friedman's repeated-measures ANOVA revealed no significant effects of TENS on sensitivity over time. As shown in Figures 2 and 3, Wilcoxon matched pairs signed rank tests revealed no significant changes in sensitivity at postintervention or follow-up relative to baseline (all *P*s > .05).

Control group. Friedman's repeated-measures ANOVA revealed no significant sensitivity changes over time in any of the tested fingers (all *P*s > .05). As shown in Figures 2

Table 2. Sensitivity Measurements for All Subjects at Baseline, Postintervention and Follow-up[a]

		Baseline					Postintervention					Follow-up				
	Finger	N	DLT	DPS	LPT	U	N	DLT	DPS	LPT	U	N	DLT	DPS	LPT	U
Intervention																
MS																
Target																
	I	0	7	7	0	1	5	9	1	0	0	2	8	4	1	0
	II	0	6	8	1	0	8	7	0	0	0	1	10	4	0	0
	V	0	5	10	0	0	3	10	2	0	0	1	5	9	0	0
Nondominant																
	I	0	6	7	1	1	0	7	7	1	0	0	6	7	1	1
	II	0	6	7	2	0	0	8	7	0	0	0	6	7	2	0
	V	0	5	9	1	0	1	6	8	0	0	0	5	9	1	0
Healthy																
Target																
	I	4	9	2	0	0	4	11	0	0	0	6	8	1	0	0
	II	5	10	0	0	0	6	9	0	0	0	7	8	0	0	0
	V	7	7	1	0	0	6	8	1	0	0	9	6	0	0	0
Nondominant																
	I	5	8	2	0	0	7	6	2	0	0	9	4	2	0	0
	II	6	9	0	0	0	7	7	1	0	0	9	6	0	0	0
	V	5	10	0	0	0	8	6	1	0	0	10	5	0	0	0
Control																
MS																
Dominant																
	I	2	5	2	1	1	2	4	3	0	2	2	5	2	1	1
	II	2	4	3	1	1	1	5	3	0	2	3	2	4	1	1
	V	2	4	3	2	0	2	4	2	1	2	2	5	2	2	0
Nondominant																
	I	3	2	3	2	1	1	5	3	0	2	3	2	3	1	2
	II	3	2	3	1	2	1	5	2	1	2	2	3	3	1	2
	V	3	3	1	3	1	3	3	1	2	2	2	4	3	1	1
Healthy																
Dominant																
	I	6	6	3	0	0	6	7	2	0	0	10	3	2	0	0
	II	7	7	1	0	0	10	4	1	0	0	8	7	0	0	0
	V	7	8	0	0	0	8	7	0	0	0	9	6	0	0	0
Nondominant																
	I	5	7	3	0	0	7	6	2	0	0	9	3	3	0	0
	II	6	7	2	0	0	8	6	1	0	0	7	8	0	0	0
	V	7	8	0	0	0	8	7	0	0	0	8	7	0	0	0

Abbreviations: MS, multiple sclerosis; N, normal; DLT, diminished light touch; DPS, diminished protective sensation; LPS, loss of protective sensation; U, untestable.

[a]The black shading indicates the shift in sensitivity for the target hand of MS patients. After the intervention sensitivity increased when compared with baseline and follow-up measurements. The data indicate the number of subjects represented in each clinical category.[35]

and 3, Wilcoxon matched pairs signed rank tests revealed no significant changes in sensitivity at postintervention or follow-up when compared with baseline (all *P*s > .05).

Impact of the Intervention on Sensitivity in MS Patients

To evaluate the impact of the intervention on MS patients, additional analysis was carried out to compare baseline sensitivity measures of the target hand of MS patients with those of healthy subjects (intervention group). Mann–Whitney *U* tests showed that, at postintervention, there were no significant differences in sensitivity of all tested fingers between MS patients and healthy subjects (all *P*s > .05). In contrast, when baseline and follow-up measures of MS patients were compared with baseline measures of healthy subjects, MS patients were less sensitive in all tested fingers (all *P*s < .05) except for the thumb at follow-up ($P = .219$). These results indicate that MS patients reached a level of sensitivity comparable with healthy subjects immediately after the intervention (Table 2). Nevertheless, 3 weeks after the end of the intervention, sensitivity in MS patients was similar to healthy subjects for the thumb only.

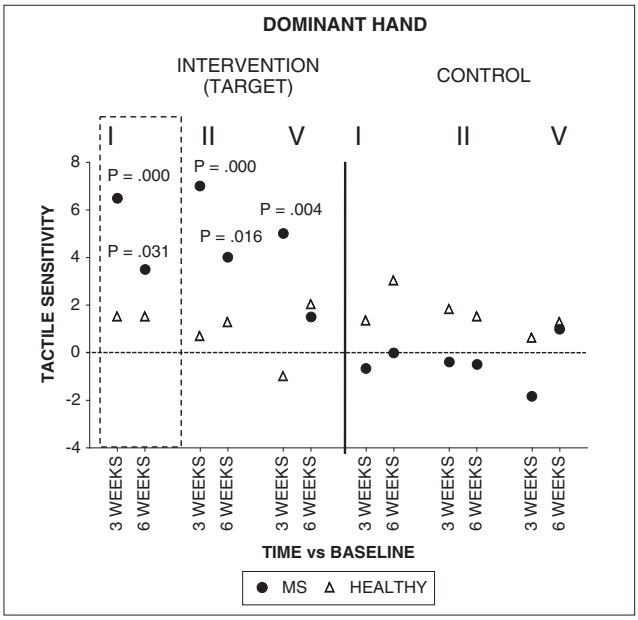

Figure 2. Semmes–Weinstein monofilaments for the dominant hand. Improvement scores (Wilcoxon matched pairs signed rank test) for the thumb (I), index finger (II), and fifth finger (V) for the intervention (target) and control groups are given as a mean rank. Mean ranks were higher when sensitivity increased. The dashed rectangle on the left represents the target finger

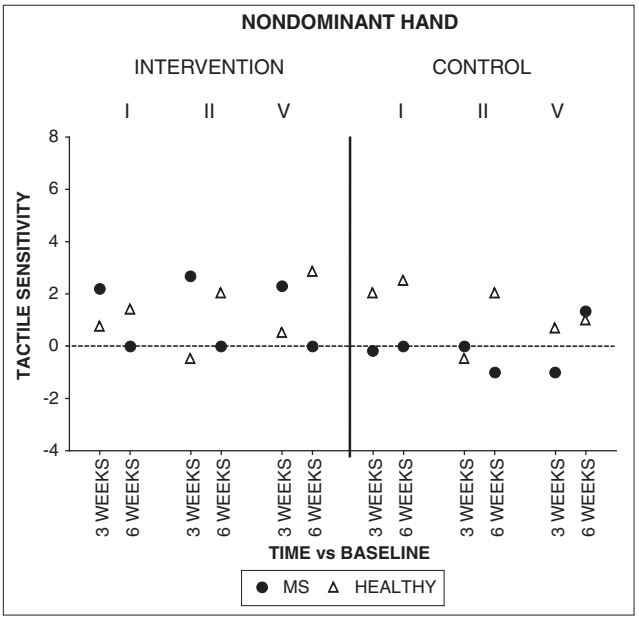

Figure 3. Semmes–Weinstein monofilaments for the nondominant hand. Improvement scores (Wilcoxon matched pairs signed rank test) for the thumb (I), index finger (II), and fifth finger (V) for the intervention and control groups are given as a mean rank. Mean ranks were higher when sensitivity increased

Discussion

The present study shows for the first time that a long-lasting increase in tactile sensitivity can be achieved by repetitive stimulation of sensory afferents with TENS in MS patients but not in healthy subjects. Moreover, increased sensitivity in MS patients was not only restricted to the median nerve area but also expanded to the ulnar nerve area. Remarkably, MS patients reached a level of sensitivity comparable with healthy subjects immediately after the intervention and long-term effects were reported 3 weeks later. Whereas Mima et al[15] reported that a short-term intervention with TENS increased sensory thresholds during and immediately after intervention, we demonstrated evidence for long-lasting changes induced by a repetitive sensory stimulation protocol. Additionally, sensitivity was still significantly increased in some fingers 3 weeks following the end of the intervention.

Potential mechanisms accounting for these long-lasting changes are long-term potentiation and depression,[19,20] but these mechanisms have neither been proven to be necessary nor sufficient for cortical map reorganization. Other physiological mechanisms refer to short-term synaptic dynamics that are altered by sensory experience[21] and alterations in inhibitory circuits.[22]

The observed increase in sensitivity was not restricted to the stimulated area but extended beyond this. Cortical reorganization as a result of the present TENS paradigm could possibly account for this finding but convincing evidence to support this claim is currently lacking. That an increase in sensitivity was also found in the fifth finger in our study is rather surprising as the thumb and index finger share different neural pathways (median nerve) when compared with the fifth finger (ulnar nerve). Although speculative, this phenomenon can perhaps be accounted for at the peripheral as well as cortical levels. At the peripheral level,[23] evidence exists for ulnar to median nerve communication. At the cortical level, spatial and temporal overlap in the human somatosensory cortex has been established.[24,25] More specifically, somatotopic overlapping representations of all 5 fingers of a single hand have been demonstrated in the primary somatosensory cortex by means of electrical stimulation.[26] Overall, this suggests that spread of activation from stimulated to nonstimulated parts of the somatosensory network might occur at different levels.

Interestingly, MS patients reached levels of sensitivity that were similar to healthy subjects immediately after the end of the intervention. Long-term effects were reported even 3 weeks later. This result shows that TENS can be

used as a valuable neurorehabilitative tool for patients with stable MS and with limitations in daily activities according to the EDSS score. Remarkably, healthy subjects showed no significant increase in sensitivity. Perhaps this result is not surprising because the healthy subjects behaved already close to their highest sensitivity level, limiting further improvements.

An interesting question for future MS research is whether such TENS interventions also result in improvement of fine motor function, as was found in stroke patients.[27,28] Evidence from animal research suggests that somatosensory input acts as a "teacher" to help shape motor system plasticity.[29] Moreover, stimulation of the somatosensory pathway in the thalamus or the somatosensory cortex induces long-term potentiation in the motor cortex, mediated by excitatory glutamatergic synapses.[30,31] Additionally, synaptic density in the motor cortex can be modified by means of somatosensory stimulation.[32] In humans, clinical studies also indicate that a prolonged period of electrical peripheral nerve stimulation induces short-term plasticity at multiple levels of the motor system.[33]

To summarize, this article demonstrates that long-lasting improvement in tactile sensitivity can be induced in MS patients by means of TENS and that these patients can reach comparable levels of sensitivity to those of healthy subjects after a long-term repetitive intervention protocol. An important future goal is to assess the role of the TENS protocol parameters. In this respect, several studies[8,15,34] have reported varying outcomes using different stimulation parameters. Therefore, a careful selection of the appropriate stimulation parameters (ie, frequency, intensity, and duration of the stimulus applied) is crucial to obtain the desired therapeutic result. The present observations highlight the potential advantage of TENS as a meaningful and valuable therapeutic tool in neurorehabilitation.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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