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RESEARCH REPORT

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Median nerve stimulation induced motor learning in healthy adults: A study of timing of stimulation and type of learning

Sandra Carvalho[1,2,*] | **Melanie French**[1,*] | **Aurore Thibaut**[1,3] | **Wilrama Lima**[1] | **Marcel Simis**[4] | **Jorge Leite**[1,2,5] | **Felipe Fregni**[1]

[1]Spaulding Neuromodulation Center, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

[2]Neurotherapeutics and Experimental Psychopatology Group, Psychological Neuroscience Laboratory, CIPsi, School of Psychology, University of Minho, Campus de Gualtar, Braga, Portugal

[3]Coma Science Group, GIGA-Consciousness, University and University Hospital of Liege, Liege, Belgium

[4]Instituto de Medicina Fisica e Reabilitacao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, São Paulo, Brazil

[5]Univ Portucalense, Portucalense Institute for Human Development – INPP, Oporto, Portugal

Correspondence
Felipe Fregni, MD, PhD, MPH, MMSc, Spaulding Neuromodulation Center, 96 13th Street, Charlestown, MA 02129.
Email: fregni.felipe@mgh.harvard.edu

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Abstract

Median nerve stimulation (MNS) has been shown to change brain metaplasticity over the somatosensory networks, based on a bottom-up mechanism and may improve motor learning. This exploratory study aimed to test the effects of MNS on implicit and explicit motor learning as measured by the serial reaction time task (SRTT) using a double-blind, sham-controlled, randomized trial, in which participants were allocated to one of three groups: (a) online active MNS during acquisition, (b) offline active MNS during early consolidation and (c) sham MNS. SRTT was performed at baseline, during the training phase (acquisition period), and 30 min after training. We assessed the effects of MNS on explicit and implicit motor learning at the end of the training/acquisition period and at retest. The group receiving online MNS (during acquisition) showed a significantly higher learning index for the explicit sequences compared to the offline group (MNS during early consolidation) and the sham group. The offline group also showed a higher learning index as compared to sham. Additionally, participants receiving online MNS recalled the explicit sentence significantly more than the offline MNS and sham groups. MNS effects on motor learning have a specific effect on type of learning (explicit vs. implicit) and are dependent on timing of stimulation (during acquisition vs. early consolidation). More research is needed to understand and optimize the effects of peripheral electrical stimulation on motor learning. Taken together, our results show that MNS, especially when applied during the acquisition phase, is a promising tool to modulate motor leaning.

KEYWORDS
explicit motor learning, implicit motor learning, median nerve stimulation, peripheral stimulation, serial reaction time task

1 | INTRODUCTION

There have been great advances in the science of motor learning in recent years with many novel interventions, including neuromodulation tools investigating the mechanisms of motor learning. In recent decades, several noninvasive stimulation techniques, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS),

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*These authors contributed equally.

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were developed to improve motor and cognitive rehabilitation. These interventions have shown promising results in terms of motor function enhancement in healthy volunteers (Focke, Kemmet, Krause, Keitel, & Pollok, 2017; Saimpont et al., 2016; Samaei, Ehsani, Zoghi, Hafez Yosephi, & Jaberzadeh, 2017), and as rehabilitation tools for stroke, spinal cord injury, Parkinson's disease or dementia, among others (Adeyemo, Simis, Macea, & Fregni, 2012; Fregni & Pascual-Leone, 2007; Kwon, Park, Kang, Chang, & Kim, 2016; Saiote, Polanía, Rosenberger, Paulus, & Antal, 2013; Wagle Shukla et al., 2016; Williams, Imamura, & Fregni, 2009; Yozbatiran et al., 2016).

Although these techniques have shown substantial results in modulating motor plasticity (Kaelin-Lang et al., 2002; Ridding, McKay, Thompson, & Miles, 2001; Veldman, Maffiuletti, Hallett, Zijdewind, & Hortobágyi, 2014), their main effects are focused on the primary motor cortex, and thus, they do not take into account an important component of motor plasticity: the sensory system. Indeed, other techniques, such as median nerve stimulation (MNS) that target the sensory system, can have a significant impact on motor cortex plasticity (Lai et al., 2016). The cortical and subcortical effects of MNS are thought to be mediated by bottom-up mechanisms, namely by a mechanism of coactivation that can trigger activation of the primary and secondary somatosensory areas (Hodzic, 2004), as well as the insula (Ferretti et al., 2007; Hodzic, 2004; Ibanez et al., 1995), and other cortical areas (Golaszewski et al., 2004; Manita et al., 2015; Wu, Van Gelderen, Hanakawa, Yaseen, & Cohen, 2005). Moreover, it has already been shown that the motor cortex and the sensory cortex can be comodulated by peripheral electric stimulation (Schabrun, Ridding, Galea, Hodges, & Chipchase, 2012) and that this sensorimotor integration is crucial for the acquisition and performance of motor skills (Arce-McShane, Ross, Takahashi, Sessle, & Hatsopoulos, 2016). For instance, Veldman et al. (2014) examined the effects of sensorimotor stimulation (SES) on motor learning and showed that there was no effect of SES if performed with no concurrent motor task. The same group evaluated the direct and delayed effects of SES in healthy adults and found that low-intensity SES did not improve direct visuomotor performances but produced delayed effects which could be linked to a motor memory consolidation improvement after SES (Veldman, Zijdewind, Maffiuletti, & Hortobágyi, 2016). Other studies have shown similar results on motor learning consolidation following MNS (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007; Conforto, Cohen, Santos, Scaff, & Marie, 2007; Conforto, Kaelin-Lang, & Cohen, 2002; Klaiput & Kitisomprayoonkul, 2008; McDonnell, Hillier, Miles, Thompson, & Ridding, 2007; Wu, Seo, & Cohen, 2006). In other words, based on a bottom-up mechanism, MNS could change brain metaplasticity and enhance motor skill learning. However, to date, the mechanisms underlying these effects are not entirely understood.

One of the most validated tasks for motor learning is the serial reaction time task (SRTT). This task consists of a sequence of connected events comprised of higher-order associations across events, temporal organization of behavior and the forecast of future events (Chafee & Ashe, 2007; Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003). These features make it suitable to explore the underlying cognitive and biological principles of learning and memory (Robertson, 2007). This task uses a sequence of motor responses in order to promote and measure performance that is thought to reflect learning. It relies on a sequence of visual cue positions that need to be successfully predicted in order for faster responses to be produced. Therefore, during this task there is a progressive learning process and prediction of when and where the next cue will appear (Robertson, 2007).

Thus, we aimed to explored how MNS, applied during acquisition and consolidation stages, can impact the process of implicit and explicit motor learning during these two stages of memory formation (acquisition and consolidation). In fact, the timing of stimulation is an important factor to be understood. To date, most protocols were designed for assessing the priming effects of MNS on motor learning (e.g., (Celnik et al., 2007; McDonnell et al., 2007; Conforto et al., 2010), or the acquisition phase of motor learning (Nitsche et al., 2003), while studies focusing on the consolidation phase were only looking at the offline improvements or stabilization of the newly learned skill (Reis et al., 2008). We therefore aimed to look at the interaction between type of learning and timing of MNS stimulation. Firstly, based on the required sensorimotor integration for the acquisition and the performance of a motor skill, we hypothesize that MNS applied during the acquisition stage will increase SRTT performance when compared to sham MNS at this stage of memory formation (i.e., acquisition). Secondly, we want to explore whether MNS can increase SRTT performance if applied during the early consolidation stage of motor leaning, similar to other brain stimulation techniques, and verify whether it can modulate performance during the early consolidation phase, which emerged between 5 and 30 min after the training phase (Hotermans, Peigneux, Maertens de Noordhout, Moonen, & Maquet, 2006).

2 | METHOD

2.1 | Participants

This study included a total of 36 healthy volunteers (age: 29 ± 8.1, 16 females—see Table 1 for baseline characteristics) and was approved by the Spaulding Rehabilitation Hospital institutional review board (Partners Human Research Committee). It was conducted in compliance with

TABLE 1 Baseline characteristics

	Sham	Acquisition	Consolidation	Significance
Age	36 (28–45)	25.5 (21.5–28)	24 (23–25)	0.024[a]
Gender (%male)	90.91%	41.67%	40%	0.013[a]
Education (Median)	Bachelor's degree	Bachelor's degree	Bachelor's degree	0.955
Ethnicity	8 White, 1 Hispanic, 1 Black, 1 Asian)	7 White, 1 Hispanic, 1 Black, 2 Asian; 1 Mixed)	7 White, 1 Hispanic; 1 Black; 1 Mixed	0.990
Baseline VAS	0.35 (0–3)	1.05 (1–2.5)	1 (1–2)	0.6599
ANT Alerting	10.89 (−29.75 to 27.08)	−22.46 (−29.91 to 7.14)	7.27 (−16.31 to 23.93)	0.2652
ANT Orienting	−9 (−26.29 to 15)	35.08 (7 to 59.20)	17.00 (9.42 to 43.5)	0.0524
ANT Executive	112.38 (97.28 to 161.55)	100.39 (72.66 to 107.54)	79.98 (70.45 to 125.81)	0.1855
Explicit learning index	0.1250 ± 0.0843	0.1229 ± 0.0366	0.1175 ± 0.0858	0.9696
Implicit learning index	0.1157 ± 0.0659	0.1132 ± 0.05898	0.1254 ± 0.0571	0.8875

Note. [a]Stands for a significant difference between groups ($p < 0.05$).

the Declaration of Helsinki (Declaration of Helsinki, 1964). Written informed consent was obtained from each participant before inclusion in the study.

Participants were excluded if they reported a history of neurological and/or psychological disorders; acute thrombosis, hypertension, cardiac arrhythmias or other unstable heart conditions (less than 12 months ago); diabetes; pacemakers and/or implanted cardioverter defibrillators; any physical disability, medical condition precluding safe and adequate testing; history of alcohol or drug abuse within the past 6 months; history of smoking in the past 6 months; history of unexplained fainting spells; head injury resulting in more than a momentary loss of consciousness; history of neurosurgery; epilepsy; any person with metal implants; or if they were pregnant (as assessed by the pregnancy test on the day of the experiment). All participants were right-handed (as assessed by the Edinburgh Handedness Inventory-Short Form: EHI-SF$\geq$ 61).

2.2 | Design

In this double-blinded, sham-controlled, randomized parallel trial, subjects were allocated to one of three groups using a double-dummy design (Figure 1):

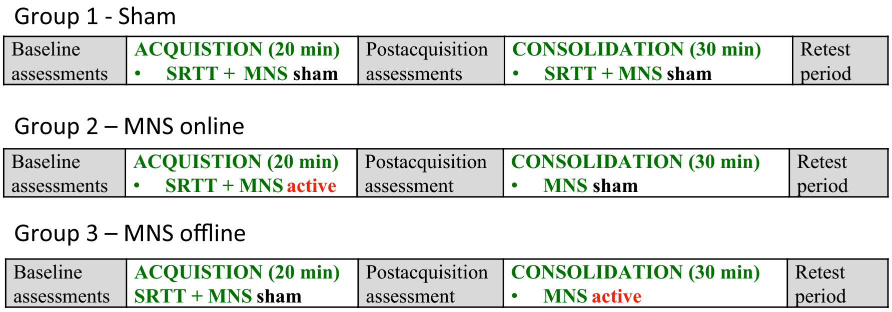
- Active online acquisition group: participants received active MNS during the acquisition period (i.e., during SRTT training), and sham MNS during the consolidation period.
- Active offline early consolidation group: participants received sham MSN during the acquisition period, and active MSN during the consolidation period.
- Sham group: participants received sham MNS both during the acquisition and the consolidation period.

2.3 | Primary outcome

2.3.1 | Serial Reaction Time Task

This is a self-paced task where participants need to reproduce a finger movement based on visual cues. These visual cues can represent a repeating sequence of positions (e.g., 2-3-1-4-3-2-4-1-3-4-2-1) or random trials where the cues do not present that repeating pattern (Robertson, 2007). We used the SRTT version proposed by Willingham and colleagues (Willingham, Salidis, & Gabrieli, 2002), in which there were two different repeating sequences occurring. One sequence consisted of black dots (a covert implicit pattern that the subject was not asked to pay attention to), while the other had colored dots (the explicit sequence, which subjects were instructed to try to pay attention to). Therefore, it would be possible to assess the implicit learning in the condition in which the subject is not aware of the repeating sequence (black dots only), and the explicit learning condition in which the repeating sequence is signaled to the subject (colored dots). These sequences were presented in three blocks: pretest (288 trials), acquisition training (1,296 trials) and retest (288 trials). In both the pretest and retest, the explicit sequence was covered and presented without any cues (i.e., no color).

In addition, at the end of the experiment, subjects were asked to reproduce the overt sequence of the "red dots" in a recall test. The instructions asked them to reproduce the entire sequence to the best of their ability, with the specification that the sequence is 12 units long being the only cue. Similarly, they were asked to reproduce "any other sequence" they might have remembered, as a measure of implicit recall.



Group 1 - Sham

Baseline assessments	ACQUISTION (20 min) • SRTT + MNS sham	Postacquisition assessments	CONSOLIDATION (30 min) • SRTT + MNS sham	Retest period

Group 2 – MNS online

Baseline assessments	ACQUISTION (20 min) • SRTT + MNS active	Postacquisition assessment	CONSOLIDATION (30 min) • MNS sham	Retest period

Group 3 – MNS offline

Baseline assessments	ACQUISTION (20 min) SRTT + MNS sham	Postacquisition assessment	CONSOLIDATION (30 min) • MNS active	Retest period

FIGURE 1 Session outline, from baseline assessments to postconsolidation assessments. MNS: median nerve stimulation; SRTT: serial reaction time task. [Colour figure can be viewed at wileyonlinelibrary.com]

2.4 | Control tasks

2.4.1 | Attention Network Task

The attention network task (ANT) allows the assessment of three attentional networks: alerting, orienting and executive control (conflict resolution), as proposed by Posner (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). The task was presented in e-prime 2.1.0 (Psychology Software Tools, Sharpsburg, PA, USA), and the stimuli were presented on a computer screen. A cue (i.e., asterisk) was presented in the center of the screen for 100 ms, followed by a target (i.e., an arrow) for 1,700 ms, pointing left or right. The test had four cue conditions—no cue, central cue, double cue and spatial cue—and three target conditions—congruent, incongruent and neutral. All combinations of conditions (cue and target) were randomly presented in one block of 96 trials. Twenty-four sample trials were performed before the task block, in order for the subjects to get familiarized with the task. Subjects were required to identify the direction to which the center arrow was pointing as quickly as possible. The efficiency on alerting and orienting is assessed by changes in reaction times through the presentation of cues and targets. The efficiency in the executive control is assessed by asking the participant to press two different keys indicating the direction of a central arrow surrounded by congruent, incongruent or neutral flankers. For more details, please see Fan, McCandliss, Sommer, Raz, and Posner (2002), Mezzacappa (2004), Rueda et al. (2004). In order to address possible outliers, scores over two standard deviations from the mean were removed (which represents less than 5% of the total number of scores). As the SRTT requires attentional resources in order to reproduce the motor sequences, the ANT was chosen to control attentional changes that could explain the motor learning results.

2.4.2 | Visual Analogue Scale for mental fatigue

Visual Analogue Scale (VAS) is a common instrument to assess self-reported mental fatigue on a scale from 0 to 10. The VAS was used to assess mental fatigue in three different moments of the experiment: baseline, immediately after the training period, and after the 30-minute consolidation period. This was performed because physical or mental fatigue has been shown to have a detrimental effect on performance.

2.5 | Median nerve stimulation

Median nerve stimulation is a form of electrical median nerve stimulation, a noninvasive neuromodulation procedure, where electrical pulses from two transcutaneous electrodes (cathode and anode) are transmitted along the wrist to the median nerve. Each session consisted of 20 min of sensorial stimulation (active or sham) delivered by standard electrodes to the left wrist. The shape of the wave was a constant rectangular wave with random frequency ranges (1–4 Hz, 8–12 Hz, and 60–90 Hz) and intensity levels (2–6 mA) that changed throughout the protocol every 2 min. The device parameters were the same across subjects. Recent studies show the effects of varying intensity and random frequency ranges of stimulation on neural effects (Chen, Lin, Chen, & Fregni, 2016; Chen et al., 2017; Morales-Quezada, Saavedra, Rozisky, Hadlington, & Fregni, 2014; Morales-Quezada et al., 2015). In the sham procedure, the device setup remained unchanged, and excepted active stimulation was only applied for the first and last 30 s. We have successfully used this method in our other studies using pulsed peripheral stimulation with similar intensities (Thibaut et al., 2017; Vasquez, Thibaut, Morales-Quezada, Leite, & Fregni, 2017; Vasquez et al., 2016). Labuschagne Foundation (Luzerne, Switzerland) provided the MNS stimulation devices.

2.6 | Data analysis

The learning index is presented as a ratio, in which implicit and explicit conditions were divided by the random condition (i.e., implicit learning index = 1—implicit/random; explicit learning index = 1—explicit/random) using reaction times. For baseline and retest periods, response times for all correct responses were used. We chose to use the last four sequences of each condition (explicit, implicit and random), as these sequences would be a good indicator of practice effects (similar approach has been used recently to estimate the effects at the end of training; Focke et al., 2017). Normality was assessed using Shapiro–Wilk test, and the index was not normally distributed.

To perform the end of training analysis, Kruskal–Wallis test was used to assess group differences for each of the independent variables (i.e., implicit and explicit) at baseline, at the end of the training session and at retest. For post hoc analyses, we used the Wilcoxon signed rank test within each group to assess performance differences between groups at the end of training and at retest.

We compared the proportion of subjects between the three groups able to recall the entire explicit and implicit sequences using a chi-square test. We did this analysis at the end of the experiment (after the end of the retest period on the free recall test). We then compared each group using a 2X2 table.

For the attention network task (ANT), the data were normally distributed, and we performed a one-way repeated measures ANOVA.

Statistical significance was set at $p < 0.05$. The effect sizes (Cohen's d effect size) were calculated from the difference in means and standard deviations between the two active conditions and sham MNS. The data were analyzed using StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP.

3 | RESULTS

Three participants had to be excluded from the analysis for the following reasons: One participant did not complete the experimental session, reporting some discomfort with the tingling sensation during the stimulation; one participant failed to start the serial reaction time task on time due to a computer error, and one technical error occurred during the SRTT leading to unreliable data. Thus, 33 participants were included in the analyses: 12 in the online MNS during acquisition group, 10 in the offline MNS during early consolidation group and 11 in the sham group.

3.1 | Serial Reaction Time Task

3.1.1 | Learning effect (implicit and explicit learning)

Explicit learning index scores were not normally distributed (Wilk–Shapiro test, $p = 0.045$); therefore, we used nonparametric tests for our analysis. There were no differences between groups for the implicit sequence. A sensitivity analysis, adjusting for gender and age, did not change our results. However, for the explicit sequence, the group that received MNS during the acquisition phase showed a significantly higher learning index when compared to the group that received MNS during early consolidation phase ($Z = 1.956$; $p = 0.050$; effect size = 0.63) and the group that received sham ($Z = -2.490$, $p = 0.0128$; effect size = 1.16). Moreover, during the last trials of the retest phase, the two active groups that received MNS during the acquisition phase ($Z = -2.223$, $p = 0.0262$; effect size = 1.11) and the consolidation phase ($Z = -2.040$; $p = 0.0414$; effect-size = 0.94) showed an increased learning index when compared to sham. See Table 2 for explicit, implicit and random SRTT scores at each time point and for each group.

3.1.2 | Explicit and implicit sequence free recall

In addition, we then looked at the number of subjects able to recall the explicit sequence at the end of the retest. Only one (of 11, i.e., 9%) subject in the sham group and one (of 10, i.e., 10%) subject in the group that received offline MNS during early consolidation stage correctly recalled the sequence, compared to seven (of 12) (58%) in the group who received online MNS during acquisition. A significant group difference was found when comparing the proportion of subjects able to recall the explicit learning sequence between the three groups ($\chi^2 = 9.174$; $p = 0.010$). Thus, the group that received active MNS during the acquisition stage recalled the explicit sequence significantly more than

TABLE 2 Mean and standard deviation for the three subscales of the serial reaction time task (SRTT) per group and at each time point

SRTT	Group	Baseline	Postacquisition	Postconsolidation
Explicit	Sham	624.76 (157.39)	595.23 (190.28)	534.70 (137.47)
	Acquisition	595.74 (88.79)	397.79 (150.32)	400.77 (103.97)
	Consolidation	506.90 (97.44)	501.68 (177.75)	423.27 (91.81)
Implicit	Sham	615.56 (135.04)	614.06 (195.71)	540.56 (121.34)
	Acquisition	504.09 (106.56)	444.34 (110.02)	421.59 (77.99)
	Consolidation	514.27 (116.15)	517.53 (166.56)	441.69 (65.18)
Random	Sham	706.45 (166.96)	670.94 (177.34)	608.82 (145.21)
	Acquisition	575.51 (143.85)	507.66 (143.38)	511.22 (137.66)
	Consolidation	576.14 (94.57)	592.43 (137.61)	497.17 (99.58)

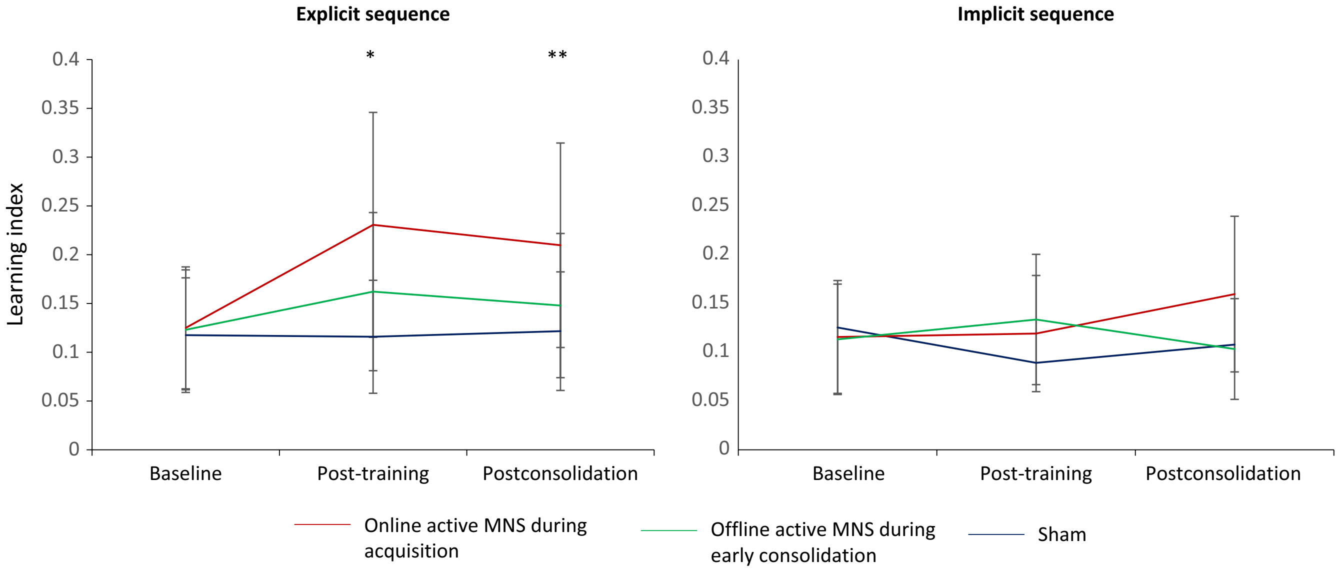


FIGURE 2 Mean and *SD* of the learning index for the explicit sequence (left) and the implicit sequence (right), for the three groups: 1—online active MNS during acquisition; 2—offline active MNS during early consolidation; and 3—sham MNS. Group 1 (red) had a higher learning index for the explicit sequence as compared to group 3 (blue) and to group 2 (green) posttraining (*). Postconsolidation, both groups (1 and 2) were significantly higher than sham (group 3) (**). Statistical significance (* and **) was set at $p < 0.05$. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Mean and standard deviation for the three subscales of the attention network (ANT), per group and at each time point

ANT	Group	Baseline	Postacquisition	Postconsolidation
Alert	Sham	3 (39.12)	−10.5 (33.23)	−34.11 (53.15)
	Acquisition	−12.19 (25.017)	−13.22 (31.36)	−14.93 (23.62)
	Consolidation	−1.91 (24.5)	−5.74 (36.071)	−2.35 (37.07)
Orient	Sham	1.05 (34.36)	14.43 (56.39)	20.08 (45.98)
	Acquisition	26.08 (43.21)	32.23 (36.69)	37.31 (35.25)
	Consolidation	21.5 (16.06)	10.056 (67.22)	27.27 (47.36)
Executive	Sham	81.75 (44.01)	98.8 (42.61)	124.63 (43.68)
	Acquisition	101.14 (30.50)	99.86 (33.84)	90.61 (39.07)
	Consolidation	121.64 (45.56)	103.32 (32.42)	110.38 (41.09)

the group that received active MNS during early consolidation ($\chi^2 = 5.51$; $p = 0.019$) and the group that received sham ($\chi^2 = 6.13$; $p = 0.013$). No differences were found between the group that received offline MNS during early consolidation and the sham group ($\chi^2 = 0.01$; $p = 0.934$) (Figure 2).

In addition, none of the participants were able to recall the correct implicit sequence in any of the three groups.

3.1.3 | Attention network task

Mean and standard deviations reaction time for the ANT are presented in Table 2. The mixed model ANOVA revealed no significant main effects for alert [F (2, 60) = 1.175, $p = 0.316$], orienting [F (2, 60) = 0.74, $p = 0.908$] nor executive [F (2, 60) = 0.705, $p = 0.498$] attention networks (see Table 3).

3.1.4 | Visual Analogue Scale for mental fatigue

No significant results were revealed between groups (sham, acquisition or consolidation group) or within groups (baseline, after acquisition period or after early consolidation period) [F (2,60) = 1.641, $p = 0.259$]. Overall, VAS fatigue scores remained low for all groups and at all time points.

4 | DISCUSSION

This pilot exploratory study investigates the effects of MNS applied during (online acquisition learning) or after (offline early consolidation learning) a motor learning (explicit or implicit) task (SRTT). Our results show that during the last trials of the retest phase, the group that received MNS during acquisition and consolidation phases showed an increased learning index for the explicit sequence when compared to sham. Furthermore, participants who received MNS during the acquisition period were able to explicitly recall the explicit sequence better (58% versus about 10% in the other two groups), which has been considered one of the optimal measures to assess learning of the explicit sequence (Galea, Albert, Ditye, & Miall, 2010; Wilkinson & Shanks, 2004). For the implicit sequence, none of the participants in any of the three groups were able to recall the full implicit sequence, supporting the assumption that this sequence was, in fact, learned mostly implicitly. There were no differences in the attention network task or the VAS for fatigue scale.

This is not the first time that peripheral stimulation has been shown to improve motor skills in healthy volunteers. Two previous studies demonstrated improvement of motor skills immediately following the peripheral stimulation by itself (Koesler, Dafotakis, Ameli, Fink, & Nowak, 2008; Veldman et al., 2016). Although these studies explored other parameters, neither looked at implicit vs. explicit motor learning nor phase of training. In addition, there are a limited number of studies combining motor training with stimulation in healthy volunteers. Most of the trials have been carried out with clinical populations. For example, several studies using peripheral stimulation in stroke patients measured the effects of stimulation before motor training and found positive results on motor function using either a single session (Celnik et al., 2007; Conforto et al., 2002) or multiple sessions (Fleming et al., 2015; McDonnell et al., 2007). The motor benefits of a single session of stimulation have been shown to last from 24 hr after a single stimulation (Celnik et al., 2007) to 30 days (Conforto et al., 2002), thus showing its effects on motor learning and learning consolidation. However, these studies did not investigate the effects on different types of learning (explicit vs implicit) or other timing of stimulation (during the acquisition or the early consolidation phase). Therefore, one of the novel aspects of this study was to investigate the effects of implicit and explicit motor learning during different phases of learning in healthy subjects using peripheral stimulation.

4.1 | Explicit vs implicit knowledge

The rationale for why MNS can affect implicit vs. explicit motor learning differently is based on the distinct neural circuits associated with the respective motor learning. For instance, the medial temporal lobe seems to be involved in explicit, but not implicit motor learning (Reber, 2013). Therefore, this study tests, in a preliminary manner, the extent of MNS effects on different networks in order to assess whether its effects were more prominent when focused on more localized brain networks (motor cortex–basal ganglia) or on more distributed networks (which include, for instance, the medial temporal lobe).

In our study, we found that only explicit learning was significantly increased by MNS. It is well known that implicit and explicit motor learning processes are not driven by the same neural mechanisms, even within the motor cortex (M1), which plays a role in the development of implicit motor learning (Kantak, Mummidisetty, & Stinear, 2012; Nitsche et al., 2003). Motor learning is dependent on spatiotemporally cortico-cortical communications between sensory and motor regions (Arce-McShane et al., 2016; Schabrun et al., 2012; Zagha, Casale, Sachdev, McGinley, & McCormick, 2013). Often this coordination results in decreased activity over motor regions, coupled with increased activation over the basal ganglia (Gobel, Parrish, & Reber, 2011). For instance, Pascual-Leone, Grafman, and Hallett (1994) showed that the acquisition of implicit knowledge was associated with increases in M1 cortical excitability. Another study showed that the acquisition of implicit, but not explicit, knowledge during the performance of SRTT induces different effects on motor cortical reorganization, as assessed by changes in MEP latency (but not MEP amplitude) (Hirano, Kubota, Koizume, Tanaka, & Funase, 2016). However, another study suggested that M1 cortical excitability was not changed by implicit learning, but instead decreased during explicit motor learning (Tunovic, Press, & Robertson, 2014). Furthermore, the medial temporal lobe seems to be involved in explicit, but not implicit, motor learning (Schendan, Searl, Melrose, & Stern, 2003). This clearly suggests that the learning of implicit and explicit sequences in the SRTT is at least partially dependent on distinct mechanisms and brain regions, with distinct levels of cortical activity over M1.

Median nerve stimulation is thought to coactivate the brain in a bottom-up manner, in which sensorial information reaches the cortex by a pacemaker system that generates and synchronizes activity through thalamocortical circuitries (Blethyn, Hughes, & Crunelli, 2008; Cooper, Scherder, & Cooper, 2005; Drover, Schiff, & Victor, 2010; Hindriks & van Putten, 2012). Thus, this lack of effects on the implicit sequence may be related to the fact that this sequence is able to induce cortical reorganization. In contrast, the explicit sequence may be more susceptible to the indirect cortical coactivation induced by median nerve stimulation as it depends on a broader (nonmotor) network. Research targeting the networks involved in explicit and implicit learning seems to provide support to this claim. Implicit learners seem to engage a direct fronto-striatal network, whereas explicit learners use a broader network of frontal and parietal structures (Yang & Li, 2012). Therefore, if implicit learners use a more direct network, which ultimately is associated with motor cortex reorganization, the broader frontoparietal network will not be as dependent on the motor cortex. Instead, it will tend to be indirectly activated by information arising from other cortices, such as the somatosensory cortex. This may also explain the differences found between our study and those utilizing other types of noninvasive brain stimulation, such as tDCS. For instance, tDCS has been shown to facilitate the learning of the implicit sequence during the SRTT task (Nitsche et al., 2003). One potential mechanism for the effects of tDCS would be a gating mechanism for sensorial processing in which increased sensorial input would enhance sensorial processing of a specific type of stimulus on which attention is oriented, in this case the SRTT. Our present results do not support the same tDCS attention dependence mechanism of action, as there were no effects on attentional networks. Moreover, results were specific for explicit rather than implicit learning; therefore, it is possible that MNS facilitated the engagement of other areas, such as the DLPFC (Grafton, Hazeltine, & Ivry, 1995; Hazeltine, Grafton, & Ivry, 1997), or even the insula which has been shown to be a key mediator for explicit learning (Yang & Li, 2012). To support this hypothesis, MNS has been shown to activate the insulta as well as somatosensory regions (Ferretti et al., 2007; Hodzic, 2004; Ibanez et al., 1995).

4.2 | Timing—when to stimulate and when to measure learning: comparison across studies

Our results show that MNS when applied during the SRTT acquisition period is particularly effective on the early consolidation of a newly learned explicit motor sequence, as shown by the increased learning index at both the end of training and at retest. This is supported by the fact that 58% of participants receiving MNS during the acquisition period were able to correctly recall the entire (12 letter-long) sequence of the explicit condition. However, no differences were found between the group that received active MNS during the early consolidation period or the sham group. When MNS was applied during the 30-minute posttraining period (early consolidation phase), it also increased performance on the SRTT task for the explicit sequence at the retest period when compared to sham. Furthermore, there were no effects on sequence recall when MNS was applied during the early consolidation stage. Therefore, it seems that the effects of MNS are more effective if the peripheral stimulation is applied during the acquisition period, rather than during the early consolidation period of motor skill learning. Interestingly, electrical stimulation of the motor cortex after motor training also seems to have no effect as compared to immediately before motor training (Cabral et al., 2015).

4.3 | Recall

Participants who received MNS during the acquisition period were able to recall the explicit sequence better (58% versus about 10% in the other two groups). This measure of free recall of the SRTT sequence has been used as an index of learning (Galea et al., 2010; Wilkinson & Shanks, 2004). In our study, we found that subjects who received MNS during the acquisition phase were able to decrease the response time while still improving explicit recall. As improvements in explicit recall are normally associated with longer reaction times (Galea et al., 2010), it is especially interesting to show that MNS can improve both the execution and declarative knowledge of motor skills simultaneously, allowing participants to process information faster while still recalling the sequence better.

Learning a procedural skill comprises at least two distinct stages: a rapid learning stage and a slower one, the consolidation phase, focusing on retention and automaticity of the skill (Barakat et al., 2011). The present results show that MNS can improve learning as well as retention of learning in healthy volunteers. These results are somewhat different from those of Veldman and colleagues (Veldman et al., 2016). The authors tested the acute and delayed (consolidation) effects of low-intensity peripheral electrical nerve stimulation on visuomotor performance in healthy young volunteers. Results showed consolidation effects on visuomotor performance but not acute effects. In this study, we show that MNS can impact both the fast acquisition learning and the early consolidation stages.

On the other hand, our results are similar to studies using another electrical stimulation technique, namely tDCS. For example, one study in which anodal tDCS was applied over M1 *during* a serial reaction time task showed that performance on the SRTT improved in the acquisition and the early consolidation periods (Nitsche et al., 2003). M1 tDCS has also been shown to improve procedural consolidation performance when applied after the training session (Tecchio et al., 2010). In addition, another study using anodal tDCS applied over M1 during the acquisition phase demonstrated that tDCS was able to increase performance during the acquisition stage, as well as during the 24-hour consolidation period (Kantak et al., 2012). However, no effects on motor learning were observed if tDCS was applied "offline" (i.e., before motor learning), or during sleep consolidation after learning (Nitsche et al., 2010). This latter study assessed the effects of stimulation after learning, which was also one of our aims in the current study. However, we did not assess any sleep consolidation effects.

Moreover, our results are also similar to the ones found previously with sensorial stimulation in stroke patients. For instance, one study showed motor learning improvement immediately after 2 hr of MNS in stroke patients (Conforto et al., 2002). Moreover, this increase in rapid skill learning following sensorial stimulation has also been shown to transfer to other domains. Lin and colleagues showed that the combination of mirror therapy with somatosensory stimulation significantly improves motor performance and motor transfer, as compared to mirror therapy alone (Lin et al., 2014). Another study by Lee and colleagues, using a similar approach of combining mirror therapy with sensory afferent stimulation, showed improved muscular, sensorimotor and daily functioning after chronic stroke (Lee et al., 2015). These studies show that MNS can increase rapid learning but also transfer to other domains. Together, these findings support that MNS can improve the execution and transfer to declarative knowledge of motor skills simultaneously when MNS is delivered during the early acquisition stage.

4.4 | Mechanisms of MNS

It will be important to understand in the future the neurophysiological basis of these immediate and delayed effects of MNS on learning. Despite the fact that the neurophysiological mechanisms of MNS are not fully understood, some neuroimaging and neurophysiology provide us with insights. A study using somatosensory stimulation (peripheral stimulation over the radial and median nerve) suggests that it can increase cortical excitability over the motor cortex immediately after stimulation; however, no changes were found at later time points (Veldman et al., 2016). If this suggests that there are no long-lasting effects induced by peripheral stimulation, other studies do not support this claim (Andrews et al., 2013; Ridding et al., 2001; Volz et al., 2013). These MNS induced neurophysiological changes include increased intracortical facilitation (Kobayashi, Ng, Théoret, & Pascual-Leone, 2003) through long-term potentiation (LTP)-like mechanisms (Andrews et al., 2013; Ridding et al., 2001), and decreased short-interval intracortical inhibition (SICI) (Classen et al., 2000). Therefore, it is possible that increased intracortical facilitation coupled with decreased SICI primes early memory consolidation through long-term potentiation (LTP)-like mechanisms. Frequency has also been shown to influence motor learning in previous trials. Some studies suggested that somatosensory electrical stimulation at lower frequencies (below 10 Hz) increases motor performance and corticomotor excitability (Veldman et al., 2016), while higher frequencies decrease corticomotor excitability (Schabrun et al., 2012). However, these results may not be entirely comparable to our stimulation parameters because, unlike most peripheral stimulations, in our study we used a random-noise frequency range that was jittered throughout the study to minimize habituation. Therefore, our results would be better comparable to the ones of transcranial random-noise stimulation (tRNS). A large range of frequencies seem to be able to increase implicit learning (Ambrus et al., 2011; Fertonani, Pirulli, & Miniussi, 2011; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008), and higher tRNS frequencies seem to increase motor excitability as well (Terney et al., 2008). Interestingly enough, one study showed that tRNS was able to increase participants' ability to inhibit irrelevant information during an inhibition task in both older and younger adults (Cappelletti, Pikkat, Upstill, Speekenbrink, & Walsh, 2015). Thus, it is possible that the effects of this type of MNS are mediated through sensory gating. This early process of gating leads to better performance that is then transferred to the free recall after the 30-minute consolidation period. Another possible mechanism is that random-noise works by stochastic resonance. By adding "noise" to a neural system that has a low signal, as well as noise, tRNS allows a weak signal to exceed the threshold by summing two signals at a sensitive period depending on what is needed for a particular task (Antal & Herrmann, 2016; van der Groen & Wenderoth, 2016). Nonetheless, these are only hypotheses that future studies should test, to explore the effects of random-noise MNS on cortical entrainments.

4.5 | Future directions and limitations

Given our results, MNS could be used in different neurological conditions, such as stroke, to improvement motor learning. MNS could be easily applied in rehabilitation while performing a motor task or combined with motor cortex stimulation in chronic pain (Boggio et al., 2009). These could be single sessions, or similarly to other noninvasive stimulation techniques, performed repeatedly. The use of repeated sessions could be preferable, as repeated sessions may be needed to induce long-lasting and clinically relevant effects (Castillo-Saavedra et al., 2016).

The present results are not without some caveats. We tested implicit and explicit learning over a single session of 20 min. As motor learning skills are often learned over multiple sessions (Luft & Buitrago, 2005), perhaps more training sessions could have increased learning. Also, motor learning can take up to 24 hr to peak; studies with a longer follow-up assessment may detect additional behavioral results on retest (Veldman et al., 2016). In addition, as proposed before (Focke et al., 2017), we used the last four sequences of the SRTT task in our main analysis and reported these results (rather than using all the sequences) since during the SRTT phase, the learning process does not start from the very first sequence, and therefore, the effect of learning is smoothed by the early phase of the SRTT. Therefore, results should be interpreted considering this type of analysis. A separate extra assessment following the SRTT training could be added to overcome this issue. Moreover, we only tested the effects of MNS during the early consolidation stage, and thus, future studies should test the effects of MNS during the late consolidation stage (e.g., 10 or 24 hr after training). However, our sample was too small to account for such differences. Larger clinical trials should overcome this issue. As aforementioned, the results of our study rely on behavioral measurements; therefore, coupling behavioral outcomes to neurophysiological measurements would help to improve our understanding of the underlying mechanisms of MNS on motor learning and related cortical networks.

5 | CONCLUSION

Overall, our study shows that MNS effects on motor learning are learning-specific and timing-dependent. When applied during the acquisition phase (and not during the consolidation phase), MNS can improve both the execution and declarative knowledge of motor skills simultaneously, meaning that participants can process information faster while still recalling the sequence better. Even if there are still several factors to be tested as to optimize and understand further the potential of peripheral electrical stimulation to change and modulate motor learning, this technique is worth investigating, especially in clinical populations.

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CONFLICT OF INTERESTS

The authors declare no competing financial interests.

DATA ACCESSIBILITY

For additional tables and data, please go to figshare https://doi.org/10.6084/m9.figshare.6198386 or please contact the corresponding author.

AUTHORS' CONTRIBUTION

SC, JL and FF conceived the study; SC, MF and WL collected the data; SC, MF, AT, JL and FF did the statistical analyses, interpreted the data and wrote the manuscript. All authors critically review of manuscript for intellectual content and approved the final version.

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