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Effect of Modulated TENS on Corticospinal Excitability in Healthy Subjects

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Abstract—Conventional transcutaneous electrical nerve stimulation (TENS) has been reported to effectively alleviate chronic pain, including phantom limb pain (PLP). Recently, literature has focused on modulated TENS patterns, such as pulse width modulation (PWM) and burst modulation (BM), as alternatives to conventional, non-modulated (NM) sensory neurostimulation to increase the efficiency of rehabilitation. However, there is still limited knowledge of how these modulated TENS patterns affect corticospinal (CS) and motor cortex activity. Therefore, our aim was to first investigate the effect of modulated TENS patterns on CS activity and corticomotor map in healthy subjects. Motor evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS) were recorded from three muscles before and after the application of TENS interventions. Four different TENS patterns (PWM, BM, NM 40 Hz, and NM 100 Hz) were applied. The results revealed significant facilitation of CS excitability following the PWM intervention. We also found an increase in the volume of the motor cortical map following the application of the PWM and NM (40 Hz). Although PLP alleviation has been reported to be associated with an enhancement of corticospinal excitability, the efficiency of the PWM intervention to induce pain alleviation should be validated in a future clinical study in amputees with PLP.

Key words: modulated TENS pattern, motor evoked potentials, TMS, corticospinal excitability, motor cortical plasticity, pain alleviation.

INTRODUCTION

Transcutaneous electrical nerve stimulation (TENS) is widely used as an inexpensive and non-invasive rehabilitative intervention for neurological conditions such as acute pain (Johnson et al., 2015; Elboim-Gabyzon et al., 2019; Peng et al., 2019), chronic pain (Mulvey et al., 2013; Hu et al., 2014a; Macedo et al., 2015; Tan et al., 2016; Gibson et al., 2019), and stroke (Conforto et al., 2007; Hatem et al., 2016; Sharififar et al., 2018). Generally, TENS is delivered in two different manners: "conventional" TENS with a high stimulation frequency (~40–100 Hz) and low intensity within range of eliciting perception to strong but non-painful sensation (below motor threshold) (Jones and Johnson, 2009; Macedo et al., 2015; Peng et al., 2019); and "acupuncture" TENS with a low stimulation frequency (~2–20 Hz) and a high stimulation intensity eliciting painful but tolerable sensations (Han, 2003; Peng et al., 2019).

Depending on the TENS parameters (i.e., frequency, intensity), the induced changes in the cortical activity of the sensorimotor cortex and the subsequent rehabilitative effect may differ (Mang et al., 2010; Chipchase et al., 2011a, 2011b; Andrews et al., 2013; Saito et al., 2015; Jadidi et al., 2020). Previous studies have indicated that conventional TENS leads to greater cortical activity suppression at the primary somatosensory cortex (S1) and to pain level reduction compared with acupuncture TENS among acute pain patients (Peng et al., 2019). Meanwhile, it has been shown that the alternation in excitability of S1 and the primary motor cortex (M1) is co-modulated due to anatomical connections between M1 and peripheral afferent input by S1 (Ridding et al., 2000). Transcranial magnetic stimulation (TMS) has been widely used as a non-invasive therapeutic measure (Rossini et al., 1994, 2015) to evaluate the reflection of sensory deprivation (Kew et al., 1994; Rossini et al., 1996; Rosenkranz et al., 2014; Nardone et al., 2019) and peripheral input (Ridding et al., 2000; Kaelin-Lang et al., 2002; Chipchase et al., 2011c; Lagerquist et al., 2012; Andrews et al., 2013) on corti-

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Abbreviations: ADM, Abductor digiti minimi; APB, Abductor pollicis brevis; BM, Burst modulation; CoG, Center of gravity; CS, Corticospinal; EMG, Electromyography; GUI, Graphical user interface; M1, Primary motor cortex; MEP, Motor evoked potential; NM, non-modulated, S1, Primary somatosensory Cortex; NM_HF, Non-modulated high frequency; NM_LF, Non-modulated low frequency; nparLD, Nonparametric analysis of the longitudinal data; PES, Peripheral electrical stimulation; PLP, Phantom limb pain; PWM, Pulse width modulation; RMS, Root mean square; rMT, resting motor threshold; tDCS, Transcranial direct current stimulation; TENS, Transcutaneous electrical nerve stimulation; TMS, Transcranial magnetic stimulation.

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cospinal (CS) tract excitability. In recent TMS studies the effect of conventional TENS patterns on modulating CS excitability has shown an enhancement in the activity of corticomotor circuits and strengthening of the CS pathway between M1 and skeletal muscles (Kaelin-Lang et al., 2002; Mang et al., 2010; Jadidi et al., 2020). In contrast, articles reported no significant changes in CS excitability following acupuncture TENS (Chipchase et al., 2011a).

Conventional TENS interventions have been reported to be beneficial for chronic pain patients, including low back pain patients (Khadilkar et al., 2008) and amputees with phantom limb pain (PLP) (Mulvey et al., 2013, 2014; Tilak et al., 2016). While the methodological aspects of TENS as a therapeutic intervention for pain alleviation is not fully resolved, spinal gating mechanisms (Melzack and Wall, 1965), activation of the pain inhibitory system (DeSantana et al., 2008), neural inhibition at S1 (Peng et al., 2019; Zarei et al., 2019, 2021), and reverse cortical plastic changes (MacIver et al., 2008) are the possible explanations.

In recent years, there has been a growing interest in the investigation of alternative temporal patterns of TENS rather than the conventional, non-modulated patterns to improve the efficiency and efficacy of rehabilitation (Chipchase et al., 2011a; Tan et al., 2016; Cassar et al., 2017; Grill, 2018). Pulse width modulated (PWM) electrical stimulation is one of the interesting approaches which has been examined in chronic pain patients (Tan et al., 2016; Bouafif and Ellouze, 2018). The results demonstrated that this pattern leads to a more comfortable perception compared with the non-modulated pattern, while providing the same level of pain reduction (Tan et al., 2016). Furthermore, the burst modulated TENS pattern has been extensively used as a non-invasive strategy to treat chronic pain patients. This pattern is generally applied with a high-frequency pulse train (5 to 7 pulses at 80–100 or 500 Hz) modulated in low frequency (2–5 or 40 Hz, respectively), and the results have revealed a significant improvement in pain alleviation compared with non-modulated TENS interventions (Schu et al., 2014; Macedo et al., 2015).

It still remains unresolved how these modulated TENS patterns influence the CS excitability and the possible CS biomarkers for pain alleviation. This study is the first to compare CS excitability and possible modulation in the motor cortex following the application of modulated (PWM and BM) and conventional TENS patterns. We investigated motor evoked potentials (MEP) evoked by TMS for the assessment of the TENS patterns' effect on the CS pathway and corticomotor responses. Further, we investigated healthy subjects to include a larger subject population. Several studies have used the same strategy to evaluate the effects of a novel intervention for neuroplasticity modulation with the future goal of utilizing this method for therapeutic purposes (i.e., in patient populations) (Chipchase et al., 2011a; Jiang et al., 2019; Zarei et al., 2021). However, additional studies are needed to validate our results in a population of patients with chronic pain (e.g., PLP).

EXPERIMENTAL PROCEDURES

Participants

Forty-four healthy, right-handed individuals (24 men, 20 women; 26.6 ± 2.7 SD years, range 23–30) were included. All subjects received written and verbal instruction and signed the consent form. The experiment procedure was conducted with the approval of the North Denmark Region Committee on Health Research Ethics (N-20190016) and performed in accordance with the Declaration of Helsinki. Moreover, each participant completed a TMS safety screening questionnaire prior to study commencement (Keel et al., 2001) and received financial compensation for the participation. Subjects were excluded if they had peripheral or central nervous system diseases, injuries, or contraindications to peripheral electrical stimulation or TMS, including pregnancy, having a pacemaker, or a family history of epilepsy.

Experimental overview

Eleven subjects matched in sex and age were randomly assigned to one of four groups. Each participant completed one experimental session that lasted approximately three hours. The outline of the protocol design is summarized in Fig. 1. First, all outcome measurements were performed before the application of the TENS pattern (Pre). Subsequently, the TENS intervention was delivered to the right median nerve for 30 min. Outcome measures were repeated immediately (Post) and 30 min after (Post30) completion of the intervention period.

TENS intervention

All electrical stimulation patterns were generated with a custom-made graphical user interface (GUI) in Matlab and delivered from a current stimulator (DS5, Digitimer, UK) by a pair of surface electrodes (Dura Stick premium, contact size 4 × 6 cm, oval) placed over the right median nerve (one electrode at the wrist on the palmar side and 2 cm proximal inter-electrode distance).

Four different TENS patterns were applied; A) **NM_LF:** Non-modulated, low frequency (40 Hz, 500 μs pulse width), B) **NM_HF**: Non-modulated, high frequency (100 Hz, 500 μs pulse width), C) **PWM:** Pulse width modulated (100 Hz, 1 Hz sinusoidal modulated, pulse width range 0–500 μs), and D) **BM:** Burst modulated (100 Hz carrier frequency, groups of five pulses modulated at 4 Hz followed by a single repolarization pulse, 500 μs pulse width). All patterns consisted of bipolar rectangular pulses.

The TENS parameter values (i.e., intensity, frequency, and pulse width) were chosen based on previous studies in which pain alleviation had been reported (Hu et al., 2014b; Mulvey et al., 2014). NM_LF pattern was added to the protocol since a wide range of frequencies (~20–120 Hz) had been used in PLP therapy sessions in the literature (Hu et al., 2014b; Mulvey et al., 2014).

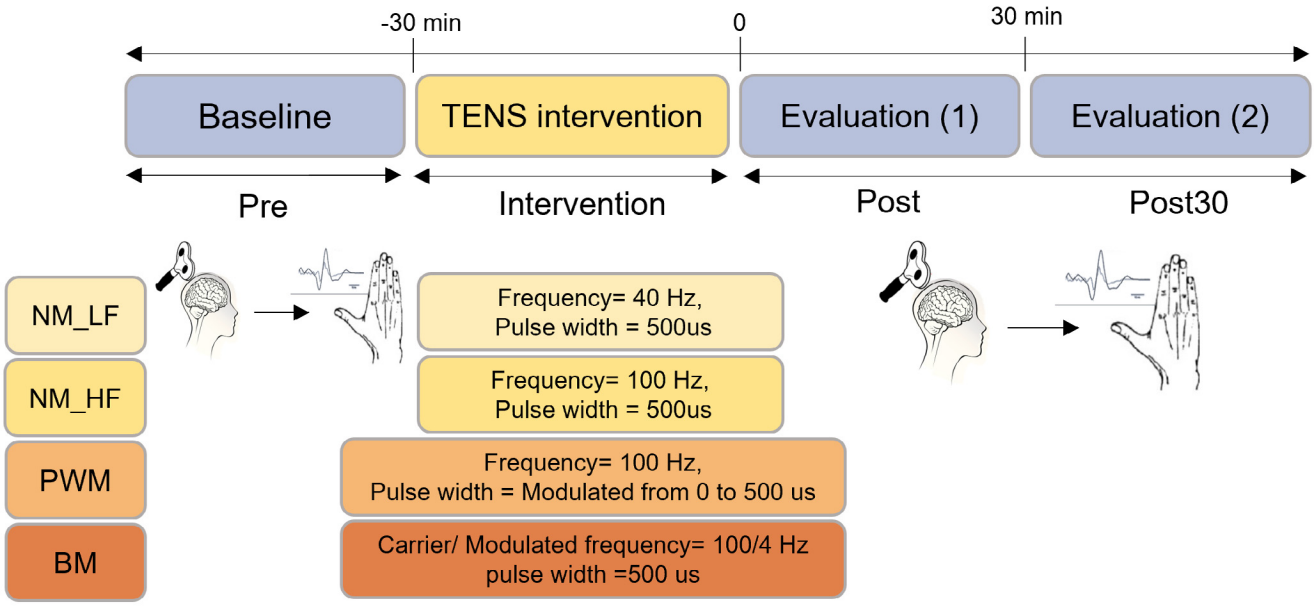

Fig. 1. Overview of the experimental protocol. The effect of the different TENS patterns on the excitability of the CS pathway was assessed at two different time points, immediately (Post) and 30 min (Post30) after stimulation and compared with the outcome measurements recorded before the intervention (Pre). NM_LF, non-modulated low frequency (40 Hz); NM_HF, non-modulated low frequency (100 Hz); PWM, pulse width modulated; BM, burst modulated.

Each intervention lasted for 30 min, with a 20 s on-time, 10 s off-time cycle (Mang et al., 2010; Ishibashi et al., 2021). The TENS intensity was set at 80% of the individual discomfort level (without pain and below the motor threshold) by a staircase procedure (Manresa et al., 2018). First, the stimulus was adjusted at an intensity of 0.5 mA and increased in steps of 0.5 mA until the subject perceived the stimulation. Next, the intensity was increased in 0.5 mA steps until the subject reported that the sensation was uncomfortable. This procedure was repeated three times. If the defined intensity caused visible hand muscle movement, the intensity was decreased by 0.1 mA steps until the movement disappeared.

Data collection (electromyography)

The participants were asked to sit in a comfortable armchair in a relaxed position. Electromyography (EMG) signals were recorded from the abductor pollicis brevis (APB) and abductor digiti minimi (ADM) muscles of the right hand and from the APB muscle of the left hand as a target, non-target, and control muscle, respectively. Signals from each muscle were collected using surface recording electrodes (Bipolar, Ambu Neuroline 720). EMG signals were pre-amplified (1000×), band-pass filtered (50 Hz–2 kHz), and stored (5 kHz sampling rate) by custom-made software (“Mr. Kick,” Knud Larsen, Aalborg University, Aalborg, Denmark).

Transcranial magnetic stimulation

TMS pulses were delivered through a figure-of-eight shaped magnetic coil (MagVenture, MC-B70 Butterfly Coil) connected to a Magstim 200 stimulator. The coil was adjusted on the scalp with a 45-degree angle to the sagittal plane to induce a field in a posterior-to-anterior direction. The optimal scalp sites (i.e., hotspots) of the right and left APB muscles were defined as the coil position that evoked the maximal MEP peak-to-peak amplitude for a constant TMS stimulation intensity. Furthermore, the resting motor threshold (rMT) was defined as the minimum TMS pulse intensity required to evoke at least 5 out of 10 MEPs with a peak-to-peak amplitude $\geq$ 50 μV (Rossini et al., 2015; Zewdie and Kirton, 2016). All MEPs were elicited while the subject was asked to remain relaxed.

Outcome measures

Corticospinal excitability. To measure the excitability of the CS tract, ten single TMS pulses were delivered at the identified optimal scalp sites. First, TMS pulses were applied over the hotspot of the right APB muscle at 120% rMT, with an inter-stimulus interval (ISI) of 5–8 s, and MEPs were recorded from the right APB and ADM muscles. Second, TMS pulses were delivered to the hotspot of the left APB muscle at 120% rMT (Rossini et al., 2015; Cavaleri et al., 2019; Nguyen et al., 2019), and MEP signals were obtained from the control APB muscle. Trials with background activity in the 55 ms to 5 ms interval preceding the TMS stimulation were discarded (less than 4% of MEPs were contaminated by noise) (Cavaleri et al., 2019; Nguyen et al., 2019). The peak-to-peak MEP amplitude in the 20–50 ms window following the TMS pulse (Cavaleri et al., 2019) was averaged across each muscle in Pre, Post, and Post30 time phases for each subject to quantify the changes in the corticospinal excitability.

Motor cortical maps. To extract the cortical map of the target muscle (right APB) over the motor cortex, an electroencephalogram (EEG) cap (g.GAMMAcap2, g.tec) was fitted on the participant's head, and the cranial vertex was determined based on the 10–20 international EEG electrode placement system. The left half of the cap was marked with a 1 by 1 cm spatial resolution grid, oriented towards the cranial vertex as point (0,0). Five single TMS pulses at 120% rMT were delivered at each site (over a 9 by 9 cm grid, pseudo-random order, 4–6 s between pulses).

MEP signals containing background EMG activity prior to the TMS pulse were excluded (less than 6% of all recorded MEPs). Due to the complex shape of some MEPs, the Root mean square (RMS) value was chosen rather than the peak-to-peak amplitude to quantify the MEP amplitudes (Tsao et al., 2010). For each trial, the RMS of the MEP response was measured within a 20 to 50 ms window after the TMS stimulation. Background EMG (55 to 5 ms prior to TMS stimulation) was subtracted, and the MEP magnitude was calculated (Tsao et al., 2010; Schabrun et al., 2014). The cortical map was then generated offline using a custom-made MATLAB GUI by averaging the MEP area of the trials at each site and time point (Pre and Post). For each subject, the maps were normalized to the maximum activity at the baseline map.

Three features were extracted from the cortical motor map. First, the whole map volume was measured as the sum of the averaged net MEP amplitude of all active sites (Tsao et al., 2010; Schabrun et al., 2014). As the second feature, the number of active sites was calculated to assess the effect of the interventions on the cortical area. A site was defined as "active" if the averaged MEP amplitude of the five MEPs at that site was $\geq$20% of the peak response of the whole map (Tsao et al., 2010; Schabrun et al., 2016; Grab et al., 2018). Finally, the center of gravity (CoG) was considered as the amplitude-weighted center of the map. It was calculated for target APB using this formula;

$$CoG = \left(\frac{\sum MEP_i.X_i}{\sum MEP_i}, \frac{\sum MEP_i.Y_i}{\sum MEP_i}\right) \quad (1)$$

where MEP_i represents the averaged net MEP amplitude of each site with the coordinates (X_i, Y_i) (Schabrun et al., 2014, 2016; Rossini et al., 2015; Grab et al., 2018).

Statistical analysis

The normality of the collected data was tested using the Shapiro-Wilk test. To compare the effect of the different TENS patterns on the excitability of the CS pathway over the three time phases with a fixed-model, mixed ANOVA was applied. If Levene's test (most common assessment for homogeneity of variance) was violated, the nonparametric analysis of the longitudinal data (nparLD) package for R Software was considered an appropriate alternative due to the nonparametric nature of the extracted features and non-equal variance across groups (Noguchi et al., 2012; Qian and Ricci, 2020). The TENS pattern ("type": BM, NM_LF, NM_HF, and PWM) was a between-subject factor, and the "time" (Pre, Post, and Post30) was considered as a within-subject factor.

In addition, the longitudinal performance of each TENS pattern on the MEP amplitude was evaluated. If the data were normally distributed, a one-way repeated measures ANOVA was conducted on the amplitude of the averaged MEPs (main dependent variables) with "time" as a within-subject factor. The nonparametric Friedman test was conducted for the non-normally distributed data. Furthermore, in case of a significant difference over time phases, post hoc multiple comparisons were applied with adjusted p values using Bonferroni corrections.

To compare the effects of different TENS patterns on the extracted cortical map features (fixed-model), we performed a mixed ANOVA or nparLD (based on Levene's test result) with a between-subject factor ("type": BM, NM_LF, NM_HF, and PWM) and a within-subject factor ("time": Pre and Post) on (1) whole map volumes, (2) the number of active sites, and (3) the CoG location of the right APB muscle. Moreover, to evaluate the effect of each TENS pattern on these features (main dependent variables) before and after interventions ("time" as a within-subjects factor), paired samples t-tests were applied to normally distributed data. Non-normally distributed features were evaluated statistically by the Wilcoxon signed-rank test.

RESULT

CS excitability changes of target muscle

The mean MEPs recorded from the right APB before and after stimulation (Post and Post30) are shown in Fig. 2A for a representative subject. Furthermore, the mean MEP amplitudes across all participants for all TENS patterns are presented for the three time phases in Fig. 2B. The results of the nparLD test performed on the MEP amplitude of the right APB muscle showed strong evidence for a main effect of "time" ($F_{1.7,77.6} = 7.67$, $p < 0.001$), while no significant effect was found for "type" ($F_{2.8,37.2} = 2.2$, $p = 0.10$), or "time $\times$ type" interaction ($F_{5,77.6} = 1.43$, $p = 0.13$).

The longitudinal performance of each TENS was analyzed, and the induced changes by the PWM TENS intervention on the mean MEP amplitude in the right APB muscle revealed a significant main effect of "time" with the Friedman test ($\chi^2_2 = 6.54$, $p < 0.05$). The post hoc analysis (with Bonferroni correction) indicated a significant increase immediately after the TENS intervention ($p < 0.05$). While this enhancement remained for 30 min following the TENS (Post30) intervention, it was no longer statistically significant compared with Pre amplitude (Pre-Post30: $p = 0.6$ and Post-Post30: $p = 0.6$). The reported p values for multiple comparisons are adjustments by Bonferroni correction and the level of significance was still considered $p < 0.05$.

In contrast, no significant effect of the 'time' factor was found after NM_HF, NM_LF, or BM TENS patterns ($p = 0.06$, $p = 0.06$, and $p = 0.59$, respectively). However, Fig. 2A shows that the NM_HF and NM_LF

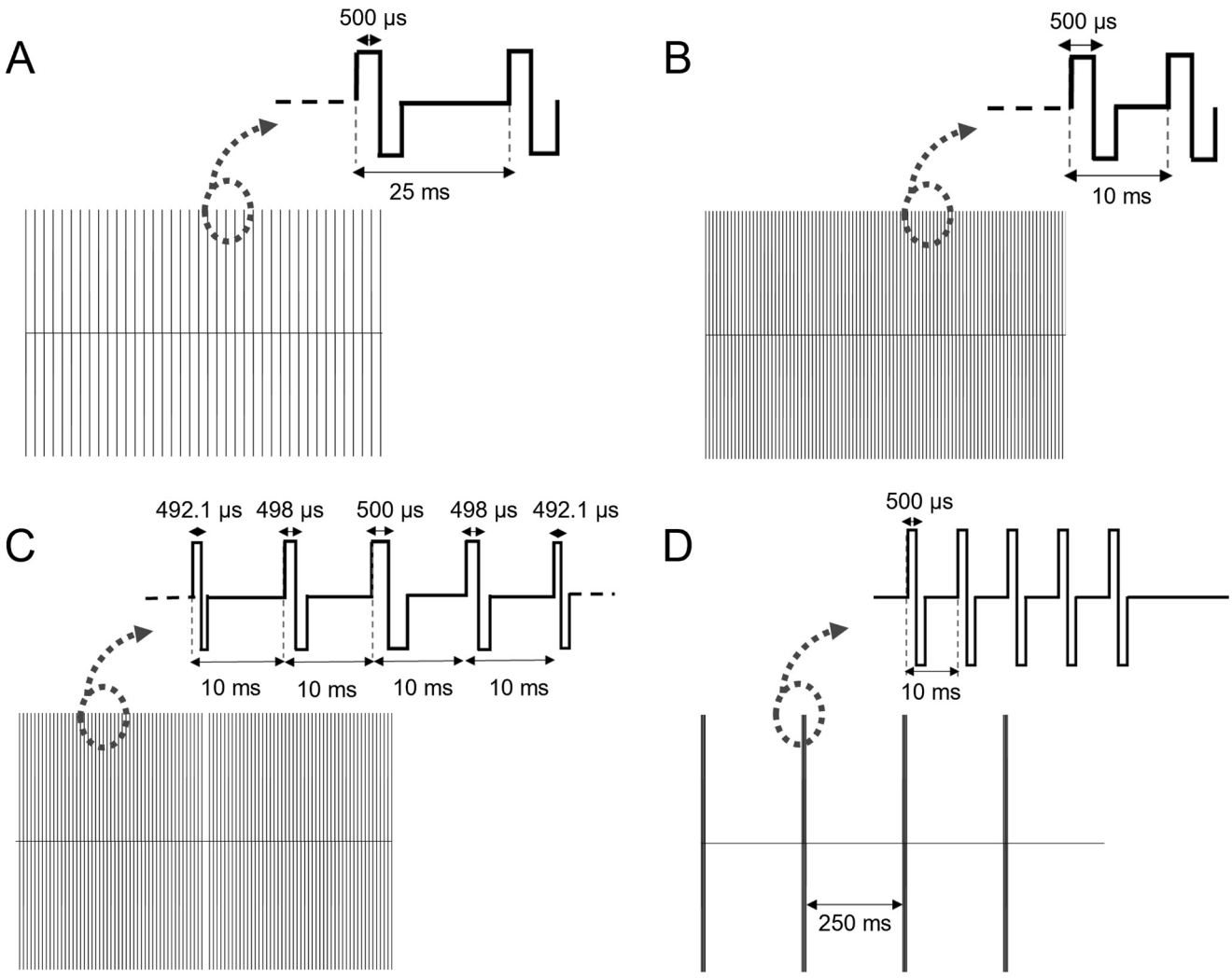

Fig. 2. TENS patterns. **(A)** Non modulated low frequency pattern (40 Hz), NM_LF. **(B)** Non modulated high frequency pattern (100 Hz), NM_HF. **(C)** Pulse width modulated (100 Hz) pattern, PWM. **(D)** Burst modulated pattern, pulses with 100 Hz carrier frequency modulated at 4 Hz, BM.

interventions increased the average MEP amplitude immediately after the intervention phase (Post) and finally returned towards the baseline level at Post30. Furthermore, the effect of the BM stimulation indicated no change in average MEPs at Post and Post30 compared with the baseline (Pre). The statistical results of applied tests are summarized in Table 1.

CS excitability changes of non-target muscle

The results from the mixed ANOVA test for the right ADM and the left APB muscles indicated no significant main effect of "time" ($F_{2,80} = 0.23$, $p = 0.79$ and $F_{2,80} = 0.17$, $p = 0.83$, respectively), "type" ($F_{3,40} = 0.59$, $p = 0.62$ and $F_{3,40} = 0.51$, $p = 0.67$, respectively), or "time × type" interaction ($F_{6,80} = 0.05$, $p = 0.99$ and $F_{6,80} = 0.25$, $p = 0.95$, respectively). Moreover, the data from the aforementioned muscles as non-median nerve-innervated and control muscles, respectively, showed no significant effect of on the MEP amplitude after all TENS interventions (Table 1).

Effect of TENS interventions on corticomotor map features

Average normalized cortical maps across all subjects in each intervention group for the right APB muscle before and after each TENS intervention are shown in Fig. 4.

Table 1. Statistical details of changes in the average MEP amplitude recorded from three muscles for all TENS patterns

Pattern Muscle	NM_HF	NM_LF	PWM	BM
Right – APB	$\chi^2_2 = 7.81$ $p = 0.06$	$F_{2,20} = 3.27$ $p = 0.06$	$\chi^2_2 = 6.54$ $\mathbf{p = 0.038}$*	$F_{2,20} = 0.54$ $p = 0.59$
Right – ADM	$\chi^2_2 = 2.36$ $p = 0.3$	$F_{2,20} = 0.45$ $p = 0.64$	$F_{2,20} = 0.39$ $p = 0.96$	$\chi^2_2 = 2.36$ $p = 0.30$
Left – APB	$F_{2,20} = 0.16$ $p = 0.85$	$F_{2,20} = 0.65$ $p = 0.53$	$F_{2,20} = 0.50$ $p = 0.61$	$\chi^2_2 = 1.40$ $p = 0.49$

*: $p < 0.05$.
Note: χ^2 and F values are reported based on data distribution and applied test.

The baseline map features among all patterns were not significantly different (tested by one-way ANOVA; map volumes: $F_{3,40} = 2.49$, $p = 0.08$, CoG coordinate, X-axis: $F_{3,40} = 1.98$, $p = 0.13$, Y-axis: $F_{3,40} = 0.57$, $p = 0.63$, and number of active sites: $F_{3,40} = 1.97$, $p = 0.13$). The result of the mixed ANOVA test on the whole map volume among all TENS patterns at Pre and Post showed a significant effect of "time" factor ($F_{1,40} = 14.27$, $p \leq 0.001$), while there was no main effect of "type" ($F_{3,40} = 1.72$, $p = 0.17$) or "time × type" interaction ($F_{3,40} = 0.41$, $p = 0.74$). In addition, there was no main effect of "time" ($F_{1,40} = 1.53$, $p = 0.22$; $F_{1,40} = 1.37$, $p = 0.23$; $F_{1,40} = 0.37$, $p = 0.42$), "type" ($F_{3,40} = 1.77$, $p = 0.11$; $F_{3,40} = 2.41$, $p = 0.08$; $F_{3,40} = 0.32$, $p = 0.8$) or "time × type" interaction ($F_{3,40} = 0.69$, $p = 0.56$; $F_{3,40} = 0.91$, $p = 0.59$; $F_{3,40} = 0.97$, $p = 0.41$) between two other map features (number of active sites, CoG_x and CoG_y, respectively).

In addition, individual statistical analyses of cortical motor maps following each pattern revealed a significant increase in map volume at Post following PWM and NM_LF patterns compared with Pre ($t_{10} = 2.64$, $p < 0.05$ and $t_{10} = 2.6$, $p < 0.05$, respectively). In contrast, NM_HF and BM TENS patterns induced no significant change in the map volume ($p = 0.28$ and $p = 0.15$, respectively).

Moreover, in the absence of a significant change in the number of active sites after all intervention patterns, the increase in active sites was more pronounced after PWM pattern stimulation ($p = 0.06$). Furthermore, while there was no significant alteration in the position of the CoG for any of the TENS patterns, all interventions shifted the CoG to the left in the x-coordinate (more lateral). Descriptive statistics of all map features for all TENS patterns are provided in Table 2.

Table 2. Descriptive statistic of map features recorded from right-APB muscle (mean ± SD, $N = 11$)

TENS pattern	NM_HF				NM_LF				PWM				BM			
Map Feature	Pre	Post	P	t/Z	Pre	Post	P	t/Z	Pre	Post	P	t/Z	Pre	Post	P	t/Z
Volume (mV)	8.98 ± 1.64	12.28 ± 5.2	0.28	$Z = 1.06$	7.83 ± 2.57	11.78 ± 5.3	**0.025***	$t_{10} = 2.63$	7.81 ± 1.83	10.02 ± 3.05	**0.025***	$t_{10} = 2.64$	7.74 ± 1.76	9.51 ± 3.7	0.15	$t_{10} = 1.48$
Active sites (n)	15.18 ± 4.23	15.12 ± 1.5	0.61	$t_{10} = 0.52$	12.27 ± 4.45	12.91 ± 4.23	0.56	$t_{10} = 0.59$	11.64 ± 3.2	12.91 ± 3.39	0.06	$t_{10} = 2.09$	12.27 ± 3.28	14.09 ± 3.9	0.25	$t_{10} = 1.21$
CoG_latitude (cm)	3.84 ± 0.68	3.95 ± 0.64	0.30	$t_{10} = 1.08$	3.87 ± 0.48	3.91 ± 0.31	0.71	$t_{10} = 0.38$	3.70 ± 0.71	4.21 ± 0.44	0.13	$t_{10} = 1.38$	3.86 ± 0.64	3.94 ± 0.76	0.34	$t_{10} = 0.99$
CoG_longitude (cm)	3.63 ± 0.96	3.60 ± 0.92	0.78	$t_{10} = 0.27$	3.98 ± 0.79	3.84 ± 0.75	0.24	$t_{10} = 1.24$	3.62 ± 0.98	3.5 ± 0.99	0.28	$Z = 1.06$	4.40 ± 0.58	4.47 ± 0.68	0.41	$t_{10} = 0.85$

Note: t-value and Z-value are reported based on feature's distribution and subsequently performed test (paired sample t-test and Wilcoxon signed-rank, respectively); $^*P < 0.05$.

DISCUSSION

The results of the present work indicate that the effect of the TENS intervention on the CS excitability and cortical map of the target muscle (right APB) depends on the delivered TENS pattern and parameters. We found that PWM TENS enhanced the excitability of the CS tract of the target muscle (right APB) significantly compared with the non-modulated patterns. Moreover, while all selected patterns increased the volume of the motor cortical map of the right APB muscle, the induced changes were only statistically significant following PWM and NM_LF.

Pattern-dependent changes in CS excitability

Similar to previous reports, the results from the present study indicated that conventional TENS patterns, with frequencies of 100 Hz and 40 Hz (NM_HF and NM_LF), induced changes with a facilitation trend in the CS activity (Mang et al., 2010; Jadidi et al., 2020). A particularly novel finding is that the PWM pattern induced a statistically significant enhancement of the CS excitability immediately after the intervention. This difference may be explained by previous evidence that the expanding

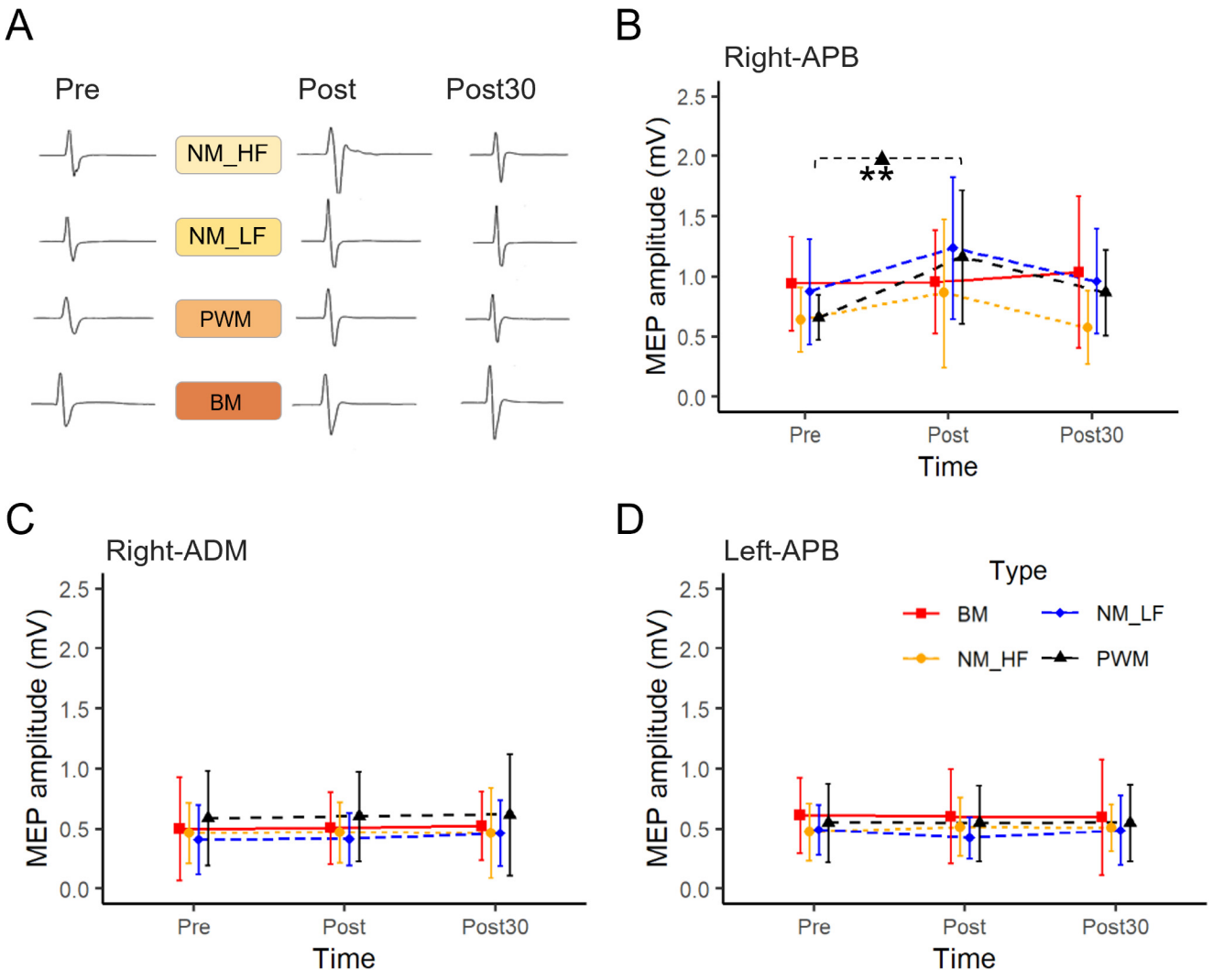

Fig. 3. Averaged peak-to-peak amplitude. **(A)** Mean of 10 MEPs waves recorded from the right APB muscle of one representative subject for each TENS pattern over time phases. **(B)** Averaged MEP amplitude before (Pre), immediately after (Post), and after 30 min (Post30) of intervention from right APB, **(C)** right ADM, and **(D)** left APB. NM_HF, non-modulated high frequency pattern; NM_LF, non-modulated low frequency pattern; PWM, pulse width modulated pattern; BM, burst modulated pattern; **:$p < 0.05$.

electrical field of PWM TENS leads to more dynamic fiber recruitment and sequentially activates different axonal populations. In contrast, the application of the conventional TENS pattern seems to uniformly stimulate a single population of fibers (Grill and Mortimer, 1996; Tan et al., 2016). In addition, while the focus of the present work was on healthy subjects, enhancement of the CS activity may also play a role in chronic pain relief, including PLP. Our results support the clinical studies covering interventions leading to facilitation of the CS activity and chronic pain alleviation such as high-frequency rapid TMS and anodal transcranial direct current stimulation (tDCS) (Roux et al., 2001; André-Obadia et al., 2006; Malavera et al., 2016). In this case, the motor cortex activity enhancement may result in thalamus activity suppression indirectly by inhibitory projections, which leads to modulation of ascending nociceptive signal pathways (Garcia-Larrea and Peyron, 2007; Bolognini et al., 2013). This mechanism may also affect other pain-related brain areas such as the periaqueductal gray matter and the anterior cingulate gyri, relating to affective emotional components of nociception (Lefaucheur et al., 2006; Navarro et al., 2007).

On the other hand, while several studies have addressed improvement in pain reduction with low-frequency and high-intensity TENS (known as BM) (Buchmuller et al., 2012; Schu et al., 2014; Macedo et al., 2015), our results show that the BM TENS intervention elicited no change in the MEP amplitude. This effect might be rooted in the TENS intensity differences. For example, Macedo et al. reported the application of BM TENS with high enough intensity to induce painless but visible muscle contractions (Macedo et al., 2015). In our study, all TENS patterns were delivered below the motor threshold, and therefore it may be insufficient for the BM pattern to induce CS changes. In addition, it has previously been reported that low frequency TENS (the modulated frequency in BM is low = 4 Hz) elicits μ-opioid

receptors in the CS tract given that BM analgesia will not happen immediately but last longer (DeSantana et al., 2008; Macedo et al., 2015). In accordance with this, our data show a slight increase 30 min after ending the BM intervention session, while the MEP amplitude after the rest patterns experienced a reduction at Post30 compared with Post. A long-term evaluation may help to investigate the later and lengthier effect of the BM intervention on the MEP amplitude.

Focality of excitability changes

A previous study regarding the effect of PWM and non-modulated electrical stimulation patterns on chronic back pain patients reported focal perception at the stimulated site, while PWM TENS elicited a more focal sensation than a non-modulated pattern (Tan et al., 2016). In line with this, our results following the TENS interventions (PWM, NM_HF, and NM_LF) reveal that while the MEP amplitude from the median nerve-innervated muscle (right APB) changed, the MEP signals recorded from the right ADM (non-target) and left APB (control) muscles remained unaffected. These findings suggest a focal and specific rather than a global effect of the delivered TENS patterns on the stimulated nerve-innervated muscle (Kaelin-Lang et al., 2002; Tan et al., 2016; Peng et al., 2019). In addition, the ADM muscle is innervated by the deep branch of the ulnar nerve. Despite the size of the stimulation electrode and median-ulnar nerve distance at the wrist, the result confirms that the sensory input just affected the target nerve and muscle.

Facilitation effect on motor cortical maps

Fig. 3 depicts all selected TENS patterns enhanced cortical motor map volume. PWM and NM_LF patterns induced significant modulation, while the two other patterns did not. Therefore, the PWM TENS pattern increased both the CS excitability at the hotspot and the whole representative map of the right APB muscle. This modulation of the corticomotor map has been shown to be beneficial in chronic pain alleviation. Experimental investigations using parallel tDCS and peripheral electrical stimulation (PES) on chronic back pain have revealed that the combined interventions increase the motor map volume and induce greater reductions in pain levels compared with application of single PES or tDCS sessions (Schabrun et al., 2014). In addition, a recent article by Seminowicz et al. divided the participants into two corticomotor facilitation and suppression groups following pain onset (Seminowicz et al., 2019). The preliminary results suggest that a reduction in the corticomotor map in the early stage of pain could be a biomarker for higher susceptibility of pain (Seminowicz et al., 2019). Then, increasing the volume of motor cortical map by therapeutic interventions may lead to chronic pain reduction. In addition, it has been recently shown that sensory electrical stimulation leads to enhancement in amputees' ability to move and perceive their phantom hand and eventually facilitation in prosthesis usability due to improved movement decoding and increased motor-related neural activity (Ding et al., 2020; Osborn et al., 2020). Since we found an increased motor pathway excitability following TENS in the present work, this may also assist in enhancing prosthesis function and control by amputees.

Moreover, clinical and experimental evidence indicate the important role of cortical reorganization in the pathophysiology of chronic pain, especially among patients with PLP (Raffin et al., 2016; Gunduz et al., 2020; Makin and Flor, 2020a). It has also been reported that PLP severity and level of reorganization are correlated (Makin and Flor, 2020b). Makin et al. showed changes in the location of the CoG of the amputated limb in both sensory and motor cortices after amputation of the upper limp (hand amputees) compared with the control group (Makin et al., 2015). The results of the present work also reveal a lateral shift (in the opposite direction of the reorganization caused by amputation to induce re-plasticity) after all TENS interventions. However, the results were not statistically significant. An explanation for such an effect could be that the 30 min of TENS intervention used in the present study might be insufficient to induce significant plasticity (Chipchase et al., 2011a) as the majority of treatment sessions are longer and repeated more than one time (Mulvey et al., 2014; Tilak et al., 2016).

The present work has some limitations that must be taken into consideration. First, the observed alternation in excitability following TENS interventions might also be influenced at spinal level. However, several studies reported no changes induced by PES on H-reflexes, M-waves, and F-waves, and therefore indicated that altered changes by PES origins at the supraspinal level (Ridding et al., 2000; Kaelin-Lang et al., 2002; Tinazzi et al., 2005; Lagerquist et al., 2012). Nevertheless, further studies will be needed to reveal any alternation of spinal mechanisms following the modulated TENS patterns. Secondly, the effect of sensory electrical stimulation on the motor cortical map has only been evaluated on the contralateral hemisphere to the target muscle. The reason lies in the time limitation and subjects' comfort as the number of delivered TMS pulses was high (over the entire experimental session). However, comparative analysis on motor cortical maps of both target and control muscles (right and left APB) might help to emphasize more how focal the effect of TENS patterns is.

To conclude, conventional and non-modulated TENS has been used for a long time as a treatment intervention for patients with chronic pain. Today, the relationship between effectively modulated TENS in pain alleviation and corticospinal excitability changes is not fully understood. In the present study, we aimed to investigate and compare the alternations of the CS tract excitability and cortical motor map following non-modulated and modulated TENS interventions in healthy subjects. The results revealed that PWM TENS delivered to the right median nerve enhanced the CS activity and corticomotor map recorded from the right APB muscle. Meanwhile, PLP alleviation has previously been associated with cortical motor map enhancement and facilitation in the CS tract excitability. Therefore, the PWM pattern may be considered as a beneficial therapy

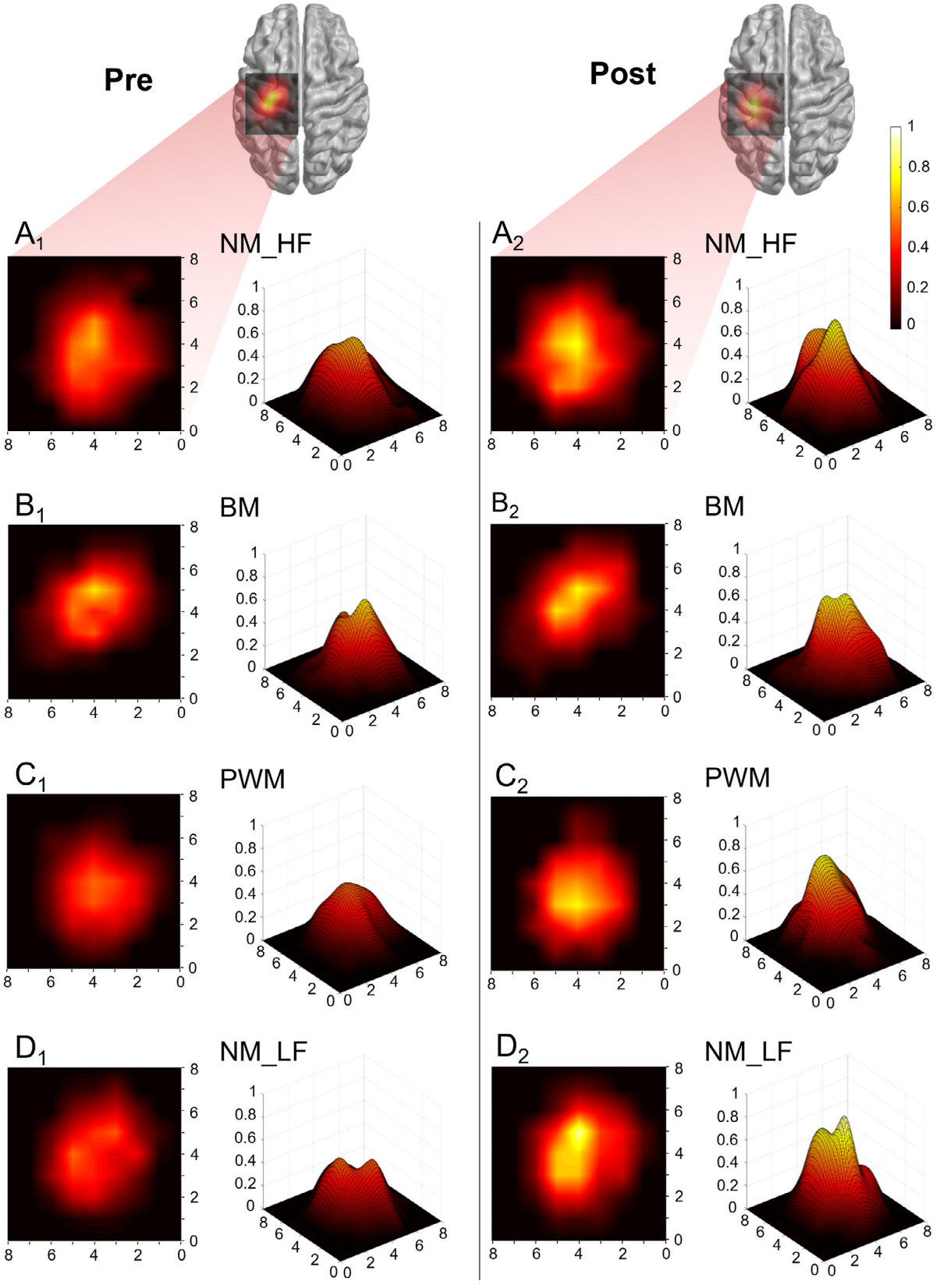

Fig. 4. Averaged cortical motor maps of the right APB muscle across all subjects. For each subject, the Pre and Post maps were normalized to the maximum MEP of Pre map. Map area and map volume representations are shown side by side at Pre (1) and Post (2), respectively. The vertex is located at coordinate (0, 0) and all maps followed the same scale bar from 0 to 1 (as shown in A_2). **(A)** NM_HF, non-modulated high frequency pattern, **(B)** BM, burst modulated pattern, **(C)** PWM, pulse width modulated pattern, and D) NM_LF, non-modulated low frequency pattern.

for PLP alleviation in the future. Further studies are required to validate our results on a population of PLP patients.

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