Alteration in Cortical Activity and Perceived Sensation Following Modulated TENS

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***Abstract*— Over the last decades, conventional transcutaneous electrical nerve stimulation (TENS) has been utilized as an efficient rehabilitation intervention for alleviation of chronic pain, including phantom limb pain (PLP). However, recently the literature has increasingly focused on alternative temporal stimulation patterns such as pulse width modulation (PWM). While the effect of non-modulated high frequency (NMHF) TENS on somatosensory (SI) cortex activity and sensory perception has been studied, the possible alteration following PWM TENS at the SI has not yet been explored. Therefore, we investigated the cortical modulation by PWM TENS for the first time and conducted a comparative analysis with the conventional TENS pattern. We recorded sensory evoked potentials (SEP) from 14 healthy subjects before, immediately, and 60 min after TENS interventions (PWM and NMHF). The results revealed suppression of SEP components, theta, and alpha band power simultaneously associated with the perceived intensity reduction when the single sensory pulses applied ipsilaterally to the TENS side. The reduction of N1 amplitude, theta, and alpha band activity occurred immediately after both patterns remained at least 60 min. However, the P2 wave was suppressed right after PWM TENS, while NMHF could not induce significant reduction immediately after the intervention phase. As such, since PLP relief has been shown to be correlated with inhibition at somatosensory cortex, we, therefore, believe that the result of this study provides further evidence that PWM TENS may also be potential therapeutic intervention for PLP reduction. Future studies on PLP patients with PWM TENS sessions is needed to validate our result.**

***Index Terms*— Modulated TENS pattern, sensory feedback, sensory evoked potentials, pain alleviation.**

I. INTRODUCTION

PERIPHERAL electrical stimulation (PES) is extensively used as a neurorehabilitation modality for patients with musculoskeletal (e.g., stroke [1], [2]) or neurological conditions such as acute [3], [4], [5] or chronic pain [6], [7]). PES parameters (i.e., frequency, pulse width, and intensity) have been investigated to optimize the efficacy of the intervention in pain therapy [3], [7], [8], [9].

Conventional transcutaneous electrical nerve stimulation (TENS) is classified as a sensory stimulation (below pain and motor thresholds) delivered at high frequency (60-120 Hz) to target the large-diameter afferent fibers (Aβ). The underlying mechanism of conventional TENS is based on the gate control theory of pain [10], suggesting that activation of Aβ fiber prevents nociceptive signal transmission (by Aδ and C fibers) by blocking the pain gate at dorsal horn level. Moreover, the effect of conventional TENS has recently been investigated at both the central and peripheral levels of the nervous system. A suppression of cortical activity and perceived intensity at the stimulation area have been reported following TENS intervention in healthy subjects [11]. Recently, Peng et al. have conducted a comparative analysis regarding the effect of conventional and acupuncture TENS on brain responses [3]. The results indicate a greater reduction of N100 and P200 by means of the conventional TENS pattern. Suppression of the power spectrum in different frequency bands, including beta, alpha, and gamma, has also been demonstrated as a result of a TENS intervention in previous studies [11], [12], [13]. Furthermore, the alteration of functional connectivity between pain-related brain areas, including the insular cortex, the primary somatosensory cortex (SI), the anterior cingulate cortex (ACC), and the prefrontal cortex (MPFC) [14], [15] has been presented following TENS [3].

Conventional TENS has gained popularity as a therapeutic intervention for amputees with phantom limb pain (PLP) by delivering sensory electrical stimulation at both amputated and intact hands ([7], [16], [17], [18], [19]. While the neurobiology of PLP is not fully understood, it is widely considered a combination of peripheral contributions [20], facilitation in the activity of the somatosensory cortex, and corticomotor reorganization [21], [22], [23]. Conventional TENS is believed to assist PLP alleviation by suppression of cortical activity and reversing the cortical reorganization [11], [24].

To enhance the rehabilitation efficacy, the literature has recently focused on alternative temporal stimulation patterns rather than conventional TENS [25], [26], [27], [28], [29]. It has been reported that a modulated stimulation pattern (with dynamic characteristics) may minimize the habituation phenomenon that can occur when using stationary stimulation

Manuscript received 3 October 2022; revised 16 December 2022; accepted 2 January 2023. Date of publication 13 January 2023; date of current version 3 February 2023. This work was supported in part by the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie Grant under Agreement 754465; and in part by the Center for Neuroplasticity and Pain (CNAP), Danish National Research Foundation, under Grant DNRF121. *(Corresponding author: Armita Faghani Jadidi.)*

This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by The North Denmark Region Committee on Health Research Ethics under Application No. N-20190016.

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Digital Object Identifier 10.1109/TNSRE.2023.3236038

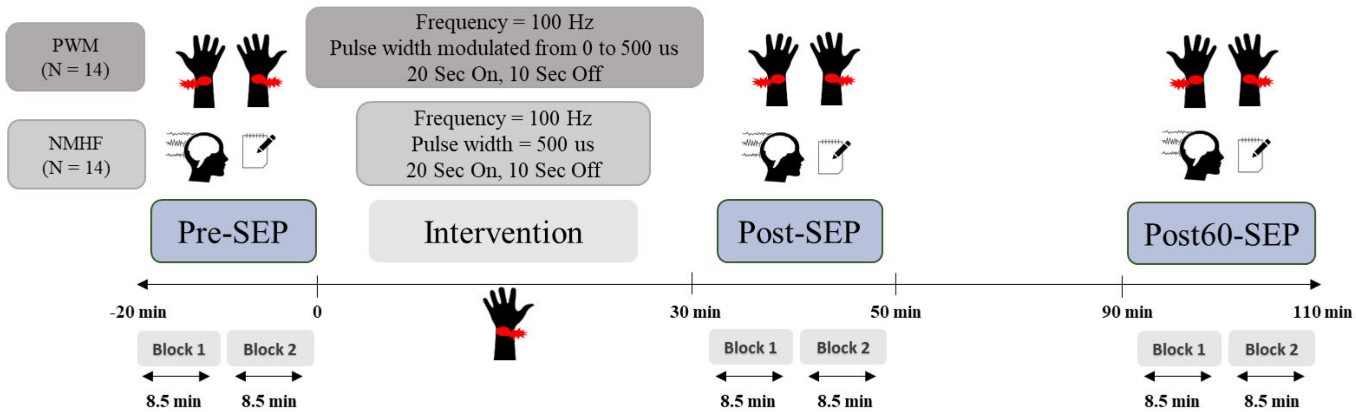

Fig. 1. Overview of the experimental design. The effect of two TENS patterns on cortical activity was investigated immediately and 60 min after the intervention compared with the baseline cortical signals. The sensation profile was also recorded in addition to EEG signal over SEP phases.

patterns [30]. Tan et al. investigated the effect of pulse width modulated (PWM) electrical stimulation on patients with chronic low back pain. The patients reported a more comfortable and natural sensation during PWM stimulation with the same level of pain reduction [27] compared with conventional TENS. Moreover, PWM TENS has been reported to result in facilitation of the corticospinal pathway activity and expansion of the motor cortical map [31], [32], which have both been suggested as possible desired effects to reduce PLP [33], [34], [35].

While there is clinical evidence on pain rehabilitation following PWM electrical stimulation [27], [36], the underlying neurobiological mechanism on the cortical activity has not yet been explored. Therefore, we conducted novel study utilizing somatosensory evoked potentials (SEPs) for assessing the change in cortical response and measured the perceived sensation following PWM TENS. Moreover, comparative analysis was conducted with induced alteration by NMHF TENS. We also explored whether the application of TENS might lead to changes in sensory-induced brain activity by contralateral limb stimulation as delivering TENS at a contralateral intact limb has been reported to be effective for patients suffering from pain [3] including PLP ([16]. In this paper, we studied healthy subjects intending to include a larger and homogeneous subject population. Investigation of novel intervention effects on healthy populations with a further therapeutic purpose for the patient population has been common strategy [11], [28], [37], [38]. However, future studies on PLP patients with PWM TENS sessions are needed to validate our results.

II. Methods

A. Participants

A total of 14 healthy subjects (all right-handed, aged 26.6 ± 2.7 SD, range 19-36, seven men) participated in the study. Subjects with central or peripheral nervous system disease, injuries, or contraindications to the surface electrical stimulation were excluded. All participants were given verbal and written instructions on the experimental procedures approved by The North Denmark Region Committee on Health Research Ethics (N-20190016). The subjects signed a written consent form and received financial compensation for their participation.

B. Experimental Overview

The procedural outline of the experiment is shown in Fig. 1. Each session consisted of three outcome measurement phases, including SEP recording, perceived sensation area, and intensity. Baseline measurements were performed as a pre phase (Pre) followed by 30 min TENS intervention delivered to the right (dominant hand) median nerve. On completion of the TENS intervention, two post outcome measurements were recorded following (Post) and 60 min after (Post60) the application of TENS.

C. TENS Interventions

Each subject completed two experimental sessions each lasting approximately 3.5 hours and at least four days apart. The sessions comprised two different TENS patterns as follows: (1) Conventional non-modulated high frequency (NMHF) with a frequency rate of 100 Hz with a 500 μs pulse width, (2) Pulse width modulated (PWM) with a carrier frequency of 100 Hz and pulse width varying from 0 to 500 μs by sinusoidal modulation (1Hz) [11], [27], [31]. The stimulus intensity was individually adjusted to 80% of the discomfort threshold (painless) with no visual movement. Both electrical stimulation patterns consisted of a series of bipolar rectangular pulses and lasted 30 min with 20s on and 10s off repetitions [31], [39]. The TENS patterns were generated by a custom-made Matlab script and delivered by a DS5 stimulator (Digitimer, UK) using two oval-shape surface electrodes (Axelgaard PALS Electrodes, 4 × 4.6 cm).

D. Data Collection

The cortical responses (continuous EEG) elicited by single sensory electrical pulses on both the dominant and non-dominant hand were recorded at Pre, Post, and Post60 time phases to assess the effect of the TENS intervention. The subjects were instructed to sit in an armchair in a quiet room (temperature ranging 23-26 °C) and instructed to gaze at the fixed cross sign displayed at a screen. A 64-channel EEG (actiCAP, Brain Products GmbH, Germany) was used with electrode location according to the international 10-20 system. The EEG data were continuously amplified and digitized (5 kHz sampling rate) by the BrainAmp MR plus amplifier (Brain Products, GmbH) with a low passband filter of 250 Hz. The FCz electrode was set as a reference.

To elicit SEP signals in both hemispheres, two blocks of 50 single square-wave pulses (pulse width of 500 μs) were delivered by a pair of surface electrodes positioned on the median nerve of both the TENS stimulated (right) and non-stimulated (left) hand [3]. In each block, 50 pulses were distributed alternately between the two hands with a random inter-stimulation interval (7-9 s uniformly distributed), to avoid habituation phenomena. The intensity was individually set at 2.5 times of the perception threshold (with no muscle twitch) determined by a staircase procedure [31], [40], [41].

In addition to cortical responses, perceived sensation information was assessed following single electrical pulses on each hand over the SEP phases. The subjects were instructed to report the perceived sensation by stimuli on both hands based on a numerical rating scale (NRS) (0 = no sensation, 10 = strongest non-painful sensation imaginable). Furthermore, participants drew the area of the elicited sensation on the right hand (TENS stimulated) by means of a custom-made software.

E. EEG Signal Analysis

EEG signals were analyzed with BrainVision Analyzer software (Version 2.2.2 Brain Products, GmbH) and analyzed further by a custom-made Matlab script and EEGLAB (v14.1.2) [42]. Firstly, a low-pass filter (115.2 Hz, 24 dB/oct) was applied to the continuous EEG data of all channels. Then the data was down-sampled to 256 Hz and band-pass filtered at 0.5-45 Hz (8th order Butterworth filter). The independent component analysis (ICA) algorithm was applied to correct the eye blink and muscle movement artifacts. Subsequently, EEG signals with an amplitude exceeding ± 100 μV were indexed for rejection and the remaining signals were rereferenced to a common averaged reference [3], [41], [43]. Epochs were extracted by segmenting the continuous EEG data into 2 s epochs from 500 ms before to 1500 ms after the stimulus onset and assigned to the right and left hand segments. Then, epochs baseline were corrected based on the 500 ms signal preceding the stimulus. Eventually, pre-processed epochs from two blocks for each time phase were merged, and individual SEP signals for each side and time phase were measured by averaging the respective epochs.

N1 and P2 subcomponents were defined as the most negative and positive peaks, respectively, across a time window of 100-250 ms at Cz after stimulus onset [11], [41]. Extracted N1 and P2 wave amplitudes elicited by delivering single pulses to each hand and over three time phases were considered for statistical analysis.

Furthermore, we conducted a time-frequency analysis by EEGLAB (v14.1.2) to assess the event-related spectral perturbation (ERSP). For calculating the ERSP, a wavelet transform with fixed Hanning window (2000ms window and 3-45 frequency range) was applied on epochs within the time window −500 to 1500 ms. The ERSP maps induced by sensory pulses on the right hand (TENS side) were extracted individually before and after the intervention (Pre, Post, and Post60) at the Cz channel for each TENS pattern.

F. Statistical Analysis - Sensation Modulation

To investigate the possible changes in the perceived sensation by the two different TENS patterns, a one-way repeated measure ANOVA or Friedman test was used depending on the normality of the data distribution evaluated by the Shapiro-Wilk test. The 'sensation rate' and 'time' were the main dependent and within-subject factors, respectively. Post hoc multiple comparisons were performed (p values were Bonferroni-corrected) when ANOVA/Friedman test revealed a significant main effect of "time". Furthermore, to compare the effect of the two TENS patterns on the perceived sensation, an independent t-test or Mann-Whitney test was conducted on the difference of the post measures (Post and Post60) and pre phase (Post-Pre and Post60-Pre) with "pattern" (NMHF, PWM) as a between-subject factor.

G. Statistical Analysis – Cortical Alterations

The normality of the SEP components (i.e., N1 and P2 amplitudes) was evaluated using the Shapiro-Wilk test. Due to normal distribution of variables, a three-way repeated measure (RM) ANOVA was used to assess the possible effects. The amplitude of the SEP components was the main dependent variable with three within-subject factors as follows; "time: Pre, Post, and Post60", "pattern: NMHF and PWM", and hand "side: left and right". In a case of a significant three-way interaction, a post hoc analysis was conducted (p values were Bonferroni-corrected and the significance level was remained as $p < 0.05$).

The longitudinal performance of each TENS pattern on SEP components for both hand sides was evaluated using a two-way RM ANOVA was conducted with "time", and hand "side" as the within-subject factors. When a significant interaction was detected, a post hoc analysis (Bonferroni-corrected p-values) was performed.

The significant differences in the time-frequency activity between the two time phases (Pre vs. Post) in all time-frequency regions were assessed by a non-parametric, cluster-based permutation test to correct the multiple comparisons [44]. Moreover, the changes in the dynamic activity of SEP components between Pre and Post time phases were evaluated in all channels and both TENS patterns over the alpha band (8-12 Hz). Channels with significant changes in ERSP activity over aforementioned time phases were detected for each pattern with a false discovery rate (FDR) correction ($p < 0.05$).

III. Results

A. Sensation Modulation

The group averaged intensity and area of perceived sensation before and after TENS interventions on the right hand (TENS stimulated hand) are compared in Fig.2. The results are in line with the statistical result that indicated the dramatic

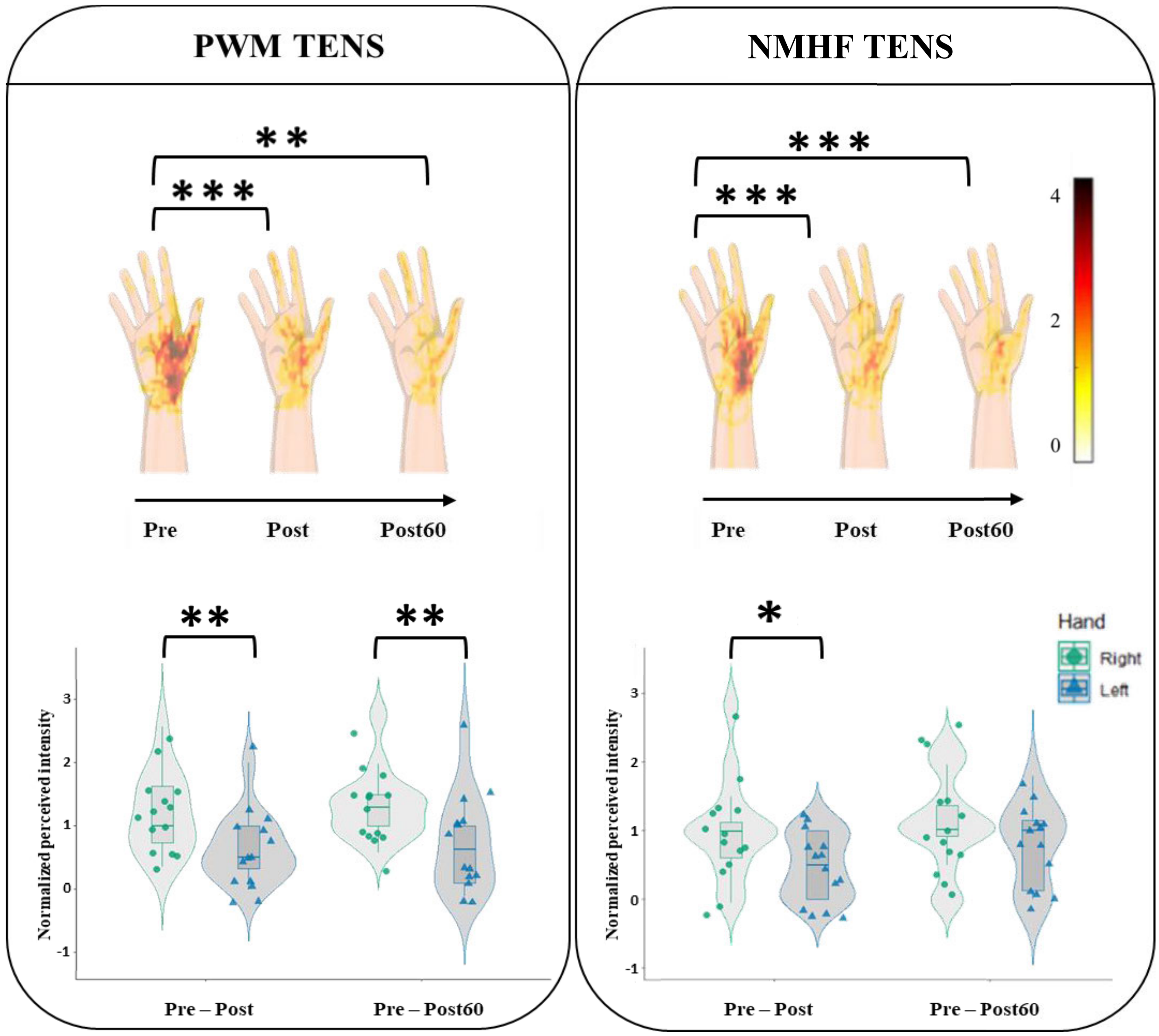

Fig. 2. Perceived sensation profile. Top row: Averaged perceived sensation map of each time phase (Pre, Post, Post60) for PWM (left column) and NMHF TENS (right column) pattern. The colored area represents the location and magnitude of perceived sensation. Bottom row: Violin plot of normalized Post evoked sensation to the baseline (Pre-Post and Pre-Post60) in both hands and TENS patterns. *: P-value < 0.05, **: P-value < 0.01, and ***: P-value < 0.001.

decrease in the perceived sensation over time phases (one-way RM ANOVA, NMHF: F2,26 = 22.21, P < 0.001 and Friedman test, PWM: $\chi^2_2 = 24$, $P < 0.001$). The post hoc analysis showed that the reduction effect occurred immediately after the intervention phase (NMHF: P = 0.001 and PWM: P < 0.001) and lasted at least 60 min after TNES (NMHF: P < 0.001 and PWM: P = 0.002).

In addition, a Wilcoxon or paired t-test (for PWM and NMHF, respectively) was performed on the difference of post perceived sensation data to the baseline (Post-Pre and Post60-Pre). The results (Fig. 2 bottom row) indicated that while sensation intensity was suppressed following both TENS patterns (Post) in both hands, this reduction was significantly greater in the right hand (the same hand stimulated by TENS) compared with the left hand (NMHF; Post-Pre, Z = 2.51, P = 0.012, and PWM; Post-Pre, Z = 2.73, P = 0.006). Interestingly, this greater reduction in right vs. left hand remained at least 60 min after PWM TENS (Post60-Pre, = 2.41, P = 0.01). Moreover, no meaningful differences were found in the changes of perceived sensation intensity between the two different TENS patterns. However, the average level of sensation suppression was higher following PWM compared with NMHF (44.8 % and 29%, respectively).

B. Cortical Alterations

The group averaged SEPs from the Cz channel (N1 and P2 waves) for both intervention patterns and stimulated hands are illustrated in Fig. 3.

N1 amplitude: The result of the three-way RM ANOVA showed a strong effect of the "time" factor (F2,26 =17.23, P < 0.001), indicating significant suppression of the N1 amplitude over time phases and moderate evidence for the effect of the three factors' interaction "time*side*pattern" (F2,26 = 3.98, P = 0.03). A post hoc analysis was performed to interpret the three-way interaction using a two- way RM ANOVA for each TENS pattern with "time" and hand "side" as within-subject

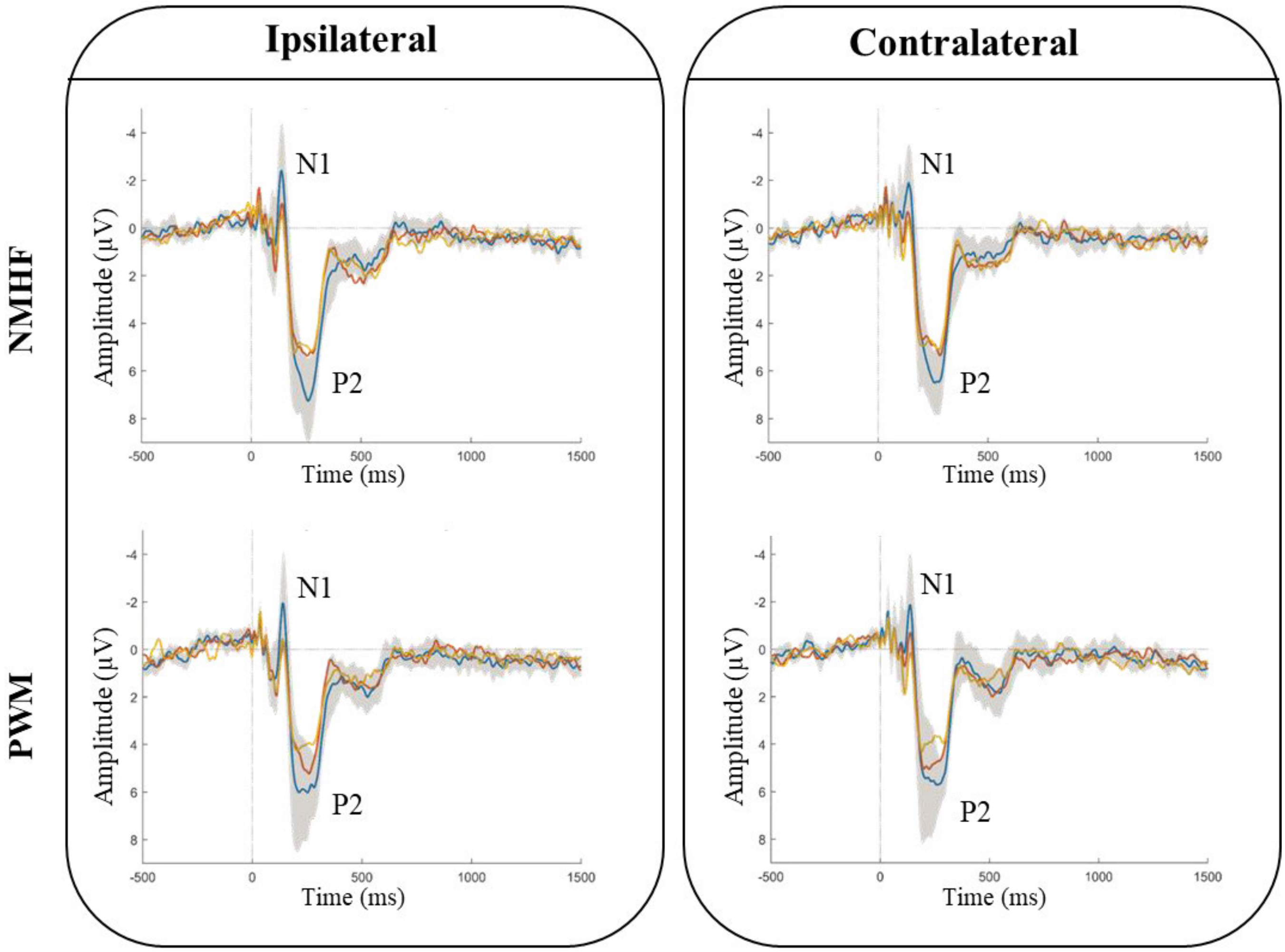

Fig. 3. Group average SEPs elicited by single electrical pulses delivered to the hands ipsilateral (right column) and contralateral (left column) to the TENS side, over three time phases as follows. Pre (blue), Post (red), and Post60 (yellow). Grey shades showing 95% of the confidence interval for the Pre SEP phase.

factors. The result for both patterns revealed a significant effect of ”time” (NMHF: $F_{2,26} = 13.29$, $P < 0.001$ and PWM: $F_{2,26} = 8$, $P = 0.002$) and ”time*side” interaction (NMHF: $F_{2,26} = 3.43$, $P = 0.47$ and PWM: $F_{2,26} = 3.98$, $P = 0.03$). Further, the post hoc analysis (Bonferroni correction) revealed a significant suppression of the N1 wave amplitude immediately after both TENS patterns when SEP induced by the right-hand stimulation (ipsilateral to the TENS side) was assessed (NMHF: $P < 0.001$ and PWM: $P = 0.005$). The reduction lasted at least 60 min after the intervention phases (NMHF: $P = 0.009$ and PWM: $P = 0.001$). However, for the left hand (contralateral to TENS) there was only a significant depression of the N1 amplitude at Post60 compared with baseline following NMHF intervention ($P = 0.01$).

P2 amplitude: A significant main effect of the ”time” factor ($F_{2,26} = 7.52$, $P = 0.003$) on the P2 wave amplitude was found in the result of the three-way RM ANOVA, representing the suppression of P2 following NMHF and PWM TENS patterns compared with the baseline amplitude. However, there was no significant effect of the pattern factor ($F_{1,13}=0.53$, $P = 0.47$) and three-way interaction (”time* side*pattern”, $F_{2,26} = 1.44$, $P = 0.25$).

The two-way RM ANOVA conducted to assess longitudinal performance of each TENS showed a significant effect of the ”time” factor (NMHF: $F_{2,26} = 5.47$, $P = 0.01$ and PWM: $F_{2,26} = 3.79$, $P = 0.036$) and ”time *side” interaction (NMHF: $F_{2,26} = 3.83$, $P = 0.035$ and PWM: $F_{2,26} = 3.59$, $P = 0.042$). Subsequently, the post hoc tests (Bonferroni correction) indicated a significant suppression of the P2 amplitude immediately (Post) after PWM patterns on the right hand as the TENS-affected side ($P = 0.003$), and this effect lasted at least 60 min (Post60, $P = 0.02$). In contrast, following the NMHF intervention a significant decrease of the P2 amplitude only occurred 60 minutes after the intervention phase ($P = 0.006$). In addition, while the P2 waves elicited by the stimulus in the contralateral hand to the TENS side showed a reduction trend following both patterns, the suppression was not statistically significant. The alteration in the magnitude of N1 and P2 peaks over time phases is presented in Fig.4.

To this point, the results revealed that both NMHF and PWM TENS reduced the perceived sensation following sensory electrical stimulation. However, the suppression effect following PWM TENS was maximal when the sensory stimulations were delivered ipsilaterally to the TENS side

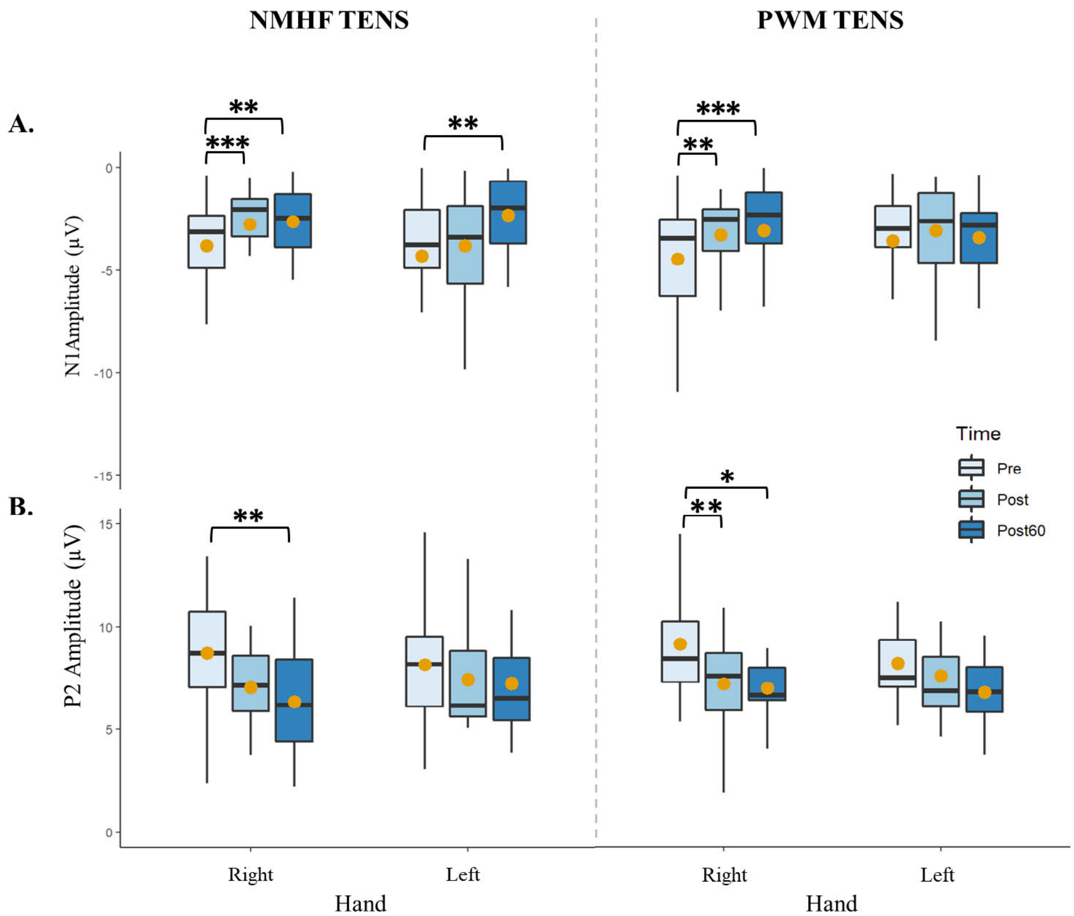

Fig. 4. Effect of NMHF (left column) and PWM (right column) TENS patterns on the amplitude of SEP components over three time phases (Pre, Post, and Post60). (A) N1 wave amplitude. (B) P2 wave amplitude. *: P-value < 0.05, **: P-value < 0.01, ***: P-value < 0.001.

(i.e., right hand) and lasted at least up to 60 min. In contrast, NMHF TENS induced a greater suppression effect in the TENS side (right hand) immediately after the intervention only. The reported perceived intensity at Post60 was notably reduced regardless of the hand receiving sensory pulses.

Furthermore, an analysis of the sensory-evoked brain activity following both patterns led to physiological support of changes in the sensory responses. Right after PWM and NMHF TENS (Post), the amplitude of the SEP components (N1 and P2) decreased maximally when the sensory pulses were delivered homotopically to the TENS side (right hand). This effect remained at least 60 mins after the PWM TENS intervention.

Dynamic activity: In Fig. 5, the group-level time-frequency maps induced by single pulses are presented for both TENS patterns and two time phases (Post and Pre) at the Cz electrode.

In addition, statistically significant differences in ERSP activity following the comparative analysis between the aforementioned time phases are depicted for both patterns. The time-frequency analysis showed a significant reduction in ERSP activity after both TENS interventions in a 100 – 220 ms time window at theta (4 – 8 Hz) and low beta (13-17 Hz), and in the range of 0 - 280 ms for alpha band (8-12 Hz). Further comparison of the ERSP map at Post60 with Pre phase revealed that the inhibition remained at least 60 min after both intervention patterns, while the significant time-frequency regions expanded (∼ 0 - 350 ms) in the lower frequency band (theta). Moreover, the ERSP activity for the N1 and P2 components in the alpha band was calculated across all 64 electrodes. Channels with statistically significant differences between time phases are highlighted in Fig. 5. The results illustrate that following both TENS interventions, the alpha band power within the N1 wave (120 - 150 ms) was significantly suppressed at the Cz and central/frontal channels. However, more frontal channels experienced a significant reduction of the alpha band power within the P2 component (180 - 220 ms) following PWM TENS compared with NMHF TENS.

IV. Discussion

In the current work, we investigated the possible alterations in sensory profile and cortical response following modulated and non-modulated TENS interventions.

A. Sensation Modulation

Previous studies (on both animal and human populations) have demonstrated the analgesic and sensory suppression effects by conventional TENS with high frequency and an intensity below the motor threshold [3], [11], [45], [46].

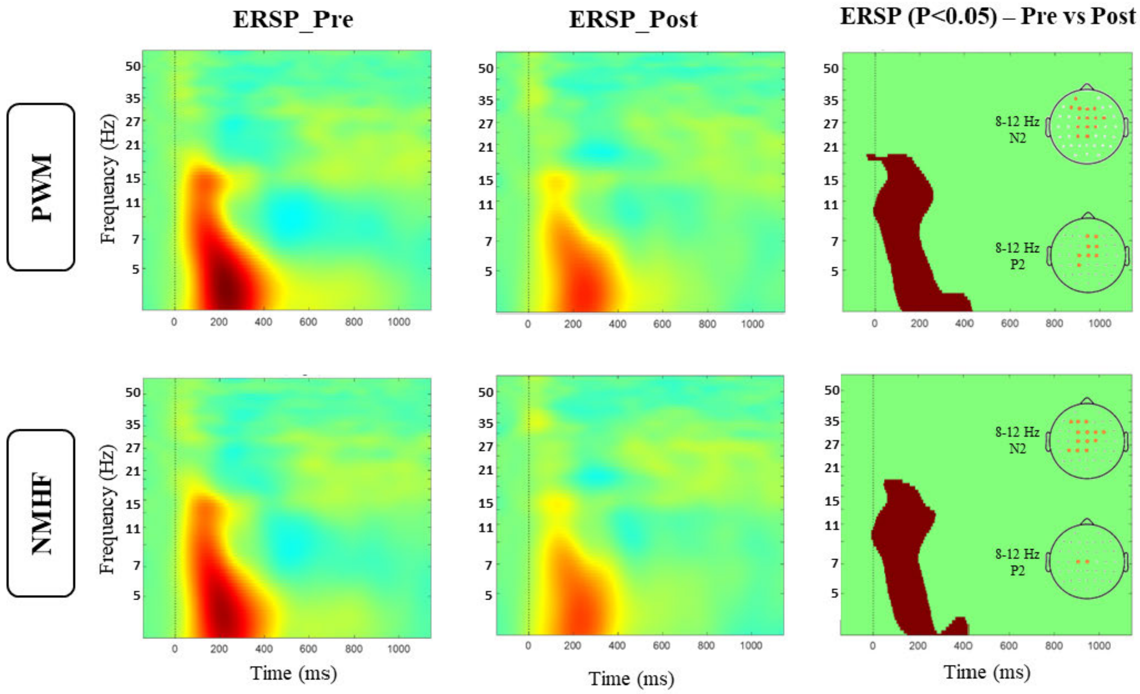

Fig. 5. Group-level time-frequency responses. ERSP maps of cortical dynamic activity following single stimulation on the right hand (ipsilateral to TENS side) before and following TENS interventions. The right column represents significant time-frequency activity in Pre vs. Post time condition (channel Cz). Orange dots in the scalp map display the statistically significant channels in alpha-band activity for the N1 wave ($p < 0.05$).

Similarly, our results indicate a sensation reduction following both NMHF and PWM patterns up to at least 60 mins. Recent research has shown that non-modulated electrical stimulation with constant pulse width uniformly elicits a single axonal population [27]. Instead, PWM electrical stimulation leads to a more dynamic fiber recruitment by sequential activation of distinct axonal populations (A β fibers with different diameters), which can replicate a more natural sensation [27], [47], [48]. This might be the explanation for the minor difference in suppression effect in our study following PWM TENS.

In addition, the present findings from the perceived sensation by sensory stimulation of the right hand are supported by the gate control theory [10]. However, the reduction trend following both patterns (specifically NMHF at Post60) on the left hand (contralaterally to the TENS side) was in line with studies suggesting the concomitant effect of the supraspinal (cortical) inhibition mechanism [3], [11].

B. Cortical Alterations

In terms of cortical modulation, we also observed a clear suppression in SEP components and time-frequency activity after both non-modulated and modulated TENS patterns. These observations are consistent with previous research demonstrating that conventional TENS (non-modulated) reduced the sensory-related potential amplitude and oscillations in healthy subjects [11].

Importantly, no statistically significant difference was detected between the induced alterations by the two patterns on the sensory-evoked components. The amplitude of the N1 wave elicited by sensory pulses on the right hand decreased equally following both patterns, and at Post60 the suppression remained similar in NMHF and was slightly increased by PWM TENS. A significant suppression effect also appeared 60 min after the NMHF intervention when sensory pulses were delivered contralaterally to the TENS side (left hand). These findings are in line with the sensation recording of the left hand in this study and provided further evidence for the contribution of cortical mechanisms [3], [11]. It may also explain the pain alleviation following the TENS interventions delivered contralaterally to the affected limb in the clinical studies ([3], [16]. Furthermore, a reduction in the P2 amplitude following the TENS interventions only presented when the sensory pulses were delivered to the TENS hand and not contralaterally. Interestingly, this alteration occurred after PWM TENS at both Post and Post60, while NMHF TENS could only induce a significant reduction in the P2 wave after 60 min (Post60).

On the other hand, several fMRI and EEG studies have indicated a reorganization and facilitation of the SI activity (N1 and P2) in patients with acute and chronic pain [21], [49], [50], [51], [52], [53]. N1 has been reported to be responsible for the early processing stage of sensory stimulus and greater N1 magnitude correlated with pain memory. In contrast, the P2 wave is believed to represent the translation of the perceived stimulus, and the larger amplitude of the P2 wave compared with early components indicates conscious detection in the sensory process of the nociceptive stimulus [49]. Meanwhile, recent work from Peng et al. demonstrated suppression of nociceptive-elicited cortical activity by conventional TENS (non-modulated) associated with analgesic effect and clear local pain alleviation [3].

Regarding dynamic activity, chronic pain has also been claimed to be associated with an enhancement in the frequency spectrum, including theta, alpha, low, and high beta bands [14],

[54], [55], [56], [57], [58], [59], [60]. In line with this, our results indicate a significant suppression in the spectral power of the aforementioned frequency bands following both PWM and NMHF TENS which could be considered as another possible signature of the TENS mechanism on pain alleviation [11], [12]. In addition, human and animal studies have demonstrated the increase in dynamic activity in the frequency bands from theta to beta in central (somatosensory cortex) and frontal brain regions [14], [61], [62]. Our results also show a higher density of central/frontal channels in a significant reduction of alpha band activity within the N1 and P2 waves.

Several clinical studies have confirmed the effectiveness of a conventional TENS intervention in chronic pain alleviation (e.g., patients with PLP [7], [17], [63]). The gate theory at the spinal level, inhibition at S1 cortex, and reverse cortical plasticity by compensating the lack of efferent input might be considered as the possible underlying mechanisms of TENS on PLP reduction [3], [10], [24], [64]. Since both selected TENS patterns in this study produced suppression at both cortical (SEP components and spectral power) and peripheral levels (sensation profile), our results show that PWM TENS with the effect on perceived sensation and simultaneous cortical inhibition (specifically the P2 wave) might also be considered as effective alternative therapies for PLP patients. PWM TENS has also been demonstrated to cause greater facilitation in the corticomotor map compared with conventional TENS, which has been suggested as a cortical biomarker associated with PLP alleviation [31].

V. Conclusion

Recently, modulated TENS has been gaining much attention to enhance the effectiveness of the intervention in pain therapy. We aimed to understand the induced alterations at the cortical activity and sensory perception by PWM TENS for the first time. We also conducted further comparative analysis with elicited changes by non-modulated patterns to support the application of PWM pattern as therapeutic intervention for PLP alleviation. Our findings revealed that PWM TENS could lead to a similar suppression effect compared with NMHF TENS on the N1 component of the SEP signal and dynamic oscillation (theta, alpha, and low beta) up to 60 mins after the intervention phase. Interestingly, the reduction of the P2 wave occurred right after PWM TENS (and not immediately following the NMHF pattern). The effect of the PWM TENS pattern on the cortical activity elicited by stimulation of the TENS affected hand was also associated with remarkable perceived sensation reduction. As such, this work opens a neuropsychological window to the underlying mechanism and provides further evidence for the potentials of PWM TENS in PLP treatment. However, future studies including PLP patients are needed to examine and validate our results.

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