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Short-term Suppression of Somatosensory Evoked Potentials and Perceived Sensations in Healthy Subjects Following TENS

Ali Asghar Zarei, Armita Faghani Jadidi, Romulus Lontis, Winnie Jensen

***Abstract*—Transcutaneous electrical nerve stimulation (TENS) has been reported to alleviate pain in chronic pain patients. Currently, there is limited knowledge how TENS affects can cause cortical neuromodulation and lead to modulation of non-painful and painful sensations. Our aim was therefore to investigate the effect of conventional, high-frequency TENS on cortical activation and perceived sensations in healthy subjects. We recorded somatosensory evoked potentials (SEPs) and perceived sensations following high-frequency TENS (100 Hz) in 40 healthy subjects (sham and intervention group). The effect of TENS was examined up to an hour after the intervention phase, and results revealed significant cortical inhibition. We found that the magnitude of N100, P200 waves, and theta and alpha band power was significantly suppressed following the TENS intervention. These changes were associated with a simultaneous reduction in the perceived intensity and the size of the area where the sensation was felt. Although phantom limb pain relief previously has been associated with an inhibition of cortical activity, the efficacy of the present TENS intervention to induce such cortical inhibition and cause pain relief should be verified in a future clinical trial.**

***Index Terms*— TENS, Sensory feedback, Sensory evoked potentials.**

I. Introduction

Transcutaneous electrical nerve stimulation (TENS) is a popular, non-invasive, and inexpensive technique for acute or chronic pain relief and stroke rehabilitation [1]–[5]. In conventional TENS, low-intensity, high-frequency electrical stimulation is applied at peripheral sensory nerves with the aim to activate large-diameter peripheral afferents to elicit segmental analgesia [6]. Conventional TENS was inspired by the gate-control theory of pain proposed by Melzack and Wall [7]. The gate-control theory suggested that activation of large diameter (Aβ) sensory afferents closes a *pain gate* in the spinal cord that inhibits the transmission of nociceptive afferent signals (Aδ and C fibers) to the brain [8], and the theory predicted local pain relief in the area of stimulation [9]. Pain regulation is now accepted as a more complex process, with the involvement of the thalamus, insular cortex, primary somatosensory cortex (SI), secondary somatosensory cortex(SII), the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) [10]–[12].

It has been reported that reorganization and facilitation in the somatosensory cortex activity occurs in neuropathic pain or phantom limb pain (PLP) patients [13][14]–[16]. However, studies have been suggested different approaches such as mirror training or neurofeedback (i.e., the imagination of movement) resulted in suppression of cortical activity and neuropathic pain reduction [17], [18]. Modulation of cortical activity through the application of various sensory feedback therapies, such as TENS, to the stump or amputation zone, has shown to be correlated with onset and relief of PLP [17]–[19].

Although the excitability of SI and other brain areas such as M1 is co-modulated following TENS, the frequency and stimulus intensity play an important role [20]. Chipchase et al. reported that electrical stimulation at the periphery with an intensity below the motor threshold decreased the corticomotor excitability, while the corticomotor excitability increased if the electrical stimulation was applied at a level that could produce muscle contraction [21].

The understanding on how TENS can revert the cortical neuromodulation and lead to the reduction of non-painful and painful sensations is still not well known. In addition, specific stimulation parameters of the TENS may lead to either cortical inhibition or cortical excitability. To overcome some of these current limitations, our objective was to evaluate possibly altered cortical and perceptual responses after a conventional, high-frequency TENS intervention in healthy subjects. We used somatosensory evoked potentials (SEPs) for tracking the effect of the TENS on the cortical responses, which is a well-known technique for examining the functionality of neural pathways, see e.g. [22]–[24].

In the present work, we tested our objective in healthy subjects to allow the inclusion of a sufficiently large and homogeneous subject population. Studies to investigate the effect of novel interventions to modulate neuroplasticity with the later aim to use these for therapeutic purposes in particular patient populations are common [25]–[27]. Our findings, however, ultimately needs to be validated in a clinical setting with phantom limb pain patients.

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II. Methods

The procedural overview of the experiment is summarized in Fig. 1. Each experimental session consisted of four SEP phases to evaluate the effect of the TENS intervention phase; a Pre phase considered the baseline and then three post-intervention phases immediately after (Post0), 30 min after (Post30) and 60 min after (Post60). In each of the four SEP phases we applied two blocks of forty double-pulse stimuli. Between the two blocks, we recorded the reaction time, perceived sensation intensity, and location of the perceived sensation.

A. Participants

Forty healthy, right-handed subjects (20 men and 20 women, aged 26.9 ± 4.3 [mean ± std]) were included. Subjects were randomly assigned to either TENS group (n=20) or a sham group (n=20). All subjects in the sham group and 15 out of 20 subjects in the TENS group had no prior experience with electrical stimulation. All subjects signed an informed consent form and received financial compensation for their participation. All procedures were approved by The North Denmark Region Committee on Health Research Ethics (N-20180049).

B. Data Collection

During all sessions, the subjects were seated in a comfortable chair (room temperature 24 - 26 ^{o}C). They were instructed to focus their gaze fixed on a cross displayed at the center of a computer screen placed in front of them. Continuous 64-channel EEG data were recorded. The electrodes were placed according to the international 10–20 system and amplified using a BrainAmp MR plus amplifier (Brain Products, GmbH). The common ground electrode was located along the sagittal midline between the Fz and Fpz electrodes, and the reference was set as the FCz electrode. The EEG signals were digitized using a sampling rate of 5 kHz The EEG signals were digitized using a sampling rate of 5 kHz, and a built-in hardware low-pass filter with a cutoff frequency of 250 Hz. Also, the electrode impedances were kept below 20 kΩ, as assessed by the Brainvision Recorder (Brain Products, GmbH).

Electrical stimulation of all SEP phases consisted of two succeeding constant-current square-wave pulses (referred to as “double pulses”) with a pulse width of 500 µs and 10 ms inter-pulse interval [28]. To avoid habituation, the inter-stimulation interval between the applied stimuli was randomly varied between 6 to 8 s (uniformly distributed) [29]. Although Cuypers et al. reported no difference in the effect of TENS on sensation between the dominant and non-dominant hand [30], we only recruited right-handed subjects in the present work to avoid adding a confounding factor in our results. The electrical pulses were delivered using a DS5 constant-current stimulator (Digitimer, UK) to the left-median nerve of the non-dominant hand. The surface electrodes were placed close to the wrist with two surface electrodes (Axelgaard PALS Electrodes, skin contact size 4 × 4.6 cm, oval).

The intensity was individually adjusted to twice the detection threshold of a double electrical pulse (without muscle twitch) determined as follows. By using a staircase procedure, stimuli were first delivered at an intensity of 0.5 mA and increased in 0.5 mA steps until the subject perceived the stimulus [31]. The participant was instructed to push a button as soon as the stimulus was perceived. Then, the current intensity was decreased in steps of 0.3 mA until the subject did no longer perceive the stimulus. Next, the current intensity was raised again in steps of 0.1 mA until the stimulus was re-detected. This staircase procedure was applied three times, and the average intensity of the last stimulus intensities was defined as the detection threshold. The same individual stimulus intensity was used through all SEP phases.

To assess the perceived intensity following stimulation in the four SEP phases, participants were asked to rate the perceived intensity of the stimuli using the numerical rating scale (NRS) ranging from 0 (no touch) to 10 (maximum non-painful sensation). Additionally, information on the areas of elicited sensation were collected by custom-made software. Behavioral responses to double-pulse electrical stimulation were obtained by recording the reaction time (RT) [32]. When the stimulation was applied, the subjects were instructed to react to each stimulus as fast as possible by releasing a button, held in the right-hand (opposite to the arm being stimulated).

C. TENS Intervention

Several studies have shown that high-frequency TENS (100 Hz with a strong sensation intensity but below the motor threshold) is an effective stimulation pattern in the management of acute pain, chronic pain, and stroke rehabilitation [1]–[5]. The intervention consisted of two blocks of 40 trials of high-frequency electrical pulses delivered at 100 Hz with a pulse width of 1 ms. Each trial included a 20 s on-time stimulation and a 10 s off-time interval between stimulation trains, applied for 20 min. The electrical pulses were delivered through the same electrodes as used in the SEP procedure.

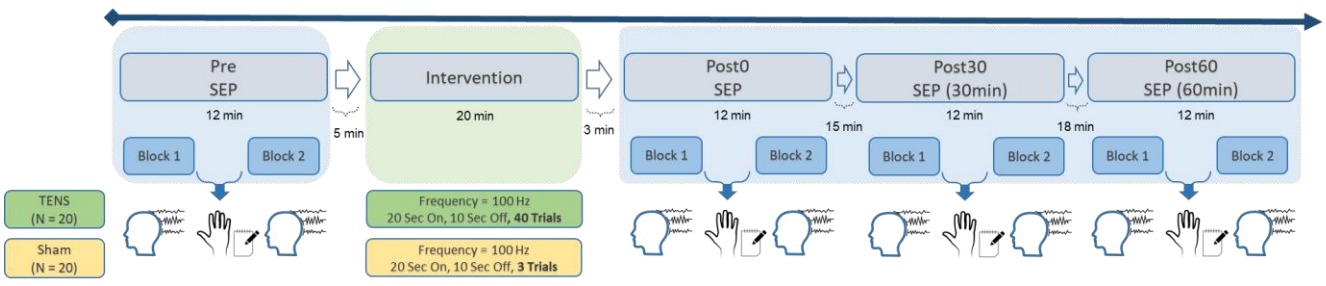

Figure 1. Overview of the experimental procedures. The effect of the TENS was assessed at three different time points (right after stimulation, 30 min and 60 min after) and compared with the measurements obtained before (i.e. baseline). The EEG signals and the associated sensation profile were recorded during the sensory evoked potential (SEP) phases.

The stimulation intensity for the intervention group was adjusted to 80% of the discomfort level (i.e., without causing motor response and pain and using a 1 s stimulation pulse width) while the intensity of the sensation threshold was selected for the sham-controlled group. The duration of the intervention sessions was the same for the two groups; however, the number of trials in the sham group was three (i.e., stimulation onset lasted for 1 min), and no high-frequency electrical stimulation was delivered to the subjects for the next 19 min. The participants received the following instructions; "For the next 20 min, the electrical stimulation will be delivered to your median nerve. The perceived sensation corresponds to no/weak sensations to intense sensations".

D. Data Analysis

SEP responses were analyzed using EEGLAB (v14.1.2) [33] and custom-made programs in Matlab. EEG data were downsampled to 2.5 kHz, band-pass filtered (0.3 Hz and 45 Hz, a 8th order zero-phase Butterworth filter, using 'filtfilt' Matlab function), and filtered with a notch filter (50 Hz, 4th order Butterworth notch filter) for line noise removal. Channels contaminated by artifacts which mostly located at the temporal lobes (e.g., TP7, and TP8) with low SNR were rejected and no interpolation was done on those channels. Eyeblink and muscle artifact components were detected and extracted using an independent component analysis (ICA) algorithm (FastICA) [33], [34]. The ADJUST algorithm [35] was then used to identify and eliminate contaminated ICs based on the unsupervised method and then verified manually. Next, the reconstructed EEG data were re-referenced to the averaged reference. EEG data were then segmented into 2000 ms epochs (from -500 ms to 1500 ms relative to the stimulus onset). Baseline correction was performed using a 500 ms time window before the stimulus onset to remove the pre-stimulus interval offset. Furthermore, epochs exceeding an amplitude threshold of ±100 μv were excluded as these were assumed to be contaminated by artifacts. Finally, individual SEPs were extracted by averaging the epochs from the combination of two blocks for each time phase.

To determine the latency window for each SEP component, the grand-average global field power (GFP) was calculated by averaging the standard deviation of epochs (mentioned above) across all scalp channels, all phases, and all participants.

Time-frequency analysis was conducted to examine the event-related spectral perturbations (ERSP) as indexes for changes in power. For computing the ERSP, the amplitude of a frequency component for the time windows -500 to 1500 ms were extracted by a three-cycle Morlet-based wavelet transformer (Hanning-tapered window, frequency range from 3 to 45 Hz, and window length of 2500ms). The time-frequency map of ERSPs were computed for each subject in four phases. A two-way ANOVA based on permutation test was applied and regions with significant ERSP for the Cz channel between two conditions were calculated (p<0.05). To correct the multiple comparisons across all time-frequency windows, false discovery rate (FDR) correction was applied [16], [36]. In addition, the comparisons between the scalp map of pre and Post0 phases in TENS and sham groups over the alpha band (8-12 Hz) and the group average SEPs for each SEP component were conducted and statistically significant channels with $p < 0.05$ (FDR corrected) were extracted.

A two-way repeated-measures ANOVA was used to assess differences in the reaction time, N100, P200, and N400 amplitudes and latencies (main dependent variables) with a between-subject factor (TENS and sham as group) and one within-subject factor (SEP phases: Pre, Post0, Post30, and Post60 as the effect of time). However, the magnitude of SEP components in TENS and sham group were different in baseline (pre phase). The normality of all the data was examined, and outlier analysis was performed by box-plot analysis. The assumption of sphericity was tested using Mauchly's test and F-values were corrected using Greenhouse-Geisser where necessary. In case of significance, a post hoc analysis was performed by Bonferroni test. The level of significance was $p < 0.05$. While visual inspection of the Q-Q plot and the histogram for perceived sensation revealed that the data were not normally distributed, statistical evaluations were performed using nonparametric tests. Friedman tests were applied to compare the perceived sensations in different time phases (Within-subject factor). Also, Mann–Whitney tests were used to test the significance of the difference (% change in sensation compared to the Pre phase) between TENS and Sham groups (between-subject factor). Bonferroni correction was applied for multiple comparisons and significant level was set to 0.012. Log-transformation was used to normalize the distribution of reaction times.

III. RESULTS

A. Behavioral Responses

The reaction times show distribution peaks for both TENS and sham groups with a conduction velocity that correspond to activation of Aδ fibers and shows that the variation of stimulus intensity had the expected effect (i.e. touch perception intensity) on both group (Fig. 2).

Due to technical issues, the reaction times were not recorded on five subjects (one in the TENS and four in the sham group). Results of the RM-ANOVA on the log-transformed (to correct

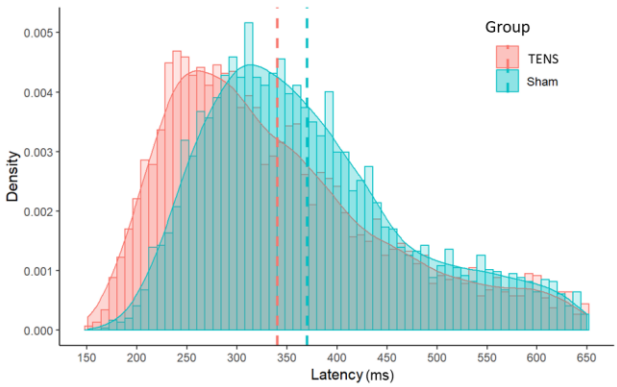

Figure 2. Histogram and density plot of reaction times for intervention and sham group across all time conditions. Blue and red lines are indicated the mean value of RTs in each group.

the left-skewed distribution) reaction times of all 35 subjects show no significant main effect between the different time phases ($F_{(3,140)} = 0.095$, $p = 0.96$, $\eta 2 = 0.002$), no effect of group (intervention vs. sham)($F_{(1,140)} = 2.58$, $p = 0.11$, $\eta 2 = 0.021$) or time × group interaction ($F_{(3,140)} = 0.14$, $p = 0.94$, $\eta 2 = 0.004$).

B. Perceived sensation

The sensation threshold for subjects was recorded as 2.30 ± 0.52 mA and 2.32 ± 0.59 mA for TENS and Sham group, respectively. Normalized, individual rating of the evoked sensation for three conditions and two groups are presented in Fig. 3. In addition, the error bar (mean ± std) were calculated and shown in the same figure. All reported sensations in each TENS and sham group were individually normalized to the baseline (pre) phase.

Perceived sensation tended to decrease during the time in the TENS and Sham group. Friedman tests showed a statistically significant difference in perceived sensation for time phases in the TENS ($\chi^2(3) = 54.20$, $p < 0.001$) and the Sham group ($\chi^2(3) = 36.95$, $p < 0.001$). Mann-Whitney tests were also performed to compare the changes in perceived sensation (Post0-Pre, Post30-Pre, and Post60-Pre) between the TENS and the Sham group. Results showed the perceived sensations were significantly lower in the TENS group for Post0 ($p = 0.005$), Post30 ($p = 0.002$), and Post 60 ($p = 0.002$) compared with the sham group.

Location and quality of perceived sensation following a block of SEP recording were analyzed for each subject, and group average of the maps of hand sensation was illustrated in Fig. 4. for each SEP phase and groups.

The map is showing that the electrical current was delivered to the median nerve and not involved the ulnar nerve as we expected. Results show that although the area and quality are the same for the pre phases in both TENS and sham groups, the quality of evoked sensations is significantly dropped following the intervention phase in TENS group. At the same time, no meaningful change in quality and location of perceived sensations were found in the sham group following the intervention.

C. Cortical Response

Grand-average global field power was calculated across all electrodes, SEP phases, groups, and subjects. Three SEP components N100, P200, and N400 were determined. We selected the N100 as the most negative peak within the 80–140 ms time interval, P200 as the most positive peak within the 180–240 ms time interval, and N400 as the most negative peak within the 350–450 ms time interval. Group average SEPs and scalp topographic map for intervention and sham groups are illustrated in Fig. 5. Results of two-way ANOVA and post hoc analysis are summarized in Table 1. The two-way ANOVA on SEP components peak latencies examined, and no significant effect of time and group was observed.

1) N100 Magnitude.

The results of the RM-ANOVA revealed a significant main effect between the different time phases ($F_{(3, 114)} = 16.67$, $p < 0.001$, $\eta 2 = 0.305$), but no significant main effect of group (TENS vs sham) ($F_{(1, 38)} = 2.50$, $p = 0.12$, $\eta 2 = 0.062$), and significant effect of time × group interaction ($F_{(3, 114)} = 3.54$, $p = 0.036$, $\eta 2 = 0.085$). Post hoc pairwise comparisons showed a significant difference in the TENS group for all time conditions after intervention compares to the baseline ($p < 001$ *for all time conditions*). In contrast, no significant effect of the intervention was found for different time conditions in the Sham group ($p = 0.42$, $p = 0.51$, and $p = 0.47$ for Post0, Post30, and Post60 compare to the baseline respectively).

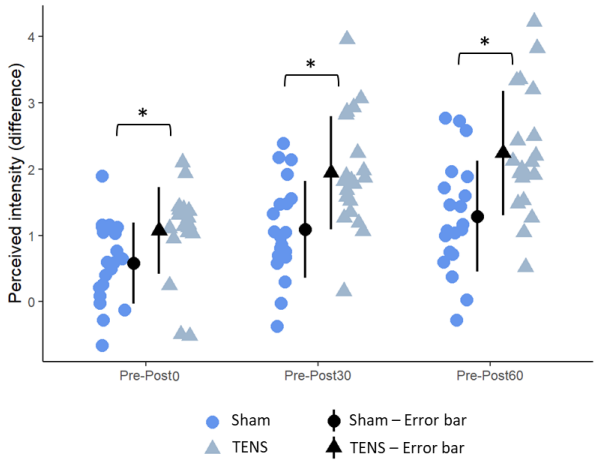

Figure 3. Difference of individual perceived sensation. Reported sensation by NRS were normalized to the baseline (pre) phase for each TENS and sham group. Mean ± standard deviation is depicted by black filled circle and back filled triangle for TENS and sham group, respectively. * p<0.05

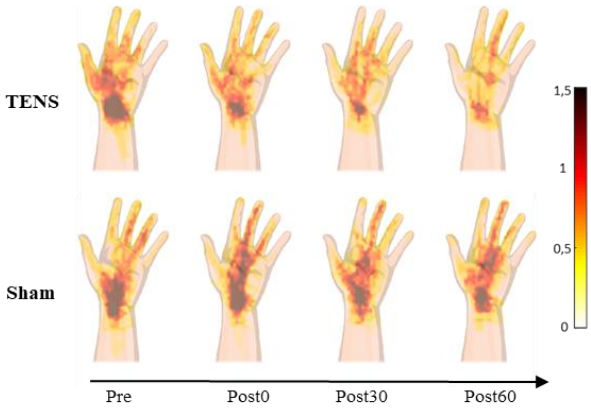

Figure 4. Map of the perceived sensations for each phase for the TENS and sham group (group average). The colored area indicates the intensity and area of evoked sensations. The perceived sensation is more focused on the electrode locations, which was left-median nerve close to the wrist.

2) P200 Magnitude.

The two-way RM-ANOVA conducted on the P200 magnitude indicated a significant main effect between the different time phases ($F(3, 114) = 31.10$, $p < 0.001$, $\eta 2 = 0.457$), and no significant effect of the main impact of group ($F(1, 38) = 1.90$, $p = 0.177$, $\eta 2 = 0.047$). However, the ANOVA revealed a significant effect on time × group interaction ($F(3, 114) = 3.74$, $p = 0.36$, $\eta 2 = 0.090$). Post hoc pairwise comparisons showed that the magnitude of the P200 component in the TENS group is significantly larger than those in the Sham group for Pre vs. Post0 time condition ($p < 001$ in TENS and $p = 0.93$ in Sham group). Post hoc analysis indicated that the effect of TENS on the P200 would recover 15 minutes following the TENS intervention.

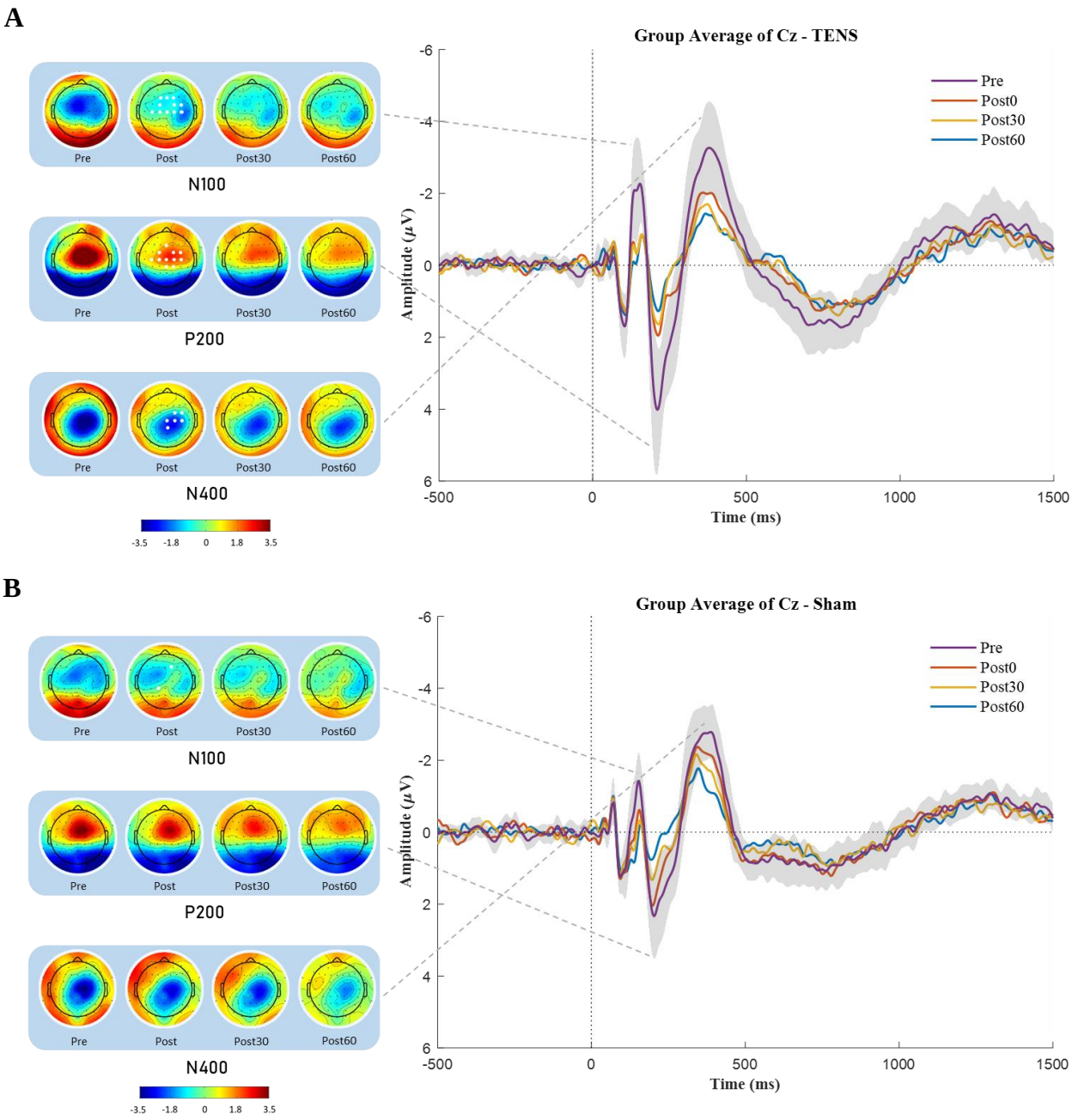

Figure 5. Group average somatosensory evoked potentials (SEPs) following double pulse surface electrical stimulation are displayed for intervention (**A**) and sham (**B**) for the Cz channel. Grey shades showing 95% of the confidence interval for the Pre SEP phase. Scalp topographies of each subcomponent (N100, P200, and N400) are plotted with the same scale bar. White dots in scalp topographies show channels with statistically significant differences between pre and post0 phases.

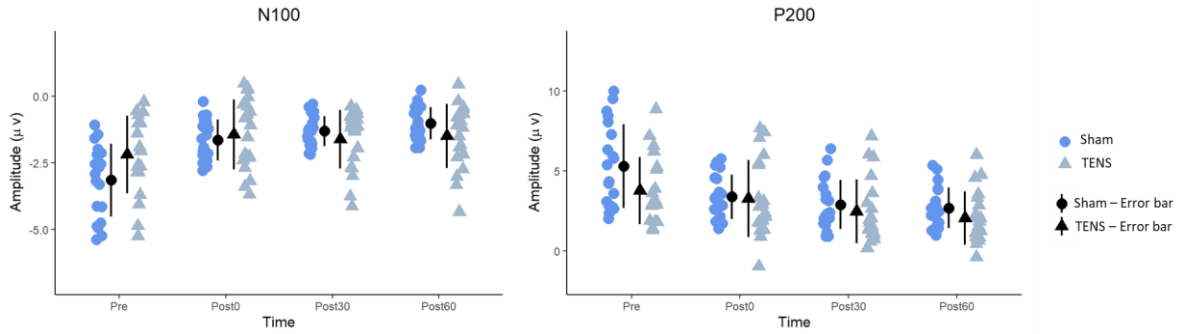

Figure 6. Individual magnitudes of SEPs subcomponents (N100, P200) over four assessment time conditions in TENS and sham groups. Mean ± standard deviation is depicted by black filled circle and back filled triangle for TENS and sham group, respectively.

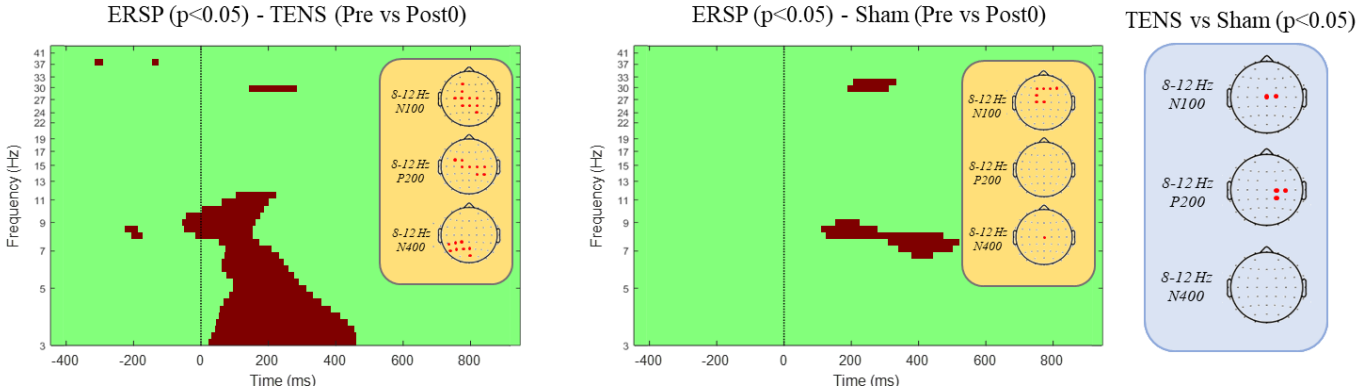

Figure 7. Statistically significant time-frequency map from one-way ANOVA for pre and post time conditions for the TENS and sham group (channel Cz). Red dots in the scalp map show the statistically significant channels in alpha-band activity for different SEP components. The far-right scalp map shows the statistically significant channels from two-way ANOVA for time × group ($p<0.05$).

3) N400 Magnitude.

The two-way RM-ANOVA conducted on the N400 magnitude revealed a significant main effect of time ($F(3, 114) = 31.98$, $p < 0.001$, $\eta 2 = 0.457$). However, no significant main effect of group ($F(1, 38) = 0.241$, $p = 0.626$, $\eta 2 = 006$), or time × group interaction ($F(3, 114) = 2.554$, $p = 0.059$, $\eta 2 = 0.063$) was found.

Dynamic Activity

The time-frequency map was compared between pre and post0 time conditions for both the TENS and sham group at electrode location Cz, and statistically significant ERSP activity is depicted in Fig. 7. Statistically significant SEPs activity in the theta and alpha band power in time windows of 300 ms (100 to 400 ms) in the TENS group was comparable with the same time-frequency windows in the sham group.

Statistically significant ERSP activity in the alpha band for SEP components was calculated across all 64 electrode locations, and channels with a significant main effect of time ($p<0.05$) are depicted as red dots in Fig. 7. Moreover, the far-right column in Fig. 7 shows the electrode location with the statistically significant differences for the effect of group (TENS vs. sham). FDR correction was used to avoid type II error due to multiple comparisons over 64 electrodes.

IV. Discussion

The results of the present work showed that TENS decreased the cortical activity of the somatosensory cortex and suppressed the perceived sensations.

Effect of TENS on the perception response

The TENS intervention on the evoked perception has shown a significant effect not only between groups but also over time. We have used the VAS scale to rate the perceived sensation following each block of SEPs. Although these measurements are subjective and have limited reliability, we have recorded the location of the subject's evoked sensation as supplementary measurements. We have shown that both cortical and sensation responses suppressed following TENS. Further experiment with recording sensation following each stimulation impulse is needed to correlate the suppression of cortical activity and perceived sensation responses.

Effect of TENS on the cortical activity over time

Despite the fact that the long-lasting analgesic effect of TENS on chronic pain reduction depends on the TENS characteristics (e.g., frequency, intensity, and TENS period) [2], [20], here, the lasting effect of 20 min TENS with a strong but comfortable stimulus intensity on cortical activity was investigated up to an hour after the intervention phase. The effectiveness of TENS on the cortical activity was evaluated by comparing the N100, P200, and N400 SEP waves, ERSP, and ITC in four time steps. Although results have shown that TENS suppresses all the mentioned SEP waves, the lasting effects of TENS on the amplitudes of these waves were different. The suppression of the magnitude of the N100 wave lasted at least an hour. However, the effects of TENS on the magnitude of P200 only remained for 30 min after the intervention.

Effect of TENS on cortical dynamic oscillation

In terms of power spectra, it has been shown that chronic pain is linked with the enhancement of delta (0.5-4 Hz) [37], theta (4-8 Hz) [16], [37], [38], and alpha band power (8-12 Hz) [37], [39], [40]. Moreover, neuropathic pain patients have shown enhanced alpha power at resting state [37], [39], [40]. The activated brain areas with the changes in theta and beta were localized in multiple pain-related areas such as SI, SII, ACC, insula, and supplementary somatosensory cortices [41]. Here, we have shown that the alpha oscillation was significantly suppressed following TENS and that central cortical areas were statistically significant between TENS and sham group, Cz and C2 for N100 wave and C2, C4, and Cp2 for P200 wave (Fig. 7). The organization of pain-associated cortical areas may be a possible explanation for the reduction of alpha and theta power following TENS intervention [39], [42]. Our findings in ITC activity demonstrate a statistically significant reduction of ITC in the theta band following TENS in a time window from 100 to 300 ms after stimulus onset, which could be considered as another biomarker of the effect of TENS on brain activity (in

the supplementary).

Although the focus of the present study was on healthy subjects, suppressed theta and alpha oscillations may also play a role in pain relief. While previous research has claimed that the alpha power might be reduced in painful conditions [43]–[45], our results are in line with previous findings in the literature covering theta and alpha enhancement in chronic pain patients.

Effect of TENS on the cortical activity in different brain areas

The N100 wave has been mentioned to represent the early stage of sensory processing that is independent to conscious awareness of the stimulus. It is thought to originate mainly from primary and secondary somatosensory cortices [46]. In line with this, Fig. 5 depicts the maximum activity at central electrodes contralateral to the stimulation site in the scalp topographies of the N100 wave in both groups, while the influence of the TENS intervention showed a reduction of cortical activity over time. Moreover, the enhancement of the N100 wave magnitude in chronic pain patients has been correlated with the memories of pain [47], [48]. The lasting effect of TENS on suppression of the N100 wave magnitude supports that SI is more sensitive to electrical sensory stimulation and can be used as a biomarker for future TENS therapy.

The cortical area which represents the P200 has been reported to correlate with the anterior cingulate cortex (ACC), which is believed to be responsible for translating a perceived stimulus as a conscious perception [49]. For example, Peng et al. noted that TENS could induce a reduction in the amplitude of the P200 wave and this was correlated with the analgesic effect of the pain perception [2]. Furthermore, the larger magnitude of P200 in comparison with early components is related to the perceptual outcome of sensory processing [50]. Therefore, our results show that the amplitude of the P200 may be suggested as a cognitive biomarker of sensory processing induced by TENS. Although chronic pain has shown to alter the sensory processing and increase the cortical activity [51]–[53] and as TENS may decrease the cortical activity, the present study suggests that the amplitude of the N100 and P200 waves could be possible biomarkers to explore the influence of TENS on suppression of cortical activity in chronic pain relief.

Possible use of TENS for pain relief

TENS may be beneficial to decrease chronic pain, such as PLP or low back pain, since both conditions are correlated with facilitation of cortical activity. This idea is supported by the hypothesis that chronic pain is increased by sensorimotor disturbances and that the pain may decrease by artificially restoring the sensorimotor congruence in patients with chronic pain and PLP [54]–[57]

One condition where TENS has been applied for pain relief is PLP. PLP is a frequent consequence of amputation [58], [59]. The underlying mechanisms of PLP are still unknown, but it is believed to be related to neurobiological changes in both the peripheral and central nervous systems (CNS). At the central level, PLP is correlated with the structural and functional reorganization of SI contralateral to the amputation [60], [61]. A possible explanation for these changes is the loss of afferent input, which leads to an invasion of the former limb representation area in SI from surrounding cortical regions [62], [63].

Cortical brain activity has been reported to change in different ways following acute and chronic pain. Several studies have addressed the suppression of cortical activity in experimentally induced acute pain [64], [65]. In contrast, several studies have shown that individuals who experience chronic pain show an increase in SI activity and a change in the location of SI activation [51], [66], [67]. It has been reported that SI reorganization plays an important role in chronic pain following a peripheral injury [68]. Moreover, experimental investigations using fMRI and EEG techniques have been suggested the reorganization and increased sensorimotor cortex activation as a notable signature of neuropathic pain [16], [69]. Neural indexes of physiological measures such as peak amplitude of all different SEP components (time-domain) and the magnitude of the SEP oscillation (time-frequency domain) have been suggested and used widely as an index for the neural activity in pain perception [47], [50], [70], [71]. The modulated SI activity is one of the mechanisms leading to changes in the pain perception and the associated cortical representation [51]–[53].

Limitations

Although our findings indicated that the TENS alter the cortical activity in healthy subjects, the present study has some limitations that must be taken into account. First, our objective has been evaluated in healthy subjects, but further study is needed to validate our results with patients experiencing phantom limb pain. Secondly, our study analyzed behavioral data with ANOVA following a log-transformation. Since generalized linear mixed-effect models do not require normalized data for statistical analysis, this may be an attractive alternative for analyzing the behavioral data [72].

V. Conclusions

Transcutaneous electrical nerve stimulation (TENS) has been reported to alleviate pain in chronic pain patients. Today, there is limited knowledge on the relation between modulation of cortical neuroplasticity and how this leads to modulation of perceived sensations (i.e. pain relief). In the present study, we explored the alterations of cortical activity and perceived evoked sensation following a TENS intervention in healthy subjects. The results showed that TENS delivered to the left-median nerve simultaneously suppressed (up to 60 min) the cortical activity, the perceived sensation intensity and the size of the area where the sensation was felt. Since phantom limb pain relief has previously been associated with an inhibition of the cortical activity, the type TENS as examined in the present work may be beneficial as a possible therapy.

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