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Transcutaneous Electrical Stimulation Influences the Time-Frequency Map of Cortical Activity - A Pilot Study

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***Abstract*— Phantom limb pain (PLP) is pain felt in the missing limb in amputees. Somatosensory input delivered as high-frequency surface electrical stimulation may provoke a significant temporary decrease in PLP. Also, transcutaneous electrical nerve stimulation (TENS) is a somatosensory input that may activate descending inhibitory systems and thereby relieve pain. Our aim was to investigate changes in cortical activity following long-time sensory TENS. Time-frequency features were extracted from EEG signals of Cz and C4 channels (contralateral to the stimulation site) with or without TENS (2 subjects). We found that the TENS caused inhibition of the spectral activity of the somatosensory cortex following TENS, whereas no change was found when no stimulation was applied.**

***Clinical Relevance*— Although our preliminary results show a depression of the cortical activity following TENS, a future study with a larger population is needed to provide strong evidence to evaluate the effectiveness of sensory TENS on cortical activity. Our results may be useful for the design of TENS protocols for relief of PLP.**

I. Introduction

Amputation of a limb is often followed by intractable phantom limb pain (PLP) that is perceived in the missing amputated limb. While the prevalence of PLP is reported to be as high as 85% of amputees, the underlying mechanisms of PLP are yet not well understood. Both peripheral and cortical mechanisms and have been mentioned as possible contributors to PLP [1]. Previous studies have reported that the functional and structural reorganization of the primary sensorimotor cortex (SI) following amputation is correlated with PLP [2], [3]. It has also been reported that the inhibition caused by the formation of neuromas in the peripheral nervous system may contribute to the mechanism of PLP [4].

Transcutaneous Electrical Nerve Stimulation (TENS) is a popular method in neurorehabilitation for pain and spasticity relief. The delivered electrical current activates the peripheral somatosensory afferents and has shown to decrease both acute and chronic pain [5], [6]. Although the delivered electrical currents are varied in frequencies, pulse durations, and intensities, the sensation evoked is most often perceived as an intense tingling. In the last decades, studies have shown the effectiveness of sensory TENS on pain relief after a period of stimulation [7], [8]. For example, Kara et al. [9] reported that TENS treatment to patients suffering from carpal tunnel syndrome induced a significant inhibition in cortical activity up to 35 minutes after the intervention period, while no changes were observed in a sham group. Several clinical studies illustrated that sensory feedback by electrical stimulation can be mentioned as a type of treatment for temporary PLP reduction [10], [11]. In a recent study at Aalborg University (FP7-health-2013-innovation-1 Project no 602547: EPIONE) steady-state surface electrical stimulation was delivered to the phantom limb (PL) and induced significant temporary changes in PL sensation [12]. The electrical current delivered as the surface electrical stimulation of referred sensation areas reduced the PLP up to 40 %, with the lasting effects varied between minutes to hours beyond the stimulation period.

Event-related potentials (ERPs) can be used to reveal changes in evoked electroencephalogram (EEG) that is the direct result of various external stimuli (e.g., motor, sensory, or cognitive). Recently, the ERP components features have been used to investigate the lasting effects of long-time steady-state electrical stimulation [13]. Spectral analysis of ERPs can also be applied to investigate cortical processing, which has been demonstrated in different conditions such as movement [14], audition [15], and painful stimuli [16].

To our knowledge, the changes in the time-frequency map of cortical activity following sensory TENS have not been dealt with in-depth. The aim of the present work was therefore to investigate changes in time-frequency representation of cortical activity following long-time sensory TENS. We collected pilot data from two subjects (one subject to TENS, and the other to sham stimulation) and compared time-frequency features from the EEG data from Cz and C4 (contralateral to the stimulated hand) channels. We analyzed the functional power-based connectivity of these two channels for two subjects.

II. Methods

A. Subjects

Two healthy right-handed subjects (one male aged 26 and one female aged 21) participated in this study. Subjects were assigned into two groups: intervention and sham. Both subjects have not participated before to experiments with electrical stimulation and signed a written informed consent form. Neither of the subjects suffered from any neurological disorders. The study was approved by the North Denmark Region Committee on Health Research Ethics (N-20180049).

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B. Experimental paradigm

The experimental paradigm was as follows. Each subject were subjected to three phases: Pre-TENS, TENS, and Post-TENS. Event-related potentials were recorded in Pre-TENS and Post-TENS phases and followed the same procedure for both intervention and sham groups. Each Pre-TENS and Post-TENS phase consisted of 80 trials of two succeeding constant-current square-wave pulses with a pulse width of 500 µs, 10 ms inter pulse interval, and a random inter-stimulus interval between 6-9 s. Electrical stimulation were generated with a DS5 constant-current stimulator (Digitimer, UK) and delivered to two PALS electrodes (40 × 64 mm, oval) attached to the left-median nerve. The intensity of the double pulses electrical stimulation to record SEPs was chosen as twice the sensation threshold, which determined before the Pre-TENS condition by using the staircase procedure, as mentioned in [17]. The sensation threshold was chosen as the average of maximum intensities of a double-pulse at which the subject reliably could percept the stimulation. The discomfort threshold was defined as the highest stimulation intensity, in which the participant reported an uncomfortable sensation. The sensation and discomfort thresholds of TENS were extracted by one second of TENS stimulation (high-frequency electrical stimulation) with the same procedure mentioned before.

The TENS consisted of 40 trials of high-frequency surface electrical stimulation (biphasic pulses, frequency = 100 Hz, pulse width = 1 ms, on-time = 20 s, off-time = 10 s) delivered to the attached electrodes (20 min in total). On the other hand, sham stimulation delivered by just two high-frequency surface electrical stimulation trials (1 min in total). Although the TENS intensity for the sham group was adjusted based on the sensation threshold, the stimulation level of 80 % of the current intensity that evoked discomfort sensation was chosen for the intervention group.

During both experiment sessions, participants were seated in a comfortable arm-chair and instructed to focus on the stimuli while their eyes were open. EEG data were recorded by using a 64-channel EEG system (10-20 system, BrainAmp MR plus amplifiers, Brain Products, GmbH). A sampling rate of 5 kHz digitized the EEG data, and the impedance of all electrodes was kept < 20 kΩ.

EEG data were preprocessed and analyzed using the EEGLAB toolbox [18]. First, the raw EEG signals were downsampled to 2.5 kHz and then filtered (band-pass 0.5 to 45 Hz, notch 50 Hz). Secondly, the filtered signals were visually inspected, and EEG channels affected by large artifacts were manually removed. Then, independent component analysis (ICA) was applied to transform the channel domain signals to the ICs domain. The ADJUST algorithm was used to extract and select the ICs contaminated by blink and other artifacts, and the processed data were reconstructed from the rest of ICs. Then, data were re-referenced to average reference and SEPs were extracted by segmenting data into epochs of 1000 ms (from 200 pre-stimulus to 800 ms following stimuli onset). Finally, the baseline correction with reference interval at 200 ms prior to stimulus onset was applied for each trial.

The effectiveness of the intervention on the central nervous system was evaluated by comparing the time-frequency features extracted from Pre-TENS and Post-TENS phases. The time-frequency map of the extracted ERPs was calculated using the Morlet wavelet (umber of cycles 4 to 10). The frequency range for wavelet analysis was 2- 40 Hz in steps of 0.95 Hz. The power values of the desired time-frequency window were calculated for each trial and channels. The desired T-F window was selected based on the window with higher amplitude in the T-F map of average trials, which is correlated with ERP response following sensory stimulus. Finally, the Pearson correlation of the extracted T-F features for channel Cz and C4 as channels close to SI was calculated over trials separately for each intervention and sham intervention group.

III. RESULTS

The average power amplitude of selected time-window over trials in Pre-TENS and Post-TENS conditions for two channels in both intervention and sham groups is illustrated in Fig 1. The same time windows of 100 - 400 ms (referred to stimulus onset) and frequency windows from 4 - 12 Hz were used for both groups and conditions. The time-frequency representation of two channels, Cz and C4 (contralateral to the stimulation site) in Pre-TENS and Post-TENS conditions for intervention and sham, are depicted in Fig 2.A and Fig 2.B respectively.

Fig 3.A shows a scatter plot of the selected power from two channels for Pre-TENS and Post-TENS conditions following the intervention. The same results for the sham group are illustrated in Fig 3.B. In the intervention group, spectral features for Pre-TENS phase have a correlation coefficient of R = 0.71 while the Post-TENS has the correlation coefficient of R = 0.4. For the sham group, spectral features for Pre-TENS phase have the correlation coefficient of R = 0.54 while the Post-TENS have the correlation coefficient of R = 0.48.

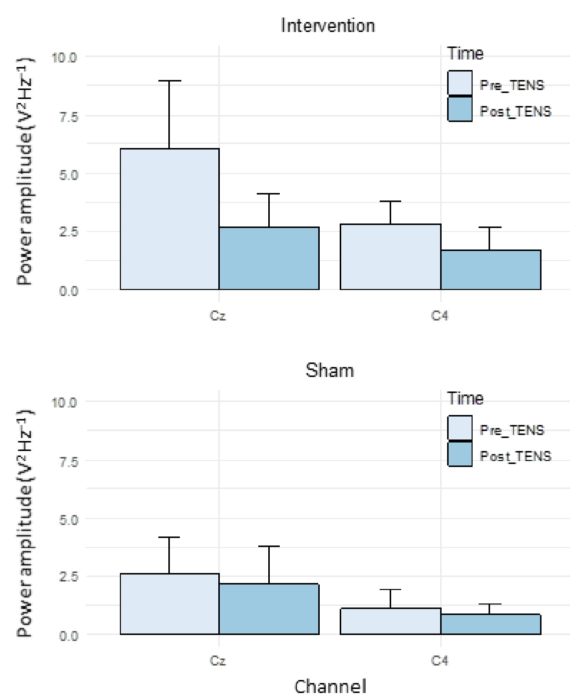

Figure 1. The average spectral power of two channels for Pre and post TENS conditions and intervention and sham groups

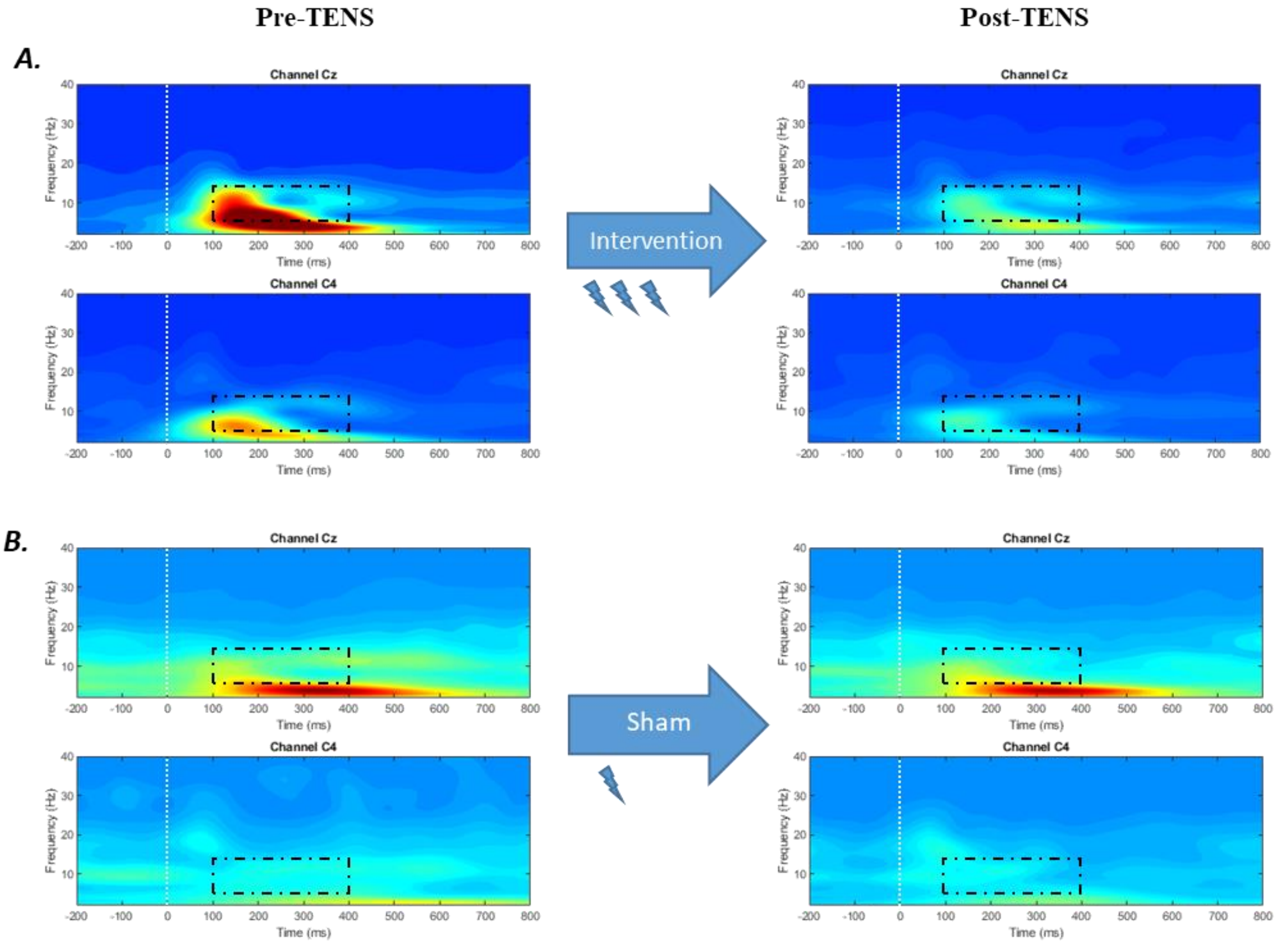

Figure 2. A) Time-Frequency representation of Pre-TENS and Post-TENS in Cz and C4 channels for subject one (intervention). B) Time-Frequency representation of Pre-TENS and Post-TENS in Cz and C4 channels for subject two (sham). Dash lines demonstrated the desired window for power feature extraction (frequency of 4-12 Hz and time window of 100-400ms after stimulation onset).

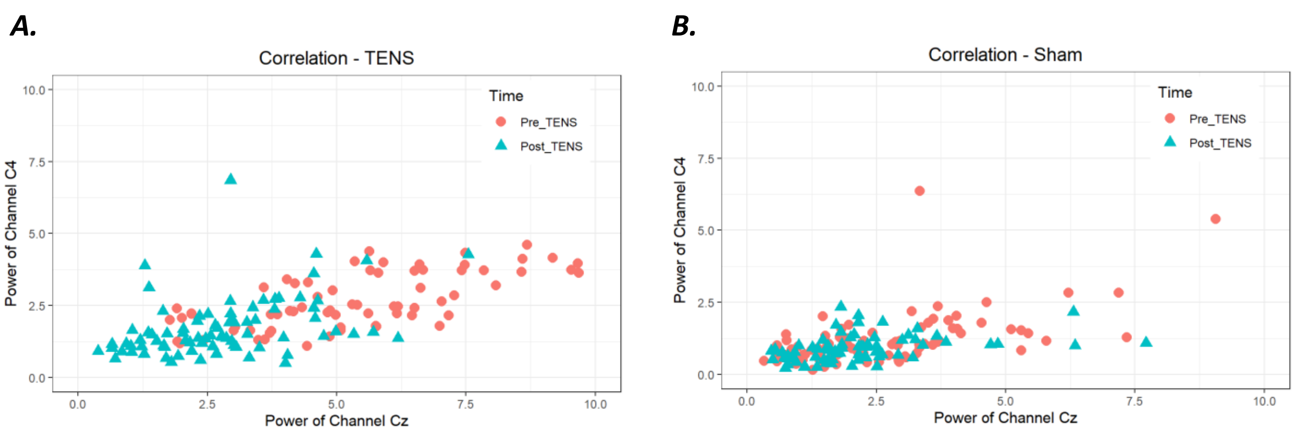

Figure 3. A) Scatter plot of the extracted power (from selected time-frequency window) of Pre-TENS and Post-TENS in Cz and C4 channels for intervention group B) Scatter plot of the extracted power of Pre-TENS and Post-TENS in Cz and C4 channels for sham condition.

IV. Discussion and Conclusion

Sensory TENS for 20 min delivered to the left-median nerve at the wrist suppressed the event-related synchronization of ERPs from Cz and C4 channels and functional power-based connectivity. Results showed that the time-frequency activity of Cz and C4 channels decreased after applying TENS (Fig - 2A). At the same time, in the sham condition, there was no significant change in the time-frequency patterns. The functional power-based connectivity of two channels over 80 trials following sensory TENS decreased the correlation coefficient, while the correlation coefficient remained stable for the subject with sham stimulation. These results are supported by the decrease in the average spectral power amplitude of selected time-frequency windows in Cz and C4 channels following sham and intervention phases (Fig.1). Although the results have covered the functional connectivity via time-frequency power, further study may investigate the casual inferences for functional connectivity on larger population samples.

The evoked significant phase-locked responses following surface electrical stimulation have previously been used as biomarkers of brain activity following different stimulation [14]–[16]. Here we have used the same biomarkers to evaluate the sensory TENS on cortical activity. Our results showed that inhibition in event-related synchronization may be used as possible markers in the transient state of cortical activity following TENS therapy.

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