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Modulation of Corticospinal Excitability by Two Different Somatosensory Stimulation Patterns; A Pilot Study*

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

***Abstract*— Following amputation, almost two-thirds of amputees experience unpleasant to painful sensations in the area of the missing limb. Whereas the mechanism of phantom limb pain (PLP) remains unknown, it has been shown that maladaptive cortical plasticity plays a major role in PLP. Transcutaneous electrical nerve stimulation (TENS) generating sensory input is believed to be beneficial for PLP relief. TENS effect may be caused by possible reversing reorganization at the cortical level that can be evaluated by changes in the excitability of the corticospinal (CS) pathway. Excitability changes are dependent on the chosen stimulation patterns and parameters. The aim of this study was to investigate the effect of two TENS patterns on the excitability of the CS tract among healthy subjects. We compared a non-modulated TENS as a conventional pattern with pulse width modulated TENS pattern. Motor evoked potentials (MEPs) from APB muscles of stimulated arm (TENS-APB) and contralateral arm (Control-APB) were recorded. We applied single TMS pulses on two subjects for each TENS pattern. The results showed that both patterns increase the CS excitability, while the effects of the conventional TENS is stronger. However, the amplitude of MEPs from control-APB after TENS delivery remained almost the same.**

Clinical Relevance— The primary results revealed changes in the activity of CS pathway for both patterns. A future study on a larger population is needed to provide strong evidence on the changes in CS excitability. The evaluation part with more factors such as changes in intracortical inhibition (ICI) may be beneficial to find an optimal modulated TENS pattern to enhance pain alleviation process in PLP.

I. INTRODUCTION

Phantom limb pain (PLP) is experienced by most subjects (up to 80%) following amputation. Painful sensations localized in or around the area of the lost limb are frequent symptoms [1]. While PLP influences the quality of life amputees negatively, the mechanism and nature of this phenomenon are yet not fully understood. Some researchers believe that the peripheral nervous system may be involved due to spontaneous discharges caused by the formation of neuromas [2]. However, recent studies have reported that significant cortical reorganization in the somatosensory map may also play a major role in PLP [3], [4]. Some studies also reported a significant reduction of intracortical inhibition in the affected side in comparison to the non-affected side or in comparison with healthy subjects [5], [6]. These changes may be considered as markers of PLP.

Despite the lack of understanding the underlying mechanism of PLP, several interventions have been applied with the aim to reduce PLP (e.g., mirror therapy, virtual reality, and transcutaneous electrical nerve stimulation). Also, several clinical trials showed that high-frequency stimulation (HFS) delivered on the affected or contralateral limb can temporarily relieve pain [7]–[9]. In EPIONE (an EU project at Aalborg University) application of non-painful steady-state electrical stimulation on the surface of the residual limb, caused significant temporary changes in the perception of PLP and a reduction of PLP up to 40 % [10].

Transcutaneous electrical nerve stimulation (TENS) may induce plasticity in the central nervous system. In healthy subjects, changes in the amplitude of motor-evoked potentials (MEPs) have been observed after TENS delivery [11]-[14]. Depending on the TENS parameters (i.e., frequency, amplitude, pulse width, and duration), MEPs evoked by TMS pulses was found to either increase or decrease. For instance, Miyata studied the impact of short-duration (120 s) high-frequency (100 Hz) electrical muscle stimulation on corticospinal (CS) excitability and reported considerable reduction in MEP amplitude from APB muscle after TENS [12]. Furthermore, two hours of low-frequency somatosensory stimulation (10 Hz) of the ulnar nerve increased the excitability of the ADM muscle (target muscle) more than APB and FDI (non-target muscles). It depicts that the effects of this electrical stimulation pattern on all three muscles were apparent, but changes in the ulnar-nerve-innervated muscle (ADM) is stronger than APB and FDI. [13]. However, Mang in 2011 conducted an experiment where 40 min of neuromuscular electrical stimulation (1ms pulse width, 20s on - 20s off cycle) could improve the excitability of CS for both the leg and the hand. This enhancement was more focused in the hand muscle [14]. In another study, he investigated the effect of electrical stimulation with different frequencies. The result showed that 100 Hz TENS increased the amplitude of MEPs more than 10, 50, and 200 Hz TENS [11].

While the neural mechanism of TENS action is yet to well-known, it is believed to be likely the combination of cortical reorganization, strengthening the CS pathway, and neural inhibition effect in local and cortical level [15]–[18]. Long-duration TENS has been used as rehabilitation method for chronic pain patients such as back pain and PLP [19] or patient with performing function movement problems disease like stroke [20]. Recent articles have been a focus on investigating alternative temporal patterns of electrical stimulation instead of conventional non-modulated pattern to enhance therapies [21], [22]. Pulse width modulated (PWM)

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electrical stimulation is one of the novel approaches which has been tested on patients with back pain, and the quality of pain relief results was equivalent to non-modulated tonic stimulation, but it produced a more comfortable perception for patients. Daniel et al. reported that despite conventional TENS (with constant parameters), this stimulation pattern activated the population of axons sequentially and replicates physiological neural signals [19].

Different TENS patterns may affect differently on CS activity. For improving the PLP reduction process, the way that the TENS patterns influence the excitability of CS pathway needs to be further investigated. To our knowledge, the changes in the CS activity following PWM TENS have not been studied. Our aim in this paper was to compare the effect of two different TENS patterns on the excitability of the CS tract. Conventional TENS pattern (i.e., a rectangular pulse with constant parameters) and modulated TENS (PWM) were used as an intervention phase. MEPs were recorded by applying single TMS pulses with two intensities before and after delivery of the TENS interventions. The peak-to-peak amplitudes of MEPs before and after electrical stimulation delivery were studied in two subjects for each TENS pattern.

II. Methods

A. Subjects

Four healthy, right-handed volunteers (two males and two females, age from 29 to 32 years) with no history of peripheral and central nervous system diseases participated in the experiment. The subjects had no prior experience with electrical stimulation (TENS) and provided their written informed consent. The North Denmark Region Committee on Health Research Ethics (N-20190016) approved the protocol of this study.

B. Peripheral sensory stimulation (TENS)

Electrical stimulation was generated by DS5 stimulator (Digitimer, UK) and delivered with a pair of surface electrodes (Axelgaard PALS Electrodes, contact size 4 × 4.6 cm, oval) placed on left-handed median nerve close to the wrist. Two electrical stimulation patterns were applied; 1) non modulated conventional TENS (100 Hz bipolar rectangular pulses with 1ms pulse width) and 2) a novel PWM TENS (bipolar, rectangular pulses, pulse rate = 100 Hz, sinusoidal modulated pulse width from 0 to 1ms. Each TENS pattern lasted 20 min (20s on, 10s off cycle) and delivered with intensity at 80% of the discomfort level. Subjects were randomly selected for stimulation with one of the two TENS patterns.

B. Recording

Excitability of the CS pathway was evaluated by analyzing the MEPs elicited by TMS pulses in the following time phases; 1) Pre-TENS as baseline MEPs, 2) Post-TENS (immediately after intervention), and 3) Post30-TENS (30 min after intervention phase) (Fig.1).

MEPs were recorded from APB of stimulated hand (right hand) as TENS-APB and APB muscles of the left hand as Control-APB. During all sessions, subjects were aske to seat in a comfortable chair and keep their muscle completely relaxed. MEP from each muscle was collecting with bipolar surface recording electrodes (Ambu Neuroline 720). The signals were pre-amplified, band-passed filtered (50 Hz to 2 kHz) and then stored by a sampling rate of 5 kHz by custom-made software (“Mr. Kick”, Aalborg University, Aalborg, Denmark). MEPs were recorded with the length of the sweep of 400ms (100ms before to 350ms after TMS onset).

TMS was performed thorough a figure-of-eight shaped magnetic coil (MagVenture, MC-B70 Butterfly Coil) to optimal scalp sites (hotspots) to stimulate the target muscle of each hand. The coil was connected to the stimulator (DANTEC Magnetic Primer TwinTop & MagLite r-25) and placed on the scalp with the intersection of both wings at a 45º angle with the midline. While the subjects were asked to relax the muscles, rest motor threshold (rMT) was measured. It was defined as the minimum intensity of TMS pulse needed to elicit MEP with a peak to peak amplitude more than 50 mV in at least 5 out of 10 trials. Each session of the experiment approximately lasted for two hours.

MEPs by TMS stimulation with intensities at 20% and 30% over rMT were obtained. Eight pulses were delivered for each intensity with a 5s interval. Changes in CS excitability pathway induced by TENS patterns for each muscle were analyzed. We averaged the sixteen MEPs from two subjects for each TENS pattern at each TMS intensities and time phase. The peak-to-peak of averaged MEPs amplitude were measured and expressed as a feature to compare changes in excitability over time conditions.

III. Results

Averaged MEPs amplitude of Pre-TENS, Post-TENS, and Post30-TENS for TENS and control muscles with 120% TMS intensity are shown in Fig.2. As can be seen, the MEP amplitude for the TENS-APB increased following both the TENS patterns phase. Changes after PWM TENS were less significant than conventional TENS, increased by 31% and

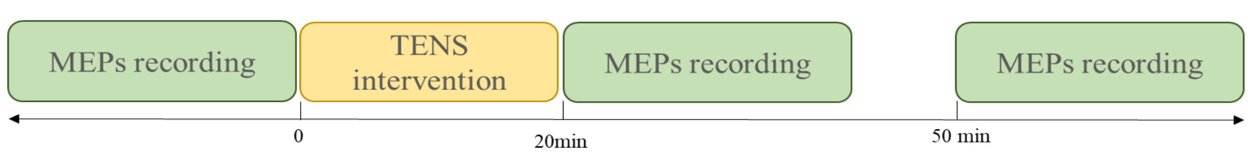

Figure 1. overview of proposed protocol: baseline, intervention, and evaluation

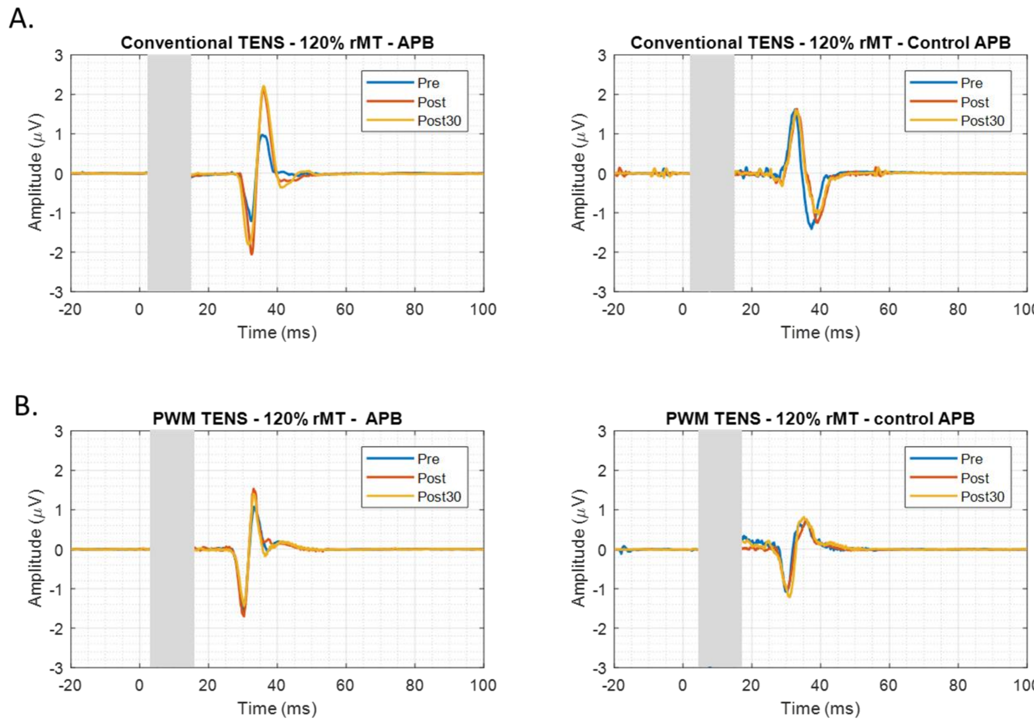

Figure 2. 16-MEPs (for two subjects) averages at 120% of rMT. MEP amplitude was measured at three different time conditions. A: Right-APB as the target muscle. B: Left-APB as the non-target muscle.

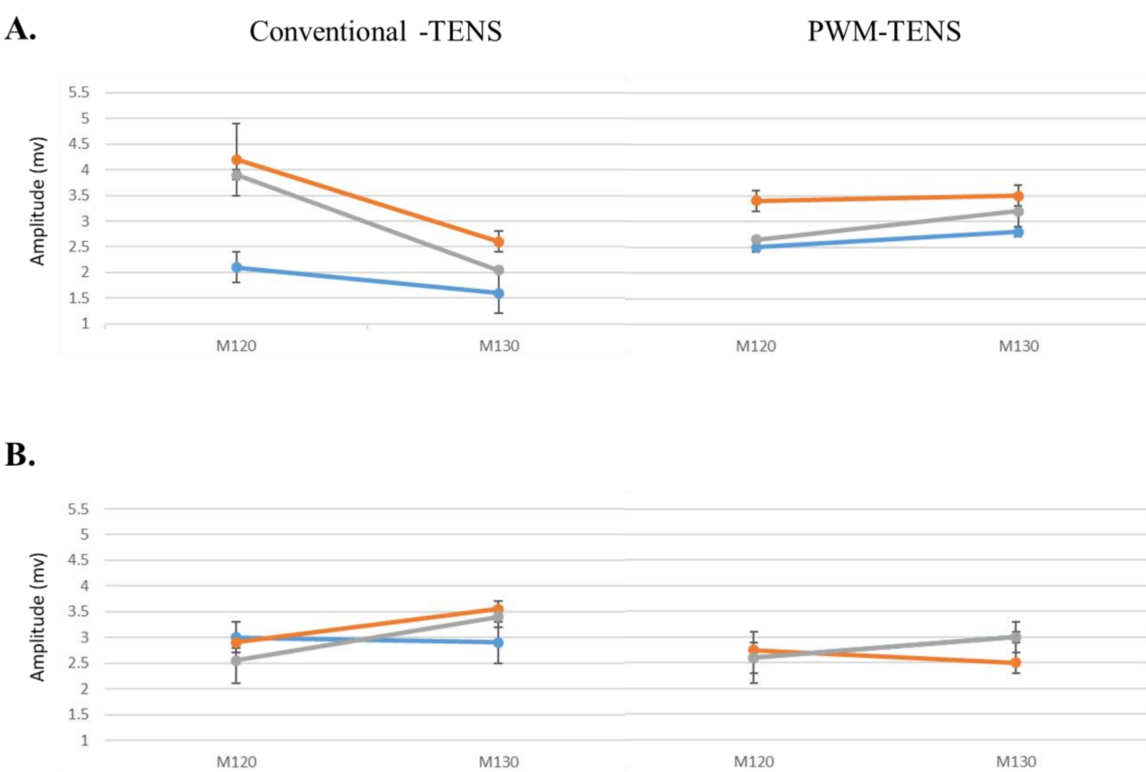

Figure 3. Recruitment curve, averaged MEPs of two subjects in both muscles and intervention patterns with intensities of 120% and 130% of rMT over three different time conditions with standard division. A: TENS-APB. B: Control-APB.

95%, respectively. An enhancement in activity is maintained after 30 min while the MEP amplitudes in Post30-TENS became weaker than Post-TENS. Moreover, the MEPs amplitude of control APB (left APB) remained almost unchanged over three time phases. 6% reduction with conventional TENS and 9% increase immediately after PWM TENS were shown in control muscle.

In Fig.3, MEPs changes for muscles are presented before and after the TENS session at TMS pulse 20 % and 30% above the rest motor threshold. Results for TENS-APB showed enhancement of MEPs amplitude after TENS delivery at 130% rMT as well. The increase of activity in stimulated muscle became 62% and 30% after conventional and PWM TENS pattern, respectively. Furthermore, by increasing TENS intensity, the impact of PWM TENS became stronger than results with 120% rMT pulses. In addition, TENS intervention effects on control muscle have changed reversely between TMS intensities.

IV. DISCUSSION

The present experiment was designed to investigate the influence of two different TENS patterns on CS excitability (non-modulated pattern with constant pulse width and PWM pattern). MEPs from APB muscles of stimulated and the contralateral hands were collected by applying single TMS pulses. The average MEPs of two subject for each pattern was measured. Our main finding was that both TENS patterns induced changes and increased excitability of the CS pathway of stimulated hand, while MEPs amplitude of control muscle maintained almost unchanged. In addition, the conventional pattern had a stronger effect on MEPs amplitude. To our knowledge, it is the first time that the effects of this PWM TENS pattern on the excitability of the CS tract were studied in healthy subjects. This pilot study can provide stronger evidence with a larger population. The future work can be investigating the impact of conventional and modulated TENS patterns on CS excitability by applying paired TMS pulses. In this way, changes in intracortical inhibition (ICI) and intracortical facilitation (ICF), before and after interventions, can be studied and compared as other factors between two TENS patterns. The result may show markers of cortical plasticity and possible reorganization effect after stimulation delivery leading to improve PLP relief process.

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