2023 45th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) | 979-8-3503-2447-1/23/$31.00 ©2023 IEEE | DOI: 10.1109/EMBC40787.2023.10340377

Exploring Psychophysical and Neurophysiological Responses to Intra-Epidermal Electrical Stimuli in Patients With Persistent Spinal Pain Syndrome Type 2 with a Spinal Cord Stimulator

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***Abstract*— There is a lack of measures that provide insights into how spinal cord stimulation (SCS) modulates nociceptive function in patients with persistent spinal pain syndrome type 2 (PSPS-T2). Recently, we observed altered nociceptive detection thresholds (NDTs) in response to intra-epidermal electrical stimulation (IES) on the feet of PSPS-T2 patients when dorsal root ganglion stimulation was turned on. Furthermore, we observed altered NDTs and evoked potentials (EPs) in response to IES on the hands of PSPS-T2 patients. To explore whether EPs were obstructed by SCS artifacts, we applied IES twice to the hands of patients with SCS turned on (SCS-ON/ON group). To explore possible confounding effects of SCS outside the stimulated area, we repeated IES on the hands of these patients, once with SCS turned off and subsequently once with SCS turned on (SCS-OFF/ON group). The results demonstrated that EPs were not obstructed by SCS artifacts. Additionally, NDTs and EPs did not significantly change between measurements in the SCS-ON/ON and the SCS-OFF/ON groups. Therefore, the results suggested that possible confounding effects of SCS outside the nociceptive system did not interfere with the detection task performance. This work warrants further exploration of NDT-EP phenomena in response to IES at the painful feet of patients.**

***Clinical Relevance*—This work contributes to developing a clinical tool to explore psychophysical and neurophysiological biomarkers for observing modulating effects of SCS in patients with PSPS-T2.**

I. Introduction

Spinal cord stimulation (SCS) is an effective treatment for patients with persistent spinal pain syndrome type 2 (PSPS-T2) suffering from chronic low back and leg pain after surgery [1,2,3,4,5]. SCS efficacy has not improved since the spinal mechanisms of action of SCS are still not completely understood [6,7]. Therefore, there is a need for clinical measures providing mechanistic insights into the modulating effects of SCS on nociceptive function [8,9,10]. Current measurement tools (e.g., pain questionnaires and quantitative sensory testing methods) depend on subjective judgment of sensation quality and provide limited insights into underlying nociceptive processing responsible for chronic pain [11].

We are developing a measurement technique for observing nociceptive function using intra-epidermal electrical stimulation (IES). This technique can recruit preferential nociceptive Aδ nerve fibers and tracks nociceptive detection thresholds (NDTs) from multiple trials of different stimulus types using an advanced electrical stimulation paradigm [12]. In a previous study, we used the so-called NDT method at the feet (i.e., L5 dermatome) of PSPS-T2 patients who have been treated with a dorsal root ganglion (DRG) stimulator [13]. NDTs were found to alter in response to IES once the DRG stimulator was turned on. Besides possible psychological effects, confounding effects of neurostimulation outside the nociceptive system (e.g., paresthesia) might have affected the patient's detection task performance.

The psychophysical (NDT) measurement technique has been combined with an electroencephalogram (EEG) to observe brain responses associated with cortical processing and conscious perception. The so-called NDT-EP method quantified the function of the nociceptive system by the effect of stimulus properties (e.g., varied stimulus amplitudes, number of pulses, and inter-pulse intervals) on features of the EPs (e.g., signal-to-noise ratio (SNR) and amplitude of the P2 peak) measured at the vertex derivation (i.e., CPz-A1A2) [14]. Previous laboratory experiments used IES of the dorsum of the hands (i.e., C7 dermatome) in healthy subjects [14,15]. Hence, clinical feasibility studies explored NDT-EP phenomena using IES performed on (non-painful) hands of patients (e.g., with PSPS-T2), which showed altered task performance compared to pain-free controls [16,17]. However, it is uncertain whether altered detection task performance in patients was related to nociceptive dysfunction. Before we could explore cortical responses using IES on painful and stimulated areas of SCS, we first need to know whether the measurement of EPs is not obstructed by SCS artifacts [18,19]. Furthermore, possible confounding effects of neurostimulation outside the nociceptive system need to be uncovered.

Therefore, the primary objective of this study was to explore NDT-EP phenomena in response to IES of the hand of PSPS-T2 patients who have been treated with SCS. Due to the different stimulation areas between SCS and IES, we did not expect significant influences of SCS on the IES detection threshold and evoked potential of the hand. We estimated psychophysical (i.e., psychometric slopes and detection thresholds) and neurophysiological (i.e., EPs) outcomes of collected stimulus-response pairs from two groups of PSPS-T2 patients implanted with a spinal cord stimulator, of which the experimental conditions were identical to previous studies. The first group repeated the measurement using the NDT-EP

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method when the spinal cord stimulator was turned on (i.e., SCS-ON/ON group). The second group had the first measurement when the stimulator turned off and subsequently once when it turned on (i.e., SCS-OFF/ON group).

II. Methods

A. Patients with PSPS-T2

Twenty-five patients with PSPS-T2 enrolled in the study. The patients were recruited at the outpatient pain clinic of the St. Antonius Hospital Nieuwegein, the Netherlands. Inclusion criteria were patients aged between 18 and 65 years, a diagnosis of PSPS-T2, and a successful (i.e., at least 50% VAS-score reduction) implanted spinal cord stimulator for at least three months because of radiating leg pain. Exclusion criteria were diagnosis of diabetes mellitus, central or peripheral nerve disorders, (surgical) intervention (e.g., spinal cord stimulator revision) less than three months to minimize possible influence of nociceptive (wound) pain, another implanted electrical stimulation device, patient's refusal, communication problems, consumption of alcohol or drugs within 24 hours before the measurement, and pregnancy. Medication intake was allowed during the study. The patients were divided into one of the two subgroups: (1) SCS-ON/ON or (2) the SCS-OFF/ON. Patients with poor task performance (i.e., a false positive detection rate higher than five percent per setting, of which false positive detections were defined by stimuli with response times below 150 ms) were excluded from data analysis. No formal sample size calculation was made because of its explorative character. All patients signed a written informed consent. The study was approved by the Medical research Ethics Committees United (MEC-U; file-number: NL66136.100.18).

B. Study Design

In this explorative mono-center study, the division of patients into SCS-ON/ON or SCS-OFF/ON was done by stratified randomization based on age (i.e., ≤50 or >50 years old) and sex to minimize potential influences. Both groups had one session at the hospital, consisting of an administration of (pain) questionnaires (i.e., case report form including numeric rating scale (NRS) scores) followed by two measurements using the NDT-EP method. The hand side for IES during the measurements was determined by randomization. Patients in the SCS-OFF/ON group were asked to turn off the spinal cord stimulator four hours before the session time at the hospital. The stimulator was turned on again after the first measurement, and the second measurement started after a 60 minute break.

B. Procedure

During the measurements using the NDT-EP method, patients sat in a comfortable chair in a clinical room shielded from acoustics. They controlled an AmbuStim 1-channel (NociTRACK B.V., Enschede, the Netherlands) with their hand, connected to two stimulation electrodes placed on the dorsum of their contralateral hand. The cathodic IES electrode (containing five needles of 0.5 mm) was positioned in the unaffected C7 dermatome, distally located from the anodic (9x5 cm) TENS electrode. An ANT Neuro Waveguard electroencephalogram (EEG) cap was placed on their head, of which the impedance of the 64 Ag/AgCl electrodes (modified international 10-20 system was kept below 5 kOhm, and was connected to the TMSi 72-channel REFA EEG amplifier. A ground electrode was placed on their forehead, and two electrodes were placed on their ear lobes. Brain activity was continuously measured with a sample frequency of 1 kHz during the measurements. Before the main measurements started, patients were familiarized with detection tasks and test stimuli using a simple staircase procedure (with a step size of 0.05 mA). Subsequently, 450 stimuli consisting of three stimulus types (i.e., 150 trials per stimulus type) were applied around the detection threshold using an advanced stimulus selection procedure. NDTs were tracked over time for each stimulus type consisting of 210 µs square-wave pulses: (1) single pulse stimuli, (2) double pulse stimuli with 10 ms inter-pulse interval (IPI), and (3) double pulse stimuli with 40 ms IPI. Patients were instructed to press-and-hold the button of the AmbuStim until they felt a sensation which they ascribed to the stimulus. When the patients felt a stimulus, they were instructed to release the button as soon as possible. Then, the stimulus was labeled as detected, and the following stimulus amplitude of the stimulus type decreased by 0.025 mA. If the patient did not respond within 1000 ms, the stimulus was labeled as non-detected. The next stimulus amplitude of the stimulus type increased by a step size of 0.025 mA. This program continued until the end of the measurement.

C. Psychophysical Responses

Psychophysical responses were observed from stimulus-response pairs (Figure 1). Individual mean detection rates and the response times were calculated from the stimulus detection responses (i.e., detected and non-detected stimuli) to evaluate the detection task performance. Individual mean NDTs and effect coefficients (i.e., psychometric slopes) were calculated using linear regression models. The NDT was determined by the stimulus amplitude of the psychophysical curve with a detection probability of 0.5. The log-odds of stimulus detection ($ln\left(\frac{P_d}{1-P_d}\right)$) was modeled as a function of the intercept, amplitudes of the stimulus pulses (*PU1, PU2*$_{10}$*,* *PU2*$_{40}$), and the number of trials (*TRL*), as described in Wilkinson notation in Equation 1. Individual mean effect coefficients (i.e., psychometric slopes) on the detection probability were calculated.

$$ln\left(\frac{P_d}{1-P_d}\right) \sim 1 + PU1 + PU2_{10} + PU2_{40} + TRL \quad (1)$$

D. Neurophysiological Responses

Neurophysiological responses were observed from the EEG activity (Figure 2). EEG signals were preprocessed using the FieldTrip toolbox of MATLAB (version 2021b; The MathWorks Inc, Natick, Massachusetts, US). The data was filtered by a band-pass filter from 0.1 to 40 Hz. In response to each stimulus, a time window of -0.5 s to 1.0 s was extracted from the EEG signal. Eye movements and muscular artifacts were removed by using independent component analysis. The CPz-A1A2 derivation was chosen for analysis of stimulus-related EPs based on previous results [15]. The grand average, P2, and SNR was computed at CPz-A1A2 from detected and non-detected stimulus response pairs. The grand average was the mean of EEG signal from 450 trials (i.e., detected and non-detected stimuli). The P2 amplitude was defined by the maximum peak between 300 to 600 ms post-stimulus. The individual mean amplitude of the P2 peak was estimated for each measurement using a linear regression model, as

described in Wilkinson notation in Equation 2. The mean P2 amplitude was modeled as a function of the intercept, the amplitude of the stimulus pulses (*PU1, $PU2_{10}$, $PU2_{40}$*), the number of trials (*TRL*), and stimulus detection (*D*).

$$U_{EEG} \sim 1 + PU1 + PU2_{10} + PU2_{40} + TRL * D \quad (2)$$

The mean individual SNR was calculated by the individual mean P2 amplitude divided by the standard deviation of the mean EEG baseline signal (i.e., -0.5 to 0 s).

III. Results

Twenty-five patients with PSPS-T2 implanted with a spinal cord stimulator completed both measurements using the NDT-EP method. Two patients, one patient in each group, were excluded because of poor detection task performance (i.e., more than five percent false-positive stimulus detections) during both measurements. A total of twelve patients in the SCS-ON/ON group (8 males; 51.3 ± 5.5 years) and eleven in the SCS-OFF/ON group (5 males; 52.8 ± 7.7 years) were included for data analysis. The patient's NRS score in the SCS-ON/ON group was 3.4 ± 1.9 during the first measurement and decreased to 0.3 ± 0.9 during the second measurement. In the SCS-OFF/ON group, the NRS score was 4.0 ± 2.3 and decreased to 1.4 ± 1.3.

A. Psychophysical Responses

NDTs and the effect coefficients of the pulses on the detection probability are depicted in Figure 1. NDTs and the psychometric slopes were not significantly different between the first and second measurements in both groups.

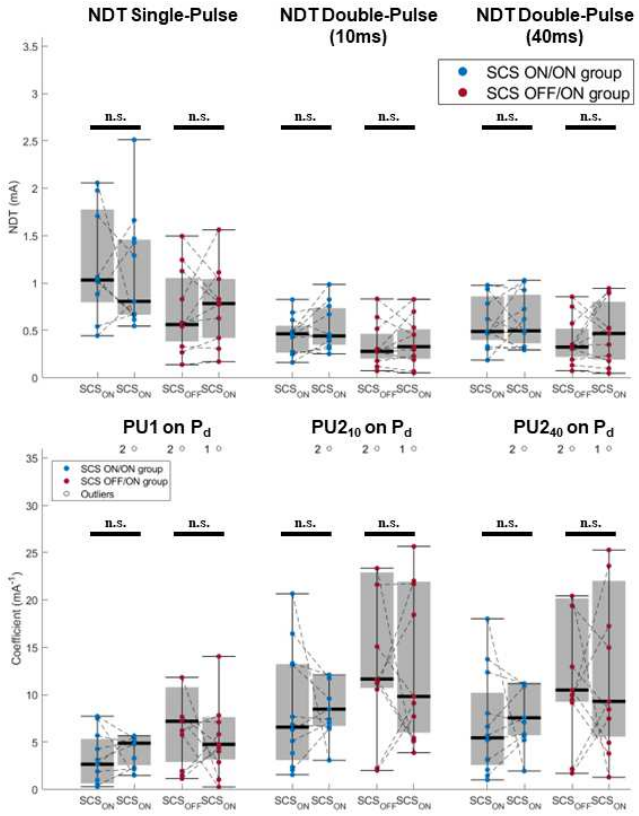

Figure 1. Individual mean NDTs and psychometric slopes from different stimulus types were estimated using linear regression models and tested not significant (n.s) between the first and second measurements using a two-sample t-test. Individual outliers were excluded before statistical testing.

B. Neurophysiological Responses

The grand average EP, the SNR of the P2 amplitude, and the individual mean amplitude of the P2 peak are shown in Figure 2. The grand average EP for detected stimuli was clearly observed in patients with PSPS-T2. The SNR and the P2 amplitude were not significantly different between the first and second measurement for both patient groups (Figure 2).

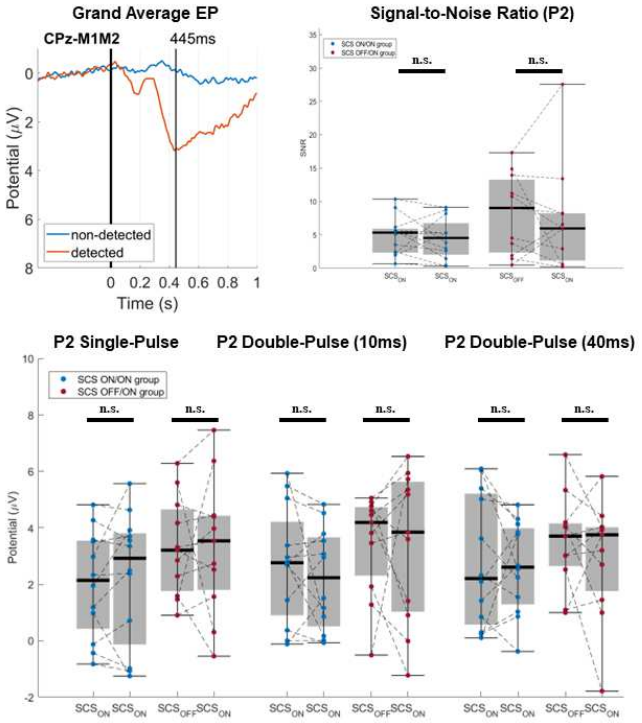

Figure 2. The grand average EP from all patients with PSPS-T2, with the signal-to-noise ratio, and mean amplitude of the individual P2 were estimated by linear regression. The outcomes tested not significant (n.s.) between the first and second measurements using a two-sample t-test.

IV. Discussion

This study explored the NDT-EP phenomena in response to IES on the hands of patients with PSPS-T2, who were treated with SCS for radiating limb pain. We evaluated whether the measurement of EPs was not obstructed by SCS artifacts during SCS and assessed whether the NDT-EP outcomes might be confounded by SCS effects outside the nociceptive system.

NDTs and slopes were estimated for each stimulus type performed on the dorsum of the hands in the SCS-ON/ON group (Figure 1). The increased variability in NDTs and slopes for single-pulse stimuli and its values for double-pulse stimuli were consistent with previous results in patients with PSPS-T2 on the dorsum of the hands [9]. Furthermore, the mean P2 amplitude and the SNR did not change between both measurements during SCS (Figure 2). The grand average, P2 amplitude, and latency are also in line with previous results from patients with PSPS-T2 [19,20]. These findings demonstrate that we measured EPs without the interference of SCS artifacts, which supports the potency for observation of nociceptive processing during SCS using the NDT-EP method [9,21].

We found that NDT-EP outcomes did not significantly change in response to IES at the hands of PSPS-T2 patients in the SCS-OFF/ON group (Figures 1 and 2). For example, paresthesia in response to tonic SCS could have influenced sensory perception [22], but it did not lead to changes in NDT-EP outcomes. Additionally, pain relief once SCS turned on could have affected the NDT-EP outcomes but was not observed. Current results suggest that possible confounding effects of SCS outside the nociceptive system did not interfere with the detection task performance. Therefore, this work permits further exploration of SCS modulating effects on NDT-EP outcomes by IES performed in the painful area of PSPS-T2 patients.

In future studies, the underlying (nociceptive) mechanisms responsible for altered NDT-EP outcomes in patients need to be understood. The influence of psychological factors (e.g., attention, learning effects) remains relevant to reduce as much as possible since it potentially affects the detection task performance and cortical responses. Exploring NDT-EP outcomes that provide mechanistic insights into nociceptive (dys)function and the modulating effects of SCS should lead to improved clinical patient outcomes.

V. Conclusion

This study explored NDT-EP phenomena in response to IES in the hands of patients with PSPS-T2 during SCS. The EPs were not obstructed by SCS artifacts. Furthermore, the NDT-EP outcomes did not significantly alter when SCS turned off and on. These results suggest that confounding SCS effects did not strongly influence the findings. Hence, this work highlights the need for further exploration of the cortical processing and conscious perception associated with SCS modulating effects in response to IES in the painful area of PSPS-T2 patients.

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