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Combined Evaluation of Nociceptive Detection Thresholds and Evoked Potentials during Conditioned Pain Modulation: A Feasibility Study

Niels Jansen, Ruben Dollen, Boudewijn van den Berg, Tom Berfelo, Imre P. Krabbenbos, Jan R. Buitenweg

Abstract— **Deficient top-down inhibitory control via diffuse noxious inhibitory control (DNIC) is a mechanism known to be responsible for the maintenance and development in several chronic pain syndromes. Experimentally, DNIC is often induced by conditioned pain modulation (CPM) paradigms such as a Cold Pressor Test (CPT). Recently, a method called the NDT-EP method has been developed with the aim to evaluate the nociceptive function, which it does via simultaneous tracking of nociceptive detection thresholds (NDT) and evoked potentials (EP). It remains to be investigated whether we can evaluate DNIC via the NDT-EP method. In this study, we take the first step to investigate this by evaluating the feasibility to combine the NDT-EP method with a 7 minutes CPT. In total 20 participants of a wide age-range were measured before, during, and after a CPT. All except 1 participant were able to complete the protocol, and enough stimulus-response pairs could be obtained for psychophysical as well as electrophysiological evaluation. Preliminary analysis of the NDT's and EP's showed results in line with earlier research such as a higher threshold for nociceptive stimuli and a lower EP amplitudes. Several NDT's of mostly elderly people (59±16 years), however, exceeded the maximum applicable stimulus strength during (7/20) or after (9/20) CPT and consequently had to be excluded from the analysis. To what extent this is a consequence of the CPT or other factors such as strong habituation associated more with elderly people, is subject to further investigation. In conclusion, the results of this study show that with the present protocol, it is feasible to combine the NDT-EP method with a CPM paradigm in almost all subjects, but that the NDT data of mostly older subjects could not be properly analyzed. Further directions for research and improvements are outlined.**

Clinical Relevance— **The results enable further research in both a clinical and research setting to investigate descending inhibitory mechanisms using the NDT-EP method.**

I. Introduction

Several different mechanisms of nociceptive central sensitization have been identified to contribute to the development and maintenance of chronic pain. One important mechanism is called Diffuse Noxious Inhibitory Control (DNIC), which inhibits nociceptive input from afferent fibers in a top-down manner and has a whole body effect [1]. A deficient DNIC has been observed in many different chronic pain syndromes, such as Fibromyalgia and Osteoarthritis [2]. Experimentally, DNIC can be activated by a conditioned pain modulation (CPM) paradigm. Most often the CPM paradigm is conducted by having the participant keeping an extremity (hand or foot) in a cold water bath (Cold Pressor Test, or CPT) for as long as the participant can tolerate. Subsequently, the efficiency of DNIC is then evaluated via psychophysical evaluations such as pain threshold measurements before and after the CPT. A higher pain threshold after CPM is interpreted as a result of DNIC being activated [3].

Pain threshold measurements, however, provide insights only at one point in time. For the evaluation of DNIC, continuous evaluation of the nociceptive system would be preferred as the activation of DNIC is strongest during the CPT and returns to baseline within about 5 minutes (or less) [3]. In addition, as DNIC is a top-down process, electrophysiological evaluation could provide further insights. It should be noted, however, that the extent to which these changes are related to DNIC is debated [4, 5]. Recently, our group has developed the NDT-EP method, which is able to measure nociceptive detection thresholds (NDTs) while simultaneously evaluating evoked potentials (EPs) to intra-epidermal electrical stimulation (IES) over time [6]. Furthermore, different stimulus types, such as a single (SP) and double pulse (DP) stimulus can be simultaneously tracked [7].

Combining the NDT-EP method with a CPM paradigm could enable an improved observation of DNIC efficiency. The response of the NDTs to a CPM paradigm has readily been evaluated in an earlier study by Doll et al [7] on young, healthy subjects. Here, mainly an effect of the SP stimuli was observed. Simultaneous observation of EP's during a CPM paradigm, however, is challenging as the maximum immersion times of participants can be short due to the pain tolerance threshold being reached, for instance two minutes or lower [8].

In this exploratory study, we evaluate the feasibility of combining the NDT-EP method with a CPM paradigm in a healthy population including a wide variety of ages. Psychophysical (thresholds, slopes and detection rates) as

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N. Jansen, B. van den Berg, T. Berfelo and J.R. Buitenweg are with the department of Biomedical Signals and Systems, Technical Medical Centre, University of Twente, Enschede, the Netherlands (e-mail: n.jansen@utwente.nl).

R. Dollen and I.P. Krabbenbos are with the Department of Anesthesiology, Intensive Care and Pain Medicine, St. Antonius Hospital, Nieuwegein, the Netherlands.

well as electrophysiological (signal-to-noise ratio (SNR), P2 amplitude) outcomes are explored and compared before, during and after CPT.

II. Methods

A. Subjects

In total 21 healthy, pain-free subjects were included in the study. One participant was excluded during the first measurement due to getting cramps during the CPT. This resulted in the inclusion of 11 females and 9 males, with a mean age of 41 (σ=20, ranging from 19-72). All included subjects were measured two times, approximately one week apart at St. Antonius Hospital Nieuwegein (the Netherlands). Only the first measurement is analyzed for this paper. Subjects were excluded, amongst others, in case they had a (1) medical history of chronic pain or any other disorders affecting the nociceptive system, (2) cardiac disease or (3) open wound at the foot to be immersed. Ethical approval for the experiments were obtained (MEC-U, NL71927.100.19) and experiments were conducted in accordance with the declaration of Helsinki.

B. Procedure

The IES-electrode for selective activation of intra-epidermal nociceptive (Aδ) fibers [9, 10] was placed on the dorsum of the dominant hand (15 right-handed). Two cathodic stimulus types were provided by a one-channel, current-controlled stimulator called the AmbuStim. A single-pulse (210 µs PW) and a double-pulse (210 µs PW, 10 ms IPI) stimulus were used for this study, which participants were familiarized with prior to initiating the experiment. Stimulus-response pairs (SRP) as well as EP's were evaluated before (80 SRP's per stimulus type), during (maximum of 7 minutes) and after (until 225 SRP's per stimulus types were obtained) CPM. Before putting the right foot in the cold water bath (µ=0.5°C, σ=0.8), subjects were instructed to put the same foot in a warm water bath for 2 minutes (µ=35.1°C, σ=0.7). During the cold water bath, a blood pressure cuff around the lower leg was applied and inflated 20 mmHg below diastolic blood pressure [11]. The cold water bath was manually recirculated every 3 minutes by the experimenter. During the experiment, participants were instructed to press the button on the stimulator and release the button as soon as a stimulus was perceived. Stimuli were selected in accordance to the method developed by Doll and colleagues [7]. EEG signals were obtained via a 64-channel EEG cap (10-20 system) from ANT Neuro Waveguard and recorded with a sampling frequency of 1000 Hz on a TMSi 72-channel Refa amplifier.

C. Nociceptive Detection Thresholds

The psychophysical data were analyzed per participant and per condition (pre-CPT, CPT, post-CPT) as within-subject measurements. Per measurement, the log-transformed individual thresholds (T_{SP}, T_{DP}) and slopes (S_{SP}, S_{DP}), as well as the detection rates (D_{SP}, D_{DP}) were determined via a generalized linear model (GLM). Measurements were excluded in case no threshold was tracked (evaluated via visual inspection wherein the measurements were randomized and the experimenter was blinded) or the result of the GLM was above (>1.6 mA) or below (<0 mA) the limits of the experiment. T_{SP} and T_{DP} were defined as the stimulus amplitude with a detection probability of 0.5. The effect of condition on these NDT outcome measures were evaluated via a linear mixed effects analysis.

D. Evoked Potentials

The electrophysiological data were also analyzed per participant and per condition as within-subject measurements. Preprocessing of the EEG signals was performed using FieldTrip [12] and subsequently analyzed using MATLAB (2019b). The signal was band-pass filtered (0.1-40 Hz) and a window was extracted 0.5s before and 1s after providing the stimulus. Baseline correction was performed based on the pre-stimulus signal. EOG and EMG artifacts were removed using independent component analysis. Grand average EP and the P2 latency (highest peak between 200-500ms) were extracted based on the CPz-A1A2 derivation [13, 14]. At the selected latency, the SNR was determined as well as, per stimulus type, the mean amplitude (µ) and standard deviation (σ) were determined. The effect of condition on these EP outcome measures were evaluated using a linear mixed effects model.

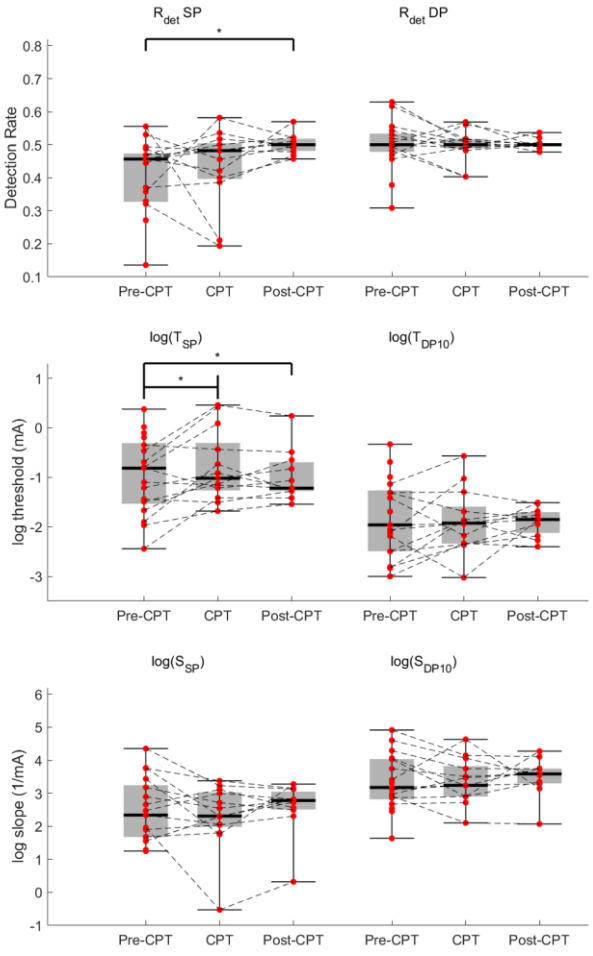

Figure 1. Detection rates (R_{det}), mean log-transformed thresholds (T) and log-transformed slopes (S) per condition (pre-, during- and post-CPT). Higher T_{SP}'s were found during- and post-CPT ($p<0.05$). The dotted line links the outcomes per phase per participant. Points without dotted line present excluded participants.

III. Results

A. Measurement Exclusion

Pre-CPT, 3 measurements were excluded, while during and post-CPT, respectively 7 and 9 measurements were excluded. All subjects who had a measurement excluded pre-CPT or during CPT, also had the measurements in the following phases excluded. The age of the group of subjects that were excluded before or during CPT (μ=59, σ=16) was significantly higher ($p<0.05$) than the group that had no measurements excluded or only post-CPT (μ=38, σ=18).

B. Nociceptive Detection Thresholds

In Figure 1, the detection rates (a), mean thresholds (b) and slopes (c) per stimulus type per condition are depicted. For the SP stimuli, higher mean thresholds can be observed during CPT ($p<0.05$) and post-CPT ($p<0.01$) as compared to pre-CPT. Simultaneously, post-CPT, the detection rates of the SP stimuli were significantly higher compared to pre-CPT. No significant differences were observed in the slopes for neither the SP nor the DP stimuli.

C. Evoked Potentials

In Figure 2, the grand average (a) of all participants from derivation CPz-A1A2 as well as the SNR (b) and per stimulus type the mean amplitude (c) of P2 are shown. No differences were found between the SNR. A statistically significant lower mean amplitude in response to the SP ($p<0.05$), but not to the DP stimuli, was found post-CPT.

IV. Discussion

In this feasibility study, we evaluated to what extent the NDT-EP method can be combined with a CPM paradigm for the evaluation of descending inhibitory control mechanisms. We did so by measuring before, during and after having participants undergo a CPT.

It was found that 20 out of 21 subjects were able to complete the procedure. In literature, immersion times differ greatly with some reporting no ceiling time [5, 15], while others report immersion times of 3 minutes and lower [3]. In general, females report lower immersion times as compared to men [8]. In this study, 11 out of the 20 participants were female, and the subjects' age ranged from 19-72. This enables us to conclude that we can, procedurally, combine the NDT-EP method with CPM in a population with a wide variety of ages and in both sexes. To what extent this procedure can also be performed in clinical populations with a dysfunctional nociceptive system, however, remains to be evaluated.

While all subjects were able to complete the procedure, a significant number of subjects was unable to track the provided stimuli during (7/20) and after CPT (9/20). An analysis on the subject's demographics showed that this phenomenon mostly occurred with people of older age. This is an undesired result as this hampers the applicability of this procedure in clinical research, given that the mean age of chronic pain patients is above 50 years old [16]. Based on the visual evaluation of the NDT's, it was observed that almost in all cases, only the SP stimuli, and not the DP stimuli, were

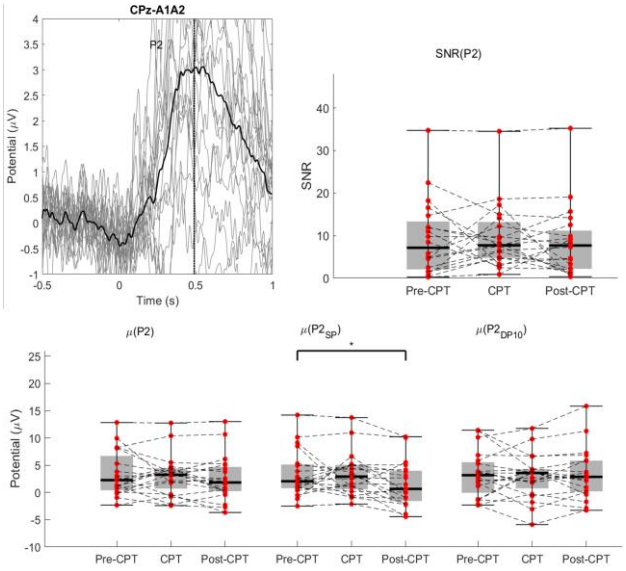

Figure 2. Grand average (CPz-A1A2) and SNR and mean amplitude pre-, during and post-CPT of P2 (490 ms latency post-stimulus). The mean amplitude and SNR were averaged per participant per condition. The mean P2 post-CPT to SP stimuli was found to be lower ($p<0.05$) as compared to pre-CPT.

responsible for this phenomenon. Due to the T_{SP} and T_{DP} being evaluated by the same GLM, both measurements were removed for the analysis. Given that the task performance of the DP stimuli was stable throughout all conditions in almost all subjects, the likely reason why the T_{SP} could no longer be tracked, is that it eventually exceeded the maximum applicable stimulation strength of 1.6 mA. Consequently, the actual effect of CPM on the SP and DP could not be evaluated effectively: possibly the thresholds of the subjects whose thresholds were most affected by DNIC were now excluded. For that reason, for future experiments with this procedure, a higher maximum stimulation is recommended at least for the SP stimuli. Furthermore, the effect of age on the NDT's should be investigated, as now it remains uncertain whether this phenomenon is a consequence of the CPT being applied, or that people of older age tend to habituate stronger to SP stimuli.

In the psychophysical data a higher T_{SP} was found during CPT and post-CPT as compared to before CPT (Figure 1). This finding is in line with the results of Doll and colleagues [7] and in line with the expectation that the thresholds would increase during and shortly after the CPT. To what extent this effect can be attributed to DNIC or to habituation, cannot be evaluated with the present experimental design.

In the electrophysiological data, we found the mean P2 amplitude to SP data to be significantly lower post-CPT (Figure 2). This finding is also in line with earlier research, wherein lower EP amplitudes were reported during a CPM paradigm [5]. At present, it is debated whether this is a biomarker of DNIC efficiency, or just habituation to the stimulus [4, 17]. Evaluation of the EEG data with analyses of more statistical power such as an LMM [18] could be helpful in evaluating the influence of the individual stimulus

parameters to the signal. In addition, for both the psychophysical as well as the electrophysiological data, future research with a control CPM paradigm could shed light as to whether the effects that we measure are related to DNIC or more to habituation.

V. Conclusion

The present study shows that procedurally, the NDT-EP method can be successfully combined with a CPM paradigm in almost all subjects. In mostly older subjects, the NDT's could however not be properly analyzed. Directions for future research and improvements to the NDT-EP method are outlined. These results enable future research in both a research and clinical setting to investigate descending inhibitory mechanisms with the NDT-EP method.

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