The Relationship between Nociceptive Detection Thresholds and Pressure- and Electrical Pain Thresholds: An Explorative Study in Rheumatoid Arthritis Patients

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Abstract — **Recently, methods have been developed enabling the characterization of the nociceptive function at the detection threshold level by measuring nociceptive detection thresholds (NDTs), rather than at the level of the pain threshold via pain threshold (PT) measurements. Both NDT and PT measurements aim to characterize (parts of) the nociceptive system. To date it is unclear if, and if so to what extent, the two outcomes relate to one another. In this study, the primary aim is to explore the relationship between the two measures in patients with rheumatoid arthritis (RA). As secondary aim, we explore differences in NDT between these RA patients with age- and sex-matched healthy controls (HC) from a readily existing dataset. In total 46 RA patients have been recruited, whereby the pressure- (PPT; bilaterally at two locations) and electrical (EPT) pain threshold were evaluated, as well as the NDTs. Significant, positive correlations were found between the EPT and PPT (R=0.54-0.60), but not with the NDTs (R≤0.25). As compared to HC, higher NDTs were found in the RA group. As the presence of a statistically significant weak relationship can only be evaluated using a larger sample size, our results indicate that there is no moderate or stronger relation between PT and NDT outcomes. This implicates that the two outcomes are not strongly driven by the same (nociceptive) mechanism(s). Future research into NDTs and what factors and/or mechanisms affect the outcome, could yield relevant insights into how to use and interpret the results of this relatively new method.**

Clinical Relevance — **The evaluation of nociceptive detection thresholds, in isolation or together with conventionally evaluated pain thresholds, might provide valuable and complementary insights into nociceptive (dis)function in man.**

I. Introduction

Pain threshold (PT) measurements can be conducted using a variety of tools with different modalities (e.g. pressure, thermal or electrical), and are widely-used within pain research to characterize the nociceptive system in an experimental and clinical setting, in patients and in healthy subjects. With these methods, differences in PTs are observed in various chronic pain syndromes such as osteoarthritis [1] and temporomandibular disorders [2]. Moreover, amongst others, PT measurements have been shown useful in identifying responders to medication such as pregabalin [3], as well as to pre-operatively identify patients at risk of having persistent pain after surgery [4]. While these observations indicate that PT measurements reflect variations in nociceptive (dis)function, PTs are also found to vary dependent on, amongst others, expectations [5], values [6] and social context [7]. This might, at least in part, be caused by pain being a subjective and unpleasurable experience, of which the concept is learned through life experience [8].

More recently, methods have been developed able to selectively activate the nociceptive system, which enables researchers to characterize the nociceptive system already at detection threshold levels (nociceptive detection thresholds, or NDTs), rather than at the level of the pain threshold. Selective activation of nociceptive fibers can be reliably achieved [9] using, amongst others, intraepidermal electrical stimulation (IES). By stimulating the cutaneous nociceptive fibers with single- (SP) and/or double- (DP) pulse, the peripheral and/or central sensitivity of the nociceptive function are probed [10]. NDTs have been evaluated and often also shown effects in multiple studies in which human pain models are used, such as capcaisin [11], lidocaine [12], sleep deprivation [13], a cold pressor test (CPT) [14] and high frequency stimulation (HFS) [15]. Lately, NDTs have also been successfully evaluated in a clinical setting such as in patients with small fiber neuropathy [16], (painful) diabetic neuropathy [17], failed back surgery syndrome [18], or neuropathic pain [19], whereby often higher NDTs were observed in the patient groups. These findings indicate that NDTs can measure characteristics of the nociceptive system, of which it is at present unknown to what extent these characteristics are relevant for the development and maintenance of chronic pain syndromes.

In the above-referenced studies, compared to studies with a similar design and subject group yet performed with PT measurements instead of NDTs, different results in terms of effect size and direction of the effect are observed. These observations raise the question to what extent NDT and PT measurements – both which are methods expected to characterize the nociceptive system – relate to one another. In this study, the primary aim is to explore the relation between NDTs and PT measurements with an electrical and pressure modality. These measurements are conducted in patients with rheumatoid arthritis (RA) in which various pain generating mechanisms (peripheral and/or central) can be expected to be present in different intensities. As secondary aim, differences in outcome between the RA patients with age- and sex-matched healthy controls are explored.

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II. METHOD

The data obtained for this study is part of a larger study, which has been approved by the Medical Research Ethics Committee United (MEC-U, reference number: NL73282.100.20). Prior to the experiment, the participants received written information and signed an informed consent.

A. Subjects

Rheumatoid Arthritis. In total 46 patients have been included from the Rheumatology Department of the Medical Spectrum Twente (MST) hospital (Enschede, The Netherlands). All patients have been diagnosed with RA with an average disease duration of 11.4 (±7.7) years. Subjects were excluded from participation if the patient was also diagnosed with diabetes mellitus or arthritis psoriatica, or in the case the patient had an implanted stimulation device, was pregnant, or was unable to understand the verbal instructions provided during the experiment. The mean age of the group was 57.7 (±11.7), with in total 18 (39%) subjects being male.

Healthy Controls. Using a readily existing dataset of healthy subjects (N=64) which were measured and recruited at the St. Antonius Hospital (Nieuwegein, the Netherlands), each patient was age- and sex matched to a healthy control subject not already selected with the same sex and the closest age. This resulted in a group of 46 healthy control subjects with a mean age of 53.0 (±12.7), with a total of 18 (39%) being male.

B. Procedure

Rheumatoid Arthritis. After the PT measurements, the NDT measurement was performed. For the PT measurements, the applied stimulus strengths which subjects indicated to perceive as annoying were noted. Three subsequent attempts were performed and averaged into one final outcome. For the pressure PT (PPT), a battery-powered, handheld algometer (Algometer type II, SBMedic Electronics) was used with a 1 cm^2 probe and a pressure increase of 50 kPa/s. PPTs were evaluated bilaterally at both the supraspinatus muscle and at the lateral epicondyle [20]. For the electrical PT (EPT), a handheld stimulator with a constant current generator (AmbuStim PT, University of Twente) was used to produce square-wave pulses of 100 Hz with a width of 210 ms. The current increased with 0.3 mA/s until a maximum current of 20 mA, and measurements were performed on the intermediate part of the right deltoid muscle using patch electrodes (Red Dot 2560, 3M). For the NDT measurements, nociceptive-selective stimuli are provided by intraepidermal electrical stimulation using custom-built electrodes containing 5 micro-needles (IES-5) placed on the dorsum of the right hand. The square-wave pulses are generated using a hand-held stimulator (AmbuStim PT, University of Twente, Enschede) with a constant current generator. Detection thresholds to two different stimulus types were tracked simultaneously [see also 10]: a single, 210 us pulse (SP) and a double-pulse (DP) in which 10 ms inter-pulse interval (IPI) was used, for which the pulse-width for both pulses was 210 us. Prior to initiating the tracking task, participants were familiarized with the stimuli by to pressing the button (resulting in a stimuli of increasingly higher stimulus strength

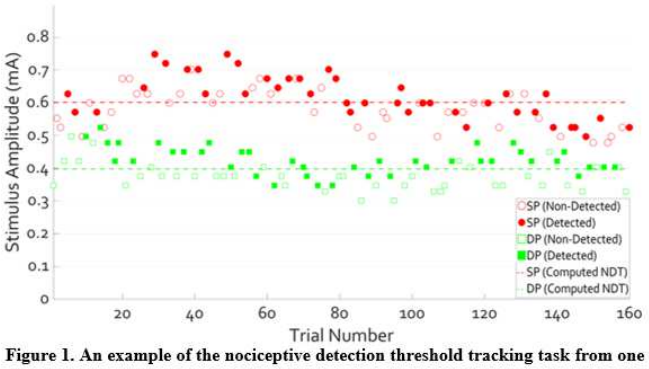

Figure 1. An example of the nociceptive detection threshold tracking task from one measurement with an RA patient. Here it can be observed how single- (SP; red circles) and double (DP; green squares) pulse stimuli are tracked over time. The filled symbols represent detected stimuli; unfilled symbols present undetected stimuli. Using a general linear model, one nociceptive detection threshold (NDT) per stimulus type is computed for the measurement, which is represented as the dashed horizontal line.

with a step size of 0.025 mA) until the stimulus was clearly perceived. Thereafter, per stimulus type, the starting stimulation strength was determined by asking participants to press and hold the button until a stimulus was perceived for the first time. During the experiment, subjects were asked to press and hold the button until a stimulus was perceived (button released within 1000 ms after stimulus application) until 80 stimulus-response-pairs (stimuli per stimulus type; SRPs) per subject were provided. Stimulus amplitudes were selected based on an adaptive staircase method [21].

Healthy Control Subjects. Only NDT measurements were conducted in this group. Most of the procedures were identical to the procedures followed with the RA patients, but there are some notable differences. First, two measurements were performed in one session, once on both hands in a randomized order. Second, one additional stimulus type was simultaneously tracked: a DP stimulus with 40 ms IPI. Third, a measurement was finished when 150 stimuli SRP's were obtained. Fourth, neurophysiological responses were simultaneously tracked using electroencephalography (EEG). Fifth, the maximal applicable stimulus strength was 1.6 mA. Sixth, the measurements were performed in a different location and by a different experimenter.

C. Statistical Analysis

The relationship between the NDT and EPT/PPT was evaluated by a two-tailed Pearson correlation. NDTs and slopes were calculated per subject using the model coefficients of the below generalized linear model. The model quantifies the effect of the first (PU1) and second (PU2) pulse, and the trial number (TRL) on log-odds of stimulus detection.

$$\ln\left(\frac{P}{1-P}\right) \sim 1 + PU1 + PU2 + TRL$$

Between-group differences were evaluated using an independent samples t-test. For all analyses, measurements were excluded in case the calculated NDT was below the experimental minimum (0 mA). For the comparison between the RA and HC subjects, measurements were also excluded if the calculated NDT was above the experimental maximum (1.6 mA). From the HC measurements, data only from the first 80 SRPs of the SP- and DP stimuli (10 ms IPI) were selected. Moreover, the measurement from the age- and sex-

matched HC subject was selected to match the handedness (dominant or non-dominant) of the RA patient.

III. Results

A. Correlation Coefficients

Multiple statistically significant correlations were observed, of which all with a $p<0.0001$. Strong, positive correlations were observed between the EPT and the PPT performed at both the supraspinatus muscle (0.54) and lateral epicondyle (0.60). Further strong and positive correlations were found between the computed SP and DP thresholds (0.74) and slopes (0.77). Strong negative correlations were found between the DP slope and the SP- (-0.65) and DP thresholds (-0.58), and between the SP slope and the SP threshold (-0.57). No statistically significant correlations were found between the EPT or PPT with any of the outcome measures of the nociceptive detection threshold tracking task. In Table 1, all correlation coefficients can be observed.

Table 1. Correlation Matrix between the PPT and EPT, and the psychophysical outcomes (NDTs and slopes) of the nociceptive detection threshold tracking task to single- (SP) and double- (DP) pulse stimuli. Correlation coefficients made bold are statistically significant with a $p<0.0001$. Sup = Supraspinatus; Epi = Epicondyle.

		EPT	PPT		NDT		Slope	
			Sup	Epi	SP	DP	SP	DP
EPT		-	**.54**	**.60**	-.04	-.11	.03	.12
PPT	Sup	**.54**	-	**.69**	.22	.25	.08	.03
	Epi	**.60**	**.69**	-	.07	.10	-.02	.10
NDT	SP	-.04	.22	.07	-	**.74**	**-.57**	**-.65**
	DP	-.11	.25	.10	**.74**	-	-.21	**-.58**
Slopes	SP	.03	.08	-.02	**-.57**	-.21	-	**.77**
	DP	.12	.03	.10	**-.65**	**-.58**	**.77**	-

B. Comparison with age- and sex-matched HC

Significant higher NDTs were observed in RA patients as compared with the HC subjects for both the SP ($p<0.001$; RA = 0.79 ± 0.36; HC = 0.42 ± 0.28) and DP ($p = 0.02$; RA = 0.42 ± 0.25; HC = 0.28 ± 0.25) stimuli. Significant lower slopes were found in RA patients as compared to HC subjects for only the SP stimuli ($p<0.02$; RA = 7.9 ± 4.9; HC= 14.9 ± 19.2). In Figure 2, the NDT's (Figure 2A) and slopes (Figure 2B) per stimulus group and per group can be found.

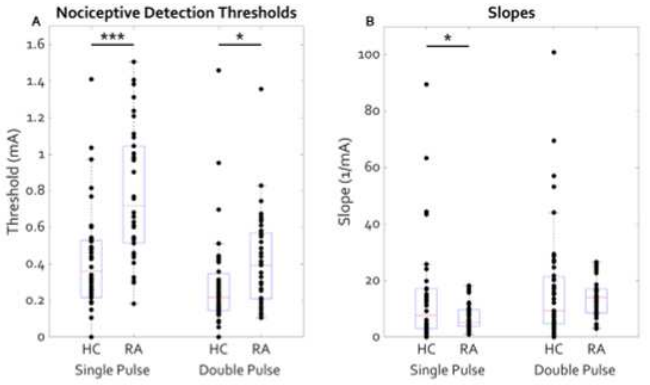

Figure 2. Exploration of differences between RA and age- and sex matched HC subjects in NDTs and Slopes. In panel A, the NDTs of both groups are shown. In panel B, the slopes of both groups are shown. On the left of each panel the responses to single-pulse stimuli are shown; on the right the responses to double-pulse stimuli.

IV. Discussion

In this study the primary goal was to evaluate the relationship between the PT and NDT in RA patients. As a secondary goal we explored differences in psychophysical outcomes between the RA patients and age-, sex- and handedness-matched HC subjects.

A. Relation between PTs and NDTs

No significant correlations have been observed between the psychophysical outcomes of the nociceptive detection threshold tracking task (NDT and slope) of any stimulus type (SP and DP) and the PPT measured at the lateral epicondyle or supraspinatus muscle, or the EPT. While this study did thus not find any relation between the psychophysical outcomes of the NDT and EPT/PPT measurements, the number of included participants only provides sufficient power to find statistically significant relations of moderate or stronger effects. As such, a weak relationship might still be present but which could not be adequately assessed given the sample size of the present study.

Only in the case the outcomes the NDT as well as the outcomes of the EPT/PPT measurement would be strongly driven by the same underlying (nociceptive) mechanism(s), could a moderate or strong relationship have been expected. For instance, such a relationship could be expected and is also found between the two pain threshold measurements in this study. Not finding a (moderate or stronger) relation between the NDT and EPT/PPT measurements, thereby indicates that the two outcomes are not strongly driven by the same (nociceptive) mechanism(s). This observation might provide opportunity, as it could implicate that the two measurements provide complementary insights into the characteristics of the nociceptive system. Simultaneously however, this observation raises questions as to which (nociceptive) mechanism(s) predominantly drive the outcome of NDT and EPT/PPT measurements.

For NDT measurements it is at present largely unknown what (nociceptive) mechanisms affect the outcome of the measurement. This is in contrast to PT measurements, which – upon strictly following a test protocol – are widely thought to predominantly reflect characteristics of nociceptive (dis)function that are relevant for the development and maintenance of chronic pain syndromes [22]. In multiple studies which have evaluated NDTs, interesting and relevant results using pain models [11-15, 23] or patient groups [16-19, 24] are obtained, but few studies have yet evaluated factors affecting the NDT outcomes. One factor which is well-known to affect the outcomes of NDT measurements, is the electrocutaneous interface [25]. In fact, many of the cited studies use pain models which affect the integrity (e.g., capcaisin) or functioning (e.g., lidocaine) of the cutaneous nociceptive fibers, or have included patient groups in which the peripheral nociceptive fibers are affected [11, 12, 16, 17, 19]. As such, these studies provide evidence for NDTs to be sensitive to peripheral mechanisms. Other studies with pain models which are thought to act predominantly on central nociceptive processes (e.g. sleep deprivation, CPT or HFS) [13-15, 23] or whereby patient groups are included where peripheral nociceptive disfunction can largely be excluded

[18, 24], suggest that NDT outcomes are also sensitive to changes in central nociceptive functioning. Recently, it was found that the NDT can be affected by criterium formation, with some stimulus types being more sensitive than others [26]. Lastly, it is thought – but not yet evaluated – that NDTs are affected by factors such as the level of attention and internal noise. Performing research on which factors affect the psychophysical responses to nociceptive-selective stimuli could yield relevant insights into this relatively new method.

B. Exploration of NDT Differences between RA and HC

As compared to age- and sex matched HC, in RA patients we observed higher NDTs to both single- and double pulse stimuli, and lower slopes to SP stimuli. Other studies in patient groups with the same method have been able to make similar observations, yet with a lower slope in response to both the single- and double pulse stimuli [17, 18]. While more research is required to understand these differences, factors which are known to contribute differentially to the SP slope as compared to the DP slope, are the peripheral- and central sensitivity of the nociceptive function [10], as well as the internal criterion [26]. As such, it is recommended that future research not only evaluates what factors affect the outcome of NDT measurements, but also whether identified factors might affect NDTs of different stimulus types differently. Overall, the observations in the present study implicate that measuring NDTs is feasible in RA patients, and that the outcomes could be useful in observing altered nociceptive processing.

V. Conclusion

The (electrical and pressure) pain threshold and the nociceptive detection threshold, both outcome measures with the aim of characterizing the nociceptive system, do not show a moderate or stronger relationship. Further research into NDTs and what factors and/or mechanisms affect the outcome, could yield relevant insights into how to use and interpret the results of this relatively new method.

References

[1] C. Fingleton, *et al.*, "Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis," *Osteoarthritis Cartilage,* vol. 23, no. 7, pp. 1043-56, 2015.

[2] R. La Touche, *et al.*, "Evidence for Central Sensitization in Patients with Temporomandibular Disorders: A Systematic Review and Meta-analysis of Observational Studies," *Pain Pract,* vol. 18, no. 3, pp. 388-409, Mar 2018.

[3] S. S. Olesen, *et al.*, "Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis," *PLoS One,* vol. 8, no. 3, p. e57963, 2013.

[4] A. Wright, *et al.*, "Abnormal quantitative sensory testing is associated with persistent pain one year after TKA," *Clin Orthop Relat Res,* vol. 473, no. 1, pp. 246-54, Jan 2015.

[5] K. J. Peerdeman, *et al.*, "An integrative review of the influence of expectancies on pain," *Frontiers in Psychology,* vol. 7, p. 1270, 2016.

[6] O. Alabas, *et al.*, "Gender role affects experimental pain responses: a systematic review with meta-analysis," *European journal of pain,* vol. 16, no. 9, pp. 1211-1223, 2012.

[7] C. Krahé, *et al.*, "The social modulation of pain: others as predictive signals of salience–a systematic review," *Frontiers in human neuroscience,* vol. 7, p. 386, 2013.

[8] S. N. Raja, *et al.*, "The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises," *Pain,* vol. 161, no. 9, pp. 1976-1982, 2020.

[9] A. Mouraux, *et al.*, "Low intensity intra-epidermal electrical stimulation can activate Adelta-nociceptors selectively," *Pain,* vol. 150, no. 1, pp. 199-207, Jul 2010.

[10] R. J. Doll, *et al.*, "Effect of temporal stimulus properties on the nociceptive detection probability using intra-epidermal electrical stimulation," *Exp Brain Res,* vol. 234, no. 1, pp. 219-27, Jan 2016.

[11] R. J. Doll, *et al.*, "Responsiveness of electrical nociceptive detection thresholds to capsaicin (8 %)-induced changes in nociceptive processing," *Exp Brain Res,* vol. 234, no. 9, pp. 2505-14, Sep 2016.

[12] M. Kodaira, *et al.*, "Evaluation of nociceptive Adelta- and C-fiber dysfunction with lidocaine using intraepidermal electrical stimulation," *Clin Neurophysiol,* vol. 125, no. 9, pp. 1870-7, Sep 2014.

[13] B. van den Berg, *et al.*, "Simultaneous measurement of intra-epidermal electric detection thresholds and evoked potentials for observation of nociceptive processing following sleep deprivation," *Experimental brain research,* vol. 240, no. 2, pp. 631-649, 2022.

[14] N. Jansen, *et al.*, "Combined Evaluation of Nociceptive Detection Thresholds and Evoked Potentials during Conditioned Pain Modulation: A Feasibility Study," in *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, 2021: IEEE, pp. 1427-1430.

[15] J. Biurrun Manresa, *et al.*, "High frequency electrical stimulation induces a long-lasting enhancement of event-related potentials but does not change the perception elicited by intra-epidermal electrical stimuli delivered to the area of increased mechanical pinprick sensitivity," *PLoS One,* vol. 13, no. 9, p. e0203365, 2018.

[16] D. Mueller, *et al.*, "Electrically evoked nociceptive potentials for early detection of diabetic small-fiber neuropathy," *European journal of neurology,* vol. 17, no. 6, pp. 834-841, 2010.

[17] T. Berfelo, *et al.*, "Exploring Nociceptive Detection Thresholds Combined with Evoked Potentials in Patients with Diabetes Mellitus," in *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, 2021: IEEE, pp. 1358-1361.

[18] B. van den Berg, *et al.*, "Combining psychophysical and EEG biomarkers for improved observation of altered nociceptive processing in failed back surgery syndrome," in *2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*, 2021: IEEE, pp. 174-177.

[19] S. Omori, *et al.*, "Pain-related evoked potentials after intraepidermal electrical stimulation to Aδ and C fibers in patients with neuropathic pain," *Neuroscience research,* vol. 121, pp. 43-48, 2017.

[20] M. Lofgren, *et al.*, "Pain sensitivity at rest and during muscle contraction in persons with rheumatoid arthritis: a substudy within the Physical Activity in Rheumatoid Arthritis 2010 study," *Arthritis Res Ther,* vol. 20, no. 1, p. 48, Mar 15 2018.

[21] R. J. Doll, *et al.*, "Observation of time-dependent psychophysical functions and accounting for threshold drifts," *Attention, Perception, Psychophysics,* vol. 77, pp. 1440-1447, 2015.

[22] L. Arendt-Nielsen, *et al.*, "Assessment and manifestation of central sensitisation across different chronic pain conditions," *Eur J Pain,* vol. 22, no. 2, pp. 216-241, 2018.

[23] R. J. Doll, *et al.*, "Tracking of nociceptive thresholds using adaptive psychophysical methods," *Behav Res Methods,* vol. 46, no. 1, pp. 55-66, Mar 2014.

[24] T. Berfelo, *et al.*, "Observing Altered Nociceptive Detection Thresholds in Patients With Persistent Spinal Pain Syndrome Type 2 With a Dorsal Root Ganglion Stimulator," *Neuromodulation: Technology at the Neural Interface,* 2022.

[25] A. H. Poulsen, *et al.*, "Comparison of existing electrode designs for preferential activation of cutaneous nociceptors," *Journal of Neural Engineering,* 2020.

[26] B. van den Berg, *et al.*, "Observation of nociceptive detection thresholds and cortical evoked potentials: Go/no-go versus two-interval forced choice," *Attention, Perception, & Psychophysics,* vol. 84, no. 4, pp. 1359-1369, 2022.