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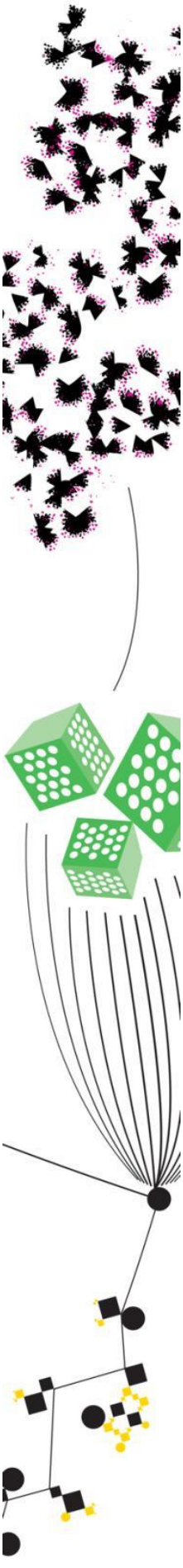

The feasibility of measuring nociceptive detection thresholds and electrical brain responses during spinal cord stimulation while electrical stimuli are applied to the foot dorsa

An explorative study in patients with persistent spinal pain syndrome type 2

M.L. Nelissen
March 2023

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A thesis submitted to the University of Twente in partial fulfilment of the requirements for the degree of

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By

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Voorwoord

Daar ligt ‘ie dan: mijn master thesis. De afgelopen jaren heb ik erg veel geleerd en heb ik de kans gekregen om zowel op professioneel als persoonlijk vlak te groeien. Als sluitstuk van de opleiding Technische Geneeskunde, heb ik het afgelopen jaar de mogelijkheid gekregen om mee te helpen aan het exploreren van een potentiële meetmethode voor het verkrijgen van nieuwe inzichten in het nociceptieve systeem op de afdeling Anesthesiologie en Pijnbestrijding in het St. Antonius ziekenhuis. Ik heb veel kunnen en mogen leren en heb me zo verder kunnen ontwikkelen tot de technisch geneeskundige die ik wil zijn. Hiervoor wil ik graag mijn dankbaarheid uitspreken naar de mensen die mij de afgelopen tijd hebben gesteund en met wie ik heb samen mogen werken.

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Marit
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Abstract

Introduction: Chronic pain is a significant, global issue, and neuroplastic alterations underlying chronic pain are difficult to identify due to a lack of methods adequately measuring neurophysiological processes. This potentially hinders the development and limits the effect of treatment methods such as spinal cord stimulation (SCS). Recently, a method was developed to observe nociceptive processing mechanisms using nociceptive detection thresholds (NDTs) and evoked potentials (EPs) after intra-epidermal electrical stimulation (IES). This method has been studied in several patient populations including patients with persistent spinal pain syndrome type 2 (PSPS-T2), with promising results showing differences between healthy individuals and chronic pain patients. Preliminary results in PSPS-T2 patients treated by SCS indicated that applying stimuli to the foot dorsa could be the next step in the development of the NDT-EP method and the exploration of effects of SCS, as the feet are usually affected by PSPS-T2. However, it is unclear whether nociceptive processes can also be measured during SCS when stimuli are applied to an area that is affected by SCS.

Research aim: to investigate feasibility of the NDT-EP method and stimulus application to the foot dorsa during SCS in PSPS-T2 patients, and further explore effects of SCS on NDTs and EPs.

Methods: Twenty-three PSPS-T2 patients (11 male, 54.9 $\pm$ 8.6 years old) who were effectively treated by SCS ($\geq$50% pain reduction) were included and randomised over two trial arms. Twelve patients (5 male, 55.9 $\pm$ 8.8 years old) underwent 'SCS-OFF vs SCS-ON' protocol, in which two NDT-EP measurements were performed with SCS turned off (SCS-OFF), followed by two NDT-EP measurements with SCS turned on (SCS-ON). Eleven patients (6 male, 53.7 $\pm$ 8.7 years old) underwent 'SCS-ON1 vs SCS-ON2' protocol, in which four measurements were performed during SCS-ON. During each measurement, 3 stimulus types were applied to the foot dorsum of either the affected or unaffected side: single pulse (SP), double pulse with a 10 ms inter-pulse interval (IPI) (DP10), and double pulse with a 40 ms IPI (DP40). Individual NDTs and slopes of the psychophysical curves were determined using a generalised linear model (GLM), and P2 and N1 amplitudes were analysed from a central (Cz-M1,M2) and a contralateral (T7-F4) EEG derivation, respectively.

Results: 87 measurements were performed, of which 56 were deemed acceptable based on GLM fit, 67 based on signal-to-noise ratio (SNR) of P2, and 70 based on SNR of N1. EPs were identified in nearly all measurements used in respective EP analyses. After selection of adequate task performance (detection rate > 30%, false positive rate < 5%), 52 measurements were selected for NDT analysis, 52 for P2 analysis, and 53 for N1 analysis. NDTs and P2 amplitudes during SCS-OFF seemed higher on the unaffected side than the affected side, and were more similar during SCS-ON. N1 amplitudes were similar during SCS-OFF and SCS-ON, and seemed to present higher amplitudes on the affected side. When compared to healthy controls (HCs), SCS-ON seemingly showed slightly higher NDTs and N1 amplitudes. Generally, thresholds and slopes for SP stimuli seemed respectively higher and less steep than those of double pulse stimulus types.

Conclusion: The NDT-EP method with stimulus application to the foot dorsa seems practically feasible, but technical feasibility is slightly questionable, due to great variability in detection rates and signal-to-noise ratios, occasionally high false positive rates, and the number of incorrectly fitted GLMs. Findings regarding NDTs on the affected and unaffected sides contradict those of previous work. It is recommended to investigate why task performance of SP stimuli is generally lower than both double pulse stimuli.

Keywords: *Chronic Pain, Persistent Spinal Pain Syndrome type 2, Spinal Cord Stimulation, Nociception, Nociceptive Detection Threshold, Evoked Potential*

Contents

List of abbreviations

AC	Anticonvulsant
AD	Antidepressant
BMI	Body mass index
BSS	Biomedical signals and systems
CIPN	Chemotherapy induced peripheral neuropathy
CSI	Central sensitisation questionnaire
CSS	Central sensitisation syndromes
DM	Diabetes mellitus
DP10	Double pulse with a 10 ms inter-pulse interval
DP40	Double pulse with a 40 ms inter-pulse interval
DR	Detection rate
DRG	Dorsal root ganglion
EEG	Electroencephalography
EP	Evoked potential
FPR	False positive rate
GFP	Global field power
GLM	Generalized linear model
(G)LMM	(Generalized) linear mixed model
HC	Healthy control
HRQoL	Health-related quality of life
IASP	International Association for the Study of Pain
ICA	Independent component analysis
IES	Intra-epidermal electrical stimulation
IPI	Inter-pulse interval
ITDD	Intrathecal drug delivery
MPQ	McGill pain questionnaire
MTT	Multi-threshold tracking
NDT	Nociceptive detection threshold
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
ODI	Oswestry disability index
OP	Opioid
PDPN	Painful diabetic polyneuropathy
PSPS-T2	Persistent spinal pain syndrome type 2
QST	Quantitative sensory testing
RT	Response time
SCS	Spinal cord stimulation
SFN	Small fibre neuropathy
SNR	Signal-to-noise ratio
SP	Single pulse
SSEP	Somatosensory evoked potential

1 Introduction

Chronic pain is a global health issue, affecting roughly one in five adults in Europe[1]. In the Netherlands, over two million people are estimated to suffer from moderate-to-severe chronic pain[1,2]. It negatively impacts both quality of life and the socioeconomic burden of chronic pain patients and society in general[3,4]. Additionally, up to 79% of chronic pain patients in the Netherlands perceive their treatment as inadequate[2]. This percentage emphasizes the difficulty of treatment, due to the poor understanding of mechanisms underlying chronic pain and of the nociceptive system[5].

While much is still unknown about the mechanisms of chronic pain, central sensitisation is considered to be one of the mechanisms involved in chronic pain syndromes[6]. Central sensitisation is a form of maladaptive neuroplasticity characterized by a hypersensitivity for noxious stimuli (hyperalgesia) and a painful response to non-noxious stimuli (allodynia)[7,8]. One chronic pain syndrome that is associated with central sensitisation, is persistent spinal pain syndrome type 2 (PSPS-T2)[6]. The term PSPS-T2 is used to describe patients with persistent or recurring chronic pain following spinal surgery[9]. Its pathophysiology is complex and both neuropathic and nociceptive pain components are involved[10]. Management of PSPS-T2 is often multidisciplinary but remains challenging with varying success rates[11]. One treatment method for PSPS-T2 patients that seems promising is spinal cord stimulation (SCS)[12]. However, the success of SCS is limited, which is partly attributed to the poor understanding of its analgesic mechanisms[12,13].

More insight into the underlying pathophysiology of PSPS-T2 may be valuable to guide methods of treatments, like SCS. Adequate assessment of the neurophysiological processes underlying chronic pain might provide that insight. Current tools to evaluate pain include the numerical rating scale (NRS) score, the central sensitisation questionnaire (CSI)[14] and the McGill pain questionnaire (MPQ)[15]. These tools mainly rely on subjective assessment however, and do not provide insight into the neurophysiological processes underlying chronic pain. In addition to the current evaluation tools, quantitative sensory testing (QST) methods are commonly used in research to assess nociceptive processing via pain thresholds, among others[16]. However, pain thresholds measured with QST methods can be influenced by patient- and observer-related factors[17,18].

A new method was proposed to provide a psychophysical measure for nociceptive processing[19]. This new method may provide a more objective, supplemental measurement to gain insight into nociceptive processing in those with and without chronic pain. This method combines nociceptive detection threshold (NDT) analysis and evoked potentials (EPs), derived from electroencephalography (EEG) recordings, and is therefore called the NDT-EP method[19,20]. NDTs are analysed through intra-epidermal electrical stimulation (IES) of nociceptive Aδ-fibres with varying stimulus properties. By tracking a subject's response in combination with information about the stimulus properties, the NDT can be estimated with a generalized linear mixed model (GLMM). The NDT measurements are combined with EEG recordings to increase objectivity[20].

The NDT-EP method has been studied in several patient populations, for instance, healthy and pain-free individuals, PSPS-T2 patients and patients with painful diabetic polyneuropathy (PDPN)[20–22]. Preliminary results indicated that the altered behaviour of NDTs and EPs in chronic pain patients compared to healthy, pain-free individuals could help identify chronic pain patients[21,22]. More recently, the NDT-EP method was applied to PSPS-T2 patients implanted with SCS[23]. Preliminary results showed that the NDT-EP method seemed feasible with stimuli applied to the hand, and no differences were observed between the situations where the stimulator was turned off and where it was turned on[23]. This led to a preliminary, tentative conclusion that SCS does not seem to influence outcomes of the NDT-EP method in other manners than through nociceptive processing.

The question arose whether nociceptive processes can also be measured during SCS when stimuli are applied to the feet, as this is usually a symptomatic area for PSPS-T2 patients. Furthermore, it would be interesting to explore the behaviour of NDTs and EPs during SCS and stimulus

application to the feet in order to investigate whether effects of SCS can be measured using the NDT-EP method. Its feasibility in a new stimulus location should be investigated first however, as the NDT-EP method has not been used during SCS and stimulus application to the feet. A study by Berfelo et al.[16] showed measurement of NDTs is feasible during dorsal root ganglion (DRG) stimulation, but EP measurements were omitted from the study procedures. Previous results of the NDT-EP method during SCS and stimulus application to the hand has shown that EPs can be measured when SCS is turned on[23]. However, it is unclear whether we can also measure nociceptive processes when SCS is turned on and stimuli are applied to the foot, as somatotopic mapping of afferent fibres in the feet is less extensive than of those in the hands. Changing the location where stimuli are applied will help increase understanding of the clinical applicability of the NDT-EP method, and potentially increase understanding of the mechanisms underlying PSPS-T2 and the working principles of SCS.

1.1 Research objective

The main goal of this exploratory study is to determine the feasibility of the NDT-EP method while stimuli are applied to the feet during spinal cord stimulation and to further explore the effect of spinal cord stimulation on nociceptive detection thresholds and evoked potentials in patients with persistent spinal pain syndrome type 2.

1.2 Thesis outline

An overview of relevant background information is provided in Chapter 2 - Background, which contains knowledge about the physiology of pain and nociceptive processing, the pathophysiology of PSPS-T2, insight into assessment of pain through questionnaires, quantitative sensory testing, and the NDT-EP method, and more insight into SCS. Finally, implications are summarised, after which the primary and secondary objectives were identified. In Chapter 3 - Methods, general methods are described, which includes how the study was executed and how data was prepared for analysis. One chapter per primary or secondary objective provides information about data analysis, results, and discussion: Chapter 4 is dedicated to the experimental feasibility and data quality, Chapter 5 focuses on effects of SCS and session effects, and Chapter 6 concentrates on a comparison between PSPS-T2 patients and healthy controls. Each chapter contains a detailed overview of data analysis related to that objective, the findings belonging to the objective, after which these are discussed and related to literature. Chapter 7 - Discussion contains a general discussion which discusses results overarching objectives, an analysis of strengths and limitations of this study, and recommendations for future research. Finally, the research questions are answered in Chapter 8 - Conclusion, which concludes this thesis.

2 Background

Relevant background information is provided in this chapter. More information will be given about the (patho)physiology of pain and the chronic pain syndrome PSPS-T2. Then, I will elaborate further on assessment of pain, including the NDT-EP method. Previous work regarding the NDT-EP method will also be summarised here. Next, information is provided regarding the treatment of PSPS-T2, specifically SCS. The chapter concludes with the implications, research goal and primary and secondary objectives of this thesis.

2.1 Pain

The International Association for the Study of Pain (IASP) has defined pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'[24]. It can therefore be considered a warning or defence mechanism to prevent potential or further damage to the body. However, the experience of pain should always be seen as a subjective experience[25]. Pain is best regarded as an experience combining a physiologic sensation with an emotional reaction to said sensation[26,27].

Pain can be subdivided in nociceptive and neuropathic pain. Nociceptive pain is caused by activation of nociceptors due to actual or threatened damage to non-neural tissue[24,28]. Neuropathic pain, on the other hand, results from a lesion or disease of the somatosensory nervous system[24,29]. More recently, the term nociplastic pain was introduced to describe pain that 'arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain'[24].

2.1.1 Nociceptive processing

Somatosensation is the physiologic process of neural substrate activation by physical stimuli resulting in the perception of touch, pressure, and pain. The physiologic process of neural pathway activation by potentially or currently damaging stimuli, is called nociception[30]. It is important to discern nociception from the experience of pain, as activation of nociceptors is not the sole factor influencing the perception of pain[25,30]. The nociceptive process consists of transduction, transmission, modulation, and perception [30].

Nociceptors are free nerve endings widely distributed throughout the body, sensitive to noxious stimuli[31]. The two main types of primary afferent nerve fibres are fast, myelinated Aδ-fibres and slow, unmyelinated C-fibres. Sensations of sharp, intense pain are elicited by Aδ-fibres, and more persistent feelings of dull, burning pain are mediated by C-fibres[30,31]. The activation of nociceptors through noxious stimuli starts the process of transduction. If a potential induced through activation of transduction channels is sufficient, action potentials are then transmitted through the nervous system.

The nociceptive information is sent to the dorsal root ganglia (DRG), where the cell bodies of primary afferent fibres are located. The DRG are responsible for ascending sensory transmission to the central nervous system. This is achieved via synapses to the dorsal horn of the spinal cord, which is the synaptic terminal of peripheral afferent nerve fibres[30]. The dorsal horn is anatomically organized in laminae, based on shape, location, and function. Nociceptive primary afferent fibres terminate in the dorsal horn ipsilaterally to their input. Second order neurons bring the nociceptive information to higher centres via anterolateral, contralateral tracts. The nociceptive information then reaches the thalamus via the spinothalamic tract. Third order neurons are then projected deeper into the brain, to, among others, the primary and secondary sensory cortices, the limbic system and the prefrontal cortex. The primary and secondary sensory cortices process incoming nociceptive signals, thereby recognizing and localizing regions of pain. The limbic system is involved in the affective component of pain processing. Furthermore, the prefrontal cortex is associated with long-term pain perception and psychosocial pain behavior[32].

After nociceptive information has reached the higher centres, descending pathways are involved in pain modulation. Activity at descending pathways is thought to influence transmission of nociceptive information by, for instance, excitation of inhibitory neurons or inhibition of excitatory dorsal horn neurons[32].

2.1.2 Pathophysiology

If pain persists or recurs for longer than 3 months, it is considered chronic pain[33]. Beyond this time, it no longer performs its original function to protect the body against potential or actual damage. Research evidence suggests that maladaptive neuroplasticity plays a role in chronic pain. Functional and/or structural changes in the brain due to maladaptive neuroplasticity, may be associated with pain persisting beyond healing, and developing and maintaining chronic pain[34–39]. These changes in brain structure can be reversed, however, which can be associated with improvement of symptoms, including chronic pain[34,40,41].

Peripheral and central sensitisation are both examples of changes due to maladaptive neuroplasticity[8]. The process of peripheral sensitisation is defined as 'increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields' by the IASP, and is characterized by primary hyperalgesia and/or primary allodynia[24]. Central sensitisation, on the other hand, is characterized by secondary hyperalgesia and/or secondary allodynia[6,24]. Bazzari et al.[8] stated that central sensitizatoin is mediated by neuroplasticity mechanisms, affecting nociceptive processing in such a way that 'pain "perception" would no longer be coupled to the presence, intensity or duration of noxious inputs'. Central sensitisation is therefore thought to account for experienced pain without noxious input.

The use of the term "central sensitisation" has been a source for discussion in this field, however. Originally, central sensitisation was described as a phenomenon of increased spinal excitability triggered by peripheral noxious output that was spatially restricted and provided an explanation for the increased pain perception[42–45]. In 2011, the IASP defined central sensitisation as 'increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold input'[24]. In more recent years, central sensitisation has received increased attention as shown by Li et al.[46], and its description has shifted to refer to a general state of central nervous system hypersensitivity[47,48]. Some researchers suggest this broad interpretation of central sensitisation might not be clinically helpful, as it increases the heterogeneity of underlying mechanisms[49,50]. The recently proposed term 'nociplastic pain' has been suggested as a replacement for central sensitisation but is still relatively unknown[51]. The discussion regarding terminology of central sensitisation highlights the scientific knowledge gap that unfortunately still exists surrounding mechanisms of the nervous system.

2.2 Chronic pain: Persistent spinal pain syndrome

Low back pain is one of the most common health complaints with an estimated lifetime prevalence of 60 to 80%[11,52]. Approximately 10% of patients have low back pain persisting for longer than three months, turning into chronic pain[53]. Possible risk factors contributing to developing chronic low back pain are severe functional limitations, radiculopathy, or psychiatric comorbidity[54]. Chronic low back pain was ranked as the greatest contributor to global disability and sixth contributor to overall global burden, with an estimated total of 83.0 million disability-adjusted life years in 2010[52]. The increasing number of patients seeking treatment has led to increasing rates of spinal surgery[55,56]. Despite proper surgery, an estimated 10 to 40% of patients suffer from persistent or reoccurring low back pain with or without radiating pain to one or both legs[57,58]. The term commonly used to describe this phenomenon is 'failed back surgery syndrome', or FBSS. The cause for FBSS is poorly understood, but patient-related factors, as well as operative and post-operative factors likely contribute to development of FBSS[11,55,56].

The IASP has defined FBSS as: "lumbar spinal pain of unknown origin either persisting despite surgical intervention or appearing after surgical intervention for spinal pain originally in the same topographical location'[26]. The term FBSS has received criticism in recent years for being vague and suggesting failure[59,60]. Several replacements have been proposed over the past years, for instance chronic pain after spinal surgery (CPSS)[33] or postsurgical spine syndrome (PSSS)[61]. The

new International Classification of Diseases (ICD-11) has adopted CPSS as of January 2022[33]. CPSS has failed to gain traction, largely by having a narrow definition[33,62]. Persistent pain after spinal surgery (PSPS) was proposed as a broader term[9,62–64]. Two types of PSPS were suggested; type 1 (PSPS-T1) applies when there was no surgery, type 2 (PSPS-T2) applies where surgery occurred. PSPS is considered more coherent and fundamental than FBSS[62]. In contrast to previous theses[21,23], it was decided to adopt PSPS-T2 in this thesis. Although FBSS is still predominantly used in clinical practice, the use of PSPS-T2 is in line with the most recent considerations and convictions, and current studies performed by this research group[16,62,63].

Patients suffering from PSPS-T2 are often severely affected by the disease. Chronic pain in general negatively impacts a patient's daily activities, quality of life, and social environment[3]. In comparison with other pain populations, reported levels of pain are greater, and health-related quality of life (HRQoL) is lower in PSPS-T2 patients[57,65]. This often leads to depression, financial stress, and unemployment[57].

Management of PSPS-T2 is often multidisciplinary and should be modified to individual needs[56]. One approach is conservative management, which includes pharmacological treatment, physical therapy, or psychological therapy[56,58]. Especially cognitive behaviour therapy is thought to help reduce pain scores both immediately after surgery and during long-term disability[66]. Many PSPS-T2 patients will unfortunately not achieve sufficient pain reduction and functional improvement with only conservative management[65]. If conservative management is insufficient, minimally invasive interventions could be employed in addition to the conservative strategies[56]. Interventional management options for PSPS-T2 include medial branch blocks, epidural injections, and adhesiolysis[56,67]. However, limited evidence exists for the long-term therapeutic effect of these interventions[67]. Even though revision surgery can also be part of treatment, success rates are generally low and decline further after each additional surgery[68].

For patients with predominant leg pain whose other treatments have failed, neuromodulation therapies, such as SCS, are indicated[58,69]. Although neuromodulation therapies are often considered a last resort, some suggest it should be considered in an earlier phase of treatment[67,69,70]. In a systematic literature review of treatment options for PSPS-T2 patients by Amirdelfan et al.[67], the strongest, long-term evidence was found for SCS, confirming that it is a promising option for PSPS-T2 treatment that reportedly provides adequate pain relief[65,67,71,72]. However, Amirdelfan et al.[67] also report varying success rates, which indicates not every PSPS-T2 patient can be treated by SCS. This highlights the need for more insight into the mechanisms of SCS.

2.3 Assessment of pain

Quantification of pain perception is needed for several reasons, e.g., a broader understanding of pain mechanisms or the improvement of treatment techniques. Current tools to evaluate pain in clinical practice are often based on self-report from the patient, using measures such as the numerical rating scale (NRS) score. Patients rate their pain on a scale from 0 to 10 or 0 to 100, where 0 represents 'no pain' and the upper limit represents 'the most pain imaginable'[73]. Additionally, questionnaires such as the MPQ, the CSI, and the Oswestry disability index (ODI), can be deployed for more insight into subjective pain experience. The MPQ is designed to provide a multidimensional insight into pain experience, addressing sensory, affective, and evaluative properties of pain[15]. The CSI is a screening tool used to assess physical and mental symptoms that often occur in central sensitisation syndromes (CSS) and help identify patients with CSS[74,75]. The ODI is a questionnaire that aids in quantifying the degree of functional limitations due to low back pain[76]. Although widely used in practice, measures such as pain scores and questionnaires rely on subjective assessment and self-report. Therefore, these measures do not provide insight into neurophysiological processes underlying chronic pain.

2.3.1 Quantitative sensory testing

Psychophysics describe the relationship between physical stimuli and the response of a subject, which can be used to systematically assess somatosensory and nociceptive function[77]. Quantitative sensory testing (QST) is a method based on psychophysics. QST is often used to

assess somatosensory function and can evaluate both an increase and a decrease in somatosensory function as well as large and small fibre dysfunction. The QST battery consists of several tests representing submodalities of the somatosensory system, e.g., thermal or mechanical stimuli[17]. Detection or pain thresholds are often used as outcome measures of QST. However, pain thresholds are thought to highly depend on a subject's attitude and motivation to endure painful stimulation[78]. Although an objective physical stimulus is applied in QST, the response is a participant's subjective report[17]. Additionally, inter-observer reliability is reliant on extended training of examiners to minimize inter-observer effects[18]. Furthermore, standardisation of QST protocols is challenging; therefore, comparing outcomes between different QST studies is potentially impeded[79]. Moreover, QST usually relies on short measurements, which makes it difficult to assess phenomena like habituation and neural plasticity. Finally, selective stimulation of nociceptive nerve fibres is not possible with QST[80].

2.3.2 NDT-EP method

Recently, a method to provide a psychophysical measure for nociceptive processing was proposed by the Biomedical Signals and Systems (BSS) group from the University of Twente. This method combines NDT tracking with EPs, derived from EEG recordings. Therefore, it is called the NDT-EP method.

2.3.2.1 Nociceptive detection thresholds

Nociceptive Aδ-fibres can be selectively stimulated using IES with a stimulus amplitude lower than twice the detection threshold[5,81]. IES is considered to be non-invasive, as the needles on the electrode only protrude the stratum corneum, which is the outermost layer of the skin. The IES electrode is shown in Figure 2.1.

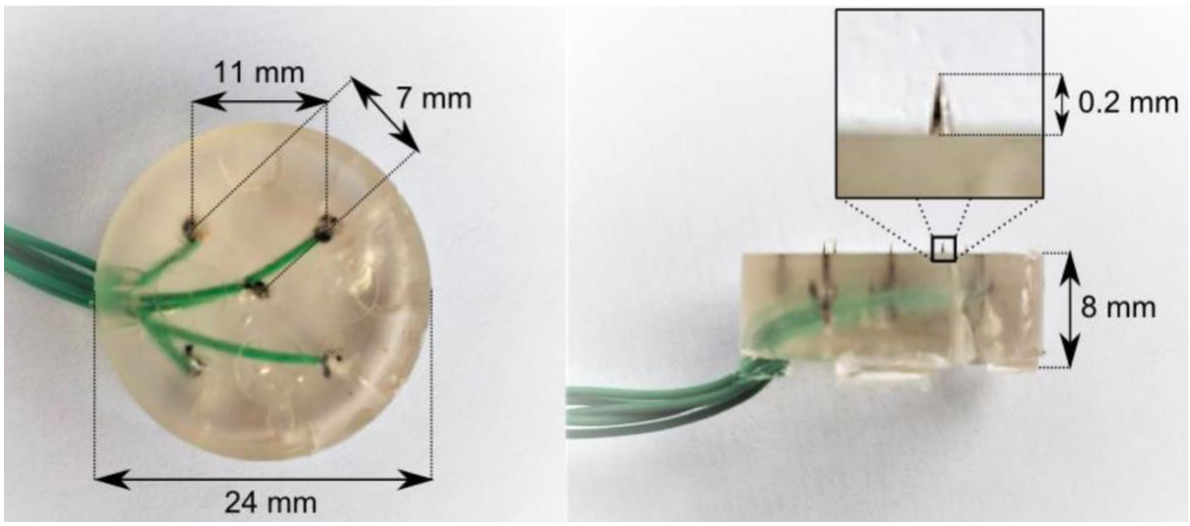

Figure 2.1: The electrode used for intra-epidermal electrical stimulation (IES) and its dimensions.

The relation between stimulus amplitude and the response of a subject can be described in a sigmoidal psychophysical curve. This psychophysical curve depicts the probability of a stimulus with a certain amplitude being detected. The amplitude where the detection probability is 50%, is referred to as the detection threshold. Furthermore, the slope of the psychophysical curve can provide insight into the reliability of the stimulus detection of a subject; a steeper curve reflects a higher reliability. Features of the psychophysical curve are thought to potentially reflect specific characteristics of disease[7]. An example of a psychophysical curve is shown in Figure 2.2, showing the sigmoidal curve for various detection thresholds and slopes.

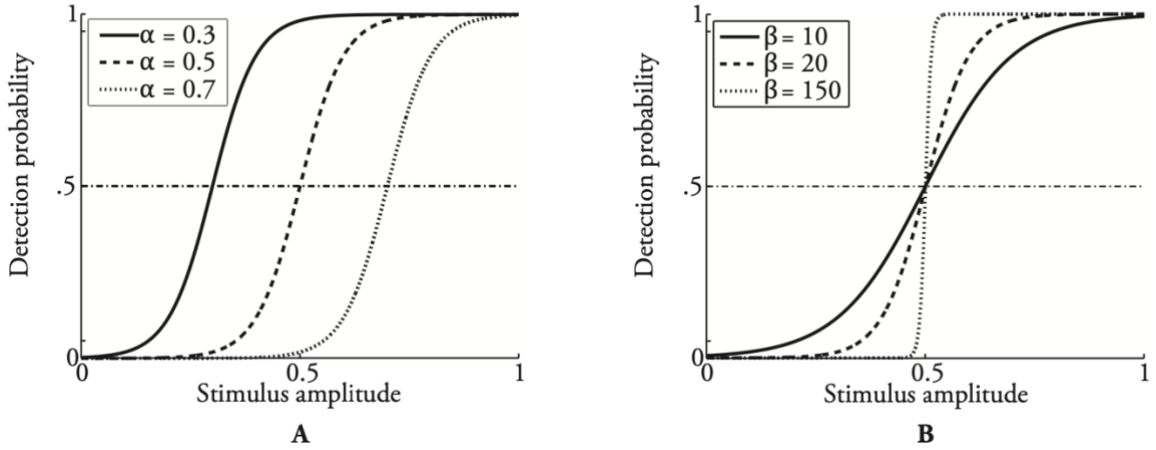

Figure 2.2: Examples of the psychophysical curve showing the effects of a change in (A) the detection threshold (α) and (B) the slope (β). The dashed line depicts a detection probability of 50%, which represents the detection threshold. Adapted from Doll[5].

Varying temporal stimulation properties allows for assessment of several aspects of the nociceptive system. Temporal properties include pulse width (PW), number of pulses (NoP), and inter-pulse interval (IPI). A multi-threshold tracking (MTT) paradigm was designed to track multiple thresholds simultaneously by randomizing stimulus order. This minimises both subject and observer bias. The MTT paradigm is illustrated in Figure 2.3A. A random-staircase procedure is used to vary stimulus amplitudes, which allows for NDT tracking over time. In a random-staircase procedure, stimulus amplitudes are randomly chosen from a predefined interval of amplitudes between 0 mA and 1.5 mA. The interval decreases when a stimulus is perceived, and increases when a stimulus is not perceived. The decrease as well as increase are by a randomly selected fixed step size (either 0.05, 0.1 or 0.2 mA). This random-staircase procedure was proposed by Doll et al.[19] and is illustrated in Figure 2.3B. It was found to be more precise in tracking non-stationary processes in comparison with a simple staircase procedure. In a simple staircase procedure, a detected stimulus consistently results in a lower stimulus amplitude, and a non-detected stimulus consistently results in a higher stimulus amplitude.

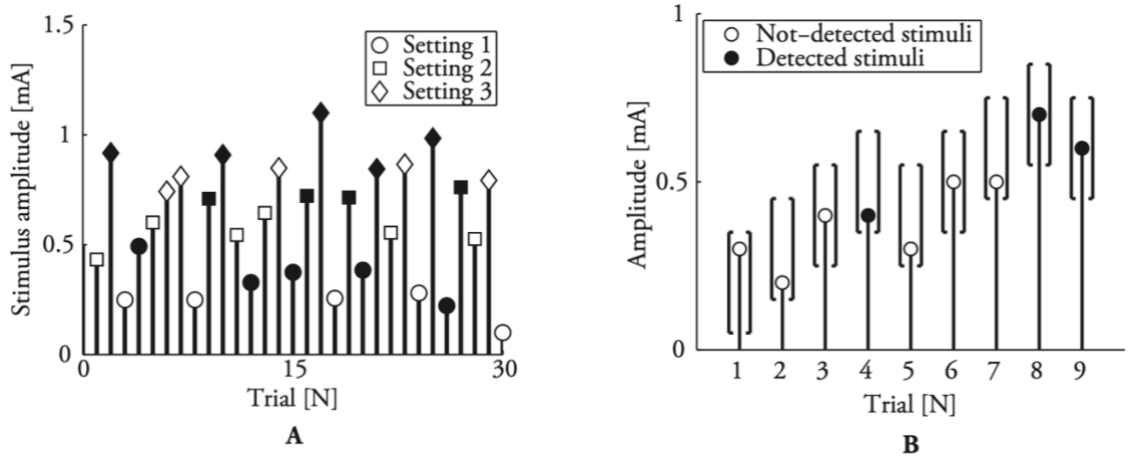

Figure 2.3: (A) A typical example of an experiment where stimuli with three different property combinations are presented in a random, intermingled order, according to the multi-threshold tracking (MTT) paradigm. (B) A typical example of the stimulus selection procedure using a random-staircase procedure. The brackets represent the set of stimulus amplitudes within which a stimulus can be randomly chosen. Detected stimuli will result in a decrease of the set, whereas non-detected stimuli will result in an increase of the set. Adapted from Doll[5].

The analysis of NDTs is performed using a GLMM. Earlier research found the statistical GLMM fits best to estimate non-stationary psychophysical curves to analyse estimated average detection thresholds for a longitudinal data set[20]. Linear mixed models (LMM) are a type of regression model, which can be used to estimate a threshold, because the stimulus responses are binary: perceived or not perceived[5]. GLMMs are an extension of LMMs to allow response variables from different distributions[82]. A GLMM evaluates the effect of stimulus properties on the detection probability. These properties must be included as fixed effects, i.e., independent variables. Interaction between certain properties also need to be included as fixed effect(s). Random effects are between-subject variables of which the variation is not explained by the independent variables of interest. Examples of random effects are intercept, stimulus amplitude, stimulation time and environment. Between-subjects random effects were included for the stimulus properties[20].

2.3.2.2 Evoked potentials

EEG recordings were added to tracking of NDTs to increase objectivity and give insight into underlying neurophysiological processing. EPs, i.e., the neurophysiological response to a stimulus, can be captured from EEG recordings. In order to evoke a large potential with a high Signal-to-Noise ratio (SNR), the hand was originally chosen as the stimulus location. As afferent fibres in the hand can be expected to have a large somatotopic mapping in the somatosensory cortices of a subject, stimulation of those fibres will generally result in a large EP[84]. Additionally, EPs have been shown sensitive to changes in stimulus parameters[85,86].

Peak amplitudes and latencies can be used to characterise EPs. Both latencies and amplitudes are suggested to provide valuable insight into underlying neurophysiological processing. Two important components of a nociceptive EP are a second negative peak (N2), followed by a second positive peak (P2). The N2 and P2 peaks are best analysed by a contralateral and central EEG component respectively, as shown by earlier studies regarding the NDT-EP method[87]. Relevant EP characteristics can be found in the central derivation around 400 ms as a positive peak (P400), and in the contralateral derivation around 200 ms as a negative peak (N200)[83].

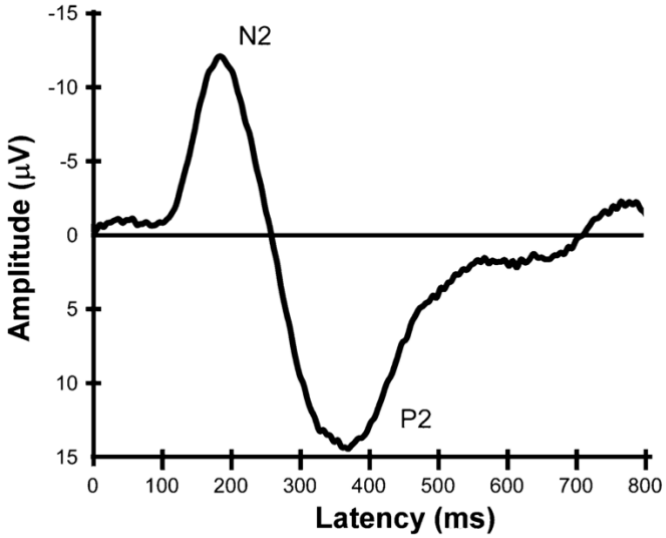

Figure 2.4: An example of a laser evoked potential following nociceptive somatosensory input, obtained from cortical activity measured with EEG. Note: the y-axis is inverted. Adapted from Hu & Zhang[83].

The N2/P2 complex is thought to express the medial pain system, which reflects sensory processing and awareness. N2 and P2 are suggested to depend on pain perception and the saliency of the eliciting nociceptive stimulus[88]. Results have shown that EPs can be modulated by stimulus detection, amplitude, and number of applied stimuli. Habituation of the nociceptive system can therefore also be seen in EPs. Habituation leads to a decrease in EP amplitude over time[89]. A reduction in N2 or P2 amplitude could also indicate the top-down inhibitory control described as conditioned pain modulation[88]. An example of an evoked potential is shown in Figure 2.4 and illustrates N2 and P2 peaks of EPs.

Van den Berg et al.[20] suggested the best statistical approach to study the effect of stimulus properties on time-locked EPs is an LMM. LMMs also consider fixed effects and random effects. Further details about these effects can be found in Section 2.3.2.1 - Nociceptive detection thresholds. An LMM improves EP analysis, because the poor signal-to-noise ratio was not

improved sufficiently by averaging EP signals[5,20]. Furthermore, the use of an LMM in EP analysis accounts for intra- and inter-subject variations and habituation[89].

2.3.2.3 Previous work using the NDT-EP method

Previously, the feasibility of the NDT-EP method has been shown in pain-free individuals (or healthy controls, HCs)[20]. Next, the results in HCs were reproduced in a clinical setting and the NDT-EP method was studied in patients with alterations in the central nervous system. PSPS-T2 patients were chosen since central sensitisation is thought to play an important role in that syndrome. In comparison to HCs, higher NDTs were found in the patient population. Furthermore, EPs in PSPS-T2 patients were modulated only by response, whereas EPs in HCs were modulated by response and stimulus amplitudes[21]. Subsequently, the NDT-EP method was studied in patient populations with small fibre neuropathy (SFN). Patients with PDPN, diabetes mellitus (DM) without pain, sarcoidosis, and chemotherapy induced peripheral neuropathy (CIPN) were evaluated using the NDT-EP method[22,90]. In general, no distinct differences in NDTs were found between patients and HCs, and EP amplitudes were decreased in the patient populations compared to HCs.

Most recently, the NDT-EP method was studied in PSPS-T2 patients treated by SCS. The NDT-EP method seemed feasible with stimulus application on the hand. Moreover, the NDT-EP method seemed reproducible in PSPS-T2 patient treated by SCS, but no generalised difference in NDTs or EPs was seen between the situations where the stimulator was turned off and where the stimulator was turned on. Furthermore, the behaviour of NDTs was studied in PSPS-T2 patients with DRG stimulation for unilateral limb pain[16]. NDT measurements were performed with IES application to the feet when DRG stimulation was turned off and on. When the stimulator was turned off, higher NDTs were observed on the affected side than the unaffected side. During stimulation, NDTs for the affected and unaffected side were comparable[16].

The effects of certain subject characteristics, such as sex, age, and BMI, were also studied. On one hand, preliminary results indicate no clear difference in NDTs and EPs between male and female HCs. On the other hand, age does influence NDTs and EPs, with increasing NDTs and decreasing EPs observed in older age groups. Furthermore, BMI was found to influence NDTs. In a comparison between HCs and pain-free, obese (BMI $\geq$ 40 kg/m^2) individuals, higher NDTs for single-pulse stimuli were found in obese individuals. Additionally, in a comparison between HCs and obese individuals with chronic pain, higher NDTs were observed for all single- and double-pulse stimulus types. In comparison to HCs, the EP amplitude was decreased in both obese individuals with and without chronic pain for double-pulse stimuli with a 10ms inter-pulse interval.

The previous work regarding the NDT-EP method provides valuable insight into its feasibility and clinical applicability, and has helped explore characteristics of nociceptive processing in healthy, pain-free individuals, as well as chronic-pain patients.

2.4 Treatment of pain: Spinal cord stimulation

The treatment of PSPS-T2 is complex and consists of many options. A full summary of treatment options is out of the scope of this thesis. This section will therefore focus exclusively on neuromodulation therapies. More information regarding treatment of PSPS-T2 can be found in the article by Amirdelfan et al.[67].

Neuromodulation therapies include various technologies that directly affect the nervous system, e.g., neural stimulators or microinfusion pumps[91]. For PSPS-T2 patients with radiating pain to the legs, SCS is currently the only indicated neuromodulation therapy in the Netherlands. Previously, dorsal root ganglion (DRG) stimulation and intrathecal drug delivery (ITDD) were used for PSPS-T2 patients, but both are no longer indicated due to limited levels of evidence[92]. For SCS, patients have to undergo a trial period of 1 week, for which electrode leads are placed in the posterior epidural space for electrical stimulation of the dorsal columns of the spinal cord[93]. The target for lead placement for ideal stimulation in PSPS-T2 patients is at vertebrae level T7[94]. During this trial period, patients carry an external stimulator. After a successful trial, defined as pain relief of 50% or more, a stimulator is implanted. The stimulator is usually placed in the lower abdominal area or the posterior superior gluteal area[93].

The foundation for SCS was laid by Melzack and Wall's gate control theory, proposed in 1965[95]. The gate control theory describes how Aδ fibres, C fibres and Aβ fibres are in competition to pass through a single-lane physiologic "gate". If the "gate" is flooded with non-painful input from Aβ fibres, input from the nociceptive Aδ and C fibres should not be transmitted. In other words, non-painful stimuli can supersede and reduce painful stimuli[93]. Two years later, Shealy et al.[96] described a case of a 70-year-old male patient suffering from chronic pain due to metastases. A monopolar SCS was successfully implanted in his intrathecal space near the dorsal column, and electrical stimulation of the dorsal column led to a decrease in pain[96]. While the gate control theory is considered to be the base concept underlying conventional SCS, clinical evidence suggests the working mechanism additionally involves activation of multiple inhibitory systems at segmental and suprasegmental levels.[58]

Conventional SCS, or tonic SCS, leads to paraesthesia due to electrical stimulation of the spinal cord, which ideally covers the painful areas[58]. However, effect rates for tonic SCS are varying[93,97]. More recently, other stimulus paradigms were proposed to possibly increase the success rate of SCS. Burst SCS offers minimal paraesthesia to the patient by delivering bursts of five spikes at 500 Hz, 40 times per second[98]. In high frequency (HF) SCS, electrical stimulation is applied to the spinal cord using a frequency of 10 kHz to provide pain relief without paresthesia[99]. In closed-loop SCS, evoked compound action potentials (ECAPs) are monitored to automatically adjust the stimulation current, which is thought to maximize the therapeutic effect by maintaining consistent spinal cord activation[100].

Research into effects of different types of SCS has been proven difficult for several reasons. Specifically in tonic SCS, it is difficult to perform sham-controlled trials due to patients experiencing paresthesia[93]. More generally speaking, heterogeneity of device designs and settings makes it difficult to combine SCS groups in studies. Furthermore, nearly all prospective studies are funded by the industry, which leads to conflicts of interest and potentially introduces bias[97]. Additionally, neuromodulation is highly associated with placebo effects[101,102]. High patient expectations, repeated visits, physician interaction, and, in case of paraesthesia, an obvious treatment effect are thought to contribute to the powerful placebo effect[102]. These factors have complicated accurate evaluation of effect and working mechanisms of SCS. Therefore, the exact working mechanisms remain unclear, which is thought to be one of the major causes of the limited success of SCS[103].

Sankarasubramanian et al.[104] recently performed a literature review into objective measures for characterizing the physiological effects of SCS for neuropathic pain. This review described the current body of knowledge regarding the mechanisms of action of SCS. They found that non-nociceptive, somatosensory processing is largely inhibited by SCS, as seen by significant decreases in amplitudes of somatosensory evoked potentials (SSEPs). Furthermore, they found that SCS inhibits spinal nociceptive processing, which is illustrated by a decrease in nociceptive flexion reflexes, or RIII activity. Lastly, the review described effects of SCS as measured by QST. Measurements of QST studies suggested that sensory hypersensitivity is decreased by SCS, as shown by increases in sensory-detection thresholds. These findings are illustrated in Figure 2.5[104].

Common shortcomings of SCS studies were also highlighted by Sankarasubramanian et al.[104]. These limitations may also hinder our understanding of the mechanisms of action of SCS. Studies regarding SCS are often performed with small sample sizes and heterogeneous populations. Furthermore, SCS studies were rarely performed placebo- or sham-controlled. In the future, well-designed studies with objective measures, homogeneous populations, and sufficient statistical power could provide further insight into mechanisms of action of SCS[104]. This is considered crucial in the further development of SCS[103].

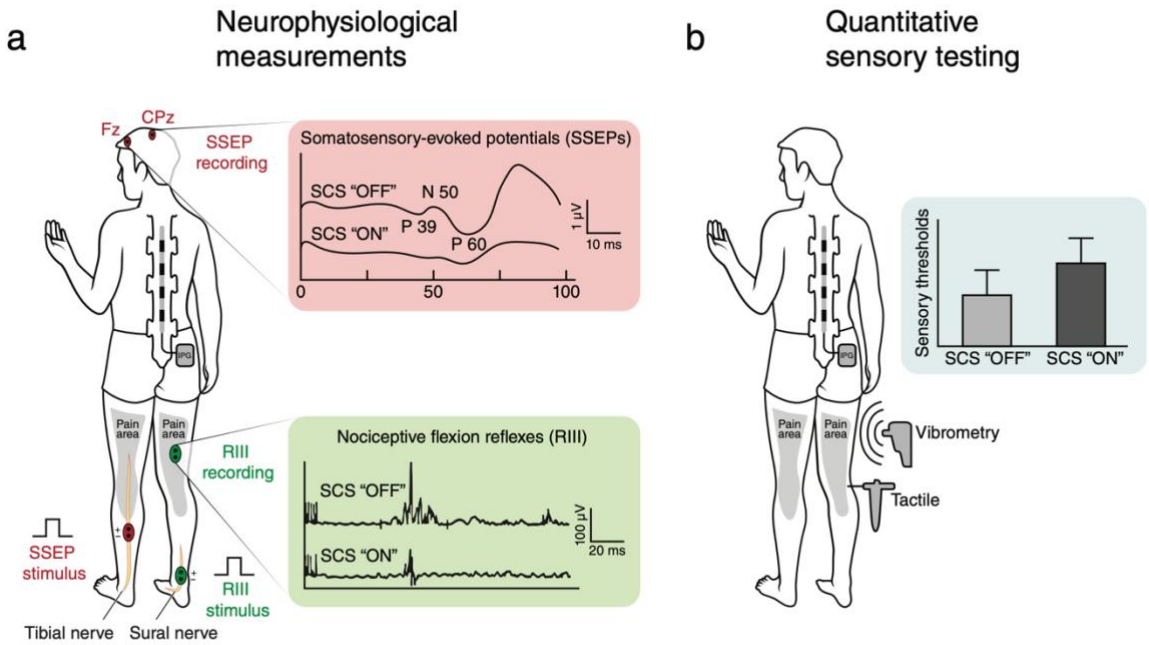

Figure 2.5: The effects of spinal cord stimulation (SCS) characterized by (a) neurophysiological measurements, and (b) quantitative sensory testing. Figure adapted from Sankarasubramanian et al.[104].

2.5 Implications

Increasing our understanding of mechanisms underlying chronic pain, specifically PSPS-T2, and its treatment is important, which was underlined in the previous sections. Previous studies regarding the NDT-EP method have shown the technique is feasible in pain-free subjects, PSPS-T2 patients without SCS and PSPS-T2 patients with SCS. It was demonstrated that NDTs and EPs can reliably be observed when SCS was turned on and electrical stimuli were applied to the hand dorsa. However, the stimulation effect on NDTs that was observed during DRG stimulation[16], was not observed with the conventional NDT-EP method. A possible explanation for the discrepant results is the location for stimulus application; the study regarding the NDT-EP method in PSPS-T2 patients treated by SCS conducted measurements on the hand, i.e., an unaffected area, whereas the study regarding NDTs in patients treated by DRG stimulation conducted measurements on the foot, i.e., an affected area. It was therefore decided to conduct the measurements for this study on the foot as well.

Although the feasibility and reproducibility of the conventional NDT-EP method have been explored during SCS, its feasibility must be investigated once more when conducting measurements on the feet. To obtain large EPs with a high signal-to-noise ratio, the hand was originally chosen as the stimulus location due to its extensive somatotopic mapping. Afferent fibres in the foot may have smaller somatotopic mapping in the somatosensory cortices of subjects which may lead to lower signal-to-noise ratios or lower EP amplitudes; the feasibility of measuring EPs specifically must thus be further investigated.

Exploring the NDT-EP method while applying stimuli to the foot dorsa in PSPS-T2 patients treated by SCS is a next step in the development of the NDT-EP method. While NDT measurements have been performed with stimulus application to the foot dorsa, it has not been investigated in combination with EP measurements yet. Furthermore, exploring the feasibility of the NDT-EP method with stimulus application to the foot dorsa is important because several patient populations experience more symptoms of pain in their lower limbs than in their upper limbs, i.e., PDPN. Lastly, the current body of knowledge will be expanded regarding the behaviour of NDTs and EPs when measurements are performed in different locations and regarding the effect of SCS on nociceptive processing.

2.5.1 Research objective

The central aim of this study is: "*To determine the feasibility of the NDT-EP method in PSPS-T2 patients during SCS while electrical stimuli are applied to the foot, and further explore effects of SCS*".

2.5.2 Primary objectives

Two primary objectives were formulated and are listed below:

- To investigate the feasibility of NDT-EP measurements during SCS in patients with PSPS-T2 while electrical stimuli are applied to the feet (affected as well as unaffected).
- To explore effects of SCS on NDTs and EPs in PSPS-T2 patients while electrical stimuli are applied to the feet (affected as well as unaffected).

2.5.3 Secondary objective

Additional to the primary objectives, one secondary objective was formulated:

- To compare NDTs and EPs between PSPS-T2 patients (both SCS-OFF and SCS-ON) and healthy controls when stimuli are applied to the feet (unaffected in case of HCs and affected in case of PSPS-T2 patients).

3 Methods

This study is part of a more extensive study of the St. Antonius Hospital (Nieuwegein, Netherlands) named “Electrical Brain Responses during Processing of Nociceptive Stimuli around the Detection Threshold: an Explorative Study in Pain Patients”. It has been approved by the regional ethical committee (MEC-U, Nieuwegein, the Netherlands) and is registered under NL66136.100.18. Solely essential information for this part of the study is described in this section. A more extensive, detailed description can be found in the study protocol of Berfelo[84].

3.1 Study population

For this study, 23 PSPS-T2 patients were recruited from the department of Anesthesiology and Pain Medicine at the St. Antonius Hospital. Recruitment happened from the St. Antonius Hospital via advertisements between March and September 2022. Subjects of the previous study by De Beer[23] were eligible for participation in this study again. These patients were informed about the current study after providing them with an update of the previous results. Newly potential subjects were informed after a regular visit at the outpatient clinic. Patients were eligible for inclusion when they were aged between 18 and 75, had signed informed consent, had been diagnosed with PSPS-T2, had an implanted spinal cord stimulator for at least 3 months due to radiating leg pain, and the implantation must be considered successful, which is determined as a pain reduction of at least 50% as measured by NRS or VAS. Patients with unilateral radiating leg pain as well as bilateral radiating leg pain were included in this study. Exclusion criteria were diabetes, pregnancy, communication issues, an implanted stimulation device other than SCS, alcohol and/or drug consumption within 24 hours before the experiment, and non-intact skin on (at least) one of the foot dorsa. Medication intake of PSPS-T2 patients was not restricted during this study.

3.2 Study design

Included PSPS-T2 patients were randomized over two trial arms. Age and sex are thought to influence the outcomes of the NDT-EP measurements; therefore, we strove for equal distributions in both trial arms. Randomization was therefore performed using stratified block randomization based on sex and age (≤50 or >50 years old). The cut-off age of 50 was chosen based on the previous study and the expectation that included patients would predominantly be aged between 35 and 65 years old. Patients in the first trial arm underwent a ‘SCS-ON1 vs SCS-ON2’ protocol, where two measurements were performed with the spinal cord stimulator turned on. Patients in the second trial arm (‘SCS-OFF vs SCS-ON’ protocol) were asked to turn their spinal cord stimulator off 12 hours before the experiment, where they started with a measurement while their stimulator remained turned off. Before the second measurement, these patients turned their stimulator on. Both patients and observers were not blinded for trial arm allocation.

3.3 Study procedures

NDT-EP measurements of PSPS-T2 patients were conducted during one five-hour visit to the St. Antonius Hospital in Nieuwegein. The CSI, NRS, questionnaire regarding demographic data, and the Oswestry Disability Index (ODI; or Oswestry Low Back Pain Disability Questionnaire) were used to gather subject information. Next, the first set of NDT-EP measurements was performed. Block randomization per two subjects based on handedness determined whether the foot ipsilateral or contralateral to the dominant hand was stimulated first. Patients in the second trial arm, who had turned off their spinal cord stimulator, turned it back on after the first measurements. After a 60-minute break for patients in both trial arms, the second set of NDT-EP measurements was performed. An overview of the study procedure for PSPS-T2 patients is shown in Figure 3.1.

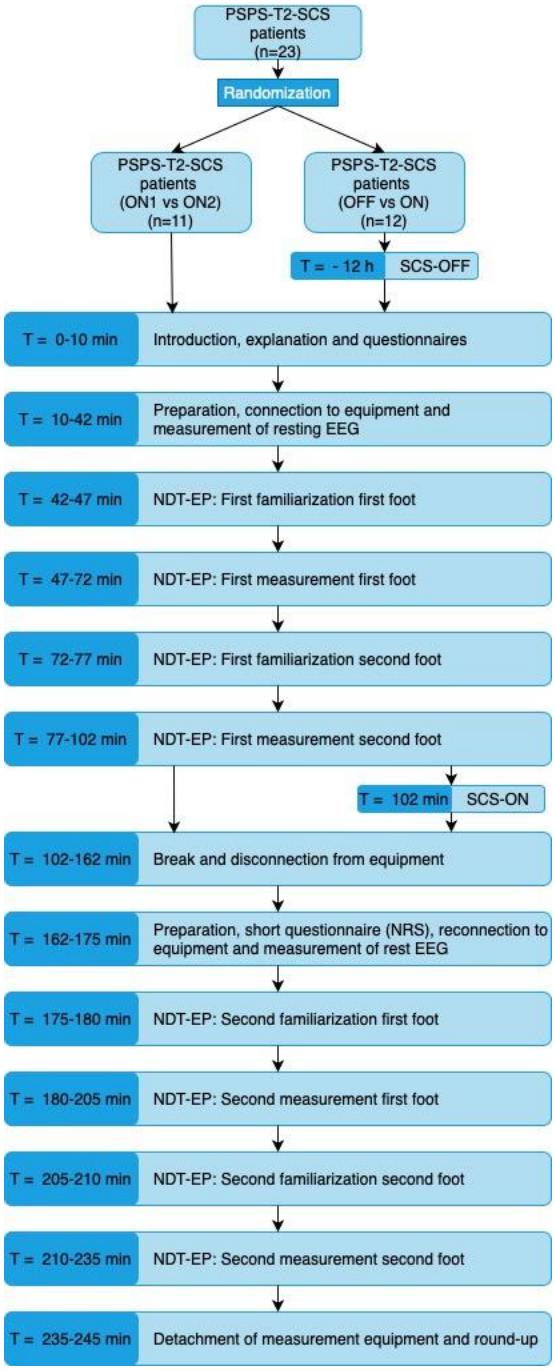

Figure 3.1: Overview of the study procedures for patients with persistent spinal pain syndrome type 2 (PSPS-T2) treated by spinal cord stimulation (SCS). Arrows placed centrally represent actions that apply to the entire study population. Arrows placed on the left and right respectively represent actions for the 'SCS-ON1 vs SCS-ON2' and 'SCS-OFF vs SCS-ON' population. NDT-EP – nociceptive detection threshold – evoked potential method; PSPS-T2-SCS – Persistent Spinal Pain Syndrome patients treated by Spinal Cord Stimulation; NRS – numerical rating scale.

3.3.1 Nociceptive detection thresholds

Using non-invasive IES, nociceptive Aδ-fibres in the dorsa of both feet were selectively stimulated through the NociTrack Ambustim stimulator. A cathodic, sterilized IES electrode with an array of five 0.2 mm needles was placed on the dorsum of the foot in dermatome L5 and fixated with tape. Dermatome L5 was chosen as (1) this dermatome provides a mostly flat surface on the foot dorsum and (2) most patients presented with complaints in this dermatome. A rectangular 9x5 cm TENS electrode placed proximally to the IES electrode on the foot, served as anode. Stimulation procedures were controlled and registered by a custom program written in LabVIEW 2013 (National

Instruments Corporation, Austin, TX, USA). Applied stimuli were rectangular shaped pulses with a standard pulse width of 0.21 ms and a varied amplitude per stimulus, ranging from 0 to 1.5 mA. Three stimulus types were applied using the multiple threshold tracking (MTT) protocol. These types were (1) a single pulse (SP), (2) a double pulse with an inter-pulse-interval (IPI) of 10 ms (DP10), and (3) a double pulse with an IPI of 40 ms (DP40).

An NDT measurement consists of a familiarization phase and a measurement phase. The familiarization phase is intended to familiarize subjects with the stimulations and to determine the initial threshold before starting the measurement phase. To identify this initial detection threshold, subjects were instructed to press and hold a button on the NociTrack Ambustim stimulator. This allowed stimuli of 1 Hz to slowly increase with 0.05 mA $\cdot$ s^{-1} from 0 mA to a maximum amplitude of 1.5 mA. Subjects were instructed to release the button after the first sensation ascribed to a stimulus.

During the measurement phase, a minimum of 450 stimuli were applied per foot, divided over the three settings, i.e., a minimum of 150 stimuli per setting per foot. While the number of stimuli per setting was equal, the order was randomized to decrease observer and subject bias. The inter-stimulus interval was randomized as well, between 3 and 5 seconds. Subjects were instructed to press the button on the NociTrack Ambustim stimulator continuously and shortly release the button immediately when they felt any sensation ascribed to a stimulus. A stimulus was classified as 'detected' when the button was released within 1000 ms after the stimulus, and as 'non-detected' when the button had not been released after 1000 ms. Stimulus amplitudes were based on whether the previous stimulus of that setting was detected by the subject, following a random staircase procedure[19]. If subjects needed a short break or a slight position change, they were allowed to release the button, which paused stimulus transmission.

3.3.2 EEG recordings

EEG measurements was performed using a 64-channel EEG cap with Ag/AgCl electrodes (ANT Neuro Waveguard, Hengelo, the Netherlands). Additionally, the ground, M1 and M2 electrodes were placed on the forehead, left ear and right ear, respectively. To reduce electrode impedance to below 5 kΩ, conductive gel was used. EEG was recorded continuously during the NDT measurement with a sampling frequency of 1000 Hz using TMSi Polybench Software (TMSi B.V., Oldenzaal, the Netherlands). Trigger codes at the moment of stimulation were sent through a connection of the NociTrack Stimulator to the EEG amplifier. To minimize EEG artefacts, subjects were asked to focus their eyes on one spot and avoid movement or talking during the measurements. Subjects were observed from within the room to prevent them from closing their eyes.

3.4 Data preparation

NDT and EEG data were prepared for analysis using MATLAB (2020b, MathWorks, Natick, MA, USA).

3.4.1 Nociceptive detection thresholds

False positive detections, defined as stimuli registered as detected with a response time below 150 ms, were registered. The percentage of detected stimuli, the percentage of false positive detections, and average response time were determined per stimulus setting and in total. To estimate NDTs per setting, a moving window of 30 stimulus-response pairs was used and values of twice the previous detection threshold were removed.

3.4.2 Evoked potentials

EEG data were pre-processed per study group with MATLAB (2015b, MathWorks, Natick, MA, USA) and the Fieldtrip toolbox[105]. Time windows of interest (epochs) were 500 ms before and 1000 ms after stimulations. EEG data were bandpass filtered between 0.1 and 40 Hz and were cleaned using independent component analysis (ICA). The ICA was deployed to remove artefacts, such as eye blinks, muscular activity or signal drift.

Following data cleaning, a butterfly plot was created which included all subjects. A butterfly plot displays grand average EPs and the corresponding global field power (GFP) for all channels. For analysis of contralateral (T7-F4) and central (Cz-M1,M2) derivations, latencies at N1 and P2 were determined. These latencies were calculated based on maximum values in the GFP between 150 and 200 ms post-stimulus and between 300 and 600 ms post-stimulus for the N1 and P2 peak, respectively. These latency ranges were chosen based on previous studies regarding the NDT-EP method and other literature regarding N1, N2 and P2 peaks[23,106,107]. The computed latencies were used as a guide in later analyses. The butterfly plot can be found in Appendix A1.

4 Experimental feasibility and data quality

This chapter focuses on the primary objective "to investigate the feasibility of NDT-EP measurements during SCS in patients with PSPS-T2 while electrical stimuli are applied to the foot". Demographics of all patients are also included in this chapter. First, methods specific to this objective are described, after which the results will be described. Then, the results are evaluated in the discussion and a preliminary conclusion is drawn regarding the feasibility of NDT-EP measurements during SCS in PSPS-T2 patients while electrical stimuli are applied to the foot.

4.1 Methods

The methods regarding study population, study design, study procedures and data preparation are described in Section 3 – Methods. Statistical analysis was performed with MATLAB, R-4.0.5 (R Foundation for Statistical Computing, Vienna, Austria), and SPSS (27.0, IBM Corp., Armonk, NY, USA). Demographic data was tested for normality with Shapiro-Wilk tests. A two-tailed independent sample t-test was used for normally distributed data, and a Mann-Whitney-U test was used for not-normally distributed data. The demographic characteristics were then compared between both populations to possibly detect between-group differences. A significance level of α=0.05 was applied to all tests.

4.1.1 Data analysis

Feasibility is subdivided in practical and technical feasibility. Practical feasibility entails the measurement experience of subjects and observers, whereas technical feasibility entails the feasibility of obtaining appropriate outcomes of NDTs and EPs after analysis.

4.1.1.1 Practical feasibility

Measurable outcomes of practical feasibility were (1) percentage of subjects that completed all 4 NDT-EP measurements, and (2) the duration of the entire experiment in minutes. Furthermore, the measurement notes were reviewed for challenges reported by subjects and other effects potentially influencing outcomes of the NDT-EP measurements.

4.1.1.2 Technical feasibility

For the technical feasibility of NDT measurements, detection rates (DRs) and false positive rates (FPRs) were analysed. Intra-group differences, i.e., differences between the first two and the second two measurements, were evaluated with two-tailed paired sample t-tests or Wilcoxon sign rank tests, depending on the distribution of the data. Inter-group differences, i.e., differences between both study groups, were assessed with a two-tailed independent sample t-test or a Mann-Whitney-U test, dependent on the distribution of the data. A significance level of α=0.05 was applied to all tests.

$$\ln\left(\frac{P_d}{1-P_d}\right) \sim 1 + A_{SP} + A_{DP10} + A_{DP40} + TRL \qquad \text{Equation 1}$$

To further explore the technical feasibility of NDT measurements, NDTs and slopes of individual psychophysical curves were estimated. A generalized linear model (GLM) was used to describe the detection probability as a function of the model intercept, pulse amplitudes (A_{SP}, A_{DP10}, A_{DP40}). and the trial number (TRL). The equation used for the GLM is shown in Equation 1. The NDT is defined as the stimulus amplitude at which the detection probability is 50%. Individual average NDTs were estimated based on the GLM coefficients. Estimation quality was evaluated in general and per stimulus type (i.e., SP, DP10 and DP40). This evaluation was performed based on whether estimated values for either the threshold or slope were in a realistic range. The realistic range for thresholds was between 0 and 2.5 mA, and the realistic range for slopes was higher than 0 mA. When one predictor (i.e., either threshold or slope of a stimulus type) was estimated incorrectly, all

predictors were classified as incorrect, as all GLM outcomes become unreliable when one predictor is incorrectly estimated.

For evaluating technical feasibility of EP measurements, two derivations were used: Cz-M1,M2 as a central derivation for the P2 peak and T7-F4 as a contralateral derivation for the N1 peak. For each individual measurement, grand average EPs were made for detected and non-detected stimuli in both derivations. The P2 was defined as the most positive peak between 300 and 600 ms post-stimulus in the grand average EP of detected stimuli in Cz-M1,M2, and the N1 was defined as the most negative peak between 150 and 200 ms post-stimulus in the grand average EP of detected stimuli in T7-F4. Individual latencies for the P2 and N1 peaks were calculated by determining the moment where P2 was maximal and N1 was minimal. Furthermore, signal-to-noise ratios (SNRs) were determined for both derivations. The SNR(P2) was defined as the amplitude of P2 divided by the standard deviation of EEG activity at baseline (500 ms pre-stimulus to moment of stimulus). The SNR(N1) was defined as the negative amplitude of N1 divided by the standard deviation of EEG activity at baseline.

For further analyses, a selection was made which measurements could be included in which analysis. For NDT analysis, this selection was made based on realistic GLM estimations and adequate task performance. Adequate task performance was defined as a total DR of higher than 30% and a total FPR lower than 5%. Selection criteria for EP analysis were a sufficient SNR, i.e., higher than 2 in the central and higher than 1 in the contralateral derivation, and adequate task performance.

4.2 Results

Measurements for PSPS-T2 patients were conducted between June and September of 2022. 23 patients were included in this study, of which 12 in the 'SCS-OFF vs SCS-ON' group and 11 in the 'SCS-ON1 vs SCS-ON2' group. A total of 90 measurements were performed by these 23 subjects.

4.2.1 Subject characteristics

Demographic characteristics of the 'SCS-ON1 vs SCS-ON2'-group and the 'SCS-OFF vs SCS-ON'-group are shown in Table 4.1. The populations did not differ significantly regarding sex, age, BMI, NRS of the past week, change in NRS between the first and third NDT-EP measurements, CSI, ODI, duration of pain or duration of SCS. Significant differences can be seen in the NRS scores of the first and third NDT-EP measurements, with a higher NRS observed in the 'SCS-OFF vs SCS-ON'-group. In both populations, three and two patients took anticonvulsants and antidepressants respectively. Only in the 'SCS-OFF vs SCS-ON'-group, two patients used opioids within 24 hours before the experiment. Other medication included paracetamol and NSAIDs. In the 'SCS-ON1 vs SCS-ON2'-group, most patients were treated with burst stimulation, whereas most patients were treated with closed loop stimulation in the 'SCS-OFF vs SCS-ON'-group. Detailed individual subject characteristics can be seen in Table 4.2. The heterogeneity of the population regarding the location of the previous surgery, pain duration, pain side and pain medication can be noted by looking at this table.

Table 4.1: Subject characteristics for the 'SCS-OFF vs SCS-ON' group and the 'SCS-ON1 vs SCS-ON2' group. NRS – Numeric Rating Scale; CSI – Central Sensitisation Inventory; ODI – Oswestry Disability Index; SCS - Spinal Cord Stimulation.

	SCS-OFF vs SCS-ON (n=12)	**SCS-ON1 vs SCS-ON2** (n=11)	**p-value**
Sex (M/F)	5/7	6/5	-
Age (years)	55.9 ± 8.8	53.7 ± 8.7	0.555
BMI (kg/m^2)	28.9 ± 3.5	27.9 ± 4.2	0.555
NRS Score			
Past week	3.8 ± 2.1	3.0 ± 1.0	0.285
NDT-EP measurement 1	4.8 ± 2.3	2.4 ± 1.2	0.005*
NDT-EP measurement 3	4.1 ± 2.0	2.5 ± 1.3	*0.040**
Δ NRS (measurement 1 – measurement 3)	0.8 ± 2.8	0.2 ± 0.8	0.522
CSI	34.8 ± 11.2	31.2 ± 11.0	0.462
ODI	14.1 ± 4.5	14.2 ± 6.5	0.967
Pain medication intake[a] (n)			
Anticonvulsants (n)	3 (25.0%)	3 (27.3%)	-
Antidepressants (n)	2 (16.7%)	2 (18.2%)	-
Opioids (n)	2 (16.7%)	-	-
Affected side			
Left (n)	6 (50%)	5 (45.5%)	-
Right (n)	5 (41.7%)	3 (27.3%)	-
Left and right (n)	1 (8.3%)	3 (27.3%)	-
Duration of pain (years)	11.0 (5.3 – 33.5)	9.0 (7.0 – 16.0)	0.449
Duration of SCS[b] (months)	25.5 (7.8 – 61.8)	32.0 (19.0 – 39.0)	0.651
SCS settings			
Tonic stimulation (n)	1 (8.3%)	-	-
Closed loop stimulation[c] (n)	7 (58.3%)	4 (36.4%)	-
Burst stimulation (n)	4 (33.3%)	7 (63.6%)	-

Data is presented as mean ± standard deviation, median (minimum – maximum), or n (%) unless stated otherwise.
* Indicates significant difference (α=0.05)
[a] In the 24 hours prior to the experiment
[b] Duration since definitive implantation
[c] Closed loop stimulation as proposed by Saluda Medical[108]

Table 4.2: Individual clinical and treatment characteristics. AC – anticonvulsants; PCM – paracetamol; NSAID – non-steroid anti-inflammatory drugs; AD – antidepressants; OP – opioids; TR – Test-Retest population; OO – SCS-Off – SCS-On population.

Subject ID	Sex/ Age	Location previous surgery	Pain duration (years)	Pain side	Pain description	Pain medication	Lead location (tip)	Type of stimulation	Stimulator manufacturer	Clinically effective stimulation parameters[a]
ON1 vs ON2										
1	M/51	L4-L5	13	L+R	Nagging	AC	Bottom T7	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.6mA
2	F/43	L5-S1	7	L	Nagging	PCM, NSAID	Bottom T7	Closed loop	Saluda Medical	30 Hz, 400 µsec, 26 µV, 17 mA max
3	M/61	L4-L5	8	L	Stabbing	-	Top T8	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.7mA
4	F/51	L5-S1	8	R	Sharp, burning	PCM, AC	Top T7	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.3mA
5	F/57	L5-S1	10	R	Nagging, burning	AD	Bottom T8	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.4 mA
6	F/56	L3-L4-L5	16	L+R	Burning	-	Bottom T7	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 1.0 mA
7	M/61	L3-L4	3	L	Stabbing	AD	Top T8	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.3 mA
8	M/72	L3-L4-L5	17	L	Throbbing	AC	Top T8	Closed loop	Saluda Medical	30 Hz, 300 µsec, 33 µV, 20 mA max
9	F/47	L5-S1	2	R	Stabbing, nagging	-	Bottom T8	Closed loop	Saluda Medical	30 Hz, 300 µsec, 72 µV, 16 mA max
10	M/45	L4-L5	19	L+R	Nagging, pulling	-	Bottom T8	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.5 mA
11	M/47	L4-L5	9	L	Stabbing	PCM, NSAID	Mid T7	Closed loop	Saluda Medical	30 Hz, 240 µsec, 5 µV, 16 mA max
OFF vs ON										
1	M/44	L4-L5	6	R	Stabbing	-	Mid T7	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.5 mA
2	F/55	L5-S1	7	L	Stabbing	NSAID, AC, OP	Bottom T6	Closed loop	Saluda Medical	30 Hz, 230 µsec, 23 µV, 17 mA max
3	M/58	L4-L5 + L5-S1	44	L	Nagging, sharp	PCM, AC, AD	Top T9	Tonic	Abbott	30 Hz, 300 µsec, 14 mA
4	M/43	L4-L5	9	L	Nagging	-	Top T8	Closed loop	Saluda Medical	10 Hz, 260 µsec, 18 µV, 9 mA max
5	F/49	L5-S1	21	L	Burning, pressing	AC, OP	Top T8	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 1.0 mA
6	F/60	L3-L4 + L4-L5	4	R	Pressing, nagging	NSAID, AD	Bottom T7	Closed loop	Saluda Medical	30 Hz, 400 µsec, 12 µV, 16 mA max
7	M/51	L4-L5 + L5-S1	32	R	Stabbing	NSAID	Mid T8	Closed loop	Saluda Medical	30 Hz, 240 µsec, 5 µV, 12 mA max
8	F/65	L3-L4	58	L+R	Sharp	-	Top T8	Closed loop	Saluda Medical	30 Hz, 240 µsec, 47 µV, 15 mA max
9	M/62	L4-L5	34	L	Throbbing, nagging	PCM, NSAID	Top T9	Closed loop	Saluda Medical	30 Hz, 480 µsec, 24 µV, 26 mA max
10	F/73	L5-S1	5	R	Nagging	PCM	Bottom T9	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.15 mA
11	F/51	L4-L5 + L5-S1	13	R	Sharp, nagging	PCM, NSAID	Bottom T7	Burst	Abbott	40 Hz, 500 Hz, 1000 µsec, 0.25 mA
12	F/60	L4-L5	5	L	Nagging	NSAID	Top T7	Closed loop	Saluda Medical	30 Hz, 240 µsec, 28 µV, 14 mA max

[a] Stimulation parameters for closed loop stimulation (Saluda Medical) include a maximum amplitude due to the variability in pulse amplitude.

4.2.2 Practical feasibility

Of all 11 subjects of the 'SCS-ON1 vs SCS-ON2' group and 12 of the 'SCS-OFF vs SCS-ON' group, respectively 9 and 11 completed all 4 out of 4 measurements during the experiment. In the 'SCS-ON1 vs SCS-ON2' group, two subjects did not complete the fourth measurement due to long duration of the previous three measurements. The unfinished measurement in the 'SCS-OFF vs SCS-ON' group was caused by a combination of equipment malfunction and long duration of the experiment. Overall average duration of the experiments was 286 minutes ($\pm$ 25 minutes). For the 'SCS-OFF vs SCS-ON' and 'SCS-ON1 vs SCS-ON2' groups specifically, the average durations were 283 minutes ($\pm$ 29 minutes) and 290 minutes ($\pm$ 22 minutes), respectively.

All subjects reported challenges in performing the experiment. Most importantly, all subjects of both groups brought up their inability to sit still for the duration of the measurements. For 9 subjects, the need to move was so great, they released the button during one or more measurements to have a short break to stretch their legs and/or back. Most button releases occurred in the third or fourth measurement, which corresponds with reported lack of concentration and need for extra encouragement. Lack of concentration and need for extra encouragement were reported after 28 and 13 measurements, respectively. Lastly, 2 out of 12 subjects in the 'SCS-OFF vs SCS-ON' group mentioned it was difficult to discern sensations of the applied stimuli from usual pain sensations in their lower limbs when the stimulator was turned off. With the stimulator turned on, 5 out of 12 subjects in the 'SCS-OFF vs SCS-ON' group reported difficulty discerning sensations of applied stimuli from the sensations caused by the stimulator. This issue was also reported by 7 out of 11 subjects in the 'SCS-ON1 vs SCS-ON2' group.

4.2.3 Technical feasibility and data quality

DRs, average RTs, and FPRs are shown in Table 4.3 for all subjects in the 'SCS-ON1 vs SCS-ON2' and 'SCS-OFF vs SCS-ON' populations. DRs in the 'SCS-ON1 vs SCS-ON2' group mostly vary between 0 and 50%, and FPRs vary between 0 and 100%. Average RTs are similar for all groups (i.e., SCS-ON1, SCS-ON2, SCS-OFF and SCS-ON). No significant intra-group differences were found for the 'SCS-ON1 vs SCS-ON2' group. In the 'SCS-OFF vs SCS-ON' group, the total FPR and FPR for DP40 were significantly higher during SCS-ON than during SCS-OFF. Significant inter-group differences were only found in the DRs. DRs were significantly different between the 'SCS-ON1 vs SCS-ON2' and 'SCS-OFF vs SCS-ON' group for all stimulus types during the third and fourth measurements. Furthermore, the total DR and DR for DP40 significantly differed between both groups for the first and second measurements. Examples of experiments with different DRs and FPRs are shown in Figure 4.1. The left panel shows an example with adequate task performance, and the right panel with poor task performance.

Table 4.3: Detection rates (%), average response times (ms), and false positive rates (%) for all subjects in both populations. Results are shown for the total measurement and per setting. SCS – Spinal Cord Stimulation; M1+2 – measurements 1 and 2 (SCS-OFF vs SCS-ON1); M3+4 – measurements 3 and 4 (SCS-ON vs SCS-ON2); SP – single pulse; DP10 – double pulse with a 10 ms inter-pulse interval (IPI); DP40 – double pulse with a 40 ms IPI.

	SCS-OFF vs SCS-ON (n=12; m=46)			SCS-ON1 vs SCS-ON2 (n=11; m=41)			p-values	
	SCS-OFF	SCS-ON	p-value	SCS-ON1	SCS-ON2	p-value	M1+2	M3+4
DR (%)								
Total	42.6 (18.1 - 48.5)	44.1 (6.0 – 49.8)	0.784	35.3 (0.7 – 46.9)	33.7 (0.9 – 48.5)	0.940	*0.039**	*0.008**
SP	36.6 (2.6 - 48.0)	37.9 (5.3 – 50.3)	0.670	22.8 (0.6 – 45.0)	22.0 (0.0 – 47.7)	0.936	0.125	*0.019**
DP10	46.6 (26.5 - 51.0)	46.4 (7.3 – 52.3)	0.976	41.8 (0.0 – 51.0)	40.7 (0.7 – 49.7)	0.970	0.119	*0.007**
DP40	45.7 (19.3 - 49.7)	46.4 (5.3 – 51.7)	0.855	39.8 (0.7-48.7)	40.0 (1.3 – 48.1)	0.881	*0.012**	*0.005**
RTs (ms)								
Total	610.8 ± 66.1	603.2 ± 77.1	0.338	613.3 ± 69.1	608.1 ± 76.3	0.581	0.447	0.998
SP	582.4 ± 58.5	598.0 ± 86.2	0.402	565.5 ± 148.6	595.1 ± 92.4	0.404	0.490	0.801
DP10	610.5 ± 71.6	590.1 ± 76.4	0.168	601.9 ± 68.7	606.4 ± 81.8	0.831	0.718	0.982
DP40	626.6 ± 69.3	621.4 ± 79.2	0.330	604.3 ± 134.2	619.1 ± 75.7	0.854	0.439	0.945
FPR (%)								
Total	1.1 (0.5 – 19.1)	1.4 (0.4 – 66.7)	*0.036**	1.7 (0.0 – 100.0)	1.7 (0.0 – 75.0)	0.809	0.419	0.820
SP	2.3 (0.0 – 50.0)	1.6 (0.0 – 75.0)	0.204	1.6 (0.0-100.0)	2.4 (0.0 – 100.0)	0.975	0.482	0.617
DP10	0.0 (0.0 – 20.6)	1.3 (0.0 – 63.6)	0.125	1.3 (0.0 – 12.0)	0.0 (0.0 – 100.0)	0.609	0.767	0.831
DP40	0.0 (0.0 – 20.7)	2.5 (0.0 – 62.5)	*0.006**	1.8 (0.0 – 100.0)	1.7 (0.0 – 50.0)	0.943	0.127	0.693

Data is presented as mean ± standard deviation or median (minimum – maximum).
* Indicates significant difference (α=0.05)

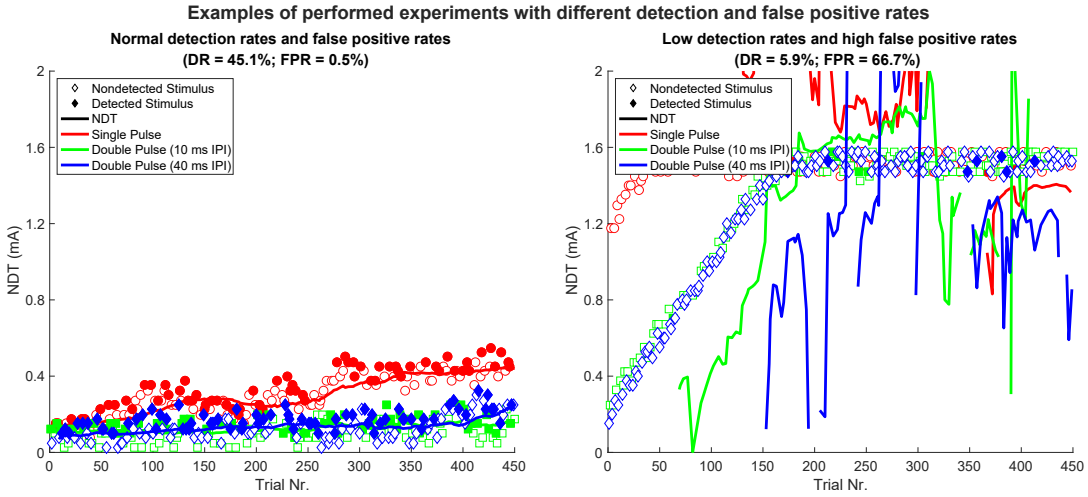

Figure 4.1: Examples of measurements with different task performance, i.e., different detection rates (DR) and false positive rates (FPR). Detection thresholds of three stimulus types (single pulse, double pulse with a 10 ms inter-pulse interval (IPI), and double pulse with a 40 ms IPI) are shown. The left panel depicts a measurement with normal task performance (relatively high DR and low FPR), and the right panel depicts a measurement with poor task performance (low DR and high FPR).

An overview of estimation quality of the GLM can be seen in Figure 4.2. Out of a total of 87 measurements, 56 estimations were realistic, whereas 31 were incorrect. Realistic estimations of an incorrect GLM are indicated in red. Most incorrect estimations stemmed from the SP thresholds and slopes, with 28 thresholds estimated either too low or too high (14 and 14, respectively) and 17 slopes too low. Two examples of psychophysical curves based on GLM estimations are shown in Figure 4.3. The left panel shows an example of thresholds and slopes estimated within realistic bounds, with a detection probability of 0% for 0 mA, thresholds of approximately 0.2 and 0.3 mA

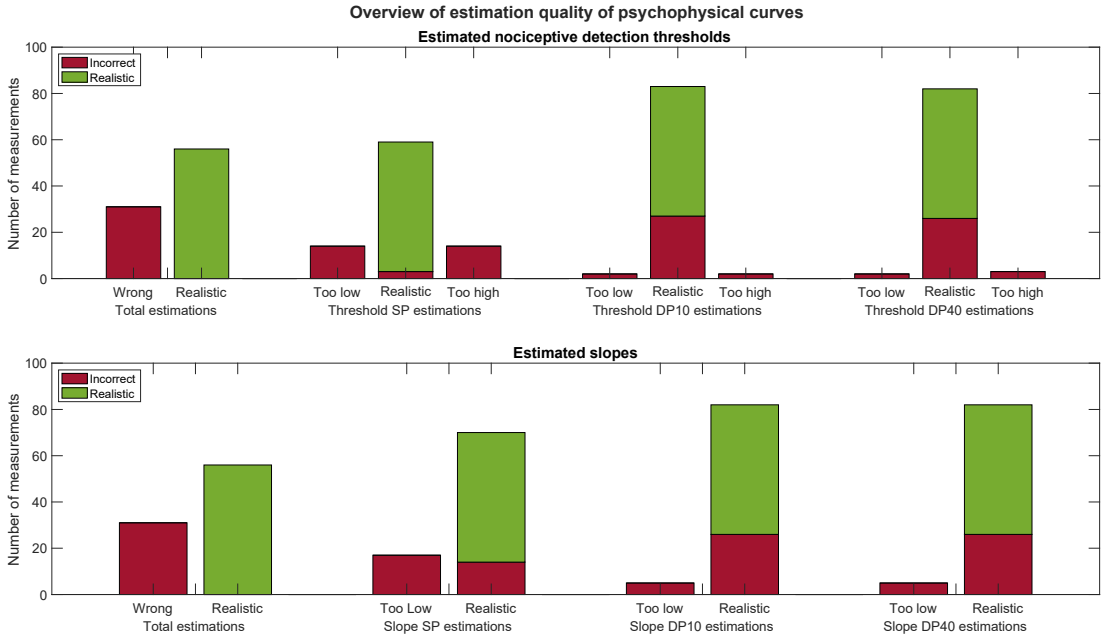

Figure 4.2: An overview of estimation quality of a generalized linear model (GLM) for characteristics of the psychophysical curve, i.e., nociceptive detection thresholds (NDTs) and slopes. Red bars illustrate measurements for which the GLM did not fit correctly in general, and green bars illustrate measurements for which the GLM did fit realistically. When red bars are shown beneath green bars, this means the characteristic (either slope or NDT for that stimulus type) was estimated within realistic bounds, but at least one predictor of the GLM was not within realistic bounds.

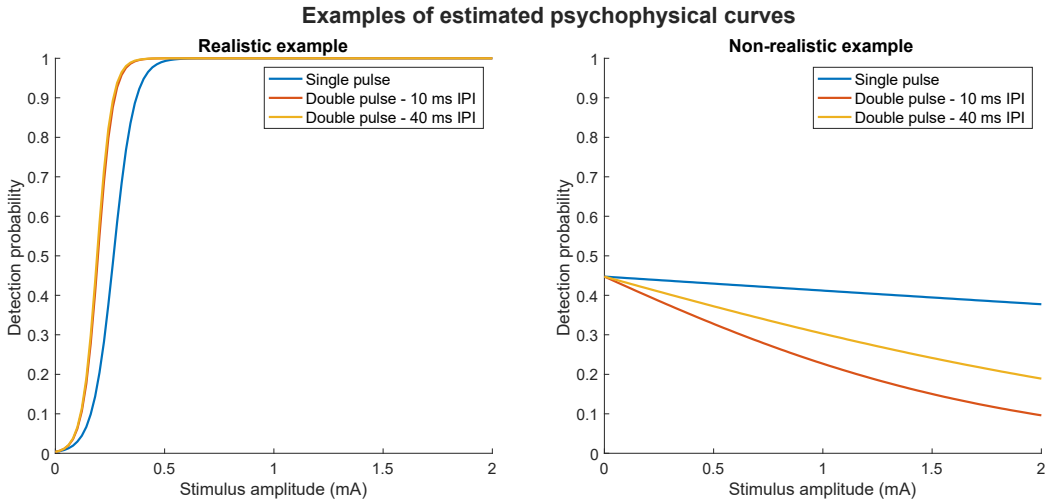

Figure 4.3: Two examples of psychophysical curves. These curves were derived from a generalized linear model (GLM), which estimated nociceptive detection thresholds (NDTs) and slopes. The NDT was defined as the amplitude at which the detection probability is 50%. Psychophysical curves are shown for the three stimulus types (single pulse, double pulse with a 10 ms inter-pulse interval (IPI), and double pulse with a 40 ms IPI). The left panel depicts psychophysical curves with NDTs and slopes estimated within realistic bounds, and the right panel depicts psychophysical curves with NDTs and slopes estimated outside realistic bounds.

and a positive slope. The right panel of Figure 4.3 shows an example of incorrectly estimated thresholds and slopes, which is emphasized by the negative slopes and a negative threshold. Furthermore, the detection probability is not 0% for 0 mA.

Signal quality of the central and contralateral derivations was evaluated using SNRs. An overview of signal quality is provided in Figure 4.4. SNRs lower than 2 in the central derivation and lower than 1 in the contralateral derivation were classified as insufficient and are shown in red. In the central derivation, 20 measurements had a SNR lower than 2, and 27 measurements had a SNR lower than 1 in the contralateral derivation. Figure 4.5 and Figure 4.6 illustrate examples of different grand average EPs in, respectively, the central derivation and the contralateral derivation, with different SNRs (high SNR in the left panels and low SNR in the right panels). All individual grand average EPs for both the central derivation (Cz-M1,M2) and the contralateral derivation (T7-F4) can be found in Appendix A2. The distribution of latencies for both P2 and N1 is shown in Figure 4.7. Furthermore, Figure 4.8 illustrates P2 and N1 amplitudes on the affected and unaffected sides. In this figure, only measurements with an SNR higher than 2 were included. As seen in Figure 4.8, almost all measurements showed an increased P2 amplitude or a decreased N1 amplitude for detected stimuli in comparison to non-detected stimuli.

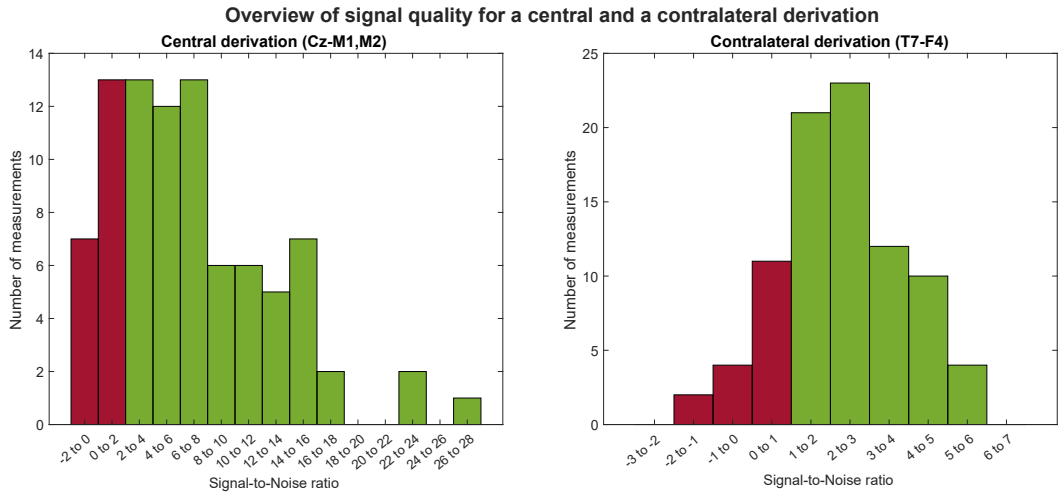

Figure 4.4: An overview of signal quality for a central (left) and contralateral (right) derivation. In the central derivation (left panel), bars shown in red have a Signal-to-Noise ratio (SNR) lower than 2, and bars shown in green have an SNR higher than 2. In the contralateral derivation (right panel), bars shown in red have an SNR lower than 1, and bars shown in green have an SNR higher than 1.

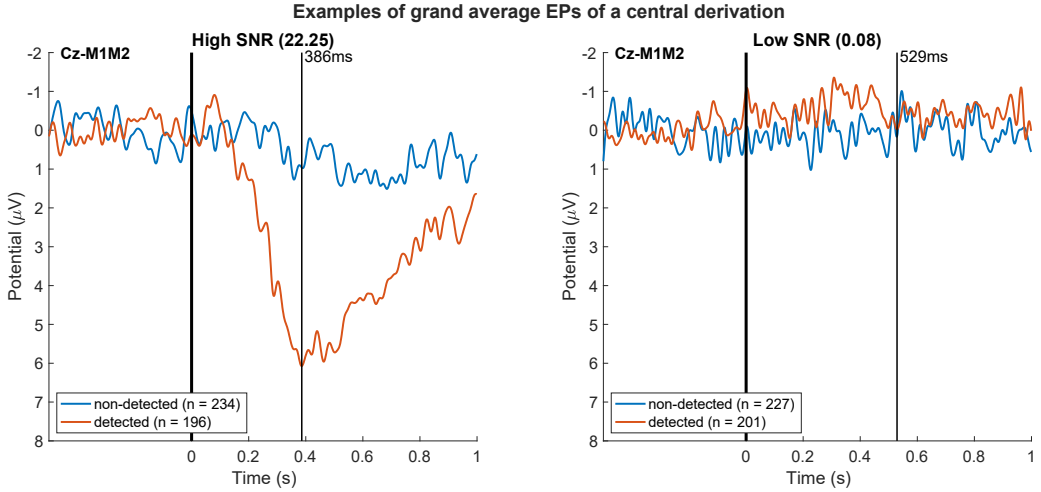

Figure 4.5: Two examples of grand average EPs in the central derivation (Cz-M1,M2) for one measurement with a high Signal-to-Noise ratio (SNR) (left panel) and one measurement with a low SNR (right panel). Orange lines indicate detected stimuli, blue lines indicate non-detected stimuli. The number of trials used for computing the grand average is shown in the legend. The vertical line at T=0 indicates the moment of intra-epidermal stimulation, and vertical lines at 386 ms and 529 ms illustrate individual latencies for these subjects.

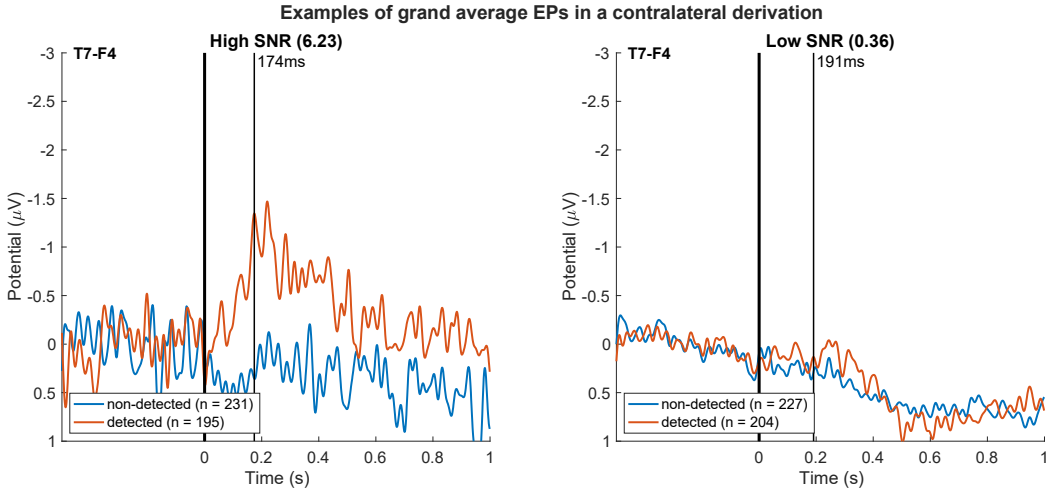

Figure 4.6: Two examples of grand average EPs in the contralateral derivation (T7-F4) for one measurement with a high Signal-to-Noise ratio (SNR) (left panel) and one measurement with a low SNR (right panel). Orange lines indicate detected stimuli, blue lines indicate non-detected stimuli. The number of trials used for computing the grand average is shown in the legend. The vertical line at T=0 indicates the moment of intra-epidermal stimulation, and vertical lines at 174 ms and 191 ms illustrate individual latencies for these subjects.

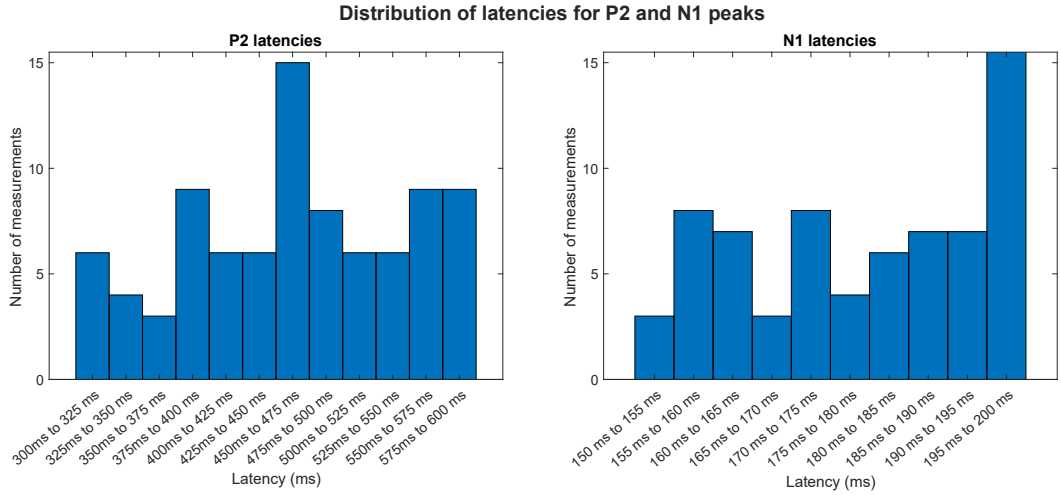

Figure 4.7: Overview of latency distributions for the P2 (left panel) and N1 (right panel) peaks. Latencies were determined per measurement.

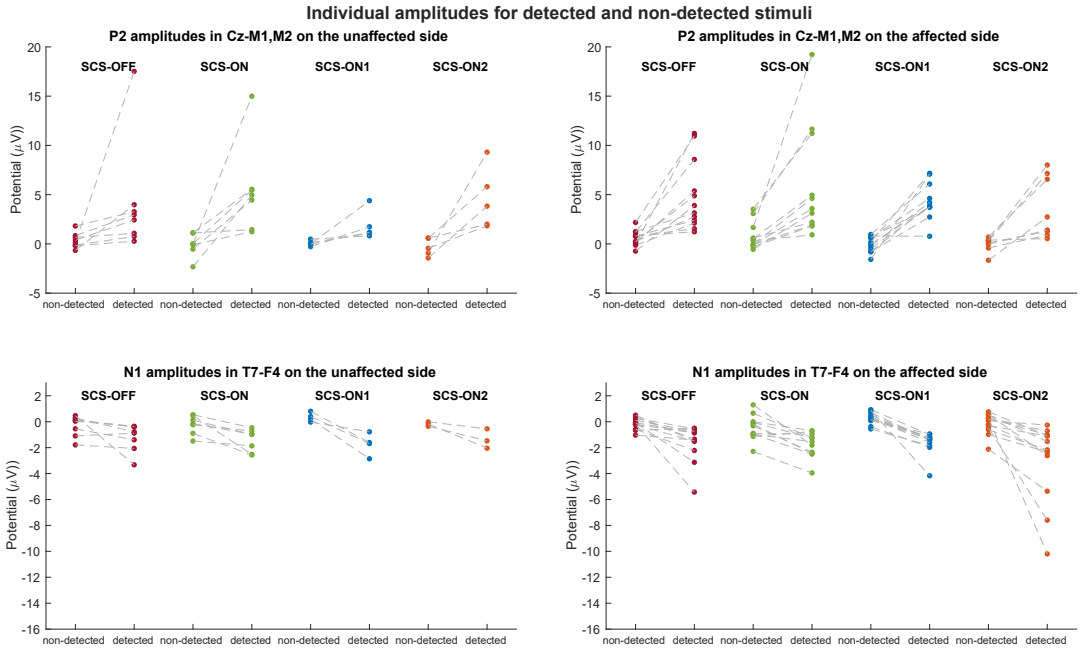

Figure 4.8: Visualisation of grand average EP amplitudes in a central derivation (Cz-M1,M2) and a contralateral derivation (T7-F4) on unaffected and affected sides. Both the amplitude of non-detected and detected stimuli are shown for the SCS-OFF, SCS-ON, SCS-ON1 and SCS-ON2 groups. Only measurements with sufficient SNR were included in this figure, i.e., SNR higher than 2 in Cz-M1,M2 and SNR higher than 1 in T7-F4. Values connected by a grey dashed line belong to the same measurement.

Based on previous results, measurements were included and excluded per analysis, i.e., NDT analysis, EP analysis of the central derivation, and EP analysis of the contralateral derivation. A flowchart representing this measurement selection is shown in Figure 4.9. 23 patients were included in this study, who performed a total of 90 measurements, of which 3 datasets were found to be incomplete and were therefore excluded from analysis. For NDT analysis, the first criterion was whether the GLM estimated NDTs and slopes within realistic bounds, i.e., NDTs between 0 and 2.5 mA and slopes steeper than 0. If this criterion was met, the task performance was classified as either adequate or inadequate. Adequate task performance was defined as a total DR higher than 30% and a total FPR lower than 5%. For EP analysis of both derivations, measurements were excluded when the SNR was lower than 2, after which task performance was evaluated. The number of included measurements per analysis can be seen in green in Figure 4.9. Which measurements of which subjects were used per analysis can be found in Appendix A3. It was found that measurements that showed equal P2 or N1 amplitudes for non-detected and detected stimuli, as shown in Figure 4.8, were excluded based on task performance.

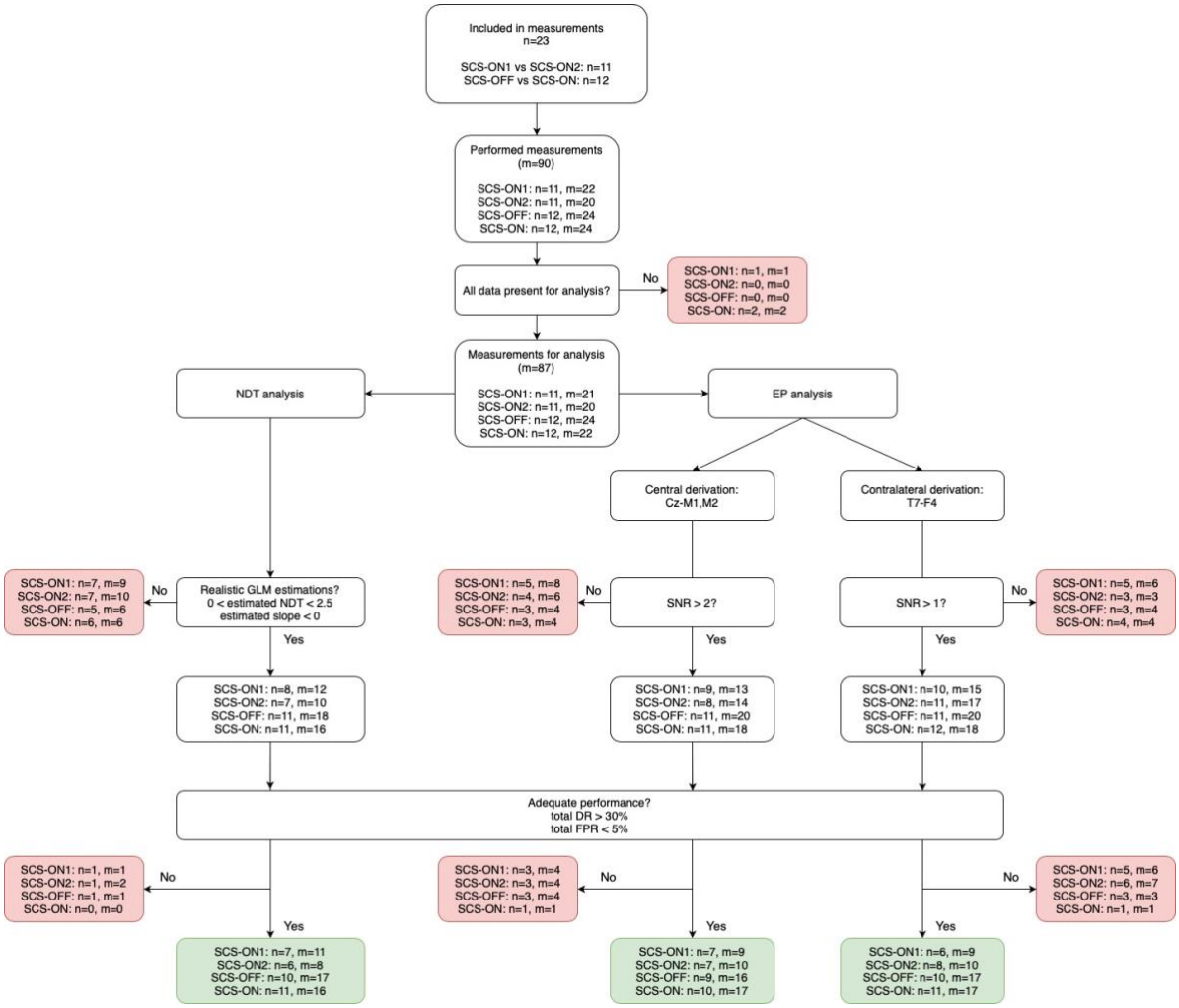

Figure 4.9: Flowchart of included subjects, performed measurements, and measurements included for either analysis of nociceptive detection thresholds (NDTs) or evoked potentials (EPs). Measurements excluded per step are shown in red, whereas eventually included measurements are shown in green.
n – number of subjects; m – number of measurements; SCS – Spinal Cord Stimulation; GLM – generalized linear model; SNR – Signal-to-Noise ratio; DR – detection rate; FPR – false positive rate.

4.3 Discussion

In this explorative study, one primary objective was to determine feasibility of the NDT-EP method during SCS in PSPS-T2 patients while stimuli were applied to the foot of affected as well as unaffected lower limbs. This protocol of the NDT-EP method appears practically feasible in PSPS-T2 patients treated by SCS. However, technical feasibility seems questionable due to great variability in DRs, occasionally excessively high FPRs, the number of incorrectly fitted GLMs, and variability in SNRs. Additionally, the number of measurements included per analysis type is lower than desired. Strengths and limitations of this study and recommendations for future research are discussed in the general discussion in Chapter 7 - Discussion.

4.3.1 Practical feasibility

The practical feasibility of this form of the experiment was determined based on the percentage of subjects who completed all 4 NDT-EP measurements, the duration of the experiment, and subject experience during the experiment. Two of 23 subjects did not complete the fourth NDT-EP measurements due to time constraints. One additional subject did not complete the fourth measurement, as equipment malfunctioned during their third measurement, which they completed approximately halfway. After restoring equipment function, the subject indicated only wanting to perform one more measurement, due to duration of the experiment.

This was the second in a line of studies regarding the NDT-EP method to perform 4 NDT-EP measurements during one experiment. It was known beforehand that this would lead to a longer duration of experiments than usual. However, the average duration of the experiment was even longer than previously expected (286 minutes and 245 minutes, respectively). The longer duration was generally caused by difficulty lowering impedance of electrodes in the EEG cap and extended duration of the familiarisation phase. In previous studies, subjects also reported challenges related to long duration of the experiment, e.g., lack of concentration[109]. These are mostly related to the duration of individual measurements, as opposed to the duration of the entire experiment. Challenges reported during the experiment included inability to sit still, lack of concentration, need for extra encouragement, difficulty discerning applied stimuli from usual pain sensations, and difficulty discerning sensations of applied stimuli from the sensations caused by SCS.

Applying the NDT-EP method to PSPS-T2 patients treated by SCS and stimulus application to the foot dorsa seems practically feasible. To improve patient comfort, measurements should be shortened, as most reported challenges are related to measurement duration. Recommendations and considerations for shortening measurements are described in Section 7.3 - Recommendations.

4.3.2 Technical feasibility and data quality

Technical feasibility of applying the NDT-EP method on the feet of PSPS-T2 patients treated by SCS was evaluated in several ways: DRs, FPRs, RTs, GLM estimation quality, and EEG signal quality. Median DRs were mostly around 40% for both groups, but the ranges were large, with a lowest DR of 0% in the ‘SCS-ON1 vs SCS-ON2’ group. While no significant differences were found between the first two and the second two measurements within both groups, DRs of all stimulus types differed significantly between both groups for the second two measurements. Furthermore, the DRs for SP stimuli were lower than those of the double pulse stimuli, especially in the ‘SCS-ON1 vs SCS-ON2’ group. Preliminary results of previous studies regarding the NDT-EP method also indicate lower DRs for SP stimuli[23,90,110,111]. A few possible causes have been hypothesised. Paired pulse facilitation presumably affects the process from transmission to perception of double pulse stimuli, which may make them more clearly perceivable. Furthermore, variations in attention or detection criterion may also play a role.

A false positive detection was defined as a response with an RT lower than 150 ms, which was pragmatically chosen. Responses with an RT lower than 150 ms are considered a result of extremely slow responses to the previous stimulus, which occur when the subject, for instance, is doubtful or randomly releases the stimulator button. Median FPRs are reasonably low, at least under 5%. However, the minima and maxima are wide, ranging from 0% to 100% for several stimulus types. The FPRs of 100% occurred in one subject who performed very poorly, with the lowest DRs in the ‘SCS-ON1 vs SCS-ON2’ group. Individual measurements with high FPRs would

have been excluded based on DR as well, except for 5 measurements of 2. This shows that most inadequate task performances would be excluded based on DR, but the FPR is an added value when it comes to assessing task performance. It is suggested to continue to implement the FPR as an exclusion criterion.

Mean RTs were presented for all stimulus settings, as well as in general. Average RTs seen in this study are approximately 100 ms higher than previously found RTs on the hands[23]. This could be explained by the additional length of nociceptive Aδ-fibres from the foot to the spinal column compared to those from the hand. However, RTs remain difficult to interpret on a group level due to a large acceptable window. During measurements, it was observed that stimuli far above the estimated threshold were detected faster than average, and stimuli below the estimated threshold were detected slower than average. On individual level, the RTs could help indicate whether a stimulus was slightly or far above the estimated detection threshold.

As could be seen in Figure 4.2, the most incorrect values were estimated for the SP stimulus type. Of the 31 incorrectly fitted GLMs in total, only three had determined a realistic value for the SP threshold. On the other hand, almost all GLMs provided realistic estimations of DP10 and DP40 stimulus types, for the threshold as well as the slope. The estimation quality coheres with task performance, as task performance is often worse for the SP stimuli, which was also the case in this study. The coherence between estimation quality and task performance is further corroborated by the number of measurements excluded after selection based on estimation quality. Only four measurements were excluded based on task performance after selection on estimation quality was performed. This was expected, as it was known beforehand that sufficient data was necessary to adequately estimate NDTs. The measurements that were excluded based on inadequate task performance, where excluded based on the FPR. This further substantiates the future use of the FPR as an exclusion criterion.

The signal quality of the central and contralateral derivations was evaluated based on SNR, where the noise was defined as the standard deviation of the EEG activity at baseline (500 ms pre-stimulus to moment of stimulus). A measurement was defined as having adequate signal quality when the SNR was higher than 2 in the central derivation and higher than 1 in the contralateral derivation. This occurred for 67 of 87 measurements in the central derivation, and 70 of 87 measurements in the contralateral derivation. When considering both derivations, this means that approximately 20% of all measurements showed insufficient SNR. Although the difficulty of measuring EPs in the contralateral derivation was expected due to lower amplitudes and therefore SNRs in general, this difficulty was not expected in the central derivation. When looking at the individual grand average EPs, shown in Appendix A2, two possible causes were identified: (1) high levels of noise at baseline or (2) no occurrence of an EP.
Increased levels of noise were also observed during the previous study performed in PSPS-T2 patients treated by SCS[23]. One explanation for increased levels of noise could be the high variance in EPs that was seen during cleaning. This may have been caused by subjects repositioning while having the button pressed. It was checked visually for a few random samples whether increases in variance corresponded to moments of repositioning, which seemed to correspond. Furthermore, increased levels of noise may have occurred due to the use of different EEG caps that were close to malfunction or had a faulty electrode. This possibility is described in further detail in Chapter 7 - Discussion. In addition to high variance in EPs and a possible effect of using different EEG caps, the increased levels of noise could also be caused by SCS.
The absence of an EP seemed to occur in specific patients, which led to the hypothesis that this could be caused by personal amplification factors of received signals, i.e., the EP amplitude is too low to be identified. In previous studies regarding the NDT-EP method, individual grand averages were rarely computed or were not shown[23,90,110]. Usually, grand average EPs are analysed on a group level, which diminishes effects of individual subjects possibly not producing EPs with sufficient amplitude to be identified as an EP.

When applying the criterion of a sufficient SNR, the measurement of EPs in both the central and contralateral derivation seems feasible. Almost all measurements showed an increased P2 amplitude or a decreased N1 amplitude for detected stimuli in comparison to non-detected stimuli.

The few measurements that did not, were later excluded for analysis based on task performance. The P2 and the N1 amplitudes were similar to those found in the previous study regarding the NDT-EP method in PSPS-T2 patients treated by SCS[23] and other previous work regarding the same patient population[21].

Technical feasibility of the NDT-EP method using IES on the foot dorsa, i.e., affected and unaffected, seems questionable. Great inter-subject variability for DRs and FPRs raises questions regarding adequate task performance and its assessment. Task performance is currently evaluated based on DRs and FPRs, but cut-off values were determined pragmatically or based on visual analysis. However, this is a first framework to further establish a window of acceptable task performance, which should consider adequate tracking of NDTs as well as NDTs reflecting detection thresholds of nociceptive fibres. The feasibility of measuring EPs was affected by increased levels of noise, for which a few possible causes were identified. Noise could be reduced by stressing the necessity of remaining in the same position to the subject or using the same EEG cap for most subjects. Furthermore, it would be interesting to investigate the effect of SCS on levels of noise. It is not completely clear what the effect of noise is on features of the EP, so it would be worthwhile to keep this into consideration for future studies.

5 Effect of Spinal Cord Stimulation

The focus of this chapter lies on the primary objective "to explore effects of SCS on NDTs and EPs in PSPS-T2 patients while electrical stimuli are applied to the foot". First, methods specific to this objective are described, after which the results will be described. Results of the 'SCS-OFF vs SCS-ON' group are included to study potential effects of SCS, whereas results of the 'SCS-ON1 vs SCS-ON2' group are included to distinguish potential SCS effects from potential session effects. Lastly, all results are evaluated in the discussion.

5.1 Methods

5.1.1 Data analysis

Measurements were included or excluded as described in Chapter 4 - Experimental feasibility and data quality and Figure 4.9. As such, different individual measurements were included in the different analyses (i.e., NDT, central EP, and contralateral EP analysis). Which specific measurements this pertains, can be found in Appendix A3. Due to small sample sizes after removal of inadequate measurements, usual analysis methods for NDT-EP outcomes as described in Section 2.3.2 – NDT-EP method do not apply. Furthermore, no statistical testing was performed due to small sample sizes.

5.1.1.1 Nociceptive detection thresholds

To evaluate NDTs, a psychophysical curve was determined using a GLM to describe the detection probability as a function of the model intercept, pulse amplitudes (A_{SP}, A_{DP10}, A_{DP40}), and the trial number (TRL). The GLM is shown in Equation 2. The NDT is defined as the stimulus amplitude at which the detection probability is 50%. Individual average NDTs (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve were then computed based on the GLM coefficients. Equation 2 was applied for two scenarios: (1) SCS-OFF vs SCS-ON and (2) SCS-ON1 vs SCS-ON2.

First, the effect of SCS (i.e., SCS-OFF or SCS-ON) and the affected side was computed using a linear model with log-transformed variables. The different situations in the first scenario (i.e., (1) affected & SCS-OFF, (2) unaffected & SCS-OFF, (3) affected & SCS-ON, (4) unaffected & SCS-ON) were included in Equation 2 as Sit, which is an abbreviation of "situation". Note that affected implies not only affected by PSPS-T2, but also affected by SCS.

Second, the session effect (i.e., SCS-ON1 or SCS-ON2) and the affected side was computed with the same model. Situations in scenario 2 were altered to (1) affected & SCS-ON1, (2) unaffected & SCS-ON1, (3) affected & SCS-ON2, and (4) unaffected & SCS-ON2. These altered scenarios were then included in Equation 2 as Sit.

$$\ln\left(\frac{P_d}{1-P_d}\right) \sim 1 + A_{SP} * Sit + A_{DP10} * Sit + A_{DP40} * Sit + TRL * Sit \qquad \text{Equation 2}$$

5.1.1.2 Evoked potentials

A central (Cz-M1,M2) and a contralateral (T7-F4) derivation were used to derive EP signals. In Chapter 4 - Experimental feasibility and data quality, P2 and N1 latencies and SNR(P2) and SNR(N1) were determined per measurement. The predetermined latencies were used to compute P2 and N1 amplitudes per epoch in their respective derivations. Mean amplitudes (μ(P2) and (μ(N1)) and standard deviations of the amplitudes (σ(P2) and σ(N1)) were then calculated.

5.2 Results

First, results are shown for the 'SCS-OFF vs SCS-ON' group for NDT analysis as well as EP analysis, after which the results for the 'SCS-ON1 vs SCS-ON2' group are shown.

5.2.1 Effect of SCS

5.2.1.1 Nociceptive detection thresholds

Figure 5.1 depicts individual NDTs (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve for the 'SCS-OFF vs SCS-ON' group. NDTs on the affected side during SCS-OFF seem lower than on the unaffected side during SCS-OFF for all stimulus types. Furthermore, NDTs seem more similar for the affected and unaffected sides during SCS-ON. Slopes seem steeper on the affected side than on the unaffected side for all stimulus types during SCS-OFF as well as during SCS-ON. However, no evident change can be seen in steepness of the slopes between SCS-OFF and SCS-ON.

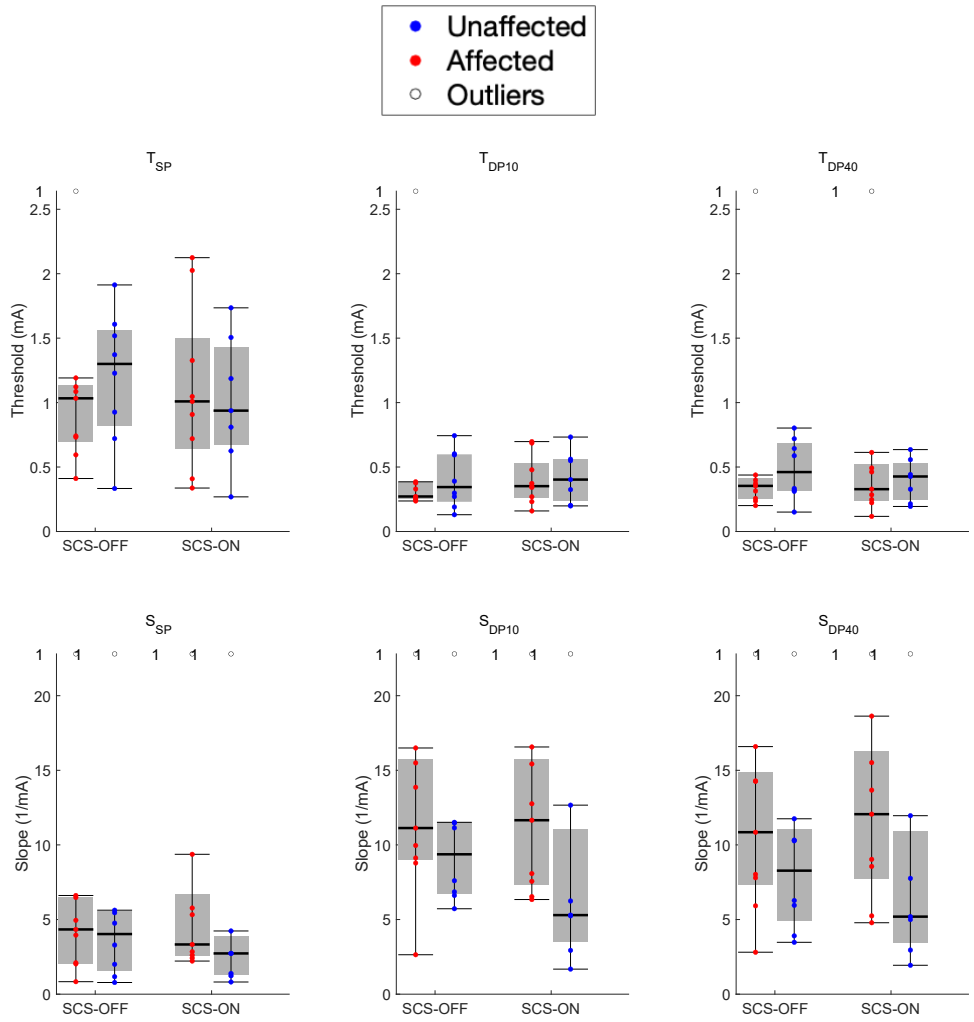

Figure 5.1: Derived detection thresholds (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve from the 'SCS-OFF vs SCS-ON' group on the affected and unaffected sides. The thresholds and slopes were averaged over the entire measurement. Values on the affected side are depicted in red, whereas values on the unaffected side are depicted in blue.

5.2.1.2 Evoked potentials

SNRs, latencies, and means and standard deviations of the P2 amplitude of individual EPs in the 'SCS-OFF vs SCS-ON' group are shown in Figure 5.2. Measurements performed on the affected side are depicted in red, whereas measurements performed on the unaffected side are depicted in blue. The distribution of SNRs and latencies are relatively similar, with a slightly longer latency on the affected side with SCS-ON. The median of mean P2 amplitudes is higher on the unaffected

side than the affected side during SCS-OFF. During SCS-ON, the mean P2 amplitudes seem more similar. Standard deviations seem higher on the affected side than the unaffected side, independent of SCS-OFF or SCS-ON.

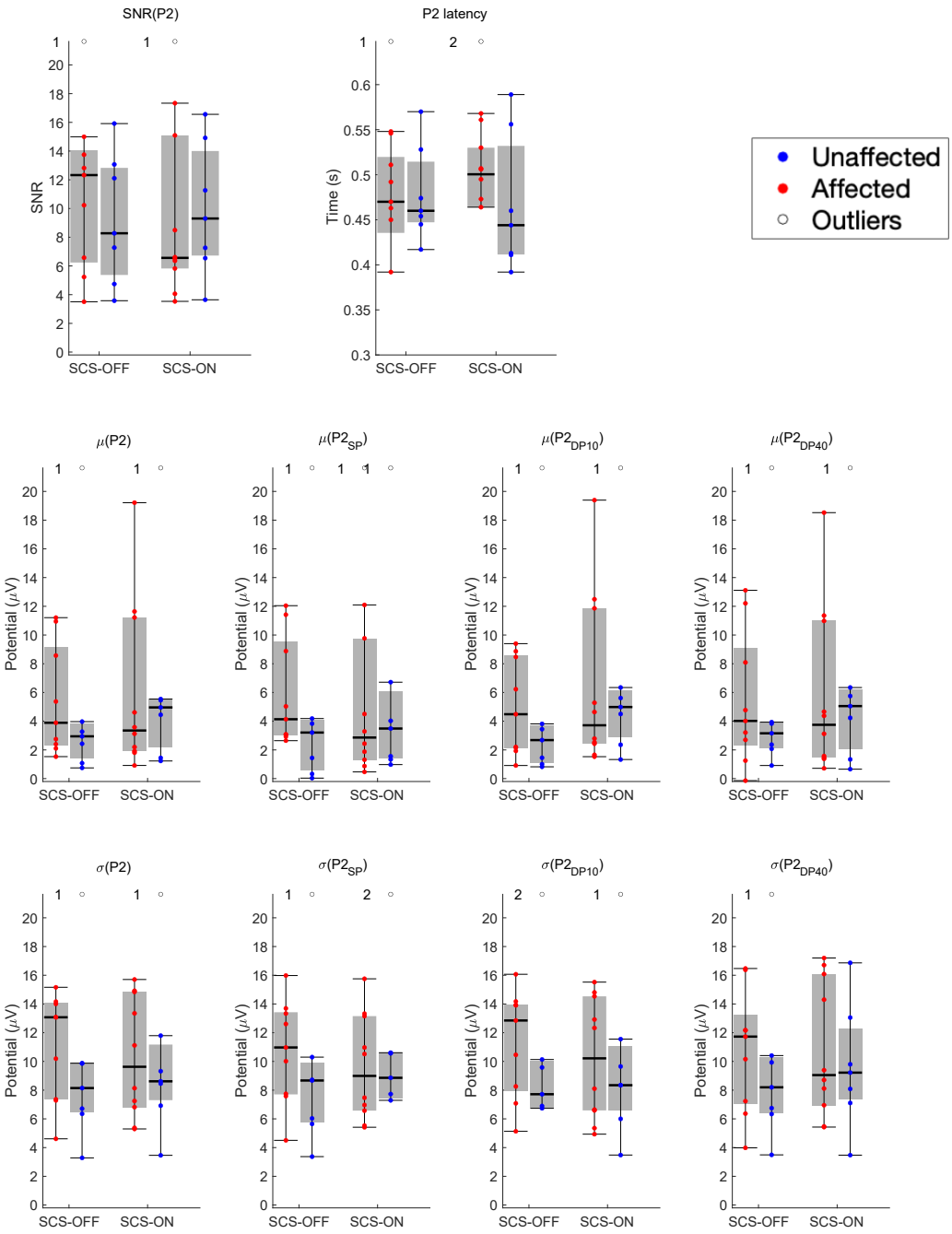

Figure 5.2: Means (μ) and standard deviations (σ) of P2 amplitudes from individual EPs in the central derivation Cz-M1,M2 from the 'SCS-OFF vs SCS-ON' group on the affected and unaffected sides. Values on the affected side are depicted in red, whereas values on the unaffected side are depicted in blue.

Figure 5.3 shows SNRs, latencies, and means and standard deviations of the N1 amplitude in the 'SCS-OFF vs SCS-ON' group. The SNR seems higher on the affected side during SCS-ON than the other situations. The distributions of latencies are similar for all situations. Mean N1 amplitudes are similar between all groups and for all stimulus types, except for the affected side during SCS-ON for DP10. Standard deviations of N1 amplitudes seem lower on the unaffected side than the affected side during SCS-OFF, but seem more similar during SCS-ON.

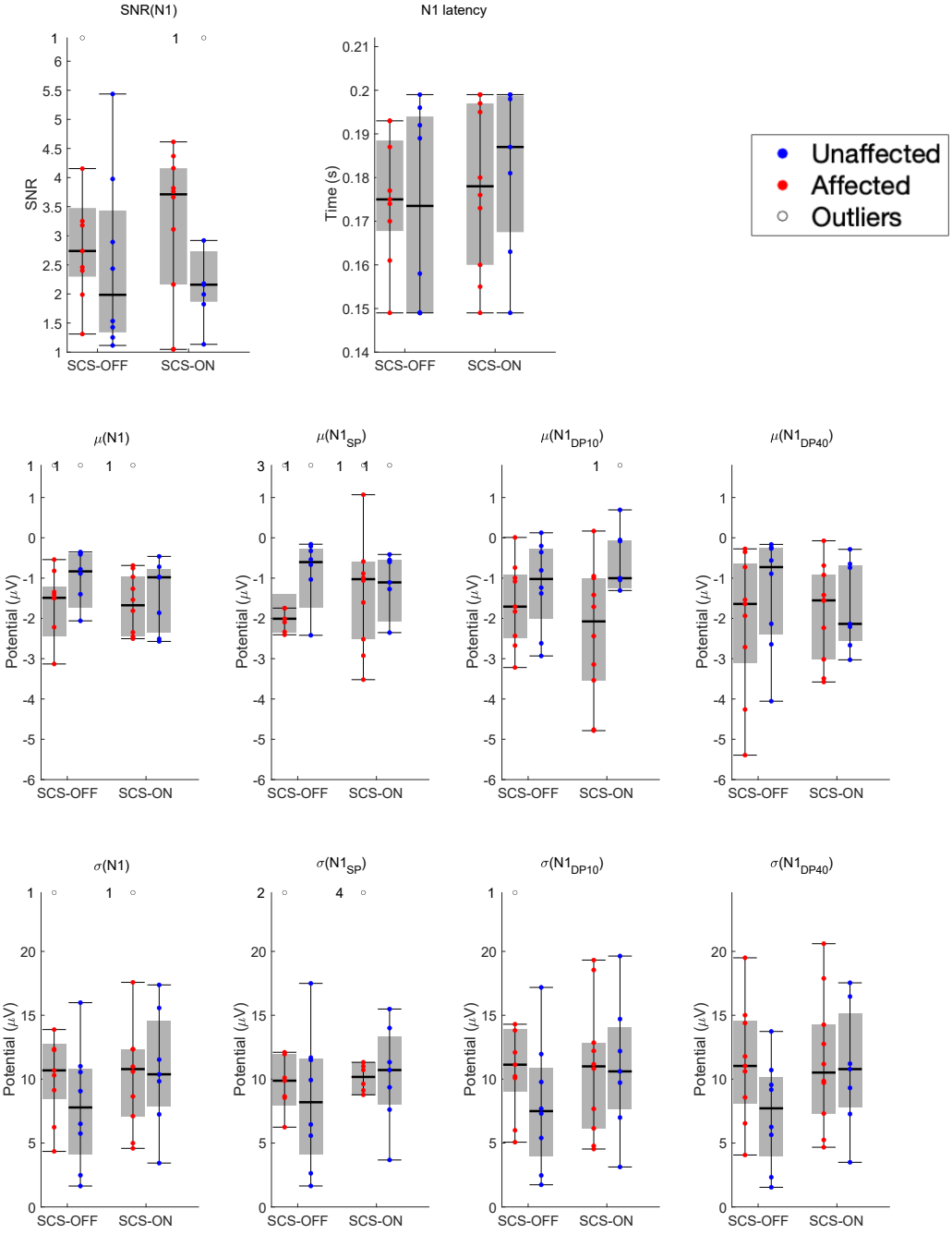

Figure 5.3: Means (μ) and standard deviations (σ) of N1 amplitudes from individual EPs in the contralateral derivation T7-F4 from the 'SCS-OFF vs SCS-ON' group on the affected and unaffected sides. Values on the affected side are depicted in red, whereas values on the unaffected side are depicted in blue.

5.2.2 Session effect

5.2.2.1 Nociceptive detection thresholds

Individual NDTs (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) for the 'SCS-ON1 vs SCS-ON2' group are shown in Figure 5.4. Only one measurement was included on the unaffected side during SCS-ON2, which hampers interpretation of these results. NDTs seem higher on the affected side during SCS-ON1 than during SCS-ON2. Slopes seem similar for all situations per stimulus type.

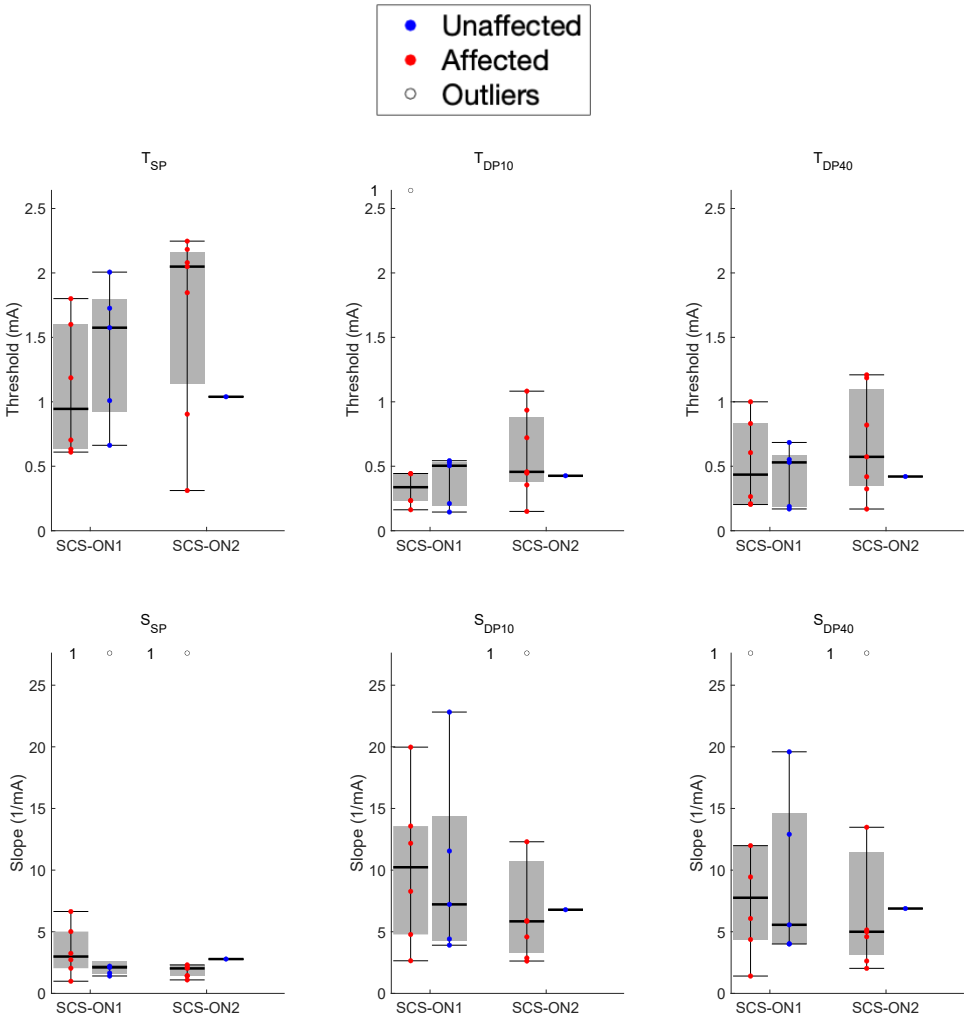

Figure 5.4: Derived detection thresholds (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve from the 'SCS-ON1 vs SCS-ON2'-group on the affected and unaffected sides. The thresholds and slopes were averaged over the entire measurement. Values on the affected side are depicted in red, whereas values on the unaffected side are depicted in blue.
Please note that only 1 measurement on the unaffected side was included in SCS-ON2.

5.2.2.2 Evoked potentials

SNRs, latencies, and means and standard deviations of the P2 amplitude of individual EPs in the 'SCS-ON1 vs SCS-ON2' group are shown in Figure 5.5. SNRs seem higher and latencies seem lower on the affected side than on the unaffected side, independent of SCS-ON1 or SCS-ON2. Mean P2 amplitudes seem higher on the affected side than the unaffected side during SCS-ON1, but seem more similar to the unaffected side during SCS-ON2. The standard deviations of P2 amplitudes show the same differences and similarities as the mean P2 amplitudes.

Figure 5.6 shows SNRs, latencies, and means and standard deviations of the N1 amplitude in the 'SCS-ON1 vs 'SCS-ON2' group. SNRs seem similar for SCS-ON1 and SCS-ON2, and latencies seem evenly distributed over the expected range (150 ms to 200 ms) on both sides. Mean N1 amplitudes and their standard deviations during SCS-ON1 seem lower (i.e., less negative) on the affected side than the unaffected side. The means and standard deviations of N1 amplitudes seem more similar during SCS-ON2.

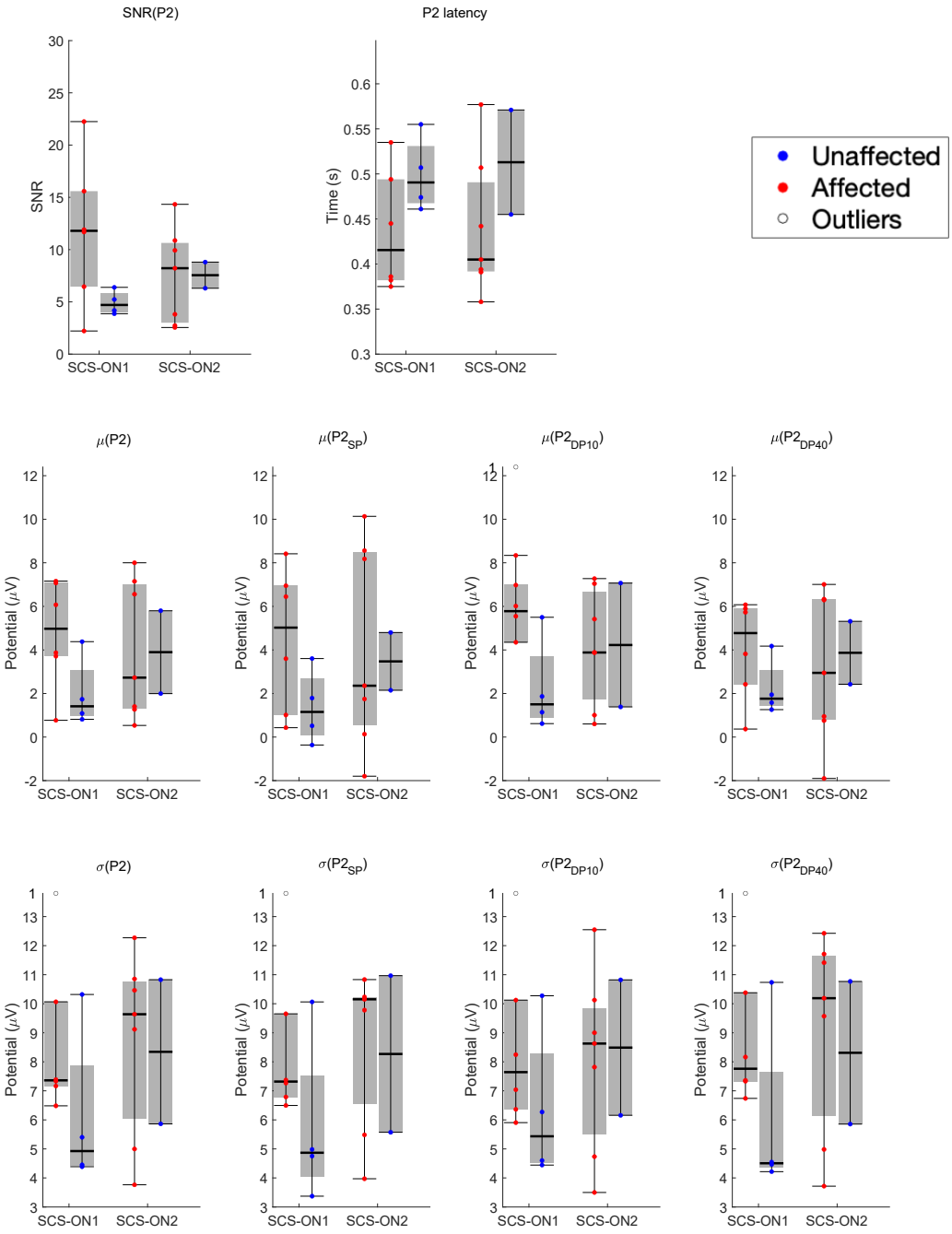

Figure 5.5: Means (μ) and standard deviations (σ) of P2 amplitudes from individual EPs in the central derivation Cz-M1,M2 from the 'SCS-ON1 vs SCS-ON2' group on the affected and unaffected sides. Values on the affected side are depicted in red, whereas values on the unaffected side are depicted in blue.

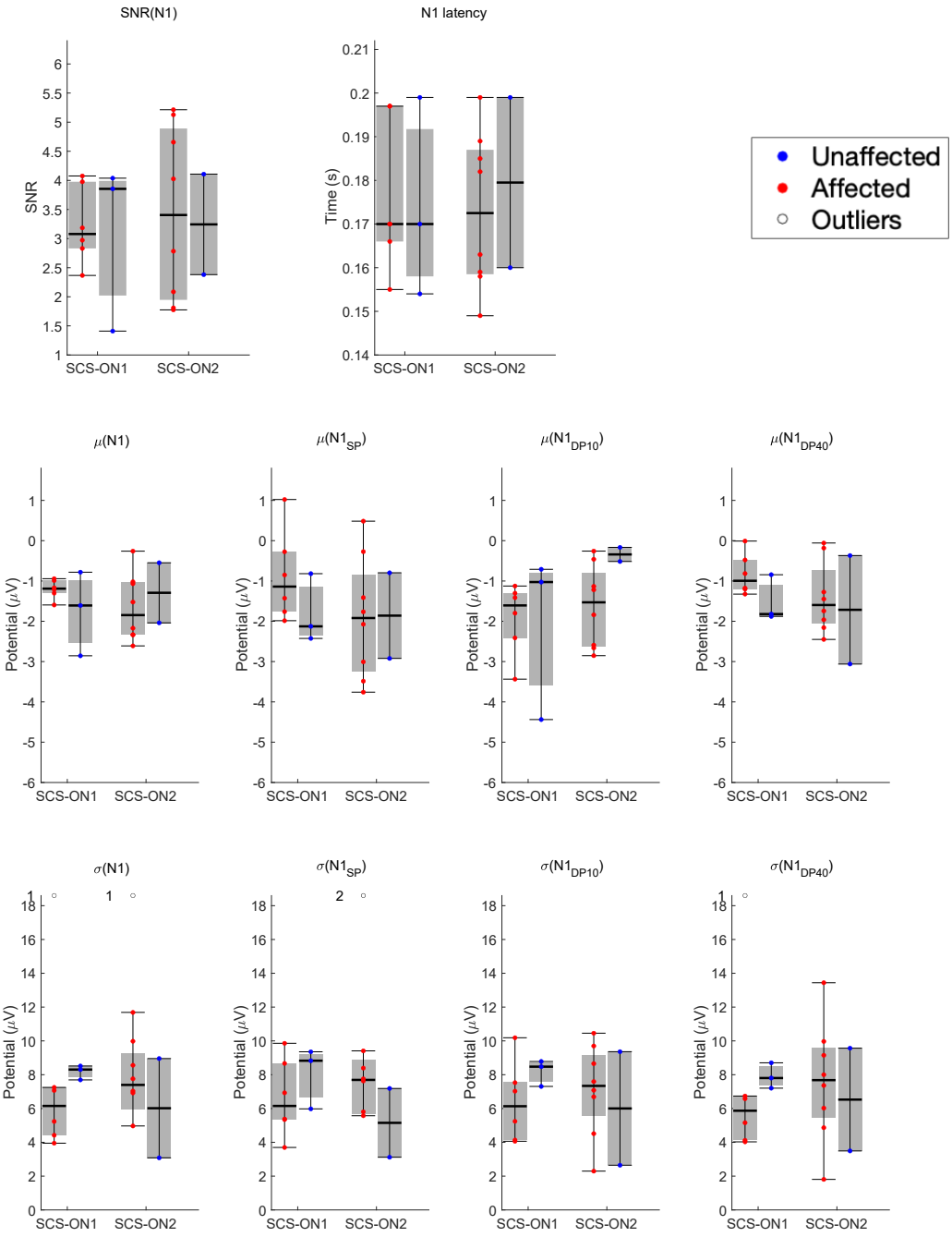

Figure 5.6: Means (μ) and standard deviations (σ) of N1 amplitudes from individual EPs in the contralateral derivation T7-F4 from the 'SCS-ON1 vs SCS-ON2' group on the affected and unaffected sides. Values on the affected side are depicted in red, whereas values on the unaffected side are depicted in blue.

5.3 Discussion

In this chapter, we aimed to explore the effect of SCS on NDTs and EPs and subsequently explore a possible session effect on NDTs and EPs. NDTs on the affected and unaffected side seemed to differ during SCS-OFF, with the lower NDT for the affected side, and NDTs were more similar during SCS-ON. P2 and N1 amplitudes are higher on the affected side than the unaffected side during SCS-OFF and are more similar during SCS-ON. Furthermore, the exploration of session effect was hampered by small sample sizes, but seem to cautiously indicate no session effect on N1 amplitudes. Strengths, limitations, and recommendations for future research are described in Chapter 7 - Discussion.

5.3.1 Nociceptive detection thresholds

The effect of SCS on NDTs was visually inspected, which revealed a difference in NDT and slope between the affected and unaffected side during SCS-OFF, with seemingly slightly higher NDTs for the unaffected side. During SCS-ON however, the difference between the affected and the unaffected side seemed to be diminished. This diminishment during SCS-ON seems to correspond to the findings of Berfelo et al.[16], but the situation during SCS-OFF seems in contrast with those findings. Berfelo et al.[16] found significantly lower NDTs on the unaffected side when DRG stimulation was turned off. However, due to altered NDT measurement procedures, different type of stimulation, different inclusion criteria, and their use of a different regression model, their results are difficult to compare to the present study. On one hand, some studies using QST methods to evaluate detection or pain thresholds also found higher thresholds in the symptomatic limb than the asymptomatic limb[112–114]. On the other hand, other QST studies have suggested an increase in sensory detection thresholds on affected limbs during SCS-ON[104]. Although these studies did not investigate differences between affected and unaffected limbs, the increase in NDT in SCS-ON when compared to SCS-OFF is in line with these findings.

Important considerations regarding the current results are the measurement exclusions and task performance. Firstly, measurements were individually evaluated and either included or excluded. As NDTs have previously shown great inter-subject variability, it could be that subjects with higher thresholds in general were excluded on the affected side, but included on the unaffected side. Secondly, it remains unknown which effect task performance has on the NDTs and slopes of psychophysical curves. The difference in NDTs may therefore also reflect a change in task performance between the affected and unaffected sides. To allow for more appropriate comparison to other studies, the data quality of the NDT-EP method with stimulus application to the foot dorsa must first be improved. This would ensure more measurements per subjects could be included, decreasing the possible effect inter-subject variability has on the current results.

Data quality should also be improved to properly evaluate a possible session effect on NDTs in the ‘SCS-ON1 vs SCS-ON2’ population. Evaluation is currently difficult, as only 19 measurements were included for this analysis, of which only one was on an unaffected side during SCS-ON2. Due to the single measurement included on the unaffected side during SCS-ON2, very little can be said about differences on the unaffected side between SCS-ON1 and SCS-ON2 or about differences between the affected and unaffected side during SCS-ON2. During SCS-ON1, thresholds were generally lower on the affected side than the unaffected side. Increased NDTs were observed on the affected side during SCS-ON2 as compared to SCS-ON1. Although this may point to a possible effect of sessions, the sample size is too small to draw an appropriate conclusion.

5.3.2 Evoked potentials

Mean P2 and N1 amplitudes were determined to investigate neurophysiological responses related to nociceptive processing. Mean P2 amplitudes were lower on the unaffected side than the affected side during SCS-OFF but were more similar during SCS-ON. This change was also seen in the ‘SCS-ON1 vs SCS-ON2’ population, with lower P2 amplitudes on the unaffected side during SCS-ON1 and more similar P2 amplitudes during SCS-ON2. However, the EP at the central derivation, i.e., the P2 peak, is thought to mainly reflect activity related to task performance. Therefore, differences in P2 amplitudes between the affected and unaffected side during SCS-OFF and SCS-ON or SCS-ON1 and SCS-ON2 are not considered to be directly associated with an effect of SCS but may rather indicate a difference in task performance.

In the ‘SCS-OFF vs SCS-ON’ group, N1 amplitudes showed similar changes as the P2 amplitude: mean N1 amplitudes were lower on the unaffected side than the affected side during SCS-OFF but were more similar during SCS-ON. Furthermore, N1 amplitudes did not increase during SCS-ON in comparison to SCS-OFF. This contradicts previous results applying the NDT-EP method in PSPS-T2 patients treated by SCS, which revealed an increased amplitude in T7-F4 during SCS-ON when compared to SCS-OFF and HCs[23]. The EP at the contralateral derivation, i.e., the N1 peak, is thought to reflect early sensory processing[106]. These results cautiously suggest SCS may not influence ascending nociceptive information. In the ‘SCS-ON1 vs SCS-ON2’ group, N1 amplitudes were fairly similar between all situations. This indicates that a possible session effect that was seen in P2 amplitudes was not reflected in these results, and therefore session may not affect N1 amplitudes.

6 Comparison to healthy controls

This chapter focuses on the secondary objective "to compare NDTs and EPs between PSPS-T2 patients (both SCS-OFF and SCS-ON) and healthy controls when stimuli are applied to the foot". First, methods specific to this objective are described, after which the results will be described. Then, the results are evaluated in the discussion and a preliminary conclusion is drawn.

6.1 Methods

To make a comparison between HCs and PSPS-T2 patients, several HCs were included to match the patient populations based on sex and age. This resulted in a dataset of 9 HCs. Subjects were eligible for participation when they were aged between 18 and 75, were pain-free, did not have a history of chronic pain complaints, did not have an implanted electrical stimulation device, and signed informed consent. Exclusion criteria were generally similar to the PSPS-T2 population. HCs performed one NDT-EP measurement on each foot; further measurement procedures were similar to those described in Section 3.3 – Study procedures for the PSPS-T2 population.

Data of PSPS-T2 patients was only used when measured at the affected side and the individual measurement was earlier included as shown in Figure 4.9. Included data was divided over two groups: SCS-OFF or SCS-ON. All measurements that were at least once included in an analysis (i.e., NDT, central EP, or contralateral EP analysis) were included in statistical analysis of demographic data. Statistical analysis was performed with MATLAB and SPSS. Demographic data was tested for normality with Shapiro-Wilk tests. A two-tailed independent sample t-test was used for normally distributed data, and a Mann-Whitney-U test was used for not-normally distributed data. The demographic characteristics were then compared between the patient populations and HCs. A significance level of α=0.05 was applied to all tests.

6.1.1.1 Nociceptive detection thresholds

DRs, FPRs, and response times (RTs) at group level were analysed. Intra-group differences were evaluated with either a two-tailed independent sample t-test or a Mann-Whitney-U test, dependent on the distribution of the data. A significance level of α=0.05 was applied to all tests. All measurements that were at least once included in an analysis (i.e., NDT, central EP, or contralateral EP analysis) were included in analysis of DRs, FPRs and RTs.

To further evaluate NDTs, a psychophysical curve was determined using a GLM to describe the detection probability as a function of the model intercept, pulse amplitudes (A_{SP}, A_{DP10}, A_{DP40}), and the trial number (TRL). The GLM is shown in Equation 3. The NDT is defined as the stimulus amplitude at which the detection probability is 50%. Individual, average NDTs (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve were then computed based on the GLM coefficients. The effect of SCS (GROUP) (i.e., HC, SCS-OFF or SCS-ON) was computed using a linear model.

$$\ln\left(\frac{P_d}{1-P_d}\right) \sim 1 + A_{SP} * GROUP + A_{DP10} * GROUP + A_{DP40} * GROUP + TRL * GROUP \qquad \text{Equation 3}$$

6.1.1.2 Evoked potentials

EP signals were derived from a central derivation (Cz-M1,M2) and a contralateral derivation (T7-F4). P2 and N1 latencies, SNR(P2) and SNR(N1) for the SCS-OFF and SCS-ON groups were previously determined in Chapter 4 - Experimental feasibility and data quality. These characteristics were determined in an equal manner for the HC population. The latencies were used to compute P2 and N1 amplitudes per epoch in their respective derivations. Mean amplitudes (μ(P2) and (μ(N1)) and standard deviations of the amplitudes (σ(P2) and σ(N1)) were then calculated.

6.2 Results

For the comparison to HCs, 9 subjects were included in this study. Therefore, 18 HC datasets were available for analysis. Measurements performed on the affected side during SCS-OFF included 9 measurements of 8 subjects, and measurements performed on the affected side during SCS-ON included 26 measurements of 18 patients.

6.2.1 Subject characteristics

Subject characteristics for HC, SCS-OFF and SCS-ON measurements are depicted in Table 6.1. No significant difference was found between the HC-population and the patient populations regarding age. However, both SCS-OFF and SCS-ON significantly differed from HCs regarding BMI, NRS and CSI, with higher values seen in the patient populations for all parameters.

Table 6.1: Subject characteristics for the populations used for a comparison between pain-free healthy controls (HCs), PSPS-T2 patients with SCS turned off (SCS-OFF), and PSPS-T2 patients with SCS turned on (SCS-ON). NRS – Numeric Rating Scale; CSI – Central Sensitisation Inventory.

	HC (n=9; m=18)	**SCS-OFF** (n=8; m=9)	**SCS-ON** (n=18; m=26)	**HC vs SCS-OFF p-value**	**HC vs SCS-ON p-value**
Sex (M/F)	10/8	5/4	10/16	-	-
Age (years)	53.2 ± 7.7	56.4 ± 8.4	55.0 ± 6.8	0.331	0.435
BMI (kg/m^2)	24.6 ± 3.1	27.8 ± 4.1	29.1 ± 4.3	*0.033**	*< 0.001**
NRS Score					
Past week	0.4 ± 0.7	3.4 ± 1.6	3.4 ± 1.4	*< 0.001**	*< 0.001**
Before measurement	0.0 ± 0.0	4.3 ± 2.3	3.3 ± 1.6	*< 0.001**	*< 0.001**
CSI	16.7 ± 8.9	35.9 ± 12.2	32.4 ± 9.1	*< 0.001**	*< 0.001**

Data is presented as mean ± standard deviation or n (%)
* Indicates significant difference (α=0.05)

6.2.2 Nociceptive detection thresholds

DRs, average RTs, and FPRs for all included measurements are shown in Table 6.2. Median DRs seem generally lower in the SCS-ON group than HC and SCS-OFF with a significantly lower total DR and DR for the DP40. Furthermore, FPRs seem higher in SCS-ON than HC and SCS-OFF, with a significantly higher total FPR. RTs seem relatively similar for all groups, with slightly lower RTs in SCS-OFF than the other groups. No significant differences were found between HC and SCS-OFF.

Table 6.2: Detection rates (DR, %), average response times (RT, ms), and false positive rates (FPR, %) for adequate measurements in the HC, SCS-Off and SCS-On populations. Results are shown for the total measurement and per setting. SP – single pulse; DP10 – double pulse with a 10 ms inter-pulse interval (IPI); DP40 – double pulse with a 40 ms IPI.

	HC	**SCS-OFF**	**SCS-ON**	**HC vs SCS-OFF p-value**	**HC vs SCS-ON p-value**
DR (%)					
Total	46.5 (34.8 – 47.9)	43.2 (35.5 – 48.5)	42.7 (31.5 – 49.7)	0.527	*0.040**
SP	41.4 (24.7 – 46.8)	39.1 (15.2 – 48.0)	38.4 (12.5 – 48.7)	0.495	0.133
DP10	47.7 (41.3 – 51.3)	47.0 (43.7 – 49.3)	45.2 (35.8 – 51.0)	0.781	0.173
DP40	47.7 (38.3 – 51.0)	45.8 (44.1 – 49.7)	44.9 (35.1 – 51.0)	0.298	*0.015**
RT (ms)					
Total	612.9 ± 77.1	576.7 ± 76.5	584.7 ± 84.6	0.259	0.265
SP	603.6 ± 72.1	551.7 ± 61.4	572.3 ± 92.9	0.077	0.237
DP10	606.2 ± 81.5	574.2 ± 87.8	576.8 ± 85.3	0.357	0.258
DP40	627.3 ± 84.7	595.9 ± 82.4	603.4 ± 82.2	0.368	0.354
FPR					
Total	0.5 (0.0 – 2.5)	0.9 (0.5 – 2.6)	1.1 (0.4 – 4.9)	0.348	*0.025**
SP	0.0 (0.0 – 3.3)	1.5 (0.0 – 5.6)	1.5 (0.0 – 8.3)	0.106	0.054
DP10	0.0 (0.0 – 4.3)	0.0 (0.0 – 2.9)	1.4 (0.0 – 3.9)	0.463	0.089
DP40	1.3 (0.0 – 3.9)	0.0 (0.0 – 3.0)	1.5 (0.0 – 5.3)	0.298	0.284

Data is presented as mean ± standard deviation or median (minimum – maximum).
* Indicates significant difference (α=0.05)

Individual NDTs (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve are shown in Figure 6.1. No significant differences were found between HC, SCS-OFF and SCS-ON regarding NDTs or steepness of the slopes. Generally speaking, SCS-ON seems to have slightly higher thresholds and slightly less steep slopes than SCS-OFF or HC.

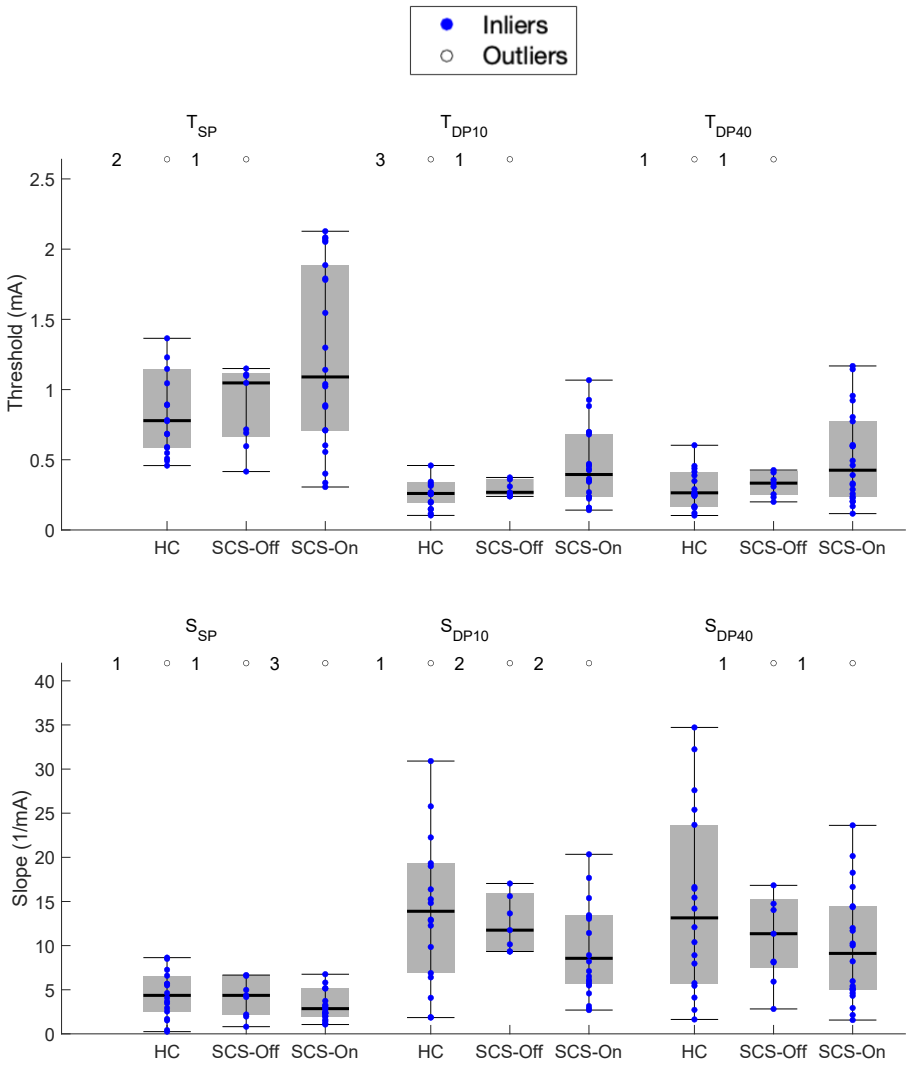

Figure 6.1: Derived detection thresholds (T_{SP}, T_{DP10}, T_{DP40}) and slopes (S_{SP}, S_{DP10}, S_{DP40}) of the psychophysical curve from adequate measurements for pain-free individuals (HC), PSPS-T2 patients with SCS turned off (SCS-Off), and PSPS-T2 patients with SCS turned on (SCS-On). The thresholds and slopes were averaged over the entire measurement.

6.2.3 Evoked potentials

Figure 6.2 depicts SNR(P2), P2 latencies, and means and standard deviations of the P2 amplitude of individual EPs. SNRs seem relatively similar between groups, with a slightly lower median SNR for HCs. P2 latencies seem higher in HC than both SCS-OFF and SCS-ON. The medians of mean P2 amplitudes seem almost equal between groups, as well as between stimulus types. Standard deviations also seem relatively similar between groups, but the distribution of values seems narrower in HCs than in the patient populations.

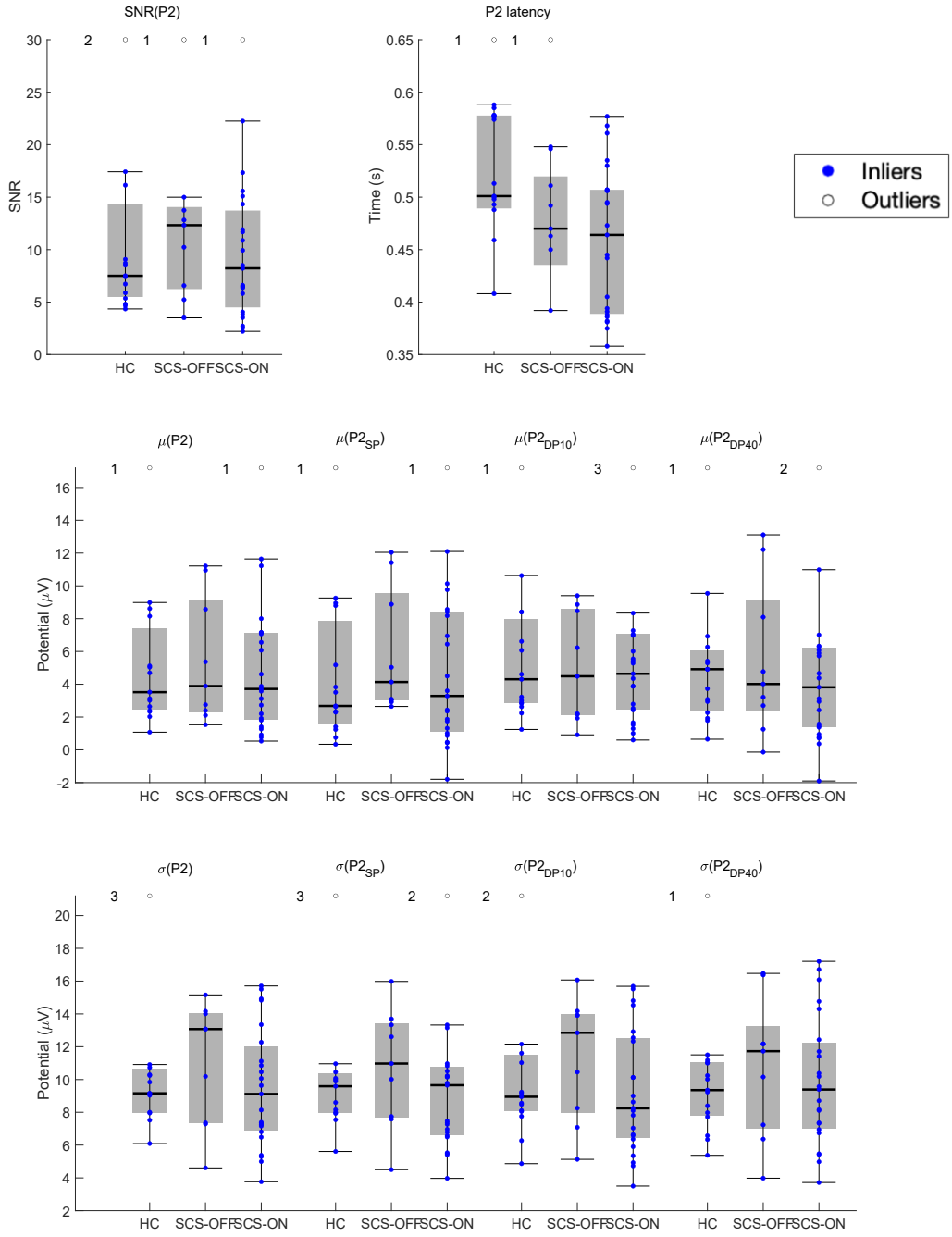

Figure 6.2: Means (μ) and standard deviations (σ) of P2 amplitudes from individual EPs for pain-free individuals (HC), PSPS-T2 patients with SCS turned off (SCS-OFF), and PSPS-T2 patients with SCS turned on (SCS-ON).

Figure 6.3 illustrates SNR(N1), N1 latencies, and means and standard deviations of N1 amplitudes. SNRs and latencies seem similar between all groups. Mean N1 amplitudes seem comparable between HC and SCS-ON for all stimulus types, and seem higher, i.e., more negative, for SCS-OFF for DP40 stimuli. The standard deviations of SCS-OFF seem higher than those of HC and SCS-ON for all stimulus types.

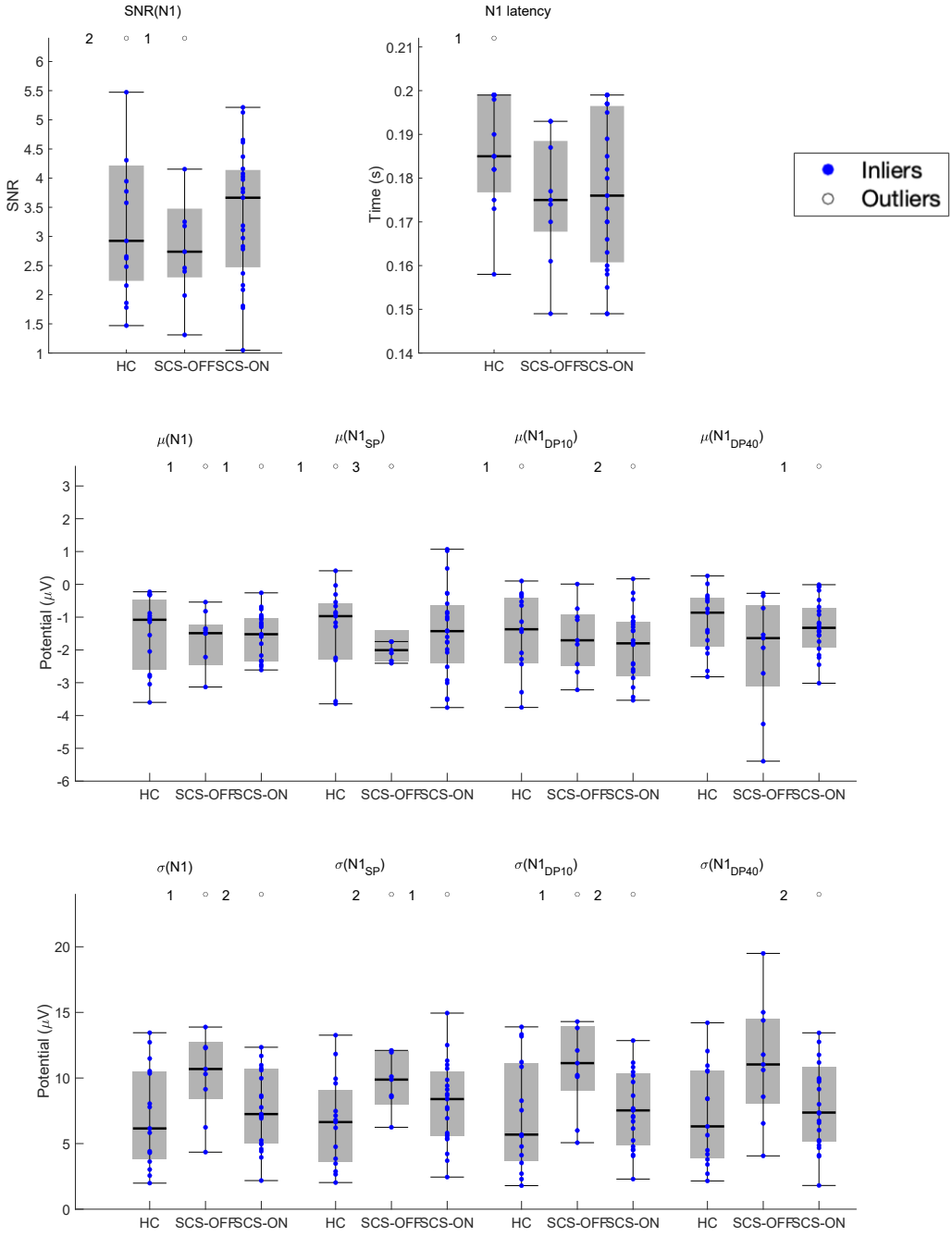

Figure 6.3: Means (μ) and standard deviations (σ) of N1 amplitudes from individual EPs for pain-free individuals (HC), PSPS-T2 patients with SCS turned off (SCS-OFF), and PSPS-T2 patients with SCS turned on (SCS-ON).

6.3 Discussion

The aim of this chapter was to compare NDTs and EPs between HCs and PSPS-T2 patients with SCS-OFF and SCS-ON. A slight increase in NDTs was observed for SCS-ON as compared to SCS-OFF and HC. Furthermore, mean N1 amplitudes seem slightly increased during SCS-OFF and SCS-ON in comparison to HC. Strengths, limitations, and recommendations for future research are described in Chapter 7 - Discussion.

6.3.1 Nociceptive detection thresholds

Visual analysis of the NDTs indicated a higher mean NDT for SCS-ON than for HCs and SCS-OFF. This difference was most visible for both double pulse stimulus types. For the SP stimulus type, median NDTs of SCS-OFF and SCS-ON were almost equal, although SCS-ON showed a wider range. As no statistical testing was performed for this analysis, whether differences are significant cannot be demonstrated. Previous work regarding the NDT-EP method in PSPS-T2 patients treated by SCS and stimulus application to the hand dorsa has also shown higher NDTs during SCS-ON as compared to HC and SCS-OFF, although not significantly[23]. However, these results seemed in contrast with a previous study, in which significantly higher NDTs were found in PSPS-T2 patients than in HCs[115]. A long-term effect of SCS was very cautiously suggested, even though literature does not provide strong evidence regarding a long-term effect of SCS on e.g. QST outcomes[116]. However, it was stressed that the influence of subject characteristics, such as age and sex, on NDTs should first be established firmly before conclusions regarding possible adaptations in nociceptive processing can be drawn. As this has not been established yet, the cautious suggestion remains that: a very cautious suggestion regarding the long-term effect of SCS.

6.3.2 Evoked potentials

In the central derivation, no evident differences were found between HC, SCS-OFF and SCS-ON, and medians of mean P2 amplitudes seemed almost equal for all groups and stimulus types. Previous work regarding the NDT-EP method in PSPS-T2 patients treated by SCS and stimulus application to the hand dorsa revealed decreased P2 amplitudes in comparison to age- and sex-matched HCs. Those findings were in contrast to earlier results, which showed seemingly similar P2 amplitudes for HCs and PSPS-T2 patients. It was hypothesised that subject characteristics may have influenced these different results. In this study, however, the findings regarding P2 amplitude seem in line with the earliest results, with similar P2 amplitudes for HCs, SCS-OFF and SCS-ON. HCs were once again age- and sex-matched, which creates doubt regarding the hypothesis subject characteristics may have been of influence. Furthermore, the EP at the central derivation, i.e., the P2 amplitude, is thought to mainly reflect task-related activity. Therefore, differences could indicate a difference in task performance, rather than be directly associated with PSPS-T2 or effects of SCS. Moreover, it was previously suggested that similarities in P2 amplitudes between HCs, SCS-OFF and SCS-ON could be a consequence of higher stimulation amplitudes during SCS-OFF and SCS-ON. Although the exact cause of observed differences and similarities between HCs and SCS-OFF and SCS-ON is unknown, subject characteristics, task performance and stimulation amplitudes could all play a role.

In the contralateral derivation, mean N1 amplitudes were slightly higher, i.e., more negative, in SCS-OFF and SCS-ON than in HCs. These results correspond to previously found results, described in Chapter 5 - Effect of Spinal Cord Stimulation, where N1 amplitudes did not increase during SCS-ON in comparison to SCS-OFF. The N1 peak is thought to reflect early sensory processing[106], and these results may therefore carefully suggest that SCS may not influence ascending nociceptive information. PSPS-T2 on the other hand, seems to influence ascending nociceptive information, as N1 amplitudes do seem increased in patient populations in comparison to HCs. This corresponds to previous results, which revealed increased EP amplitude in the contralateral derivation in PSPS-T2 patients when compared with HCs[21].

7 Discussion

In this explorative study, the main goal was to investigate feasibility of performing NDT-EP measurements on the feet of PSPS-T2 patients on the affected side as well as the unaffected side during SCS, and further explore effects of SCS on outcomes of the NDT-EP method. This NDT-EP protocol seems practically feasible, although its technical feasibility seems debatable due to variability in DRs and SNRs, outlying FPRs, and the number of incorrectly fitted GLMs. During SCS-OFF, the NDT seemed lower on the affected side than the unaffected side, and NDTs seemed more similar during SCS-ON. Furthermore, mean N1 amplitudes seem increased during SCS-OFF and SCS-ON in comparison to HCs.

7.1 General discussion

As concluded in Chapter 4 - Experimental feasibility and data quality, technical feasibility of the NDT-EP method using IES on the foot dorsa, i.e., affected and unaffected, seems questionable. Great inter-subject variability for DRs and FPRs raises questions regarding adequate task performance and its assessment. Task performance is currently evaluated based on DRs and FPRs, but cut-off values were determined pragmatically or based on visual analysis. However, this is a first framework to further establish a window of acceptable task performance, which considers adequate tracking of NDTs as well as NDTs reflecting detection thresholds of nociceptive fibres. The feasibility of measuring EPs was affected by increased levels of noise, for which a few possible causes were identified. Noise could be reduced by stressing the necessity of remaining in the same position to the subject or using the same EEG cap for most subjects. Furthermore, it would be interesting to investigate the effect of SCS on levels of noise. It is not completely clear what the effect of noise is on features of the EP, so it would be worthwhile to keep this into consideration for future studies.

A possible effect of SCS was investigated using the 'SCS-OFF vs SCS-ON' population, and the 'SCS-ON1 vs SCS-ON2' population was used to investigate a possible session effect. Based on visual inspection, NDTs and P2 amplitudes somewhat differed between the affected and unaffected limb during SCS-OFF, but seemed more similar during SCS-ON. Although interpretation of results regarding session effect was hampered by small sample sizes, a session effect seemed to occur in the NDTs and P2 amplitudes. However, differences in NDTs and P2 amplitudes could be related to a difference in task performance, rather than an effect of SCS or a session effect. Results regarding the N1 amplitude could imply that SCS does not influence ascending nociceptive information, and session does not affect N1 amplitudes. Furthermore, results from the comparison between HCs, SCS-OFF and SCS-ON seem to cautiously suggest a long-term effect of SCS. However, several measurements were excluded from further NDT or EP analysis due to poor data quality and/or task performance. As a result, inter-subject variability may have negatively affected the outcomes of this study. Therefore, the results regarding effect of SCS, session effect and the comparison to HCs should be approached with some scepticism.

When looking at Figure 5.1, Figure 5.4, and Figure 6.1, thresholds of the SP stimulus type are higher than those of the double pulse stimulus types. Furthermore, slopes are generally less steep for the SP than DP10 and DP40. Preliminary results from previous studies also indicate higher thresholds and lower slopes for SP stimuli[23,90,110,111]. As described in Chapter 4 - Experimental feasibility and data quality, it is thought that SP stimuli might be less clearly perceivable than double pulse stimuli, as the process from transmission to perception of double pulse stimuli is presumably affected by paired pulse facilitation. This may lead to less steep slopes and higher thresholds of the psychophysical curve. However, it is unsure what role variations in detection criterion and attention play in the lower performance of SP stimuli. Therefore, it could be interesting to investigate what leads to low DRs, higher thresholds and less steep slopes for SP stimuli, and whether it affects the feasibility of tracking NDTs for SP stimuli and tracking NDTs in general.

Standard deviations of P2 peaks seem higher on the affected side than the unaffected side, independent of SCS-OFF, SCS-ON, SCS-ON1 or SCS-ON2. This indicates greater intra-subject variability in symptomatic limbs than in asymptomatic limbs. Some subjects reported difficulty discerning sensations elicited by IES stimulation from sensations caused by SCS or usual pain

sensations, both of which only affect the symptomatic side. The difficulty of discerning sensations could have improved focus, as sensations elicited by IES were less evident. Improved focus may have led to stimuli closer to the threshold being detected, whereas those were disregarded on the unaffected side. Therefore, it was hypothesised that a cause for higher standard deviations on the affected side could be an improved focus due to difficulty discerning sensations.

7.2 Strengths and limitations

This study represents the next step in the development of the NDT-EP method by investigating whether NDT-EP measurements can be performed on the feet of PSPS-T2 patients on the affected and unaffected sides during SCS. Additional insight into effects of SCS on outcomes of the NDT-EP method was provided by performing NDT-EP measurements on both affected and unaffected limbs. Furthermore, a standardised protocol was used for the NDT-EP measurements and one observer performed all measurements, both of which reduced inter-observer bias. Next, the feasibility of measuring EPs during SCS was evaluated using two derivations: central and contralateral. This provided more information regarding the possibility of measuring EPs during SCS.
Despite its explorative nature, the effect of treatment could be studied by using a 'SCS-OFF vs SCS-ON' protocol with a 'SCS-ON vs SCS-ON' protocol as a reference. Moreover, the outcomes of PSPS-T2 patients treated by SCS were compared to those of HCs, which provided additional insight into long-term effects of SCS as measured by NDTs and EPs. Furthermore, randomisation of patient allocation to either trial arm led to comparable populations in both trial arms. Lastly, mean NRS scores of the week prior to the experiment suggest that included subjects were effectively treated by SCS.

Identified limitations were related to study population, methodology, measurement procedures, and data analysis. Firstly, several limitations related to the study population were observed. The study population is relatively small, which may influence the generalisability of the data. Due to the explorative nature of the study, sample size calculations were not performed. Furthermore, the existing study population shows great heterogeneity regarding subject and pain characteristics. Next, patients with unilateral as well as bilateral lower limb pain were included in this study, which negatively affects the analysis of stimulation on the affected versus unaffected side. Lastly, average BMI values of the included subjects were higher than the healthy range, which is 18 to 25 kg/m^2. Preliminary results have shown NDTs to be significantly higher in morbid obese individuals (40 kg/m^2) than HCs with a healthy BMI. Since average BMIs of the patient groups do not indicate that subjects of the current study suffered from morbid obesity, it is unsure whether NDTs could be affected by higher BMI values.

Secondly, several limitations regarding methodology were noted. Neither subjects nor observer was blinded for trial arm allocation due to practical considerations. This may have led to bias on both the observer and the subjects. Sham-controlled and observer blinded studies are thought to eliminate these effects and should be considered for future studies.
Furthermore, the order of stimulation, i.e., which side was stimulated first, was determined based on handedness. This decision was made based on previous studies where block randomization per two was performed to decide whether the dominant or non-dominant hand was stimulated first. However, in this study, it might have been better to determine the order of stimulation based on the affected side, as it remains unclear what effect order of stimulation has on NDTs and EPs measured on the affected and unaffected sides. Therefore, it is recommended to perform the block randomization based on the affected side in future studies regarding effect of SCS.
Next, the duration of the measurements was perceived as excessively long, which probably resulted in decreasing attention and increasing levels of pain. Both likely led to a decrease of focus, which is thought to lead to an increase in NDT as it can become difficult to perceive stimuli close to the threshold. While the effect of loss of focus on NDTs is not completely clear, it would be recommended to shorten the experiment.
The length of the SCS washout period of 12 hours seems sufficient, as most subjects reported increased levels of pain in comparison to the past week. The validity of an SCS washout period of 12 hours is further substantiated by other studies[116–118]. The difference in NRS between the first and third measurement does not necessarily reflect a sufficient washout period. However, a

possible explanation could be increased levels of pain due to the long duration of measurements, as previously discussed. Before reassessing the length of the washout period, it would therefore be recommended to improve the subject comfort during measurements, to ensure increased levels of pain are not caused by the measurements.
Finally, medication intake was not restricted during this study after careful ethical and practical considerations. Medications such as anticonvulsants, antidepressants and opioids are thought to affect EP amplitudes, but their exact influence on NDTs and EPs is unknown. The effect of medication intake on outcomes of the NDT-EP method should be further investigated, to substantiate a decision to do or do not restrict mediation intake.

Thirdly, some limitations regarding measurement procedures were observed. The placement of the IES electrode on the foot dorsa has shown increased difficulty in comparison to the hand dorsa. The surface of a foot dorsum is generally more uneven than that of a hand dorsum, which impedes placement in such a way that all electrodes are connected to the skin, but only protrude the stratum corneum and not other layers of the skin. Moreover, PSPS-T2 patients often face difficulty sitting still for prolonged periods. Although they were instructed to sit still for as long as possible, most patients felt the need to reposition during the measurements. This caused different angles between the foot and the lower leg than during the placement of the IES electrode, and therefore different tension on the tape that fixated it. It is unclear whether this influenced the tracking of NDTs and if so, in what manner.
Furthermore, different EEG caps were used to obtain EEG data from these subjects. However, one cap malfunctioned after having been used in several subjects beforehand. During the measurements before malfunction occurred, it was difficult to reduce electrode impedance below 5 kΩ. Although this appeared to have been achieved during these measurements, it is unclear whether the use of an EEG cap that shortly after malfunctioned, affected the EEG measurements of these subjects. Furthermore, after malfunction, two different EEG caps were used: one slightly older with all electrodes intact, and one slightly newer but which was known to have a faulty CP6 electrode. The faulty CP6 electrode was circumnavigated by disconnecting that electrode from the EEG amplifier and adding a single, so-called “fast fix” electrode which was passed through the hole near the CP6 electrode. It is unsure whether the use of these subpar EEG caps has negatively affected the outcomes of this study, but it is a possibility it has negatively affected the increased levels of noise that were observed in grand average EPs.

Lastly, some limitations related to data analysis were identified. Individual latencies were determined based on the amplitude of a grand average EP of one measurement. In some cases, this led to determining latency on the largest amplitude of noise, as no EP occurred. Therefore, it would be worthwhile to implement other methods of latency determination. A starting point would be to implement a standardised approach, either based on maximum amplitudes or the GFP.
Furthermore, individual measurements were excluded, which hampers appropriate analysis. Previous studies have shown NDTs and EPs to have great inter-subject variability; possible effects of this are usually diminished by performing group analyses. In this study however, intra-subject analyses could not be performed as some individual measurements were excluded. This could have led to skewed results as perhaps subjects with higher thresholds in general were excluded on the affected side, but included on the unaffected side. Improvement of data quality is necessary to allow for reliable comparisons to available data and draw appropriate conclusions.
Finally, it was not deemed possible to investigate possible differences between different stimulation types, i.e., tonic, burst or closed loop, due to small sample sizes and the distribution of SCS settings. Although technical feasibility does not seem to differ between stimulation types, it could be interesting to investigate whether SCS settings influence NDT-EP outcomes after stimulus application to the foot dorsa.

7.3 Recommendations

A common first recommendation would be to expand study groups to increase sample sizes. However, due to the number of excluded measurements, it is thought essential to first improve task performance so (nearly) all measurements can be included in data analysis. A first step was made to create a guide for the exclusion of data, based on quality of the GLM fit, SNR and task performance. This window of acceptable task performance should be further investigated. Factors

that could be taken into consideration as criteria for acceptable task performance include not only DR and FPR, but also the number of false negative detections, the maximum stimulus amplitude, and the moment where the maximum stimulus amplitude is reached. False negative detections are defined as detected stimuli labelled as non-detected due to a late or non-response of the subject. Although these stimuli are labelled as non-detected, they will generate an EP and could therefore influence the amplitude of non-detected grand average EPs. False negative detections could be recorded by adding registration of button releases in general, and not only during the 1000 ms after a stimulus is applied. The maximum stimulus amplitude and the moment where it is reached could be of added value because this could describe the type of fibre stimulated. The window of acceptable task performance could then be used as a framework for the exclusion of data. To then improve task performance, it would be worthwhile to investigate why task performance of SP stimuli is generally lower than both double pulse stimuli. Furthermore, its added value should be investigated, as removal of SP stimuli would lead to a reduction of experiment duration.

Shortening the experiment is considered essential to implement the NDT-EP measurement protocol in prospective studies and/or clinical practice. A decrease of duration could be achieved in several manners. First, the minimum number of stimuli necessary to study temporal characteristics of the nociceptive system should be investigated. Next, the added value of each stimulus setting should be evaluated. This could indicate a possibility to remove one stimulus setting. The results of the current study point towards the SP stimulus setting to provide the least information and potentially hamper the analysis of the double pulse stimulus settings. However, if all stimulus settings provide distinct information about the nociceptive system, a reduction of number of stimuli might be more appropriate. Furthermore, a decrease of duration could be achieved by reducing the number of EEG electrodes used. The current 64-channel set-up may be excessive since a limited number of channels is used in EP analysis. Limiting the number of channels could considerably improve the clinical applicability of the NDT-EP method.

Regarding data analysis, the central derivation Cz-M1,M2 and contralateral derivation T7-F4 were used in this study, which was in line with studies of the NDT-EP method where stimuli were applied to the hand dorsa. These derivations were originally identified as appropriate derivations for EP analysis due to high SNRs in comparison to other derivations. However, preliminary results indicated a different derivation, namely C1-AF7, provided higher SNRs in HCs when stimuli were applied to the feet than the contralateral derivation T7-F4 did. Although these results were not properly compared to available literature regarding EP analysis, it is an interesting direction for further research.

Finally, although the feasibility of applying the NDT-EP method to lower limbs of PSPS-T2 patients treated by SCS seems questionable, the current study does open the door for further research regarding the NDT-EP method with stimulus application to the feet. First, the change in location for stimulus application could possibly benefit other previously measured patient populations in which symptoms occur in the lower limbs, e.g., PDPN patients. Furthermore, inclusion criteria should be critically evaluated to limit the heterogeneity of the study population. In the current study, a broad spectrum of PSPS-T2 patients treated by SCS were included, which may have influenced results. To decrease heterogeneity, subject characteristics that could be used as inclusion criteria are unilateral lower limb pain, CSI score lower than 40, duration of pain or duration of SCS. Lastly, if task performance could be improved and the experiment shortened, this could lead to the initiation of prospective studies. Patients indicated for SCS could then perform NDT-EP measurements at various moments during the implantation process, e.g., prior to implantation, during the trial period, shortly after definitive implantation and longer after definitive implantation. Prospective studies could lead to expanded insight into effects of SCS and may ultimately lead to new ways to evaluate treatment efficacy.

8 Conclusion

The purpose of this exploratory study was to determine the feasibility of performing NDT-EP measurements on the feet of PSPS-T2 patients on both their affected and unaffected side during SCS. While the NDT-EP protocol was practically feasible, its technical feasibility was questionable due to variability in DRs and SNRs, outliers in the FPRs and incorrectly fitted GLMs. In order to improve the experimental feasibility, it is highly recommended to study factors influencing task performance, especially for SP stimuli. Following this, possible changes in the NDT-EP measurement procedure should be investigated, which could improve its clinical applicability. This could lead to a deeper insight into the mechanisms of chronic pain and SCS, which could in turn lead to new ways of evaluating treatment effect, ultimately aiding in the treatment of chronic pain.

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Appendix

A1 Butterfly plot

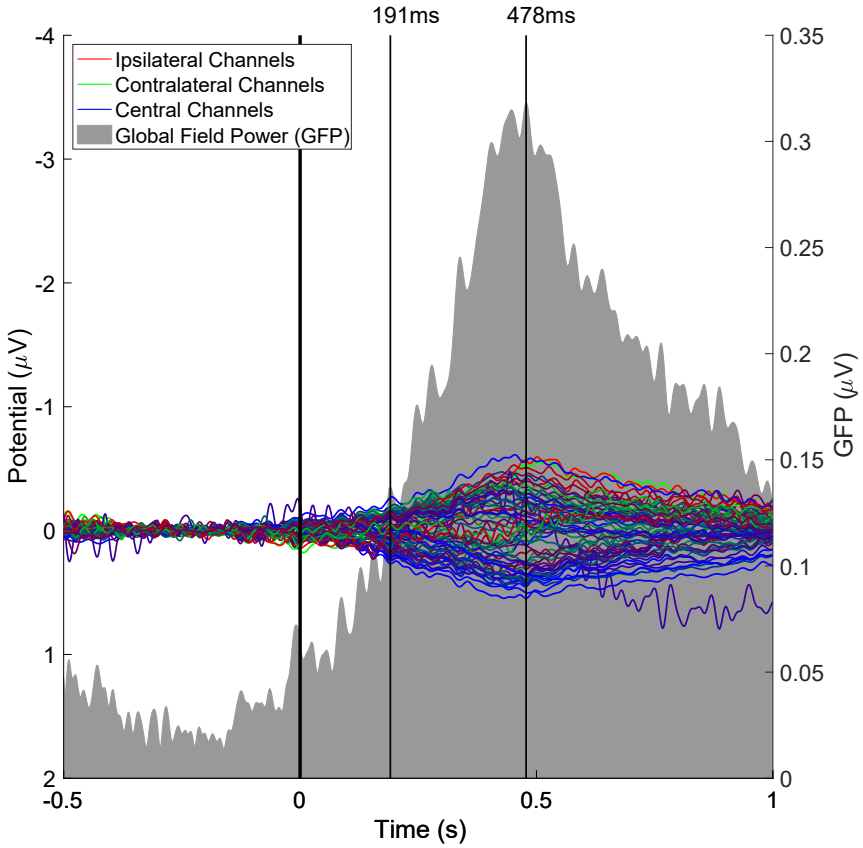
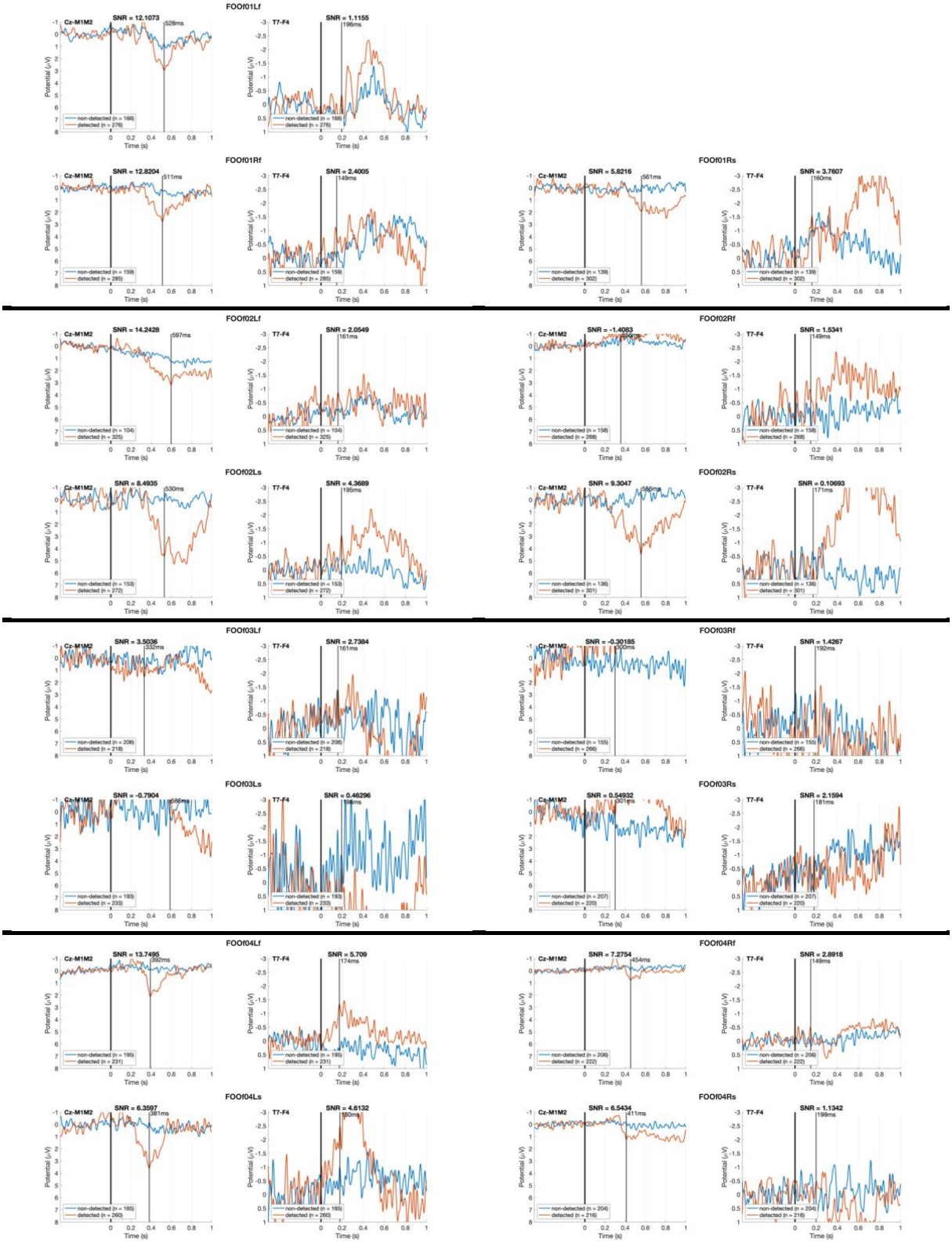
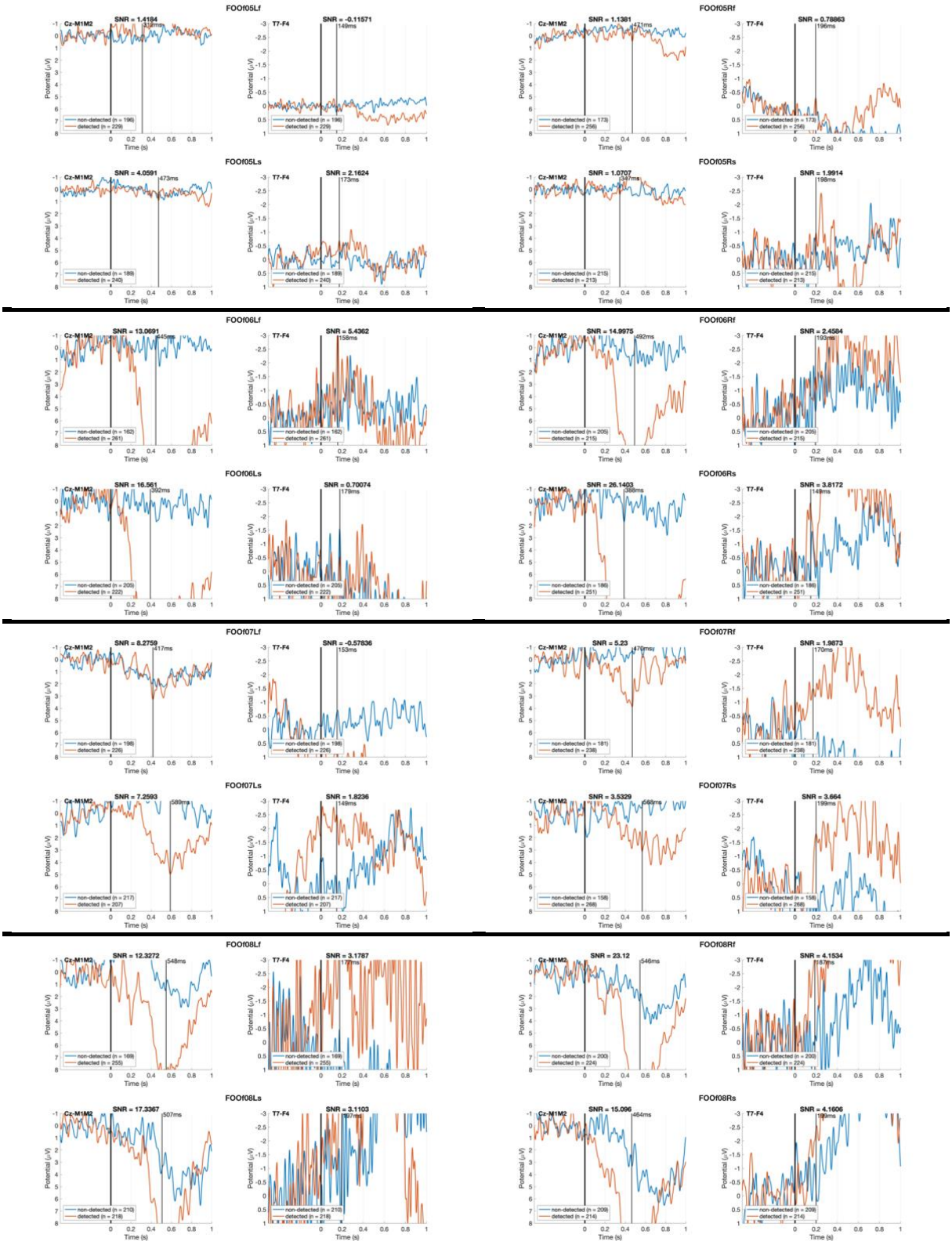
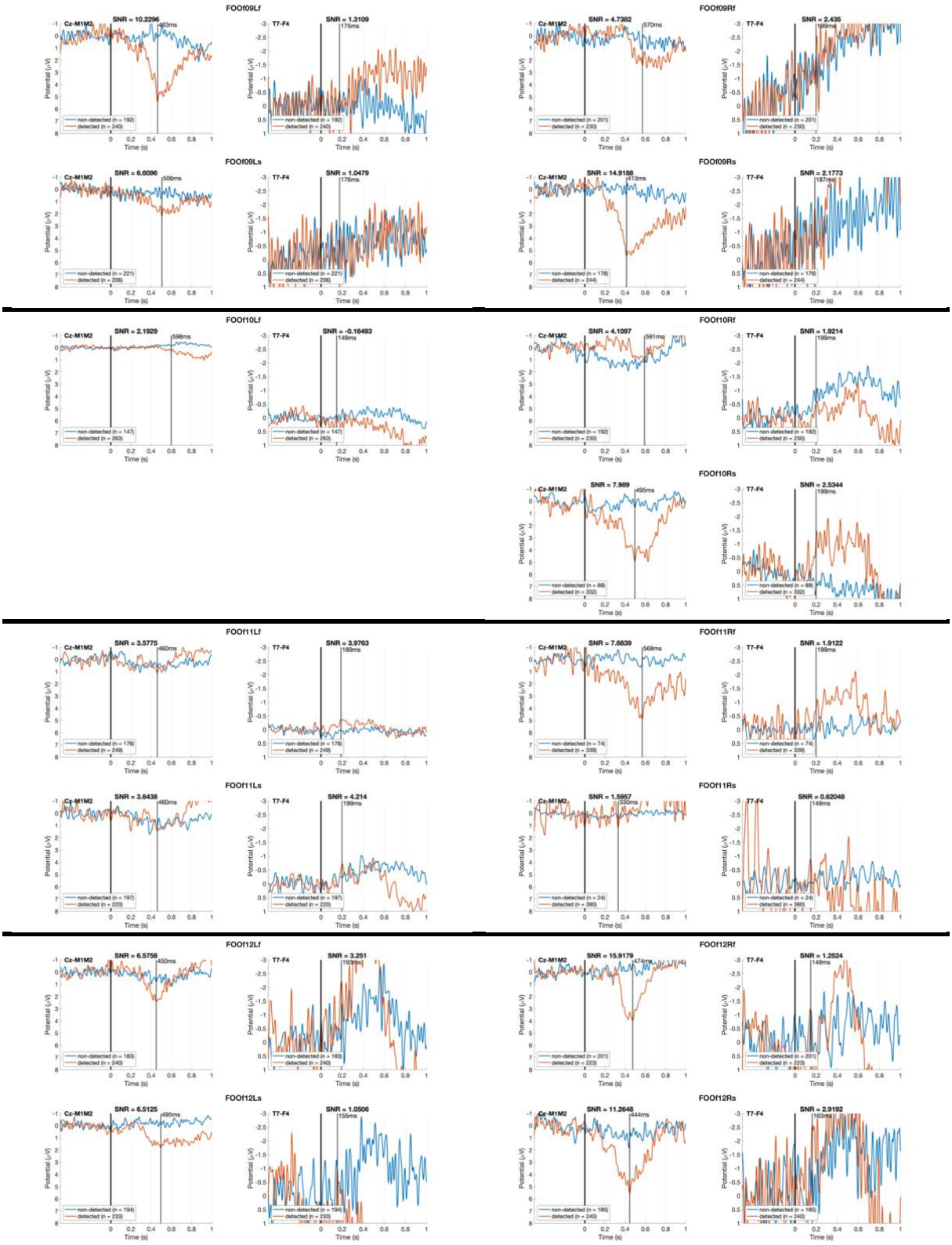


Figure A1.1: Butterfly plot for the 'SCS-OFF vs SCS-ON' and 'SCS-ON1 vs SCS-ON2' groups, depicting the grand average EP for all derivations and the global field power in grey. T=0 indicates the moment of stimulation; vertical lines indicate the latencies selected as a guide for further analysis.

A2 Individual grand average EPs in the central derivation (Cz-M1,M2) and the contralateral derivation (T7-F4) per measurement




FOOf05Lf
Cz-M1M2
SNR = 1.4184
418ms
T7-F4
SNR = -0.11571
149ms
FOOf05Rf
Cz-M1M2
SNR = 1.1381
471ms
T7-F4
SNR = 0.78863
196ms
FOOf05Ls
Cz-M1M2
SNR = 4.0591
473ms
T7-F4
SNR = 2.1624
173ms
FOOf05Rs
Cz-M1M2
SNR = 1.0707
397ms
T7-F4
SNR = 1.9914
198ms
FOOf06Lf
Cz-M1M2
SNR = 13.0691
445ms
T7-F4
SNR = 5.4362
158ms
FOOf06Rf
Cz-M1M2
SNR = 14.9975
492ms
T7-F4
SNR = 2.4584
193ms
FOOf06Ls
Cz-M1M2
SNR = 16.561
392ms
T7-F4
SNR = 0.70074
179ms
FOOf06Rs
Cz-M1M2
SNR = 26.1403
368ms
T7-F4
SNR = 3.8172
149ms
FOOf07Lf
Cz-M1M2
SNR = 8.2759
417ms
T7-F4
SNR = -0.57836
153ms
FOOf07Rf
Cz-M1M2
SNR = 5.23
470ms
T7-F4
SNR = 1.9873
170ms
FOOf07Ls
Cz-M1M2
SNR = 7.2593
589ms
T7-F4
SNR = 1.8236
149ms
FOOf07Rs
Cz-M1M2
SNR = 3.5329
588ms
T7-F4
SNR = 3.664
199ms
FOOf08Lf
Cz-M1M2
SNR = 12.3272
548ms
T7-F4
SNR = 3.1787
177ms
FOOf08Rf
Cz-M1M2
SNR = 23.12
546ms
T7-F4
SNR = 4.1534
187ms
FOOf08Ls
Cz-M1M2
SNR = 17.3367
507ms
T7-F4
SNR = 3.1103
197ms
FOOf08Rs
Cz-M1M2
SNR = 15.096
464ms
T7-F4
SNR = 4.1606
199ms
Potential (μV)
Time (s)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T7-F4
SNR = 1.3109
175ms
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Cz-M1M2
SNR = 4.7382
570ms
T7-F4
SNR = 2.435
199ms
FOOf09Ls
Cz-M1M2
SNR = 6.6096
506ms
T7-F4
SNR = 1.0479
176ms
FOOf09Rs
Cz-M1M2
SNR = 14.9188
413ms
T7-F4
SNR = 2.1773
187ms
FOOf10Lf
Cz-M1M2
SNR = 2.1929
598ms
T7-F4
SNR = -0.16493
149ms
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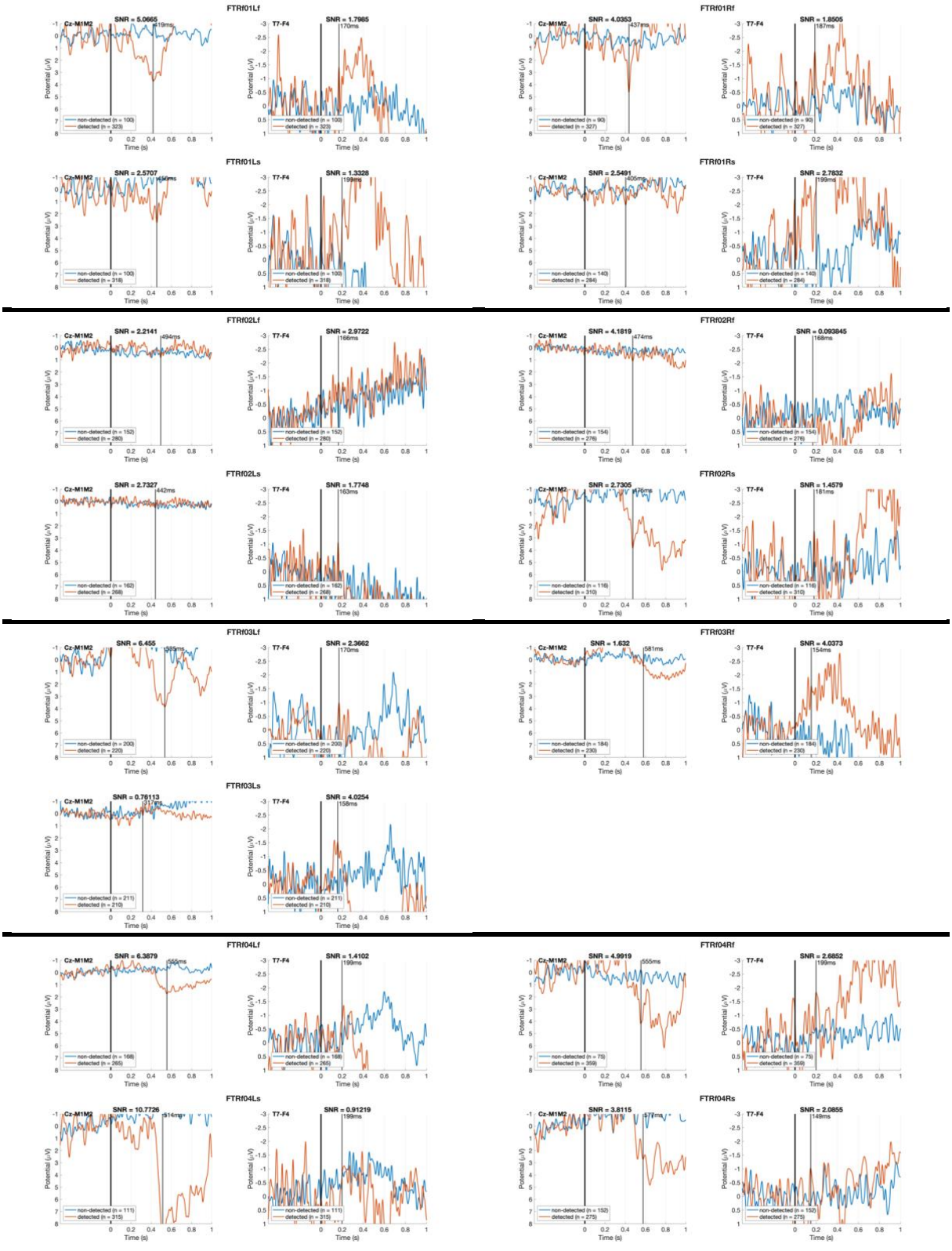
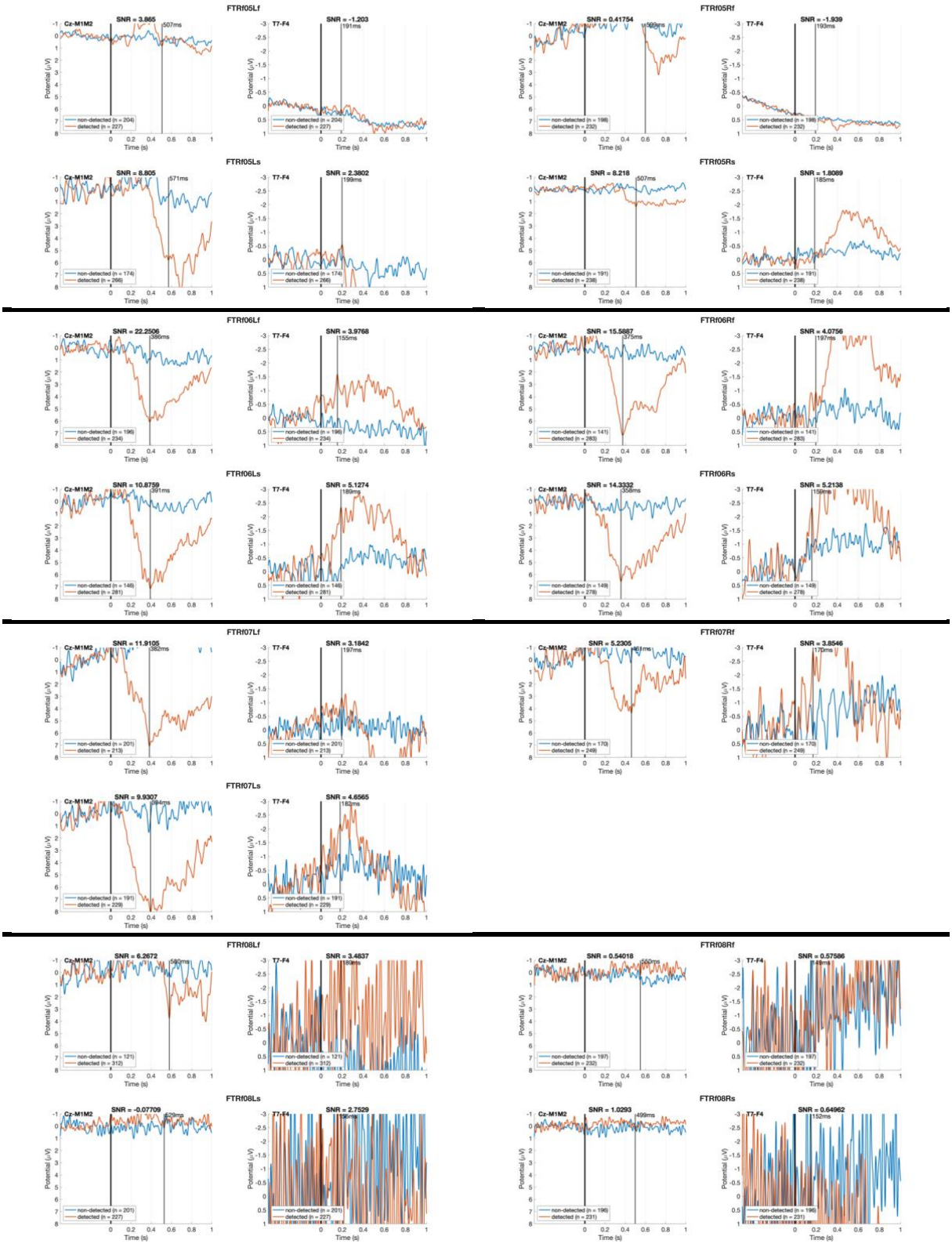
Cz-M1M2
SNR = 4.1097
591ms
T7-F4
SNR = 1.9214
199ms
FOOf10Rs
Cz-M1M2
SNR = 7.989
495ms
T7-F4
SNR = 2.5344
199ms
FOOf11Lf
Cz-M1M2
SNR = 3.5775
460ms
T7-F4
SNR = 3.9763
189ms
FOOf11Rf
Cz-M1M2
SNR = 7.6839
568ms
T7-F4
SNR = 1.9122
199ms
FOOf11Ls
Cz-M1M2
SNR = 3.6438
460ms
T7-F4
SNR = 4.214
199ms
FOOf11Rs
Cz-M1M2
SNR = 1.5957
530ms
T7-F4
SNR = 0.62048
149ms
FOOf12Lf
Cz-M1M2
SNR = 6.5758
450ms
T7-F4
SNR = 3.251
193ms
FOOf12Rf
Cz-M1M2
SNR = 15.9179
474ms
T7-F4
SNR = 1.2524
149ms
FOOf12Ls
Cz-M1M2
SNR = 6.5125
495ms
T7-F4
SNR = 1.0506
155ms
FOOf12Rs
Cz-M1M2
SNR = 11.2648
444ms
T7-F4
SNR = 2.9192
163ms
Potential (μV)
Time (s)


FTRf01Lf
Cz-M1M2
SNR = 5.0665
519ms
non-detected (n = 100)
detected (n = 323)
T7-F4
SNR = 1.7985
170ms
non-detected (n = 100)
detected (n = 323)
FTRf01Ls
Cz-M1M2
SNR = 2.5707
non-detected (n = 100)
detected (n = 318)
T7-F4
SNR = 1.3328
199ms
non-detected (n = 100)
detected (n = 318)
FTRf01Rf
Cz-M1M2
SNR = 4.0353
437ms
non-detected (n = 90)
detected (n = 327)
T7-F4
SNR = 1.8505
187ms
non-detected (n = 90)
detected (n = 327)
FTRf01Rs
Cz-M1M2
SNR = 2.5491
405ms
non-detected (n = 140)
detected (n = 284)
T7-F4
SNR = 2.7832
199ms
non-detected (n = 140)
detected (n = 284)
FTRf02Lf
Cz-M1M2
SNR = 2.2141
494ms
non-detected (n = 152)
detected (n = 280)
T7-F4
SNR = 2.9722
166ms
non-detected (n = 152)
detected (n = 280)
FTRf02Ls
Cz-M1M2
SNR = 2.7327
442ms
non-detected (n = 162)
detected (n = 268)
T7-F4
SNR = 1.7748
163ms
non-detected (n = 162)
detected (n = 268)
FTRf02Rf
Cz-M1M2
SNR = 4.1819
474ms
non-detected (n = 154)
detected (n = 276)
T7-F4
SNR = 0.093845
168ms
non-detected (n = 154)
detected (n = 276)
FTRf02Rs
Cz-M1M2
SNR = 2.7305
476ms
non-detected (n = 116)
detected (n = 310)
T7-F4
SNR = 1.4579
181ms
non-detected (n = 116)
detected (n = 310)
FTRf03Lf
Cz-M1M2
SNR = 6.455
385ms
non-detected (n = 200)
detected (n = 220)
T7-F4
SNR = 2.3662
170ms
non-detected (n = 200)
detected (n = 220)
FTRf03Ls
Cz-M1M2
SNR = 0.78113
non-detected (n = 211)
detected (n = 210)
T7-F4
SNR = 4.0254
158ms
non-detected (n = 211)
detected (n = 210)
FTRf03Rf
Cz-M1M2
SNR = 1.632
581ms
non-detected (n = 184)
detected (n = 230)
T7-F4
SNR = 4.0373
154ms
non-detected (n = 184)
detected (n = 230)
FTRf04Lf
Cz-M1M2
SNR = 6.3879
565ms
non-detected (n = 166)
detected (n = 265)
T7-F4
SNR = 1.4102
199ms
non-detected (n = 166)
detected (n = 265)
FTRf04Ls
Cz-M1M2
SNR = 10.7726
514ms
non-detected (n = 111)
detected (n = 315)
T7-F4
SNR = 0.91219
199ms
non-detected (n = 111)
detected (n = 315)
FTRf04Rf
Cz-M1M2
SNR = 4.9919
555ms
non-detected (n = 75)
detected (n = 359)
T7-F4
SNR = 2.6852
199ms
non-detected (n = 75)
detected (n = 359)
FTRf04Rs
Cz-M1M2
SNR = 3.8115
577ms
non-detected (n = 152)
detected (n = 275)
T7-F4
SNR = 2.0855
149ms
non-detected (n = 152)
detected (n = 275)
Potential (μV)
Time (s)


FTRf05Lf
Cz-M1M2
SNR = 3.865
507ms
T7-F4
SNR = -1.203
191ms
FTRf05Rf
Cz-M1M2
SNR = 0.41754
509ms
T7-F4
SNR = -1.939
193ms
FTRf05Ls
Cz-M1M2
SNR = 8.805
571ms
T7-F4
SNR = 2.3802
199ms
FTRf05Rs
Cz-M1M2
SNR = 8.218
507ms
T7-F4
SNR = 1.8089
185ms
FTRf06Lf
Cz-M1M2
SNR = 22.2506
386ms
T7-F4
SNR = 3.9768
155ms
FTRf06Rf
Cz-M1M2
SNR = 15.5887
375ms
T7-F4
SNR = 4.0756
197ms
FTRf06Ls
Cz-M1M2
SNR = 10.8759
391ms
T7-F4
SNR = 5.1274
189ms
FTRf06Rs
Cz-M1M2
SNR = 14.3332
358ms
T7-F4
SNR = 5.2138
159ms
FTRf07Lf
Cz-M1M2
SNR = 11.9105
382ms
T7-F4
SNR = 3.1842
197ms
FTRf07Rf
Cz-M1M2
SNR = 5.2305
461ms
T7-F4
SNR = 3.8546
170ms
FTRf07Ls
Cz-M1M2
SNR = 9.9307
394ms
T7-F4
SNR = 4.6565
180ms
FTRf08Lf
Cz-M1M2
SNR = 6.2672
580ms
T7-F4
SNR = 3.4837
169ms
FTRf08Rf
Cz-M1M2
SNR = 0.54018
560ms
T7-F4
SNR = 0.57586
148ms
FTRf08Ls
Cz-M1M2
SNR = -0.07709
629ms
T7-F4
SNR = 2.7529
156ms
FTRf08Rs
Cz-M1M2
SNR = 1.0293
499ms
T7-F4
SNR = 0.64962
152ms
Potential (μV)
Time (s)

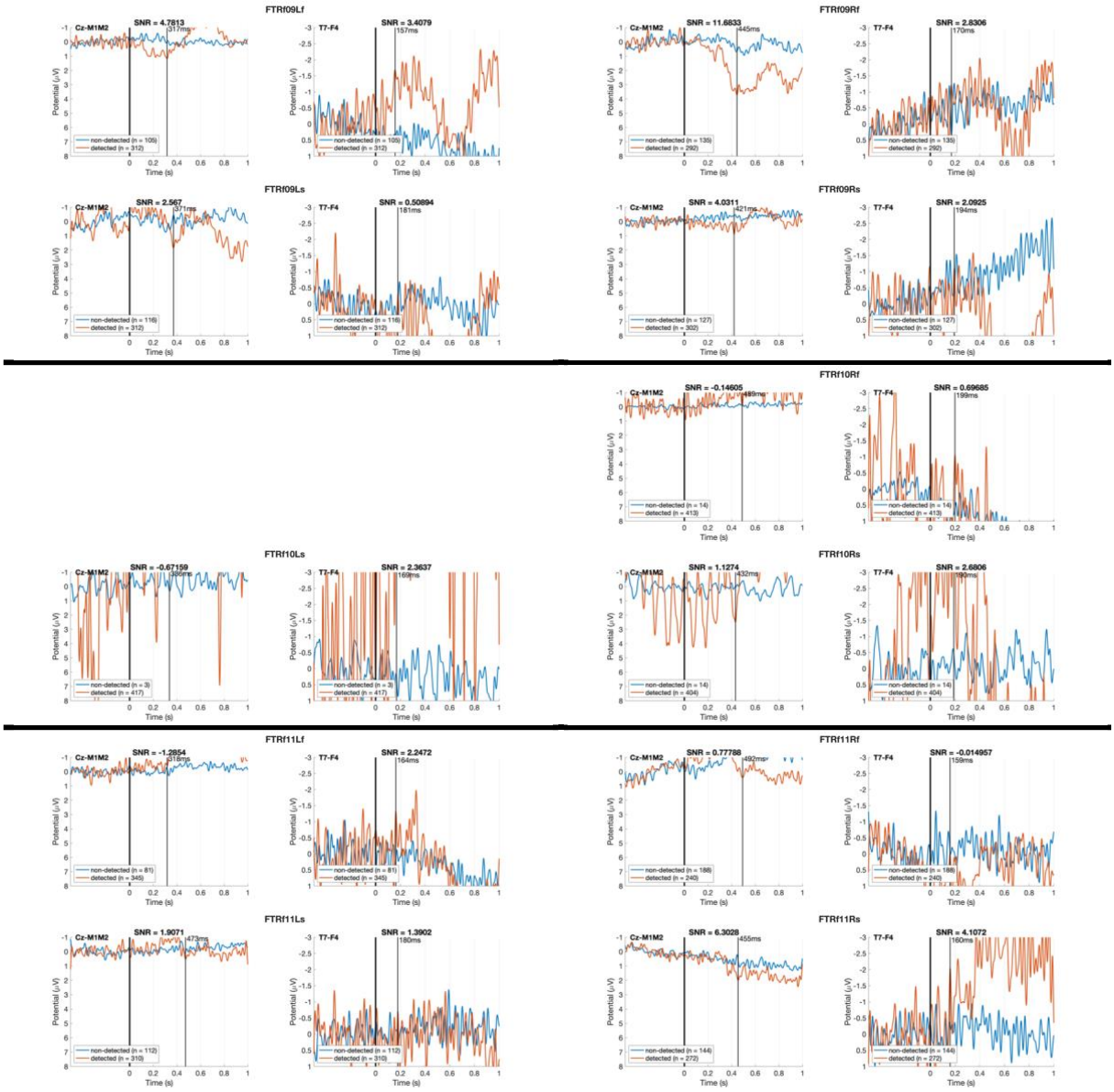


Figure A2.1: Grand average EPs in the central derivation Cz-M1,M2 and the contralateral derivation T7-F4 per measurement. Figures are categorized per subject, starting with the first subject in the 'SCS-OFF vs SCS-ON' protocol (FOOf01) and ending with the last subject in the 'SCS-ON1 vs SCS-ON2' protocol (FTRf11). Per subject, the first two measurements are in the top row, and the second two measurements are in the bottom row. Measurements performed on the left side are shown on the left side and measurements performed on the right side are shown on the right side. Orange lines indicate detected stimuli, blue lines indicate non-detected stimuli. The number of trials used for computing the grand average is shown in each legend. The vertical lines at T=0 indicate the moment of intra-epidermal stimulation, vertical lines around 150-200 ms and 300-600 ms illustrate individual latencies per measurement.

A3 Adequate versus inadequate measurements

Table A3.1: All measurement performed by all subjects. Per analysis (nociceptive detection thresholds (NDT), evoked potential in central derivation (EP_{ct}) and evoked potential in contralateral derivation (EP_{cl})), inclusion and exclusion of individual measurements was determined based on estimations of a generalized linear model (GLM) and task performance or based on Signal-to-Noise ratios (SNR) and task performance. Green represents measurements included per analysis, red represents measurements excluded per analysis, and grey represents incomplete measurements. L1 – first measurement on left foot; R1 – first measurement on right foot; L2 – second measurement on left foot; R2 – second measurement on right foot.

Subject ID	L1			R1			L2			R2		
ON1 vs ON2	NDT	EP_{ct}	EP_{cl}	NDT	EP_{ct}	EP_{cl}	NDT	EP_{ct}	EP_{cl}	NDT	EP_{ct}	EP_{cl}
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
OFF vs ON												
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												