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RELIABLE ASSESSMENT OF THE HUMAN NOCICEPTIVE WITHDRAWAL REFLEX AND REFLEX RECEPTIVE FIELDS

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INTRODUCTION OF NEW METHODS

BY
MICHAEL BRUN JENSEN

DISSERTATION SUBMITTED 2015

AALBORG UNIVERSITY
DENMARK

RELIABLE ASSESSMENT OF THE HUMAN NOCICEPTIVE WITHDRAWAL REFLEX AND REFLEX RECEPTIVE FIELDS

INTRODUCTION OF NEW METHODS

Ph.D. thesis by

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CV

Michael Brun Jensen was born in Esbjerg, Denmark in 1982. He earned his M.Sc. degree in biomedical engineering in 2010 through an elite program at the Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology at Aalborg University, Denmark. His main areas of research are biomedical signal processing with focus on EMG, evaluation of methodological validity and reliability, and the neurophysiology of spinal nociception.

PREFACE

This Ph.D. thesis is the result of work carried out between December 2011 and March 2015 at the Center for Sensory-Motor Interaction (SMI), Aalborg University.

ENGLISH SUMMARY

The nociceptive withdrawal reflex (NWR) is a polysynaptic spinal reflex responsible for moving the limbs away from a potential noxious stimulus. It is considered a reliable and objective tool in pain assessment, and is currently the only validated non-invasive physiological measure for objective assessment of spinal nociception in humans. Predominantly, the NWR is assessed by estimation of a single NWR threshold (NWR-T) from electromyography (EMG) recordings of NWRs elicited by electrical stimulation. However, a topographical methodology embracing the modular organization of the NWR has recently been introduced, resulting in more comprehensive evaluation of the NWR sensitivity by quantification of the reflex receptive field (RRF). Both of these methods have been shown sufficiently sensitive to detect abnormal spinal nociception in several groups of pain patients but have not been translated into clinical use, probably due to large variability both within and between subjects. The wide distribution of both NWR-T and RRF size in healthy subjects may reflect genuine interpersonal variation or to some extend be the result of measurement variability introduced by non-optimal assessment methodologies.

Throughout the work presented in this thesis, specific weak points or imperfections of existing methods have been addressed to enable more valid and reliable assessment of NWRs and RRFs. Novel methods have been developed and tested against the existing alternatives.

Study I demonstrated that the current practice for NWR detection is extremely sensitive to EMG crosstalk and may result in poor detection specificity. A novel method for identification of EMG crosstalk, based on analysis of muscle fiber conduction velocity was developed to improve the accuracy of NWR detection.

The NWR-T is predominantly estimated for NWRs elicited by electrical stimulation of the sural nerve at the lateral malleolus, which may be associated with substantial pain and discomfort. Study II demonstrated that the need for intolerable stimulation intensities to elicit the NWR may cause a high failure rate but that a lower failure rate can be achieved by stimulating at the sole of the foot. Furthermore, NWR-Ts for NWRs elicited by foot sole stimulation displayed superior stability over time.

In contrast to NWR-T estimation, the existing methodology for RRF quantification is not entirely objective. As demonstrated in Study III this may entail an increase in variability. A completely objective alternative methodology was developed and shown to enable more reliable quantification of RRFs. Improved stability over time makes this new methodology more suitable for multi-session and interpersonal investigations.

The present results suggest that limited reliability may be a contributing factor to why the existing methods are not suitable for discriminative assessment of spinal nociception on an individual basis. While the capability of the novel methods in this regard is still up for investigation, they are more reliable than their existing alternatives yielding more stable measures over time and hereby reducing the number of subjects needed in future experiments.

DANSK RESUME

Den nociceptive afværgerefleks (NWR) er en polysynaptisk spinalrefleks ansvarlig for at flytte lemmer væk fra en potentielt skadelig påvirkning. Den betragtes som et pålideligt og objektivt redskab indenfor smertevurdering og er på nuværende tidspunkt det eneste validerede ikke-invasive fysiologiske mål for objektiv vurdering af spinal nociception i mennesker. NWR bliver hovedsagligt vurderet ved estimering af en enkelt reflekstærskel (NWR-T) fra elektromyografiske (EMG) optagelser af NWR udløst ved elektrisk stimulation. En topografisk metode, som favner den modulære organisation af NWR, er dog for nyligt blevet introduceret, hvilket resulterer i en mere omfattende evaluering af NWR sensitivitet ved kvantificering af refleks-receptive felter (RRF). Begge disse metoder har vist sig tilstrækkelig sensitive til at detektere abnorm spinal nociception i adskillige grupper af smertepatienter men har ikke opnået klinisk anvendelse, formentlig på grund af stor variabilitet både individuelt og mellem personer. Den vide fordeling af både NWR-T of RRF-størrelse i raske mennesker kan være et udtryk for virkelige interpersonelle variationer eller i et givent omfang være et resultat af målevariabilitet introduceret på grund af ikke-optimale vurderingsmetoder.

Igennem arbejdet præsenteret i denne afhandling er konkrete svagheder og ufuldkommenheder ved eksisterende metoder behandlet for at muliggøre mere valid og pålidelig vurdering af NWR of RRF. Nye metoder er blevet udviklet og testet op imod de eksisterende alternativer.

Studie I demonstrerede, at den nuværende praksis for NWR-detektion er ekstrem følsom overfor EMG crosstalk, hvilket kan føre til detektion med dårlig specificitet. En ny metode til identifikation af EMG crosstalk baseret på analyse af muskelfiberledningshastighed blev udviklet for at forbedre nøjagtigheden af NWR-detektion.

NWR-T bliver hovedsagligt estimeret for NWR udløst ved elektrisk stimulation af suralnerven ved den laterale malleol, hvilket kan være forbundet med betydelig smerte og ubehag. Studie II demonstrerede, at uudholdelige stimulationsintensiteter kan være nødvendige for at udløse NWR hvilket kan medføre en lav gennemførelsesprocent, men at en højere gennemførelsesprocent kan opnås ved at stimulere under fodsålen i stedet. Desuden udviste NWR-T for NWR udløst ved stimulation under fodsålen forbedret stabilitet over tid.

Den eksisterende metodologi for RRF-kvantificering er i modsætning til estimering af NWR-T ikke fuldstændig objektiv. Som demonstreret i Studie III kan dette medføre en forøget variabilitet. En fuldstændig objektiv alternativ metodologi blev udviklet og vist i stand til at foretage mere pålidelig kvantificering af RRF.

Forbedret stabilitet over tid gør denne nye metodologi bedre egnet til undersøgelser med mere end en undersøgelsesgang samt til sammenligninger mellem personer.

Disse resultater antyder, at begrænset pålidelighed kan være en medvirkende faktor til, at de eksisterende metoder ikke er egnet til diskriminerende vurdering af spinal nociception på individuelt niveau. Selvom de nye metoders egenskaber i den henseende kræver yderligere afklaring, er de mere pålidelige end deres eksisterende alternativer. Den heraf øgede stabilitet over tid bevirker desuden en reduktion af det nødvendige deltagerantal i fremtidige forsøg.

ACKNOWLEDGEMENTS

I have throughout this Ph.D. project had a personal and professional relationship with my supervisors, far better than I ever could have expected. I have experienced guidance at a very high scientific level in an informal and friendly collegial tone. I would therefore like to express my sincere gratitude to Ole K. Andersen for his personal approach to supervision, his countless advices and constant support. I do appreciate your efforts, patience and confidence in me, which have been necessary to make this Ph.D. project successful despite the distance. I am also most grateful to José Biurrun Manresa for all the fruitful scientific discussions, valuable comments and suggestions, and for practically always being available and willing to assist me. I sincerely appreciate our frequent long dialogues; the professional and the personal ones alike.

I would also like to thank all the people who have helped me with the studies presented in this thesis. Those with whom I have discussed hypothesis or ideas, those who have helped me setting up pilot experiments (and been bold enough to be my guinea pig) and off course the many voluntary subjects who have participated in my experiments. Without you this work could not have been done. I also appreciate the kindness and good predisposition of all the administrative and technical staff at SMI, especially from Knud Larsen and Jan Stavnshøj who have been a tremendous help during development of software and hardware necessary to conduct my experiments.

I wish to express my gratefulness to my family; my mother Connie, my father Johannes and my sisters Charlotte and Vibeke for their constant support and confidence in me. Finally, I convey my deepest gratitude and appreciation to my greatest inspiration, the love of my life, my wife Line. I know this Ph.D. project at times has been though on the both of us. This thesis is dedicated to you.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BF	biceps femoris
CV	conduction velocity
CVA	conduction velocity analysis
DD	double differential
EMG	electromyography
iEMG	intra-muscular electromyography
LOA	limits of agreement
NWR	nociceptive withdrawal reflex
NWR-T	nociceptive withdrawal reflex threshold
RRF	reflex receptive field
SD	single differential
sEMG	surface electromyography
SOL	soleus
TA	tibialis anterior

CHAPTER 1. INTRODUCTION

Chronic pain of moderate to severe intensity occurs in 19% of the adult European population and constitutes a major health care problem in Europe [Breivik et al, 2006]. The area attains an increased focus and chronic pain conditions are today recognized as an independent healthcare problem. Chronic pain is often not associated with any apparent tissue or nerve injury but is instead related to an increased sensitivity within the central nervous system which may be denoted central hyperexcitability or central sensitization. A well-known example of this phenomenon which is caused by plasticity changes in the central nervous system is fibromyalgia [Banic et al, 2004; Desmeules et al, 2003; Woolf, 2011]. However, central sensitization is not easily assessed with sufficient validity and reliability in humans.

The nociceptive withdrawal reflex (NWR) is considered a reliable and objective tool in pain assessment [Willer, 1977], and is currently the only validated non-invasive physiological method for objective assessment of the sensitivity of the spinal nociceptive neurons in humans. It is widely used as an objective electrophysiological outcome measure in experimental studies of nociception in animals [Le Bars et al, 2001] and in humans [Andersen, 2007; Sandrini et al, 2005; Skljarevski and Ramadan, 2002]. Estimation of NWR thresholds (NWR-Ts) based on electromyography (EMG) recordings of NWRs elicited by electrical stimulation, has been shown sufficiently sensitive to detect central hyperexcitability in several groups of pain patients [Banic et al, 2004; Courtney et al, 2009; Desmeules et al, 2003; Lim et al, 2011; Sterling et al, 2008]. Still, this methodology has not been translated into clinical use, probably due to large variability both within and between subjects.

A relatively new strategy for assessing the sensitivity of the spinal nociceptive system utilizes a site-dependent modular organization of the NWR. Several studies in both animals [Clarke and Harris, 2004; Schouenborg and Kalliomaki, 1990] and humans [Andersen et al, 1999; Sonnenborg et al, 2001] have demonstrated that the NWR is modularly organized, meaning that each muscle or group of synergistic muscles has a bounded well-defined cutaneous area from which a reflex can be elicited. This reflex receptive field (RRF) is probably spatially encoded by wide-dynamic-range neurons in the deep dorsal horn [Schouenborg et al, 1995]. The receptive field of neurons of this type expands during central sensitization [Cook et al, 1987; Dubner, 1991; Herrero et al, 2000]. This dynamic nociceptive behavior suggests that spatial properties of the RRF enables non-invasive assessment of the excitability level of the spinal nociceptive system associated with experimental or chronic pain. Indeed, enlarged RRFs have been shown in groups of chronic pain patients compared to healthy controls [Biurrun Manresa et al, 2013a; Neziri et al, 2010a]. However, similar to NWR-Ts, the distribution of estimated RRF sizes in a normal population is very wide [Neziri et al, 2010b], which makes meaningful discriminative assessment on an individual level difficult.

The wide distribution of both NWR-T and RRF size in healthy subjects may reflect genuine interpersonal variation or to some extend be the result of measurement variability introduced by non-optimal assessment methodologies. To optimize the clinical and experimental value of NWR assessment and promote transition into the clinic it is of uttermost importance to ensure the highest possible level of methodological reliability.

1.1. AIMS OF THE PH.D. PROJECT

The overall aim of this Ph.D. project was to develop novel methods to improve the validity and reliability of NWR assessment. To achieve this aim, the following research questions were addressed:

1. Are existing methods for assessment of NWR and RRF sufficiently reliable to assess changes in spinal nociception and be used as objective measures of central hyperexcitability?
2. Are the conventional EMG recordings used to record the NWR selective enough to allow valid NWR detection? – If not, how can it be improved?
3. Does the conventional stimulation paradigm for elicitation of the NWR allow reliable estimation of the NWR threshold? – If not, can a change of stimulation site increase the reliability?
4. The existing methodology for RRF quantification involves estimation of subjectively identified pain thresholds. How does that influence the reliability of the evaluation? – Can a completely objective alternative assessment methodology result in more reliable RRF quantification?

These questions are addressed through three peer-reviewed articles (from now on referred to as Study I to III).

The three studies are:

Study I
Jensen M. B., Biurrun Manresa J. A., Frahm K. S., & Andersen, O. K. (2013). Analysis of muscle fiber conduction velocity enables reliable detection of surface EMG crosstalk during detection of nociceptive withdrawal reflexes. *BMC Neuroscience,* 14:39. doi: 10.1186/1471-2202-14-39.

Study II
Jensen M. B., Biurrun Manresa J. A., & Andersen, O. K. (2015). Reliable estimation of nociceptive withdrawal reflex thresholds. *Submitted to Pain.*

Study III
Jensen M. B., Biurrun Manresa J. A., & Andersen, O. K. (2015). A new objective method for acquisition and quantification of reflex receptive fields. *Pain,* 156(3), 555-64. doi: 10.1097/01.j.pain.0000460332.41009.4a.

1.2. DISSERTATION OVERVIEW

This thesis describes three methodological issues regarding the validity and reliability of existing methods for assessment of the NWR and RRF in humans, and presents to each of the raised issues a possible solution. Each of these specific issues (research question 2-4) are addressed in Study I to III respectively, and presented in respectively chapter 2-4 of this thesis. Chapter 3 and 4 cover the reliability of both existing (research question 1) and novel presented methods based on Study II and III. Finally, all four research questions are synthesized in chapter 5.

CHAPTER 2. NWR DETECTION WITH IMPROVED SPECIFICITY

Numerous different criteria for evaluation of NWRs from EMG signals are presented in the literature [Banic et al, 2004; Courtney et al, 2009; Desmeules et al, 2003; Khatibi et al, 2014; Sterling et al, 2008; von Dincklage et al, 2009]. There exists no consensus on how to evaluate the occurrence or size of elicited NWRs which makes it difficult to compare results from studies performed in different laboratories. However, in an attempt to promote a standardization of NWR-T assessment methodology, a comprehensive evaluation of both accuracy and reliability of different scoring criteria has been performed [France et al, 2009; Rhudy and France, 2007]. It was concluded that scoring criteria normalized by the prestimulus EMG activity ought to be preferred and that the scoring criteria interval peak z-score among others were considered accurate and reliable.

2.1. INTERVAL PEAK Z-SCORE – DOES A SINGLE OPTIMAL CUT-POINT EXIST?

Previous evaluation of the interval peak z-score as a scoring criterion for NWR detection has been performed in EMG signals measured over the Bicep Femoris (BF) muscle. The results of Study I indicate that a similar cut-point (interval peak z-score around 12) are suitable regardless if the NWR is measured over BF or over the Tibialis anterior (TA) muscle. This suggests that the ROC-curves and cut-points presented in [Rhudy and France, 2007] and [France et al, 2009] is not limited to one specific muscle but constitute generic entities general for the type of EMG recording. As seen in Figure 1, further investigation of the data presented in study I indicate that a slightly higher threshold for the interval peak z-score (z=14) is optimal if the NWR is measured using double differential (DD) surface EMG (sEMG) instead of the standard single differential (SD) sEMG used in previous studies. The DD sEMG configuration constitute a spatial filter capable of reducing common signal components in the recorded sEMG signal originating from external noise sources [Farina et al, 2003; Mesin et al, 2009]. The interval peak z-score is, as indicated in Equation 1 below, dependent on the baseline EMG activity measured just prior to stimulation. Superior reduction of prestimulus background noise may therefore likely result in higher interval peak z-scores and explain the slightly higher optimal cut-point for the more selective DD sEMG.

$$\textit{Interval peak } z - \textit{score} = \frac{\textit{reflex interval peak} - \textit{baseline mean}}{\textit{baseline standard deviation}} \qquad (1)$$

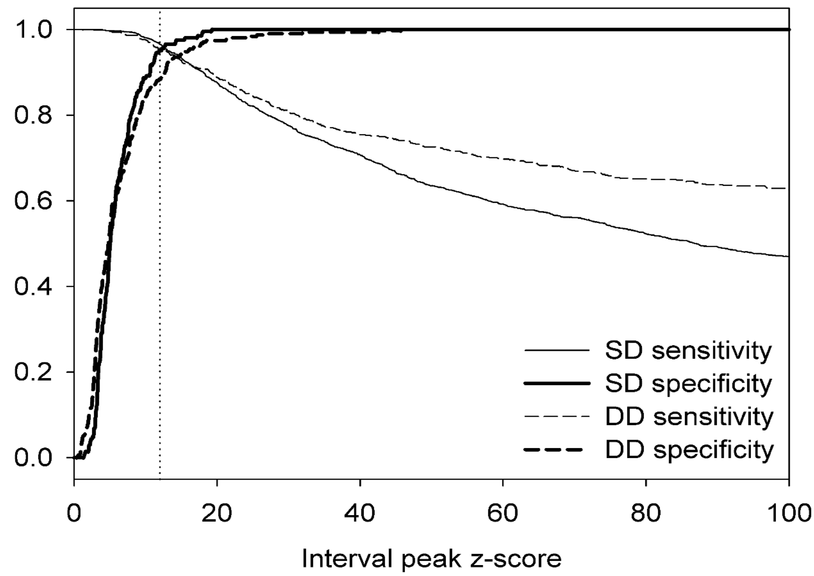

Figure 1: Plots of sensitivity (the ability to detect genuine NWRs) and specificity (the ability not to detect noise/artefacts as NWRs) with varying thresholds for the interval peak z-score. Assuming equal cost of an undetected NWR and a detected NWR not representing a genuine NWR (equal cost-functions) the optimal threshold (resulting in best possible overall accuracy) is at the intersection of sensitivity and specificity: Around 12 (the dotted line) for single differential (SD) EMG and around 14 for double differential (DD) EMG.

2.2. THE INFLUENCE OF CROSSTALK

Not only external sources of noise influence the sEMG signal. One of the main concerns of sEMG recording is the possible interference of crosstalk originating from adjacent active muscles [Farina et al, 2004]. The electrophysiological activity generated in TA by muscle contraction disperse through body tissues via volume conducting and may be measured over a relaxed Peroneus Brevis or Soleus (SOL) muscle using standard SD sEMG [De Luca and Merletti, 1988]. This electrophysiological phenomenon has also been reported during investigation of NWRs elicited by electrical stimulation at the sole of the foot, where the resulting muscle activity in TA also was detected with sEMG over the gastrocnemius muscle [Shahani and Young, 1971].

Study I showed how crosstalk may influence NWR detection based on evaluation of interval peak z-scores. Figure 1 and the optimal interval peak z-score cut-points of

12 and 14 for respectively SD and DD sEMG were based on the premise that all NWRs detected from sEMG measured over TA indeed involved muscle activity in the TA muscle. However, as shown in the study, this is not always the case. Intramuscular EMG (iEMG) exposed that many of the NWRs did not involve any activation of TA but that the activity recorded over TA was crosstalk originating from SOL. Utilizing the iEMG recordings to differentiate between genuine muscle activity and crosstalk, plots of sensitivity and specificity (Figure 2) revealed that application of a cut-point around 12 or 14 would result in NWR detection with very poor specificity. Reflex detection with much better accuracy could be achieved by applying considerable larger cut-points of 71 and 48 for SD and DD sEMG, respectively. However, the use of such very high cut-points is not compatible with the previously published plots of sensitivity and specificity of the NWR-T assessment methodology [France et al, 2009; Rhudy and France, 2007], as all small NWRs would be neglected causing an alarming reduction in detection sensitivity. This indicates that the optimal cut-point for muscle specific NWR detection is dependent on whether crosstalk occurs and on the relationship between the magnitude of genuine muscle activity and crosstalk, respectively. Information that generally is not available prior to assessment.

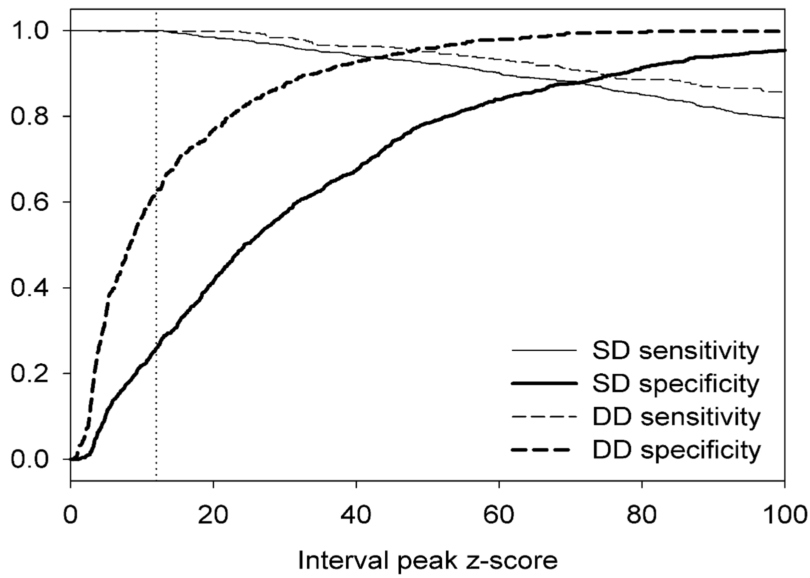

Figure 2: Sensitivity and specificity of NWR detection based on calculation of interval peak z-scores and using intramuscular EMG to differentiate between genuine NWRs and EMG crosstalk. In contrast to figure 1, this figure clearly indicates that an interval peak z-score threshold around 12 (the dotted line) may result in NWR detection with very poor specificity for both single differential (SD) EMG and double differential (DD) EMG.

2.3. CONDUCTION VELOCITY ANALYSIS (CVA)

To alleviate the influence of crosstalk during NWR detection, a novel method for distinction between genuine NWRs and crosstalk was developed and presented in Study I. This method denoted Conduction Velocity Analysis (CVA) is based on the observation that electrophysiological potentials of genuine muscle activation are propagating along the muscle fibers whereas potentials originating from other sources (e.g. external noise or crosstalk from adjacent muscles) are non-propagating [Farina et al, 2004]. By measuring the potentials using sEMG at several locations along the overall orientation of the muscle an estimate of the muscle fiber conduction velocity (CV) can be made using various simple or sophisticated methods [Arendt-Nielsen and Zwarts, 1989; Broman et al, 1985; Farina et al, 2001; Farina and Negro, 2007]. The estimated CV is indicative of the propagating/non-propagating nature of the recorded signals since a recording dominated by non-propagating signal components will result in an unreasonable high CV which may cause the authenticity of a detected NWR to be questioned (Figure 3). The CVA method was applied in Study II and III as an additional examination to determine the authenticity of NWRs detected by evaluation of interval peak z-scores. Any detected NWRs with features (CV and maximal correlation) exceeding fixed thresholds established in Study I were considered to be the result of crosstalk and thus ignored.

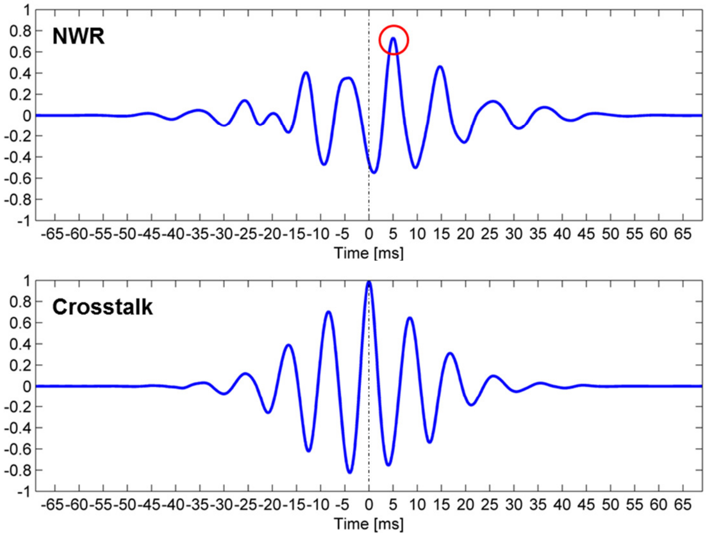

Figure 3: The muscle fiber conduction velocity may be estimated as the inter-electrode distance divided by the temporal displacement of the peak in a cross-correlogram of two adjacent EMG recordings along the orientation of the muscle fibers. Another feature utilized by the CVA method to distinguish between genuine nociceptive withdrawal reflexes (NWRs) and crosstalk is the maximum level of correlation which is close to perfect for crosstalk.

2.4. CVA ENABLES IMPROVED MAPPING OF NWR SENSITIVTY

In Study I the CVA method was applied on signals recorded during electrical stimulation at two locations under the sole of the foot causing consistent NWR elicitation in TA and SOL, respectively. The results (Figure 4) clearly showed (as previously indicated in Figure 2) that evaluation of DD sEMG resulted in NWR detection with significantly better specificity than evaluation of the conventional SD sEMG. However, even better specificity was achieved by applying CVA.

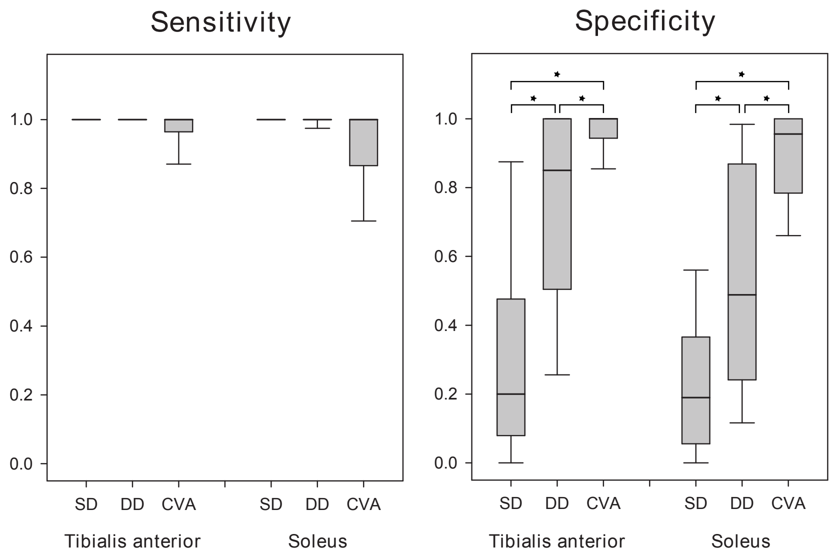

Figure 4: Sensitivity and specificity of reflex detection calculated for 14 individual subjects using three different detection methods: Evaluation of interval peak z-scores calculated for single differential (SD) EMG, evaluation of interval peak z-scores calculated for double differential (DD) EMG and application of Conduction Velocity Analysis (CVA). Asterisks indicate statistical significant differences.

These results have come about in a controlled experiment with a protocol ensuring strong NWRs causing a large degree of crosstalk. To evaluate the practical usefulness of the CVA method with respect to mapping of RRFs, the RRF of TA and SOL has been mapped both with and without CVA [Jensen et al, 2013]. The RRFs estimated in this experiment were RRF probability areas calculated as the fraction of the foot where a NWR was elicited by at least 25 percent of the stimulations. The subjects were lying in supine position which caused TA to be the predominant prime mover of the resulting reflex response. Indeed the results showed that the RRF areas estimated for SOL were significantly larger when based on evaluation of SD sEMG than if DD sEMG or CVA was utilized (Figure 5), suggesting that the NWRs detected over SOL primarily represented crosstalk. For

TA, slightly smaller RRFs were estimated when applying CVA. This could be related to the non-significant reduction in TA sensitivity observed in study I (Figure 4). However, it could also be the result of very efficient cancellation of signal components originating from external sources including a few NWRs involving genuine activity in SOL. The positive effect of using DD sEMG or CVA is also very clear on an individual level, where the RRF for SOL extracted from SD sEMG to a large extend resemble the RRF estimated for TA (Figure 6) [Jensen et al, 2013]. Due to the modular organization of the NWR, such a degree of resemblance seems suspicious. The use of either DD sEMG or CVA practically eliminates this resemblance, indicating that the SD sEMG measured over SOL is strongly influenced by crosstalk and the derived RRF mapping may not be valid.

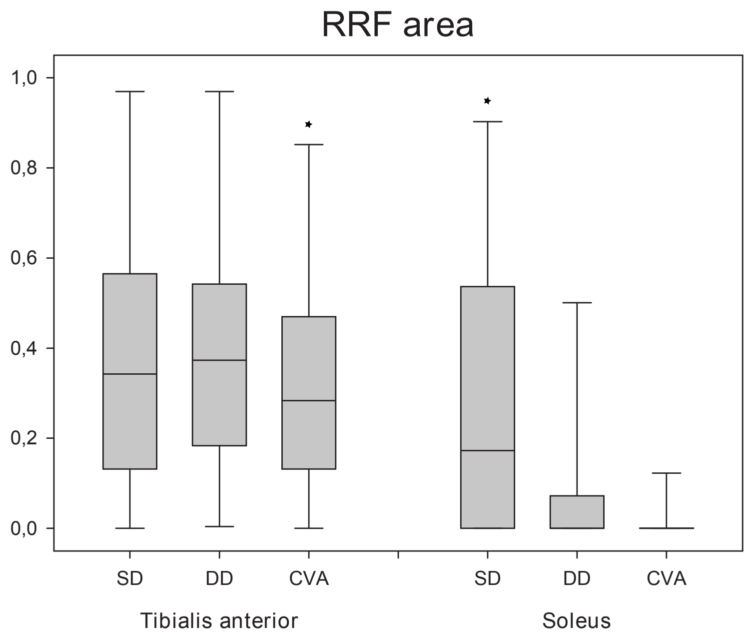

Figure 5: Reflex receptive field (RRF) areas (fraction of the foot where a reflex could be elicited by at least 25 percent of the stimulations) calculated using three different methods to detect reflexes: Evaluation of interval peak z-scores calculated for single differential (SD) EMG, evaluation of interval peak z-scores calculated for double differential (DD) EMG and Conduction Velocity Analysis (CVA). An asterisk indicates a significant difference compared to the two remaining detection methods. Compared to SD EMG, the use of DD EMG and CVA entailed significantly smaller and nearly non-existing RRF areas for the soleus muscle.

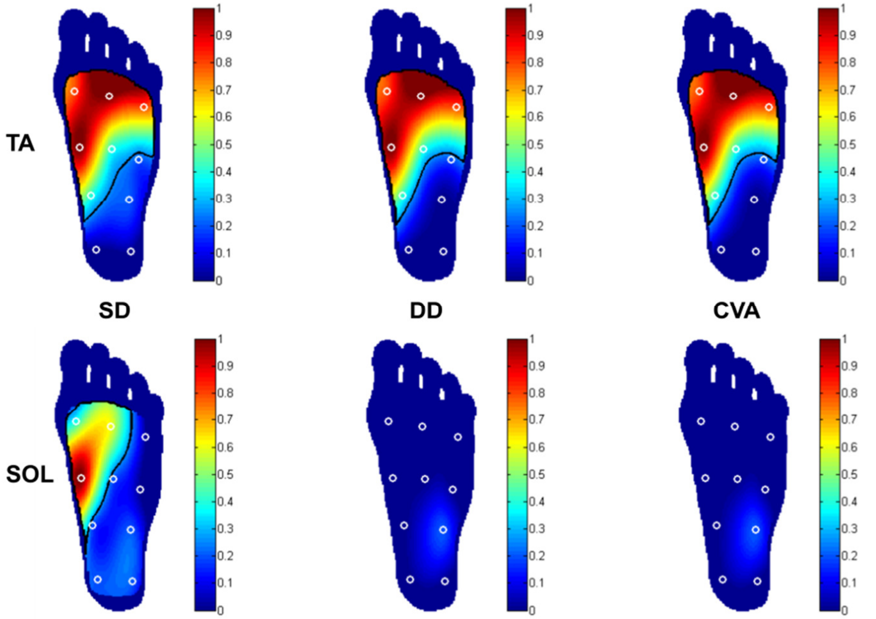

Figure 6: Example of probability maps (illustrating the likelihood that a reflex was elicited by stimulation of a given location) for the tibialis anterior (TA) and soleus (SOL) muscles produced for one individual subject using three different methods to detect reflexes: Evaluation of interval peak z-scores calculated for single differential (SD) EMG, evaluation of interval peak z-scores calculated for double differential (DD) EMG and Conduction Velocity Analysis (CVA).

2.5. PARTIAL CONCLUSION

Study I demonstrates that EMG crosstalk originating from nearby active muscles may significantly influence detection of NWRs and mappings of RRFs. Especially if the evaluation is based on standard SD sEMG signals that are very sensitive to crosstalk. In this case, NWR detection using a previously validated scoring criterion did entail very poor detection specificity. However, this issue can readily be reduced by the use of DD EMG or CVA, both of which constitute valuable measures to deal with crosstalk and enable NWR detection with improved specificity and more valid mapping of RRFs for specific muscles.

CHAPTER 3. RELIABLE ELICITATION OF THE NWR

Assessment of the NWR-T as a measure of central nociceptive processing has become very popular. For example has it been used to detect central hyperexcitability in several groups of pain patients [Banic et al, 2004; Courtney et al, 2009; Desmeules et al, 2003; Lim et al, 2011; Sterling et al, 2008] and more recently a number of studies investigating attentional or emotional descending modulation have compared NWR-Ts and measures of perceived pain to differentiate between spinal nociception and supraspinal pain perception [Khatibi et al, 2014; Rhudy et al, 2013; Rhudy et al, 2014; Terry et al, 2013; Vachon-Presseau et al, 2011]. The NWR is generally elicited by electrical stimulation of the sural nerve at the lateral malleolus and measured with sEMG recorded over the ipsilateral brevis head of the BF muscle [Sandrini et al, 2005]. However, as demonstrated in Study II, two methodological concerns limit the practical applicability of this conventional method for estimation of NWR-Ts; a relatively high failure-rate and inferior between-session reliability. Both of which may be improved by changing the stimulation site from the sural nerve to the arch of the foot.

3.1. CONVENTIONAL METHOD FOR NWR-T ESTIMATION MAY ENTAIL A HIGH FAILURE RATE

Electrical stimulation applied directly over the sural nerve is often associated with substantial pain and discomfort and conventional NWR-T assessment involving sural nerve stimulation cannot always be completed because some subjects find the painful stimulations intolerable. In Study II the NWR-T could not be consistently estimated in 29% of the subjects due to intolerable pain sensation. Prior to Study II, only a very limited number of peer-reviewed papers have reported occurrences of non-completed NWR-T estimations [Banic et al, 2004; Biurrun Manresa et al, 2014b; Sterling et al, 2008]. However, both personal communication with various laboratories using the method on a regular basis and experience from our own laboratory, suggest that more often than indicated by the literature, reliable NWR-T estimation is not feasible. To mend this limitation, Study II involved an alternative method for NWR-T estimation (Figure 7). The NWR-Ts for the same group of subjects were estimated by applying electrical stimulation at the arch under the sole of the foot, which resulted in a reduced failure rate (5%).

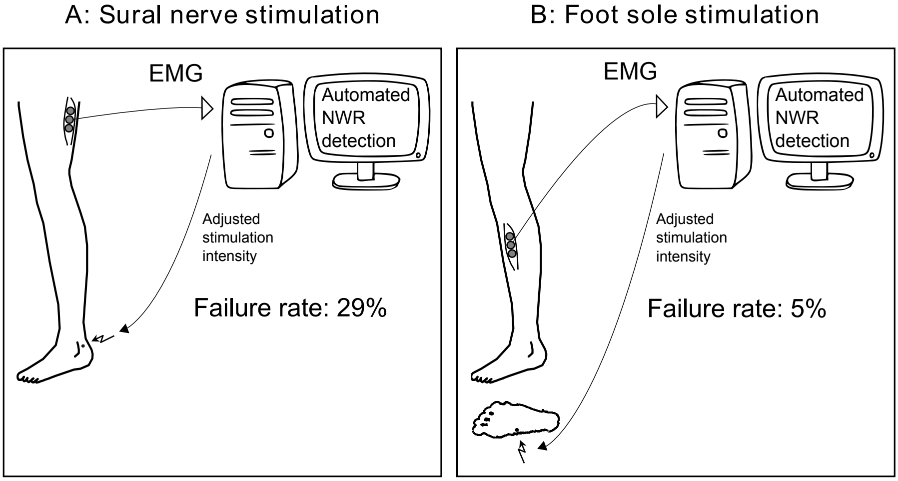

Figure 7: In study II the NWR-T were estimated using two different methods involving electrical stimulation over the sural nerve trunk (A) and at the arch under the sole of the foot (B) while measuring electromyography (EMG) from biceps femoris and tibialis anterior, respectively. The NWR-T for sural nerve stimulation could not consistently be estimated in 29% of the subjects due to intolerable pain sensation. A substantially lower failure rate was observed for NWR-Ts estimated applying stimulation at the sole of the foot.

3.2. STIMULATION AT THE ARCH OF THE FOOT YIELD MORE RELIABLE NWR-T ESTIMATION

Reliability may be defined as the consistency of repeated measurements obtained using a method. In practical terms, this means that the amount of measurement error of a reliable measurement tool does not exceed what has been deemed acceptable for the effective practical use of the method [Atkinson and Nevill, 1998]. Reliability is pivotal for any method to be clinical useful. So before a method is used for detecting differences between healthy and diseased patients, to follow-up the progression of a given disease in patients, or to investigate the effect of pharmacological interventions, its reliability needs to be analyzed. Based on the source of measurement error there exist two different types of reliability: within-session reliability, also known as internal consistency, and between-session reliability, also denoted stability over time [Baumgartner, 1989]. The former evaluates the reliability of measures that are performed two consecutive times during a single session usually within the same day (relevant for before-after experimental designs). The latter assesses the reliability of repeated measures carried out in individual experimental sessions performed on different days (relevant for cross-over designs).

In Study II the test-retest reliability of two different methods for NWR-T estimation (Figure 7) were assessed using Bland-Altman analysis [Bland and Altman, 1999].

Bland-Altman analysis compares the average and the difference between data measured at two different occasions, from which the limits of agreement (LOA) can be derived as the average difference (bias) ± 1.96 times the standard deviation of the differences. The LOA hereby delimits the range within which 95% of the differences between two repeated measurements may be expected to lie.

Previous studies investigating the reliability of the NWR-T report of excellent within-session reliability but substantial variability between sessions [Biurrun Manresa et al, 2011; Micalos et al, 2009]. The results of the Bland-Altman analysis carried out in Study II for the conventional method for NWR-T estimation involving sural nerve stimulation support these findings and show that the method has much better within-session reliability than between-session reliability (Figure 8). A corresponding difference in reliability was not observed for the method involving electrical stimulation at the arch of the foot, which is equally reliable for within- and between-session comparisons. The substantial between-session variability of the conventional method does question its use in study-designs involving more than one session and for interpersonal comparisons (e.g. case-control studies). In such cases NWR elicitation by stimulation under the sole of the foot ought to be strongly considered due to its superior between-session reliability.

3.3. PARTIAL CONCLUSION

Study II demonstrates that conventional NWR-T assessment involving sural nerve stimulation may suffer from a high failure-rate because the stimulation paradigm involves stimulation intensities reaching the pain tolerance threshold of some test subjects. By changing the stimulation site for NWR elicitation to the arch of the foot it is possible to obtain a substantially lower failure rate. Analysis of test-retest reliability indicated that the two methods for NWR-T estimation are equally reliable for within-session comparisons but that stimulation at the arch of the foot allows more reliable estimation of the NWR-T across individual sessions.

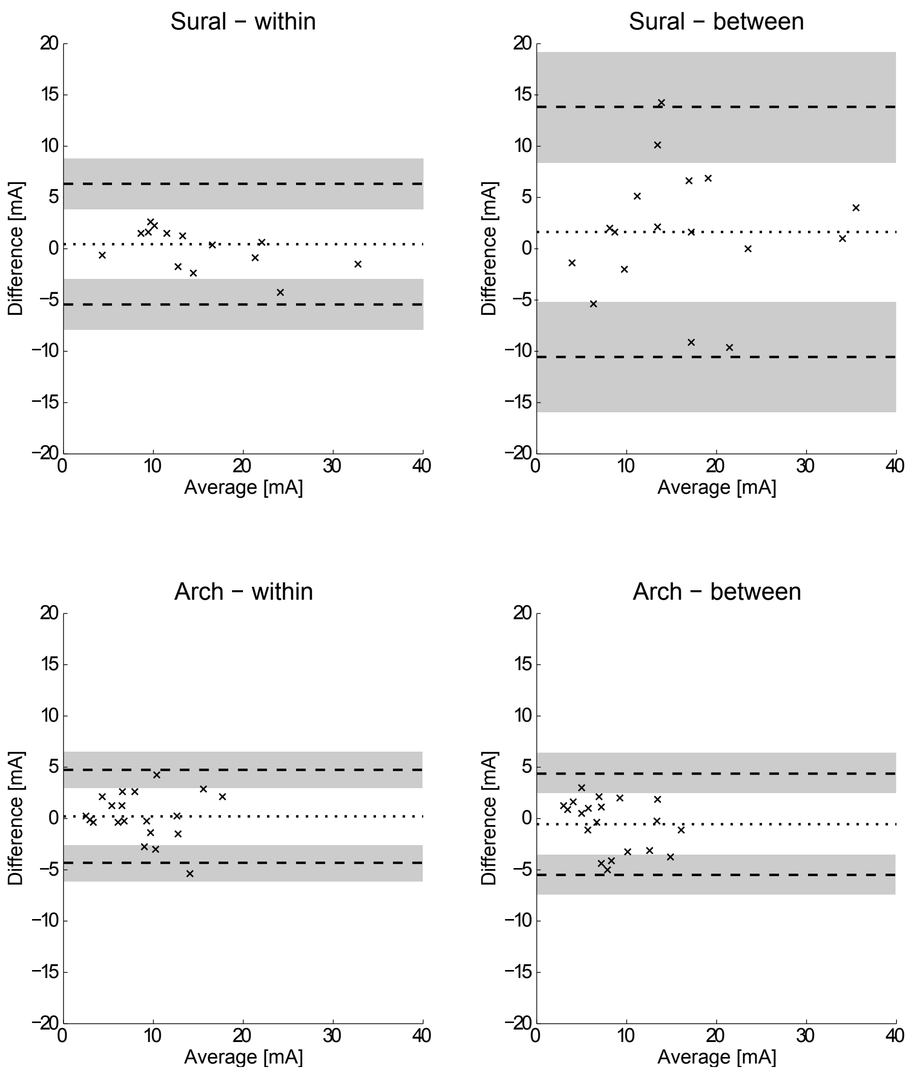

Figure 8: Bland-Altman plots for within- (left) and between-session comparison of reflex thresholds estimated by electrical stimulation over the sural nerve (top) and at the arch of the foot, respectively. The dotted lines represent the bias - the mean differences between the two measurements (measurement 2 – measurement 1), whereas the slashed lines and the grey areas indicate respectively the mean values and the 95 % confidence intervals for the limits of agreement.

CHAPTER 4. RRF ASSESSMENT WITH IMPROVED RELIABILITY

Prior to study III, two different procedures for assessment of RRFs had been published [Manresa et al, 2011; Neziri et al, 2009]. They share the same procedure for data acquisition and differ only in the way the observed NWRs are analyzed. First step in this *response methodology* (Figure 9 A) is to estimate the subjective pain threshold to electrical stimulation at a number of individual sites located under the sole of the foot. Then each site is stimulated several times with a suprathreshold intensity (the pain threshold multiplied by a fixed entity) in a randomized order while the NWR response is measured using EMG. The resulting EMG recordings may now be analyzed in two different ways. The average size (magnitude) of the NWRs elicited by stimulation of the individual sites may be interpolated and superimposed onto a graphical representation of a standardized foot. From this *sensitivity map*, the RRF can be quantified as the fraction of the interpolated image exceeding an individualized threshold. Alternatively, the probability of eliciting a NWR at the individual sites may be calculated based on the number of repetitive stimulations and another two-dimensional interpolation constitute a corresponding *probability map*. The RRF probability area can then be quantified as the fraction of the interpolated image with a NWR probability exceeding a fixed threshold. In study III a new additional variant of the RRF probability map was introduced by using CVA in the off-line NWR detection process.

4.1. SUBJECTIVE PAIN RATINGS MAY INTRODUCE ADDED VARIABILITY

A cornerstone of the NWR-T as a scientific or clinical measure is its objectivity. In contrast to any measure of somatosensory perception it does not rely on the test subject to carry out any subjective assessment. However, unlike NWR-T estimation, the response methodology currently used for RRF assessment is not completely objective. It is objective in the sense that the outcome measures (NWR size or probability of NWR occurrence) collected in response to a given painful stimulus do not directly rely on conscious decisions from the subject or the investigator. But since the intensities of the painful stimulations eliciting the NWRs are defined in relation to subjectively identified pain thresholds, the methodology does include an element of subjectivity. The results of Study III indicate that such dependency on subjective pain reports may cause an increased variability in the quantification of RRFs. In the study it was shown (Figure 10) that the between-session reliability (individual pain thresholds were estimated initially in both sessions allowing the intensities of the painful stimulations to be different on the two days) of the methodology was much poorer than the within-session reliability (two assessments based on the same set of painful stimulation intensities), suggesting that reliance on subjective pain ratings introduced added variability to the RRF quantifications.

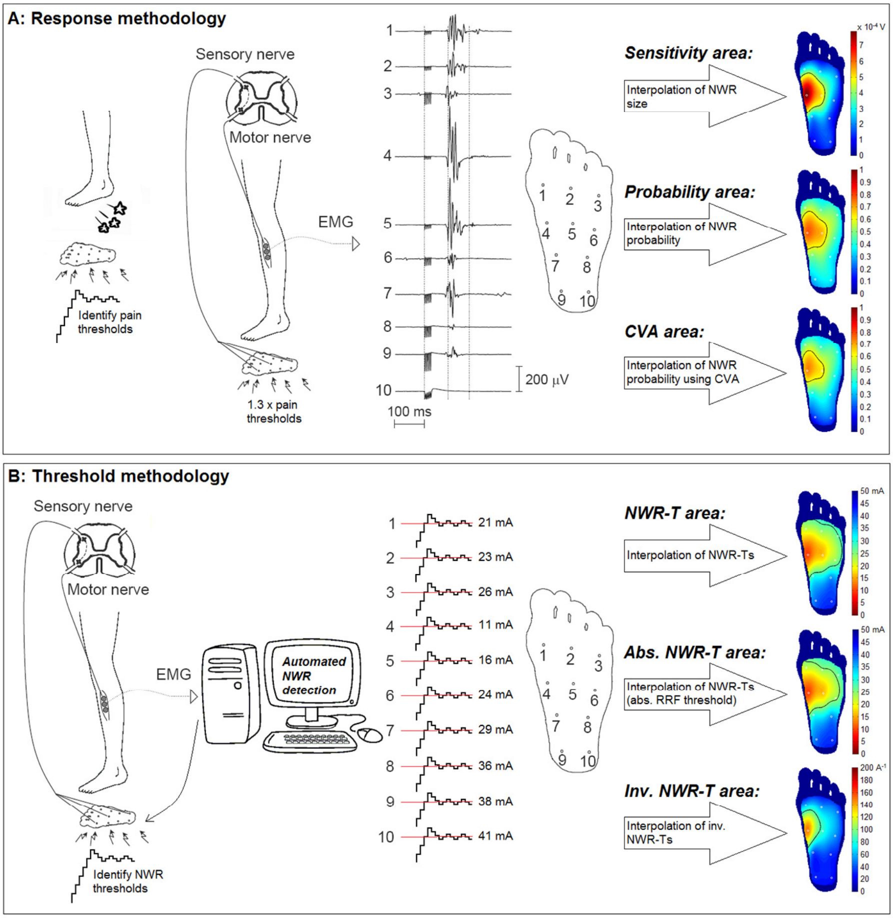

Figure 9: Existing (A) and novel (B) methodology for quantification of reflex receptive fields (RRFs). (A), Response methodology: Subjective pain thresholds to electrical stimulation are identified for each stimulation site after which the responses to suprathreshold stimulations are measured using EMG. The sizes or probabilities of occurring nociceptive withdrawal reflexes (NWRs) are interpolated to constitute a topographical mapping from which a RRF area can be quantified using three different methods. (B), Threshold methodology: NWR thresholds (NWR-T) are identified for each stimulation site using a fully automated staircase method. The NWR-Ts (or their inverse values) are interpolated to constitute a topographical mapping from which a RRF area may be quantified using three different methods.

4.2. NEW OBJECTIVE THRESHOLD METHODOLOGY DISPLAYS SUPERIOR RELIABILITY

To eliminate the need of subjective pain ratings, a novel methodology for RRF quantification was introduced in Study III. In contrast to the response methodology where it is attempted to provide an equal afferent input to the spinal cord across all stimulation sites and consider the NWR responses as an outcome measure, this new threshold methodology aims at a constant response (NWR-T) and consider the necessary input (stimulation intensity) the outcome measure. Using a similar experimental setup as for the existing response methodology, the NWR-T is estimated for a number of stimulation sites under the sole of the foot (Figure 9 B). The NWR-Ts are estimated by application of a staircase method and using CVA for NWR detection (interval peak z-score indicating a NWR which cannot be attributed to crosstalk based on CV and maximal cross-correlation). Individual staircases for each stimulation site are interleaved so the sites are stimulated in a randomized order. This novel methodology does directly lead to a topographical mapping of NWR-Ts. However, the best reliability was achieved by considering an interpolation of the inverse values of the identified NWR-Ts (a direct expression of the NWR sensitivity or ease with which a NWR may be elicited).

In contrast to the existing response methodology, this novel threshold methodology displays equally good within- and between-session reliability (Figure 11). Study III furthermore demonstrated that substantially better between-session reliability can be achieved by applying the threshold methodology compared to the response methodology. This means that a clinically relevant effect can be detected with fewer test subjects reducing the number of subjects required for future experimental or clinical studies. However, Study III constitutes the very first investigation of the threshold methodology for RRF quantification and no evaluation of the sensitivity of the methodology has yet been performed.

4.3. PARTIAL CONCLUSION

A novel methodology for completely objective assessment of RRFs was introduced in study III. It was shown that this new threshold methodology enables RRF quantification with improved reliability compared to the existing response methodology which suffers from comparatively poor between-session reliability, which could be due to a dependency on subjective pain ratings. Use of the threshold methodology hereby reduces the number of subjects necessary in future studies.

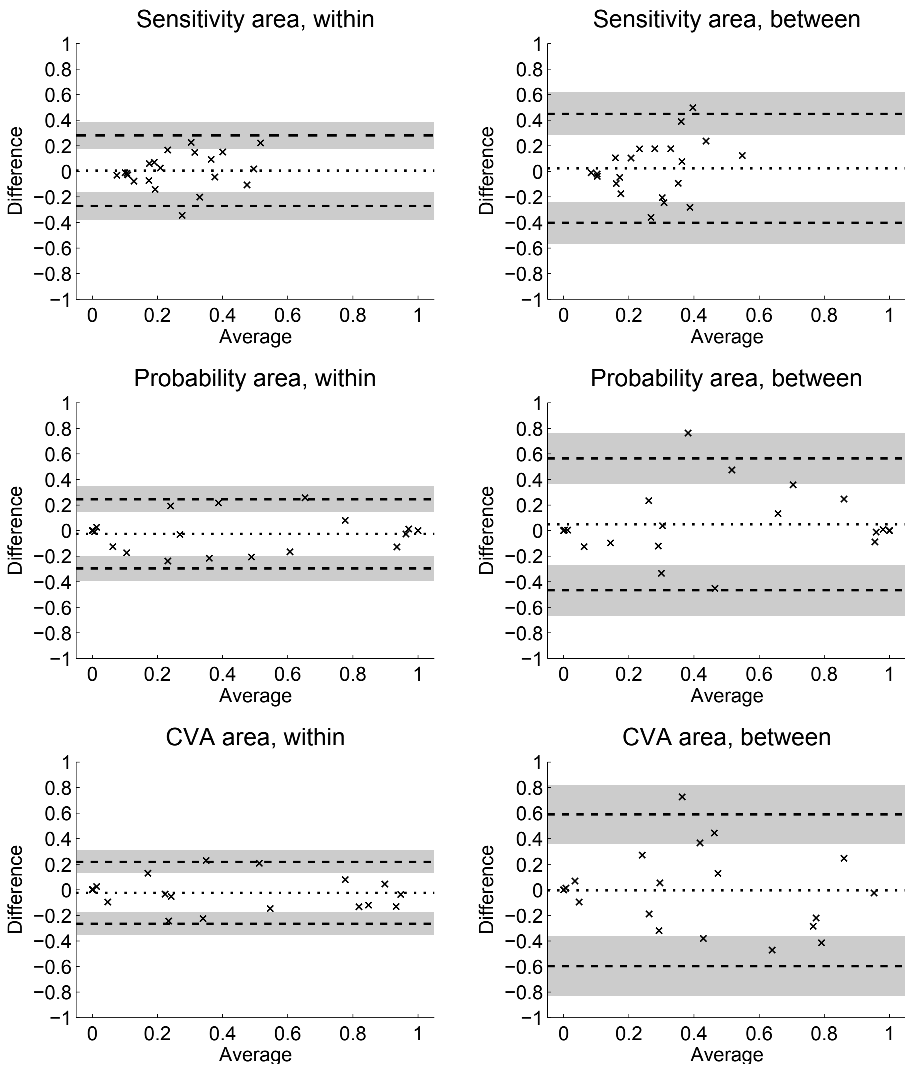

Figure 10: Bland–Altman plots for within- (left) and between-session comparisons for three different variations of the response methodology for quantification of the RRF area. Numbers on both axes represent the fraction of the sole of the foot. The dotted lines represent the bias - the mean differences between the two measurements (measurement 2 – measurement 1), whereas the slashed lines and the grey areas indicate respectively the mean values and the 95 % confidence intervals for the limits of agreement.

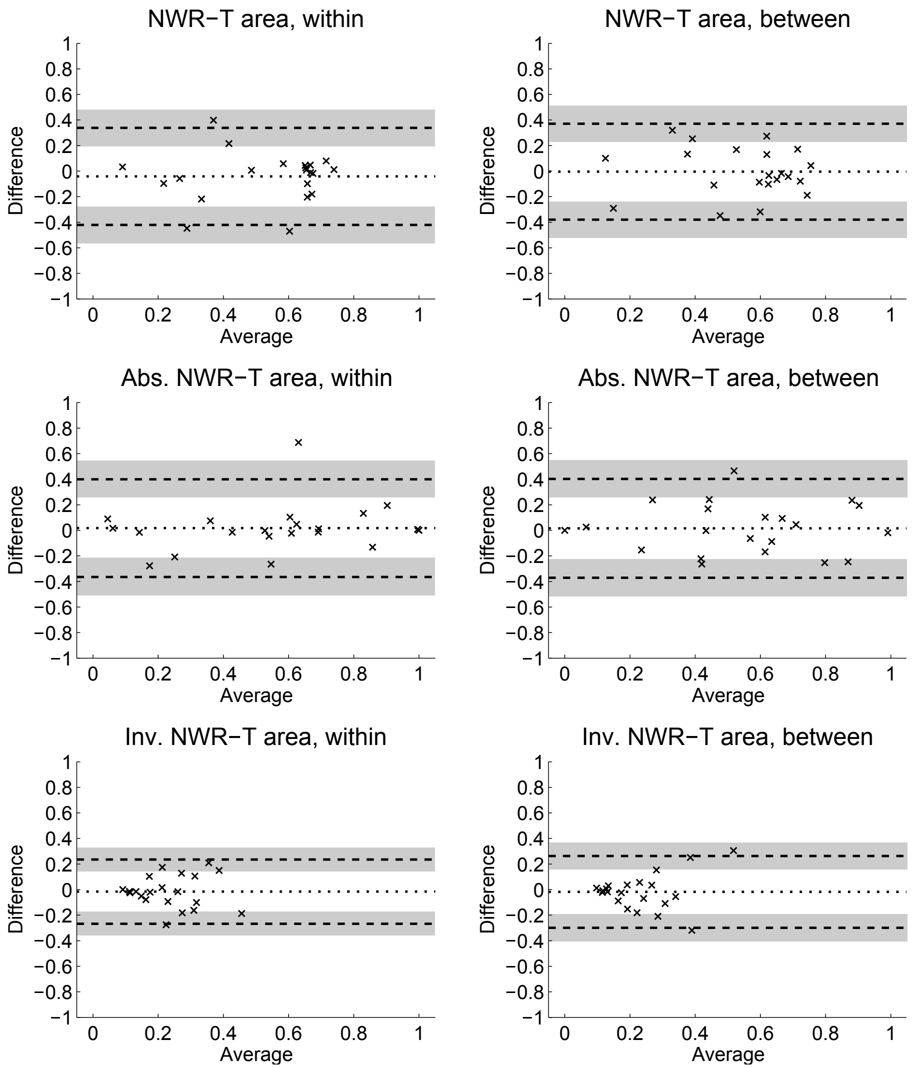

Figure 11: Bland–Altman plots for within- (left) and between-session comparisons for three different variations of the threshold methodology for quantification of the RRF area. Numbers on both axes represent the fraction of the sole of the foot. The dotted lines represent the bias - the mean differences between the two measurements (measurement 2 – measurement 1), whereas the slashed lines and the grey areas indicate respectively the mean values and the 95 % confidence intervals for the limits of agreement.

CHAPTER 5. SYNTHESIS

Measurements of both NWR-Ts and RRFs reported in the literature are generally subjects to large interpersonal variability. This was also the case for the measurements performed during the present work, although to a lesser extend when the new methods were applied. Throughout the work presented in this thesis, specific weak points or imperfections of existing methods have been addressed to enable valid and reliable assessment of NWRs and RRFs. Study I introduced CVA, a novel method for identification of EMG crosstalk developed to improve the validity of NWR detection. CVA was validated and used consequently in the following studies to ensure optimal NWR detection. To enable completely objective evaluation in the last two studies, a fully automated procedure for NWR detection was developed. Hereby the investigator exercises no influence on the outcome measure and the assessment may be performed by non-experts. This procedure utilizing CVA was developed with knowledge from Study I and applied extensively in Study II and III and is now routinely used in our laboratory.

Study II and III introduced initiatives which allow more reliable assessment of NWR-Ts and RRFs, respectively. Still, a rather large variance in the outcome measures was observed. Based on previous and present results involving different assessment methods, the NWR is extensively subject to personal differences. Consequently the large interpersonal variances observed cannot merely be considered the result of measurement errors. It may be difficult, but it is of vital importance to distinguish between the two. One way to do so is to perform the same assessment at various time points on the same test subject. Assuming that the true value of the investigated phenomenon remains unchanged, a test-retest paradigm allows a controlled quantification of the measurement error. Test-retest reliability of NWR-T estimation and RRF quantification was key aspects of Study II and III, respectively. The investigations were conducted for both existing and new methods, but it is still not trivial to interpret to which extend the interpersonal variance observed in an outcome measure is caused by measurement error and how much variance expresses naturally occurring personal differences in NWR sensitivity. The LOA delimits the range within which 95% of the differences between two repeated measurements performed on the same subject may be expected to lie. Crudely said, the upper and lower LOA quantifies the measurement error in the expected (95% confidence interval) worst case scenario. The actual measurement error on a specific sample may (very often) be far less, making it impossible to calculate the effect of an estimated measurement error on the actual measurements. Instead the LOA and other measures of reliability may purely be consulted to make an overall judgment of the expected occurring measurement errors. It is therefore also very difficult to determine if any of the investigated methods are sufficient reliable.

When can a method be considered reliable? One definition may be that the amount of measurement error of a reliable measurement tool does not exceed what has been deemed acceptable for the effective practical use of the method [Atkinson and Nevill, 1998]. Hence, the question cannot be answered unequivocally. The sensitivity of the method, the smallest clinical relevant effect of the outcome measure, and on a higher level of abstraction most importantly, the intended use of the method are of crucial importance. Existing methods for NWR-T estimation [Banic et al, 2004; Courtney et al, 2009; Desmeules et al, 2003; Lim et al, 2011; Sterling et al, 2008] and RRF quantification [Biurrun Manresa et al, 2013a; Neziri et al, 2010a] has been shown sufficiently reliable to detect central hyperexcitability in several groups of pain patients. However large interpersonal variability within the respective groups renders efficient discrimination on an individual level impossible using the existing methods [Biurrun Manresa et al, 2013b; Nguyen et al, 2011]. As previous stated interpersonal variance is caused by naturally occurring variance, which makes the measurements from the two populations overlap, but may be exacerbated by measurement errors. The results of study II and III suggest that limited reliability may be a contributing factor to why the existing methods are not suitable as decisive measures of central hyperexcitability for individual subjects. The same conclusion may turn out to apply for the novel methods too, but this depends on the sensitivity of the methods and the smallest clinical relevant effect of the outcome measures, both of which need extensive investigation. However, from the present results it can be concluded that the introduced methods are more reliable than their existing alternatives yielding more stable measures over time and hereby reducing the number of subjects needed in future experiments.

5.1. CONCLUSIONS

Based on the present work following conclusions can be made: Existing methods for NWR detection based on SD sEMG are extremely sensitive to EMG crosstalk. By using DD sEMG or the presented CVA method, more accurate NWR detection with significantly improved specificity can be achieved. The conventional method for NWR-T estimation may be associated with a high failure-rate and substantial between-session variability. Both of these issues may be substantially reduced by changing the NWR stimulation site from the skin over the sural nerve at the lateral malleolus to the arch of the foot. Whereas the existing response methodology for quantification of RRFs displays good within-session reliability, use of the presented threshold methodology yield superior between-session reliability. The improved stability over time makes the threshold methodology more suitable for cross-session and interpersonal investigations. It is not possible to judge if the assessment methods are sufficiently reliable before further investigation of the sensitivity of the methods to changes in central nociceptive excitability and identification of the smallest clinical relevant effect of the outcome measures has been carried out. However, the initiatives introduced in this thesis can all be implemented to enable more reliable assessment of NWRs and RRFs.

5.2. FUTURE PERSPECTIVES

The work described in this thesis is very focused on the introduction of new methods. More research is needed to evaluate and obtain the full value of the introduced initiatives. To promote the use of CVA its effectiveness on a broader array of muscles must be evaluated. And thorough investigation is needed to determine if specific thresholds for the two necessary CVA features must be identified for each muscle or more generic thresholds based on muscle type or fiber length may suffice for practical usefulness. Another future field of investigation regards the sensitivity of both NWR-Ts estimated stimulating the sole of the foot and the threshold methodology for RRF quantification. This work has begun. Ongoing clinical experiments apply these two methods on both chronic pain patients and healthy control subjects to test how sensitive the methods are to differences in nociceptive excitability levels. These trials are carried out by our own research group in collaboration with our external partners, as no equipment designed for neither CVA nor quantification of RRFs is commercial available. However, the methods introduced in the thesis may likely constitute a small step on the journey toward more efficient personalized pain management and evaluation of new treatment paradigms, where not only the experienced pain sensation are considered, but an objective and reliable measure of spinal nociception may be consulted.

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SUMMARY

The nociceptive withdrawal reflex (NWR) is considered a reliable and objective tool in pain assessment. It is often assessed by estimation of a single NWR threshold (NWR-T) but spatial assessment is possible by quantification of the reflex receptive field (RRF). Both methods are sufficiently sensitive to detect abnormal spinal nociception in groups of pain patients but large interpersonal variance limits their clinical use. Variability comprises personal differences but may be exacerbated by the use of non-optimal assessment methodologies.

In this Ph.D. project specific imperfections of existing methods were addressed to enable more valid and reliable assessment of NWRs and RRFs.

NWR detection from standard electromyography (EMG) is extremely sensitive to EMG crosstalk and a method to handle this type of noise, based on analysis of muscle fiber conduction velocity was developed. Conventional NWR-T estimation was found associated with a high failure rate but a change of stimulation site yielded a reduced failure rate and superior reliability. Finally, a completely objective methodology was developed to enable more reliable RRF quantification.

This work suggests that limited reliability of existing methods may contribute to the large variability observed and that the introduced initiatives can be applied to enable more reliable assessment of NWRs and RRFs.

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