

**Bilateral sensory changes and high burden of disease in patients with chronic pain  
and unilateral nondermatomal somatosensory deficits: A quantitative sensory testing  
and clinical study**

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### **Abstract**

**Objectives:** Widespread sensory deficits resembling hemihypoesthesia occur in 20-40% of chronic pain patients on the side of pain, independent of pain aetiology, and have been termed nondermatomal sensory deficits (NDS). Sensory profiles have rarely been investigated in NDS.

**Methods:** Quantitative sensory testing (QST) according to the protocol of the German Research Network on Neuropathic Pain (DFNS) was performed in the face, hand and foot of the painful body side and in contralateral regions in chronic pain patients. Twenty-five patients with NDS and 23 without NDS (termed pain-only group) were included after exclusion of neuropathic pain. Comprehensive clinical and psychiatric evaluations were done.

**Results:** NDS in chronic pain was associated with high burden of disease and more widespread pain. Only in the NDS group significantly higher thresholds for mechanical and painful stimuli were found in at least 2 of 3 regions ipsilateral to pain. In addition, we found a bilateral loss of function for temperature and vibration detection, and a gain of function for pressure pain in certain regions in patients with NDS. Sensory loss and gain of function for pressure pain correlated with pain intensity in several regions.

**Discussion:** This may indicate a distinct sensory profile in chronic non-neuropathic pain and NDS, probably attributable to altered central pain processing and sensitisation. The presence of NDS in chronic non-neuropathic pain may be regarded as a marker for higher burden of pain disease.

**Key words:** chronic pain; hemisensory loss; quantitative sensory testing; nondermatomal somatosensory deficits; sensitization

## **Introduction**

Diagnostic workup of patients with chronic pain is important for pain classification and appropriate treatment. In patients with chronic pain and sensory abnormalities, neuropathic pain may be suspected and diagnostic work up according current diagnostic criteria is recommended [1]. Some of those patients will not meet the diagnostic criteria for neuropathic pain, the cause of sensory disturbances remaining unclear. It is known that 25 to 50% of the patients with chronic pain show widespread sensory deficits often resembling hemihypoesthesia on the side of pain or worse pain [2, 3]. This phenomenon is termed nondermatomal somatosensory deficits (NDS) [2, 3]. NDS have been reported in various chronic non-neuropathic pain conditions including myofascial pain [2] and in complex regional pain syndrome (CRPS) [4]. The first description of this phenomenon dates back to the nineteen twenties [5]. It was considered to be “hysterical” or a sensory conversion disorder. Currently, NDS are recognized as a neuro-psycho-biological condition [3, 6] but cannot be fully explained by a psychiatric disorder [6, 7]. While no lesion of the central or peripheral nervous system has been identified, some functional abnormalities have been described in the literature. Functional MRI studies showed altered patterns of activation in response to sensory stimuli in somatosensory cortex and thalamus [8]. Recent neuroimaging studies identified also metabolic and structural changes in sensorimotor and temporal regions in patients with NDS [7, 9]. The occurrence of NDS in the absence of neurological cause has been suggested but not investigated systematically.

Quantitative sensory testing (QST) has been developed to provide sensory profiles in reference regions [10-12] and is widely used in research on chronic pain [13]. Sensory changes in painful regions and even beyond have been demonstrated in experimental pain, as in models of referred pain [14], heat-induced pain [15], or capsaicin induced pain [16], with a positive association between pain and sensory abnormalities, i.e. increased pain was associated with an increase in sensory changes [17]. In various chronic pain conditions sensory changes were demonstrated by QST, including the area of referred pain [18], bilateral regions in osteoarthritis [19], widespread regions in fibromyalgia [20, 21], areas within the affected segment in chronic back pain [21], outside of the pain area in chronic low back pain [22], myofascial temporomandibular joint

disorder [23, 24] and chronic back pain [25-27]. However, hemihypoesthesia in chronic pain verified using QST has been reported only in complex regional pain syndrome [4]. A comprehensive systematical neurological work up in patients with NDS and chronic pain including neurophysiology studies and sensory profiling with QST is lacking.

Therefore objectives of the study were (1) to describe prospectively clinical, neurophysiological and pain related aspects in patients with chronic non-neuropathic pain with and without NDS; (2) to investigate whether the clinical findings of NDS can be confirmed by QST; and (3) to compare QST profiles of chronic non-neuropathic pain patients with and without NDS. Potential pathophysiological mechanisms will be discussed.

## **Materials and Methods**

### **Patient recruitment**

The study cohort was the same as in a previous study [7] and will be described in brief. Local ethics committee approvals were obtained. Patients were recruited from the Centre for Pain Medicine, Nottwil, the Headache & Pain Unit, University Hospital Zurich and the Psychosomatic Division, University Hospital Berne. All patients were evaluated in a multidisciplinary setting involving psychiatrists, psychologists, neurologists, rheumatologists and orthopaedists. Eligible patients were included after informed consent. Inclusion criteria were the following: Age between 20 and 65 years, sufficient understanding of German language, pain duration for more than six months, normal neurological examination except for the presence of a reproducible unilateral sensory deficit in the NDS group (including upper and lower extremities and trunk with possible involvement of the face), normal sensation in the pain-only group, normal neurophysiology results (nerve conduction studies and somatosensory evoked potentials of tibial nerves) and normal MRI of the brain. Exclusion criteria were the following: Any neurological disease other than pain, inflammatory rheumatologic disorder, severe psychiatric disorders requiring psychiatric hospitalisation or associated with suicidality at any time. The inclusion procedure and all study related investigations were performed at the Centre for Pain Medicine Nottwil. For a rough estimate of the prevalence of NDS in one study center (Nottwil) a database research was performed retrospectively, searching for patients with chronic pain and sensory deficits.

### **Pain evaluation and psychological comorbidity**

A standardized pain history was obtained using the validated pain questionnaire of the German Society for the Study of Pain [28], including pain drawings. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS [29]). Health-related quality of life was determined by the SF-12

questionnaire [30]. Chronic pain severity was assessed using the Graded Chronic Pain Scale (GCPS) [31]. The grade of pain chronification was defined by the Mainz Pain Staging System (MPSS) [32]. This is a questionnaire consisting of 11 items (on pain characteristics, types of medication used, previous consultations of physicians, pain related interventions and hospital admissions, and participation in rehabilitation programmes) to assign the pain into one of three possible stages of disease chronification, which has been validated in several studies [33, 34]. From the pain drawings the number of affected body areas by pain (n out of 53) were counted according the areas (right, midline and left body) described elsewhere [35].

#### Clinical examination

In all patients a comprehensive neurological examination was performed focussing on the sensory system (aesthesia, thermaesthesia and algnesia), by two experienced neurologists (G.L. and F.R.) independently at different time points.

Aesthesia was assessed with a standardized brush with a force of about 200-400mN (Brush 05, Senselab<sup>R</sup>, Sweden), thermaesthesia with a cold roller (stainless steel, width 35mm, diameter 25mm, resting between investigations on a 100x40x5mm stainless steel plate to keep the temperature constant at room air about 22°C) and algnesia to pinprick with a validated 40g weighted pinprick (Neuropen<sup>R</sup>, Owen Mumford, UK). The investigation of vibration sense was performed within the QST protocol (see below). We defined 80 body areas throughout the whole body, ventrally and dorsally, where all 3 qualities were tested. The report of diminished sensation after side to side comparison by the patient was drawn in body figures for each quality in separate drawings.

#### Neurophysiological examination and imaging

All patients underwent a neurophysiological examination in a quiet air conditioned room with constant room temperature of 22.0-23.0°C. Nerve conduction studies (NCS) were performed for median and tibial nerves on the ipsilateral side (see below) and for sural nerves on both sides. Motor NCS (median and tibial nerves) included motor nerve conduction velocity, motor amplitudes and F-wave studies. Sensory NCS (median and sural nerves) included sensory nerve conduction velocity and sensory amplitudes. In addition, somatosensory evoked potentials (SEP) of tibial nerves on both sides were obtained including latency P40 and amplitude P40/N45. A neurophysiology machine type VikingSelect, software VikingSelect Master Software version 11 by Nicolet, Biomedical, USA, was used. Patients with any abnormalities indicating impaired peripheral or central neuronal conduction were excluded from the study. Procedures and normal values were used as described in the literature for NCS [36] and SEP [37].

#### Thermography

Infrared thermography was performed under room conditions described as above, after the patient had adapted to room conditions for 15min resting in a supine position. An infrared thermo camera ThermoCam™ E4 (Flir Systems, USA), was used. Thermographs were taken perpendicular to the body surface with a camera-body-distance of 100cm for the face and 50cm for the hands and feet. Thermographs were analysed using the software ThermoCam Researcher 2.7 professional, Flir Systems, USA, setting reference points in defined areas. In the face single reference points were set in a vertical line bilaterally within the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> trigeminal nerve division. At the hand reference points were set at the dorsum of the hand and dorsum of the distal phalanx of the 1<sup>st</sup>, 3<sup>rd</sup> and 5<sup>th</sup> finger (representing the dermatomes C6, C7 and C8) as well as on the dorsum of the feet and dorsum of distal phalanx of 1<sup>st</sup> and 5<sup>th</sup> toe (representing the dermatomes L5 and S1). Temperature was recorded in Celsius degrees (°C). According to the literature [38] a side to side difference of at least 1°C was considered abnormal.

#### Quantitative sensory testing

QST was performed according the standardized protocol developed by the German Research Network on Neuropathic Pain (DFNS) [10]. Room conditions were as described above. All tests were performed by the same medical technician (L.S.) who underwent a training program certified by DFNS. The tests were performed bilaterally in the face (cheek), dorsum of hand and dorsum of foot. For thermal parameters, a standardized diagnostic device (TSA-II, Medoc, Israel, temperature range: 0–50 °C, baseline temperature 32 °C) with a 9.0 cm<sup>2</sup> contact surface of the thermode and related computer software (version 5.35) was used. Thermal tests were performed, including cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT) and heat pain threshold (HPT). The mechanical testing included the mechanical detection threshold (MDT), using a standardized set of modified von Frey hairs (Opti-hair2-Set, Marstock Nervtest, Germany) and the mechanical pain threshold (MPT) using calibrated pinpricks (MRC Systems, Heidelberg, Germany). The vibration detection threshold (VDT) was examined using a Rydel-Seiffer tuning fork (64 Hz) which was applied over prominent bones, which is for the face the Zygomatic process, for hand the Ulnar styloid process and for foot the medial malleolus. The pressure pain threshold (PPT) is measured over muscles. For the face pressure algometer (FDN100, Wagner Instruments, Greenwich, USA) was applied over the masseter muscle. For hand and foot pressure algometer (FDN200, Wagner Instruments, Greenwich, USA) was applied over thenar eminence and abductor hallucis muscle respectively.



## Statistics

Clinical data were analysed with IBM SPSS Statistics (version 20, Armonk, NY: IBM Corp.). Independent samples t-tests were used to compare normally distributed data, Mann-Whitney U-tests for non-normally distributed continuous and ordinal data. Chi-square or Fisher's exact tests were used to compare categorical data between groups. In accordance with the DFNS protocol [10], all QST values except CPT, HPT, and VDT were log transformed to achieve normal distribution. QST-parameters were z-transformed before analysis, based on age and gender specific reference data for each test site from the literature, according to the formula:  $Z\text{-score} = (X_{\text{single patient}} - \text{Mean}_{\text{controls}}) / SD_{\text{controls}}$  [10]. In the NDSD group "ipsilateral" was the side of pain or worse pain, which was in accordance with the side of sensory deficits of the clinical examination, except one patient where sensory deficits were found at the opposite site to the worse pain site. In this patient the side of sensory deficit was chosen as ipsilateral. In the pain-only group "ipsilateral" was assigned to the side of pain, worse pain or based on randomisation if there was no pronounced pain side. A repeated measures ANOVA with the between subjects factor "group" (NDSD group and pain-only group) and the within subject factor "side" (ipsilateral–contralateral) was performed. As post-hoc tests, independent samples t-tests were performed to compare parameters between the NDSD and pain-only groups on ipsi- and contralateral sides, respectively, considering all  $p \leq 0.003$  as statistically significant (after Bonferroni correction). In addition, side to side comparisons were performed using paired t-tests in each patient group. The Bonferroni-Holm procedure was used to correct for multiple comparisons, analyzing 8 QST-parameters [39].

Finally, possible relations between ipsilateral sensory loss and pain intensity as well as anxiety were investigated using Spearman's correlations. These analyses included patients with NDSD and "pain-only". The Bonferroni-Holm procedure was used to correct for multiple comparisons, as described above.

## Results

Patient selection, socio-demographic data, pain related data and psychological comorbidity

For details of the selection procedure we refer to *figure Supplemental Digital Content 1*, <http://links.lww.com/CJP/A383> Seventy five patients were contacted for the NDSD group and 77 patients for group "pain-only" based on electronic chart records. Finally, 25 patients could be included in the NDSD group and 23 patients in the pain-only group. The Nottwil databank request revealed 107 patients with hemisensory deficits among 2995 unselected consecutive patients (including neuropathic pain, chronic non-neuropathic pain or chronic non-neuropathic pain with neurological comorbidity) during a 4 year time period (2007 to 2010) which equals a prevalence of 3,6%.

Socio-demographic data and pain related data and psychological variables are shown in **Table 1**. A full description of the psychological evaluation has been published elsewhere [7]. Age and gender were not significantly different between groups. The NDS group showed significantly more frequently migration background, predominantly from south-eastern Europe, higher pain chronicity, had higher grades of pain severity, lower physical health related quality of life and higher anxiety scores. The main pain diagnoses based on comprehensive multidisciplinary assessment were the following (NDS/pain-only): Headache (6/0), neck and upper extremity pain of different etiologies (non-specific 6/6, myofascial 3/0, facetogenic 0/4), back and lower extremity pain of different etiologies (non-specific 4/4, myofascial 2/3, facetogenic 0/5), non-specific abdominal pain (1/0), fibromyalgia (1/1) and non-specific hemibody pain (2/0). In addition to the main pain diagnosis most patients had multiple additional pain locations. More detailed main pain diagnoses, distributions of all pain areas and NDS localizations are shown in *table Supplemental Digital Content 2*, <http://links.lww.com/CJP/A384> for the NDS group. For the pain only group detailed data related to pain diagnoses and pain location are shown in *table Supplemental Digital Content 3*, <http://links.lww.com/CJP/A385> In the NDS group significantly more body areas were affected by pain in comparison to the pain-only group (37,3%±15,4 vs. 24%±18,5%, p=0,010).

An exception of this observation is one patient with headache only (N37 with trigemino-autonomic headache) who had pronounced hemisensory deficits for all qualities.

#### Clinical findings of somatosensory disturbances

The neurological examination was unremarkable except for hemibody sensory changes in the NDS group which were found on the right side in 15 patients and on the left side in 10 patients. In the NDS group 2 patients had a full hemibody sensory deficit for all modalities at the side of worse pain (patient N11 and N27), 22 had incomplete hemisensory deficits for all qualities at the side of worse pain, whereas one patient had an incomplete diminished hemibody sensation for all qualities at the less affected pain side (patient N35). Eleven patients had diminished sensation in a hemibody distribution only on side of pain or worse pain, whereas 11 patients had additional few areas of diminished sensation on the contralateral side. The percentage of affected areas with hypoaesthesia correlated positively with the percentage of regions with thermypoaesthesia (Spearman's rho=0.76; p<0.001) and pinprick hypoalgesia (Spearman's rho=0.76; p<0.001). In 8 patients of the NDS group the amount of body areas affected by NDS was clearly more extensive than the amount of body areas affected by pain (patient N03, N13, N21, N24, N27, N30, N35, N37), see *table Supplemental Digital Content 2*, <http://links.lww.com/CJP/A384>



## Neurophysiology and thermography

Neurophysiology and thermography studies in both groups were within normal limits and without significant side to side differences.

*Figure 1 to be placed here*

## Quantitative sensory testing

### *Group and side differences*

Increases in sensory threshold are related to loss of sensory function, and are shown with negative z-scores in

**Fig.1.** CDT was significantly higher in the NDS group compared to the pain-only group in all 3 regions investigated (Table 2). The significant interaction “group” x “side” for the region face is consistent with higher ipsilateral (as compared to contralateral) CDT only in the NDS group. This was confirmed by direct side to side comparisons. Post-hoc tests showed that patients in the NDS group had increased CDT compared to those in the pain-only group on ipsi- and contralateral sides in the region face, i.e. patients with NDS had bilateral sensory loss in the face (**Fig. 1**). WDT was significantly higher in the NDS group compared to the pain-only group in the region face but not in the regions hand and foot (confirmed by side to side comparisons). Post-hoc tests revealed bilaterally increased WDT in the NDS group compared to the pain-only group in the face. Side to side comparisons revealed increased ipsilateral compared to contralateral WDT in the face only in NDS patients. For CPT and HPT a significant interaction “group” x “side” in the region foot was found indicating a significant increase ipsilateral compared to contralateral CPT and HPT only in the NDS group (confirmed by side to side comparisons). MDT was significantly higher in the NDS group compared to pain-only group in all 3 regions investigated. The significant interaction “group” x “side” for all 3 regions is consistent with higher ipsilateral (as compared to contralateral) MDT in all regions only in the NDS group (confirmed by side to side comparisons). MPT was significantly increased in the NDS group in hand and foot, only on ipsilateral sides according to post-hoc tests. Side to side comparisons detected increased MPT on the ipsilateral compared to contralateral side in the face and feet only in the NDS group. VDT was significantly increased in the NDS group in all 3 regions investigated. Post-hoc tests revealed bilateral VDT increases in the NDS group compared to the pain-only group for all 3 regions investigated. PPT was significantly decreased in the regions hand and foot in the NDS group. Post-hoc tests showed decreased PPT in the NDS group compared to the pain-only group in the region foot on the contralateral side, while direct side to side differences showed no significant differences.

*Summary of side to side differences*

Sensory profiles using z-transformation of both groups are summarized in **Fig. 1**. Sensory thresholds in original values before z-transformation are given in *table Supplemental Digital Content 4*, <http://links.lww.com/CJP/A386> for the NDS group and in *table Supplemental Digital Content 5*, <http://links.lww.com/CJP/A387> for the pain-only group. Patients in the NDS group showed a significant increase for several thresholds on the side ipsilateral to pain: MDT was significantly increased in all 3 regions (face,  $p=0.003$ ; hand  $p=0.001$ ; foot;  $p=0.001$ ). MPT was significantly increased in 2 regions (face,  $p=0.005$ ; foot,  $p=0.035$ ). Increases in one region were found for HPT ( $p=0.002$ ) and CPT ( $p=0.002$ ) in foot, CDT ( $p=0.007$ ) and WDT ( $p=0.009$ ) in the face. Side differences were more pronounced in the regions face and foot as compared to hands. Patients in the pain-only group did not show significant side to side differences for any parameters investigated.

#### *Correlation of sensory thresholds on ipsilateral sides with pain intensity and anxiety*

Pain intensity was associated with loss of sensory function (negative z-scores) as opposed to a gain of function for pressure pain (positive z-scores), as summarized in **Fig. 2**. Pain intensity correlated negatively with z-scores for VDT (face, hand), CDT (face), MDT (hand) and positively with z-scores for PPT (face, hand). Anxiety was associated with losses of sensory function. Anxiety (HADS-A score) correlated negatively with z-scores for CDT (face), WDT (face) and VDT (face, hand, foot) (**Fig. 3**).

*Figures 2 and figure 3 to be placed here.*

## **Discussion**

The main findings of present study were the following:

- (1) The phenomenon of NDS in chronic pain is associated with high burden of disease and more widespread pain.
- (2) Changes in sensory function in patients with NDS can be objectified by quantitative sensory testing: In the NDS group significantly higher thresholds for mechanical and painful stimuli were found ipsilaterally to pain. Sensory loss correlated with pain intensity in several regions. Importantly, all patients had normal neurophysiology studies.
- (3) In addition to lateralised sensory loss, we found general alterations in sensory function in patients with NDS: These include a bilateral loss of function for temperature and vibration detection, as well as a gain of function for pressure pain in certain regions. The latter correlated positively with pain intensity.

Demography, pain characteristics and comorbidity

The NDS cohort was comparable to previous studies, concerning demographic data [2, 6, 9]. Our findings of more frequent migration background, higher pain chronicity, higher grades of pain severity, lower physical health related quality of life, and as previously published, higher pain intensity, higher anxiety scores and prevalence of absenteeism from work [7] in the NDS group in comparison to the pain-only group indicate a higher burden of pain disease. Consistent with these findings, higher pain intensities and disease related impairment in patients with NDS have been reported in various studies [2, 3, 6, 40]. In our NDS group, a relatively large proportion had migrated from south east Europe. It could be speculated that they might have experienced particularly stressful life events in war-torn countries, as NDS has been related to traumatic life events previously [6]. In our patients with NDS, traumatic life event or a diagnosis of PTSD seemed slightly overrepresented, but this was not significant [7]. The estimated NDS prevalence of 3.6% at one study centre (Nottwil) was very low compared to previous studies that found a prevalence between 17 and 38% [2, 41, 42] in certain chronic pain cohorts. This may be related to sample characteristics such as a wide variety of different chronic pain diagnoses treated at the Nottwil centre. Since the inclusion criterion to the study was a hemisensory deficit, a wide variety of chronic non-neuropathic pain syndromes was included. Accordingly, NDS have been reported in several chronic non-neuropathic pain conditions [2-4, 41-43] but extension of painful regions has not been described. Therefore our finding of more extensive pain sites in the NDS group suggests that NDS are observed particularly in widespread pain syndromes. As an exception of this observation we found NDS in one patient who had one-sided headache as the only pain location.

#### Neurophysiology, thermography and neuroimaging

The present cohort was investigated with prospective neurophysiology studies and brain imaging [7] to rule out gross functional abnormalities and structural pathology. Normal neurophysiology and imaging of the nervous system have been reported in chronic pain patients with NDS based on chart reviews, but have not been systematically studied in previous studies [2, 6, 9]. In contrast, in CRPS with NDS, several abnormalities in NCS, SEP and sympathetic skin response were found, suggesting different underlying or concomitant pathology in the case of CRPS [4]. In the literature NDS have occasionally been described in radiculopathy with SEP and MRI abnormalities [44]. Our study demonstrates that NDS can be observed in patients with chronic non-neuropathic pain syndromes in absence of neurophysiological abnormalities. Normal infrared thermography in our groups suggests lack of involvement of the vasomotor system. In contrast, the appearance of NDS in context of an injury of the sympathetic nervous system, has been suggested in the past [45].

### Clinical somatosensory findings and QST

In our cohort, diminished sensation in a hemibody distribution on the side of pain or worse pain was present in nearly all patients with NDS, although one patient with frequent migraine had NDS at the less pronounced pain side. In addition, about half of the patients with NDS had additional spots of diminished sensation opposite to the pain side. In rare cases, NDS has been described occur on the side opposite to pain [3].

In the clinical examination, we found abnormalities for aesthesia, algisia and thermaesthesia to be associated with each other, suggesting that these abnormalities are frequently observed together and should be examined in daily practice. This observation was reflected in QST were loss of function was found for MDT in 3, for MPT in 2, and for CDT, WDT, CPT, HPT in one test region ipsilateral to pain. Thus, significant side to side differences were not found for all parameters in every region. This may be explained by the following reasons: (1) incomplete expression of NDS in some patients and (2) wide variations in the extent of pain distribution at the most affected side and at the opposite side (3) some patients showed minor negative signs at the opposite side in the clinical examination, and bilateral sensory changes in QST as outlined below. (4) The extensive QST protocol could only be performed in reference regions.

Widespread sensory abnormalities in NDS involve small fibre and thick myelinated fibre function in the periphery, as well as spinothalamic and dorsal column pathways centrally at spinal cord level. This suggests the involvement of supraspinal rather than spinal mechanisms within the CNS which is consistent with neuroimaging studies discussed below. As sensory aspects of pain and sensory perception are mediated by the lateral pain system including thalamus, insular cortex and somatosensory cortex [46], chronic pain input from the same body side may interfere with sensory processing and modulate respectively suppress sensory perception. Previously, it has been hypothesized previously that NDSs may result from an attempt of the brain to shut down all input from painful regions which is however insufficient for adequate pain control but causes sensory loss for various sensory abnormalities [8]. Consistent with this idea, sensory loss correlated with pain intensity in several regions in the present study. Reduced perception for sensory or painful stimuli was associated with deactivation or lack of activation in contralateral primary and secondary somatosensory cortex, and a lack of activation in the contralateral thalamus [8, 47] in fMRI studies.

Functional and structural neuroimaging studies [7-9] showed also bilateral alterations in NDS, which could relate to the bilateral sensory abnormalities for vibration and temperature sensation, found in the present study. A PET study in NDS patients showed significant hypometabolic pattern of changes in cortical and

subcortical areas bilateral [9] involving limbic regions. Dysfunctional sensory processing in patients with NDS is associated with complex bilateral changes in grey matter volume, including the somatosensory system and temporal regions involved in multisensory integration [7].

The gain of function for pressure pain, which correlated with pain intensity, increased sensitivity to gentle palpation in the area of sensory deficits [3] and the observation of more widespread pain in NDS can be interpreted as signs of central sensitization. In this condition an increased responsiveness of neurons to their normal input occurs due to a drop in sensory thresholds probably involving a dysfunction of the endogenous pain control systems at brainstem level [48, 49]. It could be assumed that the spreading of pain is a clinical manifestation of central sensitization that has occurred in chronic pain patients under stressful conditions, as seen in various chronic pain syndromes [50]. We hypothesize that NDS may also result from maladaptive central mechanisms trying to counteract central sensitization that has already occurred in a chronic pain population, which are however insufficient to control pain but cause widespread hypoesthesia for several sensory modalities. This may involve descending inhibitory mechanisms at the level of the brainstem.

Intriguingly, bilateral localized sensory loss has been reported in experimental pain models [14] and in localized chronic pain [18, 19, 22]. In addition, increased local sensitivity to pressure pain has been consistently reported in chronic non-neuropathic pain patients [18, 51, 52] in combination with additional negative signs.

The correlation of anxiety with sensory loss for thermal and vibration sense may be an example how psychosocial stress may interact with sensory processing in chronic pain. This may be mediated by the medial pain system where motivational-affective factors interact with pain perception [49]. Afferent projections to this area have been demonstrated [53].

Considering studies on fibromyalgia, reporting evidence of small fiber neuropathy based on QST findings and skin biopsy, it could be discussed whether the observed sensory changes may be related to small fiber neuropathy, which cannot be ruled out by normal nerve conduction studies [54]. However, sensory profiles with unilateral and bilateral alterations, involving also gain of function for pressure pain, with pronounced changes also in the face are not suggestive for localized distal small fiber neuropathy. Rather, involvement of different sensory modalities points towards central dysfunction.

To our knowledge QST has not been studied systematically in patients with chronic non-neuropathic pain with NDS. QST-data have been reported in patients with CRPS I and II and NDS [4] showing significantly increased thresholds to touch, warm, and cold sensation as well as for heat pain in five tested regions at the side of CRPS.

### Limitations of the study

Although QST has been validated in several clinical trials and has been shown to provide reproducible results [55], it remains a psychophysical method, dependent on the patient's attention and compliance.

QST as a time consuming method could only be applied in selected body areas as face, hand and foot bilaterally in this study. Effort was made to demonstrate extensive sensory changes beyond the pain area. In the present study, QST was not done within the area of pain maximum. Therefore, our results were not comparable to most studies investigating sensory pain profiling within the pain maximum. Finally, vibration sense was not included into the extensive screening procedure based on aesthesia, thermaesthesia and algnesia. Thus it cannot be fully excluded that bilateral loss in VDT was observed because unilateral loss in vibration sense was not an inclusion criterion. However, bilateral changes were also found for modalities included in the screening procedure such as CDT and WDT.

### Clinical perspective and conclusion

Pain phenotyping recently becomes a major field in research to improve patients' response to treatment [56]. For psychological phenotyping the HADS and for sensory phenotyping the DFNS QST battery are recommended [56]. We showed a correlation of psychological phenotype markers such as anxiety and pain intensity with several QST parameters.

The association of affective disturbances and chronic pain is widely recognised [57]. Psychosocial phenotyping in our study revealed that the occurrence of NDS in chronic pain patients is associated with more extensive pain sites, higher ratings for anxiety, lower physical quality of life, higher grades of pain severity and chronicity and higher prevalence of migration background. NDS may be regarded as a pain phenotype expressing a higher burden of pain disease.

The combination loss of function for thermal and mechanical modalities and gain of function for mechanical pressure pain as a sign of sensitization in NDS may have impact on the management of patients with chronic non-neuropathic pain. Further studies are indicated with focus on QST in chronic non-neuropathic pain with or without NDS to evaluate conceptions of pain phenotyping and treatment response.



## Acknowledgements:

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## References

1. Treede R-D, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T and Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. *Neurology* 2008;70:1630-1635.
2. Mailis A, Papagapiou M, Umana M, Cohodarevic T, Nowak J and Nicholson K. Unexplainable nondermatomal somatosensory deficits in patients with chronic nonmalignant pain in the context of litigation/compensation: a role for involvement of central factors? *The Journal of Rheumatology* 2001;28:1385-1393.
3. Mailis-Gagnon A and Nicholson K. On the Nature of Nondermatomal Somatosensory Deficits. *The Clinical journal of pain* 2011;27:76-84.
4. Rommel O, Malin J-P, Zenz M and Jänig W. Quantitative sensory testing, neurophysiological and psychological examination in patients with complex regional pain syndrome and hemisensory deficits. *Pain* 2001;93:279-293.
5. Pette H. Das Problem der wechselseitigen Beziehung zwischen Sympathikus und Sensibilität. *Dtsch Z Nervenheilkd* 1927;100:143-148.
6. Egloff N, Maecker F, Stauber S, Sabbioni ME, Tunklova L and von Kanel R. Nondermatomal somatosensory deficits in chronic pain patients: are they really hysterical? *Pain* 2012;153:1847-51.
7. Riederer F, Landmann G, Gantenbein AR, Stockinger L, Egloff N, Sprott H, Schleinzer W, Pirrotta R, Dumat W, Luechinger R, Baumgartner C, Kollias S and Sandor PS. Nondermatomal somatosensory deficits in chronic pain are associated with cerebral grey matter changes. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry* 2015:1-12.
8. Mailis-Gagnon A, Giannoylis I, Downar J, Kwan CL, Mikulis DJ, Crawley AP, Nicholson K and Davis KD. Altered central somatosensory processing in chronic pain patients with “hysterical” anesthesia. *Neurology* 2003;60:1501-1507.
9. Egloff N, Sabbioni ME, Salathe C, Wiest R and Juengling FD. Nondermatomal somatosensory deficits in patients with chronic pain disorder: clinical findings and hypometabolic pattern in FDG-PET. *Pain* 2009;145:252-8.
10. Rolke R, Baron R, Maier C, Tölle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Bötefür IC, Braune S, Flor H, Häge V, Klug R, Landwehrmeyer GB, Magerl W, Maihöfner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M and Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain* 2006;123:231-243.
11. Magerl W, Krumova EK, Baron R, Tolle T, Treede RD and Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. *Pain* 2010;151:598-605.
12. Pfau DB, Krumova EK, Treede RD, Baron R, Toelle T, Birklein F, Eich W, Geber C, Gerhardt A, Weiss T, Magerl W and Maier C. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): reference data for the trunk and application in patients with chronic postherpetic neuralgia. *Pain* 2014;155:1002-15.
13. Backonja MM, Attal N, Baron R, Bouhassira D, Drangholt M, Dyck PJ, Edwards RR, Freeman R, Gracely R, Haanpaa MH, Hansson P, Hatem SM, Krumova EK, Jensen TS, Maier C, Mick G, Rice AS, Rolke R, Treede R-D, Serra J, Toelle T, Tugnoli V, Walk D, Walalce MS, Ware M, Yarnitsky D and Ziegler D. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *PAIN* 2013;154:1807-1819.
14. Leffler AS, Kosek E and Hansson P. Injection of hypertonic saline into musculus infraspinatus resulted in referred pain and sensory disturbances in the ipsilateral upper arm. *European journal of pain* 2000;4:73-82.

15. Apkarian AV, Stea RA and Bolanowski SJ. Heat-induced pain diminishes vibrotactile perception: a touch gate. *Somatosens Mot Res* 1994;11:259-67.
16. Magerl W and Treede RD. Secondary tactile hypoesthesia: a novel type of pain-induced somatosensory plasticity in human subjects. *Neuroscience letters* 2004;361:136-9.
17. Leffler AS, Kosek E and Hansson P. The influence of pain intensity on somatosensory perception in patients suffering from subacute/chronic lateral epicondylalgia. *European journal of pain* 2000;4:57-71.
18. Leffler AS, Hansson P and Kosek E. Somatosensory perception in patients suffering from long-term trapezius myalgia at the site overlying the most painful part of the muscle and in an area of pain referral. *European journal of pain* 2003;7:267-76.
19. Westermann A, Rönna A-K, Krumova E, Regeniter S, Schwenkreis P, Rolke R, Treede R-D, Richter H and Maier C. Pain-associated Mild Sensory Deficits Without Hyperalgesia in Chronic Non-neuropathic Pain. *The Clinical journal of pain* 2011;27:782-789.
20. Tampin B, Slater H, Hall T, Lee G and Briffa NK. Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck-arm pain. *Pain* 2012;153:2403-14.
21. Blumenstiel K, Gerhardt A, Rolke R, Bieber C, Tesarz J, Friederich H-C, Eich W and Treede R-D. Quantitative Sensory Testing Profiles in Chronic Back Pain Are Distinct From Those in Fibromyalgia. *The Clinical journal of pain* 2011;27:682-690.
22. Freynhagen R, Rolke R, Baron R, Tolle TR, Rutjes AK, Schu S and Treede RD. Pseudoradicular and radicular low-back pain--a disease continuum rather than different entities? Answers from quantitative sensory testing. *Pain* 2008;135:65-74.
23. Fernandez-de-las-Penas C, Galan-del-Rio F, Fernandez-Carnero J, Pesquera J, Arendt-Nielsen L and Svensson P. Bilateral widespread mechanical pain sensitivity in women with myofascial temporomandibular disorder: evidence of impairment in central nociceptive processing. *The journal of pain : official journal of the American Pain Society* 2009;10:1170-8.
24. Pfau DB, Rolke R, Nickel R, Treede RD and Daublaender M. Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and Fibromyalgia Syndrome. *Pain* 2009;147:72-83.
25. Clauw DJ, Williams D, Lauerma W, Dahlman M, Aslami A, Nachemson AL, Kobrine AI and Wiesel SW. Pain Sensitivity as a Correlate of Clinical Status in Individuals With Chronic Low Back Pain. *Spine* 1999;21:2035.
26. George SZ, Wittmer VT, Fillingim RB and Robinson ME. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. *The journal of pain : official journal of the American Pain Society* 2007;8:2-10.
27. Giesecke T, Gracely RH, Grant MA, Nachemson A, Petzke F, Williams DA and Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis and rheumatism* 2004;50:613-23.
28. Nagel B, Gerbershagen H, Lindena G and Pflingsten M. Development and evaluation of the multidimensional German pain questionnaire. *Schmerz* 2002;16:263-270.
29. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-70.
30. Ware J, Jr., Kosinski M and Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-33.
31. Von Korff M, Ormel J, Keefe FJ and Dworkin SF. Grading the severity of chronic pain. *Pain* 1992;50:133-49.
32. Gerbershagen U. [Organized treatment of pain. Determination of status]. *Internist (Berl)* 1986;27:459-69.
33. Huppe M, Maier C, Gockel H, Zenz M and Frettlow J. [Success of treatment in higher stages of pain chronification as well? An evaluation of the Mainz pain staging system based on the QUAST-analysis sample]. *Schmerz* 2011;25:77-88.
34. Frettlow J, Maier C, Gockel H and Huppe M. [Validation of the German Mainz Pain Staging System in different pain syndromes]. *Schmerz* 2003;17:240-51.
35. Widerstrom-Noga E, Biering-Sorensen F, Bryce T, Cardenas DD, Finnerup NB, Jensen MP, Richards JS and Siddall PJ. The international spinal cord injury pain basic data set. *Spinal Cord* 2008;46:818-23.

36. Bischoff C, Schulte-Mattler W and Conrad B. *Das EMG Buch*. Stuttgart: Georg Thieme Verlag Stuttgart, 2005.
37. Riffel B, M S and S K. Spinal and cortical evoked potentials following stimulation of the posterior tibial nerve in the diagnosis and localization of spinal cord diseases. *Electroencephalogr Clin Neurophysiol* 1984;58:400-7.
38. Feldman F. Thermography of the hand and wrist: practical applications. *Hand clinics* 1991;7:99-112.
39. Holm S. A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* 1979;6:65-70.
40. Fishbain DA, Cutler RB, Lewis J, Cole B, Rosomoff RS and Rosomoff HL. Is the Location of Nondermatomal Sensory Abnormalities (NDSAs) Related to Pain Location? *Pain medicine* 2003;4:238-243.
41. Rommel O, Gehling M, Dertwinkel R, Witscher K, Zenz M, Malin JP and Janig W. Hemisensory impairment in patients with complex regional pain syndrome. *Pain* 1999;80:95-101.
42. da Silva LA, Kaziyama HH, Teixeira MJ and de Siqueira SR. Quantitative sensory testing in fibromyalgia and hemisensory syndrome: comparison with controls. *Rheumatol Int* 2013;33:2009-17.
43. Rommel O, Malin JP, Janig W, Zenz M, Rommel O, Malin JP, Janig W and Zenz M. [Clinical findings in patients with chronic complex regional pain syndrome]. *Anaesthesist* 2004;53:965-77.
44. Rommel O, Maercklin A, Eichbaum A, Kuprian A and Jäger G. Hemisensorische Störungen bei neuropathischen Schmerzen im Rahmen chronischer Nervenwurzelreizsyndrome. *Der Schmerz* 2005;19:59-64.
45. Gross D Gefaesszone und Quadrant. *Therapeutische Leitungsnaesthesie*. Stuttgart: Thieme, 1982.
46. Treede RD, Kenshalo DR, Gracely RH and Jones AK. The cortical representation of pain. *Pain* 1999;79:105-11.
47. Egloff N, Gander ML, Gerber S, von Kanel R and Wiest R. [Chronic right-sided pain-associated nondermatomal somatosensory deficit following an accident]. *Praxis* 2010;99:797-801.
48. Loeser JD and Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. *Pain* 2008;137:473-7.
49. Westlund K. *Pain Pathways: Peripheral, Spinal, Ascending, and Descending Pathways*. Philadelphia: Elsevier Mosby, 2014.
50. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152:S2-15.
51. Kavchak AJE, Fernández-de-las-Peñas C, Rubin LH, Arendt-Nielsen L, Chmell SJ, Durr RK and Courtney CA. Association Between Altered Somatosensation, Pain, and Knee Stability in Patients With Severe Knee Osteoarthritis. *The Clinical journal of pain* 2012;28:589-594.
52. Suokas AK, Walsh DA, McWilliams DF, Condon L, Moreton B, Wylde V, Arendt-Nielsen L and Zhang W. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2012;20:1075-85.
53. Wang CC and Shyu BC. Differential projections from the mediodorsal and centrolateral thalamic nuclei to the frontal cortex in rats. *Brain Res* 2004;995:226-35.
54. Üçeyler N, Zeller D, Kahn A-K, Kewenig S, Kittel-Schneider S, Schmid A, Casanova-Molla J, Reiners K and Sommer C. Small fibre pathology in patients with fibromyalgia syndrome. *Brain* 2013;136:1857-1867.
55. Geber C, Klein T, Azad S, Birklein F, Gierthmühlen J, Hüge V, Lauchart M, Nitzsche D, Stengel M, Valet M, Baron R, Maier C, Tolle T and Treede RD. Test-retest and interobserver reliability of quantitative sensory testing according to the protocol of the German Research Network on Neuropathic Pain (DFNS): A multi-centre study. *Pain* 2011;152:548-56.
56. Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, Hansson P, Haroutounian S, Arendt-Nielsen L, Attal N, Baron R, Brell J, Bujanover S, Burke LB, Carr D, Chappell AS, Cowan P, Etropolski M, Fillingim RB, Gewandter JS, Katz NP, Kopecky EA, Markman JD, Nomikos G, Porter L, Rappaport BA, Rice AS, Scavone JM, Scholz J, Simon LS, Smith SM, Tobias J, Tockarshewsky T, Veasley C, Versavel M, Wasan AD, Wen W and Yarnitsky D. Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations. *Pain* 2016;5:5.

57. Gatchel RJ, Peng YB, Peters ML, Fuchs PN and Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological bulletin* 2007;133:581-624.

### Figure legends

**Figure 1:** Averaged QST-profiles in the NDS group (left column) and in the pain-only group (right column). Increases in sensory threshold are related to loss of sensory function, and are shown with negative z-scores $\pm$ SD. \*Significant after correction for multiple comparisons. Significant post-hoc comparisons between NDS group and pain-only group are indicated with §. §p<0.05 after correction for multiple comparisons, ipsilateral side NDS group compared to ipsilateral side of pain-only group. §§p<0.05, after correction for multiple comparisons, differences between NDS group and pain-only group on both ipsi- and contralateral sides. The grey bar indicates the normal range based on literature data from healthy controls [10].

CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. PPT: pressure pain threshold. Contralateral and ipsilateral is referred to the side of pronounced pain in the NDS group and in the pain-only group to randomized side.

**Figure 2:** Correlations between pain intensity and sensory thresholds on ipsilateral sides for CDT, WDT, MDT, VDT and PPT. \*significant after correction for multiple comparisons. In the scatterplot the x-axis corresponds to the z-transformed sensory threshold, the y-axis pain intensity (von Korff). Pain intensity is associated with a loss of function for several parameters and a gain of function for pressure pain (PPT).

**Figure 3:** Correlations between anxiety and sensory thresholds on ipsilateral sides. \*significant after correction for multiple comparisons. In the scatterplot the y-axis corresponds to the z-transformed sensory threshold, the x-axis to the HADS-A score. Anxiety is associated with a loss of function. HADS-A: Hospital anxiety and depression scale, part anxiety. CDT: cold detection threshold. WDT: warm detection threshold. VDT: vibration detection threshold.

### List of Supplemental Digital Content

Supplemental Digital Content 1.docx

Supplemental Digital Content 2.docx

Supplemental Digital Content 3.docx

Supplemental Digital Content 4.docx

Supplemental Digital Content 5.docx



**TABLE 1.** Socio-demographic and pain related data

|                            | NDS group<br>n=25 | pain-only<br>group n=23 | p-value          |
|----------------------------|-------------------|-------------------------|------------------|
| Age in years               | 42.1±9.9          | 43.1±10.5               | 0.725            |
| Sex female (n)             | 17                | 15                      | 1.000            |
| Immigration status:        |                   |                         |                  |
| none                       | 6                 | 16                      | <b>0.010</b>     |
| 1 <sup>st</sup> generation | 19                | 5                       |                  |
| 2 <sup>nd</sup> generation | 0                 | 2                       |                  |
| Immigration from countries |                   |                         |                  |
| Central Europe             | 1                 | 0                       | <b>0.006</b>     |
| East Europe                | 0                 | 1                       |                  |
| South-western Europe       | 1                 | 2                       |                  |
| South-eastern Europe       | 17                | 2                       |                  |
| Asia                       | 0                 | 1                       |                  |
| Other                      | 0                 | 1                       |                  |
| HADS-anxiety*              | 11.6±5.0          | 7.4±3.2                 | <b>0.003</b>     |
| SF-12                      |                   |                         |                  |
| physical (42.9-56.4)       | 29.8±6.6          | 37.1±8.8                | <b>0.004</b>     |
| mental (43.7-56.1)         | 36.9±10.0         | 40.9±10.8               | 0.160            |
| CPGQ (von Korff):          |                   |                         |                  |
| Mean pain intensity        | 74.8 ±14.3        | 64.5 ±17.7              |                  |
| Grade 0                    | 0                 | 2                       | 0.038            |
| Grade 1                    | 0                 | 1                       | <b>0.012</b>     |
| Grade 2                    | 2                 | 6                       |                  |
| Grade 3                    | 7                 | 6                       |                  |
| Grade 4                    | 16                | 8                       |                  |
| MPSS:                      |                   |                         |                  |
| Stage I (n):               | 0                 | 4                       | <b>&lt;0.001</b> |
| Stage II (n):              | 4                 | 11                      |                  |
| Stage III (n):             | 21                | 8                       |                  |

\*Normal  $\leq 7$ . CPGQ: Chronic Pain Grading Questionnaire. HADS: Hospital Anxiety and Depression Scale. MPSS: Mainz Pain Staging System. SD: standard deviation. NRS: numeric rating scale 0-10/10. Ordinal variables were analysed with the Mann-WhitneyTest (exact p-values).


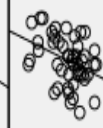






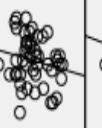
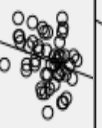

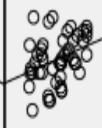
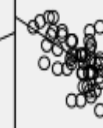


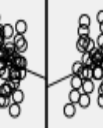
**TABLE 2.** Quantitative sensory testing (QST) in the NDSD group and pain only group

| Region / parameter | ANOVA  |        |              | Post-hoc tests NDSD vs. pain-only group |                     |
|--------------------|--------|--------|--------------|-----------------------------------------|---------------------|
|                    | Group  | Side   | Group X Side | Ipsilateral                             | Contralateral       |
| <b>Face</b>        |        |        |              |                                         |                     |
| CDT                | 0.001  | 0.010  | 0.017        | <0.001 <sup>§</sup>                     | 0.003 <sup>§</sup>  |
| WDT                | 0.001  | 0.010  | n.s.         | <0.001 <sup>§</sup>                     | 0.001 <sup>§</sup>  |
| CPT                | n.s.   | n.s.   | n.s.         | n.s.                                    | n.s.                |
| HPT                | n.s.   | n.s.   | n.s.         | n.s.                                    | n.s.                |
| MDT                | 0.001  | 0.001  | 0.013        | 0.001 <sup>§</sup>                      | 0.012               |
| MPT                | n.s.   | n.s.   | 0.001        | n.s.                                    | n.s.                |
| VDT                | 0.001  | 0.090  | 0.037        | <0.001 <sup>§</sup>                     | <0.001 <sup>§</sup> |
| PTT                | n.s.   | n.s.   | n.s.         | n.s.                                    | n.s.                |
| <b>Hand</b>        |        |        |              |                                         |                     |
| CDT                | 0.004  | 0.054  | n.s.         | 0.008                                   | 0.007               |
| WDT                | 0.085  | n.s.   | n.s.         | 0.042                                   | n.s.                |
| CPT                | n.s.   | 0.011  | n.s.         | n.s.                                    | n.s.                |
| HPT                | n.s.   | n.s.   | n.s.         | n.s.                                    | n.s.                |
| MDT                | 0.017  | <0.001 | 0.013        | 0.002 <sup>§</sup>                      | n.s.                |
| MPT                | 0.017  | n.s.   | 0.048        | 0.002 <sup>§</sup>                      | n.s.                |
| VDT                | 0.001  | n.s.   | 0.037        | <0.001 <sup>§</sup>                     | <0.001 <sup>§</sup> |
| PTT                | 0.020  | n.s.   | n.s.         | 0.021                                   | 0.053               |
| <b>Foot</b>        |        |        |              |                                         |                     |
| CDT                | 0.006  | 0.043  | n.s.         | 0.009                                   | 0.023               |
| WDT                | n.s.   | n.s.   | n.s.         | 0.082                                   | n.s.                |
| CPT                | n.s.   | 0.001  | 0.010        | n.s.                                    | n.s.                |
| HPT                | n.s.   | 0.001  | 0.022        | n.s.                                    | n.s.                |
| MDT                | 0.009  | 0.001  | 0.001        | <0.001 <sup>§</sup>                     | n.s.                |
| MPT                | 0.004  | n.s.   | 0.012        | <0.001 <sup>§</sup>                     | n.s.                |
| VDT                | <0.001 | n.s.   | 0.027        | <0.001 <sup>§</sup>                     | <0.001 <sup>§</sup> |
| PTT                | 0.012  | n.s.   | 0.083        | 0.075                                   | 0.003 <sup>§</sup>  |

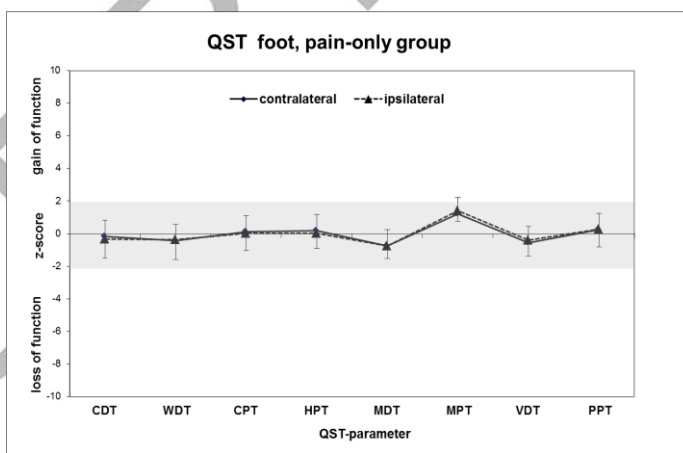
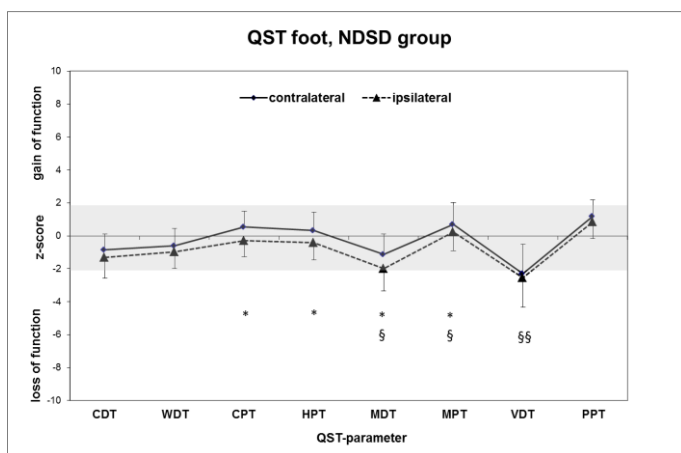
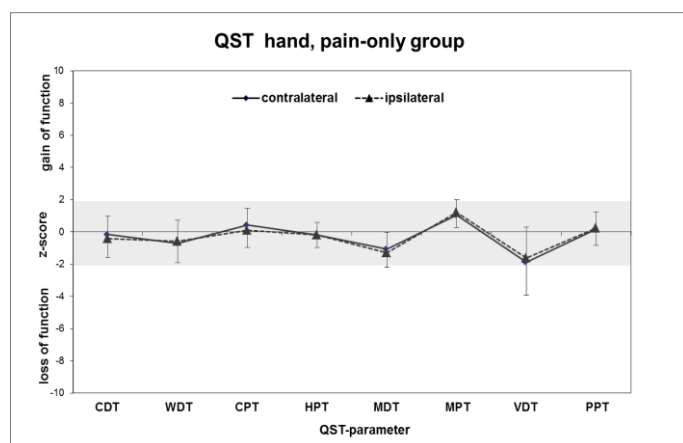
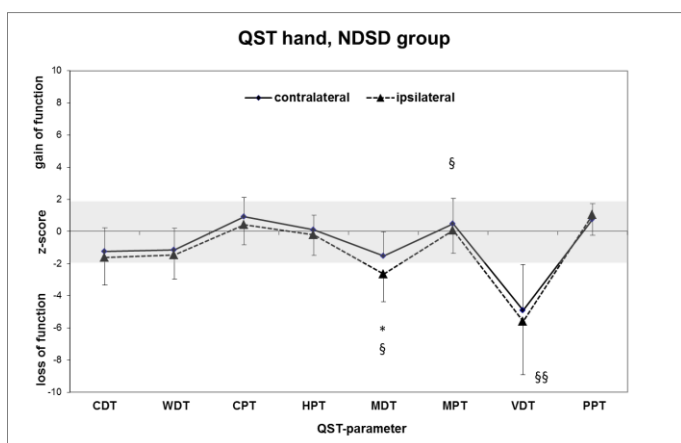
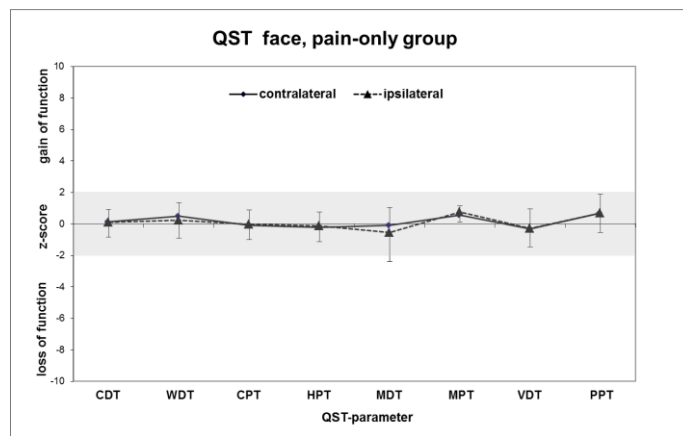
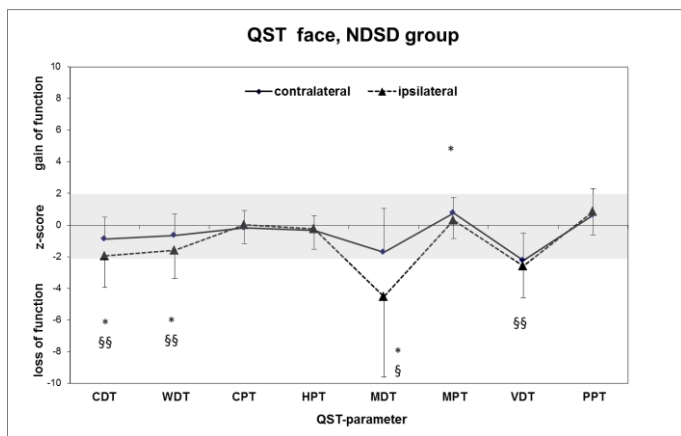
CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. PPT: pressure pain threshold. <sup>§</sup>p<0.003 was considered significant in post-hoc tests. n.s. indicates p-values ≥ 0.1



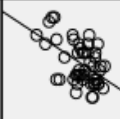








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|                        |                                                                                   |                                                                                   |                                                                                   |                                                                                   |                                                                                   |                                                                                   |                                                                                   |                                                                                    |                                                                                     |                                                                                     |                                                                                     |                                                                                     |                                                                                     |                                                                                     |                                                                                     |                                                                                     |
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|                        |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|                        | <b>Face</b>                                                                       |                                                                                   |                                                                                   | <b>Hand</b>                                                                       |                                                                                   |                                                                                   | <b>Foot</b>                                                                       |                                                                                    |                                                                                     | <b>Face</b>                                                                         |                                                                                     | <b>Hand</b>                                                                         |                                                                                     | <b>Foot</b>                                                                         |                                                                                     |                                                                                     |
|                        | CDT                                                                               | WDT                                                                               | MDT                                                                               | CDT                                                                               | WDT                                                                               | MDT                                                                               | CDT                                                                               | WDT                                                                                | MDT                                                                                 | VDT                                                                                 | PPT                                                                                 | VDT                                                                                 | PPT                                                                                 | VDT                                                                                 | PPT                                                                                 |                                                                                     |
| Spearman's correlation | -0.411<br>0.004*                                                                  | -0.346<br>0.016                                                                   | -0.213<br>0.147                                                                   | -0.214<br>0.144                                                                   | -0.224<br>0.126                                                                   | -0.389<br>0.006*                                                                  | -0.159<br>0.280                                                                   | -0.156<br>0.290                                                                    | -0.268<br>0.066                                                                     | -0.404<br>0.004*                                                                    | 0.383<br>0.007*                                                                     | -0.484<br>0.000*                                                                    | 0.539<br>0.000*                                                                     | -0.305<br>0.035                                                                     | 0.321<br>0.026                                                                      |                                                                                     |

AC



Figure

|                        |                                                                                  |                                                                                  |                                                                                  |                                                                                  |                                                                                  |                                                                                  |                                                                                   |                                                                                    |                                                                                    |
|------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
|                        |  |  |  |  |  |  |  |  |  |
|                        | <b>Face</b>                                                                      |                                                                                  |                                                                                  | <b>Hand</b>                                                                      |                                                                                  |                                                                                  | <b>Foot</b>                                                                       |                                                                                    |                                                                                    |
| HADS-A                 | CDT                                                                              | WDT                                                                              | VDT                                                                              | CDT                                                                              | WDT                                                                              | VDT                                                                              | CDT                                                                               | WDT                                                                                | VDT                                                                                |
| Spearman's correlation | -0.417<br>0.003*                                                                 | -0.459<br>0.001*                                                                 | -0.506<br>0.000*                                                                 | -0.280<br>0.054                                                                  | 0.310<br>0.032                                                                   | -0.555<br>0.000*                                                                 | -0.107<br>0.471                                                                   | -0.244<br>0.095                                                                    | 0.601<br>0.000*                                                                    |

ACCEPTED