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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 hemihypoaesthesia occur in 20-40% of chronic pain patients on the side of pain, independent of pain aetiology, and have been termed nondermatomal sensory deficits (NDSD). Sensory profiles have rarely been investigated in NDSD.

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 NDSD and 23 without NDSD (termed pain-only group) were included after exclusion of neuropathic pain. Comprehensive clinical and psychiatric evaluations were done.

Results: NDSD in chronic pain was associated with high burden of disease and more widespread pain. Only in the NDSD 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 NDSD. 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 NDSD, probably attributable to altered central pain processing and sensitisation. The presence of NDSD 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 hemihypoaesthesia on the side of pain or worse pain [2, 3]. This phenomenon is termed nondermatomal somatosensory deficits (NDSD) [2, 3]. NDSD 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, NDSD 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 NDSD [7, 9]. The occurrence of NDSD 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, hemihypoaesthesia 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 NDSD 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 NDSD; (2) to investigate whether the clinical findings of NDSD can be confirmed by QST; and (3) to compare QST profiles of chronic non-neuropathic pain patients with and without NDSD. 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 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 NDSD 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 NDSD 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 algesia), 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^{R}, 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 algesia to pinprick with a validated 40g weighted pinprick (Neuropen^{R}, 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 of 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 ThermaCam™ 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 ThermaCam 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 1st, 2nd and 3rd trigeminal nerve division. At the hand reference points were set at the dorsum of the hand and dorsum of the distal phalanx of the 1st, 3rd and 5th finger (representing the dermatomes C6, C7 and C8) as well as on the dorsum of the feet and dorsum of distal phalanx of 1st and 5th 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^2 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-score = ($X_{\text{single patient}}$ – $\text{Mean}_{\text{controls}}$) / SD_{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 contraleral 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 NDSD 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 (NDSD/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 NDSD localizations are shown in ***table Supplemental Digital Content 2, http://links.lww.com/CJP/A384*** for the NDSD 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 NDSD 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 NDSD group which were found on the right side in 15 patients and on the left side in 10 patients. In the NDSD 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 thermhypoaesthesia (Spearman´s rho=0.76; p<0.001) and pinprick hypoalgesia (Spearman´s rho=0.76; p<0.001). In 8 patients of the NDSD group the amount of body areas affected by NDSD 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 NDSD 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 NDSD group. This was confirmed by direct side to side comparisons. Post-hoc tests showed that patients in the NDSD 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 NDSD had bilateral sensory loss in the face **(Fig. 1)**. **WDT** was significantly higher in the NDSD 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 NDSD 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 NDSD 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 NDSD group (confirmed by side to side comparisons). **MDT** was significantly higher in the NDSD 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 NDSD group (confirmed by side to side comparisons). **MPT** was significantly increased in the NDSD 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 NDSD group. **VDT** was significantly increased in the NDSD group in all 3 regions investigated. Post-hoc tests revealed bilateral VDT increases in the NDSD group compared to the pain-only group for all 3 regions investigated. **PPT** was significantly decreased in the regions hand and foot in the NDSD group. Post-hoc tests showed decreased PPT in the NDSD 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 NDSD group and in ***table Supplemental Digital Content 5, http://links.lww.com/CJP/A387*** for the pain-only group**.** Patients in the NDSD 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 NDSD in chronic pain is associated with high burden of disease and more widespread pain.

(2) Changes in sensory function in patients with NDSD can be objectified by quantitative sensory testing: In the NDSD 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 NDSD: 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 characteristis and comorbidity

The NDSD 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 NDSD 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 NDSD have been reported in various studies [2, 3, 6, 40]. In our NDSD 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 NDSD has been related to traumatic life events previously [6]. In our patients with NDSD, traumatic life event or a diagnosis of PTSD seemed slightly overrepresented, but this was not significant [7]. The estimated NDSD 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, NDSD 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 NDSD group suggests that NDSD are observed particularly in widespread pain syndromes. As an exception of this observation we found NDSD 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 NDSD based on chart reviews, but have not been systematically studied in previous studies [2, 6, 9]. In contrast, in CRPS with NDSD, 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 NDSD have occasionally been described in radiculopathy with SEP and MRI abnormalities [44]. Our study demonstrates that NDSD 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 NDSD 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 NDSD, although one patient with frequent migraine had NDSD at the less pronounced pain side. In addition, about half of the patients with NDSD had additional spots of diminished sensation opposite to the pain side. In rare cases, NDSD has been described occur on the side opposite to pain [3].

In the clinical examination, we found abnormalities for aesthesia, algesia 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 NDSD 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 NDSD 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 NDSDs 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 NDSD, which could relate to the bilateral sensory abnormalities for vibration and temperature sensation, found in the present study. A PET study in NDSD patients showed significant hypometabolic pattern of changes in cortical and subcortical areas bilateral [9] involving limbic regions. Dysfunctional sensory processing in patients with NDSD 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 NDSD can be interpreted as signs of central sensitisation. 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 NDSD 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 psycho-social 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 NDSD. QST-data have been reported in patients with CRPS I and II and NDSD [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 algesia. 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 NDSD 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. NDSD 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 NDSD 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 NDSD to evaluate conceptions of pain phenotyping and treatment response.

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Figure legends

Figure 1: Averaged QST-profiles in the NDSD 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±SD. *Significant after correction for multiple comparisons. Significant post-hoc comparisons between NDSD group and pain-only group are indicated with §. §p<0.05 after correction for multiple comparisons, ipsilateral side NDSD group compared to ipsilateral side of pain-only group. §§p<0.05, after correction for multiple comparisons, differences between NDSD 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 refered to the side of pronounced pain in the NDSD 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

		NDSD group n=25	pain–only 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	**0.010**
	1st generation	19	5	
	2nd generation	0	2	
Immigration from countries				
	Central Europe	1	0	**0.006**
	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	**0.003**
SF-12	physical (42.9-56.4)	29.8±6.6	37.1±8.8	**0.004**
	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	**0.012**
	Grade 2	2	6	
	Grade 3	7	6	
	Grade 4	16	8	
MPSS:	Stage I (n):	0	4	**<0.001**
	Stage II (n):	4	11	
	Stage III (n):	21	8	

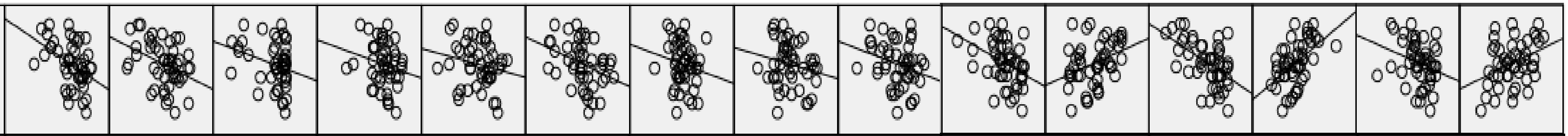
*Normal ≤ 7. CPGQ: Chronic Pain Grading Questionnaire. HADS: Hospital Anxiety and Depression Scale. MPSS: Mainz Pain Staging System. SD: standard deviation. NRS: numeric rating scale 0-10/10. Ordinal variables were analysed with the Mann-WhitneyTest (exact p-values).

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

	ANOVA			**Post-hoc tests NDSD vs. pain-only group**	
Region / parameter	Group	Side	Group X Side	Ipsilateral	Contralateral
Face					
CDT	0.001	0.010	0.017	<0.001§	0.003§
WDT	0.001	0.010	n.s.	<0.001§	0.001§
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§	0.012
MPT	n.s.	n.s.	0.001	n.s.	n.s.
VDT	0.001	0.090	0.037	<0.001§	<0.001§
PTT	n.s.	n.s.	n.s.	n.s.	n.s.
Hand					
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§	n.s.
MPT	0.017	n.s.	0.048	0.002§	n.s.
VDT	0.001	n.s.	0.037	<0.001§	<0.001§
PTT	0.020	n.s.	n.s.	0.021	0.053
Foot					
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§	n.s.
MPT	0.004	n.s.	0.012	<0.001§	n.s.
VDT	<0.001	n.s.	0.027	<0.001§	<0.001§
PTT	0.012	n.s.	0.083	0.075	0.003§

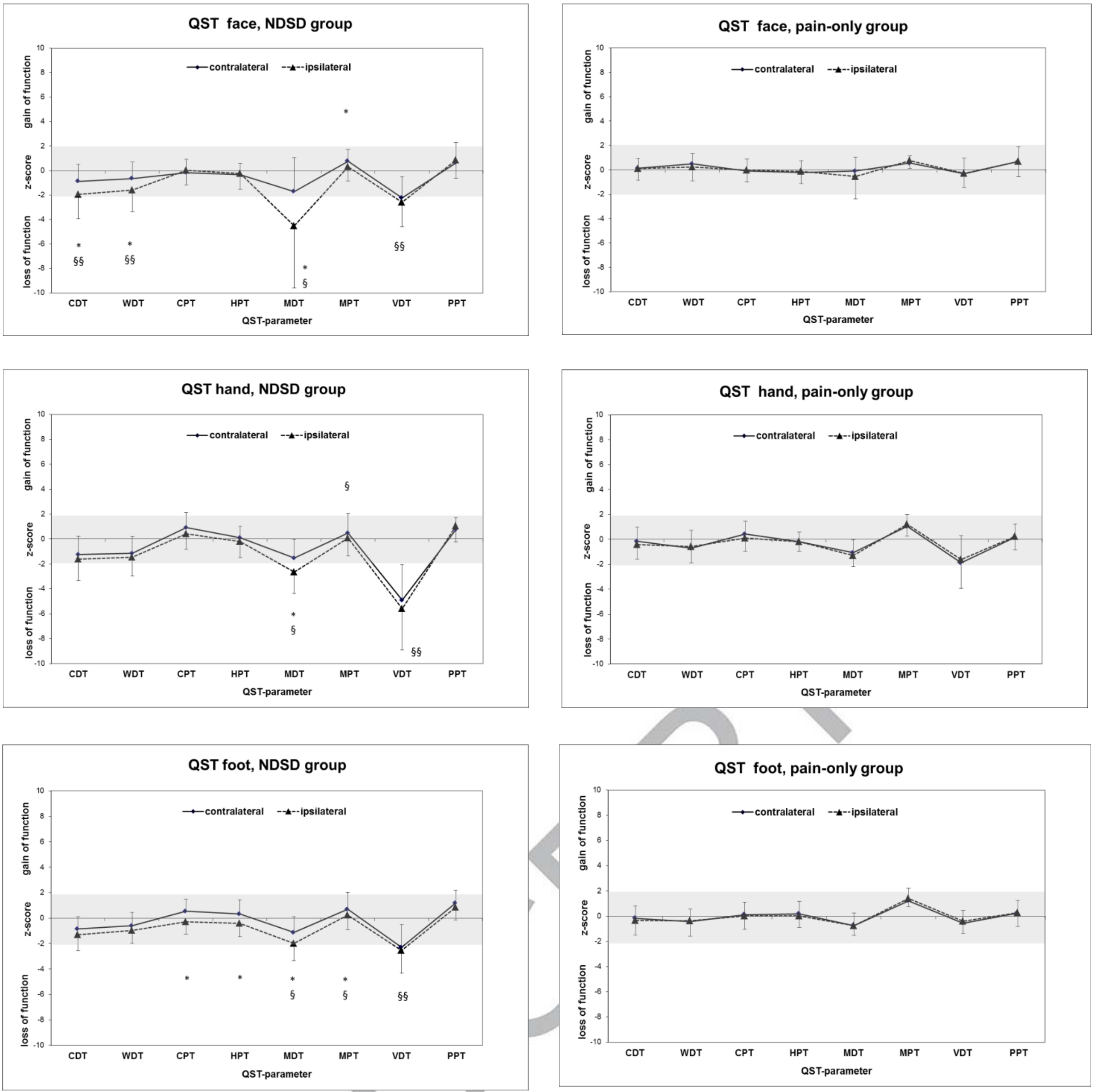
CDT: cold detection threshold. WDT: warm detection threshold. CPT: cold pain threshold. HPT: heat pain threshold. MDT: mechanical detection threshold. MPT: mechanical pain threshold. VDT: vibration detection threshold. PPT: pressure pain threshold. §p≤0.003 was considered significant in post-hoc tests.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

Figure

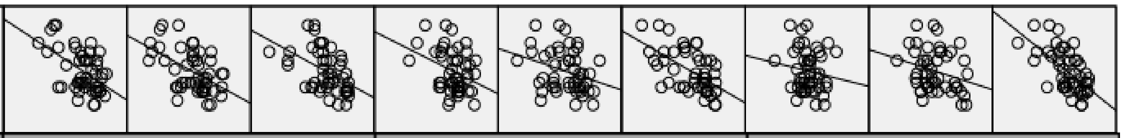


	Face			Hand			Foot			Face		Hand		Foot	
	CDT	WDT	MDT	CDT	WDT	MDT	CDT	WDT	MDT	VDT	PPT	VDT	PPT	VDT	PPT
Spear-man`s corre-lation	-0.411 0.004*	-0.346 0.016	-0.213 0.147	-0.214 0.144	-0.224 0.126	-0.389 0.006*	-0.159 0.280	-0.156 0.290	-0.268 0.066	-0.404 0.004*	0.383 0.007*	-0.484 0.000*	0.539 0.000*	-0.305 0.035	0.321 0.026

Figure


QST face, NDSD group
QST face, pain-only group
QST hand, NDSD group
QST hand, pain-only group
QST foot, NDSD group
QST foot, pain-only group
contralateral
ipsilateral
gain of function
z-score
loss of function
CDT
WDT
CPT
HPT
MDT
MPT
VDT
PPT
QST-parameter

Figure



	Face			Hand			Foot		
HADS-A	CDT	WDT	VDT	CDT	WDT	VDT	CDT	WDT	VDT
Spear-man`s corre-lation	-0.417 0.003*	-0.459 0.001*	-0.506 0.000*	-0.280 0.054	0.310 0.032	-0.555 0.000*	-0.107 0.471	-0.244 0.095	0.601 0.000*