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Continuum of sensory profiles in diabetes mellitus patients with and without neuropathy and pain

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Abstract

Background: Quantitative sensory testing (QST) assesses the functional integrity of small and large nerve fibre afferents and central somatosensory pathways; QST was assumed to provide insight into the mechanisms of neuropathy. We analysed QST profiles and phenotypes in patients with diabetes mellitus to study whether these could differentiate patients with and without pain and neuropathy.

Methods: A standardized QST protocol was performed and 'loss and gain of function' abnormalities were analysed in four groups of subjects: diabetic patients with painful (pDSPN; $n = 220$) and non-painful distal symmetric polyneuropathy (nDSPN; $n = 219$), diabetic patients without neuropathy (DM; $n = 23$) and healthy non-diabetic subjects ($n = 37$). Based on the QST findings, diabetic subjects were further stratified into four predefined prototypic phenotypes: sensory loss (SL), thermal hyperalgesia (TH), mechanical hyperalgesia (MH) and healthy individuals.

Results: Patients in the pDSPN group showed the greatest hyposensitivity ('loss of function'), and DM patients showed the lowest, with statistically significant increases in thermal, thermal pain, mechanical and mechanical pain sensory thresholds. Accordingly, the frequency of the SL phenotype was significantly higher in the pDSPN subgroup (41.8%), than expected ($p < 0.0042$). The proportion of 'gain of function' abnormalities was low in both pDSPN and nDSPN patients without significant differences.

Conclusions: There is a continuum in the sensory profiles of diabetic patients, with a more pronounced sensory loss in pDSPN group probably reflecting somatosensory nerve fibre degeneration. An analysis of 'gain of function' abnormalities (allodynia, hyperalgesia) did not offer a key to understanding the pathophysiology of spontaneous diabetic peripheral neuropathic pain.

Significance: This article, using quantitative sensory testing profiles in large cohorts of diabetic patients with and without polyneuropathy and pain, presents a continuum in the sensory profiles of diabetic patients, with more pronounced

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'loss of function' abnormalities in painful polyneuropathy patients. Painful diabetic polyneuropathy probably represents a 'more progressed' type of neuropathy with more pronounced somatosensory nerve fibre degeneration. The proportion of 'gain of function' sensory abnormalities was low, and these offer limited understanding of pathophysiological mechanisms of spontaneous neuropathic pain.

1 | INTRODUCTION

Confirmation of a lesion or disease of the somatosensory system by various tests increases the degree of certainty of the diagnosis of neuropathic pain in the context of a relevant history, pain characteristics and distribution and results of clinical sensory testing (Finnerup et al., 2016). On the other hand, lesions of the small fibres or spinothalamic tract produce sensory loss (SL) for thermal pain stimuli that are not strictly predictive of the presence or absence of spontaneous pain. Spontaneous neuropathic pain is believed to be related to the hyperactivity of residual fibres. This has increased the interest in techniques evaluating the gain of function (Forstenpointner et al., 2021).

Quantitative sensory testing (QST) may independently assess loss or gain abnormalities of various thermal and mechanical sensory modalities and has been used to phenotype both painful and non-painful neuropathic states (Forstenpointner et al., 2021; Haroun et al., 2019; Phillips et al., 2014; Üçeyler et al., 2018). There have been attempts to classify subjects into distinct sensory profiles possibly related to different pathophysiological mechanisms. This sensory profiling was believed to lead to a stratified approach and ultimately to personalized treatment and to prove the symptom-based treatment approach (Baron et al., 2012).

Recently, the use of predefined clusters of sensory phenotypes (Baron et al., 2017; Vollert et al., 2017) has offered a more nuanced view of sensory abnormalities and their combinations. This method sorts each patient into the phenotype to which the QST profile is most similar. These phenotypes resemble sensory phenotypes that can be experimentally induced in healthy subjects. The 'SL' phenotype, characterized by a loss of thermal and mechanical detection, is similar to the previously described 'deafferentation' or 'painful hypoesthesia' subgroups (Baumgartner et al., 2002; Fields et al., 1998). The 'thermal hyperalgesia' (TH) phenotype, characterized by intact sensory function combined with TH or allodynia, resembles the previously described 'irritable nociceptor' phenotype (Demant et al., 2014; Fields et al., 1998) and is likely due to peripheral sensitisation (Baron et al., 2017; Treede et al., 1992). The 'mechanical hyperesthesia' (MH) phenotype, characterized by loss of thermal detection but not mechanical

detection, accompanied by MH or allodynia, shows similarities to the previously described 'neurogenic hyperalgesia' and is probably due to a 'central sensitisation' mechanism (Baron et al., 2017; Baumgartner et al., 2002; Fields et al., 1998).

Recent studies showed the limited ability of QST to differentiate between painful and non-painful conditions and revealed the necessity to focus on more homogenous painful neuropathy patient cohorts to decrease the diversity of included patients as a source of the limitation of QST findings (Baron et al., 2012; Bordeleau et al., 2021; Forstenpointner et al., 2021; Üçeyler et al., 2018). Regarding the current knowledge of the role of QST sensory profiles in painful diabetic neuropathy, we analysed QST profiles in two large prospectively evaluated cohorts of painful and non-painful diabetic polyneuropathy patients and compared the profiles with a group of diabetic patients without polyneuropathy and a group of healthy non-diabetic individuals to confirm whether QST sensory profiling could predict the development of neuropathic pain and reveal possible mechanisms of pain development.

2 | METHODS

2.1 | Study design and patients

The data from all subjects included and analysed in the current project were derived from an observational cross-sectional multicentre cohort study, which was part of the 'ncRNAPain consortium' (http://www.ncrna-pain.eu/) and focused primarily on neuropathic pain conditions. It was approved by the respective local authorities: the ethics committees of the University Hospital Brno (No.602133) and the Rhineland-Palatinate medical association (9142-F), and registered at the German Clinical Trials Register: https://www.germanctr.de/ (Registration Number DRKS00008964).

Subjects with both painful distal symmetrical polyneuropathy (pDSPN) and non-painful distal symmetrical polyneuropathy (nDSPN) and healthy non-diabetic volunteers were recruited from two university diabetes centres in Brno (Czech Republic), from the Departments of Neurology and Anaesthesiology in Würzburg, and from

the Department of Neurology in Mainz (Germany), and they were referred for a single clinical assessment to one of three study centres (Department of Neurology in Brno, Würzburg, or Mainz). QST data from some of these subjects have already been published (Raputova et al., 2017). From 2018 to 2021, we extended the pDSPN and nDSPN cohorts and added a group of diabetic patients without polyneuropathy recruited from the patient databases of two Brno diabetes centres to analyse the influence not only of neuropathic pain but also of neuropathy on the sensory profile of patients with diabetes mellitus (DM). All participants signed written informed consent forms before inclusion in the study.

All recruited subjects first underwent a collection of diagnostic tests to confirm or reject the diagnosis of DSPN and their eligibility for the study, for example, a detailed medical and drug history, basic blood tests and a structured neurological examination. Nerve conduction studies (NCS) were done to confirm the diagnosis of DSPN.

Exclusion criteria were as follows:

- Neuropathic pain due to cause other than DSPN
- Central nervous system lesions
- History or presence of laboratory abnormalities indicating a disease, condition, or treatment that might be a potential cause of polyneuropathy other than diabetes.

Patients with DSPN were further classified as pDSPN and nDSPN. Participants classified as pDSPN had to have chronic (i.e. ≥3 months) peripheral neuropathic pain (NeuP) at the time of the clinical assessment, to meet the criteria of probable or confirmed NeuP according to the updated IASP grading system (Finnerup et al., 2016) and to have a mean NRS during the last week before the clinical examination ≥4. The nDSPN subgroup thus comprised diabetic patients with polyneuropathy who did not meet the inclusion criteria for the pDSPN group. For the purpose of more detailed analysis, we divided pDSPN group into 'true' painless patients with NRS 0 and those with very mild pain and NRS 1–3. Diabetic patients without polyneuropathy (DM) had to have no clinical neuropathic symptoms or signs and a normal NCS result.

Recruitment of study participants and the criteria used to subdivide the study participants into the different subgroups are shown in the flow diagram (Figure 1). The detailed methodology of clinical and electrophysiological assessments was the same as in the previous publication (Raputova et al., 2017).

In the recruited patients, pain and its impact on everyday life were quantified and characterized using the Graded Chronic Pain Scale (GCPS; Von Korff et al., 1992).

The Neuropathic Pain Symptom Inventory (NPSI; Bouhassira et al., 2004), a self-administered questionnaire, was used to evaluate NeuP symptoms.

The modified Toronto Clinical Neuropathy Score (mTCNS) was applied to quantify the severity of DSPN (Bril et al., 2009). The INCAT Overall Disability Sum Score (ODSS) was used to quantify disability in DSPN (Merkies et al., 2002).

The Pain Catastrophizing Scale (PCS) was used to assess negative cognitions and subjective appraisals of pain. PCS assesses a patient's propensity to develop catastrophic thinking (Sullivan et al., 1995).

Symptoms of depression and anxiety were evaluated by means of the Beck Depression Inventory II (BDI II—Beck et al., 1996) and the State–Trait Anxiety Inventory Form Y (STAI-Y—Spielberger et al., 1983).

2.2 | Quantitative sensory testing

Subjects who met the inclusion and exclusion criteria then underwent QST based on the DFNS protocol. This standardized test battery contained 13 different thermal and mechanical tests: cold detection threshold (CDT) and warm detection threshold (WDT); paradoxical heat sensations (PHS) during the procedure of alternating warm and cold stimuli (thermal sensory limen, TSL); cold pain threshold (CPT) and heat pain threshold (HPT); mechanical detection threshold (MDT) for touch and vibration detection threshold (VDT); mechanical pain thresholds for pinprick (MPT) and pressure pain thresholds (PPTs); a stimulus–response-function for pinprick sensitivity (mechanical pain sensitivity, MPS) and dynamic mechanical allodynia (DMA) as well as pain summation to repetitive pinprick stimuli (wind-up ratio, WUR). All tests were performed on the dorsum of the foot and hand, except for PPT (sole, thenar) and VDT (medial malleolus, radial styloid process) on the right. For all parameters, negative (loss of function) and positive (gain of function) phenomena were assessed (Raputova et al., 2017). The definition of QST abnormalities were based on DFNS recommendations of Z-transformation in all QST variables except for PHS and DMA to compare the individual QST data between subjects regardless of sex-, age- or body-site differences (Baron et al., 2017; Maier et al., 2010). If the individual z-values were outside of the 95% confidence interval of the reference group (i.e. z-scores >1.96 or <−1.96), the values were designated as absolute abnormalities. Z-scores of zero represent a value corresponding to the mean of the healthy control cohort, z-scores above '0' indicate a gain of function, that is, hyperaesthesia or hyperalgesia and z-scores below '0' indicate a loss of function, that is, hypoaesthesia or hypoalgesia (Baron et al., 2017).

PHS was transformed to a binary 0/2-variable: absence was coded as 0; presence was coded as +2. 1.96 SD of PHS
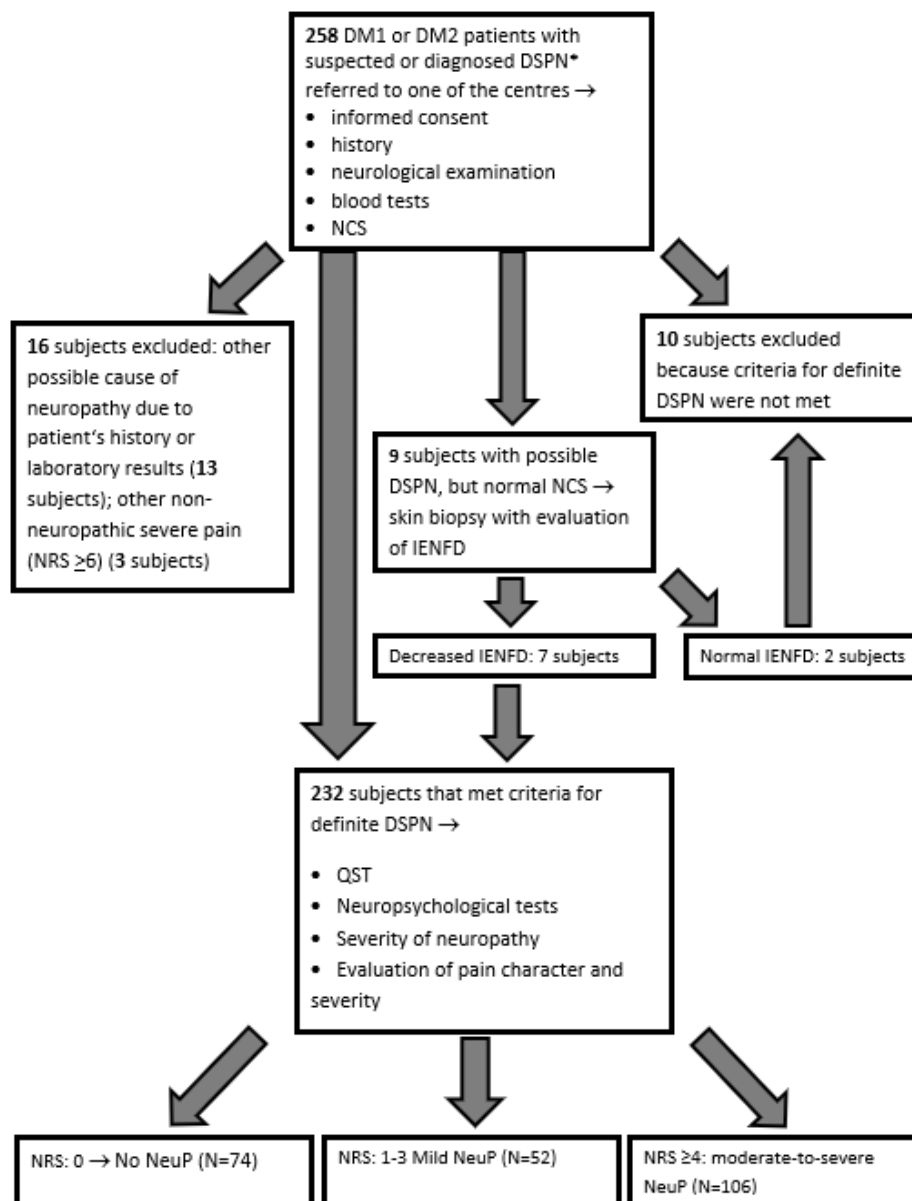
FIGURE 1 Flow diagram of study participant recruitment and the criteria used to subdivide the participants into subgroups. DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; DSPN, diabetic symmetrical polyneuropathy; NCS, nerve conduction studies; nDSPN, non-painful diabetic symmetrical polyneuropathy; NeuP, neuropathic pain; NRS, numerical rating scale; pDSPN, painful diabetic symmetrical polyneuropathy; QST, quantitative sensory testing.

above or below the reference data is considered abnormal, except for the lower extremity in older males. DMA that occurred in a wide range of intensity values (0–100) was logarithmically transformed to a 0/2/3-variable representing the absence of DMA (coded as 0), DMA with average pain ratings below 1 (coded as +2) and DMA with average pain ratings between 1 and 100 (coded as +3) (Baron et al., 2017).

To stratify subjects according to QST results into predefined sensory phenotypes, a recently suggested algorithm (Vollert et al., 2017) was used, allocating patients into one of four sensory phenotypes: (a) loss of thermal and mechanical detection—'SL'; (b) intact

sensory function, often combined with TH or allodynia –TH; (c) loss of thermal detection, but not mechanical detection, accompanied by MH or allodynia –MH; and (d) a largely normal sensory profile resembling that of healthy subjects—healthy sensory profile (Vollert et al., 2017).

2.3 | Statistical evaluation

Standard measures of summary statistics were applied to describe primary data; continuous parameters were

summarized as median (5th–95th percentile range). Categorical parameters are expressed as absolute and relative frequencies. All continuous variables were tested for normality with the Kolmogorov–Smirnov test and by visualization of N-P plots. Chi-squared tests (for categorical variables) and the Kruskal–Wallis test with post hoc tests (for continuous variables) were used to examine differences between groups (HC, DM, nDSPN and pDSPN) and other categorical variables using IBM SPSS Statistics 27. Statistical significance for multiple comparisons was established using Bonferroni's correction.

3 | RESULTS

3.1 | Study participants

Of 502 patients with diabetes mellitus type 1 (DM1) or type 2 (DM2) with suspected or diagnosed DSPN, a total of 439 met the study eligibility criteria and were able to be examined with standardized QST protocol. Similarly, of 33 DM1 or DM2 patients without symptoms and signs of polyneuropathy, 23 of them with completely normal NCS were finally enrolled (Figure 1).

The cohort of all subjects included in the study in whom QST was evaluated and sensory profiles were established consisted of the following:

- 37 controls—HC group—(median: 55 years; min-max: 32–79 years; 15 men);
- 23 diabetic patients without neuropathy—DM group—(42; 22–72 years; 9 men);
- 219 patients with non-painful diabetic polyneuropathy— nDSPN group—(61; 21–87 years; 139 men);
- 220 patients with painful diabetic polyneuropathy— pDSPN group—(64; 24–85 years; 111 men).

Further demographic and clinical characteristics are summarized in Table 1.

There were no differences between pDSPN and nDSPN patients in age, sex, degree of diabetes control, complications of diabetes or comorbidities. In comparison with the nDSPN patients, the pDSPN patients, in addition to higher scores in pain-related questionnaires (NPSI, GCPS) had significantly higher BMI, greater severity of neuropathy-related disability (ODSS, mTCNS) and higher neuropsychological scores reflecting depression (BDI II), anxiety (STAI Y) and catastrophising thinking (PCS). The DM group had lower median age and higher proportion of women, lower proportion of diabetic complications or comorbidities (diabetic nephropathy, arterial hypertension, dyslipidemia, ischemic coronary disease) compared with both neuropathic subgroups and lower BDI II and PCS

score (compared with pDSPN) and STAI Y2 (compared with both pDSPN and nDSPN).

3.2 | Quantitative sensory testing

When comparing all diabetic subgroups with painful and non-painful polyneuropathy and without polyneuropathy, the QST profiles looked very similar (Figure 2). Nevertheless, group comparisons revealed significant differences between all diabetic subgroups and healthy controls in all thermal thresholds (CDT = $p < 0.001$, WDT = $p < 0.01$, TSL = $p < 0.05$) and thermal pain thresholds modalities (CPT, HPT = $p < 0.05$) with the lowest median z-score values (the greatest loss, the highest thresholds) among diabetic subgroups in pDSPN and the highest z-score values (the least loss, the lowest thresholds) in DM (Table 2). Similar differences with the same trend towards the lowest z-score values in pDSPN and highest z-score values in DM subjects were disclosed also for mechanical pain thresholds (MPT and MPS = $p < 0.05$) and mechanical detection thresholds (MDT = $p < 0.05$, VDT = p = 0.01). We recalculated QST results after redefinition of nDSPN group divided into 'true' non-painful patients ($n = 179$) and 40 patients with very mild pain (NRS 1–3) and the results were almost the same (Table 1S).

The DM subgroup had significantly higher CPT, HPT and MPT z-scores in comparison with HC ($p = 0.02$, 0.002 and 0.02). PHS was detected in significantly higher proportions in all diabetic subgroups in comparison with healthy controls ($p < 0.006$); there was no significant difference in the frequency of DMA.

The relative number of patients affected by loss or gain of function was similar in painful and non-painful polyneuropathy subgroups (Figure 2b,c), with significantly higher proportion of patients with loss of function in CDT, WDT and TSL modalities and a higher proportion of patients with loss of function (and a lower proportion of patients with gain of function) in MPT in patients with painful compared with non-painful diabetic polyneuropathy (Table 3). The proportion of patients with pDSPN and nDSPN with loss of function, gain of function, both loss and gain of function abnormalities, and no abnormality are showed in Figure 2d. The proportion of pDSPN patients with isolated loss of function abnormality was significantly higher (60.0%) compared with nDSPN cases (38.8%; $p < 0.0063$). The frequency of sensory phenotypes derived from QST parameters was different in three diabetic patient subgroups (Figure 3). The frequency of the SL phenotype was significantly higher in painful diabetic neuropathy patients (41.8%), and lower in non-painful diabetic polyneuropathy subgroup (24.7%) and in diabetic patients without polyneuropathy (0.0%) than expected

TABLE 1 Summary of demographic, clinical and laboratory parameters related to diabetes. Parameters are summarized as median (5th–95th percentile range) and categorical parameters are expressed as absolute and relative frequencies

Parameters		Painful polyneuropathy (NRS ≥4)	Non-painful polyneuropathy (NRS <4)	Diabetes without polyneuropathy (NRS 0)	p
		$N = 220$	$N = 219$	$N = 23$	
Age (years)		63.6 (41.0;77.3)[a]	61.1 (29.9;77.0)[a]	42.0 (23.4;60.9)[b]	**<0.001**
Gender	Women	99 (45.0%)[a]	79 (36.1%)[a]	14 (60.9%)[b]	**0.03**
	Men	121 (55%)	140 (63.9%)	9 (39.1%)	
BMI		30.0 (22.4;41.5)[a]	28.7 (21.7;38.2)[b]	28.1 (21.8;35.4)[ab]	**0.02**
Type of diabetes	Type 1	36 (16.4%)[a]	72 (32.9%)[b]	10 (43.5%)[b]	**<0.008**
	Type 2	184 (83.6%)	147 (67.1%)	13 (56.5%)	
Duration of diabetes (years)		10.0 (1.4;33.1)[ab]	14.0 (2.0;31.2)[a]	9.0 (2.0;24.8)[b]	**0.02**
HbA1c (mmol/mol/[%])		65.5 (7.2) (39 (5.7); 92 (10.6))	57.0 (7.4) (39.0 (5.7); 83.1 (9.8))	52.5 (7.0) (37.1 (5.5); 83.7 (9.8))	0.23
HbA1c (mmol/mol/[%])	Controlled: <42 mmol/ mol (<6.0%)	30 (13.6%)	24 (11.0%)	4 (17.4%)	0.54
Known retinopathy	No	193 (87.7%)	192 (87.7%)	23 (100.0%)	0.20
	Yes	27 (12.3%)	27 (12.3%)	0 (0.0%)	
Diabetic nephropathy	No	176 (80.0%)[a]	189 (86.3%)[a]	23 (100.0%)[b]	**0.02**
	Yes	44 (20.0%)	30 (13.7%)	0 (0.0%)	
Arterial hypertension	No	37 (16.8%)[a]	65 (29.7%)[a]	15 (65.2%)[b]	**<0.001**
	Yes	183 (83.2%)	154 (70.3%)	8 (34.8%)	
Ischemic arterial disease of lower extremities	No	204 (92.7%)	206 (94.1%)	23 (100.0%)	0.24
	Yes	16 (7.3%)	13 (5.9%)	0 (0.0%)	
Ischemic coronary disease	No	164 (74.5%)[a]	171 (78.1%)[a]	22 (95.7%)[b]	**0.07**
	Yes	56 (25.5%)	48 (21.9%)	1 (4.3%)	
Cerebrovascular disease	No	207 (94.1%)	208 (95.0%)	23 (100.0%)	0.47
	Yes	13 (5.9%)	11 (5.0%)	0 (0.0%)	
At least 1 macroangiopathic complication	No	145 (65.9%)[a]	157 (71.7%)[ab]	22 (95.7%)[b]	**0.01**
	Yes	75 (34.1%)	62 (28.3%)	1 (4.3%)	
Dyslipidemia – at least 1 abnormality	No	69 (31.4%)[a]	83 (37.9%)[a]	14 (60.9%)[b]	**0.01**
	Yes	151 (68.6%)	136 (62.1%)	9 (39.1%)	
Chronic alcoholism— women (>1 drink per day)	No	99 (100.0%)	79 (100.0%)	14 (100.0%)	1.00
	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Chronic alcoholism— men (>2 drinks per day)	No	120 (99.2%)	138 (98.6%)	9 (100.0%)	0.99
	Yes	1 (0.8%)	2 (1.4%)	0 (0.0%)	
ODSS sum score (0–12)		1.0 (0.0;4.0)[a]	0.0 (0.0;2.0)[b]	0.0 (0.0;0.9)[c]	**<0.001**
mTCNS—symptom score	Score of symptoms (0–18)	6.0 (2.0;17.0)[a]	0.0 (0.0;4.1)[b]	0.0 (0.0;1.0)[b]	**<0.001**

(Continues)

TABLE 1 (Continued)

Parameters		Painful polyneuropathy (NRS ≥4)	Non-painful polyneuropathy (NRS <4)	Diabetes without polyneuropathy (NRS 0)	p
mTCNS—sensory test score	Score of sensory tests (0–15)	7.0 (0.0;15.0)[a]	3.0 (0.0;10.0)[b]	0.0 (0.0;2.9)[c]	**<0.001**
mTCNS sum score (0–33)	Sum score (0–33)	14.0 (3.9;29.0)[a]	4.0 (0.0;13.0)[b]	0.0 (0.0;3.8)[c]	**<0.001**
NPSI	Sum score	0.0 (0.0;71.4)[a]	0.0 (0.0;42.4)[b]	0.0 (0.0;0.0)[b]	**<0.001**
	Burning score	4.0 (0.0;10.0)[a]	0.0 (0.0;2.0)[b]	0.0 (0.0;1.8)[b]	**<0.001**
	Pressure score	0.0 (0.0;8.0)[a]	0.0 (0.0;0.0)[b]	0.0 (0.0;1.8)[b]	**<0.001**
	Attacks	2.0 (1.0;5.0)[a]	1.0 (1.0;1.0)[b]	1.0 (1.0;1.0)[b]	**<0.001**
	Evoked pain score	0.0 (0.0;6.0)[a]	0.0 (0.0;0.4)[b]	0.0 (0.0;0.9)[b]	**<0.001**
	Paresthesia/ dysesthesia score	4.0 (0.0;10.0)[a]	0.0 (0.0;2.6)[b]	0.0 (0.0;0.0)[b]	**<0.001**
GCPS disability score		16.7 (0.0;80.0)[a]	0.0 (0.0;0.0)[b]	0.0 (0.0;0.0)[b]	**<0.001**
GCPS classification (0–4)		2.0 (1.0;4.0)[a]	0.0 (0.0;1.0)[b]	0.0 (0.0;1.0)[b]	**<0.001**
PCS sum score		16.0 (2.0;35.0)[a]	11.0 (2.0;26.0)[b]	12.0 (0.2;25.9)[b]	**<0.001**
BDI II		12.0 (3.0;27.0)[a]	7.5 (0.0;21.0)[b]	8.0 (1.0;19.3)[b]	**<0.001**
STAI Y1		40.0 (23.0;57.4)[a]	35.0 (22.0;53.0)[b]	35.0 (26.3;48.7)[ab]	**<0.001**
STAI Y2		41.0 (25.5;57.5)[a]	36.0 (22.8;52.5)[b]	35.0 (26.2;44.9)[b]	**<0.001**

Note: p-value represents the comparison of patients with different levels of pain (Kruskal-Wallis test for continuous variables and Pearsons chi-squared test for categorical variables); post-hoc tests: a, b, c—same letters marking the values of categories within a given row denote mutually statistically not different groups. Significant p values ($p < 0.05$) are indicated in bold type.

Abbreviations: BDI II, Beck Depression Inventory II; BMI, body mass index; GCPS, graded chronic pain scale; mTCNS, modified Toronto clinical neuropathy score; NPSI, neuropathic pain symptom inventory; ODSS, overall disability sum score; STAI Y, state–trait anxiety inventory Y form Y1 and Y2.

($p < 0.0042$, corrected for number of comparisons). The TH phenotype was the most frequent pattern found in the DM subgroup (47.8%), less frequent in nDSPN patients (31.1%) and significantly lower than expected in pDSPN subgroup (18.2%). A similar tendency was disclosed in healthy patterns, found in 21.7% of DM patients, in 10.4% of nDSPN patients, and significantly lower than expected in 4.1% of pDSPN patients. The MH phenotype was present in approximately similar proportions in all diabetic subgroups (35.9% in pDSPN, 33.8% in nDSPN and 30.4% in DM subgroup).

QST sensory profiles were further compared between the pDSPN and nDSPN subgroups within predetermined sensory phenotypes (Figure 4). They look very similar in patients classified as SL and MH phenotypes, while more pronounced differences in mechanical pain thresholds (MPT and MPS) were seen in patients classified as TH phenotype, with higher mechanical pain thresholds and a trend towards lower MPS in painful diabetic polyneuropathy patients.

4 | DISCUSSION AND CONCLUSIONS

In this cohort study comparing sensory profiles and phenotypes of large groups of diabetic patients with painful and non-painful diabetic polyneuropathy and in comparison with diabetic patients without polyneuropathy and healthy non-diabetic controls, we disclosed very similar QST profiles in all subtypes of diabetic patients. In addition, a minor but significant trend of increased hyposensitivity for the detection of both thermal and mechanical stimuli, and a higher proportion of loss-type abnormalities of thermal modalities was found in painful diabetic neuropathy compared with non-painful neuropathy. Accordingly, the SL phenotype was dominant in pDSPN patients. The proportion of 'gain of function' abnormalities and the frequency of thermal and mechanical hypersensitivity phenotypes were not able to disclose significant differences between painful and non-painful diabetic neuropathy subgroups.

FIGURE 2 (a) Quantitative sensory testing profiles from feet of diabetic patients with painful and non-painful polyneuropathy and without polyneuropathy. The sensory profile shows thermal detection thresholds (first block), pain thresholds (second block), MPTs (third block) and MDTs (fourth block), together with allodynia and presence of PHSs (small graphs). Presented mean z scores $\pm$95% confidence interval revealed differences between diabetic subgroups in several QST parameters. (b, c) Abnormal value frequency of all patients with painful (b) and non-painful (c) diabetic polyneuropathy. (d) Proportion of patients with painful and non-painful diabetic polyneuropathy with loss of function, gain of function, both loss and gain of function abnormalities and no abnormality. CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; nDSPN, non-painful diabetic polyneuropathy; NRS, numerical rating scale; pDSPN, painful diabetic polyneuropathy; PHS, paradoxical heat sensation; PNP, polyneuropathy; PPT, deep pain sensitivity to blunt pressure; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.
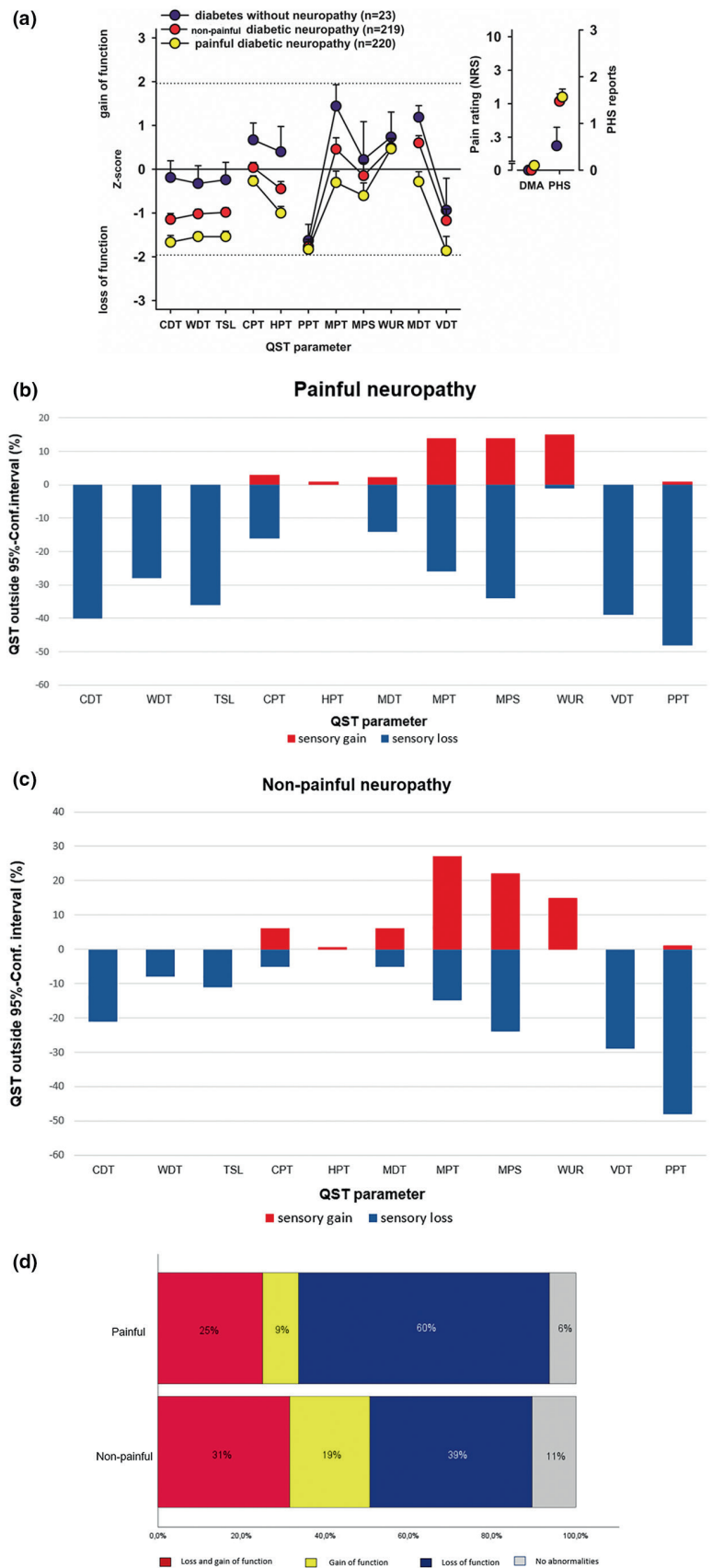
The studies mixing patients subgroups with neuropathic pain in different aetiological subtypes of neuropathies revealed that sensory profiles and possibly prevalent pain mechanisms may differ between these groups and thus studies focused on more homogenous painful neuropathy patient cohorts are needed to

TABLE 2 Quantitative sensory testing (feet). Continuous parameters are summarized as median z-scores (5th–95th percentile range). Categorical parameters are expressed as absolute and relative frequencies

Parameters		Healthy controls	Diabetes mellitus without polyneuropathy	Non-painful polyneuropathy	Painful polyneuropathy	p
		N = 37	N = 23	N = 219	N = 220	
QST parameters—Z-score						
CDT		−0.4 (−1.5;1.2)[a]	−0.3 (−1.5;1.4)[a]	−1.1 (−3.1;0.5)[b]	−1.6 (−3.3;0.2)[c]	**<0.001**
WDT		−0.6 (−2.3;0.5)[ab]	−0.5 (−1.7;1.5)[a]	−1.2 (−2.1;0.4)[b]	−1.7 (−2.6;0.0)[c]	**<0.01**
TSL		−0.5 (−2.0;0.8)[a]	−0.2 (−1.6;1.4)[a]	−1.1 (−2.2;0.3)[b]	−1.5 (−3.1;-0.1)[c]	**<0.05**
CPT		−0.2 (−1.1;1.5)[bc]	0.8 (−1.0;1.9)[a]	0.0 (−1.1;1.5)[b]	−0.7 (−1.1;1.6)[c]	**<0.05**
HPT		−0.9 (−1.9;1.3)[a]	0.2 (−1.4;3.3)[b]	−0.7 (−1.9;2.2)[a]	−1.5 (−2.0;1.4)[c]	**<0.05**
PPT		−0.6 (−2.8;0.9)[a]	−1.5 (−3.3;-0.5)[b]	−1.8 (−3.5;0.3)[b]	−1.9 (−3.8;0.5)[b]	**< 0.05**
MPT		0.6 (−2.0; 4.0)[b]	1.9 (−0.5; 2.6)[a]	0.7 (−3.3;3.1)[b]	−0.2 (−3.3; 3.0)[c]	**<0.05**
MPS		0.6 (−2.0;3.2) [a]	0.4 (−3.7;2.7)[abc]	0.1 (−3.8;3.2)[b]	−0.4 (−3.6;3.3)[c]	**<0.05**
WUR		0.2 (−1.1;1.9)	0.7 (−1.2;2.7)	0.2 (−1.5;3.3)	0.3 (−1.8;3.7)	0.720
MDT		1.2 (−0.3;2.0)[ab]	1.4 (0.4;2.0)[a]	0.9 (−2.0;2.0)[b]	0.0 (−4.2;1.8)[c]	**<0.05**
VDT		0.4 (−0.7;1.5)[a]	−0.2 (−3.7;1.0)[bc]	−0.8 (−5.6;1.4)[b]	−1.4 (−6.5;1.0)[c]	**0.01**
DMA	Normal (absent)	36 (97.3%)	23 (100.0%)	209 (95.4%)	199 (90.5%)	0.064
	Abnormal (present)	1 (2.7%)	0	10 (4.6%)	21 (9.5%)	
PHS	Normal (absent)	33 (89.2%)	18 (78.3%)	108 (49.3%)	102 (46.4%)	**<0.006**
	Abnormal (present)	4 (10.8%)	5 (21.7%)	111 (50.7%)	118 (53.6%)	

Note: p-value represents the comparison of diabetic patients without neuropathy and painful and non-painful diabetic patients (Kruskal–Wallis test for continuous variables and Pearsons chi-squared test for categorical variables); post-hoc tests: a, b, c—same letters marking values of categories within given row denote mutually statistically not different groups. Significant p values (p < 0.05) are indicated in bold type.

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MPT, mechanical pain threshold; PHS, paradoxical heat sensation; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold.

**TABLE 3** Summary of QST abnormalities—comparison of painful and non-painful groups

Parameters		Painful polyneuropathy (NRS ≥4)	Non-painful polyneuropathy (NRS <4)	p
		N = 220	N = 219	
CDT	Normal	132 (60.0%)[a]	176 (80.4%)[b]	**0.01**
	Gain	0 (0.0%)[a]	0 (0.0%)[a]	
	Loss	88 (40.0%)[a]	43 (19.6%)[b]	
WDT	Normal	158 (71.8%)[a]	204 (93.2%)[b]	**0.009**
	Gain	0 (0.0%)[a]	0 (0.0%)[a]	
	Loss	62 (28.2%)[a]	15 (6.8%)[b]	
TSL	Normal	141 (64.1%)[a]	196 (89.5%)[b]	**0.008**
	Gain	0 (0.0%)[a]	0 (0.0%)[a]	
	Loss	79 (35.9%)[a]	23 (10.5%)[b]	
CPT	Normal	219 (99.5%)	219 (100.0%)	0.99
	Gain	1 (0.5%)	0 (0.0%)	
	Loss	0 (0.0%)	0 (0.0%)	
WPT	Normal	181 (82.3%)	197 (90.0%)	0.15
	Gain	6 (2.7%)	12 (5.5%)	
	Loss	33 (15.0%)	10 (4.5%)	
PPT	Normal	113 (51.4%)	112 (51.1%)	0.93
	Gain	3 (1.4%)	4 (1.8%)	
	Loss	104 (48.2%)	103 (47.1%)	
MPT	Normal	133 (60.5%)[a]	130 (59.4%)[a]	**0.02**
	Gain	30 (13.6%)[a]	56 (25.6%)[b]	
	Loss	57 (25.9%)[a]	33 (15.1%)[b]	
MPS	Normal	116 (52.7%)	120 (54.3%)	0.48
	Gain	30 (13.6%)	46 (38.7%)	
	Loss	74 (33.7%)	54 (24.7%)	
WUR	Normal	185 (84.1%)	186 (84.9%)	0.97
	Gain	33 (15.0%)	33 (15.1%)	
	Loss	2 (0.9%)	0 (0.0%)	
MDT	Normal	185 (84.1%)	194 (88.6%)	0.13
	Gain	5 (2.3%)	11 (5.0%)	
	Loss	30 (13.6%)	14 (6.4%)	
VDT	Normal	135 (61.4%)	155 (70.8%)	0.05
	Gain	0 (0.0%)	0 (0.0%)	
	Loss	85 (38.6%)	64 (29.2%)	
DMA	Absence	213 (94.1%)	218 (95.7%)	0.85
	Gain	7 (5.9%)	0 (0.0%)	
	Loss	0 (0.0%)	1 (4.3%)	

Note: p-value represents the comparison of patients with different levels of pain (Pearsons chi-squared test), post-hoc tests: a, b—same letters marking the values within a given row denote mutually statistically not different groups. Significant p values (p < 0.05) are indicated in bold type.

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

decrease the diversity of included patients as a source of limitation of QST findings (Baron et al., 2012; Bordeleau et al., 2021; Forstenpointner et al., 2021; Üçeyler et al., 2018). Üçeyler et al. (Üçeyler et al., 2018) analysed groups of painful and non-painful polyneuropathies and small fibre polyneuropathies (SFNs) of different
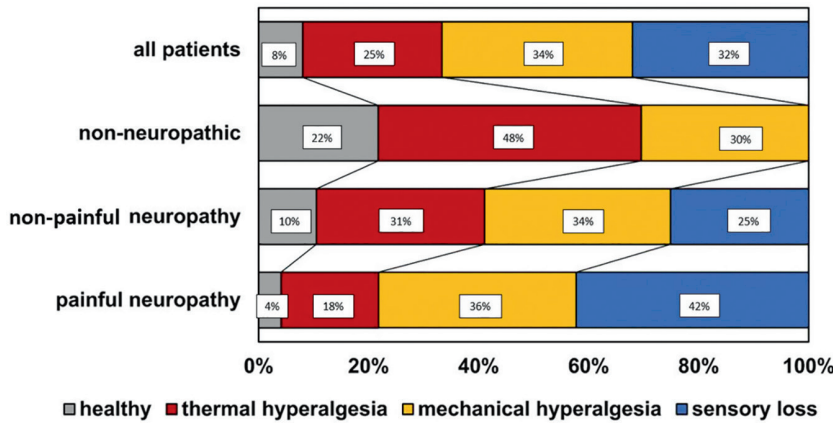
FIGURE 3 Phenotype frequencies in subgroups of diabetic patients.
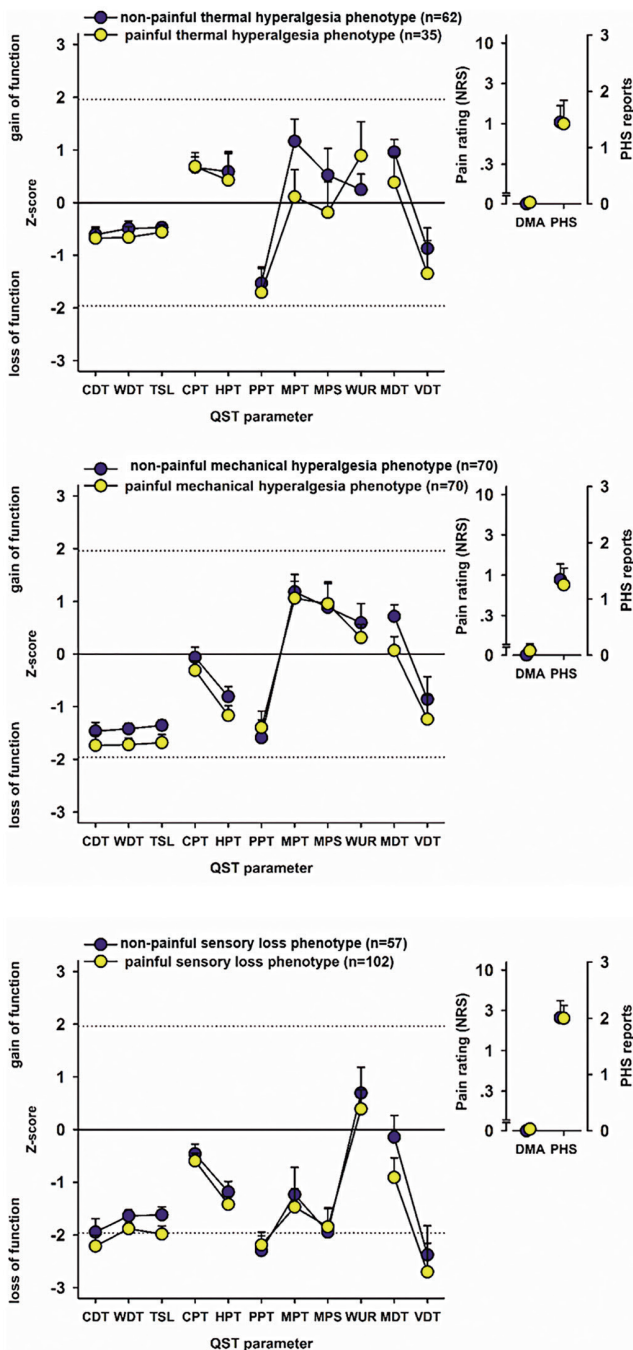
FIGURE 4 Quantitative sensory testing profiles from feet of diabetic patients with painful and non-painful polyneuropathy within predetermined sensory phenotypes. The sensory profile shows thermal detection thresholds (first block), pain thresholds (second block), MPTs (third block) and MDTs (fourth block), together with allodynia and presence of PHSs (small graphs). Presented mean z scores ±95% confidence interval revealed differences between diabetic subgroups in several QST parameters. Sensory phenotypes of painful and non-painful diabetic polyneuropathy are compared in subgroups classified as thermal hyperalgesia (upper graph), mechanical hyperalgesia (middle graph) and sensory loss phenotypes (lower graph). CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, numerical rating scale; PHS, paradoxical heat sensation; PNP, polyneuropathy; PPT, deep pain sensitivity to blunt pressure; QST, quantitative sensory testing; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

aetiology. The SL phenotype dominated in polyneuropathies while TH phenotypes prevailed in SFN. QST did not distinguish between polyneuropathies of different aetiology or painful and non-painful neuropathies regarding small fibre function but revealed higher mechanical pain ($p < 0.01$) and detection thresholds ($p < 0.05$) and lower MPS in the group of patients with painful neuropathies (Üçeyler et al., 2018).

It has already been shown that the diabetic polyneuropathy sensory phenotype is characterized by hyposensitivity to applied stimuli that was more marked in the moderate/severe NeuP group than in the mild NeuP or no NeuP groups (Raputova et al., 2017; Themistocleous et al., 2016). The greatest loss of especially thermoalgesic function is in concordance with the concept of the pathophysiology of peripheral neuropathic pain with a lesion or disease of thermoalgesic small fibres being a prerequisite for a definite diagnosis of neuropathic pain. In addition,

painful diabetic neuropathy patients also showed a greater loss of mechanical and vibration detection functions, supporting the assumption that painful diabetic neuropathy represent cases with more severe neuropathy. Loss of function of all sensory modalities are, however, also present in non-painful diabetic neuropathy with significant overlap with painful cases that prevent predicting the development of neuropathic pain and sometimes even discriminating between painful and non-painful neuropathy patients on a group level.

In response to the limited ability of QST to differentiate between painful and non-painful conditions (Forstenpointner et al., 2021), a lively discussion ensued on the value of QST to differentiate non-painful and painful conditions and to offer insight into mechanisms of the pathophysiology of neuropathic pain leading to tailored mechanism-based pharmacotherapy (Bordeleau et al., 2021; Schmelz, 2021a, 2021b; Vollert et al., 2021; Vollert & Schmelz, 2021). A dissonance between evoked and spontaneous pain, symptoms and signs and laboratory tests and patient-reported impressions are the key aspects that have been discussed (Vollert & Schmelz, 2021).

One of the key questions is whether pain directly affects sensory profiles. Gain of function abnormalities and the irritable nociceptor phenotype were found in a small proportion of patients with painful diabetic polyneuropathy: in 6.3% by Themistocleous et al. (Themistocleous et al., 2016) and in 14.6% by Raputova et al. (Raputova et al., 2017). A recent multicentre study in different painful and non-painful peripheral and central conditions revealed overall very similar sensory profiles in patients with and without spontaneous pain (Forstenpointner et al., 2021). Furthermore, it revealed the presence of hyperalgesia and allodynia in patients with central and peripheral lesions of the somatosensory system not reporting spontaneous pain. This shows that symptoms and signs of hypersensitivity may not necessarily coincide and that painful and non-painful neuropathic conditions may mechanistically blend into one another. Interestingly, hypoalgesia was more pronounced in painful polyneuropathy, whereas hyperalgesia was more frequent in painful mononeuropathies (compared with non-painful conditions) (Forstenpointner et al., 2021). Our results in a more homogenous cohort of diabetic polyneuropathy patients are similar: the proportion of 'gain of function' abnormalities of thermoalgesic and mechanoalgesic modalities including the proportion of DMA are similar in painful and non-painful diabetic polyneuropathy subgroups. The sensory profiles within the frames of predefined sensory phenotypes again shows very similar pattern in both non-painful and painful diabetic polyneuropathy patients (see Figure 4).

Interestingly, we found higher mechanical pain thresholds and a trend towards lower MPS in the group of patients with pDSPN, which is surprising, but similar to the differences between painful and non-painful polyneuropathies of different origin as published by Üçeyler et al. (Üçeyler et al., 2018). Moreover, this difference is particularly expressed in a subgroup classified as a TH phenotype, which is probably due to a definition of predefined phenotypes (see Figure 4). Even more interestingly, the DM subgroup displayed significantly higher z-scores of CPT, HPT and MPT in comparison with the HC subgroup, and TH phenotype was the most frequent pattern found in almost half of DM patients (47.8%). Similar hypersensitivity was shown using intracutaneous electrical stimulation of C-fibres and scanning the axon reflex mediated flare in diabetic patients without polyneuropathy (Krämer, Schmelzl, et al., 2004). We may speculate that patients with DM might represent a 'precondition' of DSPN, clinically asymptomatic but with ongoing subclinical processes (inflammation) leading to thermal (and mechanical) sensitisation. If PNP progresses, nerve degeneration becomes more and more important so there is little indication for TH anymore in QST.

These findings ignite discussion on the possibilities and limitations of QST within the larger picture of the relationship between nociception and pain and will promote further debate on the divergent perspectives and conceptual approaches leading to the currently available tools and possibly identifying the need for new developments (Vollert et al., 2021; Vollert & Schmelz, 2021).

The small size and relative youth of the DM patient cohort compared with the much larger nDSPN and pDSPN cohorts is a limitation of this study. We found it very difficult to collect reasonably larger DM cohorts with ages comparable with that of the DSPN cohorts, as most subjects with an established diagnosis of DM and no clinical symptoms or signs of polyneuropathy displayed at least some subclinical EMG abnormalities. We believe that our statistical analysis took these limitations into account.

To define the painful diabetic polyneuropathy subgroup (i.e. chronic ongoing definite neuropathic pain) we chose a NRS cut-off value of >4 and also criteria for probable or definite NeuP. Those diabetic polyneuropathy patients who did not comply with this criteria formed the non-painful nDSPN group with no neuropathic pain (including a small proportion of patients with NRS 1–3—i.e. mild pain). We used this definition of the pDSPN group because previous analyses showed that the sensory profiles of these mild pain cases are close to those of non-painful cases and different from moderate-to-severe ('true') painful cases. Moreover, in patients with low NRS scores (i.e. 1–3), it is frequently difficult to distinguish between true pain and other positive sensory symptoms,

such as paresthesias or dysesthesias. An additional calculation of the differences in QST parameters using the redefined non-painful group (after excluding 'mild pain') showed practically the same results (Table 1S).

In conclusion, QST profiles and phenotypes in diabetic polyneuropathy show very similar and overlapping patterns in painful and non-painful patients with a trend towards more severe loss of both thermal and mechanical sensory modalities in painful patients. These findings support the theory that painful diabetic polyneuropathy might be the 'worse' or 'more progressed' type over non-painful and reflect the ability of QST to detect small fibre neuropathy as a key element in the diagnosis of neuropathic pain (Schmelz, 2021a). QST analysis of hypersensitivity abnormalities in patients with painful and non-painful diabetic polyneuropathy currently adds limited support to understanding the pathophysiology of spontaneous neuropathic pain, which probably reflects diverse mechanisms of chronic ongoing pain and acutely evoked pain. Signs of thermal and mechanical hypersensitivity in diabetic patients without polyneuropathy needs further confirmation.

AUTHOR CONTRIBUTIONS

J. Raputova wrote the original manuscript; was involved in the literature review, data collection, data interpretation and data analysis; prepared most of the graphs; contributed to drafting the article and reviewed/edited the manuscripts. J. Vollert was involved in the calculation of prototypic sensory phenotypes; suggested and prepared some of the graphs; contributed to drafting the article and reviewed/edited the manuscripts. A. Rajdova, I. Srotova, C. Rebhorn, N. Üçeyler, F. Birklein and C. Sommer researched data, discussed the results and commented on the manuscript. E. Vlckova contributed to the study design, data acquisition, data interpretation, data analysis, drafting the article and reviewing/editing the manuscript. J. Bednarik designed the study, interpreted data and co-wrote the original manuscript. As a guarantor of this work, he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors substantially contributed to the study design and data acquisition or to data analysis and interpretation, contributed to drafting or editing the article, discussed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST

Jan Vollert received consulting fees from Casquar, Vertex Pharmaceuticals and Embody Orthopaedics, outside of the submitted work. Other authors have no conflict of interest to declare.

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