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Test–retest reliability of a simple bedside-quantitative sensory testing battery for chronic neuropathic pain

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Abstract

Introduction: The sensory phenotype is believed to provide information about the underlying pathophysiological mechanisms and to be used in the diagnosis and treatment of chronic neuropathic pain. However, the use of standardized quantitative sensory testing (QST) protocols is limited due to high expenditures of time and costs. Thus, a simple bedside-QST battery was recently developed showing good agreement when compared with laboratory QST. The aim of this study was to preliminary validate this bedside-QST protocol.

Methods: Patients experiencing chronic pain with neuropathic features (n = 60) attended 3 visits. During the first visit, laboratory QST and bedside-QST were performed by the same trained investigator. Three hours and 3 weeks later, bedside-QST was repeated. Patients completed questionnaires regarding their pain (intensity, quality), depression/anxiety, and quality of life. Test–retest reliability and convergent/divergent validity were investigated.

Results: Most of the bedside-QST parameters, including also those recommended in our first study as being indicative for sensory phenotypes, revealed a moderate to excellent test–retest reliability. Overall, results for short-term reliability and interval-scaled parameters were slightly better. Most of the bedside-QST parameters did not correlate with the depression and anxiety score, suggesting a good divergent validity.

Conclusions: Bedside-QST has good criterion and divergent validity as well as reliability. This battery consists of 5 low-cost devices that can be quickly and easily used to characterize the sensory phenotype of patients with neuropathic pain. A combination of bedside-QST parameters can be used to investigate patients' subgroups with specific pathophysiological mechanisms and to identify treatment responders.

Keywords: Bedside sensory testing, Quantitative sensory testing, Neuropathic pain, Reliability, Preliminary validation, DFNS

1. Introduction

Patients with chronic neuropathic pain experience a wide range of symptoms including positive (spontaneous/evoked pain, hyperalgesia, and allodynia) and negative sensory symptoms (hypoesthesia, hypoalgesia). These symptoms are often accompanied by comorbidities such as depression and impaired physical functioning, resulting in an overall reduced quality of life and significant burden for patients. Even first-line drugs often do not provide sufficient pain relief.[8] Moreover, several encouraging new drugs have failed recently in clinical trials. One reason for this dilemma might be that chronic neuropathic pain syndromes are multifaceted disorders with different pathophysiological mechanisms, variably expressed in each individual independent of the underlying disease. Consequently, neuropathic pain syndromes should be grouped based on the

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underlying pathophysiological mechanisms of pain generation rather than on the disease etiology to establish a so-called mechanism-based treatment.[19,28] Because no biomarkers of pain mechanisms have been discovered so far, one has to rely on surrogate markers that are believed to be closely linked to mechanisms of pain generation.[1,25]

One promising surrogate marker for dysfunction in pain pathways is the pattern of sensory symptoms and signs (sensory profile), as stratification approach[2,26] and potential predictive biomarker for treatment response.[5,11,23] The quantitative sensory testing (QST) protocol by the German Research Network on Neuropathic Pain (DFNS) is a standardized and valid method for neuropathic pain characterization through detection of sensory abnormalities of small and large nerve fibers or their corresponding pathways.[22] This protocol allows subgrouping of patients into 3 clusters based on their somatosensory profiles, which are assumed to respond differentially to specific therapeutics.[2] Consequently, the European Medicines Agency (EMA) has acknowledged in a Committee for Medicinal Products for Human Use qualification advice that sensory profiling and subgrouping of patients is an adequate stratification tool for determining specific sensory phenotypes of patients in exploratory trials on neuropathic pain.[6]

However, the use of the laboratory DFNS QST protocol (lab-QST) is limited to specialized centers due to high expenditures of time and costs and the need for training. To overcome these limitations and implement this profiling approach in clinical phase III trials and clinical practice, it is of utmost importance to develop an easy-to-use bedside assessment protocol. Recently, we presented a simple bedside-QST with good concurrent criterion validity, ie, correlation with lab-QST, which allows assignment to the 3 lab-QST clusters.[21] To establish this bedside-QST battery for its use in clinical practice and large trials, this study aimed at assessing its test–retest reliability and convergent/divergent validity.

2. Methods

2.1. Study cohort

A total of 60 patients (34 men and 26 women) experiencing chronic pain with neuropathic features for at least 3 months were included. Only adults (aged 18 years or older) with sufficient German knowledge were included. Exclusion criteria were as follows: severe depression, alcohol or drug abuse, fibromyalgia, and other pain disorders within the same testing areas that may interfere with the pain ratings. Patients were recruited from the study centre's internal patient pool and through flyers placed in pharmacies and neurological medical practices. An expense allowance of 50€ was paid out, as well as parking fees and/or travel costs.

2.2. Study design

Patients attended the study site for 3 visits over 2 days, twice at the first day and again after approximately 3 weeks (**Fig. 1**). During the first visit (t1), demographic and clinical data, including pre-existing diseases, operations, (pain) medication, and pain duration, were collected. The exact pattern of symptoms, as well as pain-influencing factors, were elaborated. Pain intensity was rated on an 11-point numerical rating scale (NRS), recording the average, minimum, and maximum pain intensity during the past 24 hours before the study visit (0 = no pain; 10 = the worst pain imaginable).

Patients underwent a clinical neurological examination to define the most affected area and to map changes over the course of the 3 weeks. Afterwards, both the lab-QST and then the bedside-QST were performed. After 3 hours, the bedside-QST was repeated (t2, short-term reliability). Approximately 3 weeks later (3 ± 1 week), patients attended the study site for a third visit (t3). After a short interview regarding changes in pain, overall health state and medication, and a clinical neurological examination, patients underwent again both the lab-QST and the bedside-QST (long-term reliability).

Bedside-QST and lab-QST were performed first in a non-affected, contralateral control area and afterwards in the most affected area (area of maximum pain). In case of a symmetric disease, the control examination was performed in a contralateral proximal area, eg, patients with a distal symmetric painful polyneuropathy were tested at the dorsum of the feet (test area) and the contralateral thigh (control area).

After both study days, patients filled out questionnaires regarding their pain intensity and quality, health, depression/anxiety, and quality of life. At t3, patients were asked about their pain course compared with that at t1 using the Patient's Global Impression of Change (PGIC; 1 = very much improved, 2 = moderately improved, 3 = minimally improved, 4 = unchanged, 5 = minimally worse, 6 = moderately worse, and 7 = very much worse).[10] The whole examination including clinical examination, and sensory testing was performed by the same examiner, who received adequate training in both testing procedures by a QST-experienced neurologist-in-training before the participants' enrollment. The same neurologist also provided supervision during the study to ensure standardized performance of testing.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee of the University Hospital of Kiel (AZ: D454/15). Before study entry, all participants gave their written informed consent.

2.3. Questionnaires

The painPREDICT questionnaire is a self-administered questionnaire that consists of 20 items covering different nociceptive and neuropathic aspects of pain, ie, pain intensity, location of pain, course of pain, and sensory symptoms rated on a 10-point NRS.[24]

The EQ-5D-5L questionnaire is a generic measurement of health-related quality of life.[7] It consists of 2 parts. The descriptive system includes 5 dimensions that are rated on a 5-point Likert scale (1 = no problem to 5 = unable/extreme problems). Based on the ratings, a 5-digit code can be calculated that reflects the patient's health state. This 5-digit code can be used to generate a country-based index value ranging from −0.661 = worst possible score to 1 = best possible score.[17] In addition, patients rate their current health state on a visual analogue scale (EQ VAS) ranging from 100 = the best health you can imagine to 0 = the worst health you can imagine.

The Hospital Anxiety and Depression Scale (HADS) is used to screen for the presence of anxiety and depression in patients with chronic diseases.[30] It consists of 14 items that are used to build 2 subscores, one for depression (HADS-D) and the other for anxiety (HADS-A). Optimal cutoff levels for possible anxiety and depressive disorders are scores ≥ 8.[3]

2.4. Laboratory quantitative sensory testing

Lab-QST was performed according to the standardized protocol of the DFNS.[22] Different thermal and mechanical sensory stimuli were applied to skin or deep somatic structures to elicit a sensory sensation (painful or nonpainful), which was evaluated by the

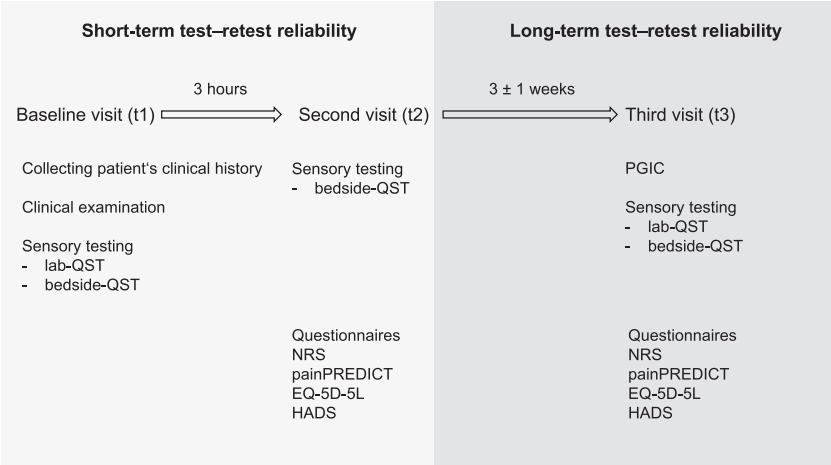

Figure 1. Study protocol. HADS, Hospital Anxiety and Depression Scale; NRS, numerical rating scale; PGIC, Patient's Global Impression of Change.

patients according to distinct criteria (intensity, painfulness). The DFNS protocol consists of 13 parameters, assessed by 7 different test devices (Supplement Table 1, available at http://links.lww.com/PR9/A179):

cold detection threshold and warm detection threshold (CDT, WDT), cold pain threshold and heat pain threshold (CPT, HPT), thermal sensory limen (TSL), presence of paradoxical heat sensations (PHS), mechanical pain threshold (MPT) and mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), pressure pain threshold (PPT), wind-up ratio (WUR), tactile (mechanical) detection threshold (MDT), and vibration detection threshold (VDT).

For statistical analysis, lab-QST *z* values were calculated that allow direct comparison with sex-matched, age-matched, and body-matched reference values of healthy controls.[14] *Z* scores of zero represent the mean value of healthy controls, *z* scores above "0" indicate a gain of function (hyperalgesia), and *z* scores below "0" indicate a loss of function (hypoesthesia, hypoalgesia). *Z* values exceeding the 95% confidence interval of reference data were defined as abnormal loss (<-1.96) or gain ($>+1.96$). Because DMA and PHS are absent under physiological conditions, calculation of *z* values is not possible. Instead, original (DMA = 0–100 numeric rating scale; PHS = numbers of PHS from 0 to 3) and dichotomous values (absent = normal; present = abnormal) were used.

2.5. Bedside-quantitative sensory testing

Bedside-QST follows a simple protocol using 11 cheap and easy-to-use devices (Supplement Table 1, available at http://links.lww.com/PR9/A179). Parameters that had achieved poor results in the previous study were excluded (brush, cotton-wool ball, 0.4-mm CMS hair). Thus, a simplification of the protocol was achieved. Because results of the 0.7-mm CMS hair were shown to be training dependent,[21] the original protocol was complemented by the inclusion of a more standardized device, ie, the Neuropen, to test for pinprick hyperalgesia and temporal pain summation. A filament of the same device was also used for statical mechanical detection in addition to the 64-mN von Frey hair. Overall, patients had to rate (1) whether the stimulus was perceived/not perceived or painful/not painful (yes/no) and (2) the perception or pain intensity of each stimuli using an 11-point NRS (0 = no perception/no pain, 10 = strongest imaginable perception/strongest imaginable pain). A painful stimulus was defined as any burning, stinging, aching, or drilling sensation. For application details of the single stimuli, see Supplement material (available at http://links.lww.com/PR9/A179).

2.6. Statistical analysis

Statistical analysis was performed using IBM SPSS statistics for Windows (Version 25.0, NY).

Descriptive analysis of bedside-QST parameters was performed by calculating minimum, maximum, and average values, standard deviations for interval-scaled parameters (NRS-11), and frequencies/detection rates for dichotomized parameters (painful/perception, yes/no).

To confirm results of our first study and to investigate properties of the newly included bedside-QST tools, comparison of lab-QST and bedside-QST parameters was repeated as previously described.[21] In brief, sensitivity/specificity, Spearman correlation coefficients, and receiver-operating characteristics (ROCs) were calculated.

Test–retest reliability of bedside-QST parameters was examined for short-term (t1–t2) and long-term (t1–t3) periods. Long-term test–retest reliability was calculated only for patients who indicated no change in their pain intensity between both study days (t1–t3) on the PGIC scale (PGIC = 4). Test–retest reliability of interval-scaled parameters (perception/pain intensity rating; NRS 0–10) was assessed using the intraclass correlation coefficient (ICC) under the random effect model according to Koo and Li: ICC of >0.9 = excellent, >0.75 = good, >0.5 = moderate, and <0.5 = poor correlation.[14] The test–retest reliability of dichotomous parameters (painful or perception, yes/no) was performed using the Cohen Kappa coefficient according to Landis and Koch: Cohen Kappa of 0.81–1.0 = almost perfect, 0.61–0.8 = substantial, 0.41–0.6 = moderate, 0.21–0.4 = fair, 0 to 0.2 = light, and <0 = poor correlation.[16]

Convergent/divergent validity was calculated by comparing the relationship of average pain intensity (NRS) and HADS scores with the bedside-QST items using the Spearman correlation coefficient. *P* values <0.05 were considered statistically significant. Based on comparing 2 ratings each, an estimated average ICC between measurements of 0.5, a desired power of 80%, and an alpha level of 0.05, Bonferroni corrected for the number of reliability assessments, a sample size of n = 60 was determined to be sufficient and robust to up to 10% dropouts.

3. Results

3.1. Characteristics of the study cohort

All included patients (n = 60, 58.1 ± 15.4 years, 34 males, 26 females) completed all 3 study visits. Baseline demographic and clinical features are summarized in **Table 1**. Patients experienced different etiologies, most frequently painful polyneuropathy. Most

of the patients (65.0%) reported no change in pain between t1 and t3, while the pain decreased in 8 (13.2%) and increased in 13 patients (21.7%).

It took a maximum of 23 minutes to perform complete bedside-QST in 2 body areas (control and test area). Sensory testing was most frequently performed in the feet (test area) and the thigh (control area). Most of the reported symptoms assessed within the battery of questionnaires remained relatively stable between the 2 study days (t1 and t3) (**Table 2**). The average pain intensity during the past 24 hours before testing was scored on average with 4/10 on the NRS on both study days. The most frequently reported symptoms of the painPREDICT questionnaire were spontaneous numbness (71.4%, 75.0%) and spontaneous tingling sensations (70.0%, 67.9%). Rather uncommonly reported symptoms were spontaneous itching (25.0%, 19.6%) and pain evoked by something warm (26.8%, 23.2%). The general health state (EQ-5D-5L) revealed an average index value of 0.7, indicating a rather little impaired health-related quality of life, although with a wide range from 0.1 to 0.9. More than half of the patients did not show any evidence for anxiety or depression.

3.2. Laboratory quantitative sensory testing results

The patient cohort was dominated by profound negative sensory signs, ie, abnormal loss to nonpainful thermal (cold detection threshold and warm detection threshold, TSL) and mechanical parameters (mechanical detection threshold and vibration detection threshold) (**Fig. 2**). Positive sensory signs were less frequently observed (most often pressure pain hyperalgesia and paradoxical heat sensations). Other positive sensory signs such as thermal hyperalgesia or pinprick hyperalgesia were rare overall.

3.3. Bedside-quantitative sensory testing results

Table 3 summarizes the results of the descriptive analysis of all bedside-QST parameters. Note that for some bedside-QST parameters, the detection rate was low, ie, PHS to 22 and 8°C metal, thermal hyperalgesia to 22 and 37°C. Comparison of lab-QST vs bedside-QST revealed similar results as previously described.[21] All parameters with good discriminative values in the previous study, ie, "loss of cold perception to 22°C metal," "hypersensitivity towards 45°C metal," "loss of tactile perception to Q-tip," "loss of pain perception to 0.7 mm CMS hair," and "Q-tip allodynia" showed comparable sensitivity and specificity values (Supplement Table 2, available at http://links.lww.com/PR9/A179). The new tools (Neuropen/Neurotip) showed comparable results to their counterpart in the original bedside-QST (64 mN von Frey hair/CMS hair).

3.4. Short-term and long-term test–retest reliability

For analysis of the short-term test–retest reliability, all 60 bedside-QST data sets were used; for the long-term test-retest reliability analysis, 39 data sets were included (PGIC pain = 4). With few exceptions, all interval-scaled parameters collectively showed a moderate to excellent agreement with slightly better results for the short-term reliability and for mechanical parameters (**Table 4**). Most of the dichotomous bedside-QST parameters revealed moderate to almost perfect test–retest reliability, although with some few exceptions (metal 22°C PHS, metal 22°C pain intensity, and metal 37°C perception/pain intensity) (**Table 5**).

3.5. Convergent/divergent validity

Correlations of bedside-QST parameters with average pain intensity and HADS-A and HADS-D subscores are summarized in **Table 6**. Only few significant but overall weak correlations ($r \leq 0.4$) were detected: anxiety with 22/8°C cold perception and 22°C cold pain intensity, depression with 22°C cold perception intensity and 8°C cold pain intensity, and average pain intensity with 8°C cold pain intensity, DMA allodynia, and postallodynia sensation pain intensity.

Table 1

Patient characteristics.

Age [mean ± SD] (range)	58.0 ± 15.3 (21–82)
Sex [n] (%)	
Male	34 (56.7)
Female	26 (43.3)
BMI [mean ± SD] (range)	27.9 ± 6.4 (18.3–56.9)
Pain duration, y [mean ± SD] (range)	4.3 ± 4.4 (0.3–22)
Diagnosis [n] (%)	
Polyneuropathy	30 (50.0)
Postherpetic neuralgia	7 (11.7)
Central pain (ependymoma, syringomyelia, ganglioglioma surgery)	3 (5.0)
Complex regional pain syndrome (CRPS)	8 (13.3)
Peripheral nerve injury	3 (5.0)
Posttraumatic neuropathic pain	4 (6.7)
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	1 (1.7)
Trigeminal neuropathy	1 (1.7)
Carpal tunnel syndrome	1 (1.7)
Unspecified sensory deficitis	2 (3.3)
Pain medication [n] (%)	
Yes (at least 1)	44 (73.3)
No	16 (26.7)
NSAID	8 (13.3)
Metamizol	8 (13.3)
Opioids	10 (16.7)
Anticonvulsants	29 (48.3)
Antidepressants	14 (23.3)
Local anesthesia	11 (18.3)
Cannabinoids	2 (3.3)
Number of pain medications [mean ± SD] (range)	1.5 ± 1.4 (0–5)
Test side [n] (%)	
Foot	35 (58.3)
Hand	12 (20.0)
Trunk	5 (8.3)
Face	3 (5.0)
Forearm	2 (3.3)
Shoulder	1 (1.7)
Thigh	1 (1.7)
Lower leg	1 (1.7)
Control side [n] (%)	
Thigh	33 (55.0)
Hand	11 (18.3)
Trunk	5 (8.3)
Foot	3 (5.0)
Face	3 (5.0)
Forearm	2 (3.3)
Shoulder	1 (1.7)
Lower leg	1 (1.7)
Upper arm	1 (1.7)
Relation between test and control side [n] (%)	
Contralateral	27 (45)
Other	33 (55)
Duration of bedside-QST, min [mean ± SD] (range)*	17.4 ± 2.4 (12–23)

* Data are only shown for the first visit (t1).
NSAID, Nonsteroidal anti-inflammatory drugs.

Table 2

Questionnaire results comparing both study days.

Questionnaire	First study day (t1, t2)	Second study day (t3)	*P*
24 hours pain intensity NRS [mean ± SD] (range)			
Average (n = 59)	4.2 ± 2.6 (0–10)	4.3 ± 2.5 (0–9)	0.729
Minimum (n = 58)	1.6 ± 1.7 (0–5)	1.7 ± 2.1 (0–7)	0.338
Maximum (n = 58)	6.7 ± 3.0 (0–10)	5.9 ± 3.0 (0–10)	**0.001**
PainPREDICT [mean ± SD] (yes, %)			
Average pain in last 7 d	4.3 ± 2.2	4.3 ± 2.1	0.712
Worst pain in last 7 d	6.2 ± 2.7	6.1 ± 2.6	0.507
Spontaneous burning sensation	3.5 ± 3.5 (57.1)	3.6 ± 3.3 (62.5)	0.876
Spontaneous tingling sensation	3.9 ± 3.1 (70.0)	3.3 ± 3.2 (67.9)	**0.016**
Spontaneous itching	1.1 ± 2.4 (25.0)	0.8 ± 2.1 (19.6)	0.294
Spontaneous numbness	4.5 ± 3.7 (71.4)	4.6 ± 3.5 (75.0)	0.956
Spontaneous pain in numb areas (6 missing values)	3.1 ± 3.4 (53.6)	3.4 ± 3.4 (58.9)	0.315
Spontaneous cold sensation	2.7 ± 3.4 (46.4)	2.8 ± 3.2 (51.8)	0.983
Squeezing	2.8 ± 3.1 (57.1)	2.7 ± 3.0 (53.6)	0.686
Deep pressure sensation	3.2 ± 3.4 (55.4)	3.1 ± 3.3 (53.6)	0.950
Swelling feeling (5 missing values)	2.9 ± 3.4 (51.8)	2.8 ± 3.2 (55.4)	0.954
Tense muscles	3.0 ± 3.6 (48.2)	3.5 ± 3.8 (53.6)	0.131
Sudden pain that occurred for no particular reason	4.4 ± 3.7 (64.3)	3.5 ± 3.7 (51.8)	**0.024**
Sudden pain caused by moving, staying in the same position, or changing positions	4.2 ± 3.7 (62.5)	4.0 ± 3.7 (60.7)	0.431
Pain when brushed against lightly	2.2 ± 3.1 (44.6)	2.0 ± 3.1 (39.3)	0.307
Pain by slight pressure	2.8 ± 3.1 (53.6)	2.4 ± 2.9 (50.0)	0.343
Pain caused by a pointed object touching (nb = 5)	2.3 ± 3.2 (41.8)	2.3 ± 3.3 (44.6)	0.730
Pain by something cold	2.1 ± 3.0 (42.9)	2.1 ± 2.9 (42.9)	0.987
Pain by something warm	1.2 ± 2.2 (26.8)	1.3 ± 2.7 (23.2)	0.652
EQ-5D-5L			0.143
Index value (−0.661–1) [mean ± SD] (range) (n = 56)	0.7 ± 0.3 (−0.2–0.9)	0.7 ± 0.3 (−0.0–1.0)	
VAS	57.9 ± 21.3 (15–95)	56.4 ± 20.7 (10–95)	
HADS-A score [mean ± SD] (range)	5.9 ± 4.4 (0–19)	5.5 ± 4.6 (0–19)	0.252
Conspicuous (≥8) [n] (%)	20 (33.3)	21 (35.0)	
Inconspicuous (<8) [n] (%)	40 (66.7)	39 (65.0)	
HADS-D score [mean ± SD] (range)	5.6 ± 3.6 (0–15)	5.9 ± 4.2 (0–15)	0.186
Conspicuous (≥8) [n] (%)	15 (25.0)	22 (36.7)	
Inconspicuous (<8) [n] (%)	45 (75.0)	38 (63.3)	
PGIC			
Pain decreased (1–3) [n] (%)	8 (13.3)		
No change (4) [n] (%)	39 (65.0)		
Pain increased (5–7) [n] (%)	13 (21.7)		

n = 4 missing values for t1 and/or t3 for all questionnaires except for the NRS and PGIC. Differences for mean values of questionnaires comparing t1 and t3 were calculated using the Wilcoxon test ($P < 0.05$ = significant). Significant correlations are marked in bold.

NRS, numerical rating scale; HADS, hospital anxiety and depression scale; PGIC, Patient's Global Impression of Change.

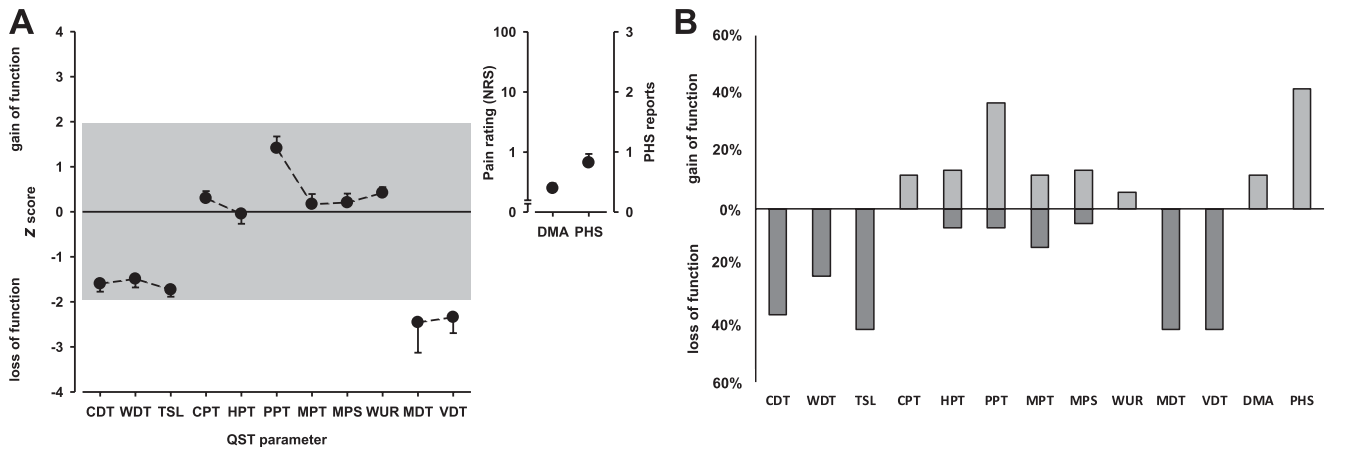

Figure 2. Lab-QST in patients (n = 60). (A) Somatosensory profile. (B) Frequencies of abnormal values. QST, quantitative sensory testing. CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; PHS, paradoxical heat sensation; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

Table 3

Descriptive analysis of bedside-quantitative sensory testing (QST) parameters (test side).

Bedside-QST	Visit	n	Min	Max	Mean (±SD)	Detection rate (yes; n, %)
Thermal parameters						
Metal 22°C Perception intensity	t1	60	0	8	2.3 (±2.4)	39 (65)
	t2	60	0	6	2.0 (±1.7)	45 (75)
	t3	60	0	8	2.2 (±2.3)	40 (66.7)
Metal 22°C Paradoxic heat sensation	t1	60	—	—	—	3 (5)
	t2	60				1 (1.7)
	t3	60				2 (3.3)
Metal 08°C Perception intensity	t1	60	0	10	3.3 (±2.5)	53 (88.3)
	t2	60	0	10	3.4 (±2.5)	52 (86.7)
	t3	60	0	10	3.3 (±2.6)	50 (83.3)
Metal 08°C Paradoxic heat sensation	t1	60	—	—	—	4 (6.7)
	t2	60				3 (5.0)
	t3	60				3 (5.0)
Metal 37°C Perception intensity	t1	60	0	8	2.3 (±2.3)	44 (73.3)
	t2	60	0	8	2.4 (±2.2)	44 (73.3)
	t3	60	0	8	2.1 (±2.3)	40 (66.7)
Metal 45°C Perception intensity	t1	60	0	10	4.4 (±3.2)	48 (80)
	t2	60	0	10	4.5 (±3.2)	50 (83.3)
	t3	60	0	10	4.4 (±3.1)	52 (86.7)
Metal 22°C Pain intensity	t1	59*	0	8	0.8 (±1.9)	11 (18.3)
	t2	60	0	6	0.2 (±0.9)	4 (6.7)
	t3	59*	0	6.5	0.6 (±1.5)	11 (18.3)
Metal 08°C Pain intensity	t1	60	0	9.5	0.9 (±2.2)	13 (21.7)
	t2	59*	0	7	0.7 (±1.6)	11 (18.3)
	t3	60	0	9	0.8 (±1.9)	12 (20.0)
Metal 37°C Pain intensity	t1	60	0	3	0.1 (±0.6)	4 (6.7)
	t2	60	0	4	0.4 (±1.0)	9 (15.0)
	t3	60	0	6	0.3 (±1.0)	6 (10.0)
Metal 45°C Pain intensity	t1	60	0	10	1.4 (±2.3)	24 (40)
	t2	60	0	9	1.8 (±2.5)	28 (46.7)
	t3	60	0	8	2.3 (±2.7)	30 (50.0)
Mechanical parameters						
Q-tip Perception intensity	t1	60	0	20	10 (±5.6)	37 (61.7)
	t2	60	0	20	9.8 (±5.4)	41 (68.3)
	t3	60	0	20	9.4 (±5.2)	38 (63.3)
CMS 0.7 mm Pain intensity	t1	60	0	10	2.4 (±2.2)	49 (81.7)
	t2	60	0	9	2.3 (±2.1)	48 (80.0)
	t3	60	0	10	2.7 (±2.6)	51 (85.0)
Neurotip Pain intensity	t1	56†	0	10	2.3 (±2.2)	44 (78.6)
	t2	56†	0	9	2.4 (±2.3)	45 (80.4)
	t3	56†	0	10	2.9 (±2.7)	47 (83.9)
Neuropen monofilament Perception intensity	t1	56†	—	—	—	43 (71.7)
	t2	56†				45 (80.4)
	t3	56†				46 (82.1)
von Frey hair 64 mN Perception intensity	t1	60	—	—	—	49 (81.7)
	t2	60				52 (86.7)
	t3	60				47 (78.3)
Q-tip allodynia Pain intensity	t1	60	0	6	0.8 (±1.7)	15 (25.0)
	t2	60	0	9	0.7 (±1.7)	12 (20.0)
	t3	60	0	8	1.0 (±2.0)	18 (30.0)
Q-tip postallodynia sensation Pain intensity	t1	60	0	9	1.1 (±2.0)	20 (33.3)
	t2	60	0	8	1.4 (±2.2)	21 (35.0)
	t3	60	0	8	1.4 (±2.2)	24 (40.0)
CMS 0.7 mm WUR single stimulus Pain intensity	t1	56	0	8	2.0 (±1.8)	—
	t2	56	0	7	2.1 (±1.7)	
	t3	56	0	10	2.3 (±2.4)	
CMS 0.7 mm WUR series stimuli Pain intensity	t1	56	0	10	3.7 (±2.9)	—
	t2	56	0	10	4.3 (±3.1)	
	t3	56	0	10	4.4 (±3.0)	
CMS 0.7 mm WUR ratio (series/single stimulus)	t1	46‡	1	5	2.1 (±0.9)	40 (87.0)
	t2	46‡	0.5	6	2.2 (±1.1)	41 (89.1)
	t3	46‡	1	7	2.4 (±1.5)	40 (87.0)

(*continued on next page*)

Table 3 (*continued*)

Descriptive analysis of bedside-quantitative sensory testing (QST) parameters (test side).

Bedside-QST	Visit	n	Min	Max	Mean (±SD)	Detection rate (yes; n, %)
Neurotip WUR single stimulus Pain intensity	t1	56†	0	8	1.9 (±1.9)	—
	t2	56†	0	10	2.1 (±1.9)	
	t3	56†	0	10	2.6 (±2.6)	
Neurotip WUR series stimuli Pain intensity	t1	56†	0	10	4.3 (±3.0)	—
	t2	56†	0	10	4.6 (±2.9)	
	t3	56†	0	10	5.1 (±3.1)	
Neurotip WUR ratio (series/single stimulus)	t1	44‡	1	7	2.8 (±1.4)	43 (97.7)
	t2	45‡	1	5	2.6 (±1.1)	44 (97.8)
	t3	50‡	1	8	2.7 (±1.9)	45 (90.0)
Vibration detection threshold	t1	60	0	8	4.9 (±2.5)	—
	t2	60	0	8	5.0 (±2.4)	
	t3	60	0	8	4.7 (±2.6)	
Pressure algometer at 4 mL Pain intensity	t1	60	0	10	3.0 (±3.4)	35 (58.3)
	t2	60	0	10	3.5 (±3.5)	40 (66.7)
	t3	60	0	10	3.2 (±3.4)	38 (63.3)
Pressure algometer Pain pressure threshold	t1	60	2	10	4.1 (±2.0)	—
	t2	60	2	10	4.5 (±2.0)	
	t3	60	1.5	10	4.3 (±2.1)	

Displayed are the number of data sets (n), the minimum (Min), the maximum (Max) ratings, the mean and corresponding standard deviation (mean ± SD), and the percentage of perceived/painful stimuli (detection rate [%]) for all 3 study visits (t1, t2, t3).

* While for the interval-scaled parameters only n = 59 patient data were available, n = 60 patient data could be included for the dichotomized parameters.

† Note that the Neurotip/Neuropen was only performed in a smaller number of patients (n = 56) because it was only applied after the study had already started.

‡ Note that some values were missing due to the dividing by zero, when patients rated the single stimulus as "no pain."

Table 4

Test–retest reliability of interval-scaled bedside-quantitative sensory testing (QST) parameters.

Bedside-QST (interval scaled)	Short term t1-t2 (n = 60)	*P*	Long term t1-t3 (n = 39, PGIC = 4)	*P*
	ICC		ICC	
Metal 22°C perception intensity	0.718	<0.001	0.710	<0.001
Metal 22° pain intensity	0.547	<0.001	0.679	<0.001
Metal 8°C perception intensity	0.890	<0.001	0.780	<0.001
Metal 8°C pain intensity	0.909	<0.001	0.720	<0.001
Metal 37°C perception intensity	0.826	<0.001	0.770	<0.001
Metal 37°C pain intensity	0.406	0.020	0.227	0.219
Metal 45°C perception intensity	0.873	<0.001	0.755	<0.001
Metal 45°C pain intensity	0.729	<0.001	0.476	0.024
Q-tip perception intensity	0.902	<0.001	0.693	<0.001
0.7 mm CMS pain intensity	0.916	<0.001	0.871	<0.001
Neurotip pain intensity*	0.929 (n = 56)	<0.001	0.788 (n = 35)	<0.001
0.7 mm CMS WUR single stimulus pain intensity	0.748 (n = 56)	<0.001	0.744 (n = 35)	<0.001
0.7 mm CMS WUR series stimuli pain intensity	0.908 (n = 56)	<0.001	0.801 (n = 35)	<0.001
0.7 mm CMS WUR ratio pain intensity†	0.244 (n = 45)	0.180	−0.002 (n = 27)	0.501
Neurotip WUR single stimulus pain intensity	0.861 (n = 56)	<0.001	0.688 (n = 35)	<0.001
Neurotip WUR serie stimulus pain intensity	0.912 (n = 56)	<0.001	0.858 (n = 35)	<0.001
Neurotip WUR ratio pain intensity†	0.700 (n = 43)	<0.001	0.085 (n = 27)	0.412
DMA allodynia pain intensity	0.849	<0.001	0.726	<0.001
DMA postallodynia sensation pain intensity	0.927	<0.001	0.884	<0.001
Pressure algometer at 4-mL pain intensity	0.851	<0.001	0.805	<0.001
Pressure algometer pain pressure threshold	0.890	<0.001	0.842	<0.001
Vibration detection theshold	0.979	<0.001	0.968	<0.001

* Note that the Neurotip/Neuropen was only performed in a smaller number of patients (n = 56), as it was only applied after the study had already started.

† Note that some values were missing due to the dividing by zero, when patients rated the single stimulus as "no pain."

ICC, intraclass correlation coefficient>0.9, excellent (dark green); >0.75, good (green); >0.5, moderate (light green); <0.5 poor (white).

DMA, dynamic mechanical allodynia; WUR, wind-up ratio.

Table 5

Test–retest reliability of dichotomous bedside-quantitative sensory testing (QST) parameters.

Bedside-QST sensation perceived (yes/no)	Short term t1-t2 (n = 60)	*P*	Long term t1-t3 (n = 39, PGIC = 4)	*P*
	Cohen's Kappa		Cohen's Kappa	
Metal 22°C perception	0.529	<0.001	0.655	<0.001
Metal 22°C PHS	−0.026	0.817	−0.035	0.814
Metal 22°C pain	0.335	0.002	0.544	<0.001
Metal 08°C perception	0.619	<0.001	0.541	0.001
Metal 8°C PHS	0.545	<0.001	0.480	<0.001
Metal 8°C pain	0.584	<0.001	0.544	<0.001
Metal 37°C perception	0.403	0.002	0.602	<0.001
Metal 37°C pain	0.397	0.001	0.473	0.003
Metal 45°C perception	0.444	0.001	0.608	<0.001
Metal 45°C pain	0.527	<0.001	0.421	0.006
Neuropen monofilament (at least 2/3)*	0.788 (n = 56)	<0.001	0.677 (n = 35)	<0.001
Neuropen monofilament (abnormal gain)*	0.650 (n = 56)	<0.001	0.340 (n = 35)	0.043
Neuropen monofilament (abnormal loss)*	0.814 (n = 56)	<0.001	0.530 (n = 35)	0.001
64 mN von Frey (at least 2/3)	0.689	<0.001	0.655	<0.001
64 mN von Frey (abnormal gain)	0.638	<0.001	0.640	<0.001
64 mN von Frey (abnormal loss)	0.609	<0.001	0.616	0.001
0.7 mm CMS pain	0.839	<0.001	0.539	0.001
Neurotip pain*	0.836 (n = 56)	<0.001	0.720 (n = 35)	<0.001
Q-tip allodynia pain	0.762	<0.001	0.652	<0.001
Q-tip postallodynia sensation pain	0.667	<0.001	0.569	0.005
Pressure algometer at 4-mL pain	0.471	<0.001	0.470	0.003

* Note that the Neurotip/Neurotip was only performed in a smaller number of patients (n = 56) because it was only applied after the study had already started.
<0 poor (white), 0 to 0.2 light (grey), 0.21 to 0.4 fair (light green), 0.41 to 0.6 moderate (lemon green), 0.61 to 0.8 substantial (green), and 0.81 to 1.0 almost perfect (dark green).
PHS, paradoxical heat sensations.

4. Discussion

This study assessed the reliability and the convergent/divergent validity of a recently developed easy-to-use bedside-QST protocol in patients with chronic neuropathic pain of different etiology. Our results indicate that most of the bedside-QST parameters are not only comparable with the corresponding parameters of the DFNS lab-QST protocol as shown previously[21] but also have satisfactory divergent validity as well as short-term and long-term test–retest reliability.

The establishment of an easy-to-use but also standardized bedside-QST could significantly improve the diagnosis and treatment of neuropathic pain. The standardized lab-QST protocol enables a detailed assessment of gain-of-function and loss-of-function parameters to create an individual sensory profile. A dysfunction of small and large nerve fibers can be detected through comparison with reference values of healthy controls.[18,20] However, the biggest limitations of the lab-QST protocol are the expensive, partly nontransportable devices, and above all, the large amount of time to perform the entire protocol, ie, 1 hour for 2 test areas (affected and nonaffected control sides). Keeping these limitations in mind, the development of comparable but easier test protocols has become the focus of current pain research.

4.1. Comparison with other bedside-quantitative sensory testing protocols

During the past 2 years, 3 additional comprehensive bedside QST protocols were developed by different research groups based on the standardized laboratory QST protocol[15,29] or a literature review of testing procedures.[27] Although these protocols seem to be very promising QST alternatives, some relevant research questions remained unanswered: Zhu et al. demonstrated significant correlations with the respective DFNS lab-QST parameters for some of their clinical sensory test tools, however, without investigating test–retest reliability.[29] The bedside QST battery by Wasan et al. was shown to be stable/repeatable over time and between 2 examiners but was not validated against a lab-QST protocol.[27] The Boston Bedside QST by Koulouris et al. was shown to have both sufficient test–retest reliability and criterion validity.[15] However, only positive phenomena (hyperalgesia/allodynia to warm/cold/pinprick stimuli) were assessed, whereas hypoesthesia to warm and cold was not part of the protocol. For the use in large clinical trials and everyday clinical practice, bedside tests such as the bedside-QST protocol presented here might be advantageous, which assess both gain-of-function and loss-of-function parameters with good criterion and divergent validity, as well as sufficient inter-rater and test–retest reliability.

Table 6

Overview of correlations of the bedside-quantitative sensory testing (QST) parameters (t1) with the pain intensity and the hospital anxiety and depression scale (HADS).

	HADS-A	HADS-D	NRS
Metal 22°C perception intensity	**0.282***	**0.393****	0.196
Metal 22° pain intensity	**0.280***	0.248	0.256
Metal 8°C perception intensity	**0.285***	0.252	0.151
Metal 8°C pain intensity	0.251	**0.262***	**0.368****
Metal 37°C perception intensity	0.087	0.018	−0.019
Metal 37°C pain intensity	0.099	0.040	0.139
Metal 45°C perception intensity	0.066	−0.029	−0.132
Metal 45°C pain intensity	0.041	0.000	0.081
Q-tip perception intensity	0.125	0.115	0.039
0.7 mm CMS pain intensity	0.131	0.108	−0.033
Neurotip pain intensity	0.123	0.035	0.052
0.7 mm CMS WUR single stimulus pain intensity	0.191	0.118	0.152
0.7 mm CMS WUR series stimulus pain intensity	0.159	0.178	0.103
0.7 mm CMS WUR ratio pain intensity	−0.185	−0.049	−0.235
Neurotip WUR single stimulus pain intensity	0.169	0.071	0.106
Neurotip WUR serie stimulus pain intensity	0.152	0.220	0.172
Neurotip WUR ratio pain intensity	−0.061	0.166	−0.109
DMA allodynia pain intensity	0.133	0.171	**0.320***
DMA postallodynia sensation pain intensity	0.147	0.211	**0.268***
Pressure algometer at 4-mL pain intensity	−0.118	0.015	0.169
Pressure algometer pain pressure threshold	−0.110	−0.032	0.043
Vibration detection threshold	0.114	0.073	0.101

Displayed is the Spearman rank coefficient between the bedside-QST parameters and questionnaires regarding depression (HADS-D) and anxiety (HADS-A) and the average pain intensity during the last 7 days (NRS). Significant correlations are marked in bold. *$P < 0.05$, **$P < 0.01$.
DMA, dynamic mechanical allodynia; WUR, wind-up ratio.

4.2. Requirements of a bedside-quantitative sensory testing

To be used in daily clinical practice and large clinical trials, a test must be feasible without requiring a great deal of time. The bedside-QST protocol presented here fulfills this criterion because an examiner only needs on average 17 minutes or a maximum of 23 minutes to perform the entire protocol on 2 testing areas. In addition, the presented bedside-QST devices are portable and inexpensive, which allows their flexible use in different medical practices and study centers. Another important requirement for a bedside test is that the devices are easy to apply without the need for extensive training. Results of our previous study suggest that inter-rater reliability is good for some bedside-QST parameters, while for others, it could be improved by training. In particular, a low inter-rater reliability between untrained and trained examiners was shown for the 0.7-mm CMS hair. To improve standardization, we therefore decided to include another tool, ie, the Neuropen with the Neurotip for investigation of pinprick hyperalgesia. Our results confirm that this tool is at least as valid and reliable as the 0.7-mm CMS hair. In addition to the Neurotip, this instrument also has a thin filament that can be used to apply not only sharp but also blunt touch stimuli. Therefore, the number of devices in or final bedside-QST protocol is reduced from 6 to 5, which in turn increases practicability in clinical practice and large studies (**Fig. 3**). Owing to better practicability, an industrially manufactured metal cube could be used instead of a metal piece because we could show strong to very strong correlations for almost all parameters (except for 22°C cold pain intensity Spearman rho = 0.029), eg, 8°C cold perception Spearman rho = 0.918.

4.3. Test–retest reliability

In clinical practice and (longitudinal) randomized controlled trials, it is of utmost importance to monitor the course of a disease, ie, to document whether the symptoms or signs of a disease worsen or improve. A corresponding biomarker must therefore remain stable over time if the severity of the disease does not change. With some few exceptions, all bedside-QST parameters showed sufficient short-term and long-term test–retest reliability. However, thermal hyperalgesia and wind-up ratio reached only poor or light reliability. One possible explanation could be that our patient cohort was dominated by patients with an abnormal loss of function, ie, hypoesthesia to thermal and mechanical parameters. Only 11.7% showed abnormal cold hyperalgesia and 13.3% heat hyperalgesia, as assessed with lab-QST. Accordingly, only a maximum of 20% of all patients rated the bedside 8°C/22°C cold and 37°C heat stimuli as painful. This unequal distribution of patients is also reflected by the answers of the painPREDICT questionnaire. The most frequent symptoms were tingling (t1, 70%) and numbness (t1, 71.4%), the latter also rated with the highest intensity (4.5/10). By contrast, only 26.8% of patients stated that their pain can be evoked by something warm. Nevertheless, this distribution reflects the patient clientele in a university hospital. As shown by Baron et al. in a multinational lab-QST study, the most frequent subgroup of patients with neuropathic pain was characterized by sensory loss, ie, hypoesthesia to thermal and mechanical parameters (42%), while the thermal hyperalgesia and mechanical hyperalgesia clusters were less frequent (33%, 24%).[2] For patients with painful polyneuropathy, the most frequently investigated disease entity in our study (50%), this uneven distribution became even more apparent. Overall, only a limited statement regarding test–retest reliability can be made for the above mentioned bedside-QST parameters.

4.4. Convergent/divergent validity

Patients with higher (post)allodynia pain intensity and 8°C cold pain intensity reported greater average pain intensity. Koulouris et al.[15] showed similar results when comparing their bedside-QST with the corresponding NPSI item, the total score, and the 0 to 10 pain intensity rating.[15] A correlation of hyperalgesia with pain intensity scores has been shown before.[4] Most of the bedside-QST parameters did not correlate with the depression and anxiety scores, suggesting a good divergent validity of our tools. The only exceptions were 22 and 8°C cold perception/pain intensity, which correlated significantly with depression and/or anxiety. A positive correlation has been described for some QST parameters with depression, indicating a hyperalgesia to some sensory modalities in patients with depression.[13] Overall, however, the calculation of convergent/divergent validity for QST based on patient-reported outcome measures is difficult because sensory testing and questionnaires are known to address different aspects of pain[9].

4.5. Quantitative sensory testing–based stratification of patients into subgroups

A QST-based stratification approach can be used in clinical trials to allocate patients into subgroups with similar sensory profiles, ie, pathophysiological mechanisms, and to develop specific

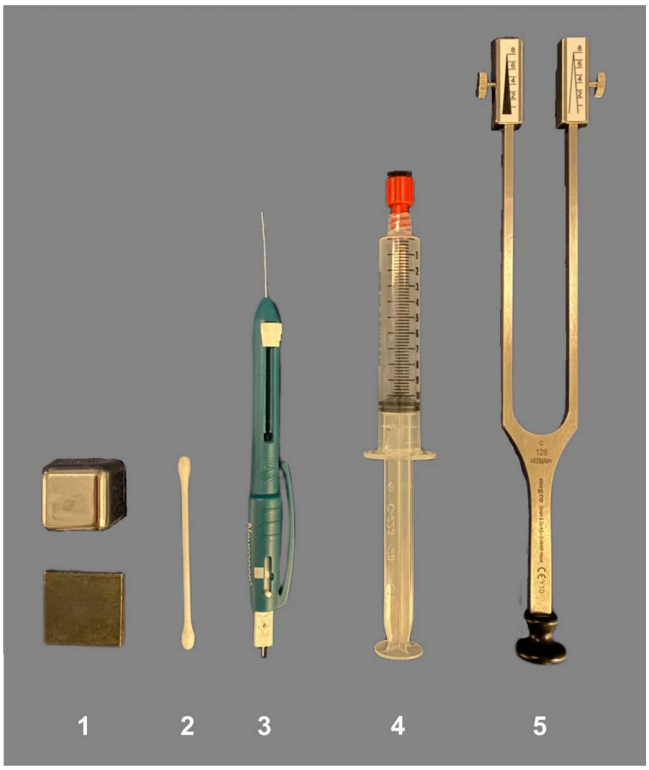

Figure 3. Bedside-QST devices. Displayed are the devices used for the final bedside-QST protocol. (1): 3 × 3-cm metal piece or 2.7 × 2.7 × 2.7-cm metal cube for thermal perception/pain, (2): Q-tip for touch sensation and dynamic mechanical allodynia, (3): Neuropen with a Neurotip for touch sensation and pinprick pain sensitivity, (4): 10-mL syringe for pressure pain sensitivity, (5): tuning fork c 128/C 64 Hz for vibration detection. QST, quantitative sensory testing.

individualized drugs. This approach was shown to potentially identify treatment responders in several (retrospective) studies.[5,11,23]

A reliable bedside-QST should also be able to identify patient's subgroups. As shown in our previous study, the 3 lab-QST clusters (sensory loss, mechanical hyperalgesia, and thermal hyperalgesia) can be identified by a combination of 5 different bedside-QST tests: 8° metal perception intensity (0–10 points), Q-Tip perception intensity difference (0–20 points), WUR single stimulus pain intensity (0–10 points), WUR series stimuli pain intensity (0–10 points), and vibration threshold (0–8 points). Test–retest reliability for these parameters was shown to be moderate to even excellent, supporting their use in clinical trials on treatment efficacy. In future studies, specific bedside-QST parameter combinations could also be used to assess patients with certain sensory characteristics, eg, combination of 8°C metal perception intensity, 37°/45°C metal perception, and Neurotip pain intensity for detecting patients with intact small (C and A delta) fibers.

4.6. Limitations

There are several limitations that should be mentioned. First, because the main aim of this study was the assessment of test–retest reliability and inter-rater observer reliability was previously investigated,[21] all test procedures were performed by the same trained investigator. For this reason, bias due to lack of blinding cannot be excluded. Furthermore, we cannot guarantee that a different examiner at a different study center would have obtained the same results. However, because most of the bedside-QST parameters had a good inter-rater reliability even between untrained and trained examiners, we assumed that this would be even higher with 2 trained examiners. Second, due to the short time interval between t1 and t2, we cannot exclude that participants remembered their ratings and that this might have led to the slightly better results for short-term test–retest reliability. Third, because most of the patients experienced painful polyneuropathy, the feet were the dominant testing area. Therefore, we cannot exclude that testing in other areas would yield different results. Lastly, although a power calculation was performed to reach a sufficient sample size, results for long-term reliability are underpowered due to reduced number of eligible patients.

5. Conclusion

This study confirmed that the bedside-QST is a valid and reliable method that can be used to assess somatosensory abnormalities in patients with neuropathic pain. Owing to its simple, fast, and cost-effective handling, the bedside-QST is a promising tool to be used in the future in clinical practice and in large clinical trials to monitor disease progression and stratify patients based on their phenotype. However, to be used as a pharmacodynamic tool, future studies should further confirm this preliminary validation and investigate particularly whether the bedside-QST is able to detect a clinically meaningful change in disease status as performed recently for lab-QST.[12] The bedside-QST could then help identify responders for already approved drugs and develop new mechanism-based approaches that could improve the treatment of patients with neuropathic pain.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A179.

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