Mechanical detection and pain thresholds: comparability of devices using stepped and ramped stimuli

Doreen B. Pfau\textsuperscript{a,x}, Omer Haroun\textsuperscript{b,c}, Diana N. Lockwood\textsuperscript{b}, Christoph Maier\textsuperscript{d}, Marc Schmitter\textsuperscript{e}, Jan Vollert\textsuperscript{c,a}, Andrew S.C. Rice\textsuperscript{c,f}, Rolf-Detlef Treede\textsuperscript{a}

Abstract

Introduction: Quantitative sensory testing is used to assess somatosensory function in humans. The protocol of the German Research Network on Neuropathic Pain (DFNS) provides comprehensive normative values using defined tools; however, some of these may not be feasible in low-resource settings.

Objectives: To compare the standard DFNS devices for assessment of mechanosensory function to a low resource tool, the Sorri-Bauru-monofilaments.

Methods: Mechanical detection thresholds (MDT), pain thresholds (MPT), and suprathreshold pinprick ratings (pain sensitivity: MPS) were measured over cheek, hand dorsum, and fingertip in 13 healthy subjects (7 female, aged 21–44 years). Mechanical detection threshold was assessed with DFNS standard glass monofilaments (0.25–512 mN, 0.5 mm tip) and nylon monofilaments (Sorri-Bauru; 0.5–3000 mN). MPT was assessed with DFNS standard cylindrical probes (8–512 mN, 0.25 mm tip), Sorri-Bauru monofilaments, and with ramped stimuli using an electronic von Frey aesthesiometer (10 mN/s or 100 mN/s, 0.20 mm tip). MPS was measured in response to stepped and ramped pinpricks (128 and 256 mN).

Results: Mechanical detection thresholds were the same for DFNS and Sorri-Bauru monofilaments. For MPT, Sorri-Bauru filaments yielded lower values than PinPricks over face but not hand. Pain thresholds were higher at all test sites for ramped than stepped pinpricks ($P < 0.01$). Suprathreshold ratings were lower for ramped than stepped pinpricks ($P < 0.05$).

Conclusion: Sorri-Bauru filaments are acceptable substitutes for DFNS standards in estimating tactile sensitivity, but are not consistent with standard probes for pinprick sensitivity because of their nonstandardized tips. Ramped stimuli overestimated MPT and underestimated MPS due to reaction time artefacts and therefore need their own normative values.

Keywords: Quantitative sensory testing, DFNS, pinprick, hyperalgesia, sensory loss

1. Introduction

Quantitative sensory testing (QST) according to the protocol of the German Research Network on Neuropathic Pain (DFNS)\textsuperscript{23} has found widespread utility as a clinical method for assessing somatosensory function. The results can be used for sensory profiling of patients, which might correspond to pathophysiological mechanisms underlying neuropathic pain.\textsuperscript{1,6,11,15,28,29} The DFNS not only provides a standardized protocol including which devices to use for which tests, they also published extensive normative data and correction factors for side-to-side comparisons.\textsuperscript{4,16,19,22} These normative data and the normalisation process they provide are particularly valuable because they allow interindividual comparisons
between patients of different age and sex, tested at different body sites and different hospitals. These normative data are accompanied by recommendations as to the type of measurement devices to be used, and it has been shown that rigorous standardization in methods, language used, and other factors reducing variance between centres and examiners is vital for the comparability between QST results. However, these recommendations have created an important limitation preventing widespread uptake of the methods because some of the devices are costly or require delicate handling, which limits their availability beyond specialised centres. In contrast to the software-controlled thermal testing devices recommended by DFNS and alternative devices, the mechanical testing devices are hand held, which necessitates standardized training in their use.

For testing the cheek, subjects were lying on a table. For testing the hand, subjects were sitting while the hand was tested, and the hand was placed in a 90˚ angle to the floor. The same position was held when the other devices were used. The tested subjects were recruited after replying to a posting at research purposes. The tested subjects were recruited after replying to a posting at research purposes.

Here, we report a comparison of DFNS recommended devices for the assessment of mechanosensory function with potential alternative devices. The specific aims were:

1. investigating the comparability of different devices using identical psychophysical methods for MDT, MPT, and mechanical pain sensitivity (MPS);
2. comparing perceived intensities of stepped vs ramped stimuli;
3. comparing the influence of different ramp rates of mechanical stimuli on the perception of "sharpness."

The Sorri-Bauru filaments were developed to detect sensory loss in leprosy patients but have been widely used by other programmes as a diagnostic technique for routine clinical and research purposes.

### 2. Materials and methods

#### 2.1. Subjects and test areas

The tested subjects were recruited after replying to a posting at the Department of Neurophysiology of the University Hospital Mannheim, Germany. They were investigated after giving written informed consent for the QST procedures (Number of Ethics committee 2007–252N–MA). Procedures were in accordance with the latest version of the Declaration of Helsinki. Tests were performed in the innervation territories of the ulnar nerve on the hand dorsum and on the palmar fingertip of the little finger, and additionally in the innervation territory of V3 (mandibular nerve) of the face (cheek). On the hand dorsum, the area below the ankles of the ring finger and the little finger was tested and the probes were placed between bones. On the cheek, the area between the corner of the mouth and the jaw anlge was tested. Subjects were sitting while the hands was tested, and the hand was lying on a table. For testing the cheek, subjects were lying on a reclined chair and the cheek was held in a position horizontal to the floor, so that the pinprick probes could be placed in a 90˚ angle to the floor. The same position was held when the other devices were used.

#### 2.2. Equipment

The Marstock NerveTest filaments (MRC Systems, Heidelberg, Germany; https://www.mrc-systems.de/en/products/pin-prick#optihair) consist of glass fiber monofilaments of different lengths and diameters, and resulting nominal bending strengths. This material is resistant to changes in humidity and temperature, and ensures the endurance of the calibration. The tips of the filaments are all coated with a tiny epoxy pearl with a defined diameter of 0.35 to 0.45 mm and are rounded (Fig. 1A). The tip is thicker than the filament in each filament force. In that way, a fairly constant contact area is ensured for each fibre diameter that varies only slightly with stimulus force depending on tissue compliance. A cylindrical tip is intentionally not used to avoid nociceptor activation due to sharp edges. Nominal bending forces logarithmically increase: 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and 512 mN (tolerance: ± 5%). These are used in the DFNS protocol to determine the MDT. The filaments are certified as medical devices (class I), CE certified, and plasma sterilization is possible.

The PinPrick (MRC systems, Heidelberg, Germany; https://www.mrc-systems.de/en/products/pinprick) are a set of 7 weighted pinprick stimulators consisting of steel tubes with different weights. The weight of each stimulator ends on a tip with potentially sharp edges, and their diameters vary between 0.12 mm and 1.14 mm (Fig. 1C). For this reason and the broad

### Figure 1. Devices for quantitative sensory testing (QST). (A) DFNS standard glass monofilaments with standardized rounded tips (Marstock Optihair), (B) DFNS standard pinpricks with 0.25-mm cylindrical tips (PinPrick), (C) Sorri-Bauru nylon monofilaments with varying diameters and sharp tips, (D) electronic von Frey aesthesiometer with 0.20-mm diameter cylindrical tips. DFNS, German Research Network on Neuropathic Pain.
range of force they cover, this set of filaments was used to test both MDT and MPT.

The electronic von Frey aesthesiometer (Somedic, Norra Melby 1129 28273 Sösdala, Sweden, http://www.somedic.com) is a device designed to apply continuously ramped mechanical stimuli. The tip diameter is 0.20 mm. The angle at the edge of the probe is ~103°. The replaceable and sterilizable tip tapers in a cylindric form to avoid skin penetration (Fig. 1D) and is connected with a handheld force and a force transducer. Data are processed using SenseBox and the SenseLab Application Suite version 0.6 build 1 (Somedic AB, Hoerby, Sweden). Visual feedback control of the applied ramp rate is given by means of flashing lights on the back of the handpiece.

2.3. Procedures

Mechanical detection thresholds were determined according to the DFNS protocol using method of limits.23

(1) with the DFNS glass monofilament, starting with a supra-threshold filament of 16 mN.

(2) with the Sorri-Bauru Estesiometro filaments, starting with a suprathreshold stimulus intensity of 2 g, corresponding to 20 mN.

Mechanical pain thresholds were tested with 2 procedures as described below:

(1) according to the DFNS protocol using stepped stimuli and the method of limits and asking the subject to differentiate between a sharp or blunt sensation evoked by

a. The PinPricks, starting with a subthreshold stimulus intensity of 8 mN

b. Sorri-Bauru Estesiometro filaments with a subthreshold stimulus intensity of 2 g, corresponding to ~20 mN.

Cutoff value for testing on the hand was 78 g, corresponding to 768 mN (face: 39 g, corresponding to 384 mN) as presenting the calculated cutoff value within the DFNS MPT procedure using the PinPricks to avoid tissue damage. This calculation is used in the case that the 512 mN (face: 256 mN) PinPrick is not perceived as painful. This value is then used as the lower value for threshold determination, and the higher value is supposed as 1024 mN (512 mN in the face). A mean value was calculated over 3 repetitions.

(2) Using a continuously increasing ramp rate at 1 or 10 g/s, using the electronic von Frey aesthesiometer with a stop button. Subjects were asked to press the stop button as soon as they perceive any sharp sensation reflecting the activation threshold of nociceptors.9

Mechanical pain sensitivity was determined

(1) using the PinPricks: a shortened procedure for testing MPS according to the DFNS QST protocol was performed, using the 128 and 256 mN PinPricks only. A numerical rating scale ranging from 0 (no pain) to 100 (most intense pain imaginable) was used for all test stimuli. Subjects were free to use integers as well as fractions. They were instructed to distinguish pain from the perception of touch or pressure (rating of 0) by the presence of a sharp or slightly pricking or burning sensation (rating above 0).

(2) using the electronic von Frey aesthesiometer; an electronic VAS is connected through the force transducer (SenseBox; Somedic, Sweden) with the computer, so that subjects continuously rated the intensity of any pain-related sensation. With the recorded ratings and applied forces, intensity coding was assessed. The corresponding pain ratings of 2 stimulus intensities as were 128 mN (intensity with the first rating above 0 using the electronic von Frey aesthesiometer) and 256 mN (highest stimulus intensity with the PinPrick in the face within the DFNS protocol to avoid damage of the skin) were noted and analysed. Applied stimulus ramps were 10 and 1 g/s, respectively, to test a possible influence of subject’s reaction time or the influence of steeper increasing pressure ramps delivered by sharp stimuli per se.14

2.4. Order of test procedures

Test procedures were performed in the following order, as recommended in the DFNS protocol: MDT, MPT, and MPS with subthreshold and suprathreshold stimuli. The order of test areas (face, fingertip, and hand dorsum) and the application order of test devices were counterbalanced.

2.5. Data analyses

Because the values of Sorri-Bauru Estesiometro filaments are given in gram, the corresponding force in mN was calculated by multiplying the factor 9.81 m3/s² kg (gravitational constant). For MDT and MPT tested with the Marstock filaments, the Sorri-Bauru Estesiometro filaments, and the PinPricks, the geometric mean values were then calculated from 5 subthreshold and 5 suprathreshold values. In addition, data of MDT were analyzed later for both filaments by the “method of the constant stimuli.” For this purpose, for each stimulus in the 5 ascending and 5 descending series, either 0 (not perceived) or 1 (perceived) was assigned. For example, when a subject perceived a 4-mN intensity, but not a 2-mN intensity, the 4-mN intensity and all intensities below were labelled as “perceived,” and the 2-mN intensity and all intensities below were labelled as “not perceived.” According to the number of perceived stimuli of each stimulus intensity, the percentage of perceived stimuli was calculated and plotted. A percentage of 50% is defined as threshold value.

The statistical difference of the Sorri-Bauru Estesiometro filaments and the Marstock filaments was calculated using paired t-tests (Excel, Microsoft Office) after calculating geometrical mean values.22,23 For MPT with the electronic von Frey aesthesiometer, the pressure intensities that were recorded when subjects pressed the stop button for the first painful sensation were averaged over 3 repetitions. Correlation analyses were performed (Excel, Microsoft Office). Correlation coefficients of r < 0.35 are considered to represent weak correlations, 0.36 to 0.67 moderate correlations, and 0.68 to 1.0 strong correlations.26

3. Results

Thirteen healthy subjects (7 female, 6 male; mean age ± SD 37 ± 16 years) were included in the study. Mean values for MDT tested by Sorri-Bauru Estesiometro filaments vs standard DFNS did not differ over all test areas and were highly correlated (Fig. 2 and Table 1). Psychometric functions for stimulus intensities reveal similar performance of both sets of filaments as well (Fig. 3A-C). Given the limited range of force, in sensitive test areas, mechanical sensitivity might be underestimated when using the Sorri-Bauru Estesiometro filaments, but elevated thresholds due to sensory loss can be quantified.

Mechanical pain threshold was significantly lower for the Sorri-Bauru Estesiometro filaments compared to standard DFNS pinpricks in the face (Table 1 and Fig. 4). By contrast, MPT did not differ on the fingertip or the dorsum of the hand. This likely reflects the fact that Sorri-Bauru filaments are thin for low forces and thick for high forces, whereas the cylindrical tip for the standard DFNS pinprick is a consistent diameter across all
forces. Correlation between the DFNS pinprick and the Sorri-Bauru Estesiometro filaments was weak to moderate in the face and on the fingertip, and strong on the hand. Thus, MPT testing with Sorri-Bauru filaments is not consistent with DFNS standards under all conditions.

Mean MPT assessed using the electronic von Frey aesthesiometer were significantly higher for both ramp rates in all test areas compared to the standard DFNS pinpricks (Table 2 and Fig. 4). The correlations between the devices were weak to moderate. A faster ramp rate of 10 g/s led to significantly higher thresholds compared to the slower ramp rate of 1 g/s (all P < 0.01; Table 2). The correlation between both electronic von Frey aesthesiometer ramp rates was moderate to strong (Table 2).

Mechanical pain sensitivity was significantly higher when tested by stepped stimuli compared to ramped stimuli (electronic von Frey aesthesiometer with ramp rates of 1 g/s or of 10 g/s, P < 0.01; Table 2 and Fig. 5). Also, the ramp rate had a significant influence on pain sensitivity in the tested areas (all P < 0.01 for 1 vs 10 g/s). However, the correlation between the stepped pinpricks and the slower ramp rate of 1 g/s was moderate (face and hand) to strong (fingertip only; Table 2), but with a ramp rate of 10 g/s weak to moderate only (Table 2). The correlation between both ramp rates was weak (fingertip) to moderate (face) and strong (hand). These data suggest that reaction artefacts add variance to MPT and MPS estimation using ramped stimuli.

4. Discussion

The Sorri-Bauru Estesiometro nylon filaments yielded similar results as the DFNS standard glass monofilaments for the testing of MDT according to the DFNS in healthy subjects. Due to larger steps of applied intensities compared to the DFNS glass monofilaments, thresholds of the most sensitive healthy subjects may be overestimated (Fig. 3), but this is not relevant in clinical use, where neuropathy leads to tactile sensory loss. Mechanical pain threshold estimated using Sorri-Bauru filaments correlated poorly with that determined by the DFNS standard pinprick. Mechanical pain threshold was systematically lower by using the Sorri-Bauru filaments in the face compared to the DFNS standard pinprick. These findings likely reflect the fact that the filaments are thin for weak forces and thick for strong forces, thus confounding stimulus intensity and sharpness. Mechanical pain threshold and MPS tested with the electronic von Frey aesthesiometer were not comparable with the DFNS standard pinpricks, although both have the same tip geometry. This is likely caused by the different mode of application (stepped stimuli vs ramped stimuli). For ramped application, the individual reaction time plays an important role, which was evidenced here by different MPT and MPS values for different ramp rates.

4.1. Use of the Sorri-Bauru Estesiometro filaments

Monofilaments, which as described by von Frey were originally made from animal hair, have been developed over time from simple, natural materials to synthetic devices. In the late 19th century, these monofilaments were also used as a method to quantify pain induced by punctate stimulation.31 Von Frey used various thicknesses of animal hair to determine the thresholds of touch recognition. Later, this technique was refined and amended by others, such as Semmes and Weinstein in the 1960s. They developed a standard set of nylon monofilaments that exert predefined forces onto the skin,25 Different forces are obtained by varying length or thickness of the nylon filament, or both.

Nylon filaments of this type were criticized for (1) being sensitive to temperature and humidity, and (1) confounding force and shape of skin contact. Sensitivity to environmental conditions has been overcome by using Von Frey filaments made from optical glass instead of nylon (Fruhstorfer et al. 2001). A testing kit comprises a standard set of glass filaments that are widely used in

Table 1

|                | DFNS Mean ± SEM (retransf.) | Sorri-bauru Mean ± SEM (retransf.) | DFNS Mean ± SEM (retransf.) | t-test | Correl |
|----------------|----------------------------|------------------------------------|----------------------------|--------|--------|
| **MDT (mN)**   |                            |                                    |                            |        |        |
| Face           | −0.338 ± 0.098 (0.46)      | −0.229 ± 0.067 (0.59)              | 0.119                      | 0.752  |
| Fingertip      | −0.241 ± 0.103 (0.57)      | −0.208 ± 0.053 (0.62)              | 0.678                      | 0.705  |
| Hand           | 0.273 ± 0.121 (1.88)       | 0.263 ± 0.129 (1.83)               | 0.900                      | 0.807  |
| **MPT (mN)**   |                            |                                    |                            |        |        |
| Face           | 1.103 ± 0.094 (12.7)       | 1.396 ± 0.041 (24.9)               | <0.01                      | 0.326  |
| Fingertip      | 1.893 ± 0.206 (78.1)       | 1.741 ± 0.074 (55.1)               | 0.422                      | 0.482  |
| Hand           | 1.844 ± 0.182 (69.8)       | 1.744 ± 0.064 (55.4)               | 0.436                      | 0.924  |

Bold text indicates DFNS standards. DFNS, German Research Network on Neuropathic Pain; MDT, mechanical detection threshold; DFNS standard = Marstock glass monofilaments (0.35–0.45-mm diameter rounded tip); MPT, mechanical pain threshold; DFNS standard = weighted 0.25-mm diameter cylindrical probes (ThePinPrick).
clinical practice by neurologists for assessing sensory abnormalities. As it became apparent that differential activation of tactile receptors vs nociceptors depends not only on stimulus force but also size and shape of the skin contact, the glass filaments received a rounded tip of standardized diameter.23 Of note, very weak forces below 1 mN can activate intraepidermal nociceptors when filaments are very thin (eg, 50 μm).8

Sorri-Bauru Estesiometro filaments are a set of nylon monofilaments ranging from 5, 200 mg, 2, 4, 10, to 300 g using a colour code for stimulus intensity (green for lightest to red for strongest force).2 When used for the hand specifically, the stimulus was found to have a cutoff 200 mg, but for the foot, the cutoff was found to be 2 g. Their use has led to a significant improvement in screening diabetic patients; for example, inability to perceive a 10-g monofilament is recognised as a risk factor for ulcer.3 Of note, it is presently unclear to what extent that sensory loss reflects tactile or nociceptive denervation or both.

In this study, the Sorri-Bauru filaments yield similar results for the testing of MDT according to the DFNS protocol in healthy subjects. Due to larger increments of applied intensities compared to the Marstock filaments, neuropathies may be underestimated in more sensitive test areas (face and fingertip). Additional variance may arise from nonstandardized tip surfaces of the Sorri-Bauru filaments. The suitability of the use on the hand should be confirmed by testing patients suffering from neuropathy, to see if results are equally similar as they are in healthy participants. Sorri-Bauru filaments cost about 20 times less than the Marstock filaments. For these reasons, they may be used more broadly in resource-limited settings to assess MDT in accordance with the DFNS protocol.12 When used to estimate MPT, the findings do not match the DFNS reference data under all conditions, and the varying filament diameters do

Figure 3. Psychometric functions for the mechanical detection threshold tested by a set of standard DFNS filaments (filled symbols) and the Sorri-Bauru Estesiometro filaments (open symbols). n = 13. A: face, B: finger, C: hand. DFNS, German Research Network on Neuropathic Pain.

Figure 4. Box-dot-plot of mechanical pain threshold (mN) tested over the face, the fingertip, and the hand dorsum. Sorri-Bauru filaments (red circles) and PinPricks (yellow squares) are comparable for fingertips and hand, but show significant deviations when applied to the face. Results of the electronic von Frey aesthesiometer differed significantly for all test areas both between 1 g/s (blue diamonds) and 10 g/s (green hexagons), and between each speed and the results yielded by the PinPricks. Tested over the face, both speeds also differed significantly from the results produced by the Sorri-Bauru filaments (P < 0.05 corrected for multiple testing by controlling the false discovery rate using Benjamini–Hochberg procedure). Higher color intensity indicates overlying data points. n = 13.
not allow a clear distinction between activation of tactile receptors vs nociceptors.

4.2. Use of the electronic von Frey

Mechanical pain thresholds and MPS tested with the electronic von Frey aesthesiometer are not comparable with the responses measured by the PinPricks due to the different mode of application (stepped stimuli vs ramped stimuli). A study comparing different devices in humans and rats has shown that ramped stimuli showed higher baseline thresholds than stepped stimuli but similar sensitivity to change at the same tip diameter. For the ramped application, reaction time plays an important role as both individual error variance and systematic variance due to ramp rate. This systematic error had first been published for thermal ramps and was confirmed here by different MPT and MPS values for different mechanical ramp rates.

The angles of the 2 probes differ (90˚ vs 103˚) and so do tip diameters (0.25 vs 0.2 mm). Both parameters could have led to systematic differences in thresholds, but in opposite directions (angle: lower for ThePinPrick, diameter: lower for aesthesiometer). So, these factors should partly cancel each other, but correlations should be high, which they are not. Thus, the reaction time artefact seems to play the dominant role, as also shown by systematic differences between 2 ramp rates.

5. Conclusions

The use of the Sorri-Bauru nylon monofilaments yield similar results as the DFNS-recommended Marstock glass filaments for assessment of tactile sensitivity (MDT). They have a slightly higher lower cutoff, which makes them less fragile; because clinical application is for detection of tactile sensory loss, this is not a relevant limitation. For research purposes, the Marstock glass filaments may deliver more precise results and detect smaller changes in sensitivity. For MPT, there was a moderate correlation with the standard DFNS pinprick; due to their confounding of filament diameter (skin contact area) and force, they likely underestimate low MPT and overestimate high MPT. Within these boundaries, they are a cheap and acceptable alternative to other devices. Due to the ramped application mode that leads to reaction time artefacts, results for mechanical pain testing with the electronic von Frey aesthesiometer are not transferable to normative values within the DFNS protocol. It might be possible to collect specific normative values for this device for a short-form QST because the ramp paradigm is faster than the stepped paradigm.

Table 2

|                  | DFNS       | EvF 1 g/s | EvF 10 g/s | T-test | T-test | T-test | Correl | Correl | Correl |
|------------------|------------|-----------|------------|--------|--------|--------|--------|--------|--------|
|                  | Mean ± SEM (retransf.) | Mean ± SEM (retransf.) | Mean ± SEM (retransf.) | evF 1 g/s vs DFNS | evF 10 g/s vs DFNS | evF 1 g/s vs evF 10 g/s | evF 1 g/s vs DFNS | evF 10 g/s vs DFNS | evF 1 g/s vs evF 10 g/s |
| MPT (mN)         |            |           |            |        |        |        |        |        |        |
| Face             | 1.396 ± 0.041 (34.9) | 1.956 ± 0.054 (90.3) | 2.245 ± 0.055 (176.0) | <0.001 | <0.001 | <0.001 | 0.133  | -0.068 | 0.691  |
| Finger tip       | 1.741 ± 0.074 (55.1) | 2.085 ± 0.060 (121.8) | 2.349 ± 0.034 (223.4) | <0.01  | <0.001 | <0.001 | 0.141  | 0.475  | 0.447  |
| Hand             | 1.744 ± 0.064 (55.4) | 2.160 ± 0.061 (144.6) | 2.379 ± 0.061 (239.6) | <0.001 | <0.001 | <0.01  | 0.241  | 0.213  | 0.407  |
| MPS (rating 0–100) |            |           |            |        |        |        |        |        |        |
| Face             | 0.942 ± 0.104 (8.75) | -0.183 ± 0.127 (0.66) | -0.601 ± 0.066 (0.25) | <0.001 | <0.001 | <0.01  | 0.403  | -0.038 | 0.608  |
| Finger tip       | 0.715 ± 0.158 (5.18) | -0.046 ± 0.143 (0.90) | -0.621 ± 0.089 (0.24) | <0.001 | <0.001 | <0.01  | 0.683  | 0.353  | 0.342  |
| Hand             | 0.641 ± 0.139 (4.37) | -0.210 ± 0.148 (0.62) | -0.758 ± 0.041 (0.17) | <0.001 | <0.001 | <0.01  | 0.438  | 0.465  | 0.801  |

DFNS, German Research Network on Neuropathic Pain; MPT, mechanical pain threshold; DFNS standard = weighted 0.25-mm diameter cylindrical probes (ThePinPrick); MPS, mechanical pain sensitivity; here, mean rating for 128 and 256 mN; evF, electronic von Frey with 0.25-mm diameter cylindrical tip. Numbers in the brackets indicate re-transformed log-values. Bold text indicates DFNS standards.

Figure 5. Mechanical pain sensitivity (NRS 0–100). Only ratings at stimulus intensities of 128 and 256 mN are reported. Pain sensitivity is significantly higher when tested by stepped stimuli (ThePinPrick, black circles) compared to ramped stimuli (electronic von Frey aesthesiometer) with ramp rates of 1 g/s (open circles) or of 10 g/s (filled triangles), (P < 0.01). Also, the ramp rate had a significant influence on pain sensitivity in the tested areas (P < 0.05 for 1 vs 10 g/s). NRS, numerical rating scale.
Disclosures
Dr. Lockwood, Dr. Maier, Dr. Schmitter, Dr. Haroun and Dr. Pfau have no conflict of interest to declare.

Dr. Rice reports personal fees from Imperial College Consultants, other from Spinfrex, outside the submitted work; in addition, Dr. Rice has a patent WO 2005/079771 pending, and a patent WO2013/110945 pending.

Dr. Treede reports grants from DFG, during the conduct of the study; grants from European Union and EFPIA companies, grants from Bayer, personal fees from Bayer, Grünenthal, GSK, Sanofi, outside the submitted work; in addition, Dr. Treede has a patent DE 103 31 250.1-35 with royalties paid to MRC Systems.

Dr. Vollert reports personal fees from Casquar, outside the submitted work.

Acknowledgements
This project was supported by the DFG (Heidelberg Pain Consortium SFB 1158, project S01; DFG grants RA 1737/2-1 and SCHW307/25-1). The authors declare no conflict of interest. The authors thank Yvonne Neu and Thomas Zahn for their support in image creation.

D.B. Pfau and O. Haroun performed the experiments, analyzed the data, and wrote the manuscript. J. Vollert and C. Maier analyzed the data. D.N. Lockwood, M. Schmitter, A.S.C. Rice, and R.D. Treede designed the study and edited the manuscript. All authors approved the submitted version of the manuscript.

Article history:
Received 2 June 2020
Received in revised form 20 August 2020
Accepted 26 August 2020
Available online 2 December 2020

References
[1] Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, Finnnerup NB, Haanpaa M, Hansson P, Hallermann P, Jensen TS, Freynhagen R, Kennedy JD, Magier W, Mainka T, Reimer M, Rice AS, Segerdahl M, Serra J, Sindrup S, Sommer C, Tolle T, Vollert J, Treede RD. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. Pain 2017;158:261–72.
[2] Bell-Krotoski J. Pocket filaments and specifications for Semmes-Weinstein monofilaments. J Hand Ther 1990;3:26–9.
[3] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[4] Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. PAIN 2006;123:231–43.
[5] Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. PAIN 2006;123:231–43.
[6] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[7] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[8] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[9] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[10] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[11] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[12] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[13] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[14] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[15] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[16] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[17] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[18] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[19] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[20] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[21] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[22] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[23] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[24] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[25] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[26] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[27] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[28] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[29] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[30] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[31] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[32] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[33] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[34] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[35] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[36] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[37] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[38] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[39] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[40] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
[41] Birke JA, Sims DS. Planar sensory threshold in the ulcerative foot. Lepr Rev 1986;57:261–7.
P, Hullemann P, Jensen TS, Magert W, Ramírez JD, Rice ASC, Schuh-Hofer S, Segerdahl M, Serra J, Shillo PR, Sindrup S, Tesfaye S, Themistocleous AC, Tolle TR, Treede RD, Baron R. Stratifying patients with peripheral neuropathic pain based on sensory profiles: algorithm and sample size recommendations. PAIN 2017;158:1446–55.

Vollert J, Mainka T, Baron R, Enax-Krumova EK, Hullemann P, Maier C, Pfau DB, Tolle T, Treede RD. Quality assurance for Quantitative Sensory Testing laboratories: development and validation of an automated evaluation tool for the analysis of declared healthy samples. PAIN 2015;156:2423–30.

Weinstein S. Intensive and extensive aspects of tactile sensitivity as a function of body part, sex, and laterality. In D. R. Kenshalo (Ed.), The skin senses. Springfield, IL: Thomas, 1968. pp. 195–222.