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The responsiveness of quantitative sensory testing-derived sensory phenotype to disease-modifying intervention in patients with entrapment neuropathy: a longitudinal study

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Conflicts of interest: DLK; DR; CMA: Nothing to declare, JV: Received personal fees from Casquar, outside of the submitted work. ASCR: IASP Council Member and Chair 18th World Congress on Pain Scientific Programme Committee, ASCR undertakes consultancy and advisory board work for Imperial College Consultants- in the last 24 months this has included remunerated work for: Abide, Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Asahi Kasei, Toray & Theranexis, ASCR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015 and from which payments continued until 2019. ASCR is named as an

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inventor on patents: Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl) hexadecanamide and related amides to relieve pain. WO 2005/079771, Okuse K. et al Methods of treating pain by inhibition of vgf activity EP13702262.0/ WO2013 110945

Abstract

The German Research Network on Neuropathic Pain (DFNS) quantitative sensory testing (QST) method for sensory phenotyping is used to stratify patients by mechanism associated sensory phenotype, theorised to be predictive of intervention efficacy. We hypothesised that change in pain and sensory dysfunction would relate to change in sensory phenotype. We investigated the responsiveness of sensory phenotype to surgery in patients with an entrapment neuropathy.

With ethical approval and consent, this observational study recruited patients with neurophysiologically confirmed carpal tunnel syndrome. Symptom and pain severity parameters and DFNS QST were evaluated prior to and after carpal tunnel surgery. Surgical outcome was evaluated by patient-rated change. Symptom severity score of the Boston Carpal Tunnel Questionnaire and associated pain and paraesthesia subgroups were comparators for clinically relevant change.

QST results (n=76) were compared to healthy controls (n=54). At 6 months post-surgery 92% participants reported a good surgical outcome and large decrease in pain and symptom severity ($p<.001$). Change in QST parameters occurred for thermal detection, thermal pain and mechanical detection thresholds with a moderate to large effect size. Change in mechanical pain measures were not statistically significant. Change occurred in sensory

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phenotype post-surgery (p<.001); sensory phenotype was associated with symptom subgroup (p=.03) and patient-rated surgical outcome (p =.02).

QST derived sensory phenotype is sensitive to clinically important change. In an entrapment neuropathy model, sensory phenotype was associated with patient-reported symptoms and demonstrated statistically significant, clinically relevant change after disease modifying intervention. Sensory phenotype was independent of disease severity and may reflect underlying neuropathophysiology.

Keywords: Quantitative sensory testing (QST); sensory phenotype; neuropathic pain; responsiveness; stratification

Background

Quantitative sensory testing (QST) is a clinical examination method for evaluating nerve fibre function in response to graded multi-modal stimuli [3;28;36;37;42;67]. Historically, variability in QST tests have impeded extrapolating findings across studies [27]. To improve standardization and interpretability, the German Research Network on Neuropathic Pain (DFNS) published a comprehensive QST protocol (DFNS QST)[70] that is now widely employed.

DFNS QST has been implemented to define reference values in healthy participants [57;64;69]. This has enabled the interrogation of sensory dysfunction and description of heterogeneous sensory profiles in a range of neuropathic pain conditions [43;58;65;76;79].

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Somatosensory dysfunction measured using DFNS QST can be clustered into three sensory phenotypes, composites of the 13 DFNS QST tests, primarily characterised by thermal or mechanical hyperalgesia or sensory loss [6]. To enhance the utility of DFNS QST as a stratification tool, an algorithm based on these three phenotypes was developed [81]; thereby affording greater sensitivity and precision in elucidating somatosensory dysfunction.

While somatosensory profile is hypothesised to reflect underlying pathophysiology of pain pathways and mechanisms in neuropathic pain conditions[2;4;18;31;59], the pathophysiology of neuropathic pain is variable, complex and not fully elucidated. The science of QST derived somatosensory profiling is, relatively speaking, in it's infancy and it's clinical importance remains under investigation. Ambiguities exist, for example there is an observed discordance for patient reported pain and pain sensitivity and the results of evoked pain measures employed in quantitative sensory testing [32;34]; these equivocal findings warrant further exploration.

Establishing that neuro-pathophysiology varies within a neuropathic pain condition is thought to be germane to improving treatment and outcomes. This has created the impetus for prescribing to target pathophysiological mechanisms [5;31]. It is unsurprising, therefore, that DFNS QST is now widely employed in clinical trials. In pain trials, it has been recommended that QST derived sensory phenotype be incorporated as a method for patient stratification [23;25;30;35;44;66]. In surgical prognosis design studies [68] somatosensory phenotype is incorporated as an exploratory risk factor for the development of neuropathic or persistent post-operative pain[1;13;83;84].

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Despite this implementation of DFNS QST and QST derived sensory phenotype in research, there is no evidence supporting their responsiveness. Fundamentally, for a tool to be psychometrically robust, it is essential that it be both internally and externally responsive; detecting small, clinically important change [26;40;47]. Accepted methods for assessing internal responsiveness include assessing patients prior to and following a treatment known to be efficacious.

A carpal tunnel surgery cohort provides an elegant model for evaluating the responsiveness of QST and QST derived sensory phenotype in patients with compression neuropathy following disease modifying treatment. Carpal Tunnel Syndrome (CTS) is a compression neuropathy of the median nerve at the wrist leading to measurable sensory disturbance and pain[19;62]. DFNS QST studies of somatosensory function in CTS patients demonstrate that whereas sensory loss to thermal and mechanical stimuli are hallmarks of CTS[7;71]; hyperalgesia to thermal and mechanical stimuli are also observed[85]. Decompression surgery is efficacious[46;72;80] and essentially, there exists a well validated comparator measure of clinically relevant change; the Symptom Severity Scale of the Boston Carpal Tunnel Questionnaire, a disease specific, reliable and responsive patient-completed questionnaire[24;50].

Study Aims:

- Investigate change in DFNS QST and QST derived sensory phenotype before and after surgery in patients with carpal tunnel syndrome to determine internal responsiveness.

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- Investigate association between DFNS QST and sensory phenotype and participant-reported measures of pain and sensory dysfunction before and after surgery to determine external responsiveness.

Methods

Ethical approval was granted by the Camberwell St Giles National Research Ethics Committee (14/LO/1436) on 29 August 2014 for a prospective, repeated measures observational study in a convenience sample of CTS participants (https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/impact-of-pain-and-somatosensory-phenotype-on-carpal-tunnel-surgery/). Study findings are reported according to STROBE guidelines for observational studies [82]; this manuscript reports a secondary analysis of an existing dataset. Adult patients listed for open carpal tunnel decompression surgery at two London National Health Service (NHS) hospitals were recruited by poster, in person at their hospital clinic appointment and by post. Participants were not paid for study participation however travel was reimbursed.

Surgical outcome measurement

The primary measure used to classify surgical outcome as good or poor (binary outcome) was a patient-reported global rating of change (PGRC) at 6 months post-surgery. Using a 5 point ordinal scale, 1 = worse; 2 = unchanged; 3 = slightly better; 4 = much better and 5 = completely cured [10;11;51;60] a grade 3 or above was interpreted as treatment success. Where previous studies [10;11] have defined treatment success as 4 or above using the same ordinal scale, these investigators concede that their patients are selected for surgery based on good prognosis and as a consequence their findings are less generalizable to the wider

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population of patients with CTS. However, comparable to the current study, Jerosch-Herold et al., (2014) investigated CTS surgical outcome in a pragmatic prospective cohort including subjects with multiple comorbidities and known risk factors for poor outcome and identified a grade of 3 (slightly better) to define treatment success. In the United Kingdom, patients with long-standing, severe median nerve compression are routinely advised they may not have complete resolution of symptoms following surgery [16]. This is in keeping with evidence of patient expectations of carpal tunnel surgery outcome; patients with long-standing and/or severe symptoms report limited expectations from surgery [49].

Case definition of neuropathic pain

To document the presence of a median nerve mononeuropathy, nerve conduction studies (NCS) were performed by the respective hospital neurophysiology departments and severity graded according to Bland [9] criteria. If this criterion was fulfilled, then pain was categorised as neuropathic where *both* of the following conditions were met [41;48;77]:

- a score of ≥4 on the Douleur Neuropathique 4 questions (DN4) questionnaire [14]. The DN4 consists of seven symptom questions and three sensory examination measures and is a validated patient and examiner completed measure for the evaluation of neuropathic pain symptoms, signs and descriptors.
- pain present in a median nerve or extra-median nerve distribution. Pain distribution was classified from a patient-completed hand symptoms diagram as originally described by Katz et al. [52], with modification based on the work of Zanette et al. [85;86]. Pain within any aspect of the median nerve distribution of the hand (thumb, index, middle or ring fingers, including the dorsal digits), distal to the carpal tunnel was defined as median nerve distribution pain. Pain localised to the median nerve distribution distal to the carpal tunnel AND the dorsal radial hand (radial nerve

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distribution) OR any portion of the small finger or ulnar nerve distribution of the hand was defined as extra-median nerve pain. Pain restricted to the ulnar nerve distribution of the hand, and/or pain occurring only proximal to the carpal tunnel was defined as non-median nerve distribution pain

This two-stage triage for categorization of neuropathic pain was repeated at 3- and 6-month visits. However, *in lieu* of repeat electrophysiological testing, two or more abnormal quantitative sensory testing findings indicative of loss of sensory function (i.e. cold detection threshold; warm detection threshold; thermal sensory limen; mechanical detection threshold; vibration detection threshold [z x ±1.96]) was taken as a confirmatory diagnostic test [41].

Participation Criteria

Exclusion criteria were significant cognitive dysfunction or lack of English language, a history of potentially confounding conditions (rheumatoid arthritis, renal failure, peripheral neuropathy of any origin other than CTS), steroid injection of the study limb within the previous four weeks or previous carpal tunnel surgical release in the study hand, anatomic abnormalities of the wrist or hand, median nerve injury or compression secondary to traumatic injury and pregnancy.

Schedule of study visits

Baseline measures were completed within 6 weeks prior to surgery; 3- and 6-months post-surgery assessments were completed within ± 21 days.

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Procedure

At baseline, demographic data and medical history was recorded. All tests and questionnaires (described below) were delivered in the same order across the participants, across visits. Pain and symptom severity parameters and median nerve somatosensory function were evaluated at three time points; prior to and at 3- and 6-months post-surgery. At three- and six-month follow-up visits, participants sealed their completed surgical outcome measures in an envelope coded with their participant identification number. Surgical outcome measures remained sealed and retained with participant case report forms until participants completed the study.

Pain and sensory dysfunction comparator measures

Symptom severity and frequency was assessed with the Symptom Severity Scale (SSS) of the Boston Carpal Tunnel Questionnaire (BCTQ) [54]. Eleven symptoms are rated on a 5-point scale with lower scores implying milder symptoms. It has been demonstrated in CTS that the SSS can be exploited to identify pain-dominant and paraesthesia-dominant subgroups with concomitant, distinct alterations in brain morphometry on structural MRI [56]. Therefore, in addition to total symptom severity score, the SSS was used to stratify participants to pain-dominant, paraesthesia-dominant and mixed-symptom subgroups for comparison with DFNS QST derived sensory phenotypes. BCTQ questions 1-5 were averaged to generate a pain score, questions 6-10 a paraesthesia score and participants were stratified based on the larger of the two. Where pain and paraesthesia scores were equivalent participants were stratified to the mixed symptom subgroup [56].

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Pain dimensions were assessed with the Neuropathic Pain Symptom Inventory (NPSI) [15], a validated patient-completed measure. Total NPSI scores range from 0 to 100 with greater scores implying more severe symptom severity; item scores of 1–3 indicate mild pain severity, 4-6 moderate and 7-10 severe [33]. Pain severity was assessed with the validated [75] Brief Pain Inventory (BPI) whereby a Pain Severity Score is calculated as the mean of four questions quantifying present pain and the least, worst, and average pain over the last week. Pain is rated on an 11-point scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) [20].

Median nerve somatosensory function

QST was performed by a trained investigator (DK) according to the German Research Network on Neuropathic Pain (DFNS) protocol [70]. All equipment was new and calibrated prior to testing. All tests were performed in the same order, as described in **Table 1.** Participants were seated in a quiet, temperature-controlled room, with the test hand (surgical hand) supported on a table. Tests were first demonstrated on the dorsal contralateral forearm. Pressure pain threshold was tested at the thenar eminence, all other tests were performed at the volar distal phalanx of the middle finger. Median nerve function was tested at the middle finger because although it innervates the volar thumb, index, middle and radial half of the ring fingers, there is evidence that the middle finger is more symptomatic and more sensitive to tests of mechanical detection in patients with CTS [12;29;50].

Full details of the DFNS QST testing procedure are reported in **Supplementary Material 1** (https://doi.org/10.6084/m9.figshare.12860003.v2). In summary, a Somedic MSA thermal stimulator (Sweden) with an 18 mm^2 metal Somedic thermode was used for thermal detection

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and pain threshold tests**.** Thermal thresholds were tested using a baseline-temperature of 32°C and ramping at 1°C/second with limits of 5°C and 50°C. Mechanical detection threshold used glass monofilaments (Optihair2-Set, Marstock Nervtest, Germany) with nominal bending forces between 0.25 and 512 mN. Mechanical pain threshold, mechanical pain sensitivity and wind up ratio were tested using blunt probes with forces ranging from 8 to 512 mN (pinprick stimulator, MRC, Heidelberg, Germany). Dynamic mechanical allodynia (DML) was tested with a cotton wisp, a cotton bud (Q-Tip) and a standardised brush designed to produce minimum friction (Somedic, Sweden). Vibration detection threshold testing used a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale). Pressure pain threshold was tested with a pressure algometer (FDN100, Wagner Instruments, Greenwich, CT, USA) with a surface area of 1 cm^2 and by applying pressure at a rate of 1 kg/cm^2 per second.

Insert table 1

Median Nerve QST Normative Data

Published normative data for DFNS QST in the hand pertain to the dorsal hand (radial nerve)[57]. Therefore, in parallel, we undertook a QST study in healthy volunteers to determine whether dorsal hand reference data is generalizable to the median nerve innervated volar hand and if not, to establish median nerve normative reference data. Imperial College Research Ethics Committee approval (IREC_13_1_10) was received on May 13th, 2014.

QST testing was performed by a single trained investigator (DK) and consistent with the DFNS QST procedure [70] employed in patients with CTS, as described in Supplementary Material 1 (https://doi.org/10.6084/m9.figshare.12860003.v2). Tests were performed at the

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dorsal hand (radial nerve innervation) and volar distal middle finger (median nerve) in one session. All Healthy Volunteer QST study procedures and results are reported in Supplementary Material 2 (https://doi.org/10.6084/m9.figshare.12860066.v2).

Significant differences were found between the dorsal and volar hand test sites for most parameters, therefore DFNS normative data for the dorsal hand [57] are not generalisable to the median nerve innervated volar hand. To generate median nerve reference data for comparison with clinical cohorts, data that was not normally distributed was transformed based on distribution properties and transformed to create a normal distribution [38;45;73]. Data was reported (not back transformed) with the mean and standard deviation as consistent with DFNS QST data analysis [57].

Statistical methods

All continuous data were tested for normality of distribution. Patient characteristics and distribution of symptom severity measures were summarized using descriptive statistics. Change in continuous measures across three time points (baseline; 3 months; 6 months) was investigated with one-way repeated measures analysis of variance (ANOVA) with post hoc Tukey HSD test and pairwise comparisons or the non-parametric Friedman test with post-hoc Wilcoxon Signed Rank Tests with Bonferroni correction, as appropriate. Magnitude of change in repeated measures was investigated with a within-subjects effect size, calculated as $r=Z/\sqrt{N}$ [22;53] and interpreted as 0.1=small, .3=medium and 0.5=large [21;63].

The distribution of QST data was assessed with skewness and kurtosis distribution parameters, statistically with the Kolmogorov-Smirnov statistic and visually with inspection

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of histograms and Normal QQ plots. Raw QST data were described with the median and interquartile range. At the group level, CTS and control QST data were compared with the Mann-Whitney U test at baseline, 3- and 6-months post-surgery. CTS QST data underwent the same data transformations as performed in healthy volunteer reference data and as reported in **Supplementary Material 2** (https://doi.org/10.6084/m9.figshare.12860066.v2). Standardised values (z-scores), were calculated for QST tests, whereby the mean control value was subtracted from the mean value of the CTS participant and divided by the standard deviation of the controls. The use of z scores enables interpretation of QST results on the individual level, values outside the range z x ± 1.96 were interpreted as abnormal [57]. Z scores with a positive value denote a gain in function (hyperalgesia) whereas a negative value a loss of function.

$$z = \frac{\text{(value of participant} - \text{mean of controls)}}{\text{Standard deviation of controls}}$$

Using the German Research Network on Neuropathic Pain (DFNS) algorithm [81], participants were defined as "healthy" or stratified to one of three sensory phenotypes primarily characterised by; 1. thermal and mechanical sensory loss (Sensory Loss); 2. preserved sensory function, associated with mild heat or cold hyperalgesia (Thermal Hyperalgesia) and 3. loss of thermal sensation, combined with mechanical hyperalgesia or allodynia (Mechanical Hyperalgesia)[6]. For clarity, and in the context of sensory testing in patients with CTS, "healthy" suggests that sensory function is not characterised by small fibre dysfunction as would be consistent with neuropathy; there may however be loss of large sensory fibre function as evidenced by reduced mechanical or vibration detection.

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Chi-square test for independence was used to investigate the relationship between categorical variables (QST derived sensory phenotype, symptom severity sub-group and surgical outcome) at baseline and 6 months post-surgery; significance is reported for the Pearson Chi-Square value or Fisher's Exact Probability Test where cell counts were less than 5. McNemar's test was used to investigate change in repeated binary measures.

Spearman's Rank Order Correlation Coefficients were performed to explore associations between symptom severity parameters and QST derived sensory phenotype. Where correlation coefficients were statistically significant ($p \leq .05$), the strength of relationship was interpreted as small r=.10 to .29; medium r=.30 to .49; large r=.50 to 1.0 [21]. Differences in symptom severity parameters, between sensory phenotypic groups, were investigated with the one-way between groups analysis of variance (ANOVA) with post hoc Tukey HSD test.

Results

Seventy-six CTS participants were enrolled between October 2014 and December 2016 and completed baseline study measures; however, 4 participants did not undergo surgery (one patient declined surgery; three patients had surgery cancelled due to ongoing medical investigations) (**Figure 1**). Baseline assessments were completed at [median (IQR)] 1(7) days prior to surgery, 3-month assessments were aimed at 90 days post-surgery and were completed at [median (IQR)] 91(31) days; 6- month assessments were aimed at 180 days post-surgery and were completed at [median (IQR)] 193(29) days. Of participants who dropped out of the study (n=3), one moved away and two reported they were too busy with work to attend.

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Insert Figure 1

Demographic data and key health parameters are reported in **Table 2.** In the majority of participants (76%) severity of nerve compression was graded from moderately to extremely severe [9]. For the generation of median nerve QST reference data, a convenience sample of fifty-four participants was selected from the Healthy volunteer QST study (Supplementary Material 2 https://doi.org/10.6084/m9.figshare.12860066.v2). Group differences for age and sex were not statistically significant (p>.05).

Insert table 2

Surgical Outcome

At 6 months post-surgery, 59 (92%) participants reported a good surgical outcome (completely cured 28%; much better 52%; slightly better 13%) while 5 (8%) reported a poor outcome (unchanged 5%; worse 3%), demonstrating that for the vast majority of participants median nerve decompression surgery was indeed an effective intervention.

Incidence of Neuropathic Pain

Prior to surgery, 58 (76%) of participants met the case definition for neuropathic pain based on nerve conduction studies, symptom distribution and DN4 score (**Table 3).** At three months post-surgery, 11 (17%) participants had two or more abnormal QST scores indicating loss of sensory function consistent with a classification of neuropathic pain; at 6 months post-surgery

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11 (18%) had two or more abnormal QST scores. At all time points, localisation of pain within the median nerve distribution was most common. Participant reported pain distribution was not associated with the severity of nerve compression on nerve conduction studies (p=.44) or duration of symptoms prior to surgery (p=.89). Improvement (decrease) in DN4 scores was statistically significant at three months post-surgery (p<.001) and from baseline to 6 months post-surgery (p<.001) with a large effect size. There was a comparable reduction in the number of patients meeting the case definition for neuropathic pain; likewise, change was statistically significant from baseline to 3 months and baseline to six months (p<.001).

Insert Table 3

Pain parameters

All pain and symptom severity parameters were normally distributed. There was a significant effect for time (p < .001) and the magnitude of the effect size was large for all pain parameters (**Table 4**). Pairwise comparisons demonstrate a statistically significant decrease in pain and symptom severity for all pain parameters from baseline to 3 months and baseline to 6 months. Symptom Severity Scale score was not associated with severity of nerve compression on electrophysiological testing (p=.88).

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Insert Table 4

Somatosensory function and sensory phenotype

Descriptive data (raw, not transformed) and differences in QST results for CTS participants and controls at baseline, 3- and 6-month assessments are reported in **Table 5**. Statistically significant differences for CTS compared to controls persist from baseline to 6 months post-surgery for cold detection threshold, thermal sensory limen, heat pain threshold, pressure pain thresholds, mechanical detection threshold and vibration detection threshold, demonstrating persistent small (Aδ, C) and large sensory fibre (Aβ) dysfunction. Dynamic mechanical allodynia is a pathological sensory response and was not exhibited by controls or CTS participants at any time point. Paradoxical heat sensations, also a pathological response, were not observed in controls and only infrequently observed in CTS participants (pre-surgery 14% participants; 3 months post-surgery 17%; 6 months post-surgery 10%.

Insert Table 5

Internal Responsiveness

CTS QST data was transformed, and Z scores calculated using transformed control group mean and standard deviations. Change in Z scores for repeated-measures QST thermal modalities from baseline to 6 months are illustrated in **Figure 2**; change in mechanical measures in **Figure 3**. Change in QST parameters across evaluations was statistically significant for thermal detection thresholds, thermal pain thresholds and mechanical detection thresholds from baseline to 3 months and baseline to 6 months. Changes in mechanical pain measures (mechanical pain threshold, mechanical pain sensitivity and pressure pain threshold) were not statistically significant at any time point. The magnitude of change (effect

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size) was large for warm detection threshold, thermal sensory limen and mechanical detection threshold. A moderate effect size was identified for cold detection threshold, cold pain threshold, heat pain threshold and vibration detection threshold; change in pressure pain threshold was statistically significant only from baseline to 3 months post-surgery and magnitude of change was small (**Table 6**).

Insert Figure 2

Insert Figure 3

Insert Table 6

QST Derived Sensory Phenotype

Prior to surgery, 21% of participants were classified as having a "healthy" QST derived sensory phenotype [81]. At all evaluations, healthy profile, thermal and mechanical hyperalgesia phenotypes were more common than sensory loss phenotypes (**Fig 4**). Statistically significant change in sensory phenotype was detected from baseline to 3 months post-surgery ($p<.001$) and 3 months to 6-months post-surgery ($p<.001$). The association of disease severity measures with sensory phenotype at baseline and 6 months was investigated.

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Neither the duration of symptoms prior to surgery, localisation of symptoms (median, extra-median or non-median distribution) or the severity of nerve compression based on nerve conduction studies was associated with sensory phenotype at either time point ($p > .05$). At 6 months post-surgery, recovering sensory function is demonstrated by normalising QST values (**Figs 2;3**) and improvement in participant reported pain and symptom severity parameters **(Tables 4;7)**. Healthy sensory profile (23%) and thermal hyperalgesia phenotype (46%) predominate, however, mechanical hyperalgesia (18%) and sensory loss (13%) phenotypes persist in one third of the sample.

Insert Figure 4

External Responsiveness

To investigate the external responsiveness of QST derived sensory phenotype we explored the association of sensory phenotype with corresponding reference measures of pain and symptom severity at baseline, 3- and 6-months post-surgery. Baseline pain and symptom severity parameters were not found to be associated with sensory phenotype, however, there was a significant correlation between pain parameters and sensory phenotype at 3- and 6-months post-surgery. (**Table 7**). Dimensions of neuropathic pain, by QST sensory phenotype, were further explored with the NPSI subscales (burning pain; pressing pan; paroxysmal pain; evoked pain; paraesthesia) at baseline and 6 months. Pain burden, again, is lower across all pain dimensions for participants with a healthy QST profile, however differences in pain dimensions between phenotypes were not statistically significant. Paraesthesia was the most common and most severe pain dimension, reported at baseline by 96% of participants and

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rated as severe by 65% of those. At 6 months, the frequency of reporting of each dimension was reduced, with 58% of participants reporting no symptoms.

Insert Table 7

Baseline Symptom Severity Scale scores (SSS) were used to stratify participants into pain dominant (n=27; 36%), paraesthesia dominant (n=37; 49%) or mixed symptom (n=12; 16%) subgroups. In participants with a baseline healthy sensory profile (21% of cohort), thermal hyperalgesia (29%) and sensory loss phenotype (18%), symptoms of paraesthesia predominate (in 69%, 50% and 71% of phenotypic group participants, respectively). In contrast, in participants with a mechanical hyperalgesia phenotype (32% of cohort), symptoms of pain predominate (in 54% of phenotype). A statistically significant association was found for QST derived sensory phenotype and SSS symptom subgroups (Fisher's Exact Test, 2-sided, p=.027) (**Fig 5**), demonstrating that QST derived sensory phenotype is consistent with or reflects patient reported pain and sensory dysfunction.

Insert Figure 5

Differences in pain and symptom severity parameters between sensory phenotypic groups were explored with the DN4, BPI Pain Severity Score, NPSI total score and Symptom Severity Scale score at base line and 6 months post-surgery (**Table 8**). At baseline, pain and symptom severity score ratings are lowest in participants with a healthy profile phenotype and highest in those with a sensory loss phenotype, however group differences were not

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statistically significant. Group differences persist at 6 months post-surgery, with statistically significant differences detected between sensory phenotypic groups for the DN4, NPSI total score and symptom severity score. Differences in pain and symptom severity parameters, between phenotypic groups at baseline, 3- and 6-months post-surgery are illustrated in **Figure 6**. Statistically significant differences were found in DN4 scores between healthy profile and sensory loss phenotypes at 6 months post-surgery. Pain severity scores are greatest in those with mechanical hyperalgesia and sensory loss phenotypes as compared to those with a healthy profile at 3- and 6-months post-surgery, however phenotypic differences do not reach statistical significance (healthy profile compared to sensory loss; p=.06). For the NPSI total score and Symptom Severity Scale score, statistically significant differences were detected at both 3- and 6-months post-surgery (healthy profile compared to sensory loss phenotype; thermal hyperalgesia compared to sensory loss phenotype).

Insert Table 8

Insert Figure 6

The association of sensory phenotype and patient-reported surgical outcome was explored with the Chi-square test for independence. Considering baseline, pre-operative phenotype, differences in outcome between phenotypic groups were observed; a good surgical outcome was reported by 100% of those with a healthy sensory profile, 95% with thermal

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hyperalgesia, 91% sensory loss and 85% with mechanical hyperalgesia, nonetheless group differences were not statistically significant (Fisher's Exact test p=.51). Sensory phenotype at 6 months was found, however, to be associated with patient reported surgical outcome (**Fig 7**). Of participants with a healthy sensory profile at 6 months, 93% reported a good surgical outcome, as did 100% of those with thermal hyperalgesia and 88% of those with sensory loss, while only 73% of participants with a mechanical hyperalgesia phenotype reported a good surgical outcome. Fisher's Exact Probability Test indicated a significant association between sensory phenotype and good versus poor outcome at 6 months, χ^2 (3, n = 61) = 7.46, p = .02. The effect size for this finding, Cramers's V, was moderate, .36 [21].

Insert Figure 7

Discussion

This novel study is the first to evaluate the responsiveness of DFNS QST and QST derived sensory phenotype in a longitudinal study of patients with compressive neuropathy following disease modifying intervention. A carpal tunnel surgery model was chosen as patients with CTS present with mixed pain and paraesthesia symptomology; there is a psychometrically robust comparator assessment of pain and paraesthesia in this clinical cohort and there is a disease modifying treatment of established efficacy for CTS. Comprehensive evidence for the responsiveness of DFNS QST and sensory phenotype were identified.

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Internal responsiveness refers to the ability of an instrument to capture change over time. In the present study, statistically significant change was detected for the majority of DFNS QST modalities and in sensory phenotype at 3- and 6-months post-surgery. External responsiveness is the degree to which change in an instrument is associated with change in a corresponding reference measure. Clinically relevant reference measures, the Symptom Severity Scale, DN4, NPSI and BPI pain severity score, demonstrated significant improvement post-surgery. Pain and symptom severity reference measures were associated with sensory phenotype at 3- and 6-months post-surgery. At 3- and 6-months post-surgery, differences in symptom severity, between sensory phenotypic groups, were statistically significant. Additionally, pain and paraesthesia subgroups, derived from the patient-reported baseline SSS, were associated with sensory phenotype. Therefore, in patients with carpal tunnel syndrome, change in sensory phenotype reflects clinically relevant change.

Establishing the responsiveness of QST derived sensory phenotype has important implications for clinical practice and research. Instrument responsiveness suggests sensory phenotype might be employed to determine if treatment is resulting in clinically important change, to evaluate the effectiveness of programs of care and might underpin the identification of subgroups of patients who most benefit from care. For research purposes, the responsiveness of sensory phenotype suggests that statistically significant, clinically important change can be identified longitudinally. Furthermore, the magnitude of change, or effect size, is relevant for determining requisite study sample size.

Previous investigations in patients with CTS report an association between the severity of nerve compression on nerve conduction studies and the distribution of paraesthesias [17;85].This association was not identified here, however, we explored pain distribution,

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rather than paraesthesia, as our aim was to establish if pain distribution supported the categorisation of pain as neuropathic. In patients with CTS, there is good evidence that the severity of physiologic nerve compression is not associated with patient reported symptom severity [39;55;78]; this dissociation was observed in the present cohort. Sensory phenotype, similarly, while not associated with the severity of physiologic nerve compression, was associated with patient reported symptoms. In patients with CTS, symptom severity and sensory phenotype are independent of electrophysiologic measures of disease severity and may reflect heterogeneity in underlying neuropathophysiology.

In this sample, a good surgical outcome was reported by 92% of participants. However, in this pragmatic cohort, a lenient cut-point of 3 (slightly better) was chosen a priori to determine surgical success. If a more stringent cut-point of grade of 4 (much better) was taken, then a good outcome would have been reported by 80% of participants and is more in keeping with the literature [10].

In patients with peripheral neuropathic pain, the frequency of DFNS QST derived sensory phenotypes, thought to reflect different neurobiological mechanisms, differ between aetiologies [6]. Tampin et al. [74] described the distribution of QST derived sensory phenotypes in a cohort of 103 patients with CTS (healthy profile 23%; thermal hyperalgesia 20%; mechanical hyperalgesia 32%; sensory loss 18%). Except for a higher frequency of thermal hyperalgesia (29%) in our cohort at baseline, phenotype distribution was similar and comparable to that reported in patients with peripheral nerve injury [6]. Variability in the

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distribution of phenotypes between CTS cohorts may result from differences in median nerve test site or in control data.

Intriguingly, we observed a decrease in the frequency of participants with a healthy sensory profile and increase in thermal hyperalgesia between 3 and 6-months post-surgery. Heat pain threshold demonstrated significant change up to 6 months post-surgery, and differences between CTS patients and controls become significant at 6 months. Change in sensory phenotype has not previously been reported in a carpal tunnel surgery cohort, however Baskozos et al. [7] similarly reported an increase in thermal sensitivity in CTS patients at 6 months post-surgery. Baskozos et al. demonstrate, histologically and electrodiagnostically, that while recovery of large and small fibre function is observed following median nerve decompression, recovery remains incomplete at 6 months. It is unclear, beyond 6 months, if small fibre function recovers further and thermal hyperalgesia resolves.

In the present cohort, prior to median nerve decompression surgery, loss of thermal detection (small fibre) and/or mechanical detection (large fibre) was more commonly observed than gain to thermal or mechanical stimuli. After surgery, while measures of large fibre function demonstrate significant improvement, at 6 months they remain reduced relative to reference data suggesting recovering but persistent dysfunction. In contrast, a mixed pattern of small fibre function recovery is observed. Cold detection threshold and thermal sensory limen improve significantly but remain reduced at 6 months, whereas warm detection threshold and cold pain threshold normalise at 3 months post-surgery.

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While less common, gain of function was observed at baseline in mechanical pain measures (wind up ratio, mechanical pain threshold, mechanical pain sensitivity and pressure pain threshold) (**Fig 3**). Wind-up ratio, a measure of pathological response of small Aδ fibre function, normalises at 3 months post-surgery while pressure pain threshold decreases across assessments and remains significantly reduced at 6 months post-surgery. However, as pressure pain threshold was tested at the thenar eminence, near to the surgical incision, increase in pressure pain sensitivity may be consistent with post-surgical nociceptive pain.

As noted, Baskozos et al. [7] previously reported longitudinal change in DFNS QST in patients following carpal tunnel surgery. Consistent with our findings, their sample presented with reduced thermal and mechanical detection thresholds pre-surgery. While improvement in small and large fibre encoded modalities was observed post-surgery, sensory function does not normalise relative to control data. Their work provides further evidence for the responsiveness of DFNS QST. While 83% of their sample report a good surgical outcome, there is persistent somatosensory dysfunction on QST that is consistent with findings on post-surgical electrophysiological studies. Furthermore, somatosensory dysfunction is consistent with participant reported symptom severity; symptoms improve however approximately 50% of patients continue to report pain and 38% paraesthesia or numbness.

Equivocal findings for individual QST modalities between the Baskozos et al. sample and our results may arise from differences in administration of the DFNS QST protocol or in control data. Whereas Baskozos et al. performed sensory testing at the volar proximal phalanx of the index finger, the present sample was tested at the volar distal phalanx of the middle finger, purported to be more sensitive to sensory change in patients with CTS [29]. We demonstrated, in our healthy volunteer QST study, that published DFNS QST reference data for the dorsum of the hand [57] are not generalisable to the median nerve innervated volar

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hand. In the absence of published median nerve reference data, investigators are reliant upon generating comparator QST control data, possibly resulting in discrepancies between studies. CTS is the most common of the entrapment neuropathies [61] and median nerve decompression surgery is one of the most commonly performed surgical procedures in the hand [8]. Future studies of median nerve somatosensory function can be anticipated and will benefit from the availability of published reference data for the DFNS QST protocol [70] for the median nerve distribution of the hand.

Study limitations

Addressing risk of bias

This study was reported according to STROBE guidelines [82] to reduce reporting bias. All patients scheduled for carpal tunnel surgery were invited to participate, however it is impossible to control for participant-selection bias. In clinical studies of this nature, the clinician-patient interaction cannot be ruled out and may influence or bias the patients' perception or judgment of outcome. To reduce the likelihood of assessor bias the investigator (D.K.) was blinded to patient reported results of surgical outcome until patients completed the trial, however, no post hoc analysis was conducted to determine if or how often blinding was broken. The completed measures were placed in pre-labeled, coded envelopes by study participants and secured in the written case report form. As the baseline and post-surgical measures were completed by one investigator in the present study, there is risk of investigator bias.

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Conclusions

In a carpal tunnel surgery model, DFNS QST and QST derived sensory phenotype identify statistically significant and clinically relevant change in somatosensory function after disease modifying intervention. Sensory phenotype at 6 months post-surgery was associated with and identified statistically significant differences in patient-reported surgical outcome. Following an efficacious intervention, significant differences were detected in persistent pain and symptom severity between phenotypic groups. QST derived sensory phenotype was not associated with disease severity measures including the duration or localisation of symptoms or severity of nerve compression and may reflect underlying neuropathophysiology. Future investigations of variables associated with sensory phenotype heterogeneity may yield evidence informing the elucidation of variability in response to intervention and underpin advances in personalised medicine. Our findings demonstrate QST derived sensory phenotype is responsive, enabling the identification of clinically important change.

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Contributions: DLK and ASCR designed the study. DR, JV CMA contributed to study concept and interpretation. DLK performed all participant testing. JV, DR and DLK performed statistical analysis. All authors contributed to drafting and critically revising the manuscript.

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Conflicts of interest:

DLK; DR; CMA Nothing to declare

JV: Received personal fees from Casquar, outside of the submitted work.

ASCR:

- IASP Council Member and Chair 18th World Congress on Pain Scientific Programme Committee
- ASCR undertakes consultancy and advisory board work for Imperial College Consultants- in the last 24 months this has included remunerated work for: Abide, Pharmanovo, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Asahi Kasei, Toray & Theranexis
- ASCR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015 and from which payments continued until 2019.
- ASCR is named as an inventor on patents:

1. Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl) hexadecanamide and related amides to relieve pain. WO 2005/079771
2. Okuse K. et al Methods of treating pain by inhibition of vgf activity EP13702262.0/ WO2013 110945

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References

[1] Andersen KG, Duriaud HM, Jensen HE, Kroman N, Kehlet H. Predictive factors for the development of persistent pain after breast cancer surgery. Pain 2015;156(12):2413-2422.

[2] Arendt-Nielsen L, Yarnitsky D. Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. J Pain 2009;10(6):556-572.

[3] Backonja MM, Walk D, Edwards RR, Sehgal N, Moeller-Bertram T, Wasan A, Irving G, Argoff C, Wallace M. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. Clin J Pain 2009;25(7):641-647.

[4] Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9(8):807-819.

[5] Baron R, Forster M, Binder A. Subgrouping of patients with neuropathic pain according to pain-related sensory abnormalities: a first step to a stratified treatment approach. Lancet Neurol 2012;11(11):999-1005.

[6] Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, Finnerup NB, Haanpaa M, Hansson P, Hullemann P, Jensen TS, Freynhagen R, Kennedy JD, Magerl 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(2):261-272.

[7] Baskozos G, Sandy-Hindmarch O, Clark AJ, Windsor K, Karlsson P, Weir GA, McDermott LA, Burchall J, Wiberg A, Furniss D, Bennett DLH, Schmid AB. Molecular and cellular correlates of human nerve regeneration: ADCYAP1/PACAP enhance nerve outgrowth. Brain 2020;143(7):2009-2026.

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

[8] Bebbington E, Furniss D. Linear regression analysis of Hospital Episode Statistics predicts a large increase in demand for elective hand surgery in England. J Plast Reconstr Aesthet Surg 2015;68(2):243-251.

[9] Bland JD. A neurophysiological grading scale for carpal tunnel syndrome. Muscle Nerve 2000;23(8):1280-1283.

[10] Bland JD. Treatment of carpal tunnel syndrome. Muscle Nerve 2007;36(2):167-171.

[11] Bland JD, Rudolfer SM. Ultrasound imaging of the median nerve as a prognostic factor for carpal tunnel decompression. Muscle Nerve 2014;49(5):741-744.

[12] Borg K, Lindblom U. Diagnostic value of quantitative sensory testing (QST) in carpal tunnel syndrome. Acta Neurol Scand 1988;78(6):537-541.

[13] Borges NC, Pereira LV, de Moura LA, Silva TC, Pedroso CF. Predictors for Moderate to Severe Acute Postoperative Pain after Cesarean Section. Pain Res Manag 2016;2016:5783817.

[14] Bouhassira D, Attal N, Alchaar H, Boureauc F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lante´ri-Minet M, Laurent B, Mickk G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 2005;114:29-36.

[15] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108(3):248-257.

[16] British Society for Surgery of the Hand. Carpal Tunnel Syndrome. London, 2016. https://www.bssh.ac.uk/patients/conditions/21/carpal_tunnel_syndrome.

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

[17] Caliandro P, La Torre G, Aprile I, Pazzaglia C, Commodari I, Tonali P, Padua L. Distribution of paresthesias in Carpal Tunnel Syndrome reflects the degree of nerve damage at wrist. Clin Neurophysiol 2006;117(1):228-231.

[18] Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52(1):77-92.

[19] Clark D, Amirfeyz R, Leslie I, Bannister G. Often atypical? The distribution of sensory disturbance in carpal tunnel syndrome. Ann R Coll Surg Engl 2011;93(6):470-473.

[20] Cleeland CS. Measurement of pain by subjective report. LJ Chapman CR, editor. In: Advances in Pain Research and Therapy, Vol. 12: Issues in Pain Measurement. New York: Raven Press, 1989. pp. 391-403.

[21] Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, New Jersey: Lawrence Erlbaum Associates, 1988.

[22] Conroy R. What hypotheses do “nonparametric” two-group tests actually test? The Stata Journal 2012;12(2):182–190.

[23] Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A, Burczynski ME, Crean C, Edwards R, Gaudilliere B, Hergenroeder GW, Iadarola MJ, Iyengar S, Jiang Y, Kong JT, Mackey S, Saab CY, Sang CN, Scholz J, Segerdahl M, Tracey I, Veasley C, Wang J, Wager TD, Wasan AD, Pelleymounter MA. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. Nat Rev Neurol 2020;16(7):381-400.

[24] De Carvalho Leite JC, Jerosch-Herold C, Song F. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire. BMC Musculoskelet Disord 2006;7:78.

[25] Demant DT, Lund K, Vollert J, Maier C, Segerdahl M, Finnerup NB, Jensen TS, Sindrup SH. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. Pain 2014;155(11):2263-2273.

[26] Deyo RA, Diehr P, Patrick DL. Reproducibility and responsiveness of health status measures. Statistics and strategies for evaluation. Control Clin Trials 1991;12(4 Suppl):142S-158S.

[27] Dyck PJ. Quantitative sensory testing: a consensus report from the peripheral neuropathy association. Neurology 1993;43(5):1050-1052.

[28] Edwards RR, Fillingim RB. Age-associated differences in responses to noxious stimuli. J Gerontol A Biol Sci Med Sci 2001;56(3):M180-185.

[29] Elfar JC, Yaseen Z, Stern PJ, Kiefhaber TR. Individual finger sensibility in carpal tunnel syndrome. J Hand Surg Am 2010;35(11):1807-1812.

[30] European Medicines Agency. Guideline on the clinical development of medicinal products intended for the treatment of pain, EMA/CHMP/970057/2011, 2016.

[31] Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 1998;5(4):209-227.

[32] Forstenpointner J, Ruscheweyh R, Attal N, Baron R, Bouhassira D, Enax-Krumova EK, Finnerup NB, Freynhagen R, Gierthmuhlen J, Hansson P, Jensen TS, Maier C, Rice ASC, Segerdahl M, Tolle T, Treede RD, Vollert J. No pain, still gain (of function): the relation between sensory profiles and the presence or absence of self-reported pain in a large multicenter cohort of patients with neuropathy. Pain 2020.

[33] Freeman R, Baron R, Bouhassira D, Cabrera J, Emir B. Sensory profiles of patients with neuropathic pain based on the neuropathic pain symptoms and signs. Pain 2014;155(2):367-376.

[34] Gierthmuhlen J, Schneider U, Seemann M, Freitag-Wolf S, Maihofner C, Enax-Krumova EK, Azad SC, Uceyler N, Birklein F, Maier C, Tolle T, Treede RD, Baron R.

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

Can self-reported pain characteristics and bedside test be used for the assessment of pain mechanisms? An analysis of results of neuropathic pain questionnaires and quantitative sensory testing. Pain 2019;160(9):2093-2104.

[35] Gilron I, Carr DB, Desjardins PJ, Kehlet H. Current methods and challenges for acute pain clinical trials. Pain Rep 2019;4(3):e647.

[36] Gracely RH. Pain measurement. Acta Anaesthesiol Scand 1999;43(9):897-908.

[37] Greenspan JD. Quantitative assessment of neuropathic pain. Cur Pain Headache Rep 2001;5(2):107-113.

[38] Grissom RJ. Heterogeneity of variance in clinical data. J Consult Clin Psychol 2000;68(1):155-165.

[39] Gursoy AE, Kolukisa M, Yildiz GB, Kocaman G, Celebi A, Kocer A. Relationship between electrodiagnostic severity and neuropathic pain assessed by the LANSS pain scale in carpal tunnel syndrome. Neuropsychiatr Dis Treat 2013;9:65-71.

[40] Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis 1987;40(2):171-178.

[41] Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, Cruccu G, Hansson P, Haythornthwaite J, Iannetti G, Jensen T, Kauppila T, Nurmikko T, Rice A, Rowbotham M, Serra J, Sommer C, Smith B, Treede RD. NeuPSIG guidelines on neuropathic pain assessment. Pain 2011;152:14-27.

[42] Haanpaa ML, Laippala PA, Nurmikko TJ. Thermal and tactile perception thresholds in acute herpes zoster. Eur J Pain 1999;3(4):375-386.

[43] Haroun OMO, Vollert J, Lockwood DN, Bennett DLH, Pai VV, Shetty V, Wakade AV, Khodke AS, Schilder A, Pfau D, Enax-Krumova EK, Maier C, Treede RD, Rice ASC. Clinical characteristics of neuropathic pain in leprosy and associated somatosensory profiles: a deep phenotyping study in India. Pain Rep 2019;4(6):e743.

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

[44] Holbech JV, Bach FW, Finnerup NB, Jensen TS, Sindrup SH. Pain phenotype as a predictor for drug response in painful polyneuropathy-a retrospective analysis of data from controlled clinical trials. Pain 2016;157(6):1305-1313.

[45] Howell DC. Statistical methods for psychology. Belmont, CA:: Thomson Wadsworth, 2007.

[46] Huisstede BM, Randsdorp MS, Coert JH, Glerum S, van Middelkoop M, Koes BW. Carpal tunnel syndrome. Part II: effectiveness of surgical treatments--a systematic review. Arch Phys Med Rehabil 2010;91(7):1005-1024.

[47] Husted JA, Cook RJ, Farewell VT, Gladman DD. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol 2000;53(5):459-468.

[48] Jensen TS, Baron R, Haanpaa M, Kalso E, Loeser JD, Rice AS, Treede RD. A new definition of neuropathic pain. Pain 2011;152(10):2204-2205.

[49] Jerosch-Herold C MR, Chojnowski A. A Qualitative Study of the Experiences and Expectations of Surgery in Patients with Carpal Tunnel Syndrome. J Hand Ther 2008;21:54-62.

[50] Jerosch-Herold C, Shepstone L, Miller L, Chapman P. The responsiveness of sensibility and strength tests in patients undergoing carpal tunnel decompression. BMC Musculoskelet Disord 2011;12:244.

[51] Jerosch-Herold C, Shepstone L, Wilson EC, Dyer T, Blake J. Clinical course, costs and predictive factors for response to treatment in carpal tunnel syndrome: the PALMS study protocol. BMC Musculoskelet Disord 2014;15:35.

[52] Katz JN, Larson MG, Sabra A, Krarup C, Stirrat CR, Sethi R, Eaton HM, Fossel AH, Liang MH. The carpal tunnel syndrome: diagnostic utility of the history and physical examination findings. Ann Intern Med 1990;112(5):321-327.

ACCEPTED

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[53] Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front Psychol 2013;4:863.

[54] Levine DW, Simmons BP, Koris MJ, Daltroy LH, Hohl GG, Fossel AH, Katz JN. A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg Am 1993;75(11):1585-1592.

[55] Longstaff L, Milner RH, O'Sullivan S, Fawcett P. Carpal tunnel syndrome: the correlation between outcome, symptoms and nerve conduction study findings. J Hand Surg Br 2001;26(5):475-480.

[56] Maeda Y, Kettner N, Kim J, Kim H, Cina S, Malatesta C, Gerber J, McManus C, Libby A, Mezzacappa P, Mawla I, Morse LR, Audette J, Napadow V. Primary somatosensory/motor cortical thickness distinguishes paresthesia-dominant from pain-dominant carpal tunnel syndrome. Pain 2016;157(5):1085-1093.

[57] Magerl W, Krumova EK, Baron R, Tolle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. Pain 2010;151(3):598-605.

[58] Maier C, Baron R, Tolle TR, Binder A, Birbaumer N, Birklein F, Gierthmuhlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihofner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uceyler N, Valet M, Wasner G, Treede RD. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain 2010;150(3):439-450.

[59] Max MB. Towards physiologically based treatment of patients with neuropathic pain. Pain 1990;42(2):131-137.

[60] Naranjo A, Ojeda S, Arana V, Baeta P, Fernandez-Palacios J, Garcia-Duque O, Rodriguez-Lozano C, Carmona L. Usefulness of clinical findings, nerve conduction

ACCEPTED

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studies and ultrasonography to predict response to surgical release in idiopathic carpal tunnel syndrome. Clin Exp Rheumatol 2009;27(5):786-793.

[61] Padua L, Coraci D, Erra C, Pazzaglia C, Paolasso I, Loreti C, Caliandro P, Hobson-Webb LD. Carpal tunnel syndrome: clinical features, diagnosis, and management. Lancet Neurol 2016;15(12):1273-1284.

[62] Padua L, Padua R, Lo Monaco M, Aprile I, Tonali P. Multiperspective assessment of carpal tunnel syndrome: a multicenter study. Italian CTS Study Group. Neurology 1999;53(8):1654-1659.

[63] Pallant J. Effect Size. SPSS Survival Manual. Maidenhead, Berkshire, England: McGraw Hill, 2013. p. 238.

[64] Pfau DB, Krumova EK, Treede RD, Baron R, Toelle T, Birklein F, Eich W, Geber C, Gerhardt A, Weiss T, Magerl W, Maier C. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): reference data for the trunk and application in patients with chronic postherpetic neuralgia. Pain 2014;155(5):1002-1015.

[65] Phillips TJ, Brown M, Ramirez JD, Perkins J, Woldeamanuel YW, Williams AC, Orengo C, Bennett DL, Bodi I, Cox S, Maier C, Krumova EK, Rice AS. Sensory, psychological, and metabolic dysfunction in HIV-associated peripheral neuropathy: A cross-sectional deep profiling study. Pain 2014;155(9):1846-1860.

[66] Reimer M, Helfert SM, Baron R. Phenotyping neuropathic pain patients: implications for individual therapy and clinical trials. Curr Opin Support Palliat Care 2014;8(2):124-129.

[67] Riley JL, 3rd, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998;74(2-3):181-187.

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

[68] Riley RD, Hayden JA, Steyerberg EW, Moons KG, Abrams K, Kyzas PA, Malats N, Briggs A, Schroter S, Altman DG, Hemingway H, Group P. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. PLoS med 2013;10(2):e1001380.

[69] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, 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(3):231-243.

[70] Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10(1):77-88.

[71] Schmid AB, Bland JD, Bhat MA, Bennett DL. The relationship of nerve fibre pathology to sensory function in entrapment neuropathy. Brain 2014;137(Pt 12):3186-3199.

[72] Shi Q, MacDermid JC. Is surgical intervention more effective than non-surgical treatment for carpal tunnel syndrome? A systematic review. J Orthop Surg Res 2011;6:17.

[73] Tabachnick BG, Fidell LS. Using multivariate statistics. Boston: Allyn and Bacon, 2007.

[74] Tampin B, Vollert J, Schmid AB. Sensory profiles are comparable in patients with distal and proximal entrapment neuropathies, while the pain experience differs. Curr Med Res Opin 2018:1-8.

[75] Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5(2):133-137.

[76] Themistocleous AC, Ramirez JD, Shillo PR, Lees JG, Selvarajah D, Orengo C, Tesfaye S, Rice AS, Bennett DL. The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. Pain 2016;157(5):1132-1145.

ACCEPTED

Copyright © 2021 by the International Association for the Study of Pain. Unauthorized reproduction of this article is prohibited.

[77] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008;70(18):1630-1635.

[78] Turgut STAİ, A; Selimoğlu, E; Atlığ, R. S; Adatepe T; Mesci E. The Relationship Between Electrodiagnostic Findings and the DN4 Questionnaire in Patients with Carpal Tunnel Syndrome. J Musculoskelet Pain 2013;21(1):19-22.

[79] Vale TA, Symmonds M, Polydefkis M, Byrnes K, Rice ASC, Themistocleous AC, Bennett DLH. Chronic non-freezing cold injury results in neuropathic pain due to a sensory neuropathy. Brain 2017;140(10):2557-2569.

[80] Verdugo RJ, Salinas RA, Castillo JL, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. The Cochrane database of systematic reviews 2008(4):CD001552.

[81] Vollert J, Maier C, Attal N, Bennett DLH, Bouhassira D, Enax-Krumova EK, Finnerup NB, Freynhagen R, Gierthmuhlen J, Haanpaa M, Hansson P, Hullemann P, Jensen TS, Magerl W, Ramirez 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(8):1446-1455.

[82] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453-1457.

[83] Wylde V, Sayers A, Lenguerrand E, Gooberman-Hill R, Pyke M, Beswick AD, Dieppe P, Blom AW. Preoperative widespread pain sensitization and chronic pain after hip and knee replacement: a cohort analysis. Pain 2015;156(1):47-54.

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[84] Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best L-A, Granot M. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain 2008;138(1):22-28.

[85] Zanette G, Cacciatori C, Tamburin S. Central sensitization in carpal tunnel syndrome with extraterritorial spread of sensory symptoms. Pain 2010;148(2):227-236.

[86] Zanette G, Marani S, Tamburin S. Extra-median spread of sensory symptoms in carpal tunnel syndrome suggests the presence of pain-related mechanisms. Pain 2006;122(3):264-270.

Figure legends

Figure 1. Participant recruitment. Flow diagram of the recruitment of study participants

Figure 2. Change in QST thermal measures

Boxes represent the standard deviation, the centre line the mean. The black upper dotted line represents + 1.96z, the bottom dotted line - 1.96z. Scores between the two are interpreted as normal, those above as gain of function and below as loss of function. Significance is denoted as * at the 0.05 probability level; ** at 0.01; *** at 0.001. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; TSL, thermal sensory limen; WDT, warm detection threshold.

Figure 3. Change in QST mechanical measures

Boxes represent the standard deviation, the centre line the mean. The black upper dotted line represents + 1.96z, the bottom dotted line - 1.96z. Scores between the two are interpreted as

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normal, those above as gain of function and below as loss of function. Significance is denoted as * at the 0.05 probability level; ** at 0.01; *** at 0.001. NS; not statistically significant. MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WUR, wind-up ratio.

Figure 4. Sensory phenotypes at baseline and 3- and 6-months post-surgery.

Figure 5. Percentage of participants with pain or paraesthesia dominant symptoms or mixed symptoms (pain and paraesthesia in equal measures) by sensory phenotype, at baseline.

Figure 6. Pain and symptom severity parameters explored by sensory phenotype at baseline, 3- and 6-months post-surgery. A. DN4; B. BPI Pain Severity Score; C. Neuropathic Pain Symptom Inventory (NPSI); D. Symptom Severity Scale score. Significance for Multiple Comparisons with post hoc Tukey test is denoted as * at the 0.05 probability level; ** at 0.01. *NS*, not statistically significant.

Figure 7. The association of sensory phenotype at 6 months and surgical outcome.

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Table 1. DFNS Quantitative Sensory Testing Battery (8)

	Stimulus	Fibre	Measure
Thermal Measures	Cold Detection Threshold (CDT)	Aδ	°C
	Warm Detection Threshold (WDT)	C	°C
	Thermal Sensory Limen (TSL)	Aδ & C	°C
	Paradoxical Heat Sensations (PHS)	Aδ & C (*PR*)	x3
	Cold Pain Threshold (CPT)	Aδ	°C
	Heat Pain Threshold (HPT)	C	°C
Mechanical measures	Mechanical Detection Threshold (MDT)	Aβ	mN
	Dynamic Mechanical Allodynia (DMA)	Aβ (*SRF*)	0-100
	Mechanical Pain Threshold (MPT)	Aδ	mN
	Mechanical Pain Sensitivity (MPS)	Aδ (*SRF*)	0-100
	Windup Ratio (WUR)	Aδ (*PR*)	ratio
	Vibration Detection Threshold (VDT)	Aβ	x8
	Pressure Pain Threshold (PPT)	C	kg/cm^2

PR, pathological response; *SRF,* stimulus response function

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Table 2.

Baseline demographic parameters

	CTS (n=76)	Controls (n=54)
Age mean years (SD)	58.5 (13.5)	54.9 (11.3)
Female sex n (%)	65 (86)	38 (70)
BMI mean (SD)	28.8 (6.8)	
Duration of CTS symptoms median months (IQR)	36 (42)	
Nerve conduction study severity (54) n (%)		
normal	3 (4)	
very mild	3 (4)	
mild	16 (21)	
moderately severe	22 (29)	
severe	14 (18)	
very severe	16 (21)	
extremely severe	2 (3)	

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Table 3

Incidence of neuropathic pain across assessments

Measure	Baseline (n=76)	3 months	6 months	ANOVA sig	Effect size
DN4 mean (*sd*)	5.39 (2.05)	1.81 (1.77)	1.29 (1.91)	<.001	.76
Pain distribution n (%)					
Pain free	7 (9)	17 (25)	25 (40)		
Median nerve	44 (60)	39 (57)	28 (45)		
Extra-median	24 (32)	9 (12)	8 (13)		
Non-median	1 (1)	4 (5)	1 (2)		
Neuropathic pain n (%)	58 (76%)	7 (11%)	7 (12%)		

Change in DN4, pain distribution and percentage of participants categorised as having neuropathic pain at baseline; 3- and 6-months post-surgery. Change in DN4 between time points was investigated with the Paired-Samples T-test. Change from baseline to 3 months and baseline to 6 months was statistically significant (p <.001); change from 3 months to 6 months was not (p=.09). 3-month sample size: DN4 and neuropathic pain n=65; pain distribution n=69. 6-month sample size: DN4 and neuropathic pain n=61, pain distribution n=62. *Sd*, standard deviation; sig, statistical significance.

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Table 4

Change in pain parameters across assessments

Measure	Baseline	3 months	6 months	ANOVA sig	Effect size
Comparisons	Baseline- 3 months	3 - 6 months	Baseline- 6 months		
BPI pain severity (1-10)	4.17 (2.73)	1.89 (2.48)	1.45 (2.15)	<.001	.49
Paired t-test sig	<.001	.35	<.001		
NPSI (0-100)	35.3 (24.2)	14.52 (18.97)	9.55 (15.0)	<.001	.57
Paired t-tests sig	<.001	.006	<.001		
Symptom Severity Score (1-5)	3.18 (.81)	1.78 (.73)	1.64 (.74)	<.001	.78
Paired t-test sig	<.001	.052	<.001		
Baseline, 3 month and 6-month data reported with mean and standard deviation. Sig, statistical significance.					

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Table 5

Comparison of QST results for CTS patients and controls

Test	Controls n=54	CTS Baseline n=76		CTS 3 months n=65		CTS 6 months n=61	
			sig		sig		sig
CDT, °C	-3.09 (3.02)	-5.65 (5.39)	**<.001**	- 4.43 (3.69)	**.05**	-3.9 (4.39)	**.04**
WDT, °C	5.75 (4.99)	7.19 (5.0)	**.004**	5.53 (4.51)	.46	6.3 (5.07)	.41
TSL, °C	9.85 (7.06)	15.01 (10.6)	**<.001**	10.67 (9)	.15	11.53 (8.33)	**.05**
CPT, °C	10.53 (10.96)	5.0 (8.72)	**.003**	8.37 (13.17)	.58	10.7 (14.3)	.65
HPT, °C	47.22 (5.31)	46.79 (5.87)	.67	45.37 (6.30)	.14	43.53 (5.59)	**.02**
PPT, kg/ cm^2	401 (208.75)	376 (173.5)	**.02**	356 (168)	**.001**	356 (175.5)	**.02**
MPT, mN	152.43 (171.6)	100.49 (195.25)	.06	119.43 (142.15)	.11	137.9 (170.27)	.51
MPS, 0-100	.29 (.37)	.36 (.92)	.15	.34 (.69)	.48	.42 (.75)	.12
WUR, ratio	1.95 (1.53)	1.56 (.95)	**.04**	1.60 (1.81)	.34	1.74 (1.13)	.58
MDT, mN	.25 (.25)	1.41 (3.44)	**<.001**	.71 (.78)	**<.001**	.71 (.61)	**<.001**
VDT x/8	8 (1)	6.67 (3)	**<.001**	7.33 (2.17)	**.03**	7 (2.17)	**<.001**

Data is reported with median (interquartile range). Statistical significance is reported for results of the Mann-Whitney U test comparing healthy volunteer control data to CTS patients at 3 time points; baseline, 3- and 6-months post-surgery. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; IQR, interquartile range; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; sig, statistical significance; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio. **Bold** represents statistical significance.

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Table 6

Responsiveness of QST

	Baseline to 3 months p=	z=	effect size	Baseline to 6 months p=	z=	effect size
CDT	**<.001**	3.51	0.44	**0.005**	2.79	0.36
WDT	**<.001**	4.03	0.50	**0.007**	2.69	0.34
TSL	**<.001**	4.25	0.53	**0.005**	2.83	0.36
CPT	**0.003**	2.30	0.37	**0.007**	2.70	0.35
HPT	**0.007**	2.69	0.33	**0.004**	2.91	0.37
MDT	**<.001**	4.73	0.59	**<.001**	5.28	0.68
VDT	**<.001**	3.52	0.44	**0.02**	2.25	0.29
PPT	**0.03**	2.17	0.27			

N=76 at baseline, N=61 at 6 months. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold, MDT, mechanical detection threshold; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold.

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Table 7

Pain Parameter	BPI pain severity score	NPSI total score	Symptom Severity Score
Sensory Phenotype	*r* (p)	*r* (p)	*r* (p)
Baseline	0.142 (0.22)	0.132 (0.26)	0.188 (0.10)
3 months	0.230 (0.06)	0.313 (**0.01**)	0.327 (**0.008**)
6 months	0.266 (**0.03**)	0.439 (**<0.001**)	0.346 (**0.006**)

Table 7. Association of sensory phenotype with pain and symptom severity parameters at baseline, 3- and 6-months post-surgery. *r* = Spearman's rank order correlation coefficient, p = statistical significance. Significant associations in **bold**.

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Table 8

		Healthy Profile	Thermal Hyperalgesia	Mechanical Hyperalgesia	Sensory loss	p=
DN4	Baseline	5.2 (2.43)	5.3 (1.96)	5.8 (1.91)	5.8 (1.76)	.70
	6 months	.43 (.51)	1.25 (1.71)	1.82 (2.56)	3.0 (2.73)	**.02**
BPI Pain Severity	Baseline	3.1 (2.05)	4.6 (2.97)	4.5 (2.83)	4.8 (3.13)	.34
	6 months	1.04 (1.60)	.67 (1.37)	2.41 (2.81)	3.38 (3.33)	.08
NPSI	Baseline	28.2 (20.6)	41.6 (28.13)	38.7 (25.12)	40.6 (23.81)	.38
	6 months	3.21 (7.32)	6.07 (9.94)	14.73 (20.48)	25.5 (23.07)	**.05**
Symptom Severity Score	Baseline	3.0 (0.59)	3.2 (0.88)	3.4 (0.81)	3.4 (1.01)	.41
	6 months	1.34 (.30)	1.44 (.52)	2.01 (.99)	2.44 (1.10)	**.03**

Differences in pain and symptom severity parameters between phenotypic groups at baseline and 6 months post-surgery reported with mean (standard deviation). Significance is reported for one way between groups Analysis of Variance (ANOVA) with post hoc Tukey HSD test; at 6 months Welch test is reported due to homogeneity in variance. Distribution of the sample across sensory phenotypes; number and percentage of patients with neuropathic pain reported in brackets [n; %]: baseline N=76 [58; 76%]; healthy profile n=16; 21% [10; 17%]; thermal hyperalgesia n=24; 32% [15; 26%]; mechanical hyperalgesia n= 24; 32% [22; 38%]; sensory loss n=14; 18% [11; 19%]. 6 months N= 61 [7; 12%]; healthy profile n=14; 23% [0]; thermal hyperalgesia n=28; 46% [1; 14%]; mechanical hyperalgesia n=11; 18% [2; 27%]; sensory loss n=8; 13% [4; 57%].

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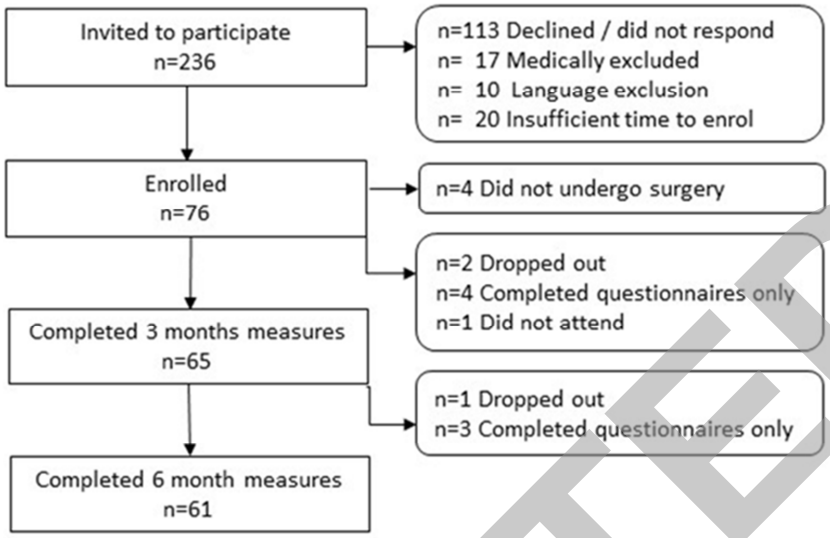

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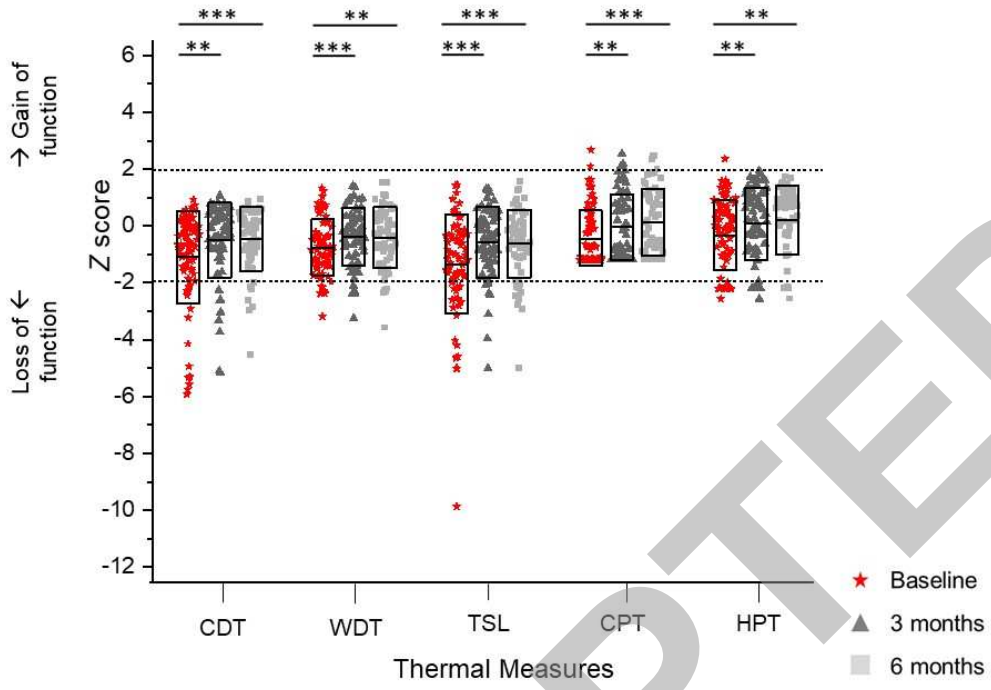

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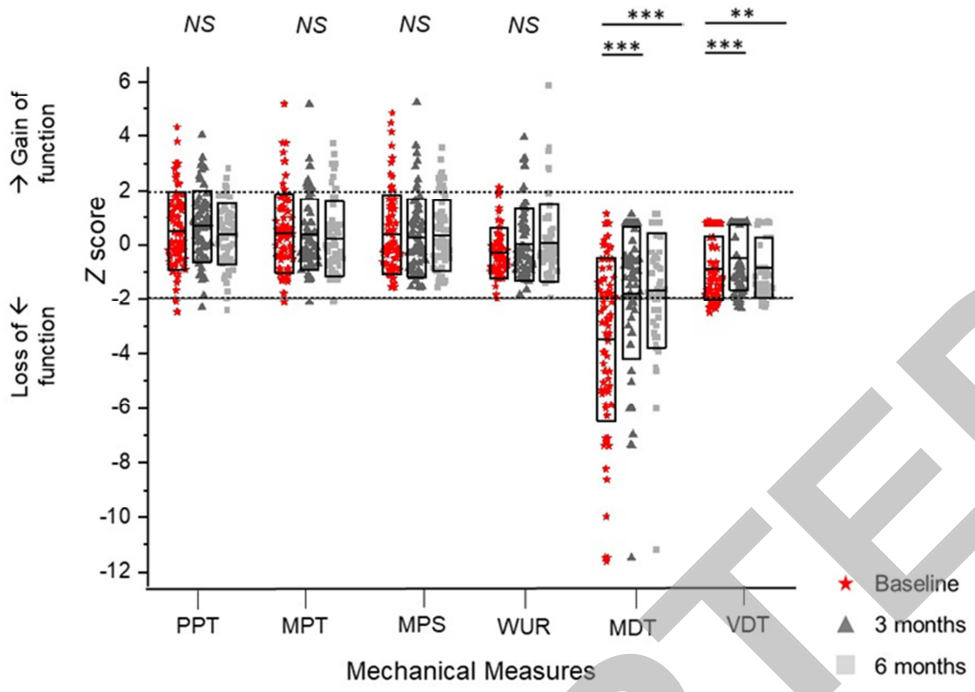

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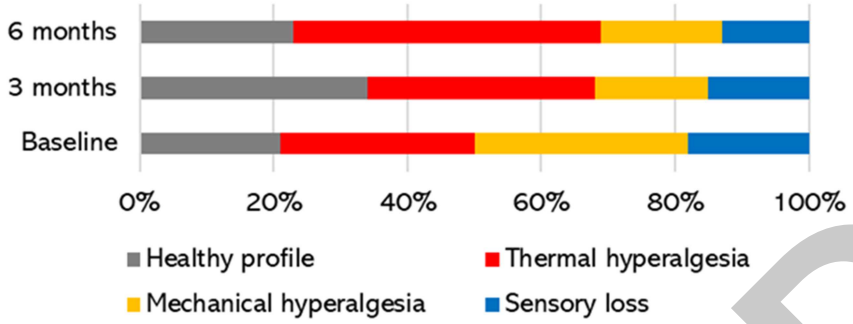

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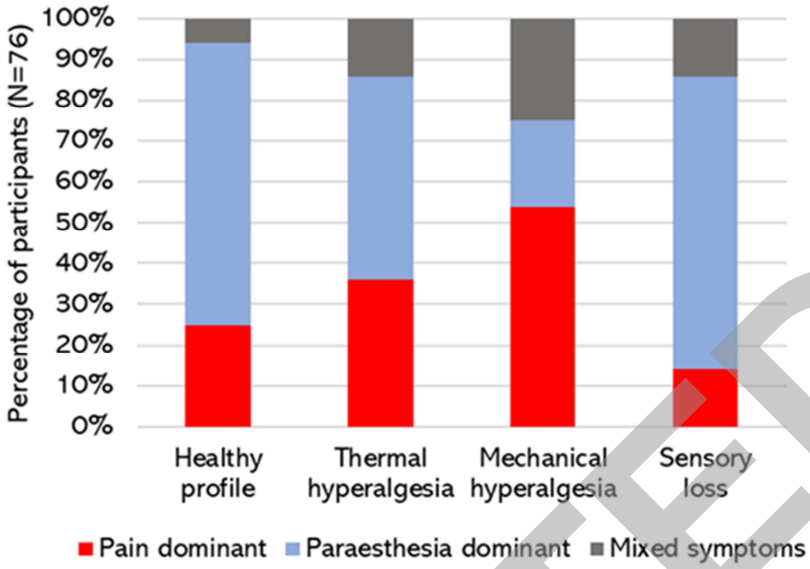

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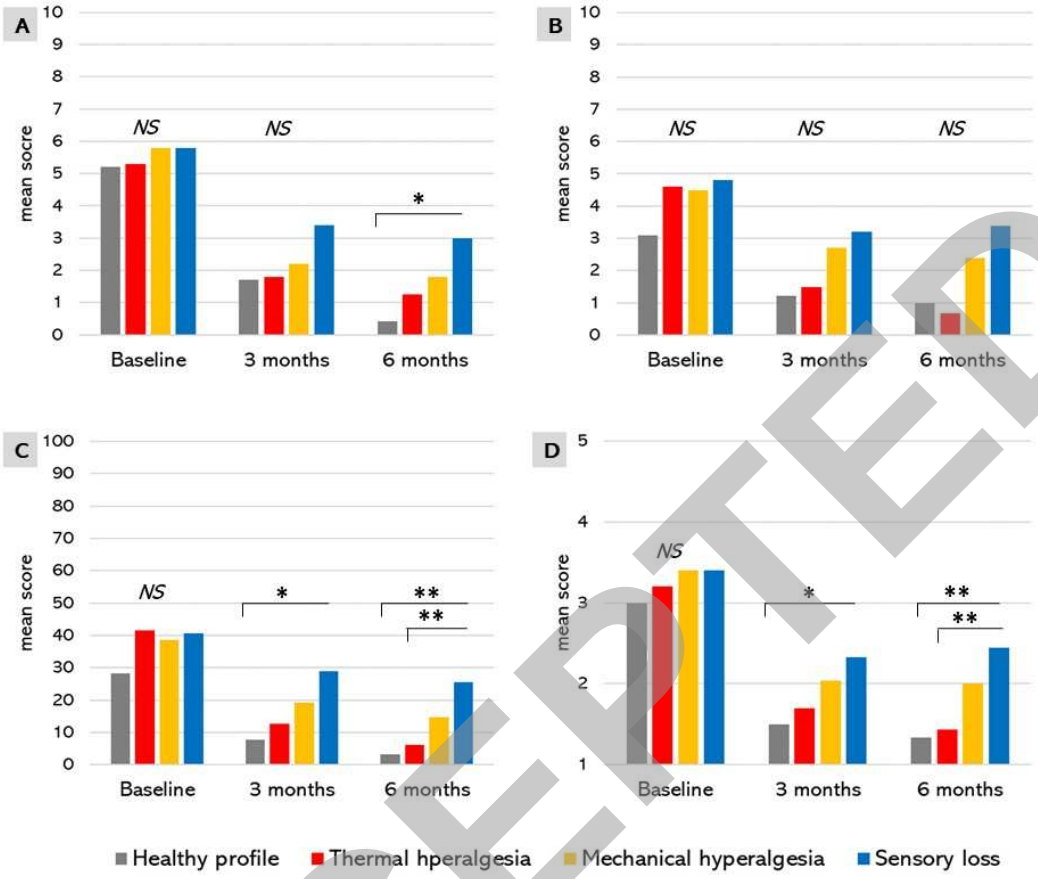

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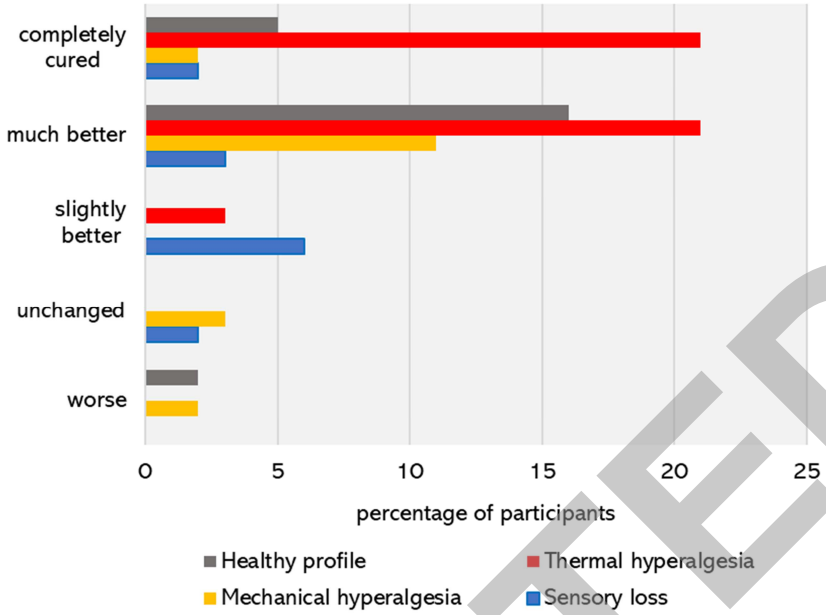

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