Title:

Phenotyping peripheral neuropathic pain in male and female adolescents: pain descriptors, somatosensory profiles, conditioned pain modulation and child-parent reported disability

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Abstract

Neuropathic pain (NeuP) can be difficult to diagnose and manage in children. Data regarding prevalence and sex-dependent differences is limited, and more detailed phenotyping is needed.

This observational cohort study recruited adolescents (10-17years) with NeuP or complex regional pain syndrome (CRPS). Following pain history and NeuP screening questionnaires, quantitative sensory testing (QST) was performed. Individual z-score plots were calculated with body-region control measures and matched to mechanism-related sensory profiles (sensory loss, thermal hyperalgesia, mechanical hyperalgesia). Conditioned pain modulation was assessed with pressure pain threshold and a contralateral cold conditioning stimulus, and meaningful conditioned pain modulation defined as twice the standard error of measurement. Patients and parents completed validated questionnaires for child quality of life (QoL), pain catastrophizing, and self-reported anxiety/depression.

Males (n=23) and females (n=43) with NeuP (n=52) or CRPS (n=14) reported moderate-severe pain with neuropathic sensory descriptors. Mixed patterns of sensory gain/loss at pain sites were not sex-dependent. Thermal hyperalgesia was common in both NeuP and CRPS, whereas sensory loss occurred only with NeuP and in a smaller proportion than adult cohorts. CPM was inhibitory in 54%, facilitatory in 14%, and non-responders had variable cold conditioning sensitivity. Males and females reported marked impairment of QoL, increased emotional distress, and pain catastrophising. Child-parent QoL scores correlated, but catastrophizing scores were discordant when parents or adolescents reported higher anxiety/depression.

NeuP in adolescents is associated with significant pain, physical impairment and psychosocial impairment. Quantifying alterations in somatosensory profiles, descending modulation, child and parent psychological function will inform individualized therapy and stratification for future clinical trials.

1. Introduction

Chronic and recurrent pain is common in children,[59] but specific neuropathic pain (NeuP) data is limited. Diagnosis based on history, sensory descriptors and examination is influenced by a child's age and developmental stage.[1; 48] Neuropathy assessment tools including sensory symptoms and signs have been developed for children with cancer[2], and NeuP screening tools[6] have shown clinical utility but not been validated in adolescents.[3; 55; 93] NeuP can be severe and prolonged, with variable response to medications. Evidence from pediatric trials is limited,[26] and pharmacotherapy is extrapolated from adult data,[2; 48] but clinical presentations and common causes of NeuP differ in children.[48] As persistent pain throughout important periods of nociceptive and/or psychosocial development can adversely affect long-term somatosensory function,[124] well-being, and educational attainment,[84] evaluation of age- and sex-dependent differences in the reporting and impact of chronic neuropathic pain in children is required.

Changes in somatosensory function and pain modulation may provide greater mechanistic insight than disease category alone.[7; 115; 131] Quantitative sensory testing (QST)[101] has identified three distinctive mechanism-related sensory profiles (sensory loss, thermal hyperalgesia, mechanical hyperalgesia)[7] associated with peripheral NeuP in adults, that despite some overlap, have high specificity for separating clinical from healthy adult populations.[122] Complex regional pain syndrome (CRPS) is now classified as a chronic primary pain condition,[87] but sensory findings have been compared with NeuP in adult QST reports.[37; 63; 71; 78] In children, QST has quantified differences associated with age and sex,[10; 12] peripheral neuropathy,[11; 68] and CRPS.[65; 108] Sex- and age-dependent differences in experimental pain sensitivity and the prevalence and intensity of different types of chronic pain are reported in adults[28; 75; 80] and children.[13; 38; 59] By contrast, pain intensity and the degree of associated sensory change did not differ between adult males and females with NeuP,[78] but this has not been evaluated in children. Alterations in conditioned pain modulation (CPM) have been identified in both adults[67] and children[52] with chronic pain. CPM can provide complementary information regarding the experience and persistence of pain,[30; 46; 47] but also be influenced by sex, age, and psychological co-morbidities.[19; 85; 117]

Detailed phenotyping informs individualized therapy and stratification for pharmacological trials in adults with NeuP.[23; 27; 34] Recommended core outcomes for pediatric clinical trials encompass measures of pain intensity, and physical, emotional and role functioning.[74] Establishing the sensitivity of psychophysical tests such as QST and CPM in children with NeuP, and validation of biomarkers such as neuroimaging, will provide additional end-points for pediatric trials.[23; 120]

This cross-sectional observational cohort study aimed to characterise the somatosensory phenotype of neuropathic pain in adolescents (10-18 years) presenting to a paediatric chronic pain clinic. We performed QST at pain and contralateral sites and hypothesized that distinct somatosensory profiles[7] would be identified in adolescents with peripheral NeuP. Sex-dependent differences in sensory thresholds and pain report were also assessed. Next, a variable pressure test stimulus and cold conditioning CPM

protocol identified the proportion of responders with inhibition or facilitation, and factors associated with CPM effect were explored. Finally, we compared the degree of pain-related disability (quality of life, emotional distress, pain catastrophizing) in males and females, and assessed correlations between patient and parental report.

2. Methods

2.1 Participants

Patients were recruited following multidisciplinary evaluation at the Great Ormond Street Hospital (GOSH) Pain Clinic, which utilises a biopsychosocial formulation to assess and manage children and adolescents with chronic pain.[69] Paediatric pain physicians can refer patients for quantitative sensory testing (QST), and nominate one of the following categories based on the child's evaluation at pain clinic: neuropathic pain (possible or probable based on clinical history, pain descriptors, examination[29]); complex regional pain syndrome (fulfilling diagnostic criteria[43]); musculoskeletal pain; visceral pain; or other. Adolescents aged 10 to 18 years with neuropathic pain were eligible for inclusion (Fig. 1). Biological sex (male/female) is reported as patients were not asked to self-report gender. Children with impaired comprehension (less than school level for 10 year old) or inadequate English language skills were excluded as sensory testing instructions can only be delivered by the Investigators in English.

The study was approved by the National Health Service West Midlands-Black Country Research Ethics Committee (Ref: 17/WM/0306; Approval: 23-8-2017). Parent and age-appropriate patient information sheets were sent to families prior to the QST appointment. At the end of clinical testing, families were approached by a separate member of the research team to answer queries, discuss the study, and seek parental consent and patient assent or consent. QST results and additional medical record data were entered in an anonymized research database, and current data relate to recruitment from 19th October 2017 to 9th March 2020. In addition, the full study protocol (clinicaltrials.gov NCT03312881) includes ongoing recruitment of adolescents with non-neuropathic pain to evaluate the specificity of a neuropathic pain screening tool, and neuroimaging in a subgroup of adolescents who agreed to a research scan.[120] Reporting is in accordance with the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines for cohort studies.[123] Throughout the manuscript, we use the World Health Organization definition of adolescents (persons aged between 10 and 19 years), and children and young people (CYP) to describe the broader age range from birth to 19 years.

2.2 Pain report

2.2.1 Pain history

A standardised case report form was used to collect a detailed pain history that included: type of pain, distribution, temporal features, duration, frequency, aggravating and relieving factors, and current and previous pharmacological and non-pharmacological management.

2.2.2 Pain intensity

Patients marked Visual Analogue Scales (VAS; 0-10cm line on paper) to indicate the intensity of current pain (How much pain do you feel right now? 0=no pain, 10=worst pain you can imagine), average pain in the last week, and worst pain in the last week (0=no pain, 10=worst pain you can imagine), interference with activity due to pain (How much does pain interfere with your usual activities? 0=not at all, 10= I can't do any of the things I want to do), and pre-test anxiety (How nervous or worried do you feel right now? 0=not at all, 10= extremely worried).[116; 127]

2.2.3 Neuropathic pain screening tool

Patients completed the Self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) to: draw the site and distribution of current pain on a body map; rate average pain in the last week on a 0-10 numerical rating scale; and report the presence or absence of 5 symptoms and 2 signs (total score 0-24). In adults, a score >12 has high sensitivity and specificity for neuropathic pain,[8] but this cut-off score has not been validated in adolescents.

2.2.4 Pain descriptors

Patients graded 11 sensory and 4 affective descriptors from the short-form McGill Pain Questionnaire on a 4-point Likert scale (0 = none, 3 = a lot) and the sum of the intensity rank was calculated (0-33 for sensory and 0-12 for affective).[76] While children over 10 can report sensory descriptors, further validation of neuropathic assessment tools is required in pediatric populations.

2.3 Quantitative Sensory Testing (QST)

Sensory testing was performed in the same temperature-controlled room with the same equipment and standardized verbal instructions. Prior to data acquisition and clinical consent/assent for testing, the sequence was described, tests were demonstrated, and participants advised they could decline or cease testing at any point.

Somatosensory function was assessed in a standardized manner as previously reported.[127] The DFNS protocol[10; 101] was adapted to reduce complexity and time for adolescents and fit within the time constraints of clinical routines.[101] Thermal sensory limen and vibration testing were not performed. Differences from the DFNS protocol for specific measures (MPT, MPS, WUR) are described below. The same methods were used for pain sites and for within-cohort control sites.

Testing was performed in the following sequence: i) thenar eminence of the self-reported non-dominant hand; ii) dynamic mapping towards the region of pain (informed by history and body map drawing) to identify the distribution and intensity of dynamic mechanical and thermal allodynia; iii) static testing at the site of maximal pain, or as close as probes could be tolerated, and adjacent to but not directly

over surgical scars where relevant; and iv) a contralateral mirror site for patients with unilateral pain, or a pain-free site within the same body region (head and neck, trunk, upper limb or lower limb) for patients with bilateral symptoms. Modalities were tested in the same sequence and included:

i) cold and warm detection, cold and heat pain (CDT, WDT, CPT, HPT). A handheld 18x18mm contact thermode with baseline 32°C, 1°C/s upslope, and limits of 10°C and 50°C (Senselab MSA Thermal Stimulator; Somedic, Sosdala, Sweden). Threshold was calculated from the mean of 5 measures for each modality. To reduce time, thermal sensory limen was not performed. Loss of the normal graded temperature sensation and a rapid transition to heat pain has previously been reported in children adjacent to surgical scars.[105; 126] Therefore, at the end of thermal testing at each site, we asked children to report if they felt the temperature had changed gradually or if there had been any rapid changes or jumps in the temperature. Children were also asked to report any paradoxical sensations (Did the temperature feel hot when we had asked you to press the button for cold, or cold when we had asked you to press the button for hot?).

ii) mechanical detection threshold (MDT). Calibrated von Frey nylon monofilaments (bending force 0.026 to 110 g; Somedic, Sosdala, Sweden) were applied sequentially in an up-down method and threshold was calculated as the geometric mean of 10 appearance and disappearance thresholds.

iii) mechanical pain elicited by von Frey filament [MP(vF)]. Von Frey monofilaments above MDT were sequentially applied until the participant reported a painful/pricking sensation. This was well-tolerated by children, but differs significantly from the DFNS protocol for mechanical pain sensitivity (MPS) which assesses a stimulus-response relationship to multiple pinprick and dynamic mechanical stimuli, with each rated at an intensity from 0 to 100 (VRS).

iv) mechanical pain threshold (MPT). A single sequence of increasing intensity PinPrick Stimulators (8-512mN) was applied until pricking pain was reported. The single sequence, rather than the series of five ascending and descending stimuli utilised in the adult DFNS protocol, reduced the number of exposures to potentially noxious stimuli and improved compliance. Reducing the time required for MPS and MPT allowed time for completion of testing at 3 sites. Two patients declined the full protocol due to feeling tired, but a further 2 had time constraints (other appointments or travel commitments).

v) wind-up ratio (WUR). Pain to the MPT stimulus was rated 0-10 (verbal rating scale, 0=touch to 10=really strong pain like a needle or blood test) at the first stimulus (VRS_1) and then following a 1/sec train of 10 repeated stimuli (VRS_{10})($WUR=VRS_{10}/VRS_1$).[44] As previously in children, the sequence was presented only once,[108] and due to individual variability in sensitivity to punctate stimuli (particularly in areas with prior surgery[127]) the patient's own threshold stimulus rather than a fixed intensity stimulus was utilised for the repeated train.

vi) pressure pain threshold (PPT). A hand-held $1cm^2$ computer-controlled algometer with optical feed-back was applied perpendicular to the body surface over underlying bone (e.g. digit for control hand, lateral knee for CPM, and the majority of limb pain and contralateral sites) or muscle (e.g. pain and contralateral

sites for head and neck and torso)(ramp 40kPa/sec, maximum 1000kPa)(SENSEBox; Somedic, Sosdala, Sweden).[127] The participant pressed a button when the stimulus became painful and threshold was calculated from the mean of 3 values. Details of PPT sites and raw data are included in Supplementary Material.

vii) dynamic mechanical allodynia (DMA). Following 3 strokes for 1-2cm length with a calibrated brush (200-300 mN; SENSELab Brush-05, Somedic, Sosdala, Sweden) at the thenar, pain and contralateral sites, participants rated the sensation between 0-10 (0=neutral; 10=unpleasant/painful).

viii) dynamic allodynia mapping. Starting at a distant site in the same body region, stimuli were applied in longitudinal and horizontal directions toward the pain site, until altered sensitivity or discomfort was reported and verbally rated from 0-10 by the child. Testing was performed with dynamic mechanical (SENSELab Brush-05) and thermal stimuli (handheld cool 25°C and warm 40°C rollers; Somedic RollTemp®, Sosdala, Sweden).

2.4 Conditioned Pain Modulation (CPM)

CPM was assessed using pressure pain threshold (PPT) on the head of the fibula (lateral knee) as a variable test stimulus and cold water immersion of the contralateral hand as a conditioning stimulus (as previously described by the current investigator[128]). The typical sequence was to measure PPT on the right knee and use the left hand for conditioning, but if patients reported pain in the left hand or right knee, this was reversed (right hand for conditioning, left knee for PPT). PPT has excellent reliability as a test stimulus[58] and was measured as described above using a computerized algometer (ramp 40kPa/sec, maximum 1000kPa)(SENSEBox; Somedic, Sosdala, Sweden). PPT on the lateral aspect of the knee over the fibula head was determined at baseline (mean of 3 measures), in parallel with (at 15 secs), and sequentially after the conditioning stimulus (50 and 90 secs following initial immersion). Cold is a reliable conditioning stimulus,[57; 132] but a range of temperatures (1^0C to 13^0C) and immersion durations (20 to 180 seconds) have been utilized in children.[52] Using a protocol previously reported in 8-17yr old children,[117] participants immersed the contralateral hand up to the wrist with the palm down and fingers spread into a 5°C circulating water bath (Techne TE-10D Thermoregulator, B-8 Bath, and RU-200 Dip Cooler; Techne, Burlington, NJ), and were instructed to leave their hand in the water for 30 seconds, or until the stimulus became too uncomfortable and could not be tolerated. Duration of immersion was recorded and subjects were asked to rate the intensity of hand discomfort (0-10 verbal rating scale) on removal.

2.5 Patient- and Parent-Reported Outcome Measures (PROMs)

Patients and their parents/carers attending the GOSH Chronic Pain Clinic complete a range of validated PROMs just prior to clinic appointments, with no specific instructions as to which parent should complete the measures. To investigate associations between patient report and parental factors,[24] we focussed on outcomes with comparable patient and parent report measures. Available data were extracted from the

medical record. All clinical assessments and questionnaires were collected before the lockdown due to the COVID-19 pandemic in the UK to avoid potential confounding effects on school, physical and emotional function.

2.5.1 Quality of life

The Paediatric Quality of Life Inventory Child (PedsQL-C) and Parent (PedsQL-P) tools evaluate 23 items relating to the child's functioning in 4 domains (physical, emotional, social, school). Parents/carers are asked to assess their perceptions of their child's quality of life. Scores range from 0 to 100, with lower scores indicating greater impairment. Clinical thresholds for total scores associated with minor, moderate, and major paediatric chronic conditions are 78, 76, and 70, respectively, for children aged 8-18yrs.[49] Total scores were included if the mean could be calculated from complete data in at least 3 domains.

2.5.2 Anxiety and depression

Patients completed the Pediatric Index of Emotional Distress (PI-ED), which has been validated for 8-17 year olds,[91] comprises 14 items related to symptoms of anxiety and depression. The maximum score is 42 and scores above of 20 indicate risk of developing comorbid anxiety and depression.[90] The PI-ED scale was developed from the adult Hospital Anxiety and Depression Scale (HADS) which also comprises 14 items and was used to assess parent/carer anxiety and depression symptoms.[135] Scores range from 0 to 21 for each scale, with suggested cut-off scores of 0-7 indicating normal anxiety/depression; 8-10 mild; 11-14 moderate; and 15-21 severe anxiety/depression.[112] For the HADS scale, normative values for anxiety are 6[4-9] (median[IQR]) in UK women and 5[2-8] in UK men, and for depression are 3[1,6].[16]

2.5.3 Pain catastrophizing

The Pain Catastrophizing Scale Child Version (PCS-C)[22] and Parent Version (PCS-P)[40] assesses the child or parents' tendency to catastrophize about the child's pain, with 13 items scored on a 5-point Likert scale (0=not at all to 4=extremely) across 3 domains (magnification, helplessness, rumination) for a maximum score of 52 (0-14 low, 15-25 moderate, ≥26 high catastrophizing).[97]

2.6 Statistical Analyses

Results relate to QST findings in a convenience sample of adolescents with neuropathic pain recruited prior to March 2020. No *a priori* power calculation for QST analysis was performed, but using the same protocol we previously constructed *z*-score sensory plots and identified significant within-cohort differences in somatosensory function in subgroups (n=11 to 15) of 19-20 year olds with prior neonatal surgery.[127]

Descriptive data are presented as mean (±SD) or mean [95% confidence intervals] (normal distribution, D'Agostino and Pearson test) or median with interquartile range [IQR 25,75]. Sex differences in pain report and questionnaire measures were compared with Student's t-test or Mann-Whitney U test. Categorical data were compared with Fisher's 2-sided exact test. Bivariate correlations are reported as two-tailed Spearman's rho (ρ), with pairwise comparisons, and bias corrected accelerated (BCa) 95% confidence

intervals. Analyses are based on available data, with no imputation for missing data, and the corrected sample size (n) is reported for clinic outcomes with incomplete data.

QST parameters are analysed in accordance with previous reports in adults[101] and adolescents.[10; 127] For thermal detection thresholds, the log-transformed difference from baseline temperature for cold and warm detection (cold difference: 32 – CDT; warm difference: WDT – 32) was calculated. Pain thresholds (CPT, HPT) are presented and analysed as raw data. Mechanical thresholds [MPT, MDT, MP(vF), PPT] were log-transformed to produce normally-distributed data. Sensory threshold analyses included mixed-model analysis of variance (ANOVA) with Greenhouse-Geisser correction, sensory modality as within-subject repeated factor, sex and diagnostic subgroup or sensory profile as between-subject factors, Bonferroni post-hoc comparisons, and reporting of multiplicity adjusted P values.

Comparisons with pain site thresholds were based on within-cohort control measures at a pain-free contralateral[60] mirror site for those with unilateral pain, or at a non-pain site within the same body region (head and neck, torso, upper limb or lower limb). This yields sensitive within-patient comparisons for clinical testing,[101] and effect sizes for threshold differences across body regions are greater than for age or sex in adults.[10; 101] To compare QST-parameters independently of their physical dimension, *z*-scores were calculated (e.g. patient with lower limb pain: *z*-score = pain site$_{patient}$ – contralateral lower limb$_{cohort\ mean}$ / contralateral lower limb$_{cohort\ SD}$). Gain of function (hyperalgesia) is indicated as a positive *z*-score, and loss of function (sensory loss) as a negative score.[101] Both absolute data and *z*-values were used to test for sex-differences in thermal and mechanical pain threshold [78].

Data from participants completing the CPM protocol are presented and analysed as both raw data and percentage change from baseline (CPM effect = [$PPT_{x\ secs}$-$PPT_{baseline}$ /$PPT_{baseline}$]x100). PPT data (kPa) were log-transformed and resultant normally distributed data was analysed: main effects with three-way mixed-design ANOVA with 2 between subject factors (sex and sensory profile), and a repeated measures factor of time; degrees of freedom were corrected with Greenhouse-Geisser estimates of sphericity; group comparisons were assessed with Bonferroni post-hoc tests; and reported P values were adjusted for multiple comparisons. Our previous measures using the same CPM protocol and PPT methodology in healthy controls (fibula head PPT =256 ± 135kPa)[128] were used to calculate the standard error of measurement (SEM = SD x $\sqrt{}$[1- ICC]). The intraclass coefficient (ICC) for repeated PPT measurements was 0.94 which is consistent with previous reports using computer-controlled algometry.[58; 70] The standard error of measurement was expressed as percentage change from baseline PPT (1SEM = ±12%). Although previously based on SEM,[70; 118] here meaningful CPM was designated as ±2SEM as recently recommended,[58] to identify inhibition (>24% increase from baseline PPT), facilitation (>24% decrease PPT) or non-responders (<24% change). Using these criteria, our previous healthy control sample[128] included 36/48 (75%) with inhibitory responses (72±39% increase in PPT), 9 non-responders, and 3/48 (6%) with facilitation (25-37% decrease in PPT). Post-hoc calculations using measures within the current cohort resulted in similar values for SEM. Bivariate correlations were assessed with factors previously shown to

influence CPM in adolescents and young adults. For CPM effect (% change in PPT at 15s), step-wise linear regression models included candidate variables based on correlations within this dataset and prior literature.[58]

Data were analyzed and plotted using SPSS® Version 24 (IBM, Portsmouth, UK) and Prism Version 8 (GraphPad, San Diego, USA).

3. Results

3.1 Demographics

Sixty-nine patients aged 10 to 17 yrs with NeuP or CRPS were recruited from October 2017 to March 2020 (Fig. 1). Three patients with possible NeuP were excluded due to changes in the clinical presentation (resolution of symptoms; no localising QST signs; not fulfilling Budapest criteria for CRPS), and data are presented for the remaining 23 males and 43 females (Table 1; see Supplementary Table 1). Clinical presentations included patients with: i) peripheral nerve injury associated with previous surgery (PPSP; n=32); ii) peripheral neuropathic pain due to other causes (PNP, n=20) including peripheral nerve trauma/compression (n=6; tumour, cyst, brachial plexopathy, injection, fracture), trigeminal neuralgia / facial pain (n=6), or distal polyneuropathy (n=8; erythromelalgia, undiagnosed sensory neuropathy, Fabry disease, Friedreich ataxia, chemotherapy); and iii) CRPS (n=14). Results of confirmatory tests[29] performed at GOSH were available for 10 NeuP patients (nerve conduction studies, n=6; genetic analysis, n=4).

3.2 Intensity and descriptors of neuropathic pain

Male and female adolescents reported moderate-severe intensity average pain and worst pain in the last week, that markedly interfered with activity (Table 1; Fig. 2). Pain was unilateral in 70%, most commonly in the lower limbs, and had persisted for over 2 years in 58% (Table 1). Older patients tended to have longer pain duration (ρ=0.29 [95%CI 0.01,0.5], P<0.05) but age did not influence self-reported pain intensity or pain-related interference.

Total S-LANSS scores were above 12 for 54/66 (87%) of adolescents, with allodynia (abnormal sensitivity to touch in 58%) and paroxysmal pain (sudden bursts for no apparent reason in 50%) the most common symptoms. A high proportion reported neuropathic signs (80% with altered sensitivity to rubbing and 88% feeling numbness or tenderness to pressing in the painful area), and 21% (5 males, 9 females) gave positive responses to all items (total score 24/24). From the McGill Pain Questionnaire, the most commonly endorsed sensory descriptors were sharp, stabbing, aching and tender (88-94%). Many adolescents asked for clarification of 'splitting', but remaining sensory descriptors were understood and graded. Affective descriptors were less frequently reported, with tiring and cruel most common (68-70%). McGill and S-LANSS scores were correlated (see Supplementary Fig. 1).

3.3 QST identifies distinct somatosensory profiles

For each adolescent, pain site z-scores were calculated using control measures in the same body region and plotted across available modalities. A deterministic approach was taken[122] for allocation to the closest matching profile (excluding TSL and VDT) reported in adults with peripheral neuropathic pain.[7] Profiles of sensory loss, thermal hyperalgesia, and mechanical hyperalgesia differed significantly from each other, with a significant main effect of sensory profile ($F_{2,66}$=67, P<0.001), modality ($F_{5.3,327}$=14.9, P<0.001), and modality x profile interaction ($F_{16,491}$=4.2, P<0.001)(Fig. 3).

Thermal hyperalgesia was the most common profile in adolescents with PNP or PPSP (25/52) and with CRPS (12/14). This included increased sensitivity to mechanical stimuli, CPT and HPT. Mild increased sensitivity to CDT and WDT was also noted, rather than the negative *z*-scores reported in adults (Fig. 3). Fourteen NeuP patients (27%) had sensory loss profiles with negative mean *z*-scores across all modalities, although the degree of reduction in MDT was less marked than in adult cohorts.[7].

A mechanical hyperalgesia profile with gain of function for MPT and MP(vF) and reduced sensitivity for all static thermal thresholds was present in 15 patients (Fig. 3). Differences from DFNS methodology and the relatively small sample size contribute to reductions in the degree of change in some modalities when compared to profiles from large adult cohorts. Z-values for MPT and MP(vF) were lower than in adults with a mechanical hyperalgesia profile, which is likely to reflect reduced sensitivity for detecting differences with the current methodology versus the repeated sequences used in the DFNS protocol. Increased variability in control PPT measures across body sites (see Supplementary Table 2) contributed to lower group *z*-values when compared to adult profiles. Higher PPT *z*-values were apparent with data restricted to a larger and less variable control sample (i.e. pain in the hand; see Supplementary Fig. 2A) or in patients with a larger effect size (i.e. CRPS; see Supplementary Fig. 2B).

As in adults, wind-up did not differentiate between clusters. A perception of rapid transition to heat was more common at pain than control sites (43% vs 15%), and 20% reported paradoxical heat sensations. Dynamic mechanical allodynia was absent at non-pain sites in adolescents (see Supplementary Fig. 2A), but was common at all pain sites irrespective of profile, whereas in adults DMA is more intense with mechanical hyperalgesia and minimal with a sensory loss profile.[7; 78] Dynamic thermal allodynia was reported across all profiles, with sensitivity to a warm roller highest in patients with a thermal hyperalgesia profile (Fig. 3A). Patient ratings of dynamic thermal sensitivity also correlated with static thresholds at the pain site: increased intensity of dynamic warm allodynia with lower HPT (ρ = -0.43 [95%CI -0.61, -0.23], P<0.01), and dynamic cool allodynia with CPT (ρ = 0.35 [95%CI 0.11, 0.57], P<0.01).

The proportion of PNP and PPSP adolescents with sensory loss, thermal hyperalgesia or mechanical hyperalgesia (27% vs 48% vs 25%) differed from a large adult neuropathic pain cohort in which sensory loss was the most common profile (42% vs 33% vs 24%).[7]

Pain intensity did not vary across somatosensory profiles, apart from a higher ‘pain now’ at the time of testing in the sensory loss group, which was not reflected in differences in average or worst pain in

the last week. Pre-test anxiety was low (median 1.8, [IQR 0.2,4.1], VAS 0-10cm), and as with measures of emotional distress and pain catastrophizing, did not differ across profiles (Table 1).

3.4 Sensory threshold evaluations in male and female adolescents

As a recent QST study in adults found lower pain thresholds in females but no sex difference in the degree to which thresholds were altered with NeuP or CRPS,[78] we compared QST data from our male and female adolescents. Static thresholds at non-pain sites were consistent with published healthy control data.[10; 12; 127] Within our cohort, control thenar values for CPT, HPT and PPT demonstrated main effects of sex with increased sensitivity in females (Fig. 4; see Supplementary Table 2).

Within the region of pain, sensitivity to CPT, HPT, MPT and PPT was increased, but thresholds did not differ significantly between males and females with lower limb pain (Fig. 4A-C). There was no main effect of sex on pain sites thresholds (see Supplementary Table 2). Similarly, z-scores across sensory loss, thermal or mechanical hyperalgesia profiles were altered to similar levels in males and females (Fig. 4D-G).

Patient age, average pain in the last week, and pain duration did not correlate with control thenar eminence or pain site sensory thresholds, and together these factors accounted for only 0.9%-4.8% variance in threshold values across the different modalities and sites (analyses not shown).

3.5 Adolescents with NeuP and CRPS show a spectrum of conditioned pain responses

Fifty-seven participants (20M, 37F) completed the CPM protocol (Fig. 1). Two patients declined and 3 patients with Fabry disease or erythromelalgia and pain triggered by temperature were excluded. In 2 patients with very high baseline PPT further increases following conditioning could not be reliably measured, and 2 removed the hand rapidly from the cold water bath and subsequent PPTs were not measured. In all patients, the conditioning and test stimuli were applied to non-painful sites. Four patients had unilateral pain in the lower arm and wrist, but could press the PPT response button with this hand and the contralateral hand was immersed for conditioning. For PPT on the knee, 26 patients had unilateral leg pain and the test stimulus was applied to the contralateral leg, and 8 patients had bilateral pain related to distal neuropathy or prior ankle/foot surgery but pain did not extend proximally to the knee.

Tolerance of the cold pressor conditioning stimulus and the intensity of discomfort reported on removal of the hand from the water bath varied similarly in males and females (Fig. 5A). Reduced tolerance correlated with increased discomfort in the hand at the time of removal (ρ= -0.34 [95%CI -.57, -.11] P<0.01) and higher anxiety (PI-ED score: ρ= -0.39 [95%CI -.61, -.10] P<0.01).

As with PPT measures at other pain-free control sites, baseline PPT on the fibula head was lower in females than males (mean difference 0.20kPa [95%CI 0.07,0.32]; $t(44.9)=3.0$, P=0.009). Across the whole group, changes in normalized PPT from baseline and during and after immersion showed a main effect of time ($F_{2.8,46}=3.7$, P=0.02) but not sex ($F_{1,46}=2.1$, P=0.15) or sensory profile ($F_{2,46}=0.7$, P=0.49). An increase in PPT during conditioning (15s) was maintained at 50 and 90s, suggesting an overall inhibitory effect (Fig. 5B).

However, this summary group data masked the spectrum of responses seen when plotting individual values for percentage change in PPT during conditioning (CPM effect)(Fig. 5C).

A 24% change in PPT (twice standard error of measurement)[58] was defined as meaningful CPM. A clear inhibitory response was identified in 32/57 (56%) and facilitation in 8/57 (14%)(Fig. 5C,D). Inhibitory CPM was associated with significant increases in PPT during (73±50% at 15s) and after the conditioning stimulus; whereas facilitation resulted in a significant decrease in parallel PPT (-49±18% at 15s) that did not persist (Fig. 5E). As recommended,[132] analyses based on the absolute change in PPT for each individual are also provided and produced comparable results (see Supplementary Fig. 3A,B). Pain site sensory thresholds did not correlate with CPM effect (data not shown).

In the remaining 17 participants, the change in PPT was less than 24% at 15s, and there were no significant changes from baseline at subsequent time points (Fig. 5E). This lack of response was most often due to inadequate conditioning: 7 patients with immersion time less than 15 seconds; 2 patients with conditioning stimulus below the intensity (>2/10) associated with consistent CPM in adults;[41; 58; 88] and 3 patients had peripheral polyneuropathy but pain at other sites. The proportion of non-responders (i.e. change in PPT less than twice standard error of measurement and/or inadequate conditioning) was highest in patients with a sensory loss profile, but comparisons are limited by the small size of the subgroups (Fig. 5F).

Factors previously shown to influence CPM in adolescents and young adults[30; 41; 45; 85; 96; 117; 128] were assessed for correlations with CPM effect (see Supplementary Table 3A). CPM effect did not differ if patients were currently taking amitriptyline (n=17)(mean difference 3.6% [95%CI -22, 30]) or any combination of anti-neuropathic treatments (anti-convulsant and/or anti-depressant and/or sodium channel blocker; n=35)(mean difference 6.0% [95%CI -29, 43]). Linear regression identified a significant contribution of immersion time but not baseline PPT to variance in CPM effect, which is consistent with the high proportion of participants with reduced conditioning tolerance in the 'non-responder' group. Age, sex, anxiety and pain catastrophizing had minimal additional impact (explained variance increased from 13% to 16%; see Supplementary Table 3B). Body mass index did not differ significantly between males (21.0 [95%CI 15,29]) and females (22 [15,38]), and did not influence baseline PPT or CPM effect (see Supplementary Table 3A).

3.6 Patient and parent-reported physical and psychosocial function

As chronic pain in CYP can be associated with significant physical and psychosocial impairment, and relationships with parental cognitive and emotional factors also have an impact,[24; 73] we have included patient and parent-reported outcome measures that formed part of interdisciplinary assessment at pain clinic. Adolescents with NeuP and CRPS reported significant and inter-related impairment of quality of life, physical, social and psychological function (Fig. 6; see Supplementary Table 4A). Mean PedsQL-Child total scores were in the range associated with severe disease (<70[49]) in 87% (Fig. 6A), correlated with parental

scores (Fig. 6B), and impairment was most marked in the physical function and school domains (Fig. 6C). Pain intensity, duration, patient age and sex accounted for only 8% of variance in PedsQL-C total scores, but including patient-reported emotional distress and pain catastrophizing in the regression model had a significant additional impact (R^2=0.59, $F_{6,48}$=11.5; P<0.001; see Supplementary Table 4B).

PI-ED scores were above the cutoff for identifying significant emotional distress (≥20) in 11/23 male and 15/43 female adolescents (Fig. 6D). Higher PI-ED scores also correlated with higher McGill affective scores (ρ =0.49 [95%CI 0.26,0.67] P<0.01). Pain catastrophizing scores were in the severe range (>26)[97] in 7/17 males and 26/38 females (Fig. 6D), and higher catastrophizing correlated with increased intensity of worst pain and pain-related interference (see Supplementary Table 4A). Increased child anxiety correlated with increased parental anxiety, and 12/65 (18%) parents reported mild-moderate anxiety (Fig. 6D,E).

Parents' perception of their child's quality of life (PedsQL-P) strongly correlated with patient self-report (PedsQL-C)(ρ =0.62 [95%CI 0.39,0.77], P<0.01, n=64) for both male and female patients (Fig. 6B) and controlling for patient age and sex had little additional impact (ρ =0.72 [95%CI 0.57,0.83]). Within the domains of PedsQL, child and parental report were highly concordant for physical function (ρ =0.79 [95%CI 0.6,0.9]P<0.01) and lower for emotional function (ρ =0.43 [95%CI 0.18,0.64] P<0.01).

Pain catastrophizing scores were available for 53 child-parent dyads, but PCS-C and PCS-P scores did not correlate (Fig. 6G). Seventeen parents reported higher (median difference [IQR] 8[6,16]) scores than their child, and 18 reported lower scores (-9[-16,-6]). Although patient age, sex, pain intensity and duration did not influence discordance in PCS scores (R^2=0.09, $F_{4,48}$=1.3; P=0.29), adding anxiety/depression scores for the child or parent had a significant impact (R^2=0.41, $F_{6,45}$=5.2; P<0.001)(see Supplementary Table 4C). Parents with higher anxiety/depression had higher levels of catastrophic thinking about their child's pain than was self-reported by the child; and children with higher anxiety/depression tended to report higher levels of catastrophizing than their parent.

Additional infrequent and mild recurrent pains (headache, abdominal, back, or chest pain) were reported by 71% (15/23 males, 32/43 females); these patients did not differ in measures related to neuropathic pain, but reported lower quality of life (PedsQL-C: mean diff [95%CI] -15[5,24],P=0.03) and higher emotional distress (PI-ED: 4.3 [0.7, 7.0],P=0.02) and pain catastrophizing (PCS-C: 7.5[0.3,14.7,P=0.043).

Forty-one patients were taking medication for NeuP at the time of testing, most commonly amitriptyline and/or gabapentin (Table 1). As patients were at different points of rationalisation of therapies commenced prior to referral and/or dose titration of medication instituted by the GOSH Pain Service, no conclusions can be made regarding relative or ongoing efficacy in this cross-sectional cohort. One quarter of adolescents had previously trialled a tricylic anti-depressant, gabapentinoid and/or opioid and ceased these medications due to lack of efficacy or side-effects (see Supplementary Table 1).

4. Discussion

Male and female adolescents with neuropathic pain and CRPS report moderate-severe pain and pain-related disability. QST identified distinct somatosensory profiles: thermal hyperalgesia was common, whereas a sensory loss profile and diagnoses associated with distal polyneuropathy were less common than in adults. Despite increased sensitivity at control sites in females, changes in sensory thresholds at pain sites were not sex-dependent. Conditioned modulation showed a spectrum of responses, with meaningful inhibitory CPM in 54% and facilitation in 14%. Patients reported major reductions in quality of life, particularly physical function, which correlated with parental perceptions. Emotional distress and pain catastrophizing were high in both males and females, and parents with higher anxiety tended to catastrophize more than their child. Detailed phenotyping with pain history, QST, CPM and patient-reported outcome measures is feasible in adolescents and highlights the significant impact of neuropathic pain.

4.1 Somatosensory phenotyping

Somatosensory signs vary within diagnostic categories, and subgrouping based on different profiles may improve mechanism-based understanding.[7] In adolescents we identified distinct sensory loss, thermal hyperalgesia, and mechanical hyperalgesia profiles, but our sample size and methodology influenced *z*-values for some modalities. These data parallel clusters reported in adults, but the relative proportions and related causes of PNP differed in adolescents.

Sensory loss is common in adults with NeuP (>50%), particularly with polyneuropathy,[7; 122] and conditions that are rare in children (e.g. postherpetic neuralgia[7]) or produce sub-clinical sensory signs (e.g. diabetes[11; 130]). Here, painful distal polyneuropathy was relatively uncommon (15% versus 55% in adult cohorts[7; 78]), but included chemotherapy-induced neuropathy in childhood cancer survivors,[68; 100] and genetic conditions with specific management implications (e.g. erythromelalgia,[4] Fabry disease[36]).

Thermal hyperalgesia was the most common profile in adolescents with NeuP or CRPS. As in adults, pain intensity, S-LANSS scores,[99] and QST findings did not clearly differentiate CRPS from NeuP,[37] thus highlighting the importance of specific CRPS diagnostic criteria.[43] Thermal and mechanical hyperalgesia, particularly increased pressure pain sensitivity, and dynamic allodynia are common features with CRPS in adults[37; 63; 71; 78] and adolescents.[65; 108] However, the increased thermal and mechanical detection sensitivity seen here and previously in adolescents[108] differs from reduced thermal detection in adults with CRPS[37; 78; 99] or the thermal hyperalgesia profile. Although anticipatory anxiety could contribute to earlier responses and lower thresholds, these factors did not differ across somatosensory profiles. As lower limb CRPS is a common pediatric pain clinic presentation,[15] associated with alterations in peripheral and central pain processing,[65; 111] potential age-related mechanistic differences require further evaluation.

Mechanical or thermal hyperalgesia or sensory loss profiles plus dynamic allodynia in the region of prior surgery accompanied self-reported sensory symptoms in adolescents with neuropathic PPSP. NeuP is a frequent component of PPSP in adults[106] and children,[55; 83; 93] particularly in the 20-40% of adolescents developing PPSP following major surgery.[18; 89; 98; 102] Mixed sensory gain/loss has been documented many years following pediatric inguinal hernia repair,[61] thoracotomy,[62] and neonatal surgery,[126; 127] but relationships with pain and self-reported sensory abnormalities vary.[54] Repeat surgery is a risk factor for PPSP in adults[107], was reported by 40% of our PPSP group, and has been associated with an increased degree and duration of post-operative pain or hyperalgesia following early life surgery in clinical[89; 95] and laboratory[82] studies. While a close temporal relationship to injury strengthens the clinical suspicion of NeuP,[29] several adolescents reported delayed onset of neuropathic PPSP. While inability to report or recognise NeuP at younger ages could contribute, significant age-dependent changes in mechanisms, including delayed emergence of allodynia, have been identified in juvenile rodents following traumatic peripheral nerve injury,[33] surgical incision,[17; 82; 125] and exposure to chemotherapy.[104] Phenotyping in specific pediatric populations is needed, with longitudinal studies evaluating effects of age at injury and presentation, and disease duration. The feasibility and role of additional confirmatory tests,[7; 21; 29; 39; 92] and biomarkers[23] also require further evaluation.

In adults, phenotyping with QST, CPM and PROMs improves response prediction for individual therapy and stratification in clinical trials.[5; 7; 23; 34; 122; 133] Within our cohort, there was marked variability in anti-neuropathic medication use prior to referral, and in tolerability and ongoing efficacy. Alongside recommended PROMs,[74] QST and CPM can provide additional standardized end-points for clinical trials.

4.2 Sensory thresholds and pain report in males and females

In healthy CYP, age- and sex-dependent influences on experimental pain sensitivity vary with stimulus intensity and methodology.[10; 12; 13] In adults, pain thresholds were lower in females but the degree of change associated with NeuP did not differ from males.[78] Here, adolescent females were more sensitive at control sites, but sex did not influence sensory thresholds within NeuP regions or *z*-score differences across somatosensory profiles.

Recurrent pain is common in children (median 40-50%), and is more intense and prevalent in girls.[24; 50; 51; 59] Chronic pain that limits activity and quality of life occurs in approximately 5% of children, but the prevalence of NeuP is unknown.[1; 56; 109] As in adults,[78] both male and female adolescents rated NeuP as moderate-severe. The predominance of females reflects overall GOSH Pain Clinic referrals (67% female)[53] and does not confirm sex-dependent differences in prevalence, as more females may seek healthcare[94] and access to specialist services is influenced by multiple factors including socioeconomic status.[53]

4.3 Conditioned pain modulation

Impaired CPM has been identified in adults with NeuP[63; 66; 67] and CYP with chronic pain.[46; 47; 52] However, differences in CPM methodology, reporting, or inclusion criteria limit comparison across populations.[57; 79; 86]

CPM produces a spectrum of individual responses[30; 114] and group data can mask the proportion with inhibition or facilitation. We identified meaningful inhibitory CPM (2xSEM[58]) in 56% and facilitation in 14%. Proportions differed when applying these criteria to our previous control data (75% inhibition, 6% facilitation),[128] and the same conditioning produced inhibition in healthy 12-17 year olds.[117] Adjusting the conditioning stimulus to achieve the same intensity for each individual may reduce variability, and comparison with matched contemporaneous controls and longitudinal studies are needed to evaluate changes with time and treatment.[133]

Inhibitory CPM responses increase throughout adolescence (12-17 versus 8-11yrs) to a similar degree in males and females.[117] Here, baseline PPT was lower in females, but CPM effect was not influenced by age or sex. As in healthy adults[35] or adults with neuralgia,[63] CPM and sensory thresholds did not correlate, likely reflecting differences in peripherally and centrally-mediated mechanisms.

4.4 Impact of neuropathic pain

Failure to recognize NeuP can delay appropriate management. NeuP screening tools have high sensitivity and specificity in adults.[6] In adolescents, DN4≥4 associated with PPSP[55; 93] and high S-LANSS scores here, suggest sensitivity for detecting NeuP but the specificity and appropriate cut-off scores for CYP require confirmation.[81] Neuropathic descriptors in the McGill questionnaire[6; 25; 76] parallel sensory symptoms reported by children over 8-10 years,[77; 129; 134] but the validity of different descriptors depends on each individual's verbal repertoire.[72]

As in CYP with chronic pain,[31; 73] disability, anxiety and depression in adolescents with NeuP and CRPS were increased and inter-related. While depression/anxiety tends to be higher in girls with chronic pain,[14] sex did not influence patient-reported scores in our NeuP cohort. Parental cognitions, behaviour and emotional factors influence child-reported pain and disability,[73; 110; 113] and as here, concordance between child-parent reported disability is high for physical function, but lower for emotional function and internalized symptoms.[9; 20; 24; 119] Pain catastrophizing was associated with increased pain intensity[9; 31; 121] but child-parent measures differed, particularly when adolescents or parents reported higher anxiety/depression.

These data highlight the need for interdisciplinary pediatric chronic pain management, and identify potential modifiable factors for psychological interventions for CYP[32] and parents.[64] Many adolescents reported persistent pain, psychosocial dysfunction and adverse effects on schooling across a prolonged period of social and emotional development. As a result, NeuP in CYP may not only incur significant health

care costs,[42; 103] but also adversely affect well-being and educational and vocational attainment in later life.[84]

4.5 Limitations

Data was obtained from a clinically-relevant but heterogenous convenience sample of patients and comparisons across smaller subgroups should be interpreted with caution. Investigators were not blinded to patient history, as the nature and distribution of pain informed clinical testing, but QST utilises assessor-independent technology.[46] To reduce testing complexity and time, some DFNS protocol measures were modified or excluded. The lack of stimulus-response assessments of mechanical pain sensitivity, and variability in pressure pain sites, limit comparison across other datasets. Somatosensory profiles were distinct from each other, and parallel but do not completely mirror adult mechanism-related profiles. Standardized methodology applicable across different ages, cognitive abilities and clinical contexts is needed. Profiles were based on within-cohort body-region specific comparisons, and additional pediatric control data will improve the sensitivity of site-, age- and sex-corrected *z*-scores. Pharmacotherapy at the time of testing was not controlled and medication use was variable. Ethnicity is not reported but the majority were Caucasian, and this may limit generalizability. Comparisons were based on biological sex not self-reported gender, and parental measures were predominantly completed by the mother. Modelling interactions between patient/parent-reported outcomes was limited by sample size, but significant co-morbidities were identified.

4.6 Conclusions

Neuropathic pain in adolescents can be severe, persistent, and adversely affect physical, emotional and social function. Sensory thresholds in the region of pain and conditioned modulation did not differ between males and females in this cohort, but potential sex-dependent differences in additional mechanism-based biomarkers and efficacy of potential interventions need evaluation. Screening questionnaires, QST, CPM, and a range of patient- and parent-reported outcomes facilitate phenotyping of adolescent neuropathic pain. This will improve recognition of neuropathic pain and ultimately contribute to individualized therapy, stratification for clinical trials, and evidence-based management.

Conflict of Interest

The authors report no conflicts of interest related to this research project or manuscript.

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Figure Legends

Figure 1. Flow chart of patient recruitment and evaluations.

Legend: PROMs, patient- and parent-reported outcome measures; QST, quantitative sensory testing; CPM, conditioned pain modulation; NeuP, clinical diagnosis of neuropathic pain; M, male; F, female; thenar, test site on thenar eminence non-dominant hand; contra, contralateral (mirror or same body region non-pain test site)

Figure 2. Pain intensity and pain-related interference do not differ between male and female adolescents with neuropathic pain. Males (n=23) and females (n=43) marked a 0-10cm visual analogue scale (VAS) to report intensity of: current pain (now); average pain in the last week (average); worst pain in the last week (worst); and the degree to which pain interfered with activity (pain interference). There was no main effect of sex ($F_{1,64}$=0.1 P=0.75) on repeated measures of pain intensity (now, average, worst pain) in adolescents with neuropathic pain or CRPS. Data points = individual values, bars = mean [95%CI].

Figure 3. Quantitative sensory testing profiles in adolescents with neuropathic pain or CRPS.

(A) Individual patient pain site thresholds were converted into *z*-scores calculated with reference to within-cohort body region-specific control data. The *z*-score plot for each individual patient was grouped according to the closest matching adult mechanism-related sensory profile: sensory loss (n=14), thermal hyperalgesia (n=37) or mechanical hyperalgesia (n=15). Dynamic allodynia to brush, cool and warm rollers at the pain sites is graded on a 0-10 numerical rating scale (NRS) and differed across profiles ($F_{2,59}$=3.4, P=0.04)(two-way mixed-effects ANOVA with sensory profile as between subject factor and repeated measures of modality). Data points = mean ± SEM. (B) The proportion of patients with a sensory loss, thermal hyperalgesia or mechanical hyperalgesia profile is represented for all patients (n=66) and for each diagnostic group: persistent post-surgical pain (PPSP, n=32); peripheral neuropathic pain (PNP, n=20); and complex regional pain syndrome (CRPS, n=14). *Legend:* CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MP(vF), mechanical pain to von Frey filament; WUR, wind-up ratio; MDT, mechanical detection threshold.

Figure 4. Thermal and mechanical pain thresholds differ between male and females at control sites, but sex-differences are not apparent at pain sites.

(A-C) Sex-specific raw data are presented for 3 sites: i) hand (thenar eminence control with no pain in the hand, n=52; 17M 35F); lower limb non-pain (contralateral control, n=30; 13M, 17F); and the most frequently affected pain region (lower limb pain, n=38; 16M 22F)(M=male, F=female). (A) Thermal thresholds (CPT, cold pain threshold; HPT, heat pain threshold) for non-pain sites (thenar, contralateral lower limb) show mild increased lower limb cold sensitivity in females. (B) Mechanical pain threshold (MPT) does not differ between males and females at control sites, and pain site thresholds are lower in both males and females. (C) Pressure pain threshold (PPT) sensitivity is increased in females at control sites, but does not differ between males and females in the region of pain. Bars=mean [95% CI]. *P<0.05 Student's unpaired t-test. Sensitivity at lower limb pain sites did not differ in males and females for any modality (see Supplementary Table 2 for additional raw data and analyses for all pain sites).

(D-G) *Z*-scores for males and females show differences in pain site sensitivity associated with sensory loss (n=14, 6M 8F), thermal hyperalgesia (n=37, 12M 25F), and mechanical hyperalgesia (n=15, 5M 10F). (D) HPT *z*-scores show a main effect of profile ($F_{2,58}$=3.6 P=0.03) but not sex ($F_{1,58}$=1.1 P=0.29). (E) CPT *z*-scores show main effect of profile ($F_{2,58}$=29.6 P<0.001) but not sex ($F_{1,58}$=0.01 P=0.93) (F) MPT *z*-scores show main effect of profile ($F_{2,58}$=17 P<0.001) but not sex ($F_{1,58}$=0.08 P=0.78) (G) PPT *z*-scores show main effect of profile ($F_{2,58}$=3.6 P=0.03) but not sex ($F_{1,58}$=1.1 P=0.30)(two-way ANOVA with sex and profile as variables). Data points=mean±SEM.

Figure 5. Conditioned pain modulation (CPM) shows a spectrum of responses in adolescents with NeuP or CRPS.

(A) Conditioning tolerance (duration of immersion contralateral hand in 5^0C water bath in seconds, s) did not differ between males (median[IQR], 30 [17,30]) and females (29 [23,30]). Conditioning pain (pain in hand on removal from water bath; 0-10 numerical rating scale, NRS) did not differ between males (8 [6,10]) and females (8 [IQR7,10]). Data points = individual patients; bars = median [IQR]. (B) Group data for normalized PPT (log_{10} kPa) during and after conditioning. PPT was significantly increased from baseline at all subsequent time points, indicating an overall inhibitory effect. *P<0.05 **P<0.01. Two way ANOVA with repeated measures and Dunnett's post-hoc comparison to baseline. Data = box and whiskers 5-95 percentile. (C) CPM effect (% change from baseline PPT at 15s) shows a

spectrum of individual responses. Clear inhibition (increased PPT) was evoked in 32 participants, facilitation (decreased PPT) in 8, and 17 participants were classified as non-responders (% change within ±24% which is less than twice the standard error of measurement). Bars = individual participants. (D) CPM effect did not differ significantly between males (mean[95%CI, 27.0[7.5,46.6]) and females (38.7[15.8,61.6])(unpaired t-test P=0.5). The standard error of measurement (±12%) is indicated within the grey box, and dotted lines mark 2SEM (±24%). Data points = individual patients; bars = mean [95%CI]. (E) The degree and duration of CPM is shown as percentage change from baseline PPT at 15s (during conditioning), 50s and 90s (after conditioning). Significant increases in PPT in the inhibition group at 15s (73±50%, mean±SD) persist at 50 and 90s. Facilitation results in a significant decrease at 15s (- 49±18%). PPT does not change with time in the non-responder group. **P<0.001 #P<0.01 (two-way ANOVA with Dunnett's post-hoc comparisons to baseline). Data points = mean [95%CI]. (F) The proportion of non-responders and participants with inhibition or facilitation are shown divided by sex or QST sensory profile (SL, sensory loss; TH, thermal hyperalgesia; MH, mechanical hyperalgesia).

Figure 6. Validated patient- and parent-reported outcome measures indicate high levels of pain-related disability and emotional distress in male and female adolescents with neuropathic pain.

(A) Pediatric Quality of Life total score reported by male and female patients (PedsQL-C, Child version), with lower scores indicating worse function, and the majority well below levels associated with moderate-severe pediatric disease (<70[49]). Total scores did not differ significantly between male and female patients (mean difference 0.5[95%CI -8.7, 9.8]). Parents (PedsQL-P, Parent version) tended to over-report dysfunction compared to children (-8.2 [-15, -1.3],P=0.02). (B) Parental PedsQL-P scores are highly correlated with PedsQL-C for male (R^2=0.51) and female (R^2=0.50) patients. (C) Within each PedsQL-C domain (physical function, emotional function, social function and school) impairment was greatest in physical function for both males (34[22,45],n=22) and females (36[29,44],n=43). (D) Pediatric Index of Emotional Distress (PI-ED) scores were high but did not differ in male and female patients (mean diff 1.2 [95%CI-3.3, 5.9]. Hospital Anxiety and Depression Scale (HADS) scores were variable but indicated mild-moderate levels of anxiety in 12/65 and depression in 6/65 parents. (E) Higher parental anxiety/depression (HADS) correlated with increased emotional distress (PI-ED) in male (R^2=0.33) and female (R^2=0.11) patients. (F) Pain catastrophizing scale (PCS-Child) scores were not significantly different in male and female patients (mean diff 4.2[-2.5,11.0]) or between parents (PCS-Parent) and patients (mean diff -0.5 [-4.7,3.5]). (G) Parental report of pain catastrophizing (PCS-Parent version) was not significantly correlated with self-report (PCS-Child version) in their male (R^2=0.18) or female (R^2=0.01) child. (A,C,D,F) Individual data points = male or female patient reported outcome scores and scores from parent/carer versions of the same or comparable questionnaires. Bars =mean [95%CI]. (B,E,G) Solid lines = regression lines for correlation of parental score with male or female child; dotted lines = 95%CI.

FIGURE 1

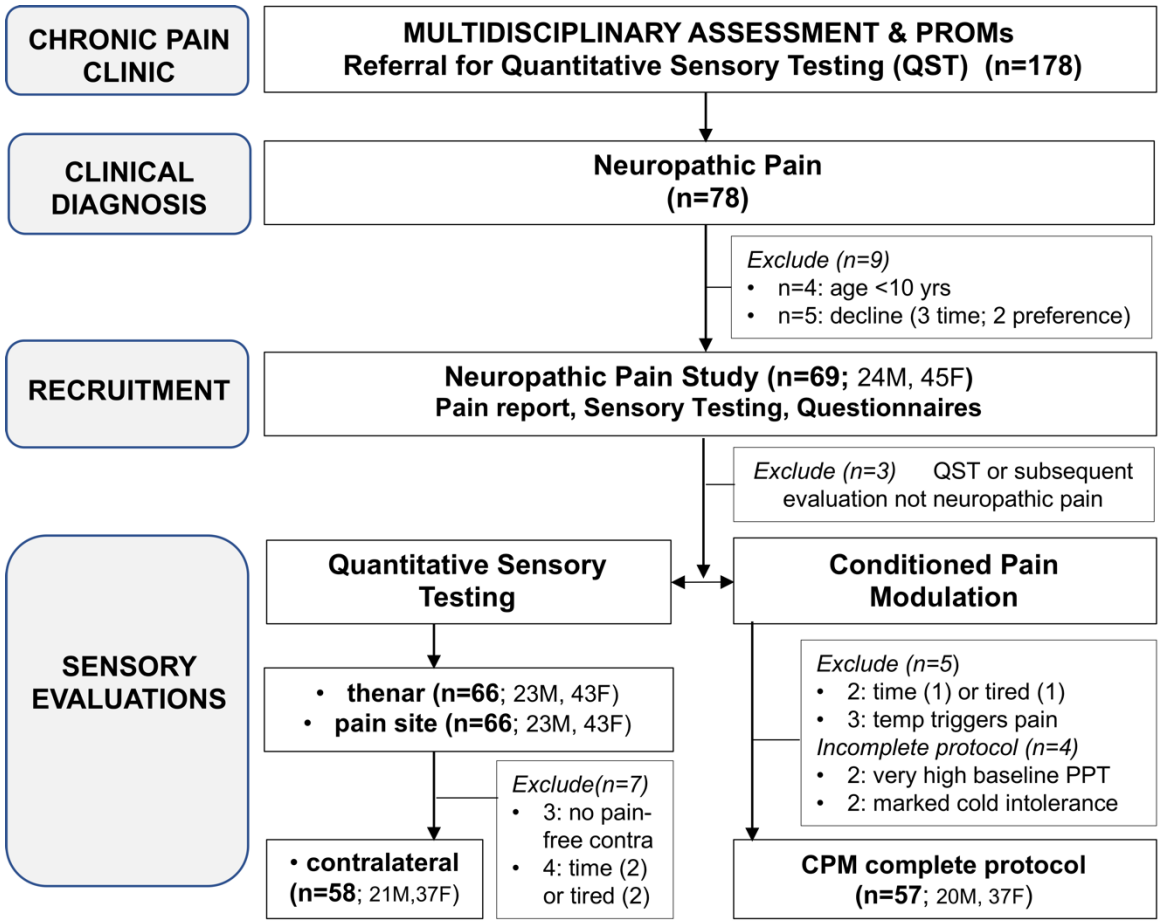

CHRONIC PAIN CLINIC
MULTIDISCIPLINARY ASSESSMENT & PROMs
Referral for Quantitative Sensory Testing (QST) (n=178)
CLINICAL DIAGNOSIS
Neuropathic Pain
(n=78)
Exclude (n=9)
• n=4: age <10 yrs
• n=5: decline (3 time; 2 preference)
RECRUITMENT
Neuropathic Pain Study (n=69; 24M, 45F)
Pain report, Sensory Testing, Questionnaires
Exclude (n=3) QST or subsequent evaluation not neuropathic pain
SENSORY EVALUATIONS
Quantitative Sensory Testing
Conditioned Pain Modulation
• thenar (n=66; 23M, 43F)
• pain site (n=66; 23M, 43F)
Exclude (n=5)
• 2: time (1) or tired (1)
• 3: temp triggers pain
Incomplete protocol (n=4)
• 2: very high baseline PPT
• 2: marked cold intolerance
Exclude(n=7)
• 3: no pain-free contra
• 4: time (2) or tired (2)
• contralateral (n=58; 21M,37F)
CPM complete protocol (n=57; 20M, 37F)

FIGURE 2

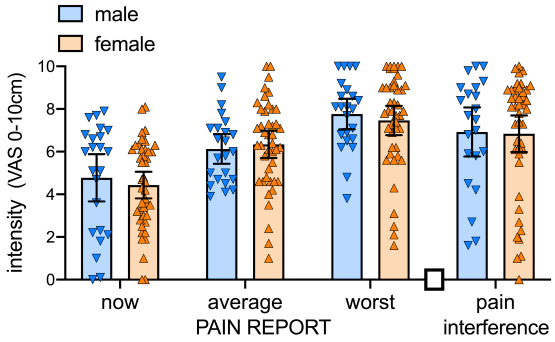

male
female
intensity (VAS 0-10cm)
10
8
6
4
2
0
now
average
worst
pain
interference
PAIN REPORT

FIGURE 3

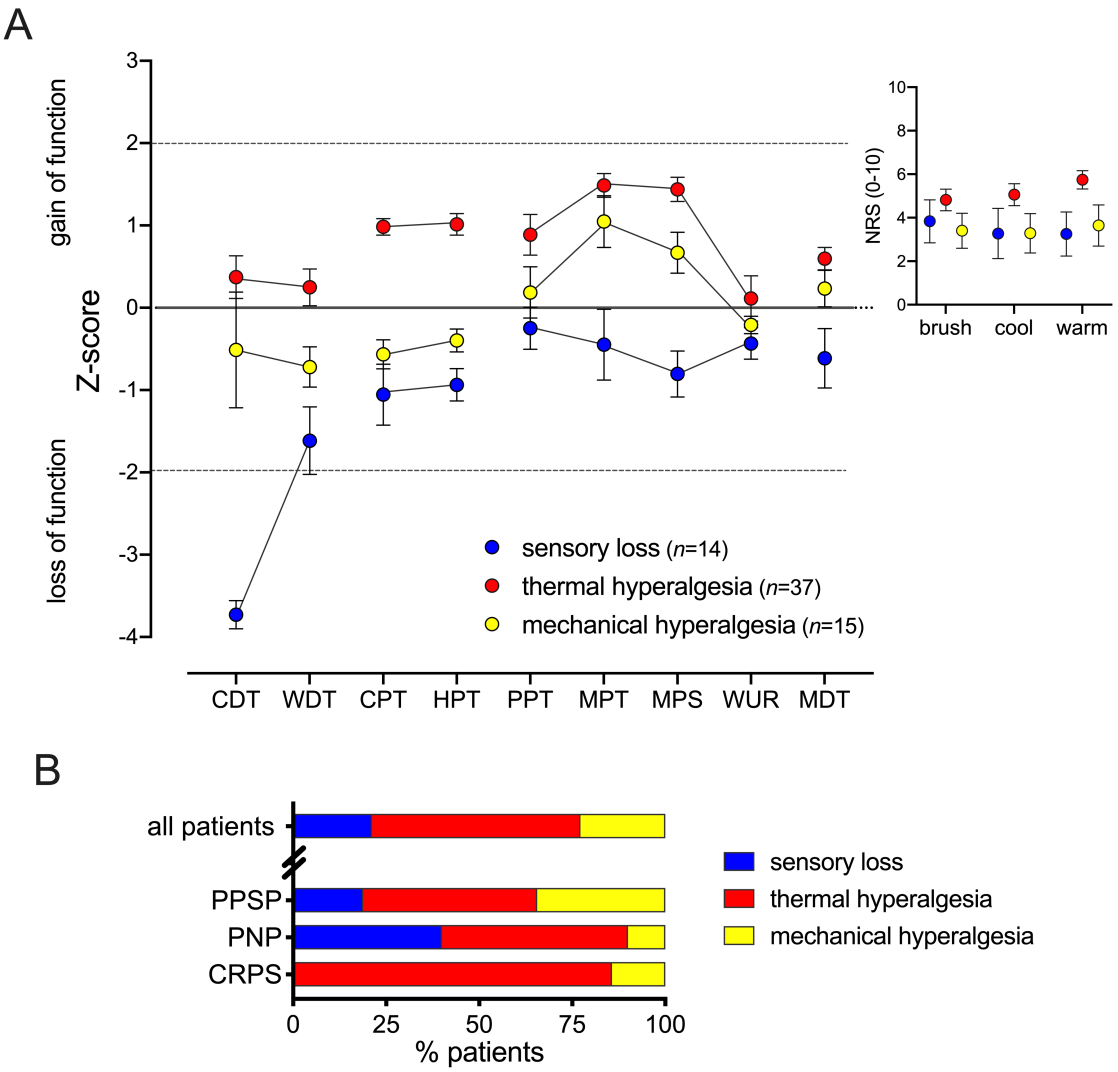

A
gain of function
loss of function
Z-score
3
2
1
0
-1
-2
-3
-4
CDT
WDT
CPT
HPT
PPT
MPT
MPS
WUR
MDT
sensory loss (n=14)
thermal hyperalgesia (n=37)
mechanical hyperalgesia (n=15)
NRS (0-10)
10
8
6
4
2
0
brush
cool
warm
B
all patients
PPSP
PNP
CRPS
0
25
50
75
100
% patients
sensory loss
thermal hyperalgesia
mechanical hyperalgesia

FIGURE 4

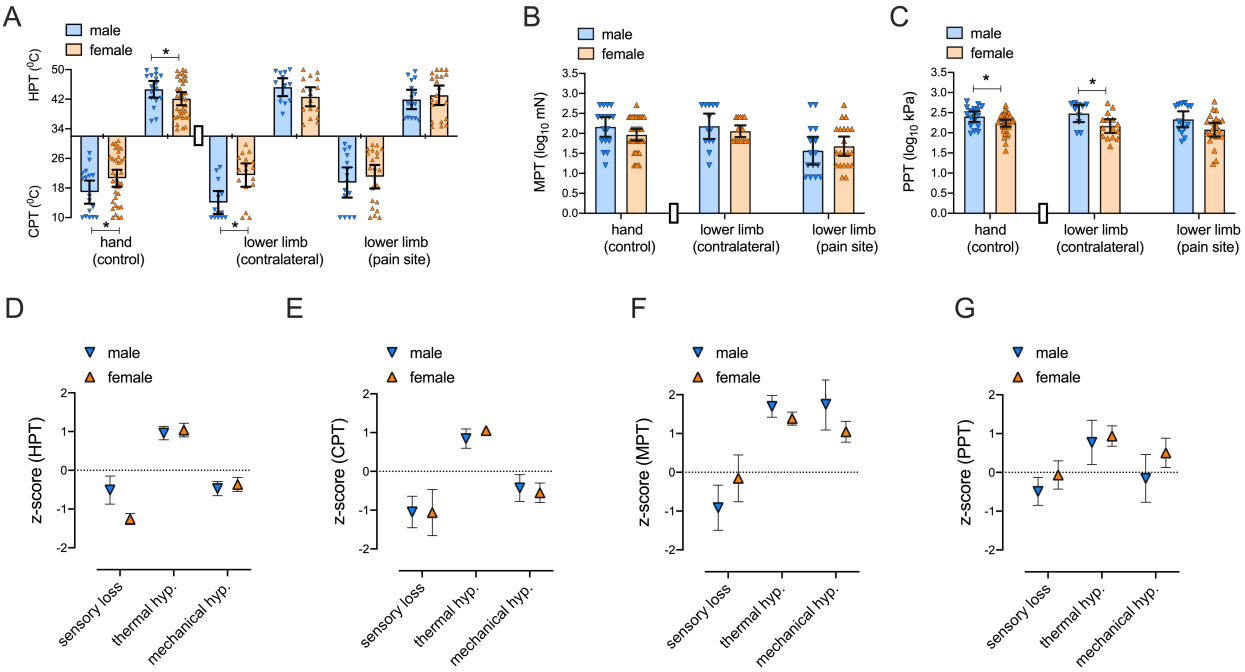

A
male
female
HPT (°C)
CPT (°C)
hand (control)
lower limb (contralateral)
lower limb (pain site)
B
MPT (log10 mN)
C
PPT (log10 kPa)
D
z-score (HPT)
E
z-score (CPT)
F
z-score (MPT)
G
z-score (PPT)
sensory loss
thermal hyp.
mechanical hyp.

FIGURE 5

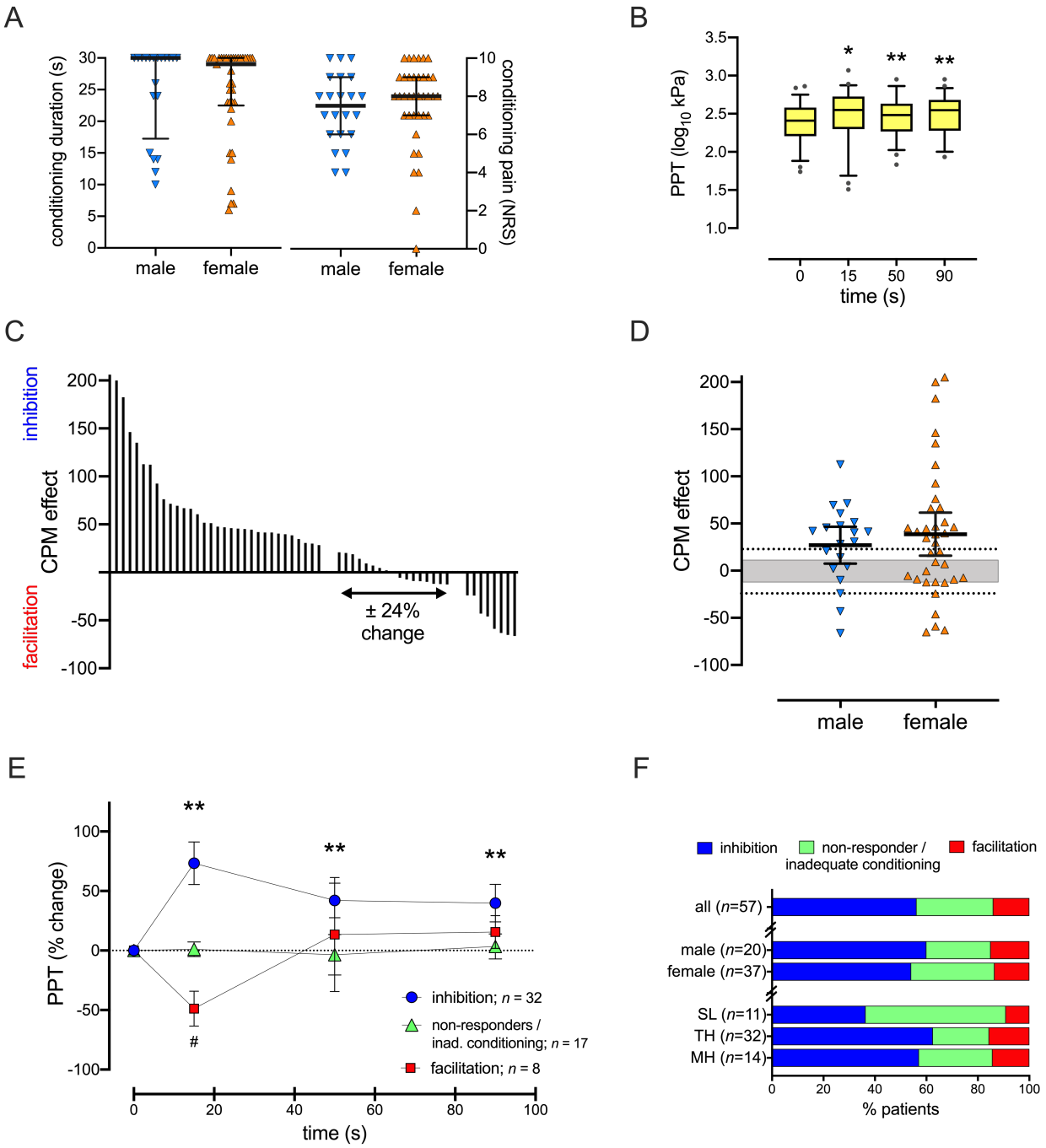
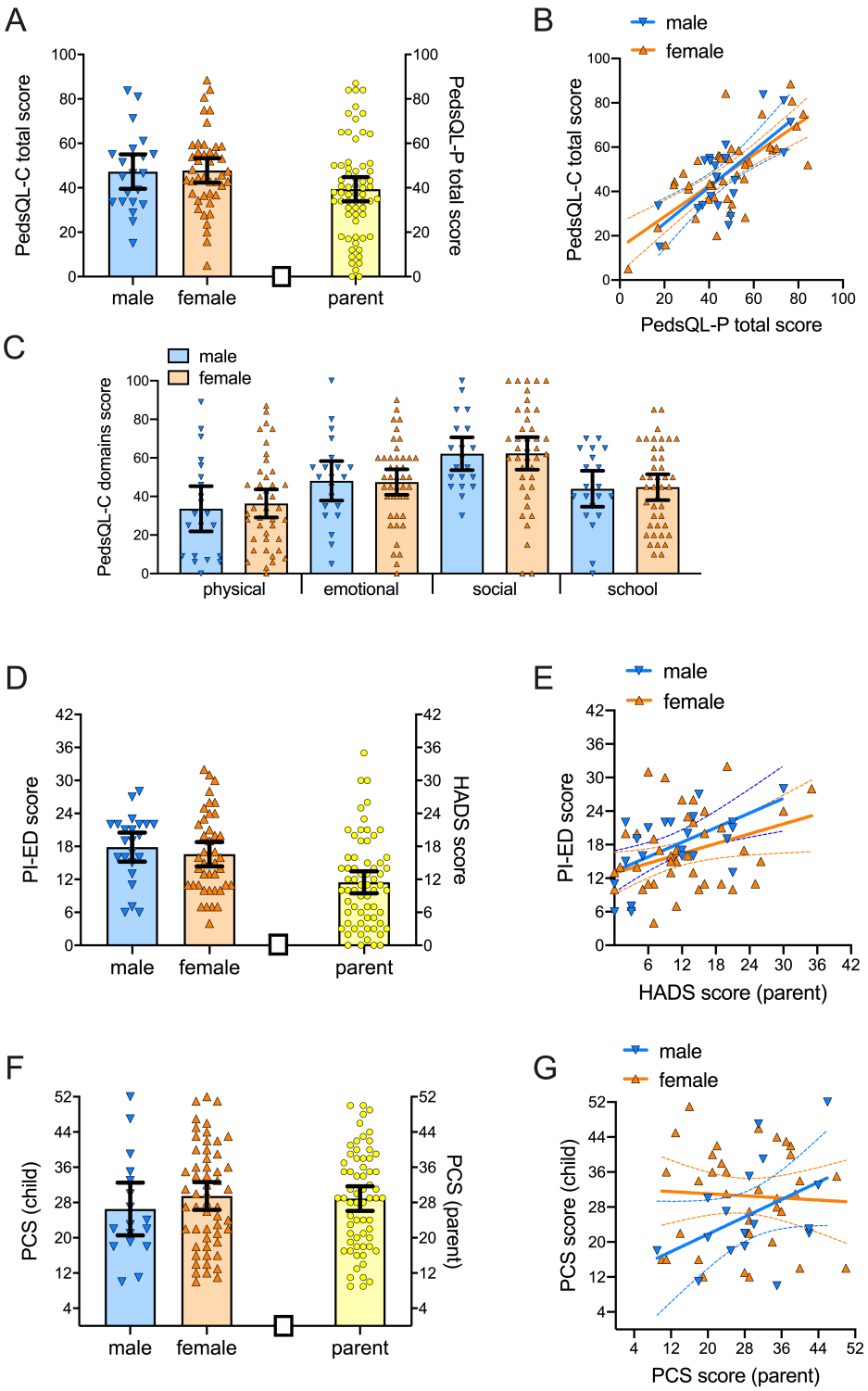
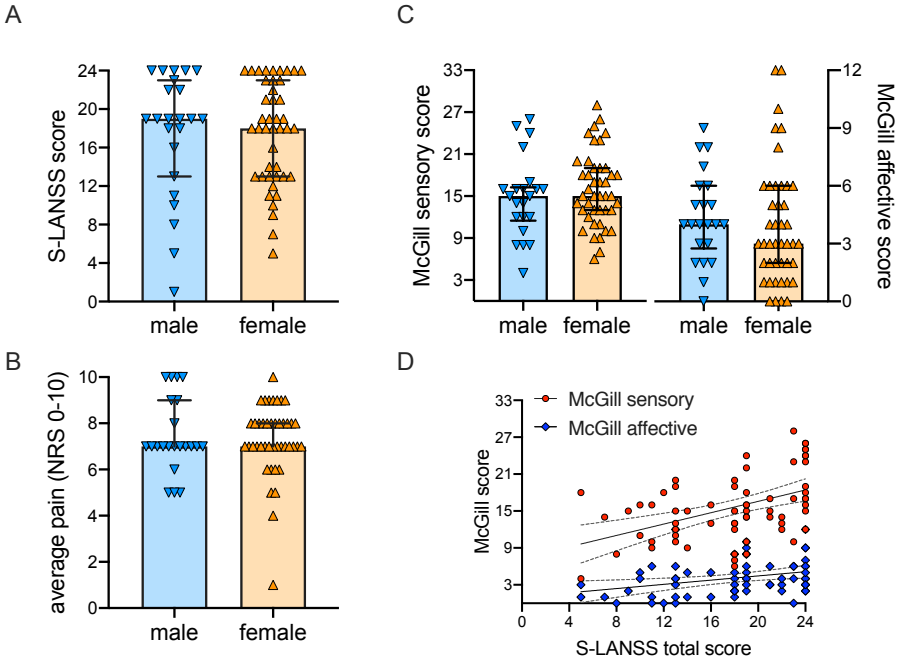
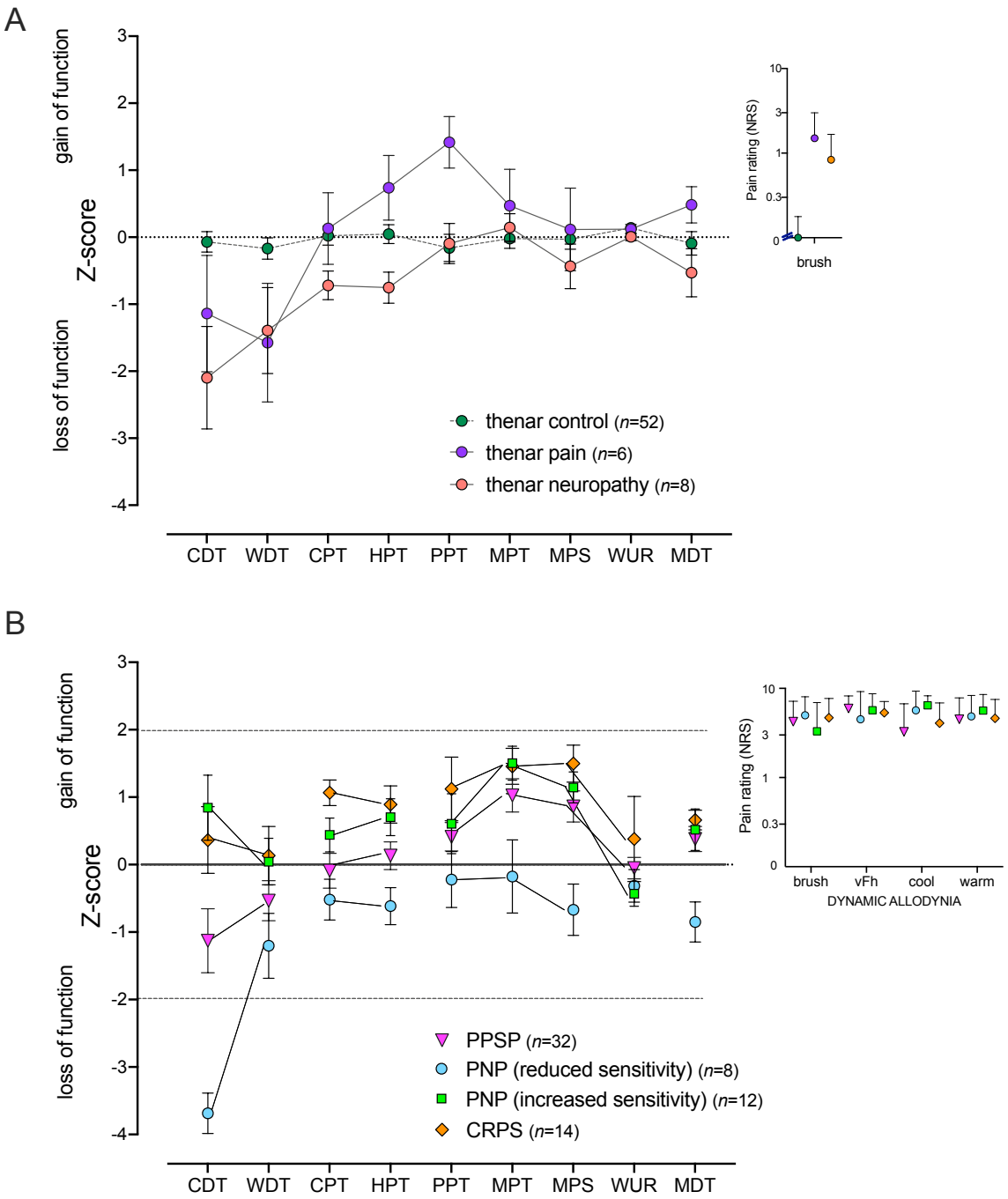

A
conditioning duration (s)
conditioning pain (NRS)
male
female
male
female
B
PPT (log10 kPa)
time (s)
C
inhibition
facilitation
CPM effect
± 24% change
D
CPM effect
male
female
E
PPT (% change)
time (s)
inhibition; n = 32
non-responders / inad. conditioning; n = 17
facilitation; n = 8
F
inhibition
non-responder / inadequate conditioning
facilitation
all (n=57)
male (n=20)
female (n=37)
SL (n=11)
TH (n=32)
MH (n=14)
% patients

FIGURE 6


A
PedsQL-C total score
PedsQL-P total score
male
female
parent
B
male
female
PedsQL-C total score
PedsQL-P total score
C
male
female
PedsQL-C domains score
physical
emotional
social
school
D
PI-ED score
HADS score
male
female
parent
E
male
female
PI-ED score
HADS score (parent)
F
PCS (child)
PCS (parent)
male
female
parent
G
male
female
PCS score (child)
PCS score (parent)



Supplementary Figure 1. Pain descriptors did not differ between male (n=23) and female (n=43) adolescents with neuropathic pain or CRPS. (A) Total scores on the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS, 0-24) (B) Average pain intensity during the last week reported on a numerical rating scale in the S-LANSS were consistent with measures indicated on a 0-10cm VAS in both males (Spearman's rho = 0.58 [95%CI 0.13,0.88]) and females (0.50 [95%CI 0.20,0.75]) (C) Total scores for sensory (0-33) and affective (0-12) pain descriptors reported on the McGill Pain Questionnaire. Data points = individual values; bars = median [IQR].
(D) Total S-LANSS scores correlated more strongly with McGill sensory (R^2 =0.22) than affective scores (R^2=0.11). Data points = individual values. Solid lines=linear regression; dotted lines = 95%CI.

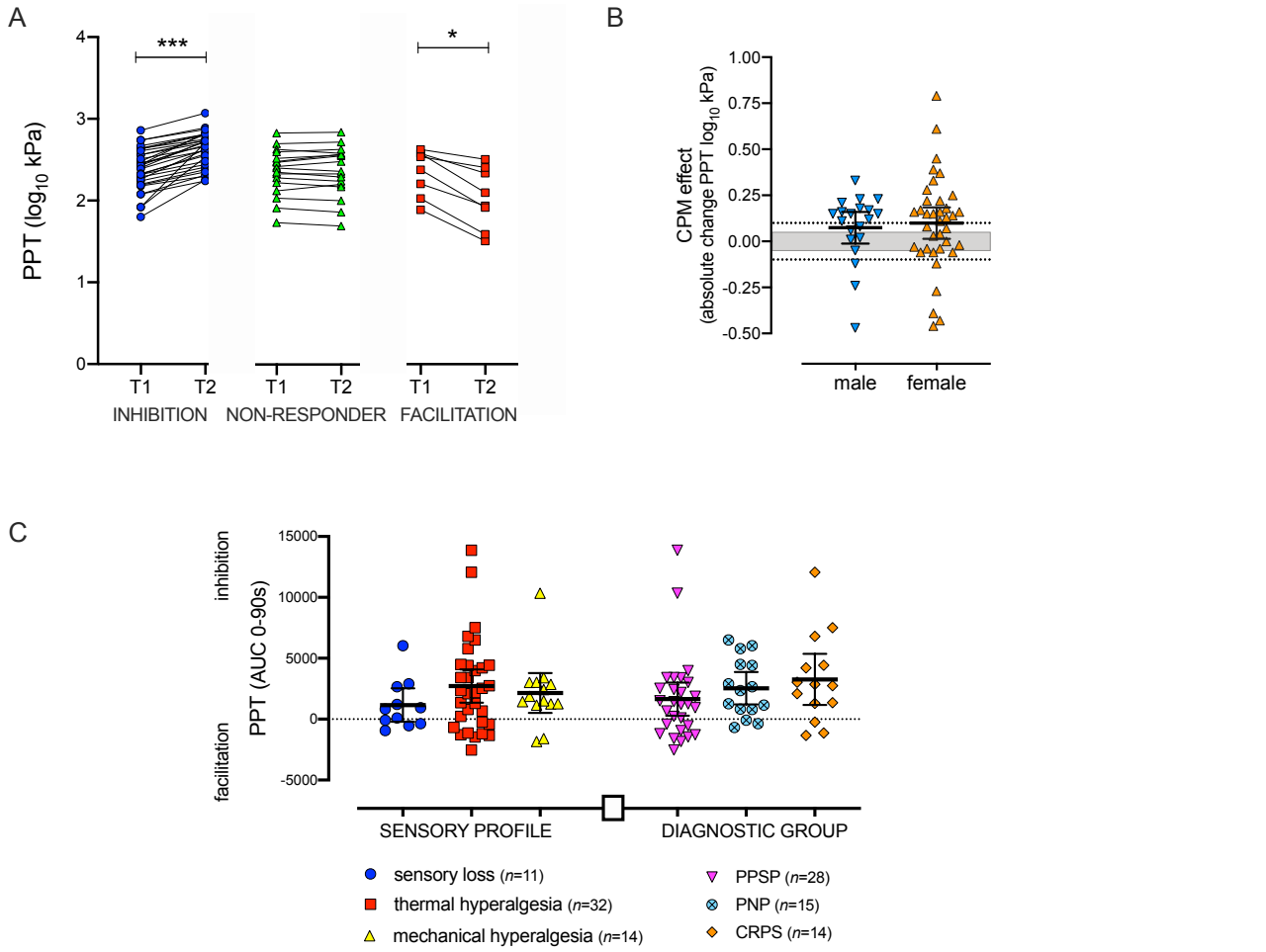


Supplementary Figure 2. Sensory profiles constructed with z-score comparisons to control values. Increased sensitivity is plotted as positive values (gain of function), and reduced sensitivity as negative values (loss of function).

A: QST modalities tested on the thenar eminence for patients with no symptoms affecting the hand (thenar control, n=52), patients experiencing pain in the hand (thenar pain, n=6), and patients with distal polyneuropathy but pain at other sites (thenar neuropathy, n=8). Data are expressed as Z-score comparisons with the thenar control group. Main effect of group ($F_{2,63}$=5.0, P=0.01), modality ($F_{4.6,268}$=6.0, P<0.001), and modality x group interaction ($F_{16,497}$=2.9, P<0.001)(two-way mixed-effects ANOVA with diagnostic group as between subject factor and repeated measures of modality). Dynamic mechanical brush allodynia was not reported at control thenar sites. Data points = mean±SEM.

B: Alterations in somatosensory function are divided into subgroups based on clinical diagnosis and signs. Z-scores were calculated by comparison of pain site measures with body region matched (head and neck,

torso, upper limb, lower limb) measures from contralateral non-pain sites. Patients with persistent post-surgical pain (PPSP, n=32) had increased sensitivity across mechanical modalities at pain sites related to previous surgical scars. Patients with peripheral neuropathic pain (PNP) were divided into those with reduced sensitivity (n=8) or increased sensitivity (n=12) based on review of the individual sensory profile. Patients with Complex Regional Pain Syndrome (CRPS) (n=14) had thermal and mechanical hyperalgesia, and z-scores for CPT, PPT MPS were highest in this group. There was a significant main effect of diagnostic subgroup ($F_{3,62}$=9.9, P<0.001), modality ($F_{5.3,306}$=10.8, P<0.001), and modality x diagnostic group interaction ($F_{24,463}$=2.0, P=0.003)(two-way mixed-effects ANOVA with diagnostic group as between subject factor and repeated measures of modality). Allodynia to dynamic stimuli (brush, 200-300mN; cool, 25^0C roller; warm, 40^0C roller) in the region of pain was rated on a 0-10 numerical rating scale (NRS). Data points = mean±SEM. *Legend:* CDT, cool detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; DMA, dynamic mechanical allodynia; PHS, paradoxical heat sensation; NRS, numerical rating scale 0-10.



Supplementary Figure 3. Conditioned pain modulation, assessed with a variable test stimulus (knee pressure pain threshold, PPT) and cold conditioning stimulus with the contralateral hand (immersion 5^0C up to 30s).

(A) Individual normalized PPT data are shown at baseline (time T1) and 15 s(T2) for patients with greater than 24% increase from baseline PPT (inhibition), ±24% change in PPT (non-responders), and >24% decrease in PPT (facilitation). Pre-post analysis of raw data similarly identifies participants with a significant increase (inhibition, blue circle, n=32), no change (non-responders, green triangle, n=17) or decrease (facilitation, red square, n=8) in PPT. Student's t-test ***P<0.001 *P<0.05.

(B) CPM effect is presented as the absolute change in normalized PPT (log_{10} kPa) at 15 seconds in males (0.07 [95%CI -0.01,0.16]) and females (0.10 [95%CI 0.01,0.18]). The standard error of measurement (±0.05; calculated from previous healthy control data) is indicated within the grey box, and dotted lines mark ±2SEM. Post-hoc analysis of current data in patients with pain resulted in similar SEM (±0.059). Values did not differ between males and females. Unpaired t-test P=0.7. Data points = individual patients; bars = mean [95%CI].

(C) As the degree of early and late phase CPM differed in adults with CRPS or neuralgia,[63] the area under/over the change in PPT versus time curve was calculated for each patient to encompass both the degree and duration of percentage change in parallel and sequential measures of PPT, the area under/over the % change in PPT vs time curve was calculated. A spectrum of responses is seen that does not differ based on pain site sensory profile (main effect of group: $F_{2,54}$ = 0.9, P=0.4) or clinical diagnostic group ($F_{2,54}$=1.2, P=0.3).

Supplementary Table 1. Demographic characteristics, pain history, sensory profile and patient/parent reported outcome measures based on clinical diagnostic group

Group	**Cohort**		**Subgroups**		
			PPSP	PNP	CRPS
N	66		32	20	14
Sex					
Male	23 (35%)		12 (38%)	6 (30%)	5 (36%)
Female	43 (65%)		20 (62%)	14 (70%)	9 (64%)
Age (yrs)	14.9 [12.9,16.1]		15.2 [12.9,16.5]	14.9 [12.9,16.0]	14.6 [11.5,16.1]
Height (cm)	160 ± 13		159 ± 13	161 ± 23	161 ± 16
Weight (kg)	57 ± 18		56 ± 15	61 ± 23	55 ± 19
Pain intensity (0-10cm VAS)					
Pain now	4.6 ± 2.2		4.5 ± 2.3	4.5 ± 2.5	4.7 ± 1.9
Average pain last week	6.3 ± 1.9		6.2 ± 2.0	6.4 ± 1.9	6.3 ± 1.9
Worst pain last week	7.6 ± 2.0		7.4 ± 2.4	7.6 ± 1.9	7.8 ± 1.3
Interference due to pain	6.9 ± 2.7		6.7 ± 2.9	6.2 ± 2.8	8.1 ± 1.6
Pain duration					
3 – 12 months	12 (18%)		5 (16%)	0	7 (50%)
1 – 2 years	16 (24%)		4 (13%)	9 (45%)	3 (21%)
2 – 5 years	25 (38%)		16 (50%)	5 (25%)	4 (29%)
> 5 years	13 (20%)		7 (22%)	6 (30%)	0
Pain site, n (%)					
Head and neck	11 (17%)		5 (16%)	6 (30%)	0
Trunk	10 (15%)		10 (31%)	0	0
Upper limb	7 (11%)		3 (9%)	2 (10%)	2 (14%)
Lower limb	38 (58%)		14 (44%)	12 (60%	12 (86%)
Pain distribution, n (%)					
Unilateral	46 (70%)		23 (72%)	9 (45%)	14 (100%)
Bilateral / midline	20 (30%)		9 (28%)	11 (55%)	0
Second pain site, n (%)*					
Head and neck	2 (3%)		1 (3%)	1 (5%)	0
Trunk	8 (12%)		7 (22%)	1 (5%)	0
Upper limb	5 (8%)		1 (3%)	4 (20%)	0
Lower limb	7 (11%)		4 (12%)	3 (15%)	0
S-LANSS					
Average pain last week (0-10 NRS)	7 [7,8]		7.5 [6,9]	7 [7,8]	7 [7,8]
Total score	19 [13,23]		18 [12,24]	18 [13,19]	22 [19,24]
McGill Pain Questionnaire					
Sensory (0-33)	15 [12,18.5]		15.5 [12,18.8]	14 [9,19]	15.5 [13,17.3]

Affective (0-12)	4 [2,6]		3.5 [1.3,5]	4 [2,6]	4 [3,6]
Current medication, n (%)					
Tricyclic antidepressant	20 (30%)		8 (25%)	7 (35%)	5 (36%)
Gabapentinoid	18 (27%)		9 (28%)	6 (30%)	5 (36%)
Lidocaine patch / mexiletine	14 (21%)		9 (28%)	3 (15%)	2 (14%)
Oral opioid**	9 (14%)		7 (22%)	2 (10%)	0
Previous medication ceased [lack of efficacy/side-effects]					
Tricyclic antidepressant	17 [12/5] (26%)				
Gabapentinoid	19 [14/5] (29%)				
Lidocaine patch	7 [6/1] (11%)				
Oral opioid***	16 [11/5] (24%)				
Patient-reported outcome measures					
Quality of life (PedsQL-C, 0-100; *n*=65)	47 [35,57]		46 [34,58] n=31	54 [36,59]	45 [36,56]
Emotional distress (PI-ED, 0-42)	17 [11,22]		16 [12,22]	17 [12,24]	21 [11,23]
Pain catastrophizing (PCS-C, 0-52; *n*=55)	30 [20,39]		27 [19,38] n=27	29 [16,40] n=18	33 [26,45] n=10
Parent-reported outcome measures					
Quality of life (PedsQL-P, 0-100; *n*=65)	45 [39,56]		49 [41,65]	45 [36,54]	42 [27,56] n=13
Anxiety/depression (HADS, 0-42; *n*=65)	11 [5,16]		10 [5,16]	12 [4,19] n=19	14 [3,16]
Pain catastrophizing (PCS-P, 0-42; *n*=64)	29 [19,38]		29 [20,38] n=31	25 [18,40] n=19	31 [18,36]

Data presented as mean±SD, (%), median [IQR 25th, 75th percentile], or n (%). Patient- and parent-reported outcome fields with missing data indicated by reduced 'n'.
Legend: PPSP, persistent post-surgical pain; PNP, peripheral neuropathic pain other causes; CRPS, complex regional pain syndrome; VAS, visual analogue scale; S-LANSS, self-report Leeds Assessment of Neuropathic Symptoms and Signs; NRS, numerical rating scale; PedsQL-C, Pediatric Quality of Life Generic scale - Child Report; PI-ED, Pediatric Index of Emotional Distress; PCS-C, Pain Catastrophizing Scale – Child; PedsQL-P, Pediatric Quality of Life Generic scale – Parent Report; HADS, Hospital Anxiety and Depression Scale; PCS-P, Pain Catastrophizing Scale – Parent Report
*22 patients indicated chronic pain at a second site on the body map that was less severe, had different characteristics (frequently musculoskeletal or visceral), and was not the focus of sensory testing. Patients with pain at a second site did not differ in age, sex distribution (7/23 males, 15/43 females), reported intensity of neuropathic pain, or patient-reported outcome scores (PedsQL-C, PI-ED, PCS).
**current opioid treatment commenced prior to referral: codeine PRN (n=4), tramadol (n=3), morphine once daily (n=1), oxycodone (weaning regime, n=1);
***opioid ceased as no benefit: codeine (n=7), 1 tramadol (n=1), morphine (n=3); opioid ceased due to side-effects: 2 codeine (n=2), tramadol (n=1), morphine (n=2).

Supplementary Table 2. Self-reported pain, pain descriptors and pain-related disability in adolescents with neuropathic pain or CRPS

		Age	Average pain	Worst pain	Pain duration	Inter-ference	S-LANSS	MPQ sensory	MPQ affective
Patient age (yrs)		1.0							
		-							
Average Pain (last week)	rho	.23	1.0						
	95% CI	-.02, .46	-						
Worst Pain (last week)	rho	.18	**.70****	1.0					
	95% CI	-.08, .41	.54, .81	-					
Pain duration	rho	**.29***	.24	.01	1.0				
	95% CI	.01, .52	-.05, .46	-.29, .26	-				
Pain-related activity Interference	rho	-.04	**.30***	.23	.06	1.0			
	95% CI	-.32, .26	.04, .55	-.01, .46	-.22, .35	-			
S-LANSS (total score)	rho	.04	.17	.17	-.08	.18	1.0		
	95% CI	-.24, .30	-.07, .38	-.11, .42	-.31, .17	-.06, .40	-		
MPQ (sensory score)	rho	**.29***	.23	.17	.09	**.29***	**.47****	1.0	
	95% CI	.05, 0.48	-.01, .44	-.11, .40	-.13, .30	.08, .48	.26, .65	-	
MPQ (affective score)	rho	.11	.10	.17	-.01	**.43****	**.37****	**.69****	1.0
	95% CI	-.16, .38	-.16, .36	-.08, .39	-.26, .22	.20, .59	.13, .56	.54, .80	-

Data represent Spearman's rho with bias corrected accelerated (BCa) 95% Confidence Interval lower and upper limits. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).
Legend: S-LANSS, self-report Leeds Assessment of Neuropathic Symptoms and Signs; MPQ, McGill Pain Questionnaire

Supplementary Table 3. Comparison between QST data from non-pain sites in current neuropathic pain cohort (NeuP cohort) and published data for the same body region.

Body Region	**Hand**					**Lower limb**			**Torso**			**Head and neck**	
Test site	thenar	thenar	dorsum	dorsum		contralateral	dorsum foot		contralateral	chest wall		contralateral	face
Data source	NeuP cohort	Walker 2018*	Blankenburg 2011**	Blankenburg 2010***		NeuP cohort	Blankenburg 2010***		NeuP cohort	Walker 2018*		NeuP cohort	Blankenburg 2010***
N sex (female, male)	52 35F, 17M	48 29F, 19M	87 43F, 44M	64 32F, 32M		31 18F, 13M	64 32F, 32M		13 10F, 3M	48 29F, 19M		7 7F	64 32F, 32M
Age range, years	10.1 – 17.4	18.1 – 20.1	14	13.0 – 16.1		10.4 – 17.4	13.0 – 16.1		10.6 – 16.6	18.1 – 20.1		14.5 – 17.3	13.0 – 16.1
Cool Diff, Log (CDT raw, ^{0}C)	0.46 ± 0.21 (28.8 ± 1.8)	0.42 ±0.27 (30.0 ± 1.01)	0.014 ± 0.21	-0.05 ± 0.17 F 0.05 ± 0.23 M		0.22 ± 0.16 (27.0 ± 2.69)	0.28 ± 0.28 F 0.35 ± 0.23 M		0.37 ± 0.26 (28.6 ± 1.8)	0.39 ±0.19 (27.6 ± 3.56)		-0.45 ± 0.2 (29.7 ± 0.9)	-0.04 ± 0.22 F 0.05 ± 0.22 M
Warm Diff, Log (WDT raw, ^{0}C)	0.50 ± 0.19 (35.5 ± 2.3)	0.46 ± 0.24 (34.7 ± 1.6)	0.11 ± 0.17	0.14± 0.15 F 0.22 ± 0.20 M		0.79 ± 0.19 (38.7 ± 3.0)	0.40 ± 0.19 F 0.51 ± 0.23 M		0.26 ± 0.39 (37.0 ± 2.3)	0.62 ± 0.20 (38.2 ± 3.76)		0.63 ±0.21 (36.8 ± 2.7)	0.09 ± 0.17 F 0.15 ± 0.16 M
CPT, ^{0}C	19.4 ± 6.7	18.0 ± 6.6	21.7 ± 6.7	18.6 ± 8.0 F 17.6 ± 9.1 M		18.1 ± 6.7	17.6 ± 9.2 F 16.6 ± 8.7 M		25.9 ± 3.4	22.6 ± 6.5		24.9 ± 3.7	17.3 ± 8.8 F 17.4 ± 8.0 M
HPT, ^{0}C	43.0 ± 5.0	43.9 ± 4.8	40.6 ± 3.6	42.1 ± 3.3 F 42.6 ± 4.1 M		43.9 ± 4.6	42.5 ± 2.9 F 43.8 ± 3.0 M		41.1 ±3.9	41.8 ± 3.98		43.0 ± 4.3	41.7 ± 3.8 F 43.1 ± 3.0 M
MDT, Log mN (MDT raw, g)	-0.11 ± 0.60 (0.16 ± 0.32)	-0.21 ± 0.42 (0.11 ± 1.0)	-0.21 ± 0.28	-0.51 ± 0.28 F -0.62 ± 0.19 M		0.26 ± 0.71 (1.31 ± 4.54)	-0.64 ± 0.19 F -0.60 ± 0.20 M		0.34 ± 0.86 (1.90 ± 5.4)	0.16 ± 0.48 (0.36 ± 0.99)		-0.17 ± 0.43 (0.09 ± 0.07)	-0.743 ± 0.01 F -0.74 ± 0.03 M
MPT, Log mN	2.03 ± 0.44	1.91 ± 0.40	1.56 ± 0.3	1.53 ± 0.31 F 1.62 ± 0.26 M		2.12 ± 0.41	1.45 ± 0.36 F 1.43 ± 0.28 M		2.0 ± 0.43	1.79 ± 0.47		1.59 ± 0.45	1.20 ± 0.31 F 1.28 ± 0.28 M
PPT, Log kPa	2.3 ± 0.30	2.37 ± 0.18	2.53 ± 0.14	2.7 ± 0.10 F 2.8 ± 0.14 M		2.29 ± 0.33	2.87 ± 0.21 F 3.02 ± 0.12 M		1.98 ± 0.41	2.35 ± 0.22 (lower limb)		1.83 ± 0.31	2.87 ± 0.21 F 3.02 ± 0.12 M

Legend: NeuP cohort, current neuropathic pain cohort; Cool Diff, cool difference = 32^{0}C minus CDT; CDT, cool detection threshold; Warm Diff, warm difference = WDT minus 32^{0}C; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; PPT, pressure pain threshold; M, male; F, female

References:

*Walker SM, Melbourne A, O'Reilly H, et al. Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery. *Br J Anaesth.* 2018;121(3):623-635.

** Blankenburg M, Meyer D, Hirschfeld G, et al. Developmental and sex differences in somatosensory perception--a systematic comparison of 7- versus 14-year-olds using quantitative sensory testing. *Pain.* 2011;152(11):2625-2631.

***Blankenburg M, Boekens H, Hechler T, et al. Reference values for quantitative sensory testing in children and adolescents: developmental and gender differences of somatosensory perception. *Pain.* 2010;149(1):76-88

Supplementary Table 4. Analysis of group sensory data: impact of sex, diagnostic group, and body region.

Modality	**Value** (mean ± SD)	**Sample** (N)	**Main effects**			**Bonferroni post-hoc comparisons, P<0.05** (mean difference [95% CI])
			sex	diagnostic group	body region (site)	
CDT (CoolDiff, Log)						
thenar	0.46 ± 0.21	52	F1,46=2.9 P=0.09	F2,46=0.6 P=0.6	n.a.	
contralateral	0.27 ± 0.21	51	F1,35=5.0 **P=0.03**	F2,35=0.5 P=0.6	F3,35=1.4 P=0.25	Male vs female: 0.19 [0.07,0.32] P=0.004
pain site	0.59 ± 0.33	62	F1,47=0.12 P=0.72	F2,47=1.0 P=0.4	F3,47=0.8 P=0.52	
WDT (WarmDiff, Log)						
thenar	0.50 ± 0.20	52	F1,46=3.4, P=0.07	F2,46=3.9 **P=0.03**	n.a	PNP vs CRPS 0.21 [0.04,0.39] P=0.03
contralateral	0.72 ± 0.20	52	F1,36=0.1 P=0.67	F2,36=0.22 P=0.8	F3,36=2.8 P=0.05	
pain site	0.75 ± 0.25	58	F1,43=0.09 P=0.76	F2,4=0.6 P=0.6	F3,43=0.7 P=0.53	
CPT (^{0}C)						
thenar	19.4 ± 6.7	52	F1,46=6.4 **P=0.02**	F2,46=1.0 P=0.37	n.a.	Male vs female: -5.8 [-10.3,-1.2] P=0.02
contralateral	20.6 ± 6.7	55	F1,39=8.1 **P=0.01**	F2,39=0.4 P=0.71	F3,39=.26 **P=0.001**	Male vs female: -5.3 [-9.1,-1.5] P=0.007; Lwr limb vs H&N: -7.1 [-13, -0.5] P=0.03; Lwr limb vs torso: -7.8 [-14,-1.3] P=0.01; Upr limb vs torso: -8.7 [-17,-1.9] P=0.04
pain site	21.8 ± 6.7	64	F1,49=0.01 P=0.9	F2,49=3.2 P=0.047	F3,49=0.8 P=0.47	PNP vs CRPS: -5.3 [-10, -0.2] P=0.04; Lwr limb vs H&N: -5.9 [-11. -0.4] P=0.03
HPT (^{0}C)						
thenar	43.0 ± 5.0	52	F1,46=5.5 **P=0.02**	F2,46=0.4 P=0.35	n.a.	Male vs female : 4.0 [0.6,7.5] P=0.02
contralateral	43.1 ± 4.4	55	F1,39=0.6 P=0.46	F2,39=1.4 P=0.24	F3,39=1.6 P=0.19	
pain site	42.0 ± 5.1	64	F1,49=0.1 P=0.79	F2,49=2.9 P=0.06	F3,49=0.4 P=0.79	
PPT (Log kPa)						
thenar	2.3 ± 0.30	52	F1,46=6.7 **P=0.01**	F2,46=1.4 P=0.26	n.a.	Male vs female: 0.22 [0.05,0.39] P=0.01
contralateral	2.14 ± 0.37	48	F1,32=5.5 **P=0.03**	F2,32=0.8 P=0.45	F3,32=5.3 **P=0.004**	Male vs female: 0.29 [0.04,0.54] P=0.03; Lwr limb vs H&N: 0.5 [0.1,0.9] P=0.02
pain site	2.0 ± 0.45	64	F1,49=2.5 P=0.12	F2,49=0.4 P=0.69	F3,49=2.1 P=0.11	
MPT (Log mN)						
thenar	2.0 ± 0.44	52	F1,46=1.9 P=0.18	F2,46=0.4 P=0.69	n.a.	
contralateral	2.0 ± 0.46	54	F1,38=0.6 P=0.5	F2,38=1.8 P=0.18	F3,38=3.0 **P=0.04**	
pain site	1.6 ± 0.58	64	F1,49=0.05 P=0.8	F2,49=0.45 P=0.64	F3,49=0.7 P=0.58	
MPS (Log mN)						
thenar	1.7 ± 0.71	51	F1,45=0.5 P=0.48	F2,45=0.5 P=0.6	n.a.	
contralateral	1.8 ± 0.69	53	F1,37=0.15 P=0.7	F2,37=0.9 P=0.41	F3,37=3.8 **P=0.02**	Upr limb vs H&N: 0.9 [0.04,1.8] P=0.037
pain site	1.1 ± 0.83	63	F1,48=1.8 P=0.18	F2,48=4.2 **P=0.02**	F3,48=0.2 P=0.91	Lwr limb vs H&N: 0.6 [0.02,1.3] P=0.038
MDT (Log mN)						
thenar	-0.11 ±0.62	52	F1,46=0.07 P=0.79	F2,46=0.08 P=0.92	n.a.	
contralateral	1.83 ± 0.69	53	F1,38=6.4 **P=0.02**	F2,38=0.7 P=0.51	F3,38=2.6 P=0.07	
pain site	0.07 ± 0.68	62	F1,47=3.6 P=0.06	F2,47=1.4 P=0.26	F3,47=3.7 **P=0.03**	Torso vs H&N: 0.8 [0.1,1.5] P=0.023; Lwr limb vs H&N: 0.65 [0.1,1.2] P=0.012

Data analysed by 3-way ANOVA with sensory modality as dependant variable and fixed factors of sex, diagnostic group and body region (H&N = head and neck; torso = chest, back, abdomen; upper limb; lower limb) for pain site and contralateral site; n.a. = body region analysis not applicable for thenar values as all at one test site. Bonferroni post-hoc comparisons with P<0.05 only reported. Reduced sensitivity is indicated by negative CPT mean difference values (as higher temperature indicates sensitivity) and positive mean difference values for all other QST parameters.

Legend: Cool Diff, cool difference = 32^{0}C minus CDT; CDT, cool detection threshold; Warm Diff, warm difference = WDT minus 32^{0}C; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; MDT, mechanical detection threshold

Supplementary Table 5A. Correlations to explore factors associated with the degree of conditioned pain modulation in adolescents with neuropathic pain or CRPS (n=57).

		CPM effect	Baseline PPT	Immersion time	Immersion NRS	Average pain	Age	Sex	BMI	Neuropathic Rx	Amitrip-tyline	PCS-C	PI-ED	HADS-Anxiety
CPM effect	rho	1.0												
	95%CI													
Baseline PPT	rho	-.12	1.0											
	95%CI	-.39, .16												
Immersion time (s)	rho	.19	.24	1.0										
	95%CI	-.07, .45	-.03, .49											
Immersion pain (NRS)	rho	.12	-.13	**-.34****	1.0									
	95%CI	-.16, .37	-.43, .16	-.57, -.11										
Average pain last week (VAS)	rho	.06	-.13	-.20	.11	1.0								
	95%CI	-.21, .33	-.41, .17	-.48, .09	-.14, .36									
Age	rho	.01	-.11	.20	-.03	.25	1.0							
	95%CI	-.27, .29	-.41, .19	-.05, .44	-.26, .20	-.05, .55								
Sex	rho	.02	**-.36****	-.06	.07	.03	.26	1.0						
	95%CI	-.26, .26	-.58, -.1	-.32, .20	-.19, .32	-.21, .28	.01, .49							
BMI	rho	-.01	.21	.18	.03	.14	.21	.04	1.0					
	95%CI	-.29, .28	-.03, .45	-.09, .42	-.24, .26	-.12, .37	-.07, .46	-.21, .30						
Current neuropathic Rx	rho	-.09	.02	-.15	-.01	**.30***	-.05	-.16	.14	1.0				
	95%CI	-.36, .17	-.29, .31	-.39, .12	-.28, .26	.02, .52	-.31, .25	-.37, .11	-.17, .46					
Current amitriptyline	rho	.01	-.05	.05	-.03	.04	-.04	-.15	.09	**.29***	1.0			
	95%CI	-.25, .27	-.32, .21	-.21, .31	-.31, .22	-.23, .31	-.32, .24	-.42, .15	-.21, .35	.10, .49				
Catastrophizing (PCS-C)	rho	-.11	-.07	-.19	.19	**.36***	.13	.14	-.02	.05	-.03	1.0		
	95%CI	-.41, .18	-.36, .22	-.46, .10	-.14, .50	.05, .62	-.15, .41	-.17, .43	-.35, .28	-.25, .36	-.35, .29			
PI-ED	rho	-.05	-.03	**-.39****	.26	.02	.04	-.13	-.04	.05	.09	**.53****	1.0	
	95%CI	-.37, .27	-.36, .30	-.61, -.1	-.08, .53	-.31, .31	-.28, .36	-.42, .20	-.38, .27	-.26, .34	-.23, .39	.28, .74		
HADS (parent anxiety)	rho	-.19	**-.39****	-.18	.24	-.02	.04	.16	-.08	.05	**.32***	.07	**.32***	1.0
	95%CI	-.51, .14	-.63, -.08	-.46, .13	-.06, .52	-.32, .27	-.31, .40	-.12, .43	-.36, .22	-.24, .32	.03, .57	-.30, .40	.02, .58	

Data represent Spearman's rho with bias corrected accelerated (BCa) 95% Confidence Interval lower and upper limits; *Correlation significant at 0.05 (2-tailed). **Correlation significant at 0.01 level (2-tailed).
Legend: CPM, conditioned pain modulation; CPM effect, % change PPT during conditioning (15 seconds); PPT, pressure pain threshold on fibula head; s, seconds; NRS, numerical rating scale; VAS, visual analogue scale; BMI, body mass index; current neuropathic Rx, current treatment with gabapentinoids and/or anti-depressant and/or sodium channel block; PCS-C, Pain Catastrophizing Scale – Child report total score; PI-ED, Pediatric Index of Emotional Distress; HADS, Hospital Anxiety and Distress scale, parent anxiety score
Parameters based on previously reports of significant correlations with CPM effect in adolescents and young adults: baseline PPT and immersion time [11], immersion discomfort/pain [3; 4; 6], pain report, age [10], sex [2; 7; 8], body mass index [9], psychological variables (pain catastrophizing and anxiety)[5] maternal anxiety [1], psychotropic medication [11], duloxetine/anti-depressant therapy [12]

Supplementary Table 5B. Correlations between the degree and/or duration of conditioned pain modulation and pain site sensory thresholds in 57 adolescents with neuropathic pain

		CPM effect	CPM area curve	CDT	WDT	CPT	HPT	MDT	MPS	MPT	PPT	WUR	DMA
CPM effect	rho	1.0											
	95% CI	.											
CPM area curve	rho	**.88****	1.0										
	95% CI	.79, .94	.										
CDT	rho	-.23	-.17	1.0									
	95% CI	-.48, .06	-.46, .13	.									
WDT	rho	-.14	-.11	**.64****	1.0								
	95% CI	-.44, .18	-.44, .23	.44, .79	.								
CPT	rho	.15	.10	**-.60****	**-.52****	1.0							
	95% CI	-.13, .42	-.21, .40	-.79, -.36	-.76, -.19	.							
HPT	rho	-.05	-.01	**.53****	**.73****	**-.72****	1.0						
	95% CI	-.36, .27	-.31, .29	.24, .75	.51, .86	-.86, -.46	.						
MDT	rho	.01	-.03	**.47****	**.38****	**-.33***	**.33***	1.0					
	95% CI	-.36, .35	-.41, .32	.22, .68	.12, .59	-.59, -.01	.05, .56	.					
MPS	rho	-.22	-.28	**.62****	**.55****	**-.57****	**.55****	**.70****	1.0				
	95% CI	-.54, .11	-.57, .04	.36, .79	.32, .74	-.75, -.32	.30, .75	.44, .89	.				
MPT	rho	-.13	-.12	**.49****	**.31***	**-.39****	**.48****	**.45****	**.60****	1.0			
	95% CI	-.39, .16	-.39, .19	.21, .70	.03, .58	-.63, -.11	.22, .69	.19, .66	.38, .77	.			
PPT	rho	-.09	-.17	**.50****	**.56****	**-.56****	**.61****	**.36***	**.53****	**.39****	1.0		
	95% CI	-.40, .23	-.44, .14	.29, .67	.34, .71	-.74, -.26	.42, .73	.06, .58	.29, .69	.09, .65	.		
WUR	rho	-.16	-.17	-.05	-.29	.13	-.28	.08	-.08	-.02	-.06	1.0	
	95% CI	-.43, .12	-.43, .08	-.35, .26	-.57, .06	-.20, .45	-.55, .03	-.19, .34	-.38, .19	-.39, .31	-.37, .27	.	
DMA	Rho	.12	.08	-.17	**-.42****	.14	-.31	-.18	-.29	**-.37***	-.29	**-.38***	1.0
	95% CI	-.23, .44	-.26, .39	-.49, .15	-.64, -.16	-.24, .50	-.56, -.01	-.49, .13	-.58, .04	-.63, -.03	-.55, .04	.07, .64	.

Data represent Spearman's rho with Bias corrected accelerated (BCa) 95% Confidence Interval lower and upper limits; *Correlation significant at 0.05 (2-tailed). **Correlation significant at 0.01 level (2-tailed).
Legend: CPM, conditioned pain modulation; CPM effect, % change PPT during conditioning (15 seconds); CPM area curve, area under/over % change PPT vs time to 90 seconds; PPT, pressure pain threshold on fibula head; CDT, cool detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; WUR, wind-up ratio; DMA, dynamic mechanical allodynia

Supplementary Table 5C Linear model of factors influencing CPM Effect (% change in PPT at 15 secs) in adolescents with neuropathic pain (n=57)

	Step 1				Step 2				Step 3			
Variables	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***
Baseline PPT (kPa)	-0.09	0.05	-.23	0.094	-0.09	0.06	-.24	0.10	-0.08	0.06	-.22	0.16
Immersion time (s)	2.7	1.01	.34	0.012	2.9	1.12	.37	0.011	2.6	1.2	.33	0.035
Age					-2.5	3.93	-.09	0.53	-1.11	4.2	-.04	0.79
Sex					0.28	18.2	0.002	0.99	0.48	18.9	.004	0.98
PI-ED									-0.62	1.3	-.07	0.65
Catastrophizing (PCS)									-0.53	0.79	-.10	0.51
R^2	**0.13**				**0.14**				**0.16**			
F for R^2	$F_{2,53}$=4.0; P=0.024				$F_{4,51}$=2.1; P=0.10				$F_{6,47}$=1.4; P=0.22			

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Supplementary Table 6A. Correlations between patient pain report and both patient and parent-reported outcome measures in adolescents with neuropathic pain (n=66).

		Average pain	Worst pain	Pain duration	Interference	PedsQL-Child	PedsQL-Parent	PI-ED (child)	HADS (parent)	PCS-Child	PCS-Parent
Average Pain (last week)		1.0									
		-									
Worst Pain (last week)	rho	**.70****	1.000								
	95% CI	.54, .81	-								
Pain duration	rho	.18	-.055	1.000							
	95% CI	-.16, .47	-.35, .23	-							
Pain-related activity Interference	rho	**.36***	.26	.038	1.000						
	95% CI	.05, .62	-.07, .57	-.27, .32	-						
Quality of life (PedsQL-Child)	rho	-.08	**-.29***	.05	**-.32***	1.000					
	95% CI	-.34, .20	-.54, .01	-.22, .30	-.56, -.02	-					
Quality of life (PedsQL-Parent)	rho	-.07	-.14	.14	-.19	**.62****	1.000				
	95% CI	-.33, .24	-.39, .14	-.14, .41	-.46, .14	.39, .77	-				
Emotional distress (PI-ED, Child)	rho	.10	.20	.03	**.45****	**-.67****	**-.49****	1.000			
	95% CI	-.18, .35	-.08, .43	-.27, .31	.22, .62	-.80, -.46	-.73, -.19	-			
Anxiety/depression (HADS, parent)	rho	-.004	.17	-.17	.13	**-.35***	**-.39****	**.40****	1.000		
	95% CI	-.26, .25	-.12, .43	-.42, .10	-.16, .42	-.56, -.07	-.62, -.11	.09, .63	-		
Catastrophizing (PCS-Child)	rho	.278	**.34***	.06	**.49****	**-.60****	**-.41****	**.61****	.14	1.000	
	95% CI	-.03, .55	.02, .62	-.22, .35	.26, .68	-.77, -.35	-.65, -.07	.40, .76	-.17, .44	-	
Catastrophizing (PCS-Parent)	rho	.12	.16	.03	.24	-.19	-.20	.22	**.44****	.21	1.000
	95% CI	-.16, .40	-.15, .42	-.26, .32	-.06, .51	-.51, .16	-.46, .14	-.07, .48	.15, .67	-.08, .48	-

Data represent Spearman's rho with Bias corrected accelerated (BCa) 95% Confidence Interval lower and upper limits; *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). Values for correlations between average pain, PCS, PI-ED, & HADS are for the full cohort, and differ from Table 5B due to the reduced sample size for conditioned pain modulation.

Legend: PedsQL-Child, Pediatric Quality of Life Generic scale - Child Report; PedsQL-Parent, Pediatric Quality of Life Generic scale - Parent Report of perceived child function; PI-ED, Pediatric Index of Emotional Distress; HADS, Hospital Anxiety and Depression Scale for report of parental symptoms; PCS-C, Pain Catastrophizing Scale – Child; PCS-Parent, Pain Catastrophizing Scale for Parents

Supplementary Table 6B. Linear model of factors influencing quality of life (PedsQL-Child total score) in adolescents with neuropathic pain

	Step 1				Step 2				Step 3			
Variables	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***
Worst Pain (last week)	-0.9	1.1	-.11	0.41	0.5	.83	.06	0.58	0.7	.8	.09	0.39
Pain duration	0.3	2.45	.02	0.89	1.7	1.8	.09	0.33	1.4	1.7	.08	0.41
Age	-2.1	1.18	-.25	0.08	-1.1	1.1	-.09	0.33	-1.8	1.1	-.17	0.12
Sex	2.1	4.70	.06	0.66	2.4	3.6	.07	0.50	3.8	3.6	.11	0.29
PI-ED (child)					-1.5	.29	-.59	0.001	-1.1	.32	-.42	0.002
PCS-C (child)					-0.4	.18	-.25	0.046	-0.6	.19	-.41	0.003
HADS (parent)									-0.5	.26	-.21	0.09
PCS-P (parent)									0.3	.19	.16	0.17
R²	**0.08**				**0.59**				**0.63**			
F for *R²*	$F_{4,60}$=1.3; P=0.29				$F_{6,48}$=11.5; P<0.001				$F_{8,43}$=9.1; P<0.001			

Legend: PedsQL-Child, Pediatric Quality of Life Generic scale - Child Report; PI-ED (child), Pediatric Index of Emotional Distress for child report of anxiety and depression; HADS (parent), Hospital Anxiety and Depression Scale for report by parents of own symptoms; PCS-Child, Pain Catastrophizing Scale – Child; PCS-Parent, Pain Catastrophizing Scale for parental report of child catastrophizing

Supplementary Table 6C. Linear model of factors influencing differences between parental report (PCS-P) and child report of pain catastrophizing (PCS-C) in adolescents with neuropathic pain (discordance = PCS-P total score minus PCS-C total score)

	Step 1				Step 2			
Variables	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***
Worst Pain (last week)	-1.6	1.03	-.23	0.12	-1.5	.83	-.22	0.09
Pain duration	0.6	2.26	.04	0.80	0.9	1.8	.06	0.63
Age	1.6	1.42	.16	0.28	1.9	1.1	.19	0.11
Sex	-7.3	4.45	-.23	0.11	-8.1	3.6	-.27	0.03
PI-ED (child)					-1.1	.27	-.51	<0.001
HADS (parent)					-0.9	.23	.49	<0.046
R²	**0.09**				**0.41**			
F for *R²*	$F_{4,48}$=1.3; P=0.29				$F_{6,45}$=5.2; P<0.001			