TITLE PAGE

Complete manuscript title: Sensory function and pain experience in Arthritis, Complex Regional Pain Syndrome, Fibromyalgia Syndrome and healthy volunteers: a cross-sectional study.

Authors' full names, highest academic degrees and affiliations: Prof Shea Palmer PhD[1], Dr Jacqueline Bailey PhD[1,2], Dr Christopher Brown PhD[3], Prof Anthony Jones MD[4], Prof Candy S McCabe PhD[1,5,6]

[1]University of the West of England, Bristol, UK; [2]Resolve Your Pain, Bath, UK; [3]University of Liverpool, Liverpool, UK; [4]University of Manchester, Manchester, UK; [5]Royal United Hospitals Bath NHS Foundation Trust, Bath, UK; [6]Florence Nightingale Foundation, London, UK.

Name and address for correspondence: Prof Shea Palmer, University of the West of England, Glenside Campus, Blackberry Hill, Bristol BS16 1DD. Tel: +44 117 3288919. Email: Shea.Palmer@uwe.ac.uk

Address for reprints: as above.

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ABSTRACT

Objectives: This study aimed to identify relationships between sensory function and pain in common pain conditions (Arthritis, Complex Regional Pain Syndrome (CRPS) and Fibromyalgia Syndrome (FMS)) and healthy participants. Sensory abnormalities are known to be concomitant with some types of chronic pain but comparison across pain conditions using existing research is difficult due to methodological differences. Pragmatic Quantitative Sensory Testing (QST) methods were used.

Methods: Hot and cold sensitivity, light touch threshold (LTT), two-point discrimination (TPD) and pressure pain threshold (PPT) were assessed in 143 participants (n=37 Healthy, n=34 Arthritis, n=36 CRPS, n=36 FMS). Outcomes were assessed in the index ('affected' or right) and contralateral arm. Participants also completed the Brief Pain Inventory and McGill Pain Questionnaire.

Results: There were statistically significant differences between groups for all QST outcomes except TPD. Relative to healthy participants, FMS displayed heat hyperesthesia in both arms and cold hyperesthesia in the contralateral arm. CRPS demonstrated no changes in thermal sensitivity. Both CRPS and FMS exhibited bilateral pressure hyperalgesia. LTT hypoesthesia was observed bilaterally for CRPS but only in the contralateral arm for FMS. CRPS and FMS had pressure hyperalgesia in the index arm relative to Arthritis patients. There were no differences between Arthritis and Healthy participants for any QST outcome. In CRPS there were significant correlations between LTT and pain outcomes bilaterally.

Discussion: People with FMS and CRPS demonstrate extensive sensory dysfunction. Arthritis patients had sensory profiles closer to healthy participants. LTT may provide a clinically relevant and accessible assessment for CRPS.

Key words: Arthritis, Complex Regional Pain Syndromes, Fibromyalgia, Pain Threshold, Sensation.

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INTRODUCTION

Sensory abnormalities have been identified in a range of chronic pain conditions and are related to pain experience. For example, increases over a three year period in mechanical hypoesthesia and hyperalgesia were associated with ongoing pain in Complex Regional Pain Syndrome (CRPS).[1] In people with knee osteoarthritis (OA) undergoing joint replacement surgery, pre-operative heat hyperalgesia predicted post-operative analgesic consumption;[2] and pre-operative pressure hyperalgesia at a distant point (the forearm) correlated with pain one year post-surgery.[3] In Fibromyalgia Syndrome (FMS) hot and cold pain thresholds were associated with pain, fatigue, anxiety and depression;[4] and with hand pain, sleep quality and number of tender points.[5] Sensory assessment may therefore represent an important part of clinical examination.

One of the difficulties in mapping sensory function across different pain conditions is the array of methodological approaches reported. The German Research Network on Neuropathic Pain (DFNS) produced a standardised QST protocol.[6] However, it takes approximately 30 minutes for each body region and uses very specialist equipment. Additionally, most QST studies investigate specific patient groups in isolation, preventing comparisons between different conditions. Three exceptions[7-9] all used the DFNS protocol. Maier et al.[7] compared somatosensory function across different neuropathic pain conditions, demonstrating hyperalgesia to cold, heat, blunt pressure and pinprick; and dynamic mechanical hyperalgesia in CRPS. Blumenstiel et al.[8] compared QST outcomes in the back and dorsum of the hand in chronic back pain, FMS and healthy controls. Back pain patients displayed pressure hyperalgesia and vibration hypoesthesia only in the back. Sensory changes were more pronounced in FMS. Tampin et al.[9] compared cervical radiculopathy, FMS and healthy participants, finding similar patterns of thermal hyperesthesia and mechanical hypoesthesia/hyperalgesia between groups, although changes were more

marked in FMS. One further study[10] used alternative QST methods of pressure algometry and cuff algometry to compare different patient groups, finding that sensory function in recurrent low back pain (LBP) was comparable to healthy controls. There was a range of sensory changes in mild and severe LBP but these were more pronounced in FMS.

The above studies demonstrate that using the same protocol facilitates comparison across clinical conditions. Sensory differences might be clinically important as they may indicate underlying pain mechanisms. Furthermore, exploring relationships between sensation and pain experience might highlight which abnormalities are most clinically relevant. However, there may be advantages in employing more pragmatic and relatively low cost assessments than the DFNS protocol.

This study therefore aimed to use pragmatic QST methods (inexpensive modalities, 20 minutes to assess multiple body regions) to assess sensory function in healthy volunteers and chronic pain patients (CRPS, FMS and Arthritis) and to explore the relationships with self-reported pain experience. It was hypothesised that the protocol would identify a) sensory abnormalities in chronic pain patients; b) greater sensory abnormalities in CRPS and FMS than Arthritis; and c) positive relationships between sensory abnormalities and two different measures of pain experience.

MATERIALS & METHODS

This was a multi-centre cross-sectional observational study conducted at the Royal National Hospital for Rheumatic Diseases, Bath, UK (RNHRD) and at Salford Hospital, Manchester, UK. The results reported here were part of a wider study investigating sensorimotor conflict and its relationship to behavioural and neurophysiological variables in these patient groups. For example, we have demonstrated that sensorimotor conflicts lead to greater self-reported sensory disturbances in CRPS and FMS than in Arthritis, and that such disturbances are

related to pain intensity.[11] The analysis of QST and pain measures is reported separately here to allow full consideration of the findings in relation to the relevant literature. Ethical approval was granted by the National Research Ethics Service Committee South West - Frenchay (11/SW/0246).

Participants

Participants were recruited from four distinct patient groups to reflect those reported in previous literature: Complex Regional Pain Syndrome Type 1 (CRPS), Fibromyalgia Syndrome (FMS), OA/Rheumatoid Arthritis (RA) (Arthritis), and healthy controls (Healthy) (Table 1). The decision to recruit a combined Arthritis group was based on the wish to have a comparator group that had predominantly joint-specific disease, regardless of the inflammatory component. The Healthy group was matched with the patient groups according to gender and age (within 10 year bands). Sample size calculations were based on Pressure Pain Threshold (PPT) data for the index finger reported by Fernández-de-las-Peña et al.[16] They found a mean PPT of 448.7kPa in healthy participants (n=20), with a standard deviation of 23.4kPa (calculated from the reported 95% confidence intervals as recommended by Higgins and Green[17]). In patients with carpal tunnel syndrome, they found a reduction in PPT of 167kPa compared to healthy participants. However, a much more conservative difference of just one standard deviation was used for the purposes of our sample size calculation. On the basis of multi-group comparisons, α=0.05 and 90% power, a sample size of n=33 in each group was calculated.

TABLE 1 HERE

Patient identification: Potential participants were identified by the multidisciplinary teams from the outpatient departments and wards at the RNHRD, Bath and the musculoskeletal pain clinic at Salford Royal, Manchester. Patients were also recruited from a database of volunteers held by the North West England Primary Care Research Network (PCRN).

Potential participants were given an invitation letter and an information sheet about the study by a member of the multidisciplinary team, or received this by mail in the case of PCRN volunteers.

Healthy volunteer identification: Healthy volunteers were recruited from hospital staff, family members of patient participants and other professional contacts known to the researchers. They were given a letter of invitation and a participant information sheet.

All potential participants were asked to contact the research team if they were interested in taking part. If they expressed an interest, the research associate employed on the project (JB) contacted them and arranged an appointment for assessment. Participants were given an opportunity to ask any questions about the study on the telephone and when attending for assessment, prior to providing written informed consent. Travel expenses were refunded and all participants were offered a £5 voucher for their time.

Outcome measures

The research associate conducted all assessments at both study sites. QST data were collected on both arms for all participants. The term ‘index arm’ has been used to identify the affected arm for those patients with unilateral arm pain. For all other participants (i.e. healthy volunteers and those with lower limb or multiple limb pain) the ‘index arm’ was randomly chosen to be the right arm (there were no statistically significant differences between left and right arms for any of the QST values in the healthy control group). The term ‘contralateral arm’ has been used to denote the unaffected limb in those with unilateral arm pain. For all other participants the ‘contralateral arm’ was the left arm. Due to variation in pathology between groups and variation in pain distribution within groups this classification was employed to facilitate comparison between groups on the effect of having pain in the limb being tested. Participants were positioned in upright sitting with the tested limb supported on

a table placed to the side. Sensory assessment took approximately 20 minutes to complete using the following procedure.

Hot and cold sensitivity: Hot and cold metal rollers (Therroll, Somedic Production AB, Sweden) were applied to both forearms. Where this was not possible with CRPS patients due to allodynia, they were tested on the area closest to the painful site that they could tolerate. The hot roller was set at 40^{o}C and the cold roller at 25^{o}C according to the manufacturer's recommendations (equivalent to 7-8^{o}C from normal skin temperature, normally within a non-painful range). Participants were asked to indicate if they could feel heat or cold and whether the stimulus was painful or not. This allowed an assessment of any paradoxical sensations such as cold stimuli being interpreted as heat.[18] The intensity of thermal sensations and any associated pain was assessed using an 11 point numerical rating scale. One half of the scale related to the intensity of cold sensations and the other half related to heat sensation intensity as follows: 0='Very painful', 1='Painful', 2='Faint pain', 3='Cold', 4='Cool', 5='No thermal sensation', 6='Warm', 7='Hot', 8='Faint pain', 9='Painful', 10='Very painful'. This was adapted slightly from the descriptors used by Berglund et al.[18] Both arms were tested three times, randomising the hot and cold rollers. The mean intensity ratings were used for analysis.

Light Touch Threshold (LTT): LTT was assessed on both hands and at a distant site (the sternum). A series of Von Frey monofilaments of decreasing stiffness were firstly applied at right angles to the centre of the sternum and the participant was asked to indicate when the sensation of touch disappeared. The stiffness value of this monofilament was recorded (in grams, g). Monofilaments of increasing stiffness were then applied and participants were asked to indicate when the sensation of touch reappeared. This monofilament value was also recorded and the LTT was calculated as the mean of the disappearance and appearance thresholds. This process was repeated on the palmar surface of both index fingers.

Pressure Pain Threshold (PPT): A digital algometer (Somedic Production AB, Sweden)[19] was used on the palmar aspect of the distal phalynx of the index finger of both hands. The device's 'pinch handle' was used to squeeze the finger at a rate of 10kPa/s (using the device's built-in slope indicator). A $1cm^2$ probe was used. Participants were asked to report when the sensation turned from one of pressure to one of pain, at which point the pressure was released and a reading was taken from the digital display (in kilopascals, kPa). Three measurements were taken from each hand and the mean used for analysis.

Two Point Discrimination (TPD): TPD, the smallest distance between two points that participants could distinguish, was assessed using a caliper, moving from a larger to smaller distance between points. Assessment was conducted on the lateral aspect of the upper arms due to the glove-like distribution of pain and allodynia in many of the CRPS patients. This distance was recorded once for each arm (in mm).

In addition to QST outcomes, patient-reported outcome measures related to pain were completed by all participants. These were the Brief Pain Inventory Short Form (BPI-SF)[20] and the Short Form McGill Pain Questionnaire Version 2 (SF-MPQ-2).[21] The BPI-SF asks participants to rate on a scale of 0-10 their pain over the previous 24 hours and the extent to which pain has interfered with physical, social and psychological aspects of functioning. It generates two scales related to pain severity and pain interference (both with a maximum score of 10). Completion takes five minutes and it has been shown to be valid and reliable in a wide range of patients, including those with osteoarthritis.[22] The SF-MPQ-2 also takes five minutes to complete and provides a comprehensive list of 22 pain descriptors rated on a scale of 0-10 that capture the quality of pain. The total score is derived as an average to generate a maximum score of 10.

Data analysis

Shapiro-Wilk tests were used to test the normality of data distributions. Non-parametric Kruskal-Wallis tests were used to compare QST values between groups (Bonferroni correction α=0.01). Statistically significant findings were followed-up using post hoc Mann-Whitney U tests to compare QST values between pairs of groups (Bonferroni correction α=0.008). The relationships between QST variables and pain measures (BPI and SF-MPQ-2) were tested using Spearman's Rank Order correlation coefficients (α=0.05).

RESULTS

A total of 143 participants took part in the research and the demographics and patient-reported outcome measures for each of the groups are reported in Table 2. The Arthritis group (n=34) comprised 13 people with OA, 17 with RA and 4 with a dual diagnosis of OA and RA. The mean ± SD BPI intensity scores in each of these Arthritis subgroups were 2.87 ± 1.60, 2.68 ± 1.81 and 3.63 ± 2.26 respectively, suggesting that pain was largely comparable, except with a dual diagnosis. The groups were largely comparable on the basis of gender. However the Arthritis group was slightly older, had a longer disease duration, less severe pain and less pain interference than the other patient groups. The CRPS and FMS groups were similar on most variables, with the exception of pain distribution.

TABLE 2 HERE

Table 3 presents the data for the QST variables. Most QST data deviated from a normal distribution. Lg10 and Ln transformation failed to improve data distributions and therefore the median and interquartile values have been presented and inferential analysis was conducted using non-parametric statistics throughout.

TABLE 3 HERE

CRPS and FMS patients were the only groups to display statistically significant sensory dysfunction relative to healthy participants. There were no significant differences in any QST measure between healthy participants and those with arthritis. There were also no significant differences in any QST measure between CRPS and FMS participants.

Thermal stimuli: FMS patients displayed heat hyperesthesia on both arms but cold hyperaesthesia only on the contralateral arm. CRPS patients failed to display changes in sensitivity to thermal stimuli. The median intensity rating for cold stimuli were 3.00 ('cold') for all groups. For heat stimuli the median was 6.00 ('warm') for the Healthy, Arthritis and CRPS groups and slightly higher at 7.00 ('hot') for FMS. No participants in any group rated the cold stimulus as paradoxically hot (or vice versa).

Light touch thresholds: LTT hypoesthesia was evident in both CRPS and FMS groups for the contralateral limb but only in CRPS patients for the index limb. There was a median increase in LTT in the index arm in the FMS group but this did not reach statistical significance. No statistically significant difference in LTT (sternum) between groups was identified.

Two point discrimination: There were no statistically significant differences in TPD between groups. There was a median increase in TPD in both the index and contralateral arm in FMS relative to Healthy participants but this was not statistically significant.

Pressure pain thresholds: Both CRPS and FMS patients demonstrated pressure hyperalgesia in both limbs relative to Healthy participants.

Relationship between QST outcomes and self-reported pain variables: QST outcomes were correlated against SF-MPQ-2, BPI Severity and BPI Interference data to investigate the

relationships between QST and clinical pain variables. In the interests of brevity, only statistically significant QST variables are reported in Table 4 below.

TABLE 4 HERE

The results suggest that hypoesthesia to light touch is correlated with clinical pain outcomes in people with CRPS, on both the index and contralateral side. These correlations were stronger for the index arm (range r=0.51-0.70) than for the contralateral arm (range r=0.39-0.57). A similar relationship was seen in FMS, but only with the MPQ and only for the index arm. There was a positive relationship between the intensity of heat sensation and the MPQ in those with Arthritis. No other QST modalities were correlated with any other clinical pain outcomes.

DISCUSSION

Overall the results suggested that sensory changes were more severe in CRPS and FMS. There was a general tendency towards cold and heat hyperesthesia, touch hypoesthesia and pressure hyperalgesia in both conditions. Differences were evident for both the index and contralateral arms, suggesting that sensory dysfunction might involve changes in central nervous system sensitivity; particularly given that the majority of participants in each group did not have arm pain as their primary complaint. There are more similarities between CRPS and FMS than the other groups, and people with Arthritis have sensory profiles that are largely similar to Healthy participants. LTT hypoesthesia seems to be closely correlated with patient-reported outcomes in CRPS. Our pragmatic QST protocol demonstrated the ability to identify sensory abnormalities in chronic pain patients.

The observed findings of heat and cold hyperesthesia in FMS reflect similar findings for warmth made by Kosek et al.[23] and cold by Berglund et al.[18] However Hurtig et al.[5] and

Desmeules et al.[24] found no evidence of changes to thermal detection and da Silva et al.[25] found evidence of thermal hypoesthesia in FMS. In CRPS thermal hypoesthesia (as opposed to the cold hyperesthesia observed in the present investigation) has been more commonly observed.[26-28] Wylde et al.[29] previously found evidence of warm and cold hypoesthesia in patients with knee OA awaiting joint replacement surgery, whilst Kosek and Ordeberg[19] found warm hyperesthesia but no changes to cold detection in hip OA patients awaiting hip replacement. The present study found no evidence of thermal hypo/hyperesthesia in Arthritis patients, although our participants are likely to have had less severe conditions than those included in those previous investigations. These differences in findings may also be a function of different methodological approaches. In particular, the current investigation rated the intensity of thermal sensations associated with two metal rollers at fixed temperatures (25^{o}C and 40^{o}C), as opposed to the more common method of determining detection thresholds using thermoelectric Peltier elements. Caution therefore needs to be taken with directly comparing findings. However, the present investigation was able to identify differences between groups using the Therroll method. Interestingly, there were no instances of paradoxical heat sensations with cold stimuli, contrary to previous evidence in FMS[18] and acute CRPS[26]; although this was not found to be a major feature of chronic CRPS[26] or in a later study by the same authors.[27]

Light touch hypoesthesia has previously been observed in FMS,[25] upper limb CRPS,[27] knee OA[29] and the feet of people with RA.[30] Kosek et al.[23] and Hurtig et al.[5] found no changes in touch thresholds in FMS and Kosek and Ordeberg[19] also found no differences in hip OA relative to a control group (although touch thresholds were found to improve following joint replacement surgery). Two-point discrimination was found to be increased in CRPS patients with dystonia[28]. The current findings are therefore largely in agreement with previous observations, although we did not see significant changes in LTT in Arthritis patients. Interestingly Reimer et al.[1] found that there was a link between mechanical hypoesthesia and ongoing pain in CRPS over a 3 year period. The associations observed between LTT

and patient-reported outcomes in the present investigation might provide further evidence of the potential importance of mechanical hypoesthesia in the generation and maintenance of pain and pain-related disability, particularly in CRPS. The correlation values for CRPS were slightly stronger for the index arm (r=0.51-0.70) when compared to the contralateral arm (r=0.39-0.57). 42% of the CRPS sample had arm symptoms as their primary complaint and this affected limb was tested as the 'index' limb in those cases. Greater mechanical hypoesthesia in the affected arm might therefore help to explain the slightly stronger relationships observed for the index arm.

Pressure pain hyperalgesia is perhaps the most consistent finding in FMS,[23,25,31] CRPS,[1,27,28,32] OA[3,19,29] and RA.[33] A systematic review and meta-analysis by Suokas et al.[34] supported evidence of pressure hyperalgesia in OA, at both the affected joint and at remote sites. However, evidence for pressure hyperalgesia in Arthritis was not found in the current study. Reimer et al.[1] observed that increased sensitivity to mechanical pain was linked with ongoing pain in CRPS 3 years later. Giesecke et al.[31] found that pressure hyperalgesia could be used in conjunction with psychological variables to identify subgroups of FMS patients. So, assessment of PPT might also prove to be an important clinical outcome. Indeed Wylde et al.[35] found that PPT demonstrated the strongest test-retest reliability in people with knee OA shortlisted for joint replacement surgery when compared with LTT, thermal sensation thresholds and thermal pain thresholds. Furthermore, PPT was one of the most prevalent somatosensory abnormalities observed[29] and correlated with post-operative pain.[3]

It is important to acknowledge potential confounders such as inflammatory status, medication, generalised versus local pain, the presence or absence of upper limb pain and psychosocial factors. All these issues have the potential to complicate comparisons both within and between groups and to influence the inter-relationships between variables, for example the potential of analgesia to induce LTT hypoesthesia. Future research should more adequately account for some of these confounders, for example through investigation

of the inter-relationships between factors in only one patient group, such as upper limb CRPS, like previous work in FMS.[36]

Strengths and limitations

A strength is that the same experimental protocol was applied to all patient groups, facilitating comparison. The protocol was designed to be pragmatic, taking approximately 20 minutes to complete, and used relatively portable and inexpensive equipment. This is an important strength of the investigation because such methods might be more accessible to researchers and clinicians. As already discussed, however, this created difficulties in controlling potential confounding variables both within and between groups.

Although the study recruited to the specified sample size, it is important to note that sample size calculations were based on PPT at the index finger.[16] Therefore, the possibility of Type II errors cannot be discounted where trends towards group differences failed to reach statistical significance for some of the other outcome measures. However, the participant numbers in the present investigation (n=34-37) are relatively large when compared to other similar studies. For example, Blumenstiel et al.[8] had groups sizes of n=20-23, Tampin et al.[9] n=22-31 per group Goubert et al.[10] had group sizes of n=15-26. Only Maier et al.[7] had a larger sample size, (n=51-403 per group).

Pain severity, as measured by the BPI and MPQ, was much lower in the Arthritis group compared to FMS and CRPS and may partly explain why the sensory profile of this group did not differ from healthy participants. It should also be acknowledged that many participants did not have arm pain, complicating comparisons between pain conditions and between the ‘index’ and ‘contralateral’ arm. For example 21/36 people with CRPS (58%) had foot/leg pain as their primary complaint and therefore testing of the index arm is not a true reflection of the sensitivity of an affected limb in CRPS. There were trends towards hot and cold hyperaesthesia, touch hypoesthesia and pressure hyperalgesia in the index limb of

those with CRPS affecting the upper limb, as compared to those with lower limb CRPS. However, those trends were not statistically significant. Nonetheless, the ability of the protocol to identify differences in sensory function between conditions despite such participant heterogeneity is very promising. Finally, it should also be acknowledged that the numerical rating scale used to rate the intensity of thermal sensation and pain has not previously been validated.

Future research

It would be interesting to determine the predictive validity of the sensory abnormalities identified in the present investigation, particularly LTT. Ideally future research should be performed on more homogenous patient populations, for example those with unilateral arm pain. That would better identify whether the protocol is able to identify differences between conditions and between affected and unaffected limbs.

Conclusion

This investigation demonstrated the ability of a pragmatic QST protocol to identify sensory abnormalities in chronic pain patients. As hypothesised, people with FMS and CRPS demonstrated extensive sensory dysfunction, whilst Arthritis patients had sensory profiles closer to healthy participants. LTT were found to correlate with patient-reported outcome measures in CRPS and may therefore provide a clinically relevant and accessible assessment for CRPS.

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LEGENDS FOR TABLES

Table 1. Inclusion and exclusion criteria.

Table 2. Demographics and patient-reported outcome measures for each group. N/A = Not Applicable. *This figure includes those with unilateral arm pain plus those with multiple limb pain, all of whom had bilateral arm pain.

Table 3. Median (Interquartile Range) values for each QST modality. Kruskal-Wallis tests were used to compare QST values between groups (* = statistically significant, Bonferroni correction [Symbol]=0.01). Post hoc Mann-Whitney U tests were used to compare QST values between pairs of groups († = statistically significant versus healthy, ‡ = statistically significant versus arthritis, both Bonferroni correction α=0.008). [+] = increased sensitivity (hyperesthesia/hyperalgesia) versus healthy. [-] = decreased sensitivity (hypoesthesia/hypoalgesia) versus healthy. Where median values were identical, decisions on [+] and [-] were based on mean values.

Table 4. Spearman's Rank Order correlation coefficients exploring the relationship between QST variables and patient reported pain scores. * = statistically significant (α=0.05)

TABLES

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
All	
• ≥18 years old. • Men or women. • Able to cooperate.	• Comorbidity affecting sensory processes. • Asymmetrical visible disfigurement of upper limbs (additional to that caused by chronic pain condition).
Complex regional pain syndrome (CRPS)	
• Meet Budapest criteria for unilateral CRPS.[12] • Upper or lower limb affected.	• Diagnosis of FMS or OA/RA.
Fibromyalgia (FMS)	
• Meet American College of Rheumatology (ACR) criteria for FMS.[13]	• Diagnosis of CRPS or OA/RA.
Osteoarthritis / Rheumatoid Arthritis (Arthritis)	
• Meet ACR clinical criteria for Rheumatoid Arthritis[14] or National Institute for Health and Care Excellence clinical criteria for Osteoarthritis.[15]	• Diagnosis of CRPS or FMS.

Healthy volunteers (Healthy)	
• Matched for age (within 10 years) and gender with patient groups.	• Formally diagnosed rheumatological disorders.

Table 2. Demographics and patient-reported outcome measures for each group. N/A = Not Applicable. *This figure includes those with unilateral arm pain plus those with multiple limb pain, all of whom had bilateral arm pain.

Variable		Healthy (n=37)	Arthritis (n=34)	CRPS (n=36)	FMS (n=36)
Age, years (mean ± SD)		50.27 ± 15.28	58.35 ± 9.19	48.94 ± 13.70	51.03 ± 9.85
Sex, Women : Men, n		29 : 8	30 : 4	29 : 7	28 : 8
Duration of Condition, years (mean ± SD)		N/A	13.69 ± 10.81	5.53 ± 3.55	6.06 ± 7.29
Limb affected, n	**Right arm**	N/A	9	9	1
	Left arm	N/A	2	6	0
	Right leg	N/A	9	10	0
	Left leg	N/A	3	11	1
	Multiple	N/A	11	0	34
Index arm tested, Left : Right, n		0 : 37	2 : 32	6 : 30	0 : 36
Proportion of participants that had pain in the		0/37 (0%)	22/34 (65%)	15/36 (42%)	35/36 (97%)

index arm, n (%)*					
Brief Pain Inventory Severity, max 10 (mean ± SD)		0.50 ± 0.73	2.86 ± 1.75	5.35 ± 2.59	5.68 ± 1.33
Brief Pain Inventory Interference, max 10 (mean ± SD)		0.05 ± 0.27	2.89 ± 2.14	6.03 ± 3.17	6.29 ± 2.10
McGill Pain Questionnaire Total, max 10 (mean ± SD)		0.00 ± 0.01	1.48 ± 1.07	4.51 ± 2.73	4.08 ± 1.51

Table 3. Median (Interquartile Range) values for each QST modality. Kruskal-Wallis tests were used to compare QST values between groups (* = statistically significant, Bonferroni correction [Symbol]=0.01). Post hoc Mann-Whitney U tests were used to compare QST values between pairs of groups († = statistically significant versus healthy, ‡ = statistically significant versus arthritis, both Bonferroni correction [Symbol]=0.008). [+] = increased sensitivity (hyperesthesia/hyperalgesia) versus healthy. [-] = decreased sensitivity (hypoesthesia/hypoalgesia) versus healthy. Where median values were identical, decisions on [+] and [-] were based on mean values.

QST Modality	**Healthy (n=37)**	**Arthritis (n=34)**	**CRPS (n=36)**	**FMS (n=36)**	**Between groups differences (Kruskal-Wallis)**
Cold, 0-10 scale (Index Arm)	3.00 (0.00)	3.00 (0.00)	3.00 (1.00)	3.00 (1.00)	p=0.048
Cold, 0-10 scale (Contralateral Arm)	3.00 (0.00)	3.00 (0.00)	3.00 (0.13)	**3.00 (0.25)† [+]**	**p=0.004***
Heat, 0-10 scale (Index Arm)	6.00 (0.00)	6.00 (1.00)	6.00 (1.00)	**7.00 (1.00)† [+]**	**p=0.001***
Heat, 0-10 scale (Contralateral Arm)	6.00 (0.00)	6.00 (1.00)	6.00 (1.00)	**7.00 (1.00)† [+]**	**p=0.005***

LTT, g (Index Arm)	0.06 (0.09)	0.06 (0.13)	**0.14 (0.69)†** **[-]**	0.10 (0.21)	**p=0.002***
LTT, g (Contralateral Arm)	0.06 (0.08)	0.10 (0.13)	**0.12 (0.31)†** **[-]**	**0.12 (0.23)†** **[-]**	**p=0.004***
LTT, g (Sternum)	0.05 (0.11)	0.01 (0.11)	0.09 (0.70)	0.12 (0.49)	p=0.018
TPD, mm (Index Arm)	4.00 (1.00)	4.00 (1.00)	4.00 (1.07)	4.50 (1.50)	p=0.162
TPD, mm (Contralateral Arm)	4.00 (0.50)	4.00 (1.50)	4.00 (1.00)	4.50 (2.00)	p=0.329
PPT, kPa (Index Arm)	280 (144)	301 (192)	**182 (102)†‡** **[+]**	**196 (130)†‡** **[+]**	**p<0.001***
PPT, kPa (Contralateral Arm)	328 (151)	286 (198)	**225 (169)†** **[+]**	**221 (237)†** **[+]**	**p<0.001***

Table 4. Spearman's Rank Order correlation coefficients exploring the relationship between QST variables and patient reported pain scores. * = statistically significant ($p<0.05$)

Group	SF-MPQ-2	BPI Severity	BPI Interference
Healthy	Nil	Nil	Nil
Arthritis	Heat (Index Arm) r=0.37, **p=0.033***	Nil	Nil
CRPS	LTT (Index Arm) r=0.69, **p<0.001*** LTT (Contralateral Arm) r=0.49, **p=0.004***	LTT (Index Arm) r=0.70, **p<0.001*** LTT (Contralateral Arm) r=0.57, **p=0.001***	LTT (Index Arm) r=0.51, **p=0.003*** LTT (Contralateral Arm) r=0.39, **p=0.027***
FMS	LTT (Index Arm) r=0.47, **p=0.006***	Nil	Nil