The Clinical Journal of Pain

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

--Manuscript Draft--

Manuscript Number:	CJP-D-19-00133R1
Full Title:	Sensory function and pain experience in Arthritis, Complex Regional Pain Syndrome, Fibromyalgia Syndrome and healthy volunteers: a cross-sectional study.
Article Type:	Original Article
Keywords:	arthritis; Complex Regional Pain Syndromes; Fibromyalgia; pain threshold; Sensation
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Manuscript Region of Origin:	UNITED KINGDOM
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TITLE PAGE

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Sources of support: C McCabe was funded by a National Institute for Health Research Career Development Fellowship (CDF/2009/02). This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgements: The research team would like to thank Lindsay Davies for her administrative support for the project.

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 ~~and cold~~ hyperesthesia in both arms and cold hyperesthesia in the contralateral arm. CRPS demonstrated no changes in thermal sensitivity ~~demonstrated cold hyperesthesia only in the index arm, with no heat hyperesthesia~~. 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), ~~Osteoarthritis~~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=0.0~~5~~1). 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 ~~. I~~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 ~~cold and~~ heat hyperesthesia on both ~~the index and contralateral~~ arms but cold hyperaesthesia only on the contralateral arm. CRPS patients ~~displayed cold hyperesthesia only on the index arm and~~ failed to display changes in sensitivity to thermal stimuli ~~heat hyperesthesia~~. 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. ~~Although a~~ No statistically significant difference in LTT (sternum) between groups was identified~~, there were no significant differences between individual pairs of groups once the Bonferroni correction for multiple testing was applied. There were non-significant median increases in LTT at the sternum in both CRPS and FMS and a median decrease in Arthritis relative to Healthy~~.

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.

REFERENCES

[1] Reimer M, Rempe T, Diedrichs C, et al. Sensitization of the nociceptive system in Complex Regional Pain Syndrome. *PLoS ONE* 2016;11(5):e0154553.

[2] Martinez V, Fletcher D, Bouhassira D, et al. The evolution of primary hyperalgesia in orthopedic surgery: quantitative sensory testing and clinical evaluation before and after total knee arthroplasty. *Anesth Analg* 2007;105(3):815-821.

[3] Wylde V, Palmer S, Learmonth ID, et al. The association between pre-operative pain sensitisation and chronic pain after knee replacement: an exploratory study. *Osteoarthritis Cartilage* 2013;21(9):1253-1256.

[4] Smith BW, Tooley EM, Montague EQ, et al. Habituation and sensitization to heat and cold pain in women with fibromyalgia and healthy controls. Pain 2008;140(3):420-428.

[5] Hurtig IM, Raak RI, Kendall SA, et al. Quantitative sensory testing in fibromyalgia patients and in healthy subjects: identification of subgroups. *Clin J Pain* 2001;17(4):316-322.

[6] Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123(3):231-243.

[7] Maier C, Baron R, Tölle TR, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* 2010;150(3):439-450.

[8] Blumenstiel K, Gerhardt A, Rolke R, et al. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clin J Pain* 2011;27(8):682-690.

[9] Tampin B, Briffa NK, Slater H. Self-reported sensory descriptors are associated with quantitative sensory testing parameters in patients with cervical radiculopathy, but not in patients with fibromyalgia. *Eur J Pain* 2013;17(4):621-633.

[10] Goubert D, Danneels L, Graven-Nielsen T, et al. Differences in Pain Processing Between Patients with Chronic Low Back Pain, Recurrent Low Back Pain, and Fibromyalgia. *Pain Physician* 2017;20(4),307-318.

[11] Brun C, Mercier C, Grieve S, et al. Sensory disturbances induced by sensorimotor conflicts are higher in complex regional pain syndrome and fibromyalgia compared to arthritis and healthy people, and positively relate to pain intensity. *Eur J Pain* 2019, 23(3):483-494.

[12] Harden RN, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the “Budapest Criteria”) for Complex Regional Pain Syndrome. *Pain* 2010;150(2):268-274.

[13] Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 2010;62(5):600-610.

[14] Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62(9):2569-2581.

[15] National Institute for Health and Clinical Excellence. *NICE guideline on osteoarthritis: The care and management of osteoarthritis in adults, NICE clinical guideline 177*. London: National Institute for Health and Clinical Excellence, 2014.

[16] Fernández-De-Las-Peñas C, Madeleine P, Martínez-Perez A, et al. Pressure Pain Sensitivity Topographical Maps Reveal Bilateral Hyperalgesia of the Hands in Patients With Unilateral Carpal Tunnel Syndrome. *Arthritis Care Res* 2010;62(8):1055-1064.

[17] Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. London: The Cochrane Collaboration, 2011.

[18] Berglund B, Harju EL, Kosek E, et al. Quantitative and qualitative perceptual analysis of cold dysesthesia and hyperalgesia in fibromyalgia. *Pain* 2002;96(1-2):177-187.

[19] Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain* 2000;88(1):69-78.

[20] Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23(2):129-138.

[21] Dworkin RH, Turk DC, Revicki DA, et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). *Pain* 2009;144(1-2):35-42.

[22] Mendoza T, Mayne T, Rublee D, et al. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. *Eur J Pain* 2006;10:353-361.

[23] Kosek E, Ekholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. *Pain* 1996;68(2-3):375-383.

[24] Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum* 2003;48(5):1420-1429.

[25] da Silva LA, Kazyiama HH, Teixeira MJ, et al. Quantitative sensory testing in fibromyalgia and hemisensory syndrome: comparison with controls. *Rheumatol Int* 2013;33(8):2009-2017.

[26] Huge V, Lauchert M, Forderreuther S, et al. Interaction of hyperalgesia and sensory loss in complex regional pain syndrome type I (CRPS I). *PLoS ONE* 2008;3(7):e2742.

[27] Huge V, Lauchart M, Magerl W, et al. Complex interaction of sensory and motor signs and symptoms in chronic CRPS. *PLoS ONE* 2011;6(4):e18775.

[28] van Rooijen DE, Marinus J, Schouten AC, et al. Muscle hyperalgesia correlates with motor function in complex regional pain syndrome type 1. *J Pain* 2013;14(5):446-454.

[29] Wylde V, Palmer S, Learmonth ID, et al. Somatosensory abnormalities in knee OA. *Rheumatology (Oxford)* 2012;51(3):535-543.

[30] Wilson O, Kirwan JR. Measuring sensation in the feet of patients with rheumatoid arthritis. *Musculoskeletal Care* 2006;4(1):12-23.

[31] Giesecke T, Williams DA, Harris RE, et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum* 2003;48(10):2916-2922.

[32] Enax-Krumova EK, Lenz M, Frettlöh J, et al. Changes of the Sensory Abnormalities and Cortical Excitability in Patients with Complex Regional Pain Syndrome of the Upper Extremity After 6 Months of Multimodal Treatment. *Pain Med* 2017;18(1):95-106.

[33] Lee YC, Bingham CO, Edwards RR, et al. Association Between Pain Sensitization and Disease Activity in Patients With Rheumatoid Arthritis: A Cross-Sectional Study. *Arthritis Care Res* 2018;70:197-204.

[34] Suokas AK, Walsh DA, McWilliams DF, et al. Quantitative sensory testing in painful osteoarthritis: a systematic review and meta-analysis. *Osteoarthritis Cartilage* 2012;20(10):1075-1085.

[35] Wylde V, Palmer S, Learmonth ID, et al. Test-retest reliability of Quantitative Sensory Testing in knee osteoarthritis and healthy participants. *Osteoarthritis Cartilage* 2011;19(6):655-658.

[36] Turk DC, Okifuji A, Sinclair JD, et al. Pain, disability, and physical functioning in subgroups of patients with fibromyalgia. *J Rheumatol* 1996;23(7):1255-1262.

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]=0.0~~5~~1). 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)

The reviewers' comments are addressed in turn below. Associated changes are highlighted in red font within the revised manuscript.

Reviewer Comments:

Reviewer #1: This study investigates 3 different groups of chronic pain patients, CRPS, FM, arthritis (rheumatoid arthritis and osteoarthritis), and healthy controls using a QST protocol to test sensory dysfunction. The authors conclude that CRPS and FM patients display high sensory dysfunction in contrast to arthritis patients and healthy controls. Further, the authors surmise that light touch threshold (LTT) examination might provide a clinically relevant and accessible assessment for the CRPS and FM groups. The study is interesting however several issues should be resolved.

RESPONSE: Thank you for these comments. We trust that we have addressed each of the issues raised below.

Hypothesis

The authors used the McGill Pain Questionnaire (MPQ) to measure pain quality as one measure. However no clear a priori hypothesis was reported in advance of the study.

RESPONSE: Apologies if this was not clear but our final hypothesis at the end of the Introduction section (*"c) positive relationships between sensory abnormalities and pain experience"*) relates to both the MPQ and BPI. We have therefore clarified this issue by adding *"…two different measures of…"* to this sentence. We have also now clarified in the data analysis section that analysis of the relationships between QST measures and pain experience involved both the MPQ and BPI. We trust that this now clarifies the a priori hypothesis in relation to the MPQ.

Method

The arthritis group consists of both osteoarthritis and rheumatoid arthritis patients. The reviewer wonders why an inflammatory rheumatic and a non-inflammatory disease is put into a single group. What is the percentage of the RA patients? What is the DAS28 in RA and OA? Is this comparable? Is the pharmacological treatment (medication) in the RA patients comparable to the osteoarthritis patients? Inflammation is a potential confounder/covariate.

RESPONSE: We agree that this is a little unorthodox and was a major point of discussion within the research team when designing the study. The overriding consideration and rationale for combining the conditions was to create a comparator group that had predominantly joint-specific disease, regardless of the inflammatory component. This was to provide contrast with the other clinical conditions, which were more likely to display symptoms associated with neurogenic pain and central sensitisation. This decision has now been justified under the 'Participants' section of the manuscript. Unfortunately we do not have DAS28 data but we have now conducted a descriptive analysis of BPI intensity between the Arthritis subgroups and have added details to the 'Results' section, as follows: *"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."* This would suggest, therefore that inflammatory/non-inflammatory status is unlikely to have been a major factor in this study. We have also now added further discussion related to potential confounders in the 'Discussion' section, as follows: *"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]*"*

The authors differed between the "index" (painful) and the contralateral arm. The right arm was used with healthy controls and bilateral pain patients. What is the reason for not applying a counterbalanced random procedure?
RESPONSE: The research team discussed a range of different options for data analysis to provide a valid comparison with the index arm. The right arm was chosen at random after identifying that there were no statistically significant differences between left and right arms for any of the QST values in the healthy control group. The proportion of left arms identified as the index arm in the patient groups was very small (only 8 out of the 106 patients) and therefore counterbalancing would equate to only 2 or 3 of the 37 healthy participants being chosen at random to present data for the their left arm as the index limb. Given the lack of difference between left and right limbs this was considered unnecessary. This rationale has now been clarified in the 'Outcome measures' section of the 'Material & Methods'.

Statistics
The authors reported that they used the Kruskal-Wallis Test instead of the ANOVA, because their data was not normally distributed. Due the significant range in pain intensity (BPI) and the wide standard deviations, the reviewer suggests looking at the lg10 transformation for normalization of the data and then to use the ANOVA with pain severity (BPI) as covariate. The influence of pain on sensory functions can also be examined in groups.
RESPONSE: Thank you so much for this suggestion. Following your advice, we have performed Lg10 transformation on the QST, unfortunately with no improvement in the normality of data distributions. We have also performed Ln transformation of the data, which similarly failed to improve the normality of distribution. We have therefore decided to maintain non-parametric analysis throughout but have now clearly reported in the 'Results' section attempts to transform the data to conduct parametric analysis. We trust that this is acceptable.

The authors used an alpha of $p<0.05$. With multi variable comparisons, a conventional alpha is suggested. A $p<0.006$ in case of 8 tested variables is appropriate.
RESPONSE: Bonferroni correction has already been applied to the alpha level for post-hoc pairwise comparisons between groups (6 pairwise comparisons = alpha 0.008). Given your suggestion, we are also happy to apply a Bonferroni correction to the results of the Friedman test to account for the multiple variables investigated. Five variables were tested (cold, heat, LTT, TPD and PPT) and therefore we have adjusted the alpha level to 0.01 for these analyses. We trust that this is acceptable. This now means that cold (index arm) and LTT (sternum) are no longer statistically significant and we have removed reference to post-hoc testing for these variables in Table 3 and adjusted the accompanying text accordingly. Please note that adjusting alpha on the basis of 8 variables, as you originally suggested, or 11 variables (to account for testing of five variables on both the index and collateral arms and LTT on the sternum) makes no difference to the statistical significance of the other variables. We therefore trust that our decision to adjust on the basis of the 5 variables is acceptable.

Results
The CRPS group included patients with arm and leg/feed pain. Are there fundamental sensory differences in CRPS patients with and without arm pain?
RESPONSE: We have now looked very closely at the differences in sensory profile between those with and without arm pain in the CRPS group, as suggested. There were 15 CRPS patients with an affected upper limb (this was therefore also their 'index' limb) and 21 with an affected lower limb. As might be expected, 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. Only cold hyperaesthesia ($p=0.033$) and pressure hyperalgesia ($p=0.016$) were statistically significant at a level

of 0.05 but this was not the case following Bonferroni correction. We have now commented on these observations in the 'Discussion' section.

The reviewer recommends a redraft taking the above into consideration and will be happy to rereview the manuscript afterwards.
RESPONSE: Thank you for your helpful comments. We hope that we have addressed these satisfactorily.

Discussion.
Since medication, inflammation, LTT and SF-MPQ 2 might correlated but vary within the groups, the reviewer recommends to discuss the influence of the confounder variables?
RESPONSE: Thank you for this point. As outlined in relation to an earlier comment, additional discussion has now been added to the 'Discussion' section to address this. We trust that this is satisfactory.

Limitations.
The limitations should mention the heterogeneity (mechanical vs. inflammatory caused pain, heterogeneous influences of medication on sensory functions, arm vs. leg/feed pain, generalized vs. localized pain) within each group that makes a reliable analysis among groups difficult. The reviewer recommends a repetition of that study, using only the CRPS and comparing psychosocial subgroups (MPI, Turk et al, 1996) with respect to differences in sensory functions as measured by QST.
RESPONSE: As already detailed, acknowledgement of the potential confounders has been added to the 'Discussion' section. This addition explicitly refers to the Turk et al 1996 paper as a potential model for exploring upper limb CRPS. This additional discussion has now been explicitly referred to in the 'Strength and limitations' section, as follows: *"As already discussed, however, this created difficulties in controlling potential confounding variables both within and between groups."*

Reviewer #2: Nice study of sensory testing in different groups. The sample size is good and the writing is clear. A few substantial suggestions:
RESPONSE: Thank you for these positive comments. We have addressed each of your suggestions below.

1) In general, it's pretty unusual to combine OA and RA. I'd strongly consider not doing that. At the very least, test for differences.
RESPONSE: We trust that our explanation in response to a similar comment from Reviewer 1 explains the rationale for doing this. This decision has now been justified under the 'Participants' section of the manuscript.

2) The testing location on the arm is interesting. I like the standard approach, but some patients will have pain there, some not. Please report the % of patients in each group (presumably 0 in the controls) who had pain in the area of the arm being tested.
RESPONSE: Unfortunately a range of slightly different test sites were used for each QST parameter (volar aspect of the forearm for hot and cold; palmar aspect of the index fingers and the sternum for LTT; palmar aspect of the index finger for PPT; and lateral aspect of the upper arm for TPD). We therefore did not specifically record the presence or absence of pain under each test site. However, we can confirm that all participants reporting 'multiple' limb pain had bilateral upper limb pain which means that the 'index' arm was painful in all of these cases. To make this clearer, we have now substituted the previous *"Proportion of participants that included tests on an 'affected' arm, n (%)"* data in Table 2 with *"Proportion of participants that had pain in the index arm, n (%)*"*. We have added a footnote to the table to clarify this, as follows: *"*This figure includes those with*

unilateral arm pain plus those with multiple limb pain, all of whom had bilateral arm pain." We have also updated the section in the 'Discussion' where this issue was discussed, adding some specific information about the CRPS group (see previous response to Reviewer 1 above). We hope that these changes are useful.

3) Compare test results in patients with and without pain in the testing area.
RESPONSE: As described in response to the previous point, and to the point made by Reviewer 1, we have presented some additional information in the 'Discussion' section specifically in relation to comparing the results of CRPS patients with and without arm pain. With respect, we do not feel that repeating such analysis for the other groups would add anything of note due to the lack of arm pain (n=0/37 (0%) in the Healthy group), the very small proportion with no arm pain (n=1/36 (3%) in the FMS group) and the observed lack of differences in QST measures (the Arthritis group). We hope that this is acceptable.

4) It may be worth computing and analyzing difference scores (results at one arm minus results at the other) in several of the groups.
RESPONSE: We have carefully considered this point and feel that it has been largely addressed in response to previous points concerning analysis of painful versus non-painful arms. We also feel that the existing text in the 'Future research' section addresses this issue, as follows: *"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."* We trust, therefore, that this issue has already been addressed.

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 included tests on an 'affected' arm, n (%)**~~		~~0/37 (0%)~~	~~11/34 (32%)~~	~~15/36 (42%)~~	~~1/36 (3%)~~
Proportion of participants that had pain in the index arm, n (%)*		0/37 (0%)	22/34 (65%)	15/36 (42%)	35/36 (97%)

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 α=0.0~~5~~1). 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.

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	0.06 (0.08)	0.10 (0.13)	**0.12 (0.31)† [-]**	**0.12 (0.23)† [-]**	**p=0.004***

(Contralateral Arm)					
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