

Title: Neuropathic Features of Joint Pain: a Community-Based Study.

Subtitle: Neuropathic Features of Joint Pain: a Community-Based Study.

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ABSTRACT

Objective

Quantitative sensory testing (QST) and questionnaire-based assessment have been used to demonstrate features of neuropathic pain in those with musculoskeletal pain. However, their direct relationship has not been investigated in the community. We conducted an observational study to describe the characteristics of joint pain and examine the relationship between QST and the PainDETECT questionnaire.

Methods

Warm detection, heat pain, mechanical pain thresholds and mechanical pain sensitivity were determined over the sternum alongside PainDETECT scores in a cross-sectional study of 462 participants from the Chingford Study. Comparisons were made between those with and without joint pain. Logistic regression modelling was used to describe the association between neuropathic pain features, determined by the PainDETECT score, and each of the QST measures individually, adjusting for age, BMI and pain-modifying medication use.

Results

66.2% reported recent joint pain with a median average pain severity of 5/10. There was increased sensitivity to painful stimuli in those with pain compared to the pain free group and this persisted after stratification by pain-modifying medication use. While only 6.7% had possible and 1.9% likely neuropathic pain features using standard PainDETECT thresholds, features of neuropathic pain

were common and present in over 50%, with at least moderate severity, of those reporting pain. Heat pain thresholds and mechanical pain sensitivity were significantly associated with features of neuropathic pain identified using PainDETECT, OR 0.88(0.80-0.97), $p=0.012$ and 1.24(1.04-1.48), $p=0.018$ respectively.

Conclusion

QST and the PainDETECT questionnaire identified features of neuropathic pain in this community-based study, with significant overlap between the two techniques.

Musculoskeletal pain is common, disabling and often poorly managed, especially in the elderly[1 2]. Current treatment and development of new effective therapies for musculoskeletal pain is hindered by poor understanding of the underlying mechanisms[3]. Whilst previous research has focused on articular and peri-articular mechanisms of pain, accumulating evidence now suggests that features of neuropathic pain may be present in some patients with musculoskeletal pain syndromes, including chronic widespread pain [4 5] and osteoarthritis [1 6-12]. The appreciation that pain can be due to not only joint pathology but also central and peripheral sensitization may then be translated to mechanism-based clinical diagnosis and management options [13].

Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”[14]. While thought to be common, affecting up to 25% of those with chronic pain[15], it is clinically under-recognized and associated with an array of comorbidity resulting in reduced quality of life[16].

A key factor in the under-recognition of patients with neuropathic pain is the lack of a gold-standard diagnostic tool. Evidence-based guidelines recommend screening questionnaires, such as the Leeds assessment of neuropathic symptoms and signs[17] and PainDETECT[18] to identify patients with possible features of neuropathic pain, particularly by non-specialists[19]. Although their use has resulted in reclassification to a diagnosis of neuropathic pain in one third

of patients with musculoskeletal pain conditions[20], such tools still fail to recognize 10-20% of patients and can only provide a guide to diagnosis[21].

Quantitative sensory testing (QST), which measures psychophysical responses to controlled stimuli with the aim of identifying neural dysfunction, is also used to identify sensory changes in patients with neuropathic pain features[22 23] and is being increasingly used in musculoskeletal research[6 24 25]. Allodynia or hyperalgesia, identified using QST may indirectly suggest sensitization of nociceptive neurons. If these phenomena are identified distant to the site of index pain, they may represent central, rather than peripheral sensitization.

Although sensitization is a feature of neuropathic pain it can also occur in the context of non-neuropathic pain, which means that QST can only be used to identify possible features of neuropathic pain rather than provide a definitive diagnosis.

Evidence for neuropathic features in musculoskeletal conditions arises from studies of QST measures[4-6 11 12 26] as well as symptom-based assessment[7 9 26] but to date no studies have examined the direct relationship between these two potential screening tools for joint pain in a community-based population.

The aims of this study were to (1) describe the characteristics of joint pain in a community-based sample and (2) examine the relationship between neuropathic features identified using the PainDETECT questionnaire and QST measures.

PATIENTS AND METHODS

Setting and Subjects

The study participants were selected from the Chingford Study, a well-described prospective population-based longitudinal study of osteoarthritis and osteoporosis, comprising 1,003 women, derived from the register of a large general practice in Chingford, North London [27-29]. The women, aged 44 – 67 years at baseline are representative of women in the UK general population with respect to weight, height and smoking characteristics[28]. The study was established in 1989 and 516 women attended the year 20 follow-up visit. A musculoskeletal pain assessment was conducted in 462 women who were included in the present analysis. The local ethics committee approved the study and written consent was obtained from each woman (Outer North East London Research Ethics Committee (formerly Barking & Havering and Waltham Forest RECs), LREC (R&WF) 96).

For each participant age, height measured in centimeters (to the nearest 0.1 cm) in a standing position, with shoes removed, using a wall-mounted stadiometer (Leicester Height Measure, Seca) and weight in kilograms (to the nearest 0.1 kg) by electronic scales with shoes removed, were recorded.

Quantitative sensory testing

QST was used to determine warm detection, heat pain and mechanical pain thresholds and mechanical pain sensitivity based on the protocol devised by Rolke et al[23]. In order to focus on potentially centrally mediated effects and minimize the influence of any local pathology associated with musculoskeletal conditions, a site 3cm distal to the sternal notch was tested. Participants were asked to close their eyes during testing.

Warm detection and heat pain thresholds

Thermal thresholds for warm and heat pain detection were assessed using the Thermotest Modular Sensory Analyzer (MSA), Somedic, Sweden, thermode 25x50mm. The method of limits algorithm was used, with a thermode adaptation temperature of 32^o C. Each stimulus was generated after a randomized 4 to 6 second interval. Both thresholds were obtained with ramped stimuli (1^o/S) that were terminated when the participant pressed a button. Each threshold was tested 5 times and the mean value from all 5 readings calculated. The MSA thermotest has an in-built safety cut-off temperature of 50^oC to ensure no harm to the patients. If the limit was reached and the participant did not report any sensation, the data was recorded at that limit.

Mechanical pain threshold

Mechanical pain thresholds were measured using a set of seven custom-made weighted pinprick simulators that exert a force of between 8 and 512 mN, following a binary logarithmic scale with a flat contact area of 0.25mm in diameter (MRC Systems, Germany). Using the method of limits, the final

threshold was the geometric mean of five series of ascending and descending stimulus intensities.

Mechanical pain sensitivity

This was tested using the same weighted pinprick stimuli as above. The 512mN pinprick was applied 3 times and the participant was asked to give a rating for each stimulus on a 0-10 numeric rating scale, "0" indicating no sharpness and "10" the most sharp imaginable. The mean of the 3 measures was taken.

Assessment of mechanical pain sensitivity was added to the protocol after the study had commenced as it was felt that supra-threshold testing might provide important additional information. The order of attendance of participants was random so the missing data was not a source of systematic bias. Sensitivity analysis subsequently confirmed that there was no significant difference in age and BMI between the tested and non-tested participants.

Pain assessment

The PainDETECT questionnaire was used to assess the features of pain experienced by participants in the preceding four weeks[18]. PainDETECT is a self-administered questionnaire, validated against expert diagnosis in patients with chronic lower back pain, to distinguish those with predominantly neuropathic pain from non-neuropathic pain[18]. It contains a body drawing for patients to indicate the sites of pain and any radiation present, assessment of pain quality with a marker of severity from 'hardly noticed' to 'very strongly',

pattern of pain and measures of current, worst and average pain severity. An overall PainDETECT score is then generated summarizing all apart from the pain severity data, resulting in a score of -1 to 38. A score above 18 indicates likely neuropathic pain, 13 to 18 possible neuropathic pain, and below 13 makes neuropathic pain unlikely[18].

In this study, each woman initially completed the body diagram and those reporting more than one painful area were asked to complete the questionnaire with a single location of pain in mind, similar to the modified PainDETECT for knee pain [7]. Up to two areas were assessed per woman, with a priority of capturing data on knee, hip and hand pain in line with our research interests.

Data on analgesia and neuropathic medications used in the preceding 72 hours, thought to potentially effect QST results, were recorded. Analgesics were defined as any compounds containing acetaminophen, non-steroidal anti-inflammatory drugs or opioids. Neuropathic medications included anti-depressants, selective serotonin and norepinephrine reuptake inhibitors and anti-convulsants, including gabapentin and pregabalin, prescribed for any indication. Participants were subsequently categorized according to whether they had used any of the above pain modifying medications or not.

Statistical methods

Demographic details, medication use and QST measures of the women were compared in those with and without self-reported joint pain in the preceding month. Wilcoxon rank sum test, unpaired t-test and Chi-squared test were used

for non-normal, normal and categorical data respectively. The groups were then further divided according to the use of pain modifying medication and ANOVA and Kruskal–Wallis one-way analysis of variance were used to assess differences in normal and non-normal data respectively. For those with pain, the proportion of women with a PainDETECT score reflecting possible or likely neuropathic pain in at least one area was calculated, using Fisher’s exact test to identify any significant effect of pain modifying medication use.

The painful sites and distribution of overall PainDETECT scores for these sites were described. The measures of pain severity, presence of radiation and presence of at least moderate severity for each of the seven pain qualities measured by the PainDETECT questionnaire were used to describe the characteristics of joint pain.

The main outcome variable was the overall PainDETECT score, dichotomized using published thresholds into unlikely neuropathic pain (<13) versus possible/likely neuropathic pain (≥ 13)[18]. This cutoff was selected as there were few PainDETECT scores above 18 in this study. Univariate logistic regression modeling, adjusting for clustering of sites within a person, was used to describe the association between the binary features of neuropathic pain variable (determined by the PainDETECT score) and each QST measure separately. In view of the binary logarithmic scale for mechanical pain thresholds, logarithmic transformation was used prior to regression analyses. This was done so that a one step increase in the transformed mechanical pain threshold variable was of the same order as the step between successive probes

used to measure this threshold. Multivariate logistic regression was used to adjust for the potential confounders age, BMI and analgesic or neuropathic medication use, determined a priori. Fractional polynomial regression modeling was used to model non-linear relationships for continuous variables.

For the QST measures found to be significant predictors of neuropathic pain, a receiver operating characteristic (ROC) curve was used to define the cutoff values that predict the binary neuropathic pain variable with optimal sensitivity and specificity. Using these cutoff values, the proportion of participants with QST measures indicative of possible or likely neuropathic pain was determined.

All statistics were performed using Stata SE v 12 (StatCorp, College Station, TX, USA).

RESULTS

Of the 462 women included in the present study, 306 (66.2%) reported joint pain in the preceding month: 125 (27.1%) experiencing pain in more than one area. BMI was found to be normally distributed. Age, PainDETECT scores and all QST measures were non-normal. Those with pain had a significantly higher BMI (28.2(4.5) v 26.8(5.2), $p=0.004$) and were more likely to have taken analgesia in the past 72 hours (39.2% v 16.7%, $p<0.001$). All the sternal QST measures, apart from the warm detect threshold, showed increased sensitivity to the experimental stimuli in those with joint pain compared to the pain-free group (45.3(42.4-47.6) v 46.4(43.7-48.3), $p=0.006$, 22.4(9.6-102.4) v 64.0(16.0-140.8), $p=0.002$, 6.0(4.7-8.3) v 5.3(3.3-7.7), $p=0.024$ for heat pain threshold, mechanical pain threshold and mechanical pain sensitivity respectively). This trend is maintained when taking account of medication use as shown in Table 1. The proportion of participants with likely neuropathic pain is significantly higher in those who had taken pain modifying medication, compared to those who had not (2.5% v 20.1%, $p<0.001$).

The 431 painful sites assessed were located as follows: knee (46.4%), hip (13.9%), back (14.2%), shoulder (10.0%), hand/wrist (8.8%), and other (6.7%).

None of the participants reported pain at the sternum, where QST was conducted. The median (IQR) pain severity for current pain, worst pain and average pain were 0(0-3), 6(4-8) and 5(3-6) respectively.

The distribution of the total PainDETECT scores for each area assessed is shown in Figure 1. 29/431(6.7%) of the areas scored between 13 and 18, representing possible neuropathic pain, and 8/431(1.9%) scored above 18, corresponding to likely neuropathic pain. Conversely, only 26/431 (6.0%) of the painful areas had no features of neuropathic pain.

The breakdown of the PainDETECT scores in terms of the presence or absence of radiating pain and at least moderate severity of the other seven qualities is shown in Figure 2. The most common qualities were pain with light pressure (20.2%); sudden pain attacks like electrical shocks (16.1%), radiating pain (13.7%) and burning pain (13.2%). Overall 47.3% of the areas didn't have associated radiating pain or any qualities with at least moderate severity, 32.5% showed a single quality, 9.5% showed 2, 6.5% showed 3 and 4.2% showed 4 or more qualities.

We then explored the relationship between QST measures and the findings from the PainDETECT. Univariate analysis showed heat pain thresholds and mechanical pain sensitivity were significantly associated with possible or likely

neuropathic pain determined by PainDETECT score and the effect remained after adjustment for potential confounders, Table 2.

Using a ROC curve analysis, cutoff values with optimal sensitivity and specificity were determined, with heat pain thresholds below 45.2°C, area under the curve 0.61 (95% CI 0.51,0.71), and mechanical pain sensitivity above 6, area under the curve 0.62 (95% CI 0.52, 0.72) predicting possible or likely neuropathic pain (as determined by PainDETECT score). Using these cutoff values, the proportion of participants with one or both QST measures indicative of possible or likely neuropathic pain was determined, Figure 3.

DISCUSSION

An important finding of this study was that QST at the sternum, a central point distant from the region of pain, demonstrated increased sensitivity to painful stimuli in those with pain compared to the pain free group and this relationship persisted after stratification by pain modifying medication use. In those with joint pain, possible or likely neuropathic pain was present in 20.1% taking pain modifying medication, compared to only 2.5% of those not taking pain modifying medication. While overall only 6.7% had possible and 1.9% likely neuropathic pain using the PainDETECT thresholds, features of neuropathic pain were common and present in over 50%, of those reporting pain, with at least moderate severity. In those with pain, heat pain thresholds and mechanical pain sensitivity were significantly associated with likely neuropathic pain identified using PainDETECT (OR 0.88(0.80-0.97), $p=0.012$ and 1.24(1.04-1.48), $p=0.018$) respectively. 34% of participants with musculoskeletal pain demonstrated increased sensitivity to both heat and supra-threshold mechanical stimuli.

The prevalence of musculoskeletal pain has previously been estimated at around 30%[2] in the general population. The higher rate seen in this study may be accounted for by the following three factors. First the Chingford Study is restricted to women, who are known to be at greater risk of developing musculoskeletal pain. Secondly the women were aged between 64 and 87 years at the time of the current study and the prevalence of musculoskeletal pain is seen to increase strongly with age. Finally, the duration and chronicity of musculoskeletal pain has varied between studies. For example in one study 58%

of 20-72 year olds reported musculoskeletal pain in the past week, compared to 15% who had musculoskeletal pain every day during the past year. The current study measured pain within the past 4 weeks, which is most similar to the former definition with a correspondingly similar estimate. The estimated prevalence of neuropathic pain varies from 1-8.8% [15 30] in the general population to 6.9-8.2% [31 32] amongst those with chronic pain. Although this study has not been designed to estimate the prevalence of neuropathic pain, the proportion of areas assessed that fulfilled the criteria for likely neuropathic pain using PainDETECT is reassuringly similar.

To our knowledge, no other studies of QST have been conducted in joint pain in the community but the results can be compared to those from a study of somatosensory abnormalities in osteoarthritis of the knee [6]. Consistent with the current study, *Wylde et al* demonstrated increased sensitivity to a pressure stimulus applied distant to the site of pain (the right forearm), in patients compared to controls and no significant difference in distant warm detection. In contrast distant heat pain thresholds were not found to be significantly different while in our study those with pain demonstrated significantly lower heat pain thresholds than the pain free group. Whilst this may represent a true difference between the populations being studied, it may also reflect the differences in analysis methods and site of assessment. Overall, these studies emphasize the potential for altered pain sensitivity in areas away from the site of pain, implicating possible central nervous system involvement.

As there is no gold standard test for neuropathic pain, we wished to compare two of the tools currently used: PainDETECT versus QST. Although there are no previous studies that specifically assess the association between PainDETECT scores and QST in the community, a study of patients with chronic pain has shown that self-reported neuropathic features identified using the Neuropathic Pain Symptom Inventory correlate to related modalities tested with QST[33]. Furthermore, a study of patients with fibromyalgia demonstrated that pain pressure thresholds were correlated with PainDETECT score[26].

Hochman et al demonstrate the same group of most common pain qualities identified in this study in patients with knee osteoarthritis, using the modified PainDETECT questionnaire: radiating pain (59.2%), electrical shocks (50.4%), sensitivity to pressure (34.9%) and burning pain (33.3%)[7]. The frequency of symptoms is much higher than in the current study, which is expected as only patients with moderate to severe arthritis symptoms were recruited. This suggests that a similar set of qualities may be important in musculoskeletal conditions in general although further exploration of this is required.

Strengths of this study include its large sample size, the use of an unselected community-based cohort with the participating women being representative of those in the general UK population and incorporation of potential confounding factors such as BMI, age and use of pain modifying medication. The main limitation is the use of PainDETECT questionnaire to assess separate areas affected by pain within an individual. Although not formally validated for use in this manner, the modified PainDETECT questionnaire, which has been found to

have adequate face and content validity, follows a similar principle[7]. A further limitation is the lack of definitive diagnostic information regarding the presence of any actual lesions of the somatosensory system. For this reason it is only possible to comment on the presence of features suggestive of neuropathic pain. As details of widespread pain were not formally collected, the effect of this on the QST results can also not be assessed. The study findings are only applicable to women between the ages of 64 and 87 years old.

We have demonstrated in the current study that pain modifying medication did not eradicate sensory changes detected with QST, but rather acted as a marker of severity. Standard practice is to cease pain medication for at least 24 hours prior to QST[22 23], which contributes to the ethical and logistical constraints of its transferability as a clinically viable tool. These data reassure us that meaningful changes can still be detected, despite pain medication use, increasing its potential clinical utility. Furthermore the presence of possible or likely neuropathic pain in 20.1% of those requiring pain modifying medication for joint pain highlights the potential burden of neuropathic pain features in this group of individuals within the community.

The association between heat pain thresholds, mechanical pain sensitivity and PainDETECT scores provides reassuring concurrent validation of significant overlap between the paradigms being measured using both techniques in this setting. Whilst this compliments the results of a neuroimaging study of patients with hip osteoarthritis, by *Gwilym* et al, which demonstrated significant correlation between PainDETECT score and periaqueductal grey activation in

response to punctate stimuli[10], further work on establishing the underlying mechanisms and benefits of treatments targeting these specifically is needed.

Furthermore the presence of increased sensitivity to heat in isolation of changes in mechanical pain sensitivity (15%) and vice versa (27%) suggests that testing multiple modalities may differentiate clinically important sub-groups of patients.

In summary, this study confirms that musculoskeletal pain is common in the community and despite the likely tendency towards mild disease and the continuation of pain modifying medication, QST and the PainDETECT questionnaire identified features suggestive of neuropathic pain with significant overlap between the two techniques. Further validation of the findings is required before transferring these techniques to the clinical setting.

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CONTRIBUTORSHIP STATEMENT

AS was involved in conception and design of the study, data acquisition, analysis and interpretation of the data, drafting the article and approval of the final version to be published. SG was involved in the conception and design of the study, critically revising the article and approval of the final version to be published. RNB, CC, NKA and IT were involved in analysis and interpretation of the data, critically revising the article and approval of the final version to be published. DH and TS were involved in acquisition of the data, critically revising the article and approval of the final version to be published. MKJ was involved in conception and design of the study, analysis and interpretation of the data, critically revising the article and approval of the final version to be published.

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TABLES

Table 1: Characteristics of women assessed for pain at year 20 visit, stratified by pain and medication use.

Characteristic	No pain reported N=156		Pain reported N=306		P-value
	No pain modifying medication (N=123)	Pain modifying medication (N=33)	No pain modifying medication (N=162)	Pain modifying medication (N=144)	
Age (years)	70 (67-75)	73 (67-78)	72 (67-77)	71 (68-75)	0.229
BMI (kg/m ²)	26.9(4.4)	26.7(5.0)	27.5(4.7)	29.0(5.5)	0.001
Warm detect threshold (°C)	4.8 (3.7- 6.7)	5.6 (4.4-6.7)	4.8 (3.7-6.2)	4.9 (3.8-6.1)	0.324
Heat pain threshold (°C)	46.4(43.7- 48.4)	46.1 (43.7-48.0)	45.5 (42.6- 48.0)	45.0 (42.2-47.4)	0.020
Mechanical pain threshold (mN)	64.0(16.0- 164.0)	40.0 (16.0- 128.0)	32.0 (11.2- 153.6)	19.2 (8.2-70.4)	0.001
Mechanical pain sensitivity (0-10)*	5.3 (3.3-7.7)	6.0 (4.0-7.7)	6.0 (4.0-8.0)	6.5 (5.3-8.3)	0.019
PainDETECT _{≥13} **	-	-	4/157 (2.5%)	29/143 (20.1%)	<0.001
N(%); Mean (SD); or Median (IQR)					

*Measures of mechanical pain sensitivity were only available for 90 participants without pain (71 had not taken pain modifying medication and 19 had), and 219 participants with pain (113 had not taken pain modifying medication and 106 had).

**using highest painDETECT score in those with more than one painful area

Table 2: Predictors of possible/likely neuropathic pain scores on PainDETECT, using a logistic regression model, clustered by person.

Predictors	Univariate model		Multivariate model*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Warm detect threshold, per °C increase	1.00 (0.86-1.16)	0.949	0.98 (0.85-1.14)	0.905
Heat pain threshold, per °C increase	0.88 (0.80-0.97)	0.012	0.88 (0.79-0.97)	0.011
Mechanical pain threshold, per step increase	0.97 (0.83-1.13)	0.657	1.01 (0.86-1.17)	0.945
Mechanical pain sensitivity, per unit increase	1.26 (1.07-1.48)	0.005	1.24 (1.04-1.48)	0.018

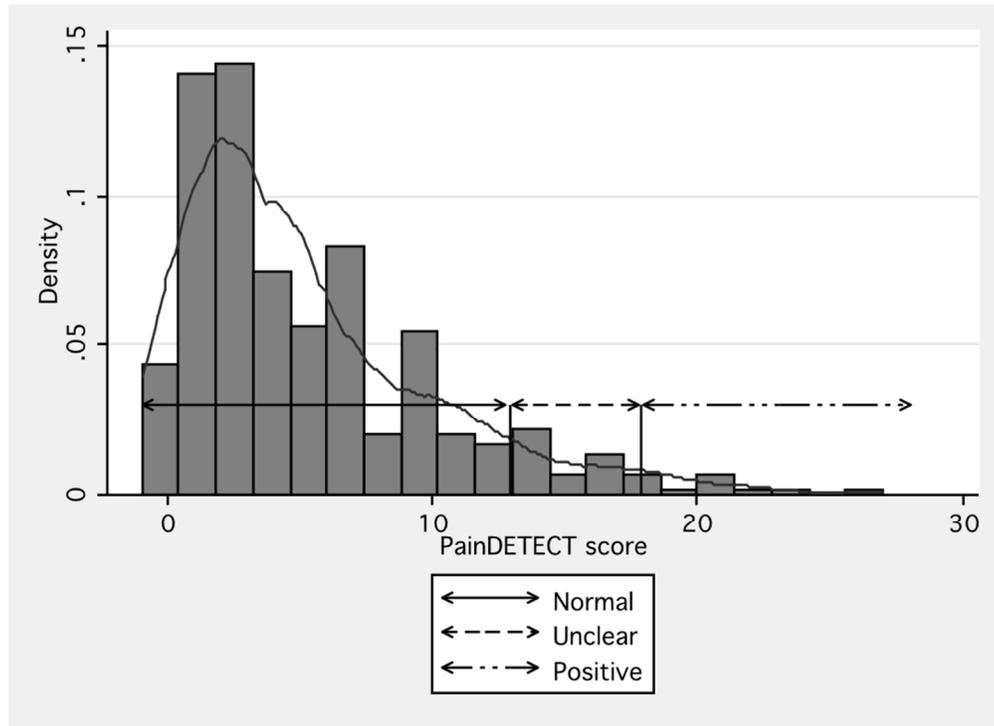
*Adjusted for age, BMI & analgesic or neuropathic medication use

FIGURE LEGENDS

Figure 1: Kernel density distribution plot of the total PainDETECT scores in those with self-reported musculoskeletal pain.

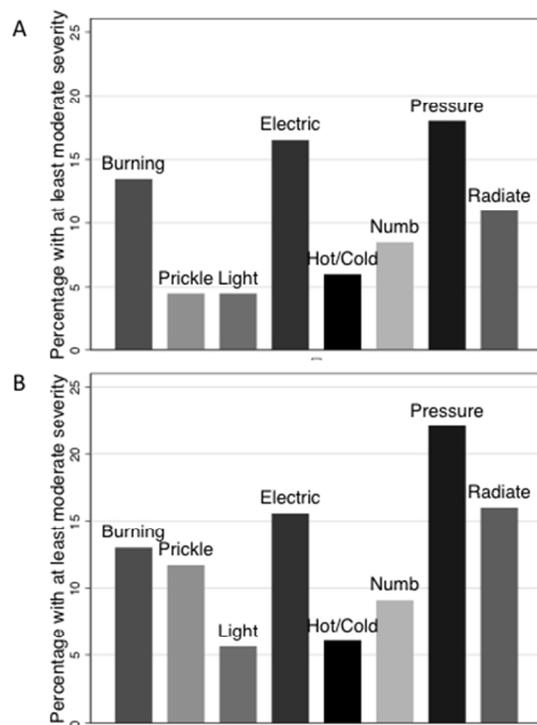
Figure 2: Bar chart demonstrating the qualities of pain, captured using PainDETECT, reported at knee (A) and other musculoskeletal sites assessed (B).

Figure 3: Venn diagram demonstrating the number of participants with one or both QST measures indicative of possible or likely neuropathic pain, n=219 (% of total). HPT= Heat pain threshold, MPS= Mechanical pain sensitivity.



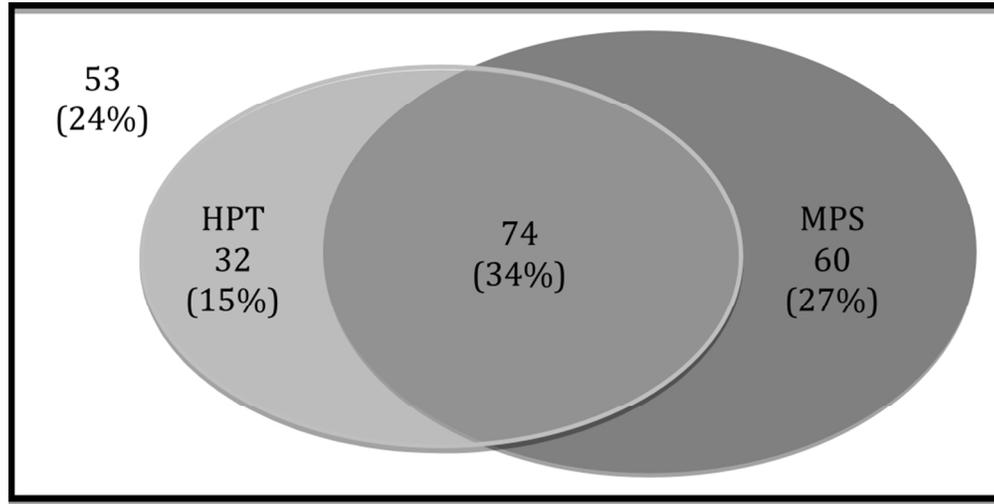
Kernel density distribution plot of the total PainDETECT scores in those with self-reported musculoskeletal pain
281x204mm (96 x 96 DPI)

Accept



Bar chart demonstrating the qualities of pain, captured using PainDETECT, reported at knee (A) and other musculoskeletal sites assessed (B).
254x190mm (72 x 72 DPI)

Accept



Venn diagram demonstrating the number of participants with one or both QST measures indicative of possible or likely neuropathic pain, n=219 (% of total). HPT= Heat pain threshold, MPS= Mechanical pain sensitivity.

281x142mm (96 x 96 DPI)

Accepted