Article Type: Original Article

Title: Location, location, location: Variation in sensitivity to pain across the body

Running head: Pain perception differs across the body

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Manuscript Type: Original Article (European Journal of Pain)

Funding Sources: This study was funded by an Australian Research Council Linkage Project Grant (LP120200033) between the Victorian Transport Accident Commission and the School of Psychological Sciences, Monash University. MJG is supported by a National Health and Medical Research Council Early Career Researcher Fellowship (APP1036124).

Conflicts of Interest: The authors have no financial or other relationship that might lead to a conflict of interest.

What's already known about this topic?

- There is some evidence that sensitivity to noxious stimuli differs between the sexes and around the body.

What does this study add?

- We tested sensitivity to acute suprathreshold thermal stimulations across a range of body sites to investigate for potential variability. We found significant differences in the perceived intensity and unpleasantness of noxious and innocuous thermal stimuli at the wrist and lower back, compared with the shoulder and leg. These results suggest that pain experience is driven by receptor density or the relative functional importance of these sites.

Keywords: pain, thermal pain, body sites, pain perception

Abstract

Background: There is evidence that sensitivity to noxious stimuli differs between the sexes and across the body, but few studies have investigated differences in the perception and experience of acute pain stimuli across the body in healthy individuals.

Methods: We recruited 52 healthy participants, aged 18-36 (50% male) and administered 39°C, 42°C, and 45°C stimuli at four body sites bilaterally to examine differences in the experience of pain intensity and unpleasantness between body sites via an 11-point numerical rating scale.

Results: Noxious and innocuous thermal heat stimuli were perceived as significantly more intense when delivered to the wrist (M = 3.98, SD = 1.93) and back (M = 4.07, SD = 1.98) compared to the shoulder (M = 3.45, SD = 1.91) and leg (M = 3.46, SD = 1.87). Pain unpleasantness ratings yielded similar findings; stimuli were perceived as more unpleasant when administered to the wrist (M = 2.83, SD = 1.93) and lower back (M = 3.04, SD = 2.11) compared to the shoulder (M = 2.63, SD = 1.85) and leg (M = 2.26, SD = 1.82).

Conclusions: These findings suggest that ~~threshold and suprathreshold~~ painful thermal stimuli delivered to the wrist and back are perceived as more intense and unpleasant compared with other body sites in healthy persons. These differences may be due to variations in receptor density, or the relative importance of these sites for daily living and survival.

Significance: Moreover, these insights are helpful for the design ~~and interpretation~~ of studies investigating pain experience in healthy persons in experimental or clinical settings.

1. Introduction

Pain is a far more complex experience than a simple indicator of potential or actual tissue damage (Loeser and Treede 2008). Peripheral neurons called nociceptors respond to nociceptive stimuli. Although some nociceptors are polymodal (i.e., they are activated by different kinds of noxious stimuli; Gold 2006), the perception of thermal stimuli – predominantly via lightly myelinated A-delta and unmyelinated C-fibres – is central in the design of the present study, which investigated variability in pain experience across the body.

Pain perception is highly subjective, and has been shown to vary in relation to sex, and the body site the stimulus is targeting (e.g., Harju 2002). An extensive systematic review identified strong evidence to suggest that females have lower tolerance for thermal (both heat and cold) pain compared with males (Racine et al., 2012a), particularly at extreme temperatures (Sarlani et al., 2003). Women have also been found to display greater wind-up effects (i.e., the temporal summation of nociceptive signals; Fillingim and Edwards 2005). Such an increase in sensitivity may be the result of sex differences in temporal summation, or the way the perception of pain intensity becomes amplified over time (Fillingim et al., 1998). A second comprehensive

systematic review from Racine et al., (2012b) concluded that various biological (e.g., hormonal factors), psychological (e.g., stress), and social factors (e.g., gender-specific pain expectations) contribute to the postulated sex differences in pain sensitivity in healthy men and women.

Patients with chronic pain frequently present with lateralised differences in pain perception. Such lateralised sensitivity can assist in an accurate diagnosis of the pain disorder, and the potential mechanisms involved. During examination it is critical that lateralised differences are interpreted with reference to normative values, without assuming that healthy individuals do not experience laterality differences in pain perception across the body (Greenspan et al., 1999). The German Research Network on Neuropathic Pain (DFNS) was founded to establish a database of phenotypically characterised patients with neuropathic pain, providing researchers with standardised protocols for somatosensory analysis of patients with neuropathic pain, and to establish age- and gender-matched reference values for quantitative sensory testing (QST) parameters (Magerl et al., 2010; Pfau et al., 2014; Rolke et al., 2006). Since the DFNS was established, further QST research has been performed in patients with a variety of neuropathic syndromes (Maier et al., 2010) and chronic postherpetic neuralgia (Pfau et al., 2014). However, these studies investigated a series of parameters relating to pain sensitivity in healthy controls and neuropathic pain conditions (i.e., cold and warm detection and pain thresholds, thermal sensory limen, as well as mechanical and vibration detection thresholds) rather than investigating the perception and experience of acute noxious and innocuous stimuli.

The current exploratory study manipulated the delivery site and temperature of thermal heat stimuli to investigate if the subjective ratings of pain intensity and unpleasantness to ~~noxious and innocuous~~ thermal heat stimuli of varying intensities differ ~~varied~~ across the body in healthy individuals. Findings from this study will provide useful insight for the planning of studies investigating pain experience in healthy individuals, as well as highlighting the importance of matching body sites in experimental tasks (i.e., that simply stimulating one body site could give different results), and potentially serving as reference values for future studies involving patients living with localised pain.

2. Methods

2.1 Participants

Fifty-two healthy volunteers, including twenty-six men, participated in this study. The mean age was 21.92 years (SD 3.51, median 21) with a range from 18 to 36 years. Exclusion criteria included: acute or chronic pain (i.e., pain that is persistent for more than three months); current analgesic or psychotropic medication use (i.e., use of medications more frequently than “as required/pro re nata”); and medical conditions known to be associated with altered pain sensitivity (e.g., diabetes, neurodegenerative diseases, previous injuries, or major trauma). These criteria were assessed via an online screening questionnaire prior to the experiment. Participants were also excluded from the study if they were identified to be at risk of anxious/depressive

disorders and/or suicidal ideation. This screening was completed at the beginning of the testing session (see 'Mood questionnaires').

2.2 Procedure

The protocol was approved by the Monash University Human Research Ethics Committee (CF14/1640 - 2014000772) and followed the Helsinki Declaration of 1975. All participants gave written, informed consent and received $20AU for their participation. Advertisement for the study was posted on electronic newsletters and forums, as well as physical fliers on the Monash University campus. Participants were free to withdraw from the study at any point during the study. Prior to the experimental testing session participants were required to abstain from alcohol for 24 hours, as well as caffeinated beverages and nicotine for four hours.

All participants were tested once between 9am and 6:30pm, and all sessions followed the same general procedure. A male experimenter greeted the participant and provided guidance throughout the experimental procedures. Before commencing the experiment, participants completed baseline demographic and mood questionnaires. ~~The current study formed part of a larger experimental study, the results of which will be are discussed elsewhere (Tracy *et al*., 2015, in preparation).~~

2.3 Magnitude estimations task

2.4.1 Method of pain induction

The Medoc Pathway Pain and Sensory Evaluation System (Medoc Advanced Medical Systems Ltd, Ramat Yishay, Israel) with Medoc Main Station software version 6.3.6.18.1 was utilised to deliver thermal stimulations to participants. The Pathway system allows for exact, controllable delivery of heat stimuli using the Contact Heat Evoked Potentials (CHEPS) thermode. The CHEPS thermode has a round contact area of 573mm^2 (27mm in diameter) and can produce temperatures between 30°C and 55°C, with the ability to increase in temperature at a rate of 70°C/second. The magnitude estimation task comprised eight blocks, with 12 trials per block.

2.4.2 Stimulus target sites

Stimuli within the eight blocks were distributed across four target sites bilaterally The exact location of thermode placement for each stimulus target site was as follows: for the *wrist* site the thermode was placed 5cm up the arm from the styloid process of the radius, on the anterior surface of the arm (proximal to the elbow); for the *shoulder* site the thermode was placed on the anterior surface of the deltoid region of the upper limb, over the acromioclavicular joint; for the *leg* site the thermode was placed 5cm up the leg from the patella, proximal to the pelvis; and for the *back* site the thermode was placed on the horizontal line indicating the supracristal plane (the highest points of the iliac crests), 3cm from the midline of the body. These sites are frequently used in pain research in healthy controls and chronic pain patients (e.g., Defrin et al., 2006; Fillingim et al., 1998). All sites were tested separately, and each block was specific to a particular body site

and side of the body (e.g., all stimuli in the first block were delivered to the left lower back, all stimuli in the second block were delivered to the right wrist, etc.). The eight body sites were tested in pseudorandomised order.

2.4.3 Trial design

Each trial started with a fixation cross (2s), and then the thermal stimulus was delivered over a four second period (modified from Loggia et al., 2011). During stimulus delivery, the thermode increased from baseline (32°C) to the target temperature (1s), remained at the target temperature for two seconds, and then returned to baseline in one second (Supplementary Fig. 1). The thermode remained at baseline until the delivery of the stimulus in the next trial. The stimuli were programmed as high pain (45°C), low pain (42°C), or innocuous (39°C). Over the course of each block, each target temperature was delivered four times in pseudorandomised order. During the trials, the CHEPS thermode was securely held in place by the participant, ensuring the surface of the thermode remained in even contact with the skin of the target area (with the exception of the volar forearm, where the Velcro strap was used to secure the thermode). Temperatures were selected after screening the literature (Thibodeau et al., 2013) and pilot testing in a separate sample, with the expectation that the 45°C stimuli would be rated at an average of seven out of ten. The stimulation temperatures used in the current study were taken from literature screening and pilot testing (rather than fixing the temperatures according to individual pain threshold levels e.g., the lowest intensity stimulus is set at the pain threshold level, while the highest intensity stimulus set at a specific number of degrees above the pain threshold level) as the authors were more interested in the potential differences in pain perception and experience to thermal heat stimuli across the human body, rather than investigating individual differences in pain threshold levels. This is more of a response-dependent methodology, rather than a stimulus-dependent methodology (e.g., Gracely et al., 1988). Prior pilot testing in six participants trialled the highest stimulus at 48°C, but many participants were not able to tolerate these temperatures for the duration of the paradigm.

2.4.4 Pain ratings

After each trial participants were asked to rate intensity and unpleasantness of the stimulus using an 11-point computerised numerical rating scale (NRS), with anchors of 0 (no pain/not unpleasant), 5 (mildly painful/mildly unpleasant), and 10 (extreme pain/extremely unpleasant). The difference between stimulus intensity and unpleasantness was described by using the analogy according to Price *et al.* (1983). In brief, the analogy relates the concepts of pain intensity and pain unpleasantness to the volume of a radio. Pain intensity is described as being similar to the loudness of the radio, where the unpleasantness of the pain depends on the intensity and other factors that may influence how pleasant or unpleasant the experience is. Participants were given 8 seconds to complete these ratings, after which the next trial started.

2.4 Mood questionnaires

The Beck Depression Inventory-II (BDI-II; Beck et al., 1996a) and the Beck Anxiety Inventory (BAI; Beck and Steer 1990) are 21-item self-report measures designed to assess the severity of current symptoms of

depressive and anxious disorders respectively. These questionnaires have excellent psychometric properties and have been recommended for use in pain research (Dworkin et al., 2008). The BDI-II has been shown to have high one-week test-retest reliability (Pearson's $r = 0.93$), indicating that it is not overly sensitive to daily variations in mood (Beck et al., 1996a), and to have high internal consistency (Cronbach's alpha = 0.91; Beck et al., 1996b). The BAI has also been proven to be highly internally consistent (Cronbach's $\alpha = 0.94$) and acceptably reliable over a period of 11 days (Pearson's r = 0.67; Fydrich et al., 1992). The Cronbach's alphas for the BDI-II and BAI in the current sample were 0.75 and 0.54, respectively. The BDI-II and BAI were used to screen the severity participants' current symptoms of depressive and anxious disorders. Participants who were identified to be "at risk" of mild depression and/or anxiety (i.e., scores ≥ eight on the BAI; ≥ 19 on the BDI-II; or ≥ two on item nine (suicidal ideation) of the BDI-II) were excluded.

2.5 Statistics

The data were analysed with IBM SPSS Version 20.0. ANOVA with contrast analyses were performed to ensure that the three stimulus temperatures selected for the paradigm were perceived as significantly different from one another (i.e., validating the temperatures), and to determine potential differences in the subjective intensity and unpleasantness of painful thermal stimulations between the target sites. For the latter analyses, the stimulus target sites were paired to investigate potential differences between the six possible paired site combinations: wrist/shoulder, wrist/back, wrist/leg, shoulder/back, shoulder/leg, and back/leg. For the contrast analysis data from the bilateral sites (e.g., the left and right shoulder) were combined to produce an overall mean rating for each of the four target sites (i.e., shoulder, back, wrist, and leg), which were then compared as part of the analysis. A p value of 0.05 was considered to be statistically significant, and Bonferroni corrections were applied where necessary by dividing the desired level of statistical significance (i.e., $\alpha = 0.05$) by the number of comparisons performed to counteract the likelihood of Type I error (Dunn 1961).

3. Results

3.1 Sample description

Fifty-two participants completed the study and were eligible for analysis. Participants had an average age of 21.92 years (SD = 3.55) and were not identified to be "at risk" of mild depressive ($M = 3.27$, SD = 3.30) and/or anxious ($M = 2.37$, SD = 1.96) disorders.

3.2 Temperature validation

The three stimulus intensities (i.e., 45°C, 42°C, and 39°C) were given significantly different ratings of intensity throughout the magnitude estimations paradigm, regardless of body site (Supplementary Fig. 2). The 45°C stimulus ($M_{45} = 6.60$, SD = 2.23) was perceived to be significantly more intense than both the 42°C ($M_{41} = 3.14$, SD = 2.00; $F(1,49) = 583.86$, $p < .001$, $\eta_p^2 = .92$) and 39°C ($M_{39} = 1.47$, SD = 1.46; $F(1,49) = 559.61$, $p < .001$, $\eta_p^2 = .92$) stimuli. The 42°C stimulus was also perceived to be significantly more intense than the 39°C stimulus ($F(1,49) = 171.02$, $p < .001$, $\eta_p^2 = .78$).

3.3 Pain intensity ratings

Using a Bonferroni adjusted alpha of .008 (.05/6), simple comparisons as part of the contrast analysis revealed significantly different ratings in subjective pain intensity in four of the six pairs of stimulus target sites. Regardless of stimulus intensity, thermal stimuli delivered to the wrist were perceived as significantly more intense compared to the stimuli were delivered to the shoulder ($F(1,49) = 14.01$, $p < .001$, $\eta_p^2 = 0.22$) and the leg ($F(1,49) = 20.99$, $p < .001$, $\eta_p^2 = 0.30$). Similarly, stimuli delivered to the back were perceived as significantly more intense than those delivered to the shoulder ($F(1,49) = 20.08$, $p < .001$, $\eta_p^2 = 0.29$) and the leg ($F(1,49) = 18.34$, $p < .001$, $\eta_p^2 = .27$). No significant differences were observed for subjective ratings of pain intensity between the wrist and the back, as well as the shoulder and the leg (Fig. 1A).

Figure 1 here

Post hoc contrast analysis (using a Bonferroni adjusted alpha of .002) investigated the source of the differences in subjective pain intensity. For the wrist/shoulder comparison, only the 39°C stimuli delivered to the wrist was perceived as significantly more intense compared to the shoulder ($F(1,49) = 13.46$, $p = .001$, $\eta_p^2 = 0.22$; Fig. 2a). For the wrist/leg comparison, stimuli were perceived as more intense at the wrist compared to the leg at both 42°C ($F(1,49) = 13.17$, $p = .001$, $\eta_p^2 = 0.21$) and 45°C ($F(1,49) = 15.28$, $p < .001$, $\eta_p^2 = 0.24$), Fig. 2b. For the shoulder/back comparison, both the 39°C ($F(1,49) = 17.90$, $p < .001$, $\eta_p^2 = 0.27$) and 42°C ($F(1,49) = 13.30$, $p = .001$, $\eta_p^2 = 0.21$) stimuli delivered to the back were perceived as significantly more intense compared to the shoulder: (Fig. 2c). Finally, for the back/leg comparison, the 42°C stimuli delivered to the back were perceived as significantly more intense compared to the leg ($F(1,49) = 12.97$, $p = .001$, $\eta_p^2 = 0.21$). In addition, the 45°C stimuli directed to the back resulted in a marginally significant increase in intensity ratings compared to the leg ($F(1,49) = 10.52$, $p = .002$; Fig. 2d). No significant differences were observed in response to the remaining stimulus intensities at these sites. Values of subjective pain intensity for all sites and temperatures can be seen in Table S1.

Figure 2 here

3.4 Pain unpleasantness ratings

Using a Bonferroni adjusted alpha of .008 (.05/6), simple comparisons as part of the contrast analysis revealed significantly different ratings in subjective pain unpleasantness in four of the six pairs of stimulus target sites. Thermal stimuli delivered to the wrist were significantly more unpleasant compared with the stimuli delivered to the shoulder ($F(1,49) = 14.29$, $p < .001$, $\eta_p^2 = 0.23$) and the leg ($F(1,49) = 22.48$, $p < .001$, $\eta_p^2 = 0.31$). Stimuli delivered to the back were perceived as significantly more unpleasant compared to those delivered to the shoulder ($F(1,49) = 20.97$, $p < .001$, $\eta_p^2 = .30$) and the leg ($F(1,49) = 22.70$, $p < .001$, $\eta_p^2 = 0.32$). No significant differences were observed for subjective ratings of pain unpleasantness between the wrist and the back, or the shoulder and the leg (Fig. 1B).

Post hoc contrast analysis (using a Bonferroni adjusted alpha of .002) investigated the source of the differences in subjective pain unpleasantness. The 42°C stimuli directed to the wrist resulted in a marginally significant increase in the perceived unpleasantness compared to the shoulder ($F(1,49) = 10.37$, $p = .002$; Fig. 2a). For the wrist/leg comparison, both the 42°C ($F(1,49) = 11.54$, $p = .001$, $\eta_p^2 = 0.19$) and 45°C ($F(1,49) = 17.06$, $p < .001$, $\eta_p^2 = 0.26$) stimuli delivered to the wrist were perceived as significantly more unpleasant compared to the leg , and $M_{L45} = 4.96$, SD = 2.63; (Fig. 2b). For the shoulder/back comparison, the 39°C($F(1,49) = 11.74$, $p = .001$, $\eta_p^2 = 0.19$), 42°C($F(1,49) = 15.94$, $p < .001$, $\eta_p^2 = 0.25$), and 45°C ($F(1,49) = 11.74$, $p = .001$, $\eta_p^2 = 0.19$) stimuli delivered to the back were perceived as significantly more unpleasant compared to the shoulder (Fig. 2c). Finally, for the back/leg comparison, the 39°C ($F(1,49) = 13.53$, $p = .001$, $\eta_p^2 = 0.22$), 42°C($F(1,49) = 18.00$, $p < .001$, $\eta_p^2 = 0.27$), and 45°C ($F(1,49) = 12.20$, $p = .001$, $\eta_p^2 = 0.20$) stimuli delivered to the back were perceived as significantly more unpleasant compared to the leg (Fig. 2d). No significant differences were observed in response to the remaining stimulus intensities at these sites. Values of subjective pain unpleasantness for all sites and temperatures can be seen in Table S2.

4. Discussion

The present study examined whether there were differences in the intensity and unpleasantness of acute thermal heat stimuli across the body in healthy individuals. Our results suggest that, in healthy ~~and otherwise pain-free individuals~~, specific body sites may be more sensitive to both noxious and innocuous thermal heat stimuli. In particular, thermal heat stimuli delivered to the wrist and back were perceived as more intense and unpleasant compared to the same stimuli when delivered to the wrist or shoulder.

Subjective ratings of pain intensity and pain unpleasantness were found to vary between specific body regions in the present study. The thermal stimuli were perceived as significantly more intense and unpleasant when directed at the wrist and back compared to the shoulder and the leg. Previous studies investigating variation in subjective intensity and unpleasantness as a function of target body sites are scarce. Harju (2002) reported that thermal heat and cold perception varies in relation to age, sex, and body area (e.g., at the knee, older women were more sensitive to both cold and heat pain compared to younger women and men at the same site). This finding was recently opposed by Hafner et al., (2015), who reported that the thermal detection threshold increased with age, and was significantly higher at the foot compared to the hand. Other studies have examined differences in sensitivity within a localised region of the body, such as the face and head, and found that thermal pain thresholds differed significantly across orofacial sites (i.e., tongue, lips, forehead etc.; Essick et al., 2004; Kim et al., 2013). Several other studies have examined differences in thermal pain thresholds across the body, with mixed results (e.g., Defrin et al., 2006; Hardy et al., 1952; Kenshalo 1986; Lautenbacher and Strian 1991).

The German Research Network on Neuropathic Pain (DFNS) has collected multicentre reference data for pain perception at the cheek, dorsal surface of the hand, and the dorsal surface of the foot in healthy adult males and females ranging from 20 to 70 years (Magerl et al., 2010). In an early publication from this reference data, Rolke et al. (2006) reported that the three aforementioned regions of the body (i.e., the cheek, hand, and foot) differed with respect to the QST parameters (e.g., cold, heat, mechanical, and pressure pain thresholds), with sensitivity in the face being higher than in the foot. Sensitivity in the hand was usually intermediate to the other two sites (Rolke et al., 2006). Although this earlier study employed different target sites and testing parameters, the results of the present study are consistent. That is, specific regions of the human body display differences in the way pain is perceived. A later study by Pfau et al. (2014) extended upon the initial DFNS dataset by examining potential differences in pain sensitivity between the upper and lower back in patients with chronic postherpetic neuralgia and healthy controls. In the Pfau study, QST revealed lower sensitivity on the upper back than the hand, and higher sensitivity on the lower back than the foot, without finding differences between the upper and lower back (Pfau et al., 2014). The present finding that the pain is perceived as more intense and unpleasant at the back compared to the leg is consistent with those reported by Pfau et al. (2014), further highlighting that pain is subjectively experienced differently across different sites of the body.

Previous research has revealed that glabrous (i.e., non-hairy) skin has a significantly higher heat pain threshold compared to hairy skin (Taylor et al., 1993). It has been suggested that this is because glabrous skin is more richly innervated with heat-sensitive receptors (unmyelinated C fibres) and high threshold nociceptors (finely myelinated Aδ fibres, AHM type I), but lacks the lower threshold heat receptors (AHM type II; Treede et al., 1995). However, more recent findings suggest that these receptors do exist, but are simply situated deeper in glabrous compared to non-glabrous skin (Iannetti et al., 2006). ~~However~~ It should be noted that~~,~~ the stimulus target sites in the present study were all nonglabrous. Other areas of the body have been found to have different tactile sensitivities based on the density of receptors that innervate that particular area of the skin (Gallace and Spence 2014). Therefore, the regional differences observed in the current study may perhaps be due to differences in the distribution of temperature-responsive nociceptors throughout the target sites.

Given that pain intensity and unpleasantness was found to differ *among* nonglabrous body sites suggests that these effects may arise not simply due to differences in innervation, but due to a combination of both functional and psychological mechanisms. The hands and arms of humans are required for many activities of daily living (e.g., object manipulation, communication, and feeding), and for maintaining survival (e.g., self-defence), while the large muscles of the back ~~and legs~~ are integral to core mobility and strength~~, and ambulation. Therefore, it is possible that hands and arms are viewed as more indispensable for survival.~~ The increased sensitivity to pain at these sites may be a protective mechanism that serves as an enhanced warning signal to prevent potential injury to body sites that are more “valuable” or necessary to survival. ~~Alternatively, as the muscles of the back are not involved in daily functioning tasks in the same way as hands and feet, and~~

~~certainly not with the same level of acuity, it is less frequently exposed to potentially damaging environments and stimulations. Furthermore, the majority of the "noxious" threats to these body parts are due to musculoskeletal strain or injury, rather than cutaneous stimulation. Therefore, the perception of danger may be enhanced in response to stimulations in the arm, potentially explaining the observed increase in subjective ratings of pain intensity and pain unpleasantness to thermal stimulation on the back.~~

Some limitations from the present investigation should be considered in making generalisations from these findings. First, the current sample mainly comprised young (< 40) participants who were all healthy and pain-free. Further research is needed to determine whether the same patterns are found in older and/or clinical populations, given that prior research has identified that pain perception (Gibson and Farrell 2004) and central pain processing (Gibson et al., 1991) changes through the aging process even in the absence of comorbid illness and disease. Second, thermal heat stimulation was the only method of sensory stimulation used. Therefore, the results of this study may not generalise across other forms of noxious somatosensory stimulation. Third, the sample size was smaller than that of prior research examining the sensory lateralisation of pain (e.g., Lugo et al., 2002). However, as our effect sizes (partial eta squared; η_p^2) can be classified as large (Cohen 1988), this suggests that this study recruited a sufficiently large sample to detect clinically important differences. Finally, the current study investigated the perception of noxious and innocuous thermal stimuli across only four bilateral sites. For a more detailed investigation of potential differences in pain perception across the body, a greater number of test sites (including both glabrous and nonglabrous skin) should be included in future studies.

In conclusion, the present study found that the wrist and the lower back are more sensitive to noxious and innocuous thermal stimuli compared to the shoulder and leg. These results suggest that pain experience is driven by receptor density or the relative importance of the site experiencing pain for daily living and survival. Such insights are helpful for the design and interpretation of future studies investigating pain in an experimental or clinical setting. These findings are important to consider when selecting target and control sites for pain-related studies.

Author Contributions

Each co-author contributed significantly to the work described and commented on the manuscript. LMT planned and executed the study, recruited and gained consent from participants, collected and analysed data, discussed the results, and wrote the paper with guidance and feedback from the co-authors. NG-K contributed to the research design, interpretation of analyses, discussion of results, and editing the manuscript. SJG contributed to the research design, discussion of results, and editing the manuscript. MJG assisted in research design, interpretation of the findings, discussion of results, and editing the manuscript.

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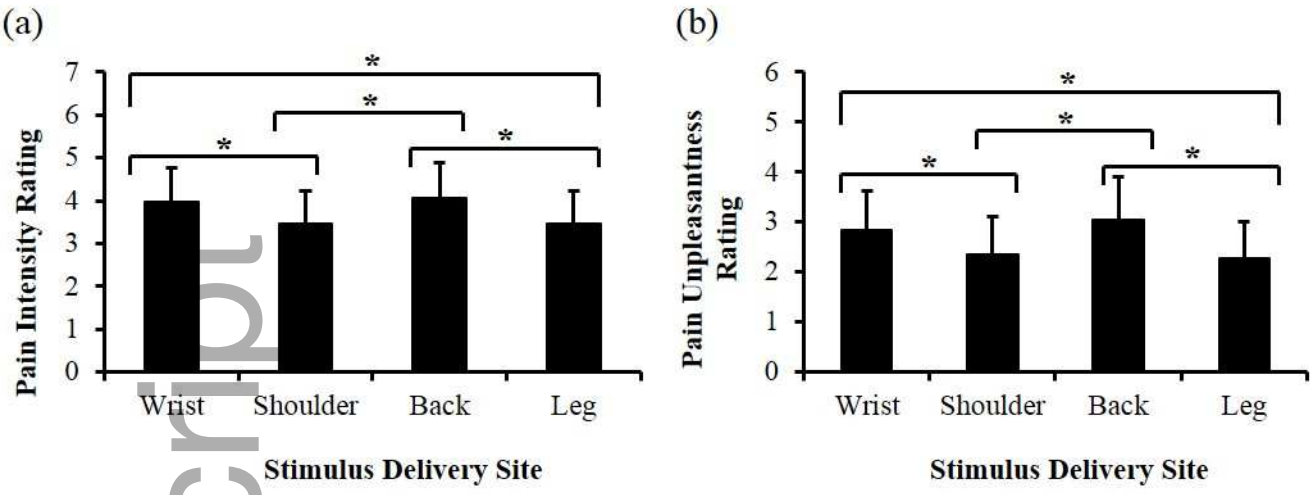

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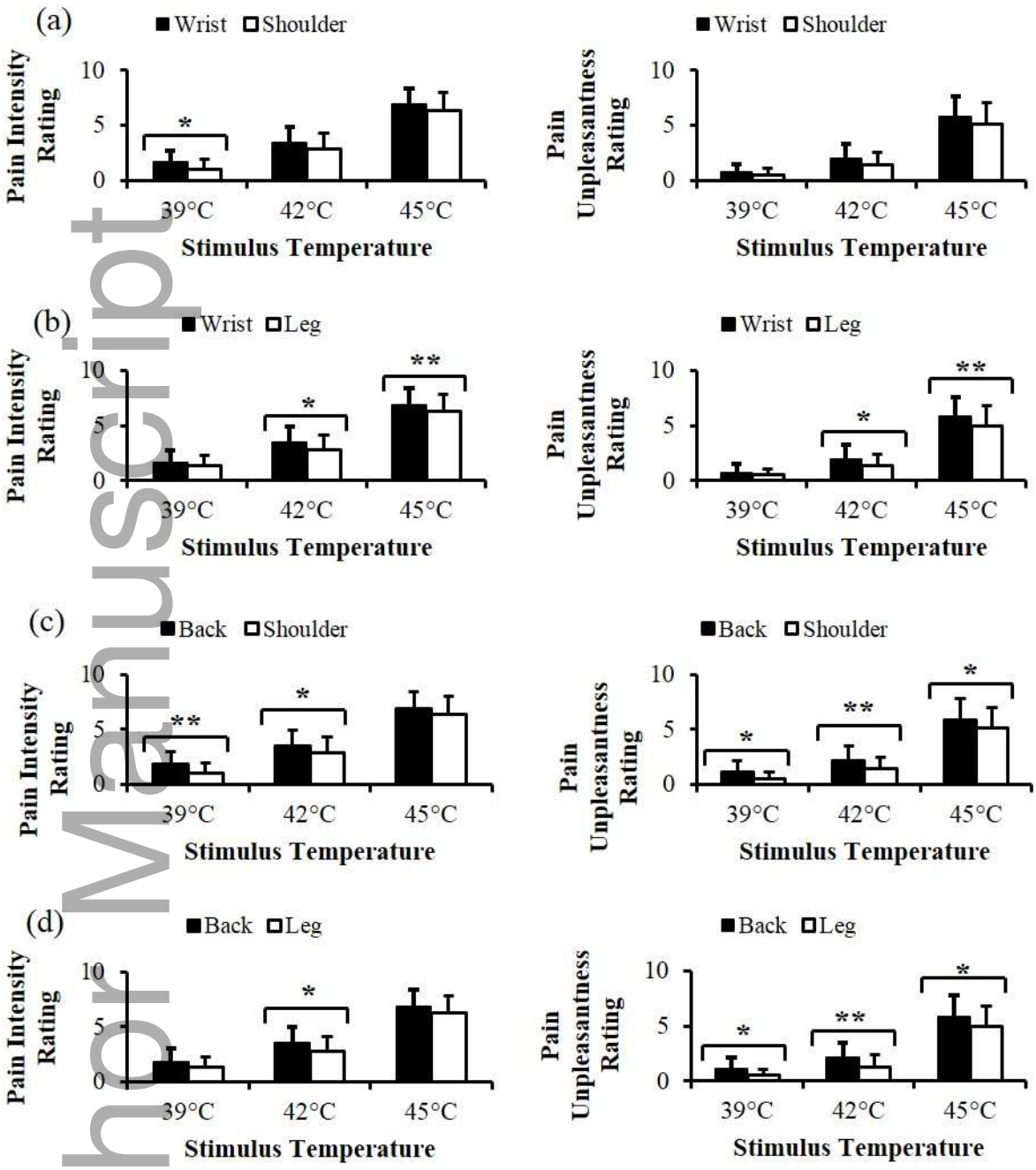

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Title:
Location, location, location: Variation in sensitivity to pain across the body

Date:
2016-11-01

Citation:
Tracy, L. M., Georgiou-Karistianis, N., Gibson, S. J. & Giummarra, M. J. (2016). Location, location, location: Variation in sensitivity to pain across the body. EUROPEAN JOURNAL OF PAIN, 20 (10), pp.1721-1729. https://doi.org/10.1002/ejp.895.