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Tactile acuity improves during acute experimental pain of the limb

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Abstract

Introduction: Chronic pain is associated with poor tactile acuity, commonly measured with the 2-point discrimination (TPD) test. Although poor tactile acuity across chronic pain conditions is well established, less is known in acute pain.

Objective: Recent conflicting findings in experimentally induced neck and back pain led us to conduct a TPD investigation in experimentally induced limb pain. We hypothesised altered TPD during experimental upper limb pain, but we did not speculate on the direction of the change.

Methods: Thirty healthy subjects immersed their dominant hand in a circulating cold-water bath at 7°C (cold pressor test [CPT]). Two-point discrimination was measured at baseline (pre-CPT), during pain (during-CPT), and after withdrawal from the water (post-CPT) in 3 different sites: (1) the dominant forearm, (2) dominant arm and (3) contralateral forearm.

Results: Repeated-measures analysis of variance revealed a significant main effect of time ($F_{(2,56)} = 4.45$, $P = 0.02$, $\eta_p^2 = 0.14$) on TPD; in all 3 sites, TPD values decreased (ie, tactile acuity improved) during pain. Interestingly, the contralateral forearm followed a similar pattern to the dominant (ie, painful) forearm, and furthermore was the only site that exhibited any correlation with pain, albeit in an intriguing direction ($r = 0.57$, $P = 0.001$), ie, the greater the pain the worse the tactile acuity.

Conclusion: The improvements in tactile acuity during experimentally induced limb pain may reflect a protective response. The changes in the corresponding site in the contralateral limb may reflect a protective spinal cross talk. Such a response, together with the interesting relationship between tactile acuity and pain, warrant further inquiry.

Keywords: Acute pain, Tactile acuity, Experimental pain, Two-point discrimination, TPD, Limb pain

1. Introduction

Chronic pain is commonly accompanied by perceptual changes and sensory deficits, such as distorted body image,[15,27,39,54] altered position sense,[8,17,51,61] and misallocation of tactile stimuli.[33,40] Across chronic pain disorders, patients are less precise at identifying the location and features of a tactile stimulus delivered to their painful body area.[2,20,33,60]

Tactile acuity, the precision with which touch information is perceived, is most commonly tested with the 2-point discrimination (TPD) test.[22] Two-point discrimination threshold refers to the shortest distance between 2 points that someone can perceive as 2 points, not 1, touching the skin. The shorter the distance (lower TPD value), the better one's tactile acuity.[29] Tactile acuity is different to simple tactile detection; it is a judgement task processed by the central nervous system and has been associated with functional representation in the brain's primary somatosensory cortex (S1).[11] Across chronic pain conditions, there is evidence of poor tactile acuity at remote sites,[6] further suggesting central nervous system dysfunction. The extent of tactile impairment has been found to correlate with pain intensity,[14,32,46] and evidence suggests that as pain reduces, tactile acuity improves.[47] Treatment aimed at improving tactile discrimination has resulted in reduced pain.[13,41]

Although it is well established that tactile acuity is altered in chronic pain, little is known about tactile acuity in early stages of

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pain. Two recent studies reported reduced tactile acuity in subjects with acute neck and back pain, respectively,[19,38] but exactly when such alterations might occur, and their possible meaning, is unknown. To our knowledge, only 2 studies have investigated tactile acuity following experimentally induced pain.[1,3] Adamczyk et al. first reported tactile acuity deterioration following induction of low back pain[3]; however, the same authors reported that tactile acuity did not change with neck pain.[1] Both induced pain with hypertonic saline injection; the authors suggested that the conflict might be due to the differences in anatomical site being tested.[1]

Besides an investigation over 48 hours (delayed onset muscle soreness) in the upper limb,[21] we are unaware of any investigation into tactile acuity in experimental limb pain. Chronic limb pain is accompanied by a complex presentation across several body systems.[36] In the healthy somatosensory system, tactile acuity is superior and arguably more important in the limbs, particularly the upper limbs,[42] than in the trunk. For these reasons, an investigation of tactile function in experimentally induced upper limb pain is warranted.

This study induced unilateral limb pain using the cold pressor test, with the aim of determining whether tactile acuity changes in the painful limb. Secondary aims were to determine whether changes occur in remote sites, and whether tactile acuity returns to baseline as pain resolves. We hypothesized alterations to tactile acuity with pain; however, given the existing conflicting findings, we were unsure whether this would result in an impairment or improvement.

2. Methods

2.1. Subjects

A sample of healthy pain-free subjects aged between 18 and 35 years were recruited from the general community, largely from the Curtin University population. Subjects reported no history of significant injury to the upper limbs or history of chronic pain. Peripheral neuropathy, peripheral vascular disease, diabetes, high blood pressure, dysrhythmia or heart disease, history of seizures or fainting, history of frostbite, any open cut or sore on the upper limb to undergo testing, or a history of Raynaud syndrome were all conditions for exclusion, as known contraindications to cold pressor test administration.[58] Subjects gave written, informed consent and were advised that they were free to withdraw from the experiment at any time without prejudice. Subjects were tested on 1 occasion for a session of up to 1-hour duration. All procedures conformed to the Declaration of Helsinki, and this project was approved by the Human Research Ethics Committee, Curtin University (HRE2021-0098).

2.2. Sample size

A sample size calculation was performed in G*Power (G*Power statistical software, version 3.1.9.4[12]). The calculation determined a minimum sample of 21 subjects to allow detection of a moderate effect with 80% power, at a significance level of 0.05. The sample size of n = 30 was chosen to account for potential dropout and for any possible differences in sample and study design to past work.[1] An additional 10 subjects were recruited for piloting, which informed study design before recruitment of the study sample.

2.3. Study design

Subjects' TPD was tested at baseline, during cold-water immersions (cold pressor test [CPT]), and at the end of the experiment, hereby referenced as pre-CPT, during-CPT, and post-CPT (**Fig. 1**). Subjects underwent 3 cold-water immersions of the dominant hand to just proximal to the wrist joint; during each immersion, a different body site was tested for TPD. The 3 sites were tested in a randomised order to control for learning effects, adaptation, and fatigue. The sites were (1) the dorsal dominant (painful) forearm, (2) the dorsal dominant upper arm, and (3) the dorsal contralateral (pain-free) forearm, hereby referred to as the dominant forearm, dominant proximal arm, and contralateral forearm. Two-point discrimination in the dominant proximal arm and contralateral forearm was measured to explore whether acute pain is associated with tactile acuity changes in locations remote from the pain. Before data collection, a piloting phase was necessary to verify whether the CPT temperature was noxious; establish the latency between immersion and stable pain intensity (ie, determine the time point at which to measure TPD); establish recovery time between subsequent CPT immersions; and confirm that basic tactile sensitivity remained intact during cold-water immersion (note that one subject withdrew from testing due to pain, leaving 9 pilot subjects, Supplementary Table, available at http://links.lww.com/PR9/A201).

2.4. Piloting

2.4.1. Stable pain intensity

Piloting confirmed that the cold pressor test, set at 7°C, was sufficiently noxious to induce pain during every immersion across all subjects. This temperature elicited moderate pain ratings among pilot subjects (mean pain rating of 6/10) and thus was maintained for the experiment to follow.

2.4.2. Cold pressor test water temperature

Two-point discrimination was to be measured during CPT immersion when pain reached a stable intensity.[1] Piloting determined the mean time spent in the cold water to reach a stable pain intensity rating. Subjects were instructed to indicate their pain using a verbal numerical pain scale ranging from 0 to 10 (0 indicating no pain and 10 indicating the worst pain imaginable) and advise when their pain was at a stable intensity, ie, neither increasing nor decreasing. The average time taken to reach a stable pain intensity was 50 seconds, and thus was determined as the time point for TPD testing for all subjects.

2.4.3. Recovery

Piloting also established a safe and consistent recovery time (ie, time before re-immersion) after removal of subjects' hands from the cold-water bath. After immersion of their hand in water at 32°C water for 1 minute,[37] the following was tested: (1) assessing capillary refill was normal (manually, by applying pressure to the nailbed of the dominant forefinger for approximately 10 seconds and thereafter visually observing colour return within 3 seconds), (2) physical observation of the hand to confirm absence of cyanosis or erythema, (3) ascertaining that pain had subsided, and (4) a tactile sensitivity check (as described below). According to these parameters, subjects recovered within 5 minutes of removing their hand from the cold bath, and thereafter 5 minutes was set as the recovery period between subsequent immersions.

2.4.4. Tactile sensitivity

A higher-order task of tactile acuity requires basic tactile sensitivity. There is evidence of altered tactile function in experimental pain.[16]

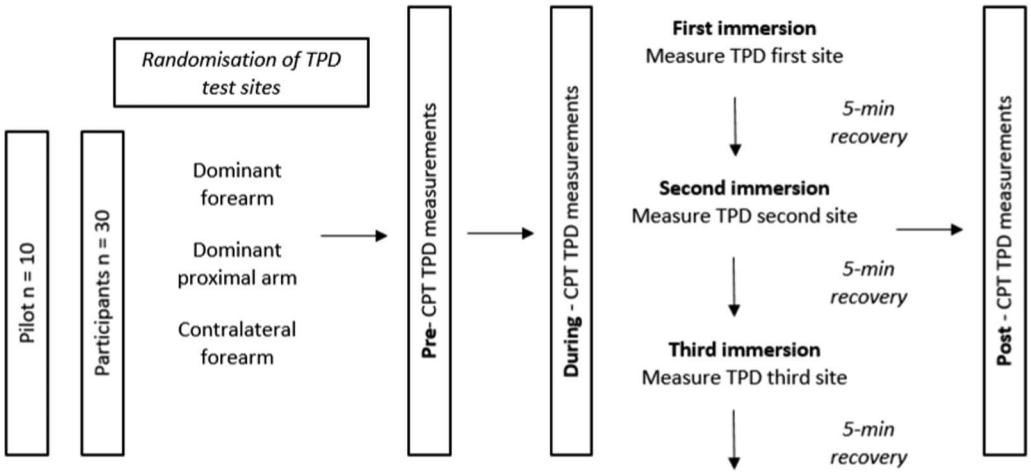

Figure 1. Study design. Following piloting, 30 subjects were recruited for the study. Two-point discrimination (TPD) was tested in 3 sites, in a randomised order. TPD testing was conducted before (pre-CPT), during (during-CPT), and after (post-CPT) 3 separate painful cold-water immersions, with 5-minute recovery periods between subsequent immersions.

Thus, although we did not test tactile thresholds specifically, piloting was important to determine that the subjects' basic tactile sensitivity was not affected by the cold-water stimulus. Sensitivity checks evaluated that transmission in both Aß fibres (light touch; tested with cotton wool) and Aδ fibres (sharp, punctuate stimulus; tested with a toothpick)[30] was not impaired in either the immersed or the contralateral forearm. Sensitivity was assessed immediately following TPD testing (ie, >50 seconds post immersion), and as part of determining the recovery period post immersion in both forearms. Sensitivity was found to be unaffected in all pilot subjects. Sensitivity checks were only conducted thereafter to confirm recovery after the 3 immersions.

2.5. Two-point discrimination test

Two-point discrimination was measured on a non-immersed skin site using a set of 3D-printed TPD callipers. A printed set of predetermined TPD distances, as opposed to a pair of traditional callipers, aided prompt administration of stimuli. Prior to use, the distance of each was verified against a commercially-available digital TPD device. The callipers were applied in a longitudinal (ie, vertical) orientation on the limb until the very first blanching of the skin.[39] Subjects were asked to respond whether they felt 1 or 2 points touching the skin as the stimulus was applied. One-point stimuli were used as catch trials, to ensure the subjects were alert. The calliper distance was altered between each stimulation; either increased by 5 mm until the subject could distinguish 2 points (ascending sequence) or decreased by 5 mm until the subject could feel only one point (descending sequence). This process was repeated 3 times, and the mean TPD score was gathered from the 6 sequences, with a lower TPD threshold indicating better tactile acuity. The order of sequences (ie, ascending or descending) was counterbalanced between subjects to control for any order effects. The specific site of skin stimulation was slightly varied with each stimulation, to avoid irritation. Subjects' eyes were closed during all TPD testing. No feedback on responses was given by the researcher.

2.6. The cold pressor test

The cold pressor test was chosen because it induces a tonic and unpleasant pain, thought to mimic that of chronic pain conditions.[50] The use of circulating water, together with the maintenance of a controlled water temperature, have been recommended to increase the method's reliability.[37] This investigation used a circulating water bath (12-L capacity, T100 model, Grant Optima Lab Gear, Melbourne, Australia), with an accessory cooling unit (C2G model) set at a temperature of 7°C. The water bath contained dual heating and cooling actions and constant circulation, which led to a safe, precise, and constant temperature, with ±0.05°C stability.

The extent to which the hand was immersed was monitored and kept consistent. The hand was immersed such that the water level was just above the wrist joint, and the hand was open and not touching the base of the tank. After 50 seconds in the water, subjects were asked to verbally express their pain rating and then TPD testing commenced in 1 of the 3 randomised TPD testing sites. Once the TPD measurements were obtained, the subject could remove their hand from the water. Thus, total immersion time was not fixed, but there was a fixed 5-minute recovery period between immersions, during which subjects immersed their dominant hand in 32°C water for 1 minute. After the third immersion and the recovery period were complete, post-CPT TPD measurements were taken.

2.7. Other pain measures

At the end of the session, subjects were asked to rate their pain unpleasantness, using a visual analogue scale (VAS).[48] The VAS tool consisted of a 10-cm sliding apparatus, which indicated "not at all unpleasant" on the left and "most unpleasant imaginable" on the right Each subject indicated their rating by sliding the nonnumerical scale; the numbered scale was only visible to the researcher. Subjects were also instructed to complete the Pain Catastrophizing Scale (PCS)[53] as a measure of their thoughts, attitudes, and beliefs when experiencing pain. The scale includes 13 items rated on a 5-point scale, with a higher score indicating a higher level of catastrophizing (maximum score 52).

2.8. Statistical analysis

All statistical analysis was performed using SPSS (IBM, version 27.0, Armonk, NY). Normality was evaluated using the Shapiro–Wilk statistic ($P > 0.05$) and visual inspection of histograms and box-and-

whisker plots. All TPD variables were normally distributed, with the exception of the dominant forearm site during CPT and post CPT. All normal data are presented as mean ± SD; non-normally distributed data are presented as median (IQR) unless stated otherwise. The changes in TPD over time and site were determined with a 2-way repeated-measures analysis of variance (ANOVA) with site (dominant forearm, dominant proximal arm, and contralateral forearm) and time (pre, during, and post CPT) as within-subject factors. The ANOVA was deemed robust despite 2 conditions being non-normally distributed.[4] *F*-tests were followed by planned comparisons of tactile acuity over site and time. The associations between TPD and pain-related variables (pain intensity, PCS score, pain unpleasantness) were tested with Pearson product coefficient (r) for normal data (pain intensity ratings, PCS scores) and Spearman rank order correlation (r_s) for non-normally distributed data (pain unpleasantness).

3. Results

3.1. Subjects

Upon completion of piloting, 30 healthy, pain-free subjects were enrolled (12 male and 18 female subjects; age, 22 ± 2.7 years). One subject's data were removed from the analysis due to outlying (ie, inconsistent and some implausible) values across sites and time. Importantly, removal of the one subject did not affect the main results of the study. The data from 29 subjects are presented below. No subjects withdrew their hand prematurely from the water bath or showed adverse effects following the CPT administration. Pain-related variables recorded throughout the experiment are presented in **Table 1**. The mean pain rating across all 3 CPT immersions was 6.6 (±2.3), and no subject reported a pain rating of 0 on any immersion.

3.2. Tactile acuity changes upon acute limb pain induction

Repeated-measures ANOVA revealed a large and statistically significant main effect of time on TPD ($F_{(2,56)} = 4.45$, $P = 0.02$, $\eta_p^2 = 0.14$), indicating that tactile acuity was indeed altered with immersion and then removal of the hand from the CPT bath. There was also a significant main effect of site on TPD ($F_{(2,56)} = 20.11$, $P < 0.005$, $\eta_p^2 = 0.42$), indicating that there was a large difference in tactile acuity across the 3 body sites. There was no significant interaction between time and site ($F_{(4,108)} = 1.028$, $P > 0.05$, $\eta_p^2 = 0.04$).

Descriptive statistics for tactile acuity for the 3 body sites across the 3 time points, ie, pre-CPT, during-CPT and post-CPT, are presented in **Table 2**. At all 3 sites, TPD values decreased, ie, tactile acuity improved, when subjects were in pain (post hoc comparisons between pre-CPT and during-CPT, Bonferroni corrected, $P < 0.05$). Site wise, the dominant proximal arm was different to both the dominant forearm and the contralateral forearm (post hoc comparisons, Bonferroni corrected, $P < 0.05$); interestingly, there was no difference between the forearms, and they followed a similar pattern of TPD change over time. Although there was only a trend toward recovery of TPD (post-CPT) over the 3 sites, a post hoc t test revealed a significant difference between TPD during and post CPT in the contralateral forearm only ($t(28) = -2.22$, $P = 0.04$; note no correction for multiple comparisons) (**Fig. 2**).

3.3. The relationship between tactile acuity and pain

Results from the correlation analyses are presented in **Table 3**. Generally, there were no significant correlations between pain ratings and TPD in the dominant forearm or the dominant proximal arm (Supplementary Figure 1a and b, available at http://links.lww.com/PR9/A201), nor were there any significant correlations between pain unpleasantness (Supplementary Figure 2a and b, available at http://links.lww.com/PR9/A201) or PCS score (Supplementary Figure 3a and b, available at http://links.lww.com/PR9/A201) and TPD in the dominant forearm or the dominant proximal arm. Notably, the contralateral forearm was the only site to exhibit (moderate) correlation trends with both PCS score and pain unpleasantness (Supplementary Figures 2c and 3c, available at http://links.lww.com/PR9/A201) and a significant moderate correlation with pain rating ($r = 0.57$, $P = 0.001$; **Fig. 3**), whereby TPD values increased (indicating worse tactile acuity), as reported pain ratings were greater.

4. Discussion

We hypothesized alterations to tactile acuity upon exposure to acute experimental pain in the limb; however, we were unsure as to the direction of the change. We further aimed to determine whether there were tactile acuity changes at remote sites, and finally whether any changes returned toward baseline as pain resolved.

We provide the first evidence of improved tactile acuity in an acutely painful limb. One might expect such a finding, given the role of acute pain in promoting protective behaviour.[59] It seems intuitive that heightened tactile awareness might accompany acute pain, in line with evidence of enhanced responses in

Table 1

Pain-related variables.

Pain variable		Mean (SD)
Pain intensity	Dom. forearm	6.59 (2.3)
	Dom. prox. arm	6.52 (2.1)
	Contra. forearm	6.66 (2.5)
Pain unpleasantness		4.6 (4.9)*
Pain Catastrophizing Score		16.17 (10.3)

Pain intensity when corresponding site tested; sites tested in random order (all/10).
Pain unpleasantness on VAS 10-cm sliding scale (/10). Pain Catastrophizing Score/52, with higher score indicating higher level of catastophizing.
* Median and IQR reported.
Contra. forearm, contralateral forearm site; Dom. forearm, dominant forearm site; Dom. prox. arm, dominant proximal arm site.

Table 2

Tactile acuity (2-point discrimination values) for each body site.

Time	Site	Mean TPD in mm (SD)
Pre-CPT	Dom. forearm	31.64 (15.0)
	Dom. prox. arm	42.21 (15.1)
	Contra. forearm	33.19 (15.2)
During-CPT	Dom. forearm	28.33 (23.3)*
	Dom. prox. arm	37.21 (16.0)
	Contra. forearm	26.64 (10.4)
Post-CPT	Dom. forearm	28.33 (16.3)*
	Dom. prox. arm	36.93 (16.3)
	Contra. forearm	30.98 (2.8)

* Median and IQR reported.
Contra. forearm, contralateral forearm site; Dom. forearm, dominant forearm site; Dom. prox. arm, dominant proximal arm site; during-CPT, during immersion (pain); post-CPT, after recovery from the bath; pre-CPT, before immersion in the bath; TPD, 2-point discrimination test value, expressed in mm, millimetres.

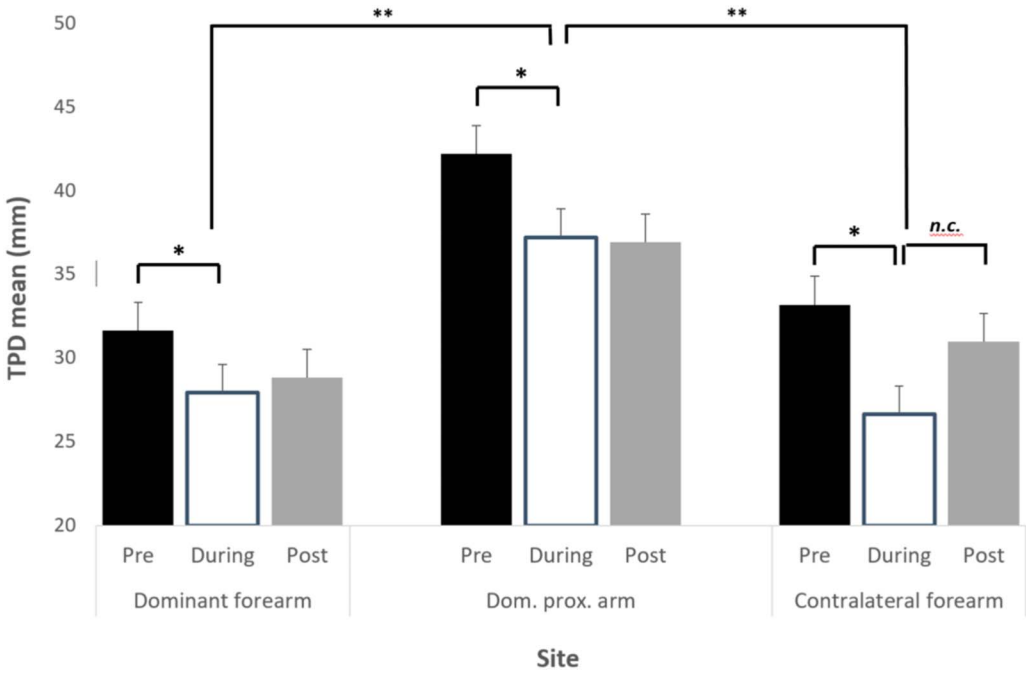

Figure 2. Tactile acuity in 3 sites over time. Two-point discrimination (TPD) data in mm, presented as mean (SEM). Note that TPD values decreased (ie, tactile acuity increased) during pain across all 3 sites, with the 2 forearms different to the proximal arm. *$P < 0.05$ Bonferroni corrected, **$P < 0.005$ Bonferroni corrected, n.c. $P < 0.05$, noncorrected.

perceptions more broadly in an acute pain state.[55,56] Interestingly though, our findings contrast with recent findings in experimentally induced low back pain, where tactile acuity deteriorated[3] and neck pain, where tactile acuity remained intact, although the authors hypothesised an improvement.[1]

The 2 notable differences between ours and the 2 existing experimental pain studies are the pain induction method and the body site tested. The former is arguably less important, given that Adamczyk et al. used the same method in both their studies and reported conflicting results.[1,3] It may be noteworthy that the pain intensity we report here (6.6) is considerably higher than that reported in both previous studies (3.8 in each). However, the conflict is likely to be better explained by the different anatomical sites tested. Baseline tactile acuity is higher in the limbs than in areas of the neck and trunk.[35] Possibly, in acute pain, extra protection is afforded to the limbs given that limbs are crucial for interaction with our environment, including in times of threat. This would explain why chronic limb pain exhibits a close relationship with distortions of body image, particularly tactile acuity.[18] Hubscher et al.[21] reported reduced tactile acuity with acute upper limb pain, but TPD was measured 48 hours after muscle pain induction. Indeed, our TPD improvement is likely transitory.

The 2 remote sites also improved in tactile acuity, with the most pronounced improvement in the contralateral limb. Although this is the first report of changed tactile acuity remote from an experimentally induced painful site, it is known that TPD is altered at remote sites in chronic pain.[6] Symmetry is a consistent feature across chronic inflammatory diseases such as osteoarthritis and rheumatoid arthritis.[52] There is compelling evidence to suggest that the symmetry is neurally mediated, at the spinal level.[23,26,52] Such a spinal cross-talk could explain our results, although the interpretation of "mirroring" or symmetry remains speculative without also testing lower limb sites. We did not test other modalities and thus cannot say that our effect was modality specific, nor did we test other sites in the contralateral upper arm and thus cannot say that our contralateral findings were topographically precise. However, the current findings align with reports of contralateral upregulation of oedema and inflammation, and such responses have been posited to reflect a biological protective role—preparing the contralateral limb for injury that has been sustained to the original site.[52] Although past literature focuses on the symmetry of inflammation, there is reason to speculate similar mechanisms with nociception, given that nociception can create inflammation.[45] Interestingly, there is

Table 3

Correlations between tactile acuity and pain measures.

TPD site tested	Pain intensity	Pain unpleasantness	Pain catastrophizing score
Dominant forearm	$\rho = 0.12$, $P = 0.53$	$\rho = 0.10$, $P = 0.6$	$\rho = 0.13$, $P = 0.52$
Dominant proximal arm	$r = 0.32$, $P = 0.09$	$\rho = 0.14$, $P = 0.47$	$r = 0.28$, $P = 0.15$
Contralateral forearm	**$r = 0.57$, $P = 0.001$**	$\rho = 0.32$, $P = 0.09$	$r = 0.37$, $P = 0.05$

Pain intensity when corresponding site tested; sites tested in random order (all/10).
Pain unpleasantness on VAS 10-cm sliding scale (/10).
All values reported as Pearson r correlation, or Spearman ρ for dominant forearm TPD values or pain unpleasantness values (non-normally distributed).
Correlations significant at $P < 0.05$ shown in bold.
TPD, 2-point discrimination test value.

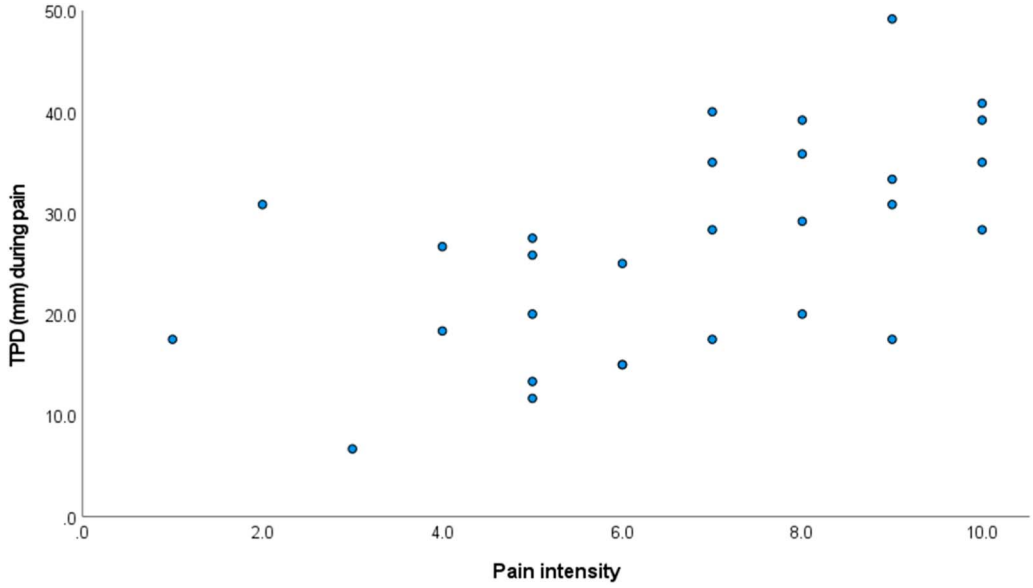

Figure 3. Correlation between tactile acuity in the contralateral forearm and pain intensity. A moderate positive correlation indicated that 2-point discrimination (TPD) values increased (ie, tactile acuity increased) with increasing pain ratings.

preclinical evidence that the findings in the contralateral or "mirrored" site are of a lesser magnitude and duration than the original lesion.[52] Here, we saw the most pronounced change in the contralateral limb. However, regarding duration, the contralateral limb recovered quickest; it was the only site to significantly recover tactile acuity within the 5-minute recovery.

Somewhat surprisingly across the sites we report only a trend toward recovery of tactile acuity after pain resolved. There was no recovery of tactile acuity at the proximal arm site. An improvement in pain has been found to be correlated with an improvement in tactile acuity in chronic limb pain.[41] Adamczyk et al.[3] found that tactile acuity restored after a 6-minute recovery period in their low back pain study; however, they did not investigate tactile acuity after pain had subsided in the neck.[1] We may have seen a significant resolution with a longer recovery. Further investigation could explore whether pain intensity relates to, or predicts, the extent of TPD recovery.

The correlations we report between tactile acuity and pain-related variables are intriguing. The only site to exhibit a significant relationship between pain intensity and tactile acuity was the contralateral forearm—and the correlation was moderate ($r = 0.57$). The contralateral forearm was also the only site to display a trend toward a relationship with PCS score ($r = 0.37$) and unpleasantness ($\rho = 0.32$). The direction of the correlation, whereby pain rating increased as tactile acuity worsened, is challenging to reconcile with the main finding. It is worth contemplating that subjects' attention was distracted away from the contralateral side, ie, towards the pain, explaining the correlation between pain and tactile acuity on the contralateral side, but this would be at odds with the improved tactile acuity contralaterally. We did not set out to investigate the pain intensity and tactile acuity relationship per se. Important work on spatial tuning in the spinal cord highlighted the need for research investigating the individual differences in pain sensitivity and how they may relate to spatial tuning specifically, ie, the precision of the receptive fields of wide dynamic range neurons responsible for pain and touch.[49] Interestingly, complex regional pain syndrome (CRPS), a chronic pain disorder of the limbs, is the only chronic pain disorder for which there is consistent evidence of correlation between pain and tactile acuity.[31,44,46]

Although it is unlikely someone in pain would seek therapy for altered tactile acuity, the issue of the onset of sensory dysfunction with pain seems important. Our findings bring to mind an important clinical correlate. Complex regional pain syndrome is a debilitating chronic limb pain disorder characterised not only by pain but also by multisystem dysfunction, including the somatosensory system—notably poor tactile acuity.[24,28] The distribution of pain and other features is not explained by peripheral nerve territories, and it is widely posited that the brain, specifically the functional representation of the painful limb in S1, is associated with the spread of pain.[34,36,57] There is brain imaging evidence of not only altered S1 representation of the CRPS-affected limb[9] but also, importantly, change to the S1 representation of the contralateral "healthy" limb.[10] The apparently bilateral change is thus far unexplained by simple neurochemical mechanisms in the cortex.[24] The possible involvement of the spinal cord cannot be ignored. Marked *bilateral* changes (amplitude and duration increases) in flexor efferent responsiveness, as well as expanded contralateral receptive fields, have resulted from unilateral injury in animals[43,62] and may apply to the contralateral findings here.

Our findings are robust for several reasons. The sample size was determined a priori to test our primary hypothesis. We randomised sites and counterbalanced sequences (commenced with TPD ascending or descending sequence), and all testing was conducted by one researcher (J.P.S.).[7] Our subjects consistently experienced pain, at an intensity consistent with the chronic pain literature.[5] Crucially, pain persisted throughout testing. As well as establishing the time point at which to measure TPD, our rigorous piloting determined that tactile sensitivity remained intact throughout testing—as has been recommended.[1] That tactile acuity improved rather than deteriorated is further evidence that the cold-water stimulus did not hinder basic sensory capacity.

Some limitations need to be acknowledged. The primary testing site was not over the site of maximal pain but proximal to the immersed hand at a standardised site. Although testing over the painful area was not feasible with the cold-water bath, it is noteworthy that many chronic pain studies test TPD at standardised sites rather than at the most painful site.[6] We maintain

that the most likely explanation of our findings is improved tactile acuity in the painful *region*, rather than in an adjacent non-painful *site*—the latter would make it difficult to explain the contralateral limb findings. The TPD testing tools were made in-house, were not validated, and were set at 5-mm increments; however, their design is simple, and their distances were checked against commercially available callipers. Although one researcher collected all data, it is important to note that they were not blinded. Our correlation findings were unexpected, and the study was not designed to investigate the pain and tactile acuity relationship question specifically. To fully investigate neurological mechanisms, further testing sites are needed. Inclusion of a nonpainful cold condition may help elucidate the effect of arousal on tactile acuity as distinct from pain—a question of great importance in the pain field more broadly.[25]

Our study is the first to demonstrate an improvement in tactile acuity in acute experimental pain not only in the painful limb but also at a symmetrical site on the nonpainful limb. Although possibly reflecting a protective nervous system response, future work should address such mechanisms, together with a more robust investigation of the recovery of sensory changes as pain resolves. Such investigations will aid our understanding of the crucial role of sensory processing in chronic pain states.

Disclosures

The authors have no conflict of interest to declare.

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Author contributions: J.P.S., M.T. and F.D.P. designed the experiment; J.P.S. recruited subjects and collected data; J.P.S., M.T., and F.D.P. analysed data; J.P.S., M.T., H.L.S., and F.D.P. prepared the manuscript.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A201.

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