



Original experimental

Comparison of spatial summation properties at different body sites

Maleea D. Holbert^a, Ashley Pedler^a, Danny Camfermann^b, Daniel S. Harvie^{a,*}^a Recover Injury Research Centre, Centre of Research Excellence in Road Traffic Injury, Menzies Health Institute QLD, Griffith University, Gold Coast, Australia^b Sansom Institute for Health Research, Division of Health Sciences, University of South Australia, Adelaide, Australia

HIGHLIGHTS

- We compared spatial integration of noxious stimuli among body regions.
- Distance-based and area-based spatial summation did not differ by region.
- Anatomical variance in spatial summation cannot account for spinal pain prevalence.
- Distance-based summation was greatest at 15- and 20-cm separations.

ARTICLE INFO

Article history:

Received 16 May 2017

Received in revised form 3 July 2017

Accepted 7 July 2017

Available online 9 August 2017

Keywords:

Spatial summation

Distance-based spatial summation

Chronic pain

Low back pain

Neck pain

Sensory processing

ABSTRACT

Background and aims: The nociceptive system appears to have evolved a range of protective characteristics that are of great interest in understanding both acute and chronic pain. Spatial summation is one important characteristic, whereby increasing area of a stimulus, or distance between multiple stimuli, results in more intense pain—not only greater area of pain. One of the mysteries of chronic pain is why spinal pain is so prevalent relative to pain at other sites. Since pathological tissue models have failed to fully explain spinal pain, we theorized that body region specific differences in sensory processing—such as a greater propensity for spatial summation—may help to explain its vulnerability. We aimed to examine this by comparing the properties of summation at different body parts: the dorsal forearm, neck, and back.

Methods: Spatial summation of pain was investigated using noxious intra-dermal electrical stimuli in healthy pain-free adults (14 males, 6 females), and the perceived pain intensity was rated on a 0–100 pain scale. Area-based stimulation was investigated by doubling the stimulation area with the addition of a second electrode placed adjacent to the first. Distance-based summation was investigated by randomly varying the separation distance between paired noxious electrical stimuli at separations of 0, 10, 15, and 20 cm.

Results: This study demonstrated that the properties of area- and distance-based summation are uniform across the neck, back, and forearm in healthy adults. Spatial summation of pain was also found to be greatest at 15- and 20-cm paired separations for all body regions tested, confirming that noxious information can be integrated over an extensive anatomical area.

Conclusion: Data from this investigation refutes the thesis that spatial summation of pain may be a contributing factor for the reported difference in chronicity rates between spinal and peripheral sites. It remains, however, a potentially important mechanism by which noxious inputs from multi-level pathology might integrate and contribute to pain.

Implications: While data from this project suggest that there are no regional differences in the properties of spatial summation of noxious stimuli, regional differences in other characteristics of the nociceptive system may yet provide insight into why some spinal pain is so highly prevalent; nociceptive distance-based summation may be highly relevant where two or more conditions co-exist in close proximity.

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1. Introduction

Chronic low back pain affects 16.3% of general [1] and 25.4–49% of older populations [2,3]. Similarly, neck pain reportedly affects 22% of females and 16% of males [4,5]. In contrast, the incidence

DOI of refers to article: <http://dx.doi.org/10.1016/j.sjpain.2017.07.018>.

* Corresponding author at: Griffith University, Gold Coast Campus, Southport, QLD 4222, Australia.

E-mail address: d.harvie@griffith.edu.au (D.S. Harvie).

of chronic arm and hand pain is only 4.1% [6]. Decades of research attempting to explain the greater prevalence of spinal pain with respect to pathological tissue models have not provided a convincing explanation. For example, degenerative disc changes are not a risk factor for neck pain [7] and tissue abnormalities often blamed for pain occur at similar rates in people without pain [8,9]. Notwithstanding the limitations of imaging techniques, tissue factors at best provide an incomplete picture of the cause of ongoing neck pain [10].

There is therefore interest in other factors that might explain the high rates of spinal pain. One possibility that has received little attention, is that the properties of the nociceptive system governing the spine, are different to those that governing regions less vulnerable to chronic pain. Reid et al. [11] found that SS of paired noxious stimuli on the arm occurs at separations of up to 10 cm, with the maximum magnitude at 5 cm, and decreasing in magnitude at 20 cm. Quevedo and Coghill [12] also found distance-based summation of pain to be most pronounced at 5- and 10-cm separations, however, also found evidence that spatial summation (SS) can occur up to 40 cm separations using heat stimuli. However, not all of the data are consistent, with other studies showing spatial summation occurs at 30-cm separations, but is abolished at 40-cm separations [13]. We aimed to examine whether there are differences in the spatial integration of noxious sensory information between different body areas, and more specifically, between peripheral sites such as the arm (where persistent pain problems are rare) and spinal regions (where persistent pain problems are in epidemic proportions). It was hypothesized that the maximum distance at which two noxious stimuli summate at the dorsal arm will be less compared to spinal areas. Further, it was hypothesized that the magnitude of area and distance-based summation would be greater at spinal sites relative to the arm.

2. Materials and methods

2.1. Participants

Subjects were recruited via a purposive sampling method; through the use of posters and fliers advertised around Griffith University Gold Coast campus. Exclusion criteria included individuals suffering from chronic or acute pain conditions, a history of arm, neck, or back pain requiring treatment in the preceding six months, systemic diseases such as diabetes, peripheral nervous system disorders, mental illnesses including somatoform disorder and conversion disorders, and individuals who take narcotic pain medications. The sample size was chosen to ensure adequate (80%) power to detect a small to medium effect ($F=0.25$) for the main analysis [3(Region: Back vs. Neck vs. Hand) $\times$ 5(Stimulus separation: 0, 10, 15, 20 RM ANOVA)]. These values were selected based on a previous investigation into nociceptive SS which used noxious electrical stimuli in humans, with an a priori power calculation for a repeated measures experimental design with power equal to 80% and a moderate effect size [11]. Twenty healthy, pain-free individuals (6 females, mean age = 23.3 years, SD = 4.46) volunteered.

2.2. Stimulus material

Two DS7A High Voltage Constant Current Stimulators (Digitimer Ltd, Welwyn Garden City, UK) were used to produce paired electrical stimuli. Spatial summation of pain was assessed using paired stimuli of equal intensity to skin overlying the cervical and lumbar spine, and dorsal right forearm, at separations of 0, 10, 15, and 20 cm (Fig. 1). Participants were asked to rate pain intensity using a 0–100 numeric rating scale (NRS); where 0 = “no pain sensation” and 100 = “worst pain sensation imaginable” after each

administered transcutaneous electrical stimulus (TES). The spatial configuration of the electrodes was counterbalanced within each region to control for any proximal-distal gradients in nociceptive distribution. Custom made intra-dermal electrodes were used for application of painful electrical stimuli. The design was based on the intradermal electrodes employed by Inui and Kakigi [14]. The electrode employs a 10 mm gold cup EEG electrode (Genuine Grass®, USA) with a modified Ambu® Neuroline stainless steel monopolar needle electrode positioned in the center, to act as the anode. The resulting configuration is a concentric bipolar electrode with a distance of 5 mm between anode and cathode, that result is a focused activation of free nerve endings in the superficial skin, and thus a relatively nociceptive-specific stimulation. The custom electrode was authorized for research after a Risk Assessment evaluation at the University of South Australia.

2.3. Protocol

Informed consent was obtained from all participants subsequent to screening and explanation. Subjects then filled out a demographic questionnaire and the pain catastrophizing scale (PCS). Participants were not informed about the experimental stimuli contingencies or the hypotheses. To ensure that subjects were naïve to the hypotheses of the study, they were informed that the study was investigating properties of pain perception and that this would involve rating how painful a series of stimulations are on their neck, back, and arm. The experiment was considered to be of minimal risk to participants, and subjects were compensated with a \$20 gift voucher for their involvement. Moreover, participants were informed they could withdraw from the study at any time with no penalty, and would still receive payment for their time; one participant withdrew and their data were discarded.

2.4. Experimental environment

Subject testing was carried out in a quiet laboratory with a maintained internal temperature ($22 \pm 2^\circ\text{C}$), lighting, and personnel throughout testing. Participants were placed in the prone position for spinal measurements (neck and lower back) and supine position when assessing the dorsal forearm.

2.5. Pretest assessment

Prior to the assessment of SS, the stimulus intensity required to elicit a pain response rated as 50 on the 100-point NRS was determined, using increasing stimulus intensities. Using the most proximal or caudal electrodes, with initial stimulation intensity of 4.0 mA and pulse duration of 200- μs , stimulation intensity was increased in 4.0 mA increments until the participant indicated that stimulation was moderately painful, experiencing pain that is equivalent to 50 out of 100 of the NRS; this scale is anchored at 0 – indicating no pain sensation and 100 – which indicates the worst pain imaginable. The strength of the single TES for all locations was individually calibrated such that it was based on the subject's perceived pain (50/100) as opposed to the magnitude of the electrical current. This acted to account for differences in sensitivity across each region.

2.6. General procedure

A within-subjects design was used for this study. All participants had SS measurements recorded from the three testing sites. Following the thresholding procedure, participants received 15 suprathreshold TES (12 paired stimuli and 3 single stimulus) in randomized order at each body region. The order of body region was also randomized. The experimenter stood alongside the participant

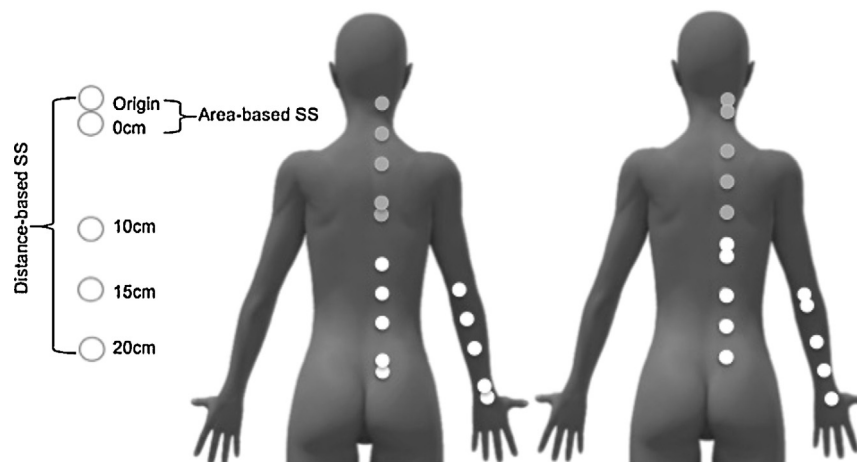


Fig. 1. Electrode placement for the neck, lower back and forearm. The person exhibits the electrode arrangement using a distal origin electrode, while the right shows the arrangement using a proximal origin electrode. The far left of figure shows the electrode configurations used to assess area- and distance-based SS of pain.

during testing and used a switch to manipulate which electrodes were activated, and a manual control to adjust intensity. The paired electrical stimuli were triggered by a single switch synchronized by a communication cable to ensure simultaneous delivery.

Inter-stimulus intervals of 15–20 s were provided between paired noxious stimuli aiming to minimize sensitization and habituation that may occur as a consequence of repeated painful stimulation. All participants were given the same instructions during the experimental protocol: (1) They will receive a number of paired electrical stimulations, (2) they will be required to report the level of pain experienced using a 0–100 NRS for pain, and (3) they must focus their gaze on a fixation point placed on the ground or ceiling (to control for spatial attention). To assist in controlling for the effects of participant fatigue, the number of stimulus separations was limited to four. To control for surprise, or anticipatory confounds, participants were verbally warned before each TES; the experimenter counted down from three prior to administering the electrical stimuli, “three, two, one, and now”.

2.7. Statistical analysis overview

2.7.1. Effect of stimulus separation on evoked pain

To determine the effect of separation distance between electrodes on NRS scores and within subject differences in SS at different body sites, a mixed model analysis was performed. Through the inclusion of random effect modeling for slope and intercept, the mixed model approach accounts for variances in the starting point (intercept) and change over repeated measures (slope) within individual participants. In addition this modeling approach does not assume that repeated measures taken from the same participant are independent. These features make the mixed model approach preferable to the general linear model in repeated measures analyses. The dependent variable used in the current study was the change in NRS reported at each electrode separation (0 cm, 10 cm, 15 cm, 20 cm) in comparison to stimulation using the origin electrode only. The factors included in the model were electrode separation (5 levels: origin, 0 cm, 10 cm, 15 cm, 20 cm) and body site (3 levels: arm, back, neck). Alpha was set at $p = 0.05$. Data was analyzed using IBM SPSS, version 23 (IBM, New York). The level of significance was set at $p < 0.05$ for all analyses.

2.7.2. Spatial summation by body region

The interactive effect of body site * electrode separation on NRS was analyzed to determine differences in SS between body sites, and this acted to answer our primary research question. The NRS

reported during stimulation with a single electrode (origin) was included in the model as a covariate. Subject and slope (change in NRS over increasing electrode separation) were entered as random effects in the model. Where significant main effects were detected, pairwise comparisons with Bonferroni corrections were performed to identify where differences were observed.

3. Results

3.1. Subjects

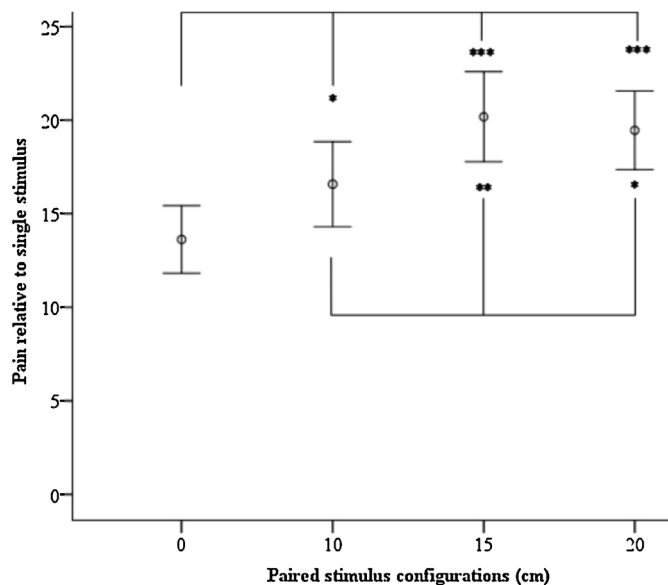
A total of 20 healthy individuals participated in this study. Mean (SD) age = 23.30 (4.46); 6 females; and 85% right upper limb dominance. Table 1 presents demographic and anthropomorphic subject information. Participants represented the following ethnic groups: Caucasian Australian ($n = 11$), Japanese ($n = 1$), Chinese ($n = 1$), Caucasian European ($n = 5$), Hispanic ($n = 1$), and Caucasian North American ($n = 1$). The mean body mass index (BMI) of the sample was 21.88 (SD = 2.74). Anthropometric measures such as height and weight were recorded for each participant as a high body fat ratio (BFR) has been shown to influence some measures of sensory function such as tactile acuity [15,16]. The vast majority of participants were within a healthy weight range; 85% of subjects had a BMI between 18.5 and 24.9; one participant was categorized as marginally overweight (BMI of 25.5); and two participants were classified as underweight (BMI of 15.61 and 16.85, respectively).

3.2. Spatial summation overall

Mixed model analysis showed a significant main effect of electrode separation distance on NRS ($F(4.0, 228.0) = 155.0, p < 0.001$). Pairwise comparisons revealed that all paired electrode separations (0, 10, 15, and 20 cm) evoked statistically greater pain intensity than TES at the origin electrode alone ($p < 0.001$ for all, see Fig. 2). That is, perceived pain intensity was greater for all paired stimuli in comparison to a single stimulus of equal intensity. Observation of the

Table 1
Participant demographic and anthropomorphic measures.

Gender	Height (M, SD)	Weight (M, SD)	BMI (M, SD)	Age (M, SD)
Male ($N = 14$)	180, 7.80	74.36, 8.41	22.83, 1.83	24.14, 5.05
Female ($N = 6$)	165, 4.20	53.08, 9.58	19.47, 3.11	21.33, 1.63
Total ($N = 20$)	175.50, 9.80	67.98, 13.14	21.88, 2.74	23.30, 4.46



*** $p < 0.001$, ** $p = 0.001$, * $p < 0.05$

Fig. 2. Presents pain ratings for paired stimuli at 10, 15, and 20-cm separations relative to a single stimulus (i.e. paired stimuli at a 0-cm separation) ($N=20$). Mean (circles) and 95% confidence intervals (error bars) for pain, relative to a single stimulus, are shown across different spatial configurations. The separation distance between paired electrical stimulation significantly affected pain ratings ($p < 0.001$). The paired 0-cm separation was significantly different from the other paired electrode configurations at 10, 15, and 20-cm separations ($p = 0.018$, $p < 0.001$, and $p < 0.001$, respectively). In addition, the paired 10-cm separation was significantly different from the 15- and 20-cm paired stimuli configurations ($p = 0.001$ and $p = 0.023$, respectively), and there was no difference in SS between the 15 and 20 cm paired stimuli ($p > 0.99$). *** $p < 0.001$, ** $p = 0.001$, * $p < 0.05$.

graph suggested that distance-based SS of pain was greatest at the 15- and 20-cm configurations (see Fig. 3).

3.2.1. Spatial summation by body region

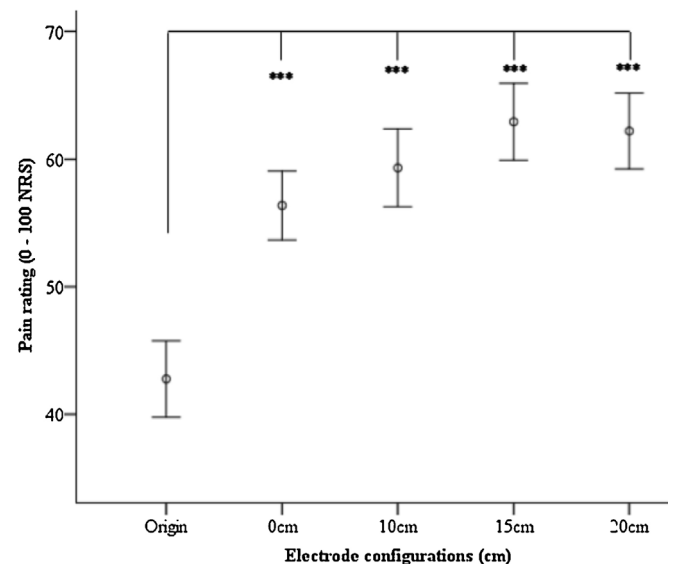
The 3(Body site) $\times$ 5(Electrode separation) Repeated measures ANOVA did not reveal an overall effect ($F(2.0, 38.0) = 0.561$, $p = 0.575$), or interactive effect of electrode separation $\times$ body site ($F(8.0, 228) = 0.585$, $p = 0.790$) (see Fig. 4). As there was no significant influence of body region found within this study, pain ratings for paired stimuli relative to a single stimulus were averaged across body sites for further analysis.

4. Discussion

This project investigated regional differences in the properties of SS of noxious stimuli between the neck, low back, and arm. Our hypothesis that the properties of SS would differ as a function of body site was refuted in that no significant differences in area- or distance-based SS was found between the three sites examined. These findings move the field forward by providing evidence against the thesis that increased prevalence of low back and neck pain might be explained by anatomical differences in the properties of spatial summation.

4.1. Anatomical differences in sensory function

The integrative characteristic of the nociceptive system was compared between the neck, back, and right forearm, aiming to determine if nociceptive SS could be a causal factor in the high chronicity rates of neck and back pain. If spinal regions were to have a unique propensity towards spatial summation of noxious input, this may have assisted to explain the higher prevalence of spinal



*** $p < 0.001$

Fig. 3. Presents pain ratings from single and paired stimuli across the neck, lower back, and forearm ($N=20$). Mean (circles) and 95% confidence intervals (error bars) for pain, scored on a 0–100 numeric rating scale (NRS), are depicted across different spatial configurations. Pain ratings for the single stimulus (origin electrode) were significantly different from all paired configurations at 0, 10, 15, and 20 cm separations ($p < 0.001$) and this trend is uniform across all body regions tested (right dorsal forearm, neck, and lower back). *** $p < 0.001$.

pain. The hypothesis was considered particularly plausible because it has been shown that there are differences in sensory processing of tactile input between different areas of the body, for example, tasks testing ability to discriminate between various letters drawn on the skin (tactile graphesthesia tasks) are performed with less accuracy and precision on the lower back relative to the forearm or abdomen [17]. Since accuracy in the tactile system also depends on ability to discriminate between stimuli (rather than integrate them), it was proposed that areas where tactile tasks were shown to have less discriminative capacity would show greater integrative tendency (i.e. greater propensity for spatial summation).

4.2. Properties of spatial summation

Overall pain ratings were significantly affected by the stimulus configuration. These data are consistent with the nociceptive phenomenon known as SS of pain; where an increase in the area of, or distance between, noxious stimuli results in increased intensity of pain, not only area of the pain. As expected, pain was lower for a single stimulus than it was for any of the paired stimuli confirming the area-based summation phenomena. Further, the pain ratings for the 10, 15 and 20 cm separations were greater than the 0 cm separation, confirming the distance-based phenomena. Moreover, pain ratings for the paired 10 cm separation were significantly lower in comparison to the 15 and 20 cm paired configuration. The maximum distance at which distance-based summation occurs, however, cannot be inferred from this study since summation was still observed at the 20 cm separation relative to the 0 cm separation. Our data does, however, provide some progress towards understanding the distance at which two stimuli summate maximally. That is, the 15 and 20 cm distance showed significantly greater summation relative to the 10 cm separation, with the peak appearing at 15 cm. This remains a debate in the broader literature, with a number of studies indicating that SS of pain is greatest for 5- and 10-cm separations, and decreases at 20-cm separations. However, previous studies have not frequently assessed the 15 cm separation, and thus we had higher resolution between 10 and

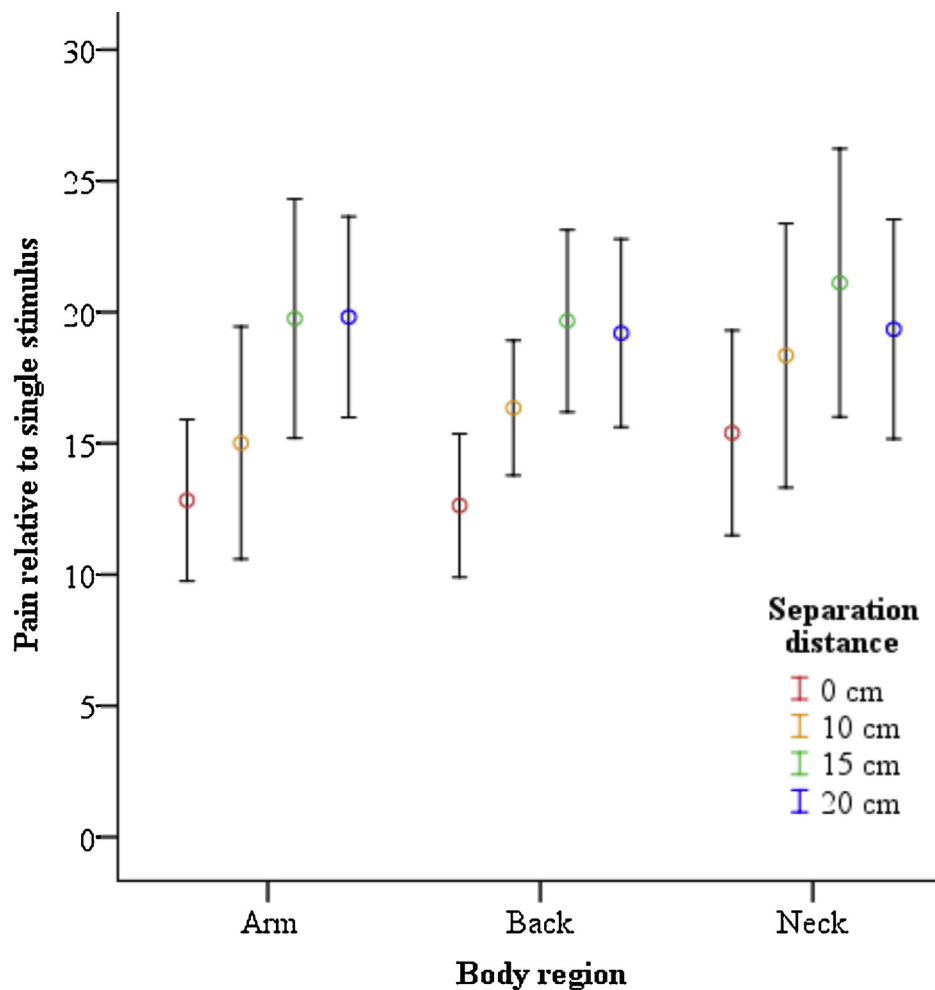


Fig. 4. Presents pain ratings for paired stimuli relative to a single stimulus (i.e. paired stimuli at a 0 cm separation) within the right dorsal forearm, lumbar spine, and cervical spine ($N=20$). There was no difference in distance-based SS of pain between the arm, neck, and back ($p=0.790$). SS of pain was greatest at the paired 15-cm configuration for both neck and back regions, and greatest at 20-cm separation for peripheral sites, however this result was not significant and statistically there was no difference in pain between 15- and 20-cm separations.

20 cm. Notwithstanding this factor, we highlight some inconsistency in the literature.

4.3. Clinical relevance

While anatomical explanations fail to account for the prevalence of back pain compared to pain in other body regions, neurophysiological explanations are also insufficient. While regional differences in properties of SS appear unable to assist in this explanation, spatial summation remains a potentially relevant contributor to spinal pain. That the lumbopelvic region appears prone to multiple pathologies in spatial proximity, spatial summation may contribute to multiple minor problems, resulting in debilitating pain. For example, Pelvic pain may involve endometriosis, ovarian cysts, lower back, and sacroiliac joint pain, and be exacerbated by cyclical/menstrual pathology. Such conditions may be tolerable when occurring in isolation, however may become debilitating when comorbid. So far evidence suggests spatial summation can occur at distances up to 20 cm (current study), 30 cm [13], and even 40 cm [12]. These distances could enable summation across multiple spinal segments, sacroiliac joint structures, and pelvic organs.

4.4. Limitations

The tested sample population was young and fit, and it is possible that the properties of spatial summation are distinct in other

healthy or clinical populations. Nonetheless, examining sensory processes in healthy individuals provides important insight into nociceptive mechanisms. Furthermore, the disproportionate number of males (14 males and 6 females) within the sample may not account for gender associated physiological differences. As noted, the current study limited the separations of electrodes to 20 cm. As such it is possible that differences in spatial summation between body areas exist beyond this distance.

5. Conclusion

Our analysis showed there were no significant differences in summation of pain between spinal and peripheral body areas, or within spinal regions (i.e. between the cervical and lumbar spine). Spatial summation of pain was found to be greatest at the 15- and 20-cm paired separation for all body regions tested, confirming that noxious information can be integrated over an extensive anatomical area, and confirming that it may be relevant where two or more conditions co-exist in close proximity. While we conclude that there are no regional differences in the properties of spatial summation of noxious stimuli, regional differences in other characteristics of the nociceptive system may yet provide insight into the high prevalence of spinal pain.

Ethical issues

Ethical approval was obtained from the Griffith University Human Research Ethic Committee (GU Ref No: 2016/176). The consent mechanism used in this study followed the guidelines of the National Statement on Ethical Conduct in Research Involving Humans, which was outlined in the Griffith University Human Research Ethics Manual.

Conflicts of interest

The authors declare no conflicts of interest.

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