

Original Reports

Spatial Summation of Pain in Humans Investigated Using Transcutaneous Electrical Stimulation

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Abstract: Spatial summation of pain is well accepted but surprisingly understudied. Area-based summation refers to the increase in pain evoked by increasing the area of stimulation. Distance-based summation refers to the increase in pain evoked by increasing the distance between multiple stimuli. Although transcutaneous electrical stimulation has several advantages over other experimental pain paradigms, whether or not this modality evokes spatial summation remains unknown. We aimed to answer this question in order to lay the foundation for critical studies of spatial summation. Twenty-five healthy participants received stimuli on their forearm, and the primary outcome, pain intensity, was compared across 5 spatial configurations—1 with a single stimulus and 4 paired configurations at 0-, 5-, 10-, and 20-cm separations. Importantly, the potential confounder of a proximal-distal gradient in nociceptive sensitivity was removed in this study. Pain intensity was higher in response to the paired stimuli than in response to the single stimulus ($P < .001$), and the paired stimuli separated by 5, 10 and 20 cm, evoked greater pain than stimuli at a separation of 0 cm ($P < .001$), thus confirming both area- and distance-based summation, respectively. We conclude that transcutaneous electrical stimulation is appropriate for future investigations of spatial summation.

Perspective: Distance-based summation is likely implicated in some clinical pain. However, current understanding for spatial summation is limited. This study demonstrates that transcutaneous electrical stimulation is safe, feasible, and valid for future investigations of spatial summation and will allow critical questions to be answered.

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Key words: Spatial summation, distance-based summation, noxious, pain, electrical stimulation.

Spatial summation (SS) of pain was first clearly shown when increasing the area of suprathreshold noxious thermal stimulation clearly increased the intensity of the pain evoked, not just the area of the pain.²⁴ Two

types of SS are now established: 1) SS with increased area of a single stimulus—area-based SS,^{7,10,14} and 2) SS with multiple adjacent stimuli moved further apart—distance-based SS.^{8,24,26,29} SS has been proposed as an underlying mechanism for certain clinical pain conditions, for example, fibromyalgia.²⁹ The proposed mechanisms of SS are as follows: peripheral integration of the nociceptive input, such that greater numbers of primary nociceptors are activated; enhanced nociceptor recruitment at the dorsal horn by activation of multiple nociceptive receptive fields; and sensory-cognitive interactions.²⁶

Although SS of pain is well accepted, so too is conditioned pain modulation (CPM), which also involves multiple noxious stimuli delivered at separate locations.^{9,31} We recently undertook a systematic review²⁷ to evaluate the evidence concerning the influence of stimulus modality on SS and the extent of its spatial

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boundaries. That is, at what spatial separation does SS give way to CPM? Surprisingly, a comprehensive search revealed only 8 published studies that had investigated distance-based SS of noxious stimuli in humans, and only thermal and mechanical stimuli had been used. One study delivered identical and paired thermal stimuli on the arm and concluded that SS is evident at a separation of 5 cm and CPM at a separation of 30 cm,⁹ but it was not able to comment on the boundary between the 2 effects.

Transcutaneous electrical stimulation (TES) has advantages over other experimental pain paradigms; for example, it is safer, and stimulus parameters can be more precisely controlled.^{2,3} However, it also has disadvantages; for example, it activates both local nociceptors and tactile receptors, as well as axons.³ Bearing these limitations in mind, TES remains very well suited to interrogating the nociceptive system in humans. Precise modulation of stimulus parameters should help us to better understand the relative and thus far only hypothesized mechanistic contributions to SS. Such knowledge may have critical implications for our understanding and treatment of clinical pain conditions. For example, that disturbances in attention have been shown to abolish SS^{9,25} supports the view that in conditions in which distance-based SS is implicated,¹² modulating attention may have an effect on clinical pain intensity. Although such proposals are premature, the current study was designed to lay the foundations for this line of research by determining the characteristics of SS in response to TES in healthy, young adults. We tested 3 hypotheses: 1) that the pain elicited by paired electrical stimulation (ES) would be greater than that elicited by a single stimulus of equal intensity (area-based SS); 2) that pain would be greater for 2 stimuli at a separation of 5 cm than for identical stimuli at a separation of 0 cm (distance-based SS); and 3) that pain would be lower at a separation of 20 cm than at 5 cm (reflecting the spatial boundary of distance-based SS).

Methods

Participants

A convenience sample of 25 healthy, Caucasian volunteers participated (mean \pm SD = 23 \pm 3 years; 13 male). The sample size was based on pilot studies and an a priori power calculation for a repeated-measures design, to detect a moderate effect ($F = .25$) with 80% power and significance set at $\alpha = .05$. Participants were recruited via posters displayed at the University that detailed the study's duration (approximately 1.5 hours), compensation for time (\$20/h), inclusion criteria, and general aim. To ensure that participants were naïve to the study hypothesis, they were told that the study was investigating properties of pain perception and that this would involve their rating how painful a series of stimulations on their arm felt. Participants were aware that they were able to withdraw from the experiment at any time and that they would still be compensated for their time; no participants withdrew. No further directions

or assessments regarding preparation prior to the study were performed. Because it is unknown if any processing differences or biases exist for nociceptive information between the 2 hemispheres (or sides of the body), as well as if there are differences related to a person's hand dominance, only right-handed participants were included, and all experimental procedures were performed on the right arm. Participants were excluded if they were suffering from any acute or chronic pain, as detailed on the recruitment poster. All of the participants provided written informed consent. The experimental protocol was approved by the institutional human research ethics committee.

Experimental Environment

Each test was conducted in a quiet laboratory with constant room temperature (22°C), lighting, and personnel throughout testing. The participants were seated at a table with their right arm positioned in front of them (Fig 1). Uninterrupted access to the arm was established for the testing, and all equipment remained in situ for the duration of the experiment.

Stimulus Materials and Apparatus

Two constant current stimulators (Model DS7A; Digi-timer, Welwyn, United Kingdom; 200 μ s pulse duration, 0–99.9 mA current) produced the TES. Five pairs of transcutaneous electrodes (1-cm diameter, silver–silver chloride sintered), applied to the skin with adhesive washers, were used to deliver the electrical current to the participant's right dorsal forearm. The skin was prepared using an abrasive gel and gauze to remove any foreign particles, and cleansed with an alcohol wipe. Conductance gel was inserted under the electrode once it was fixed to the skin using a blunt syringe. Four testing locations at 0, 5, 10, and 20 cm were measured and marked on the skin (Fig 2). Only 4 locations were tested to constrain the experimental session and to ensure that the participants maintained concentration throughout the testing session. Further, it was not possible to go beyond 20 cm without crossing either the wrist or elbow joint, which would have run the risk of introducing other confounds such as proximity to a joint and the related changes in spatial localization¹³ and distance perception¹¹ across a joint. Because pain thresholds may vary as a function of the distance from the body,^{1,15,16,18,30} the origin of the testing zone (the 0-cm marking) was alternated proximally (situated nearer to the center of the body, or close to the elbow) or distally (situated away from the center of the body, or close to the wrist) for each consecutive participant (Fig 2).

Pretesting Assessments

At the most proximal location, and starting at 5.0 mA (200- μ s pulse duration, 300 V), the electrical current was increased in 2.0-mA increments until the participant perceived the stimulation to be painful. An inter-stimulus interval of at least 15 seconds was used throughout testing. The participants had to verbally report a pain score immediately following stimulation,

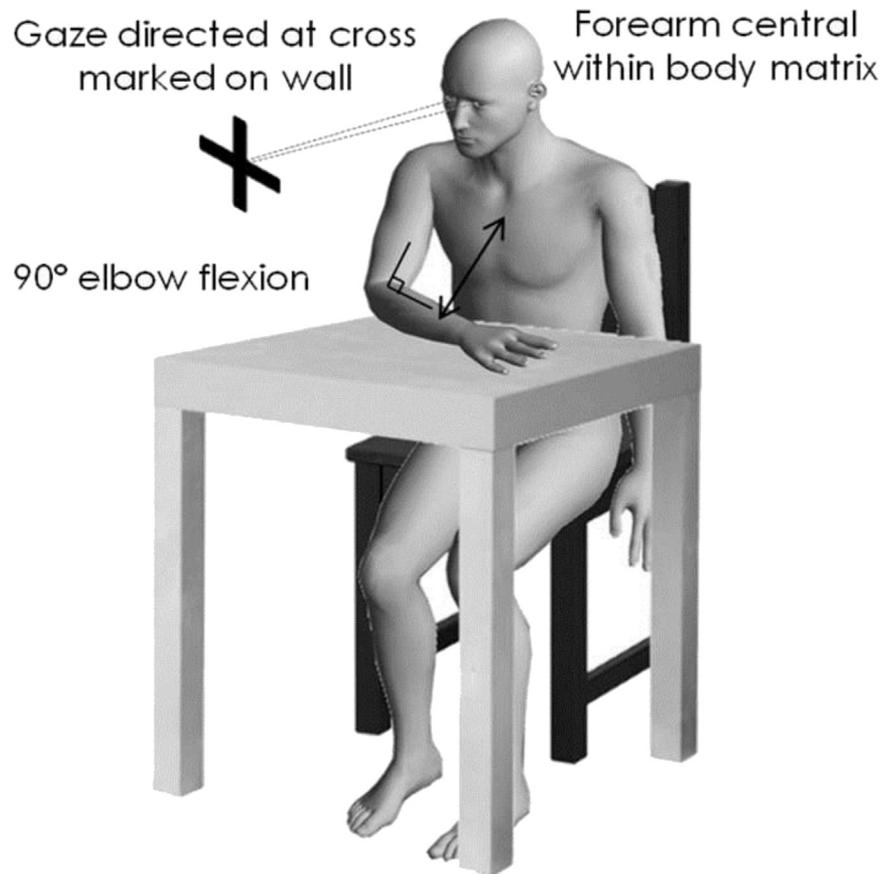


Figure 1. Participant positioning. Participants were seated in a quiet room and asked to maintain their gaze on a black cross marked on the wall in front of them. The right arm rested on the table in 90° elbow flexion and was directly parallel to their chest.

using a 0 to 100 numeric rating scale (NRS), where 0 represents no pain at all and 100 represents the worst pain imaginable. When the participant felt confident rating the ascending stimuli, a constant intensity for the single stimulus was determined. The intensity of the single stimulus for all locations was based on the participant's reported pain rather than on the magnitude of the electrical current delivered. Moreover, although the current level of the single stimulus at each location on the forearm could vary, the pain intensity was consistent, thus accounting for any site-to-site differences in skin sensitivity or thickness. In consideration of interindividual differences in scale use as well as differences in pain sensitivity, there was no upper limit for the pain rating of the stimulation intensity, and a rating at or above 20 was accepted. For the majority of the participants ($n = 23$), a pain rating between 20 and 35 on the NRS (mean, 25.6) was used; however, for 2 participants whose perception of the nonpainful stimulus becoming painful was very sudden, their pain rating was toward the higher end of the NRS (60/100 for both), despite minimal increase in the current intensity. Provided that the participant was willing to tolerate the stimulation intensity for the remaining experimental session (24 stimulations), these higher pain ratings were accepted. The intensity of the proximal single stimulus was then matched at each of the subse-

quent locations by increasing or decreasing in 1.0-mA increments until the participant perceived the single stimulus to be equally painful at each location. The proximal location was restimulated as required to ensure that the participants could remember the desired perceptual intensity. At a minimum, 3 consecutive trials of a set current that elicited a pain rating equal to that of the most proximal location was used to determine the current delivered at each location. The current levels for each location were then recorded by the experimenter to be used within the experimental session. Our approach ensured that all of the stimuli were contextually (electrode size and appearance) and perceptually identical.

Experimental Protocol

Reference electrodes located at the proximal location for proximal participants (Fig 2A), and at the distal location for distal participants (Fig 2B), were activated simultaneously with a set of electrodes at 1 of the other 4 locations (0, 5, 10, or 20 cm away from the reference electrode) to create the paired stimuli. In this way, the reference electrode paired with the adjacent electrodes at a separation of 0 cm targeted area-based SS, and the other electrodes targeted distance-based SS (see Fig 2).

In a repeated measures design, 24 paired stimulations, 6 at each separation, were delivered in a randomized

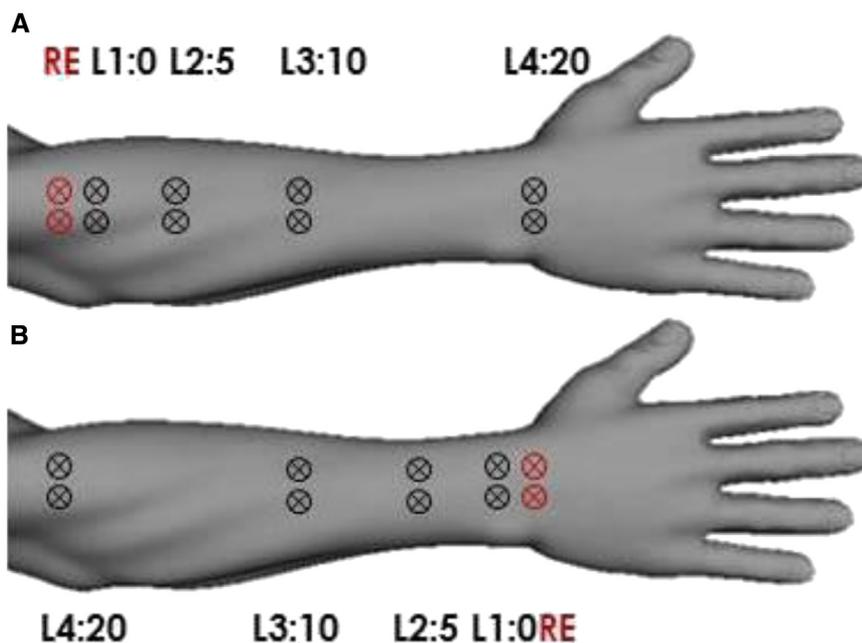


Figure 2. Electrode placement. There were 2 patterns: one with the reference electrode (RE) located proximally, close to the elbow (A), and one with it located distally, close to the wrist (B). The electrodes were labeled L1:0, L2:5, L3:10, and L4:20, respectively, to describe their location and separation from the RE.

counterbalanced order, with an interstimulus interval jittered between 15 and 20 seconds. This design aimed to minimize any effects of sensitization or habituation to the repeated stimuli; visual inspection of the data did not suggest that either one of these mechanisms significantly affected the pain ratings. All of the electrodes remained in situ and were covered by a towel throughout the entire experiment. The participants were blinded to both the experimental hypotheses and the spatial configuration of the paired stimuli throughout the experiment. All of the participants were given consistent instructions: 1) they would receive 24 paired stimulations and needed to verbally report a pain rating immediately following stimulation; 2) they must maintain their gaze on the cross marked on the wall in front of them and should concentrate on giving an overall pain rating for the pair, rather than for each individual stimulus; 3) they may or may not perceive 2 separate “pains” associated with each stimulus; 4) the intensity and location of the activated electrodes will randomly change throughout the 24 stimulations, and they can use the entire 0 to 100 NRS to rate the intensity of their pain.

The experimenter (E.R.) sat alongside the participant and manipulated which electrodes were activated and their current output. The electrical stimulators were driven by a single switch and synchronized by a communication cable. The participant was given a verbal warning from the experimenter—“and now”—immediately prior to each stimulus to minimize any influence that anticipation or surprise could have on pain ratings. A second experimenter (R.M.), who was blinded to the stimulus pairing, recorded the participants’ verbally reported pain rating.

At the completion of the experimental session, a blinding check was performed. That is, the participants were questioned regarding the experimental hypothesis and

were asked if they felt that the stimulations were more painful when the pairs were closer together or when they were farther apart. Participants were not aware that they would be required to make such judgements prior to the experimental session; rather, they were encouraged to focus their attention on the intensity of the stimulations and on providing accurate pain ratings.

Statistical Analysis

All analyses were conducted using Excel and IBM SPSS Statistics, version 21 (IBM Corp, Armonk, NY).

Primary Analyses

The hypotheses were tested using repeated-measures analysis of variance: 1) that the pain elicited by paired ES would be greater than that elicited by a single stimulus of equal intensity (area-based SS); 2) that pain would be greater for 2 stimuli at 5-cm separation than for identical stimuli at a separation of 0 cm (reflecting maximal distance-based SS); and 3) that pain would be less at the 20-cm separation than at the 5-cm separation (reflecting the spatial boundary of distance-based SS). The factor was condition (5 levels: single stimulus and paired stimuli at 4 separations), and the primary outcome was the participant’s pain rating. We used a Huynh-Feldt correction for violation of sphericity. Pairwise comparisons, with a Bonferroni adjustment for multiple comparisons, were then performed to determine which conditions were significantly different from each other. Significance was set at $\alpha = .05$.

Secondary Analyses

Effect of Proximal Versus Distal Orientation. Previous experiments in our group using laser-evoked responses

have suggested that in addition to the proximal-to-distal gradient of human intraepidermal nerve fiber density,^{15,16,18} there is similarly a proximal-to-distal gradient in the pain evoked by fixed stimuli, such that identical stimuli will evoke more intense pain if they are delivered proximally on the limb than if they are delivered distally (Stanton et al, unpublished data, 2014). Such a phenomenon would appear to confound any investigation of SS unless the direction of separation was to be alternated between trials or participants. We controlled for this possible confounder by alternating the location of the reference electrode (proximal or distal) between participants. This methodological step has not been mentioned in previous investigations of SS.²⁷ To investigate the potential involvement of such a proximal to distal gradient, we undertook a sensitivity analysis whereby we repeated the above analysis in each of the groups—those with a distal reference electrode and those with a proximal reference electrode—and we used a t-test to compare the pain evoked at the 20-cm separation between these 2 subgroups of participants. Significance was set at $\alpha = .05$.

Results

Because the assumption of sphericity was violated, we applied the Huynh-Feldt correction, which corrects for the estimated magnitude of the sphericity violation and yields noninteger degrees of freedom.

SS Exists for Noxious Electrical Stimuli

Pain was significantly affected by the stimulus configuration (main effect of condition: $F[3.61, 537.37] = 40.55$, $P < .001$). Pain was lower for a single stimulus than it was for any of the paired stimuli ($P < .001$ for all), which upheld the first hypothesis.

SS Within the Distance-Based Paradigm

Pain ratings were significantly affected by the separation between the paired stimuli ($F[2.53, 377.28] = 12.12$, $P < .001$). SS was lower when the stimuli were immediately adjacent to each other (at a separation of 0 cm) than it was at any of the other separations tested ($P < .001$ for all; Fig 3), which upheld the second hypothesis. There was no difference in SS between the 5-, 10-, and 20-cm conditions ($P > .65$ for all; see Fig 3), which did not uphold the third hypothesis. The separation at which SS is maximal or abolished could not be determined from this experiment.

Effect of Proximal Versus Distal Orientation

For the proximal-origin participants ($n = 12$), pain was affected by the separation between the paired stimuli ($F[2.71, 192.20] = 5.21$, $P < .01$), as it was for the whole group. SS was again lower at 0 cm than at 5 or 10 cm ($P < .01$ for both), but in contrast to the group data, pain at 20 cm was no greater than pain ratings at 0 cm ($P = .30$; Fig 4). For the distal-origin participants ($n = 13$), pain was also affected by the separation

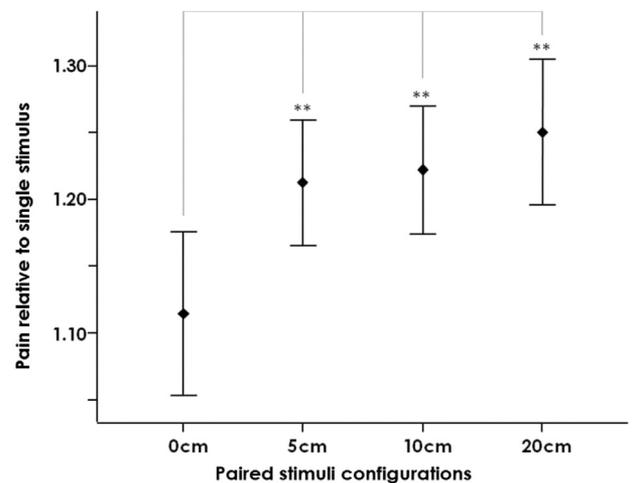


Figure 3. Pain from paired stimuli relative to single stimulus ($n = 25$). Mean (diamonds) and 95% confidence interval (error bars) for pain, relative to that evoked by the single stimulus, across different configurations. The single stimulus was significantly different from all paired configurations (** $P < .001$), and the paired 0-cm separation was significantly different from the other paired stimuli configurations (5, 10, and 20 cm) (** $P < .001$). There was no difference in SS between 5, 10, and 20 cm ($P > .65$ for all).

between the paired stimuli ($F[2.46, 189.71] = 10.15$, $P < .001$). However, in contrast to the group data, the 0-cm separation only differed from the 10- and 20-cm separations ($P < .05$ for both) and not the 5-cm separation ($P = .06$; Fig 5). Critically, the direction of the separation affected SS, insofar as the 20 cm in the distal direction pain was greater ($1.33 \pm .38$) than it was in the proximal direction ($1.17 \pm .38$; $t(148) = -3.00$, $P < .01$), even though the stimuli were actually delivered to identical locations (see Fig 2).

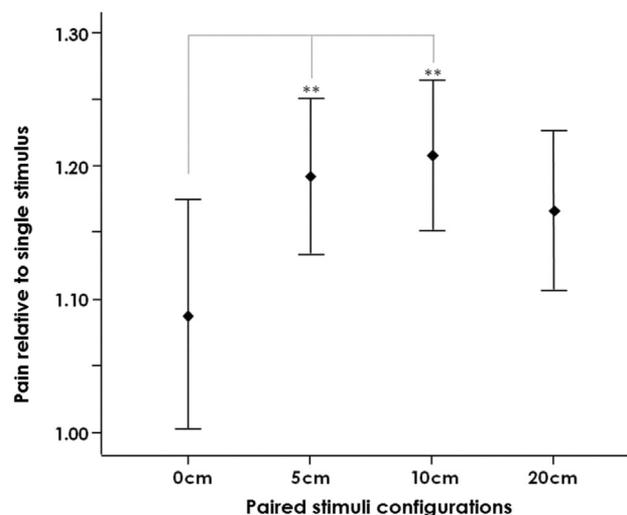


Figure 4. Proximal-origin participants: Pain from paired stimuli relative to single stimulus ($n = 12$). Mean (diamonds) and 95% confidence interval (error bars) for pain, relative to that evoked by the single stimulus located proximally (near to the elbow), across different configurations. The 0-cm separation was significantly different from the 5- and 10-cm separations (** $P < .01$) but not from the 20-cm separation ($P > .3$).

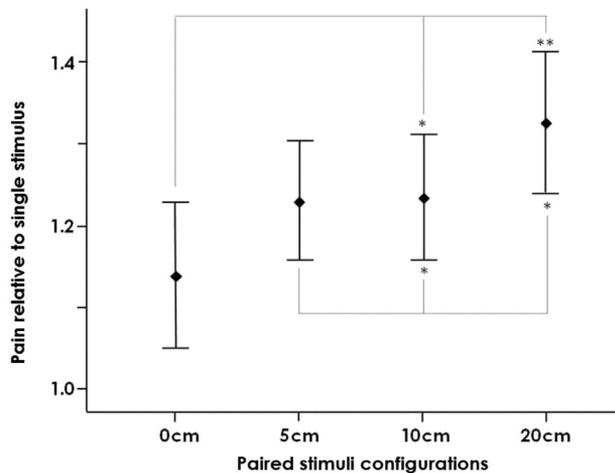


Figure 5. Distal-origin participants: Pain from paired stimuli relative to single stimulus for each separation ($n = 13$). Mean (diamonds) and 95% confidence intervals (error bars) for pain, relative to the pain evoked by the single stimulus located distally (near the wrist), across different configurations. The 0-cm separation was significantly different from the 10-cm separation ($*P < .05$) and the 20-cm separation ($**P < .01$) but not the 5-cm separation ($P = .06$). The 5-cm separation was significantly different from the 10- and 20-cm separations ($*P < .05$).

Blinding to the Experimental Hypothesis

There were no correct predictions of the experimental hypothesis when the participants ($n = 25$) were questioned at the completion of the experiment. In response to the question "Did you feel that the stimulations were more painful when the pairs were closer together, or when they were farther apart?", 13 participants reported that they were "unsure," 6 felt that the stimulations were more painful when they were closer together, and 6 felt they were more painful when they were further apart.

Discussion

We hypothesized that TES would impart area- and distance-based SS. The results clearly uphold these hypotheses, as evidenced by more intense pain from 2 stimuli as compared to 1, and more intense pain with paired stimuli at separations of 5 and 10 cm than at 0 cm. However, the results do not support our hypothesized reduction in SS at a distance of 20 cm, which suggests that the boundary of SS, and the point at which SS gives way to CPM, is greater than 20 cm. This is in contrast to previous studies, in which noxious heat, cold, or mechanical stimuli were used and maximal SS was found at separations of between 5 and 10 cm on the leg or forearm.^{8,26,29} Although there are no published data for TES on the skin, the current results are consistent with a previous study that stimulated the tooth pulp of 2 adjacent teeth and demonstrated area-based SS of ES.⁴

Effect of Proximal Versus Distal Orientations

Experiments in our laboratory (Stanton et al, unpublished data, 2013) suggest that a proximal-distal bias may exist for the processing of noxious stimuli, whereby stimuli

delivered proximally are more painful than identical stimuli delivered distally. Previous studies have presented data relevant to this issue,^{1,25,30} and such a bias is supported by the proximal-to-distal gradient of human intraepidermal nerve fiber density.¹⁵⁻¹⁷ Such a bias is of critical relevance to our understanding of distance-based SS because, until now, all our evidence of distance-based SS comes from studies in which the reference stimulus has been located distally. That is, it is possible that evidence of an apparent distance-based SS reflects a proximal-distal sensitivity gradient instead. That adds import to our result: SS at the 20-cm separation was less for the proximal-origin participants than it was for the distal-origin participants even though the locations were, in fact, identical. Specifically, when the reference electrode was located proximally, the addition of a simultaneous distal stimulus did not increase pain ($P = .3$), whereas when the reference electrode was located distally, it did ($P < .001$). This finding is consistent with the discovery that when participants were asked to divide their attention between 2 identical heat stimuli, they found the proximal one more painful than the distal one.²⁵ Relevant here is a recent proposal of the cortical body matrix,²² an integrated network of neural loops that subserves regulation and protection of the body and the immediate surrounding space, both physiologically and psychologically. According to that proposal, one would predict heightened protective responses when threatening stimuli occur closer to the body. Also relevant is the recent discovery of a kind of defensive personal space, identified by heightened eye blink responses to stimuli presented closer to the face spatially but identically distanced somatotopically.²⁸ Such concepts raise the possibility that a proximal-distal sensitivity gradient at least contributes to the apparent SS effect we see in the literature. That we still saw an SS effect in the pooled data, and at smaller separations, indicates that the proximal-distal gradient does not explain the whole effect, but it certainly urges us to revisit previous investigations of SS in humans because by ignoring this issue, the previous investigations may indeed be fundamentally confounded.

Proposed Neurophysiological Mechanisms

The observation that SS was maximal when the stimuli were spatially separated and was minimal when the stimuli were adjacent (ie, at the 0-cm separation) supports neuronal recruitment as the dominant neurophysiological mechanism underpinning distance-based SS.²⁶ Presuming that SS is still present at a separation of 20 cm and that the average receptive field diameter for primary nociceptive afferents is around 5 cm,²⁶ the recruitment is likely occurring centrally via the activation of 2 unique but overlapping (at least for the 10-cm separation) populations of neurons.²⁶ Conversely, for a single enlarging stimulus in the area-based paradigm, one might have predicted that increased activation of a peripheral nociceptor population is more likely, although once the area is large enough, this would presumably also increase spinal nociceptor recruitment. Importantly,

the mechanism of neural recruitment is 1) limited by spatial constraints (ie, at further separations the overlapping of receptive fields from the 2 neural populations would diminish) and 2) facilitated by stimulus intensity (ie, higher intensity stimuli evoke greater rostrocaudal activation in the spinal cord,⁶ which has been shown to facilitate the integration of multiple stimuli on the body).^{6,23} The involvement of cerebral cortical mechanisms must also be considered. Whereas thalamic activation, which is critical for the transmission of nociceptive input, remains consistent, greater activation in cortical regions, including the primary somatosensory, anterior cingulate, and prefrontal cortices, has been shown to correlate with increased pain to standardized noxious stimuli.⁵

The present study, in addition to previous investigations of noxious SS, supports SS to be a protective feature of nociceptive processing according to an anatomical frame of reference. One might predict, however, that SS also exists according to a spatial frame of reference. Consider this for example: One grasps an electric fence with 2 hands, thus stimulating 2 body areas that are somatotopically (anatomically) far apart, but spatially very close together. According to the published literature, this situation should evoke CPM, whereby one noxious stimulus inhibits the response to a second, remote, stimulus. However, this would seem counterproductive because the threat in that *location* remains magnified, just as it is when the stimuli are anatomically adjacent. This is clearly a speculative proposition, but not an outrageous one; that noxious and innocuous stimuli are processed within both somatotopic and spatial frames of reference is well established,^{22,28} and spatially defined sensory processing abnormalities have been identified in people with chronic pain.^{19–21} If indeed SS is spatially, rather than anatomically, defined, the significance of cortical contributions to SS mechanisms may be elucidated.

We previously evaluated the risk of bias associated with previous studies of SS as part of a systematic review.²⁷ We then implemented measures to avoid the threats to validity that we identified. For example, sample size was determined a priori; the stimuli were identical in terms of the intensity of the pain that they evoked; the participants were blinded to the experimental hypothesis; all communication with the participants was standardized; and pain ratings were recorded by a researcher who was blinded to the configuration of the stimuli and the direction of separation (proximal or distal).

There are other considerations too, however. For example, TES is not exclusive to the nociceptive system, which means that our conclusions relate to noxious stimuli but do not implicate only the nociceptive system. This consideration is also at play in previous studies,

which have used heat, cold, and mechanical stimuli.² Importantly, activation of both nociceptive and nonnociceptive mechanisms is consistent with nonexperimental pain. That said, TES is nonphysiological insofar as it directly activates peripheral nerves, including nociceptors, and therefore sidesteps the physiological transformation of input to action potential. That there are many possible mechanisms of TES stresses the importance of the current study in confirming that TES is a clinically safe and feasible modality appropriate for future investigations of SS. That only 4 stimulus separations were used clearly limits the spatial resolution of our results—we cannot tell where distance-based SS starts, between the 0- and 5-cm separations. That 20 cm was the maximum separation meant that it was not possible to identify the separation at which SS decreased. However, as discussed in the Methods section, it was not possible to go beyond 20 cm without the risk of introducing other confounds such as proximity to a joint and the related changes in spatial localization¹³ and distance perception¹¹ across a joint. Furthermore, because stimulus intensity may alter spatial integration,⁶ the inclusion of 2 participants whose stimulation intensity was rated considerably higher on the NRS than the remainder (60/100, group average 26/100) may have enhanced the SS in these participants. However, exclusion of these participants from analysis did not alter the significance of the current findings, which suggest that SS mechanisms do not vary for high- and low-sensitivity individuals. Further studies comparing stimulation intensities in a within-subjects design will be needed to clarify these properties. That separations were randomized within participants minimized the potential influence of factors such as alcohol, caffeine, drug use, sleep, or exercise on the results, but it remains possible that our main findings were influenced by such factors. As such, controlling for these factors would strengthen our result. Finally, the current results are limited in their generalizability to stimuli delivered to the right forearm of healthy, young, and pain-free students. Whether or not the same pattern occurs in pain patients will require further study.

Conclusion

We hypothesized that the pain elicited by paired ES would be greater than that elicited by a single stimulus of equal intensity and would be modulated by the distance between the paired stimuli. Our results uphold these hypotheses and demonstrate these properties of SS evoked by TES but do not reveal the degree of separation at which SS subsides, which appears to be greater than 20 cm, at least in the forearm.

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