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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.***

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 review[27] 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 ± SD = 23 ± 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 α = .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; Digitimer, Welwyn, United Kingdom; 200 μs 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 localization[13] and distance perception[11] 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-μs pulse duration, 300 V), the electrical current was increased in 2.0-mA increments until the participant perceived the stimulation to be painful. An interstimulus interval of at least 15 seconds was used throughout testing. The participants had to verbally report a pain score immediately following stimulation,