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ABSTRACT

Objectives: Tactile dysfunction in chronic pain is explained as disruption in somatotopically based processing of stimuli. We hypothesized that people with chronic back pain also demonstrate a spatially defined disruption of tactile processing.

Methods: In 3 cross-sectional experiments, 26 patients with unilateral low back pain and 12 healthy controls made temporal order judgments of pairs of tactile stimuli. We analyzed the stimulus onset asynchrony at which participants perceived them to be simultaneous (PSS). Stimuli were delivered to either side of the back or to both index fingers. For hand stimuli, the position of the hands were 1) one either side of the back or 2) in front of the body, 3) one behind the back and one in front on the affected side or 4) on the unaffected side.

Results: In patients, mean ± SD PSS for stimuli to either side of the lower back occurred when the affected side received the stimulus 25 ± 25 msec before the unaffected side. PSS for stimuli to the hands with one hand held near the affected area was similar when the other hand was behind the back on the opposite side of the midline (17 ± 17 msec) or in front of the body on the affected side (31 ± 21 msec). These PSS values were greater than that for all other conditions and in healthy controls (p < 0.01), which approached zero.

Conclusions: Spatial representation of vibrotactile stimuli is disrupted in chronic unilateral back pain. Neurology® 2012;79:327–332

GLOSSARY

ANOVA = analysis of variance; CRPS = complex regional pain syndrome; JND = just noticeable difference; PSS = perceived to be simultaneous; PSS = point of subjective simultaneity; SOA = stimulus onset asynchrony; TOJ = temporal order judgment.

Back pain is the most burdensome musculoskeletal complaint.1,2 About 30% of acute back pain episodes lead to chronic back pain,3 which incurs most of the disability and cost. Chronic back pain is associated with cortical dysfunction4 and disrupted tactile processing.5–10 Multisensory representations of peripersonal space play an important role in modulating our awareness of external events,11 which suggests that disrupted spatial representation could contribute to disrupted tactile processing in back pain.

Chronic complex regional pain syndrome (CRPS) occurs after stroke but can be triggered by tissue trauma. In chronic CRPS, tactile stimuli from the affected side of external space are given less weighting by the brain than stimuli from the unaffected side.12 This finding can be considered qualitatively similar to the poststroke phenomenon of extinction.13

One possible interpretation of disrupted spatial representation in CRPS is that it serves to limit provocation of pain. If so, one might expect similar effects in other chronic pains that are confined to a specific spatial location. We hypothesized that, in people with unilateral back pain, a stimulus delivered to the painful side of the back, or to a hand held near the painful side of the back, would have to occur before an identical stimulus delivered to the opposite side for the 2 stimuli to be perceived to be simultaneous.

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METHODS  Participants. We undertook 3 cross-sectional experiments with a total of 26 patients and 12 healthy controls (table e-1 on the Neurology® Web site at www.neurology.org). Twelve people (6 female; 11 right handers, according to self-report) with unilateral back pain and 12 age-matched controls (5 female; 11 right handers, according to self-report) with no history of back pain participated in experiment 1. People with unilateral back pain for at least a year participated in experiments 2 (n = 7, 2 female, 5 right handers) and 3 (n = 7, 4 female, 5 right handers). The experiments involved a convenience sample recruited from community notice boards. Patients reporting pain on one side of the back, below the first lumbar vertebra, were eligible. Sample size was based on data from a previous study in patients with CRPS1\(^2\) and on pilot trials. All experiments were powered to detect an effect size of 1.4 with 80% power. The first experiment allowed for missing data and withdrawal but in fact did not lose any data. Participants with evidence of neurologic impairment, and those with neurologic or psychiatric diagnoses that might affect sensation, were excluded. Medications were tabled but no effort was made to reduce or modify medications. All participants gave written informed consent. All procedures were approved by the institutional ethics committee and conformed to the Declaration of Helsinki.

Protocol. All experiments. Vibrotactile stimuli (10 msec duration; 290 Hz) were delivered through bone conduction vibrators (part no. VBW32, Audiological Engineering Corp. Somerville, MA; vibrating surface 1.6 cm × 2.4 cm). Noise-blocking ear protectors were worn to prevent the participant from hearing the stimuli. All participants confirmed that they could not hear the stimuli. Perceptual thresholds to the stimuli were determined for stimulators fixed on each side of the lower back. Experimental stimuli were 140% of the vibrotactile threshold for that location and for that participant. Stimuli were not painful. Participants made temporal order judgments (TOJs) of vibrotactile location and for that participant. Stimuli were not painful. Participants made temporal order judgments (TOJs) of vibrotactile stimuli delivered using an in-house signal generator and custom program. A trial constituted 1 stimulus from each vibrator, in random order and at different stimulus onset asynchronies (SOA): 240, 120, 60, 30, 10, –10, –30, –60, –120, –240 msec. Participants judged which of the 2 stimuli they perceived to have occurred first by verbal responses. The stimulus locations were randomly assigned numerical identifiers. That is, for some participants, the vibrator on the left was called ‘1’ and the vibrator on the right was called ‘2’, and for other participants this was reversed. Verbal responses were recorded and coded by in-house software.

Participants stood comfortably, weight evenly balanced. Spontaneous pain was assessed using an 11-point numerical rating scale. Participants put on the ear protectors. Participants completed 2 practice blocks of 50 trials, interspersed with a 2-minute rest. Pain was reassessed after these 2 blocks. After a further 4-minute rest, data collection began. For each condition, 2 blocks of 150 trials were interspersed with a rest which was the longer of either 4 minutes or until pain returned to baseline. All patients reported pain had returned to baseline by 4 minutes.

Experiment 1. In addition to the protocol described above, the following protocol was undertaken: The stimulators were placed inside a foam cube (100 × 100 × 100 mm) so that the pad of either index finger was resting on the stimulator. Perceptual thresholds were determined. The TOJ protocol was repeated, under 2 conditions, in randomized counterbalanced order: 1) hands held behind the back (~3 cm away from the back, one near the usually painful area of the back and one on the other side of the back) and 2) hands held in front of the body, either side of the midline.

Experiment 2. To control for a possible order effect of undertaking the TOJ protocol with stimulators on the back, before undertaking the TOJ protocol with the stimulators held in the hand, the order of conditions was alternated between participants. That is, in protocol otherwise identical to that described for experiment 1, the 2 hand-stimuli conditions were conducted first. Participants held both hands on one side of the body; the hands were held in a parasagittal plane about 50 mm lateral to the body and either side of the coronal plane. The order of sides was alternated between participants. Participants rested for 10 minutes and then the stimulators were placed on the back so as to repeat the protocol described above for all experiments.

Experiment 3. In addition to the protocol with stimulators on the lower back, an otherwise identical protocol was undertaken with the stimulators placed on either side of the T3 spinous process, 40 mm from the midline. The order of conditions was alternated between participants.

Analyses. The primary outcome variable in each case was the point of subjective simultaneity (PSS). PSS is that point at which participants are equally likely to report either stimulus as occurring first and is considered equivalent to the SOA at which the 2 stimuli are perceived as simultaneous. The just noticeable difference (JND), which is the half of the difference between values needed to get 25% vs 75% correct,\(^4\) estimated the accuracy of responses. Data were tested for normality using the D’Agostino-Pearson omnibus test. Assuming normality, the proportion of correct responses at each SOA was converted into z scores using a standardized normal distribution. Linear function computed the best-fitting straight line. The slope and intercept values were derived in order to calculate PSSs and JNDS. Repeated-measures analyses of variance (ANOVA) compared PSS and JND between conditions. Linear regression determined the relationship between PSS and 1) the duration of symptoms, 2) average pain over the last 2 days, and 3) spontaneous pain prior to data collection. Significant regressors were entered as covariates in the ANOVA on PSS. Normality was assessed by QQ plots. Significance was set at α = 0.05.

Standard protocol approvals, registrations, and patient consents. In each experiment, all participants gave written informed consent. All procedures were approved by the institutional ethics committee and conformed to the Declaration of Helsinki.

RESULTS  PSS data for all experiments are presented in figure 1.

Experiment 1. All PSS and JND data were normally distributed. For patients but not for controls, when vibrotactile stimuli were delivered to either side of the back, the stimulus that was delivered to the affected side had to occur 25 msec before the other stimulus for them to be perceived as simultaneous (mean ± SD PSS = 25 ± 25 msec; figure 2A; controls = 1 ± 13 msec, p < 0.01; figure 2C). The same effect was observed when the stimuli were delivered to either index finger and the hands were held behind the body (PSS = 17 ± 17 msec; figure 2B), but not when the hands were held in front of the body (PSS = 1 ± 12 msec, which was less than both other
conditions: \( p < 0.01 \). In controls, PSS approached zero in all conditions (\(-2 \text{ m sec} < \text{PSS} < 4 \text{ m sec}\) for all). Participants were more accurate when the stimuli were delivered to the hands (mean \( \pm \) SD JND = 53 \pm 18 m sec) than when they were delivered to the back (JND = 67 m sec \( \pm \) 19 m sec; main effect of position \( F_{2,22} = 5.0, p = 0.016 \)).

**Experiment 2.** All data were normally distributed. We replicated the findings of experiment 1 in patients with chronic unilateral back pain when stimuli were delivered to their lower back: mean \( \pm \) SD PSS = 36 \pm 20 m sec. When participants held one hand in front and one behind their body on the same side as the usual area of back pain, the stimuli to the back hand had to occur before the stimuli to the front hand for them to be perceived as simultaneous (\( \text{PSS} = 31 \pm 21 \text{ m sec} \)), but when the hands were held in front and behind the opposite side of the body, PSS approached zero (5 \( \pm \) 13 m sec; \( p < 0.01 \)). Accuracy was similar for stimuli to the hands (mean \( \pm \) SD JND = 60 \( \pm \) 22 m sec) and stimuli to.
the back (JND = 76 ± 24 msec; no main effect of position \( p = 0.06 \)).

Experiment 3. All data were normally distributed. We replicated the result of the first 2 experiments when stimuli were delivered to the lower back, PSS = 30 ± 12 msec. However, when the stimuli were delivered to the upper back, PSS approached zero (2 ± 9 msec; \( p = 0.013 \)). The JND was smaller when stimuli were delivered to the upper back (63 ± 14 msec) than when they were delivered to the low back (93 ± 24 msec; \( t[5] = 2.9, p = 0.033 \)).

Relations between PSS and duration and PSS and pain. PSS for the condition in which stimuli were applied to the back and duration and pain data for all patients (\( n = 26 \)) were pooled. Linear regression showed that PSS was related to duration of back pain: PSS increased about 0.5 msec for every month of back pain (figure 3; linear regression: \( B = 0.52, r = 0.73, p < 0.001 \)). PSS was not related to spontaneous pain or to average pain over the last 2 days (NS).

DISCUSSION Our results uphold the hypothesis that chronic back pain is associated with a spatially defined disruption of tactile input. In all 3 experiments, when a tactile stimulus was delivered within the space around the affected area, it had to occur earlier than an identical stimulus presented elsewhere for the patient to perceive the 2 stimuli as simultaneous. This means that the stimulus is processed more slowly when it comes from this area of space. That the effect is spatially defined means it is not attributable to dysfunction of the peripheral tissues, neural pathways, or primary sensory cortical areas that serve the somatotopic representation of that area of the body. Although functional changes within the CNS have long been held to contribute to chronic pain problems, the current results provide evidence that a persisting musculoskeletal disorder leads to a disruption of tactile processing that is qualitatively similar to that observed in brain-damaged patients affected by spatial neglect. In that group, stimuli from the contralesional side of the body midline have to occur before those from the ipsilesional side in order to be perceived as simultaneous. Indeed, spatially defined disruption of sensory processing has only ever been reported after neurologic injury or disease. The persistence of pain seems to determine an anisotropy in our neural representations of the space close to the body or in the way we deploy attention to this space.

The concept of anisotropy in neural representations (or spatial attention) is not new to the neurologic literature. In fact, it has been suggested that disorders such as neglect and extinction might indeed be caused by anisotropies at the level of higher order spatial representations or in the deployment of spatial attention. It has also been shown that anisotropies or even shrinkage of neural representations are not necessarily caused by neurologic damage but can be determined by the normal lateralized organization of the neurocognitive system, such as in pseudoneglect, or by the absence or increase of motor and proprioceptive feedback. In the case of chronic unilateral back pain, loss of movement is an unlikely explanation because it is not possible to stop moving one side of the back without also limiting movement on the other side. We would speculate instead that reduced weighting of tactile input from the body part and the space around it serves to limit the provocation of pain. That is, our representation of space assumes the signature of the part of the body that is usually close to it. Consequently, stimuli that enter that space are automatically subject to a perceptual distortion or neglect. That pain can be powerfully modulated by shifting spatial attention in healthy volunteers and is reduced or relocated in those with spatial neglect supports this idea. We have previously proposed the concept of a body matrix to describe this integration of somatotopic and spatial representations that appears to be disrupted in a body-part–specific way in people with chronic
pain.

The neural mechanisms related to this effect need to be investigated further, but we believe that interactions between sensory specific (S1) and higher order areas of the brain thought to process the stimuli in terms of peripersonal and external spatial coordinates, such as the temporal-parietal junction and posterior parietal cortex, are probably important.

The current work does not permit conclusions about causation. That the magnitude of the deficit was related to the duration of symptoms may suggest that the dysfunction increases as symptoms persist, but it may also mean that those with a smaller deficit are likely to recover from an episode of back pain more quickly than those with a larger deficit. Similarly, we have no evidence that the disruption contributes to pain. That disrupted somatotopic representation contributes to other painful conditions has been suggested and there is supportive evidence from patients. However, experimental data strongly suggest the disruption is not enough to cause pain, at least in healthy volunteers. Also, conditions characterized by disruption of somatosensory and motor representations are not necessarily painful and, remarkably, experimentally disrupting the cortical representation of a painful limb can increase or decrease pain, depending on the nature of the distortion. Nonetheless, training somatotopic representation seems to reduce pain in phantom limb pain and CRPS, which raises the possibility that training spatial representations may also reduce pain. For example, it might be feasible to test whether auditory discrimination training—which of several speakers emits a tone—can be used to improve spatial representation in the same manner as tactile discrimination training has been used to improve somatotopic representation. One consideration in this regard is that tactile discrimination behind the back seems to be better than it is in front of the body, within the visual field, which suggests that further studies are required before generalizing the current work to other areas of pain. Importantly though, this intriguing finding of improved tactile discrimination behind the back does not affect the current results, which showed a side-specific effect. Clearly, the current work suggests several areas of further study.

The current study clearly demonstrates that chronic unilateral back pain is associated with a spatially defined disruption of tactile input. That disruption of an integrated body space representation can occur in association with a persistent musculoskeletal disorder suggests that the neurologic involvement in chronic pain is more complex than was previously thought and raises the possibility of new directions for treatment.
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