Primary Somatosensory Cortex and Pain

Or, How to Handle a Hot Potato

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The Focus article by Backonja raises a number of important questions regarding the role of the primary somatosensory cortex (SI) in pain perception. It is hard to argue against his conclusion that the current challenge is to better understand the role of SI in pain. Of course, one could assert the same for every brain area and associated function. However, pain is more than a novel stimulus, and my assessment is that the role of SI in pain perception has become more dubious, not less, as more sensitive human brain imaging techniques have been applied to the problem.

There is certainly adequate single-unit electrophysiologic evidence for somatic nociceptive information flow to SI. The same is not true for other cortical areas. However, the reason for this difference is not because the evidence is more convincing for SI, but that much more concerted effort has been spent for this region of the cortex. Until the last few years there were, in fact, no systematic anatomic or physiologic studies examining specifically nociceptive inputs to regions outside of SI.

Backonja states that the recent positron emission tomography (PET) studies corroborate the participation of SI in conscious pain perception. As argued in a review [1], the spatial resolution of these PET studies cannot distinguish between activation of SI and primary motor cortex (MI), especially since the activation centers are usually located between the two regions, and since a number of recent functional magnetic resonance imaging (fMRI) studies show large MI activity, distinct from the SI activity, during pain perception. He also cites pain studies in which cortical activations were determined by electromagnetic methods (electroencephalography, magnetoencephalography, and evoked potential) as further evidence for the involvement of SI in pain perception. It should be remembered that the localization accuracy of these techniques is inferior to that of PET. Thus, the same interpretation problems exist in these studies as well. Backonja reviews evidence that shows that SI modulates pain. This may, in fact, be interpreted as the descending portion of the "pain gate" of Melzack and Wall [17], where innocuous inputs through multiple loops, including SI, inhibit pain. I do not understand why such modulation would imply that the region participates in pain perception, especially since this logic would more readily implicate the dorsal raphe or the periaqueductal grey, rather than SI, in pain perception.

Next, Backonja states that there are difficulties in interpreting the role of SI in pain. Obviously this is my position as well; however, the arguments used do not seem convincing. The first problem raised by Backonja is in relation to the relative paucity of nociceptive neurons reported in the cortex. This seems to be true in SI (it is unclear if it is true for other cortical areas, given the lack of proper studies). However, its implications are unclear, because there are no concrete brain theories as to the minimum number of neurons required for perceiving anything. There are, on the other hand, opposite examples: the number of neurons in V1 that code for color are far less than color insensitive cells, but this does not translate into a specific behavioral or perceptual deficit. Similarly, only a small number of cells seem to subserve gustatory representation in both the thalamus and the cortex, again with no obvious perceptual deficits, that is, I still enjoy the subtle taste nuances of a glass of good wine. On the other hand, the small number of nociceptive responsive cells in SI should translate into a small metabolic signal, and the ratio of the nociceptive to touch responsive cells

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(estimated to be in the order of 1:1000) should be reflected in the relative intensity of SI activation, when determined metabolically, for the respective tasks. This certainly does not seem to be true in PET, single photon emission computed tomography (SPECT), or fMRI studies, raising further doubts regarding the association between SI activation and the underlying function performed during a painful task.

Another argument that Backonja uses to explain the paucity of nociceptive cells is one advocated in different flavors by many others in the past and is the analogy of sounding the alarm. The notion is that, in a state of emergency, sounding the alarm does not need a sophisticated code. A loud scream by a few neurons can achieve the task. I disagree. Split-second decisions regarding responses to noxious stimuli are critical for the survival of the organism and the species. A starving animal needs to make millisecond decisions about the pursuit of a potential food source, which, more often than not, is a noxious experience. That is, when and how to handle a hot potato is a sophisticated fast response, for which whole body motoric responses are needed, based on accurate information regarding the location and intensity of the noxious stimulus. Whether the number of nociceptive cells in SI is sufficient for performing these sensory-motoric adjustments is presently unknown.

As Backonja acknowledges, the single-unit electrophysiologic studies in rat, cat, and monkey have concentrated on identifying SI neurons that respond to noxious stimuli lasting only a few seconds. Similarly, all human brain imaging studies in which robust SI activations were observed were done using very short-duration thermal stimuli. These observations imply that cortical activation during such phasic noxious stimuli emphasize the pathways and systems involved in the fast motoric tasks, and the activations in these tasks do tend to involve both SI and MI (for details see Apkarian [1]).

Backonja assumes that, since SI is primary somatosensory cortex and receives nociceptive inputs, it must participate in *conscious* pain perception. Although SI is the primary sensory cortex for innocuous tactile inputs, there is no definitive evidence that it is also the primary cortex for noxious inputs. One could just as well argue that other parietal cortical regions (SII, area 7b, or insula) receive the main nociceptive inputs preferentially through the dorsal spinothalamic pathway (DSTT) relaying nociceptive specific inputs from the marginal layers of the spinal cord. On the other hand, the nociceptive inputs to SI are mainly through the ventral spinothalamic pathway (VSTT), and as a result nociceptive cells in SI are mainly of wide dynamic range type [2,7,10,13]. More likely, the two pathways relay distinct nociceptive information to different cortical areas, through parallel channels. The existence of these parallel systems is analogous to the organization of the parvo and magno visual pathways, although in the latter the two routes intermingle at the level of V1. It needs to be emphasized that other nociceptive pathways, either directly [12,19] or through brainstem relays [4], have now been shown to access the hypothalamus, amygdala, ventral pallidum, and other limbic targets, all of which must contribute to pain perception. Perhaps *sustained conscious* pain perception is mediated mainly through these limbic pathways, rendering *conscious* pain perception primarily an emotional, rather than a sensory, percept.

Backonja dubs pain as a distributed phenomenon. It is not clear what he means by this. There is certainly ample evidence that noxious inputs are represented in multiple cortical and subcortical regions. This does not imply, however, that pain representation is a distributed process. Physiologic and anatomic data imply that different pain features are extracted at different cortical stations, which interact dynamically in patterns that remain to be understood. Calling this organization distributed implies a lack of functional specificity for the different nociceptive information processing stations and, instead, infers that the same information is shared diffusely among the regions.

Backonja then borrows mechanisms demonstrated in other sensory systems to explain mechanisms of perception of pain. The latter seems inevitable, given the lack of the same type of data for nociception. However, a significant role for rhythmic activity in pain perception, at least in SI and lateral thalamus, seems unlikely, because recent studies (Shi et al., unpublished data) show that lateral thalamic (at least in ventral posterior thalamic nucleus) wide dynamic range-type neurons, which as a group show oscillatory activity around 30–40 Hz during tactile stimuli, cease oscillating while responding to a noxious stimulus (the population autocorrelation becomes flat). Similar data do not exist for cortical nociceptors, but the strong interconnectivity between lateral thalamic and SI neurons implies that the same might happen in SI.

Based on studies in the visual system, Backonja wonders about activation of SI when one imagines pain. If the latter is a recommendation for performing brain imaging studies during imagined pain, I advise against it. The results of such studies are inherently uninterpretable, because there is no adequate control or knowledge regarding the subjects' performance or state during imagining something, or anything. For example, a number of studies have shown increased activation in SI at the appropriate body part when attention is directed to that region of the body [18,21], while others have shown decreased activity in SI regions subserving areas outside the body part attended [11,14]. It is not

clear how one distinguishes such effects from imagining pain. And, what if no SI activation was seen during imagining pain? How does one then interpret the results? Thus, neither the positive nor the negative results would lead to conclusive interpretations regarding the role of SI in pain perception.

Backonja next raises a number of important questions regarding cortical reorganization in chronic pain states, emphasizing differences between acute and chronic pain. There are, in fact, now a number of studies in which human brain pathophysiology was examined during chronic pain. These studies seem to differ significantly from the results obtained in animal models of chronic pain. As pointed out by Backonja, the results in rat models of chronic pain show increases in receptive field sizes and increased afterdischarges, both in the lateral thalamus and in SI. However, the opposite is observed in human chronic pain states [8,9,14,15,22], and our preliminary fMRI activation studies in four reflex sympathetic dystrophy patients. In the thalamus, metabolic activity seems diminished in chronic pain, and SI activity seems to remain mainly unchanged. It looks as if the discriminative spinothalamic representation is actively inhibited in humans during chronic pain, although the patient suffering from these pains certainly knows what body part the pain resides in but qualitatively may describe it as located diffusely within that body part.

These results, as well as the observation that sustained pain inhibits SI activity in normal subjects [3], the report that central pain may be experienced by patients with no functional thalami [20], and the report that central regions important in formalin injection-induced pain behavior (which lasts for over an hour, i.e., a sustained pain model) in rats is independent of the lateral thalamus [16], all force the conclusion that the ventral spinothalamic, lateral thalamic, SI nociceptive system is not important for clinically relevant pain states. This in turn significantly diminishes the importance one can ascribe to these structures in conscious sustained pain perception. Instead, these observations, together with the data showing activation of SI in acute pain states, imply that the nociceptive inputs to SI may in fact be involved in motoric decisions, such as how to handle a hot potato. In contrast, other cortical regions, more parietal, insular, or frontal, are probably more crucial for conscious pain states, where the percept is sustained long enough to be clinically relevant.

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