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Review

Optical imaging of nociception in primary somatosensory cortex of non-human primates

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Abstract: While the activation of primary somatosensory (SI) cortex during pain perception is consistently reported in functional imaging studies on normal subjects and chronic pain patients, the specific roles of SI, particularly the subregions within SI, in the processing of sensory aspects of pain are still largely unknown. Using optical imaging of intrinsic signal (OIS) and single unit electrophysiology, we studied cortical activation patterns within SI cortex (among Brodmann areas 3a, 3b and 1) and signal amplitude changes to various intensities of non-nociceptive, thermal nociceptive and mechanical nociceptive stimulation of individual distal finerpads in anesthetized squirrel monkeys. We have demonstrated that areas 3a and 1 are preferentially involved in the processing of nociceptive information while areas 3b and 1 are preferentially activated in the processing of non-nociceptive (touch) information. Nociceptive activations of individual fingerpad were organized topographically suggesting that nociceptive topographic map exits in areas 3a and 1. Signal amplitude was enhanced to increasing intensity of mechanical nociceptive stimuli in areas 3a, 3b and 1. Within area 1, nociceptive response co-localizes with the non-nociceptive response. Therefore, we hypothesize that nocicepitve information is area-specifically represented within SI cortex, in which nociceptive inputs are preferentially represented in areas 3a and 1 while non-nociceptive inputs are preferentially represented in areas 3b and 1.

Key words: nociception; optical imaging; primates; hand; primary somatosensory cortex

1 Introduction

Along with the discovery and development of blood oxygen level-dependent (BOLD) fMRI technique, brain regions that are involved in the processing pain information in humans now can be non-invasively visualized and examined directly while subjects are experiencing specific pains. These studies have led to the identification of neural substrates of pain perception. Among those cortical areas, somatosensory cortexes (SI and SII) and insula have been proposed to play an essential role in the processing of the sensory-discriminative components of pain such as spatial discriminative and intensity coding, while insula and anterior cingulate cortex are involved in the processing of affective-motivational components[1]. However, to fully understand the somatosensory function in humans, it is critical to understand the neural basis underlying the BOLD signal and to link the observed human brain activation to the knowledge learned from animals, which are acquired by more invasive methods such as optical imaging of intrinsic signal and single unit electrophysiology. We have previously demonstrated that optical imaging of intrinsic signals, which detects similar homodynamic-related signals as BOLD signal, has proved to be a powerful way to monitor cortical activation during tactile information processing providing much higher spatial (around 100 μm) and temporal (hundreds of millisecond) resolution in non-human primates[2,3]. Detailed methodology see the reference[4]. Toward the goal of providing more comprehensive view of how nociceptive information is processed and represented in the primary somatosensory cortex, we examined the cortical activation during nociceptive *versus* tactile stimulation of individual fingerpad with integrated optical imaging of intrinsic signal and single unit electrophysiology recordings on the same anesthetized squirrel monkey.

2 Area-specific activations to nociceptive *versus* tactile stimuli within primary somatosensory (SI) cortex

Historically, the role of SI in pain perception has long been

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in dispute. Lesions of SI have been reported to cause either hypoalgesia or hyperalgesia, or to affect pain perception not at all (for review see[5,6]). However, with the improvement of high-resolution structural or anatomical imaging technique in humans, investigators can more specifically identify the locations of injury in the brain. Recent case reports demonstrate that localization of painful stimuli was grossly impaired with SI damage[7,8]. In line with this notion, recent PET, fMRI, and MEG/EEG human studies have provided convergent evidence for participation of SI in the coding of sensory-discriminative aspects of pain[8-15]. For example, somatotopic organization of hand and foot in SI was revealed by intracutaneous injection of capsaicin (which can elicit painful sensation) into hand and foot[9]. Graded thermal noxious stimuli evoked pain-intensity related activation in multiple areas including SI[10]. An fMRI study found that distributed cortical systems, including SI, have shown pain intensity as well as temporally correlated activation[16]. It is known that four cytoarchitectonical areas (Brodmann areas 3a, 3b, 1 and 2) are defined in SI of primates[17-19] and humans[20-22]. However, the role of each sub-area in SI in pain processing is largely unknown. Few studies on the differential involvement of sub-areas within SI have reported inconsistent results. For example, area 3a was involved in the thermal nociceptive processing in monkeys[22] while areas 1 and 2 were activated in humans[23]. Due to insufficient confirmative electrophysiology conducted in monkey studies and the lack of spatial specificity of human imaging studies, the specific roles of individual areas within SI need to be further explored. Furthermore, without directly comparing the cortical responses to tactile *versus* various painful stimuli, we still do not know whether the modality and spatial information of a painful stimulus are encoded by co-localization with tactile inputs or are encoded by nociceptive inputs themselves. To address these questions, we studied squirrel monkeys with mechanical nociceptive (indentation of a sharp 0.2 mm diameter probe) and non-nociceptive mechanical (indentation of a dull 2 mm diameter probe) stimulation, which can elicit moderate sharp pain or pressure perception in humans, respectively. To examine the differences between the cortical response to mechanical pain *versus* pressure stimulation, nociceptive and non-nociceptive mechanical indentation are sequentially presented on a single digit (e.g. D3). We observed that areas 3a, 3b and 1 were all activated during nociceptive stimulation whereas only areas 3b and 1 were activated during pressure stimulation. Because it is impossible to activate mechanical nociceptors without also activating low-threshold mechanoreceptors by indentation, we sought to remove the tactile component common to both nociceptive and pressure stimuli by subtracting the pressure map from the nociceptive map. In the subtraction maps, area 3a showed the strongest preferential activation to nociceptive stimulus while activation in area 3b was eliminated by subtraction of the pressure component. A weaker nociceptive response was also evident in area 1. This subtraction data suggests that there are some differential responses in areas 3a and 1 to the nociceptive component of our stimulus. Therefore, we hypothesize that nociceptive information is preferentially represented in areas 3a and 1, while tactile information is preferentially represented in areas 3b and 1.

3 Topographic organization of SI in pain perception

Topographic maps are fundamental to sensory processing. The importance of topographic organization in pain perception was demonstrated by clinic observations that facial pain or phantom limb pain were closely associated with cortical topographic reorganization of hand or facial region in SI cortex[24,25]. For example, it has been shown that facial pain (such as trigeminal neuralgia) was positively associated with the neuroplastic changes in the somatic cortical representation of the hand[26]. A magnetoencephalographic study in amputee patients with phantom limb pain has shown that the amount of cortical reorganization of the lower lip ipsilateral to the amputation is positively correlated with the magnitude of pain experienced by subjects[24]. Suppression of phantom pain contingent upon regional anesthesia was accompanied by a clear reduction of cortical representation of the lip ipsilateral to the amputation[27]. In summary, these observations suggest that the cortical representations of ipsilateral face and hand exhibit a competitive nature with respect to cortical activation. These studies lead to the hypothesis that the changes of topographic representation of Hand-Face region in SI cortex under certain pathological conditions may lead (or at least contribute) to the generation of facial or phantom limb pain. However, without demonstrating the topographic map of pain perception in normal subjects, it would be hard to understand the neural mechanisms underlying the cortical reorganization in pathological conditions. With the relatively low spatial resolution (at least with current conventional fMRI scanners) and lack of electrophysiological support, human imaging studies cannot provide detailed somatotopic maps in each area

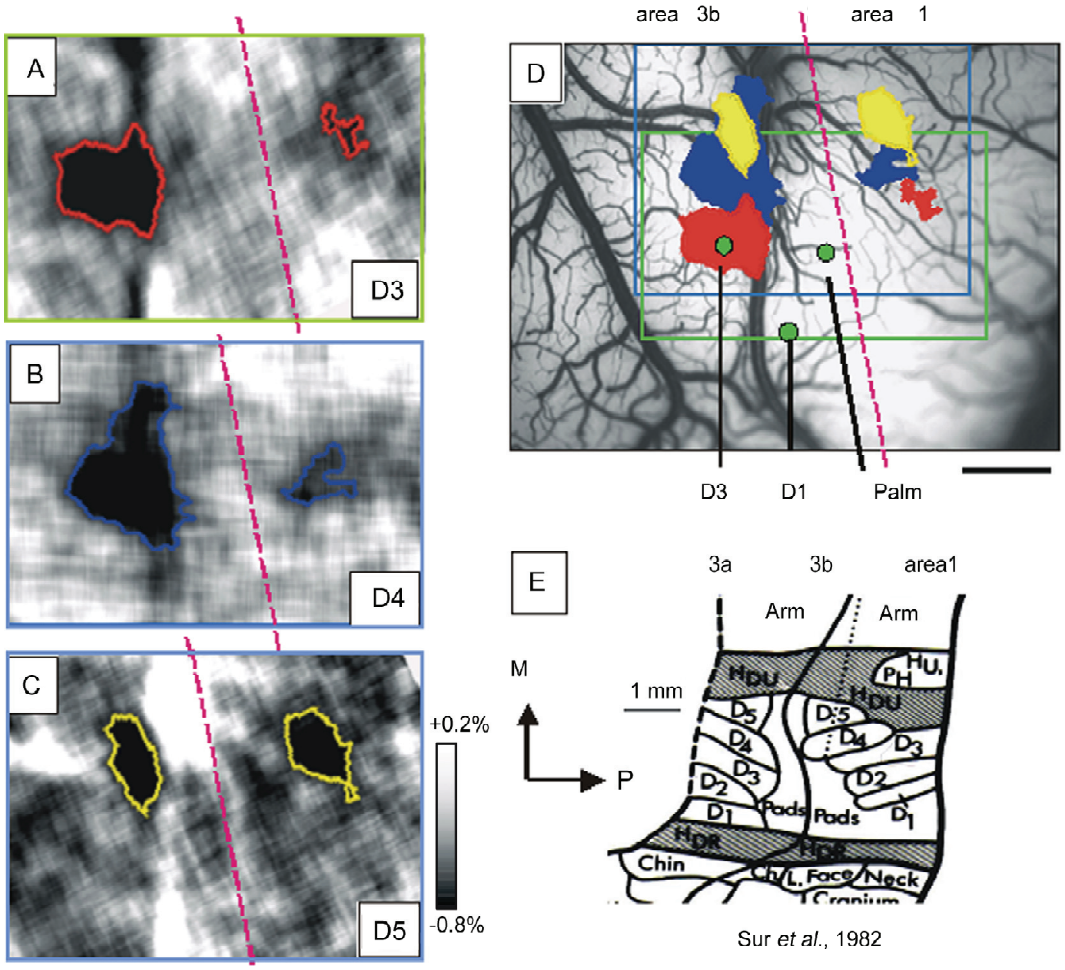

Fig. 1. Topographic organization of responses to pressure stimulation on fingerpads in areas 3b and 1 under isoflurane anesthesia. Two activation spots (highlighted with color lines) were observed in both areas 3b (left) and 1 (right) when single indentation was presented to contralateral D3-D5 distal fingerpad (*A-D*). Multi- and single unit activity recorded from sample penetrations (green dots) were consistent with the imaged somaototopy (*D*). Approximate border between areas was indicated by dotted pink lines in *A-D*. Scale bar, 1 mm. M: medial. P: posterior. Grey scale bar indicated the relative reflectance changes obtained in the images. *E*: Digit topography in areas 3b and 1 from Sur *et al*., 1982. Reproduced from Chen *et al*., 2001[2].

of SI to confirm where nociceptive information is encoded. There are several studies that have suggested some somatotopy in monkeys and humans[5,9,28,29] during pain processing. However, because there apparently are only few nociceptive neurons scattered in the large amount of low-threshold mechano-responsive neurons, it is hard to evaluate the role of these neurons in representing the topographic map of pain. We have previously shown that the topographic map of the fingerpads can be revealed simultaneously in areas 3b and 1 in response to pressure stimuli (Fig. 1) with intrinsic optical imaging[2]. Furthermore, by applying mechanical nociceptive on the individual digit, we examined whether topography of nociception is different with that of touch in each of areas 3a, 3b and 1. Our data

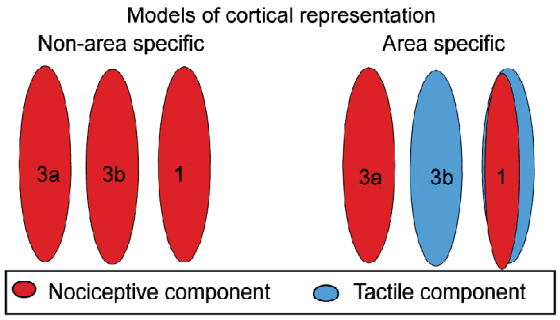

Fig. 2. Schematic illustration of models in area-specific cortical representation.

showed that mechanical nociceptive stimulation evoked somatotopically organized activations, which were spatially co-localized with tactile responses in areas 3a, 3b and 1, respectively. Our optical imaging data suggests that there is topography of nociception, but it is overlapped with tactile maps.

4 Summary

We have hypothesized two possible models for the cortical representation of nociception within SI cortex that are illustrated in Fig. 2. Within SI, nociception could be represented broadly within areas 3a, 3b and 1 (Fig. 2, left model), or in an area-specific manner (Fig. 2, right model). By using integrated high-spatial resolution optical imaging and single unit electrophysiology methods, our data support that mechanical nociceptive *versus* non-nociceptive inputs are area-specifically represented within SI cortex (right model). Since in our pilot studies we did not target or obtain activations in area 2, we do not speculate on what the roles of that area 2 could play during the nociceptive processing. Therefore, we exclude the area 2 in this model at this point.

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