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CEREBRAL COLUMNAR ORGANIZATION OF THE FIRST NOCICEPTIVE COMPONENT INDUCED BY CO_2 LASER ON THE TAIL OF THE RAT

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Abstract—The somatotopic map of the first nociceptive component in the primary somatosensory cortex (S1) is still unclear. In this study, a CO_2 laser was applied to the tail of the rat to induce nociception without the interference from large myelinated (A_β) fibers. Thus, only noxious fibers could be activated. Two-dimensional current-source-density analysis was used to analyze the evoked field potentials. Using this method, the nociceptive responses of A_δ-fibers in S1 were verified, and the somatotopic map of the first nociceptive component in S1 was identified. We found that whether light touch or laser-induced nociception was applied to the tail of the rat, the responsive topography in S1 was consistent. Discrimination of these two modalities was achieved vertically in the same column; the deeper layer represented the nociceptive response while the superficial layer encoded the response to light touch. This is quite different from that of a primate brain.

Key words: current source density, nociception, CO_2 laser, evoked potentials, cortex, rat tail.

Columnar organization in the cerebral cortex has been well known since its proposal in 1955 (Mountcastle et al., 1955). One column consists of a vertical assembly of neurons spanning whole cellular layers in the cerebral cortex (Horton and Adams, 2005). Electrophysiological data acquired from microelectrodes in the primary somatosensory cortex (S1) or visual cortex, histological evidence from Golgi stains (Lorento De No, 1949), and embryological inferences of cortical development (Rakic, 1971, 1988; Walsh and Cepko, 1992) all support the existence of columns in the cortex. Neurons in the same column share the same peripheral receptive field (LeVay and Nelson, 1991), and columns respond to similar receptive field clusters known as hypercolumns (Nicholls et al., 2001; Horton and Hocking, 1998; Sincich and Horton, 2003). These characteristics of columnar organization make exploring the function of the cortex much easier.

Lamina is the other substructure in the cerebral cortex and lies parallel to the cortical surface. From *in vitro* or *in vivo* electrophysiological recordings, distinct electrical characteristics have been found due to the morphological characteristics and composition of neurons, interneurons, and even functional receptors in different lamina (Salin and Prince, 1996; Zhang and Deschenes, 1997). Furthermore, histological evidence from immunological or fluorescent staining has further verified these findings (Bodor et al., 2005; Cauli et al., 1997).

One column in S1 is allocated to one receptive field, however, do neurons at different depths (or lamina) in one column process different functions? In 1983, it was first observed that dissimilar neural activities were displayed in the six layers of one column when applying stimuli of touch or nociception to the periphery (Lamour et al., 1983a,b). Subsequently, there have been only a few studies that have shown distinct functions in different layers of S1. In this study, two-dimensional (2D) current source density (CSD) (Jaw et al., 2008) was used to investigate the possible functions of the lamina in S1.

We adopted a CO_2 laser as an adequate and quantitative nociceptive stimuli (Bromm and Lorenz, 1998) to prevent the activation of low-threshold mechanical receptors (Bromm and Treede, 1984). After 2D CSD analysis, a single conspicuous dipole could be used to demonstrate the first nociceptive component response in S1. Hence, the dipole activated by the CO_2 laser occupied the deeper layer (or lamina) than that activated by mechanical touch. This suggests that S1 utilizes horizontal (or columnar) mapping to locate the body site being stimulated and the lamina within the same cortical column differentiates what kind of stimulus is encoded in rodents. By contrast, in primate brains, different modalities from the same receptive field maybe processed in different cortical area. This may imply that the increase in the number of cortical columns during evolution enables us to handle somatosensory information on more complex and delicate manner.

EXPERIMENTAL PROCEDURES

Preparation

Twelve male Wistar rats that weighed between 250 and 450 g were used in the present experiment. All experiments were carried out in accordance with the guidelines of the National Taiwan University College of Medicine and College of Public Health Institutional Animal Care and Use Committee (IACUC), as well as the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23). All efforts were made to minimize the number of animals used and their suffering. Rats were initially anesthetized with ketamine (50 mg/mL; intraperitoneally) and then injected with diluted ketamine (1.5 mg/mL; i.v.) using an infusion pump to maintain the required depth of

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Abbreviations: AP, anterior–posterior; CSD, current source density; FP, field potential; LEP1, early laser evoked potential; ML, medial–lateral; S1, primary somatosensory cortex; 2D, two-dimensional.

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anesthesia during the experiment. Tracheotomy was performed to enable the clearance of the airway and provide continuous respiration. The body temperature of the rat was maintained higher than 37.8 °C using a homeothermic blanket.

After the rat was positioned in the stereotaxic apparatus, a craniotomy was performed. The primary somatosensory area of the right cortex, 3.0 mm posterior to the bregma and 3.0 mm lateral to the sagittal suture, was exposed and the dura was removed carefully. A glass micropipette filled with 3 M NaCl solution was used as the recording electrode.

Stimulation and recordings

The skin in the middle portion of the tail of the rat was stimulated by heat radiation generated by a CO_2 laser (TAIEX YJS-11; TAIEX Co., Ltd., Shengang Township, Taichung Country, Taiwan, R.O.C.). Ten effective laser pulses were applied within 2 cm of the tail because the receptive field usually covers an area longer than 6 cm on the tail of the rat. A single pulse with a power of 2.5 W and 0.01 s duration was employed. To avoid damage to the tail by burning, a 10 s interval between stimuli was adopted.

The innervated nerve is the 3rd sacral root (S3), and the projected area in S1 was limited to 1.4–1.6 mm posterior to the bregma and 1.2–1.6 mm lateral to the sagittal suture. The evoked potentials were amplified 2500 times. The signals were then low-pass filtered (5th-order Butterworth, 100 Hz) to eliminate noise higher than 45 Hz (Jaw, 2001). The signals were converted through a 12-bit A/D card (PCI-MIO-16E-4, National Instrument) and stored in a computer.

To digitize the field potentials (FPs), a 1 kHz sampling rate and 1024 points were used. For each recording site, 10 cycles of the evoked FPs were averaged for noise reduction.

Data analysis

The FPs can reveal the integral response that results from volume conduction among neurons, and the interactions and interconnections manifested by neurons. CSD analysis was used to determine the activity center of the FPs (Jaw et al., 2008).

RESULTS

The consistent latency of the FPs recorded in the S1 indicated which types of afferent fibers were involved in conducting the laser-stimulated noxious sensation from the periphery. According to the previous study of mechanical stimuli, the depth of the maximal response was approximately 500 μm from the surface of the cortex (Chien et al., 2007). Hence, we mapped the range of noxious responses at this depth. After a preliminary search, CSD analysis was performed on the FPs at each plane separately. Following this, the center of the largest (major) response to the first nociceptive component was identified.

Conduction velocity of the responses

The conduction velocity is calculated by dividing the distance between the stimulus site and recording point (about 30 cm) by the latencies of the evoked FPs. The result obtained was 5 m/s. This suggested that the A_δ-fiber was engaged in the conduction of the first nociceptive component.

Response on the horizontal section

To locate the area of S1 that is responsive to the tail, systematic recordings on horizontal sections at a depth of 500 μm were performed (n=2). As the skin of the rat tail was irradiated by the CO_2 laser, point-by-point recordings were made at that depth. Higher amplitudes of the FPs waveforms were found when the recording points came closer to the mapped area of the tail (Fig. 1A). The overall range, however, was limited to a region 2.0 mm behind the bregma and 2.0 mm lateral to the sagittal suture. Although the amplitudes of the FPs varied with different recording points, the major receptive regions in S1 of the laser-induced nociceptive responses were 1.7–2.0 mm behind the bregma and 1.7–2.0 mm lateral to the sagittal suture.

As shown in Fig. 1, the latencies of the recording points were 50±5 ms, 60±5 ms, and 80±5 ms, respectively. The latencies were shorter when the recording points were more proximal to the tail.

Coronal and sagittal mapping of responses

After locating the responsive center on the horizontal section, it is important to verify the depth with the maximal FPs response. First, the coronal plane (approximately 1.7–2.0 mm right lateral to the sagittal suture and 500–1000 μm in depth) with anterior–posterior (AP) fixed at 1.9 mm behind the bregma (n=4) (Fig. 2A) was recorded. The responsive latencies on this plane were approximately 50±5 ms, and the amplitudes of the FPs were maximal at a depth of 900 μm. The CSD analysis of the FPs showed a dipole at a depth of 700–900 μm (Fig. 2B). Two sources were found at 700 μm and 900 μm, and a sink was demonstrated at a depth of 800 μm.

Second, the sagittal plane (approximately 1.9–2.2 mm behind the bregma and 500–1000 μm in depth) with medial–lateral (ML) fixed at 1.9 mm lateral to the sagittal suture, was mapped (n=1) (Fig. 3A). The responsive latencies, approximately 50–80 ms, were not as consistent as those on the coronal plane, and the FPs at a depth of 900 μm were more distinct than that seen at other depths. The CSD analysis of the FPs also showed a dipole at a depth of 700–900 μm (Fig. 3B). Two sources were found at 700 μm and 900 μm, and a sink was found at a depth of 800 μm.

Searching on the horizontal section at a depth of 900 μm

According to the previous results, the maximal response in S1 was located at 900 μm. Recordings were performed on the horizontal plane at a depth of 900 μm to obtain the maximal responsive area (n=3). The recording ranges were 1.7–2.1 mm behind the bregma and 1.7–2.1 mm lateral to the sagittal suture (Fig. 4A).

The FPs latencies varied from approximately 50–90 ms. As the recording points moved closer to the tail, the FP waveforms had higher amplitudes. The CSD analysis showed that a significant sink appeared (ML 1.8, AP 1.8–1.9) (Fig. 4B).

DISCUSSION

In this study, the first nociceptive component of the waveform showed a clear negative polarity. The later compo-

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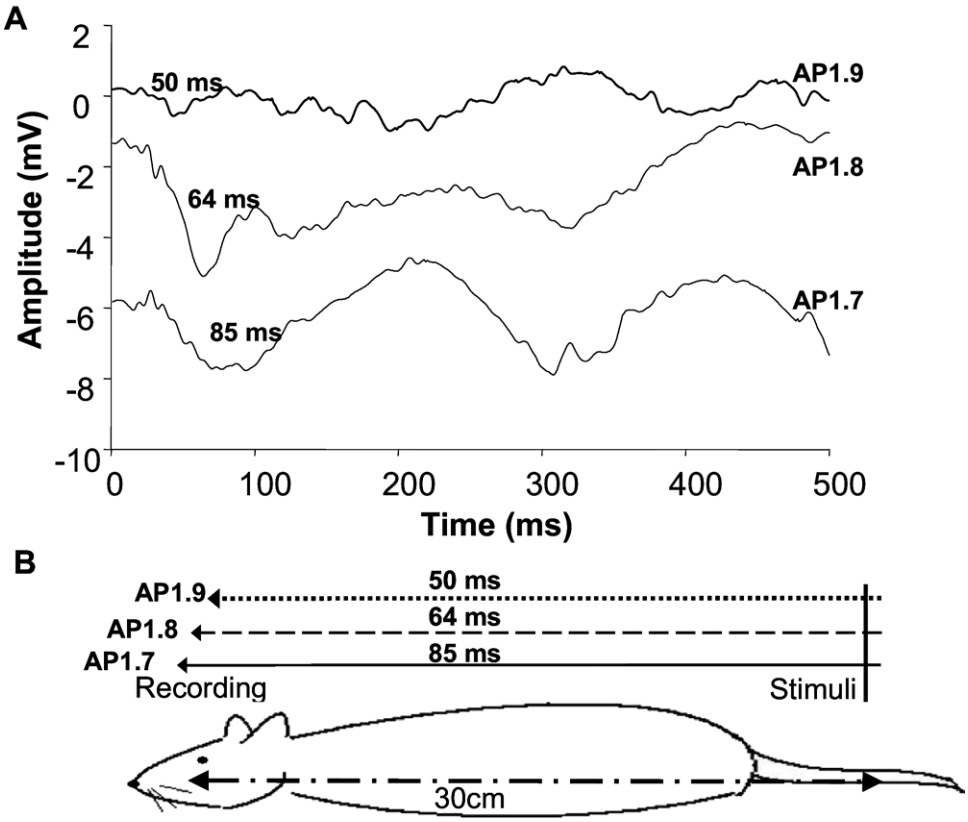

Fig. 1. The latencies of the responses on the sagittal plane, ML fixed at 1.9 mm lateral to the sagittal suture. (A) Waveforms of the laser evoked potentials. (B) Site of laser stimuli and recording points. The distances behind the bregma and their latencies are as indicated.

nent was also negative, but more variability was observed. These waveforms resembled the FPs recorded from Michigan probes in S1 (Sun et al., 2006).

The conduction velocity of the first component of the laser-evoked FPs corresponded to A_δ-fibers. Therefore, this component was identified as the early laser evoked potential (LEP1), mediated by A_δ-fibers from the periphery. LEP1 then enter the ventral posterolateral (VPL) nuclei of the thalamus and arrive at S1 (Treede et al., 1999). LEP1 can reflect the intensity of the laser stimulus (Ohara et al., 2004; Bornhovd et al., 2002; Kalliomaki et al., 1993) and is very sensitive to anesthetics (Shaw et al., 2001).

The appearance of the later negative-polarity waveform in this study was more unstable and ambiguous. Without the morphine control test (Kalliomaki et al., 1993; Sun et al., 2006), it is impossible to verify that this negative-polarity waveform is truly the late laser evoked potential (LEP2) (Kalliomaki et al., 1993), or the potentials from faster polysynaptic response in S1. Therefore, we focused on the LEP1, which is conveyed by the A_δ-fibers.

The initial hypothesis of this study is that since one of the major functions of S1 is localization (Treede et al., 1999), the variation in the response should be more related to the stimuli sites (receptive fields) than modalities. Because of previous findings from mechanical stimuli, a depth of 500 μm (Chien et al., 2007) was used to locate the responsive center in the horizontal plane. The massive pyramidal cells at this depth, which belong to laminae II/III of the cortex, helped us locate the representation of the tail in S1.

The CSD analysis from both coronal and sagittal planes showed similar results; that is the source-sink-source dipole is around 800 μm in depth. This indicated the ionic flows at this depth were very strong. It also corresponds to the dipole calculated from one-dimensional CSD analysis in lamina IV (Sun et al., 2006). Due to the specific thalamic afferents terminating in this layer, the neurons at this depth receive specific noxious inputs from the thalamus (White and Keller, 1989). The dipoles presented on these two planes were oriented vertically to the cortical surface. This confirms the columnar orientation in the cerebral cortex (Mountcastle, 1997).

The depth recordings of the maximal responses determined the main responsive regions in S1 when laser stimuli were applied to the rat's tail. In previous studies using various techniques including functional images, electro- or magneto-encephalograms, the maximal responsive depth (laminar) in S1 could not be clearly located (Bornhovd et al., 2002; Hofbauer et al., 2001; Bromm and Chen, 1995). Even the isopotential maps directly interpreted from laser evoked potentials only showed the widespread distributions in S1 (Shaw et al., 1999). The obvious dipole observed at a depth of 700–900 μm proved that there is somatotopic organization of the first laser-induced nociceptive component in S1.

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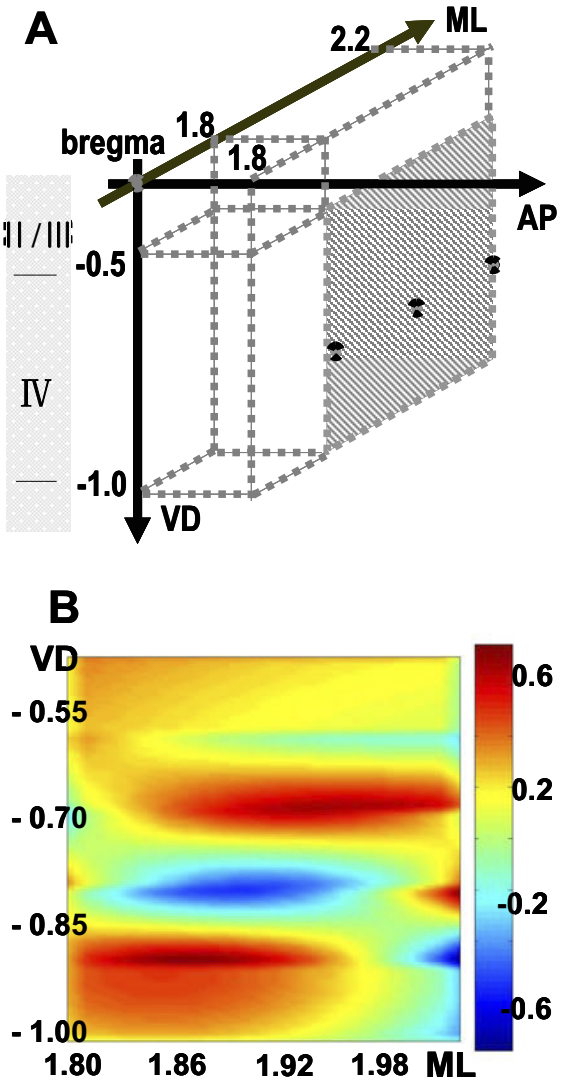

Fig. 2. The coronal plane showing the depth of maximal responses. (A) An illustration of where the recoding plane is made. (B) 2D CSD analysis on the coronal plane at 50 ms latency. A dipole (ML 1.8–2.1, VD 0.65–0.95) is obtained. (The unit of the color bar is v/mm^2.)

When stimulating the tail of the rat, the depth of the maximal response to mechanical stimuli was 500 μm (Chien et al., 2007) and that of laser stimuli was 900 μm. Previous studies support these findings that the cortical layer in the SI of rodents is more superficial when responding to mechanical stimuli compared with noxious ones (Shaw et al., 1999; Sun et al., 2006; Lamour et al., 1983a,b). In addition, some previous studies in rats (Schouenborg et al., 1986; Kalliomaki et al., 1993) and primates (Apkarian et al., 1987) have speculated that the nociception mediated by C-fibers projects to the deeper cortical layers, laminae Vb and VI, than that mediated by Aδ-fibers. These findings indicate that there are two nociceptive pathways from the periphery to the CNS and may manage different aspects of pain (Kalliomaki et al., 1993). The prominent responsive center of LEP1 obtained from CSD analysis in the more superficial lamina in S1 also supports this viewpoint.

Some previous findings from brain imaging studies show the different locations of mechanical and pain sensations, the former in area 3b and area 1, and the latter in area 3a, in the cortex of the primate (Tommerdahl et al., 1996; Craig, 2003). Since, the characteristics of traditional electrophysiological recordings and functional images are incomparable, the results from two kinds of studies may not fully correspond. Nonetheless, the inconsistence between the primate and the rat may not be attributed to the difference of functional imaging with electrophysiology only. Other studies showed the different locations between somatosensory evoked potentials (SSEPs) and (LEPs) in human S1 by using intracerebral recording (Valeriani et al., 2004). This supported that LEPs, especially the N2-P2 component, could be generated in a more posterior part of S1, e.g. area 1 or area 2 (Valeriani et al., 2004), S2 (Tarkka

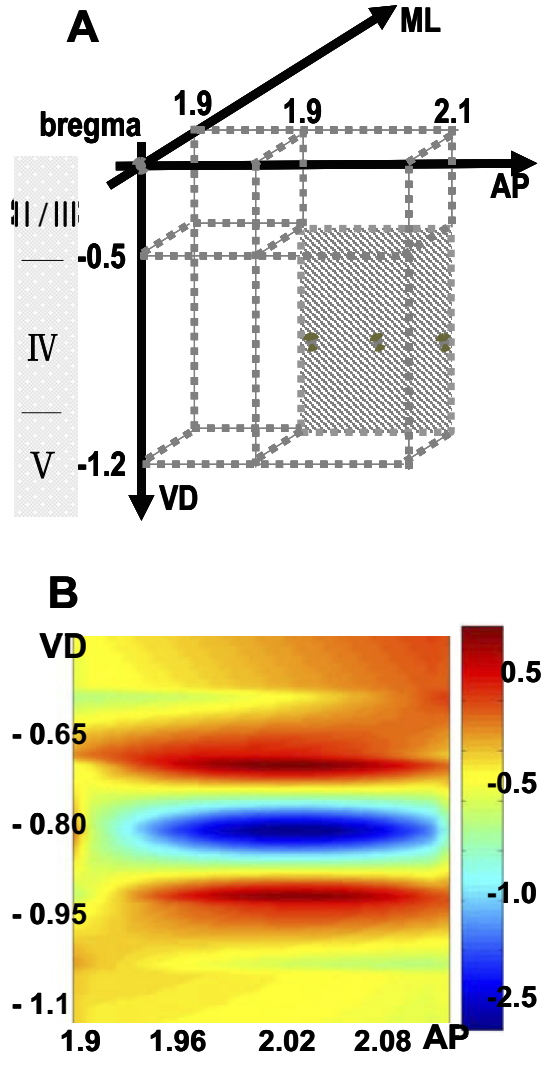

Fig. 3. The sagittal plane showing the depth of maximal responses. (A) An illustration of where the plane is recorded. (B) 2D CSD analysis on the sagittal plan at 50 ms latency. A dipole (AP 1.9–2.1, VD 0.65–0.95) is clearly shown. (The unit of the color bar is v/mm^2.)

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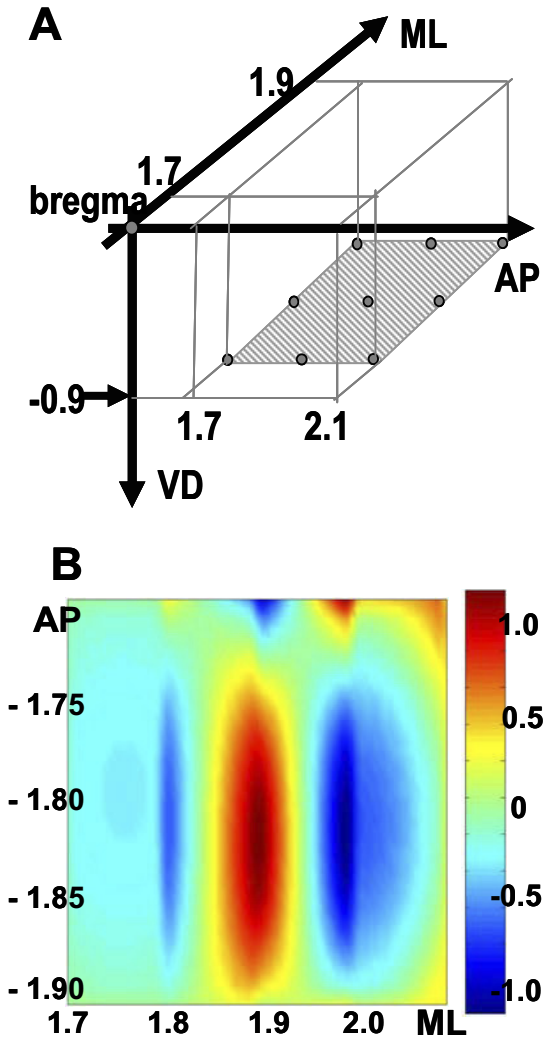

Fig. 4. Mapping at the horizontal plane. (A) Illustration of the recordings. (B) Two-dimensional CSD analysis on the horizontal plane at 55 ms latency. A dipole (ML 1.8–2.1, AP 1.75–1.9) is obtained. (The unit of the color bar is v/mm^2.)

and Treede, 1993; Bromm and Lorenz, 1998), or other posterior parietal cortex, area 5 or area 7 (Valeriani et al., 2004). Nevertheless, to compare the responsive region in S1 between painful and non-painful sensation, the more adequate stimuli should be used instead of electrical stimuli. Ultimately, there must be some differences among species. Considering the huge amount of the cerebral cortical volume of the primate, the function of localization and discrimination of modality may be accomplished at different areas, unlike the rodent that performs the two tasks in the same column. Based on the differences of methodology and species from prior researches, we just limited our suggestion in rodents.

If noxious stimuli from the same region in the periphery all induce the same topographic regions in S1, it would provide additional evidence that localization of sensory input is a definite function of S1 in the rat. Therefore, our initial hypothesis has been supported. For further confirmation, simultaneous recordings of neuronal responses to a variety of sensory modalities at different laminae in a single column should be performed. Multi-channel multi-unit simultaneous recordings could be used to further verify this hypothesis.

CONCLUSION

In summary, the A_δ-fiber-mediated component of nociception in S1 was mapped by CSD analysis. The horizontal section in S1 represents the somatotopic map of peripheral receptive fields. By contrast, the layer of S1 encodes the modality of stimuli. Thus, the S1 in the rat is a well-organized and highly structured area.

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