Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain Research 992 (2003) 263–271
BRAIN RESEARCH
www.elsevier.com/locate/brainres

Parallel pain processing in freely moving rats revealed by distributed neuron recording

Jin-Yan Wang[a], Fei Luo[a,*], Jing-Yu Chang[b], Donald J. Woodward[b], Ji-Sheng Han[a]

[a] *Neuroscience Research Institute and Department of Neurobiology, Peking University Health Science Center, Beijing 100083, PR China*
[b] *Department of Physiology and Pharmacology, Wake Forest University Health Science Center, NC 27157, USA*

Accepted 27 August 2003

Abstract

The present study was designed to examine the possible differential roles of the medial and lateral pain systems in pain perception. We used a microwire array recording technique to record the pain-evoked neural activity of multiple neurons in freely moving rats. Noxious radiant heat was delivered to either hind-paw in a randomized order. A total of 256 single units were recorded in primary somatosensory cortex (SI), anterior cingulate cortex (ACC), and medial dorsal (MD) and ventral posterior (VP) thalamus during the painful stimulation. The results showed that SI neurons displayed a strong pain-related excitatory response with short duration and significant contralateral bias; VP had very similar functional patterns to that of SI. This suggested that SI, together with VP, participate in the processing of the sensory-discriminative aspect of pain. In contrast, ACC and MD shared common characteristics of moderate and longer-lasting increase of neural activity, bilateral receptive fields without contralateral preference, as well as the anticipatory response at the start of a painful stimulus, corresponding to the specific role of ACC and MD in the affective-motivational aspects of pain. The results provide an initial demonstration of distributed activity patterns within different pain systems in awake and freely moving rats, hence, providing confirmation of the existence of the dual pain pathways.
© 2003 Elsevier B.V. All rights reserved.

Theme: Sensory systems
Topic: Pain: pathways

Keywords: Primary somatosensory cortex; Cingulate cortex; Thalamus; Nociception; Microelectrode

1. Introduction

It has long been recognized that pain is a multidimensional phenomenon. It is composed of sensory-discriminative and affective-motivational components, which are processed by parallel neural systems [2,21]. The 'lateral pain system', including lateral thalamic nuclei and somatosensory cortex, is thought to transmit information mainly about sensory features of pain stimuli, such as stimulus location, duration, intensity, and quality. On the other hand, the 'medial pain system' including the medial thalamic nuclei and cingulate cortex has been proposed to mediate the affective-motivational aspects of pain [16,33,39].

Evidence for dual pain systems is abundant. Neuroimaging studies have shown that multiple cortical regions are activated during painful stimulation. Among frequently activated cortical and subcortical regions are primary and secondary somatosensory cortex (SI and SII), anterior cingulate cortex (ACC), insular cortex (IC), and thalamus [6,10,11,15,17,26,38]. Data from anatomical and physiological studies reveal that somatosensory cortex receives nociceptive input mainly from lateral thalamic nuclei [12,14,37]. Clinical research has demonstrated that SI and SII lesions cause deficits in pain sensation without impairing pain affect, suggesting that somatosensory cortices are necessary for encoding selectively the sensory-discriminative aspects of pain [13,27]. In contrast, the nociceptive projections to ACC come largely from medial thalamic nuclei (midline and intralaminar nuclei) [36,41]. Using hypnotic suggestion, Rainville et al. [31] demonstrated that ACC was specifically related to the pain unpleasantness but not pain sensation. Also, single unit recordings in ACC of anesthetized rabbits and rats revealed nociceptive neurons that were not organized somatotopically and had large receptive fields [36,42],

* Corresponding author. Tel.: +86-10-62091152; fax: +86-10-82072207.
E-mail address: fluo@bjmu.edu.cn (F. Luo).

0006-8993/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2003.08.059

corresponding to the notion that ACC is engaged in processing pain affect.

Although it is widely accepted that nociceptive information is transmitted by separate, parallel pain systems, the neural basis for pain processing remains primarily uncertain. First, the limited temporal resolution of functional imaging does not allow for direct investigation of the pain-related activities over short durations [26,28]. Second, much of the experimental data on pain research has come from anesthetized animals [7,36,42]. The neural responses evoked by pain stimuli under anesthetized conditions should not be identical to those in the awake state, since this might interfere with the transmission and decoding of pain signals. Third, it is well known that even the simplest behaviors depend on the concurrent activation of large populations of neurons distributed across the brain [23]. Traditional single-unit recording techniques have sampled the activity of only one neuron, and the coding strategy of neural ensembles cannot ultimately be resolved without information about concurrent activity of ensembles of neurons. To date, there are no available data regarding neural ensemble activity corresponding to the cerebral coding of pain.

In the current study, we recorded pain-related neuronal activities with microwire arrays to obtain simultaneous recordings from groups of single neurons in freely moving rats. The aim of this study is to depict the time course of

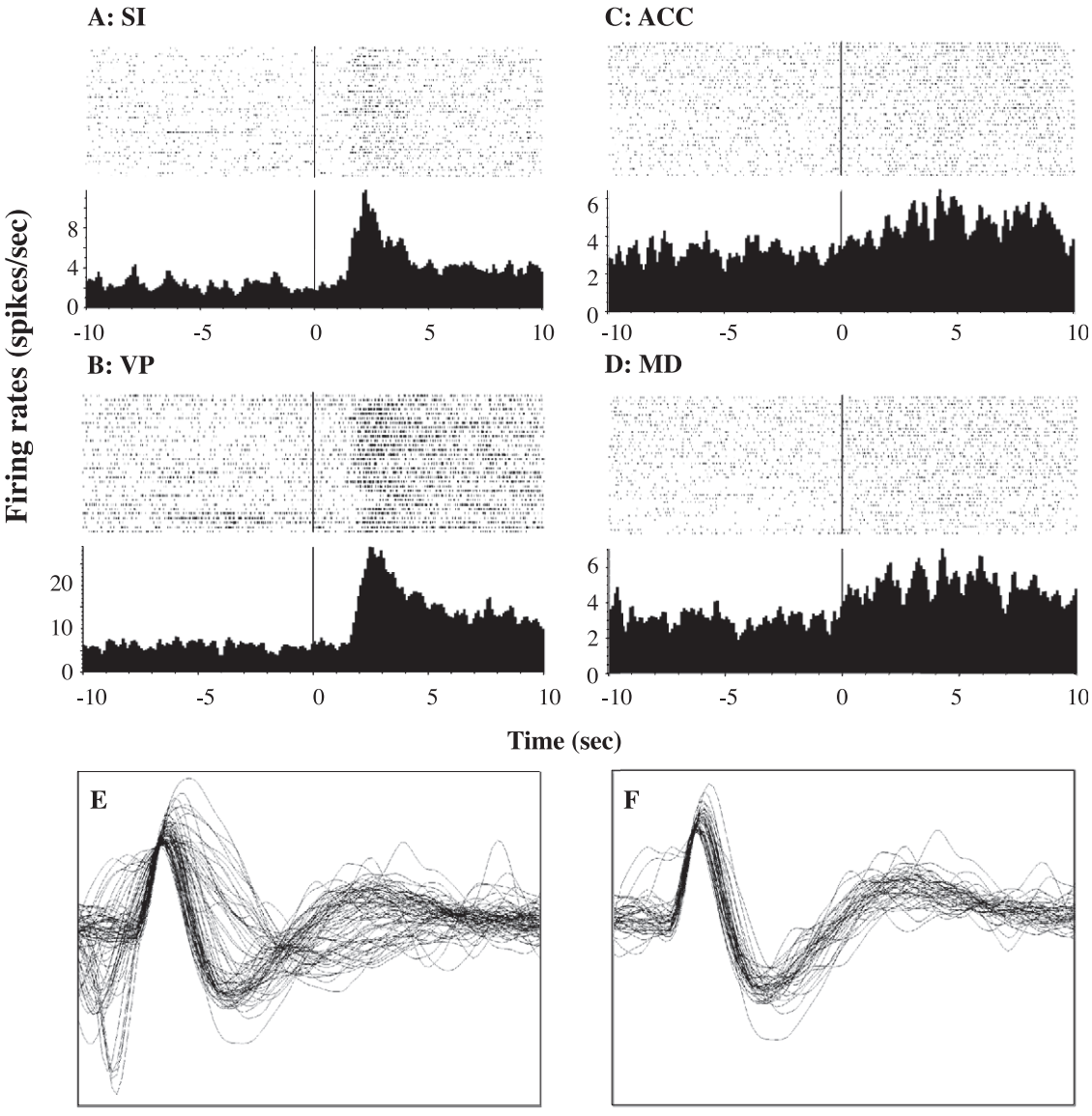

Fig. 1. Rasters and perievent histograms showed the typical excitatory neuronal response in SI, VP, ACC, and MD (A–D) during painful stimulation. Extracellularly recorded spike activity was sorted as nondiscriminated waveforms (E) and validated as single-unit discharge (F). SI (A) and VP (B) neurons displayed strong pain-related excitatory responses with short duration; in contrast, ACC (C) and MD (D) showed moderate and longer-lasting increase of neural activity. Each dot in the raster (top) depicted the time of occurrence of a neuronal spike, with each row representing an individual trial. The perievent histogram (bottom) illustrated the average firing rate of a neuron around a painful stimulus; time = 0 on the *x*-axis corresponded to the time of stimulation start. SI, the primary somatosensory cortex; ACC, the anterior cingulate cortex; MD, the medial dorsal thalamus; VP, the ventral posterior thalamus.

neuronal activity patterns in SI, ACC, and medial and lateral thalamus, and thus, to clarify the existence of parallel pain systems.

2. Materials and methods

2.1. Animals and surgery

Eight male Sprague–Dawley rats weighing 300–350 g were used in this study. Animals were housed under 12-h dark–light cycle (light phase 7:30 am–7:30 pm) for at least 1 week before surgery, with food and water available ad libitum. All experiments were carried out in accordance with the Institutional Animal Care and Use Committee of Peking University. All efforts were made to minimize animal suffering and reduce the number of animals used.

Animals were anesthetized with ketamine (100 mg/kg, i.p.), and then transferred to a Kopf stereotaxic apparatus. Supplementary doses (one third of the original) of ketamine were given when necessary to keep a sufficient level of anesthesia. Four small craniotomies were made for microelectrode array implantation. Coordinates for the craniotomies were according to the atlas of Paxinos and Watson [24] as follows: (1) for SI, 1.0 mm posterior to bregma (− 1.0 A), 2.0 mm lateral to midline (L), and 2.0 mm ventral to the skull surface (V); (2) for ACC, 3.2 A, 0.8 L, and 2.8 V; 3) for medial dorsal thalamus (MD), − 2.3 A, 0.8 L, and 5.5 V; 4) for ventral posterior thalamus (VP), − 3.0 A, 3.0 L, and 6.0 V. Arrays of eight stainless steel Teflon-insulated microwires (50-μm diameter, Biographics, Winston Salem, NC) were slowly lowered into the target areas. The microelectrode arrays were secured onto the cranium with dental cement using skull screws as anchors. Animals were administered penicillin (60,000 U, i.m.) before surgery to prevent infection and housed individually after surgery.

2.2. Experimental procedure

Experiments started 7 days after surgery. Animals were placed in a plastic chamber ($44 \times 44 \times 44$ cm^3) and allowed to move freely during the entire recording session. Lightweight cables connected the detachable headset to a rotating commutator on the ceiling of the chamber to allow for the animal's free movements. Noxious radiant heat from a 12.5-W projector bulb was used as painful stimulation, which was randomly applied to either side of the plantar surface of the rats' hind-paws via a 4-mm diameter opening and through a glass floor (1 mm thick). The nociceptive responses were measured by paw withdrawal elicited by the radiant heat. A time stamp series (resolution, 1 ms) marking stimulus start and end was recorded and synchronized with the neural spike recordings. The interstimulus interval was no less than 20 s. Each recording session lasted 1.5–2.0 h. Painful stimuli were delivered only when animal was quiet and showed no voluntary motor activity. Thus, the interstimulus intervals were not quite consistent throughout the recording session because the animal could sometimes be active (e.g. grooming or moving around the chamber).

Sham stimuli were randomly inserted among real painful stimulation (i.e., turned the light on and off to mimic the real stimulation without focusing on the rat paw). The neural responses around sham stimulation were recorded as control. The animal's behavior during the whole experimental session of experiment was recorded into a digital video file for off-line analysis.

2.3. Electrophysiological recording

Neuroelectric signals were obtained from the stainless steel microwires and passed from the headset assemblies to a preamplifier via two lightweight cables and a commutator. The signals were then filtered (0.5 and 5 kHz, 6 dB cutoff) before being sent to a multichannel spike-sorting device. The sampling rate is 50 kHz. Spike activities were monitored on a computer with a time resolution of 20 μs, picked up by setting proper parameters for amplitude and duration, and recorded into a database file with a PC-based software Magnet (Biographics). Data was then analyzed with a commercially available PC-based program (STRANGER, Biographics). The identity of clearly sorted single neurons was verified by graphical capture of waveform (see Fig. 1E and F for example). We also routinely compute inter spike interval (ISI) histograms of the spike train data. If the ISI plots reveal counts in bins close to zero, the neuron will be rejected. The time stamps of these waveforms were then stored on a personal computer for off-line analysis.

2.4. Data analysis

Bin counts for each trial (0.1 s bin size) were calculated using the analysis program NeuroExplorer (Plexon, Dallas, TX) and the results were exported to Matlab in spreadsheet form. Neural responses to pain stimulation were evaluated using a sliding window averaging technique [34], in which a

Table 1
Summary of the experimental groups and recorded neurons

Rat no.	Target areas	Side of microelectrode arrays	Number of units
1	SI, ACC, VP, MD	unilateral	32
2	SI, ACC, VP, MD	unilateral	32
3	SI, ACC, VP, MD	unilateral	27
4	SI, VP	bilateral	35
5	SI, VP	bilateral	31
6	SI, VP	bilateral	34
7	ACC, MD	bilateral	33
8	ACC, MD	bilateral	32

Total units = 256.
SI, the primary somatosensory cortex; ACC, the anterior cingulate cortex; MD, the medial dorsal thalamus; VP, the ventral posterior thalamus.

Table 2
Summary of percent of total responding units according to response type

	ACC	MD	SI	VP
Total number of neurons	59	55	74	68
Excitatory	32 (54%)	27 (49%)	54 (73%)	62 (91%)
Inhibitory	9 (15%)	4 (7%)	0	0
Sum	41 (69%)	31 (56%)	54 (73%)	62 (91%)

1-s time window was slid through the entire period of a trial at 0.1-s step. The bin counts of each window were compared with those of a preset 3-s control window 10 s before the stimulation event by Student's *t*-test. The differences were considered significant only when it reached a significance level of $p < 0.005$ in three consecutive steps, thus to achieve a global significance of $p < 0.05$ (as proposed by a Monte Carlo simulation with a program (AlphaSim) proposed by Douglas Ward (http://afni.nimh.nih.gov/afni/AFNI_Help/AlphaSim.html).

A cluster technique (K-means, SPSS) was used to sort neuronal responses depending on the similarities in patterns of excitation or inhibition around stimulation events. Normalized firing rates (z) were used to visualize activity patterns in populations. This was calculated by the following formula: $z=(x-m)/s$, where x is the raw firing rate, computed within the moving window, of a neuron at a particular time bin, and m and s are mean and standard deviation, respectively, of its firing rates throughout the whole time period (-10 to $+10$ s) around the stimulation events.

To compare the neural responses between different events (e.g., cortical responses evoked by ipsilateral vs. contralateral hind-paw stimulation), we adapted the information theory concept '*surprise*'. This is defined as the

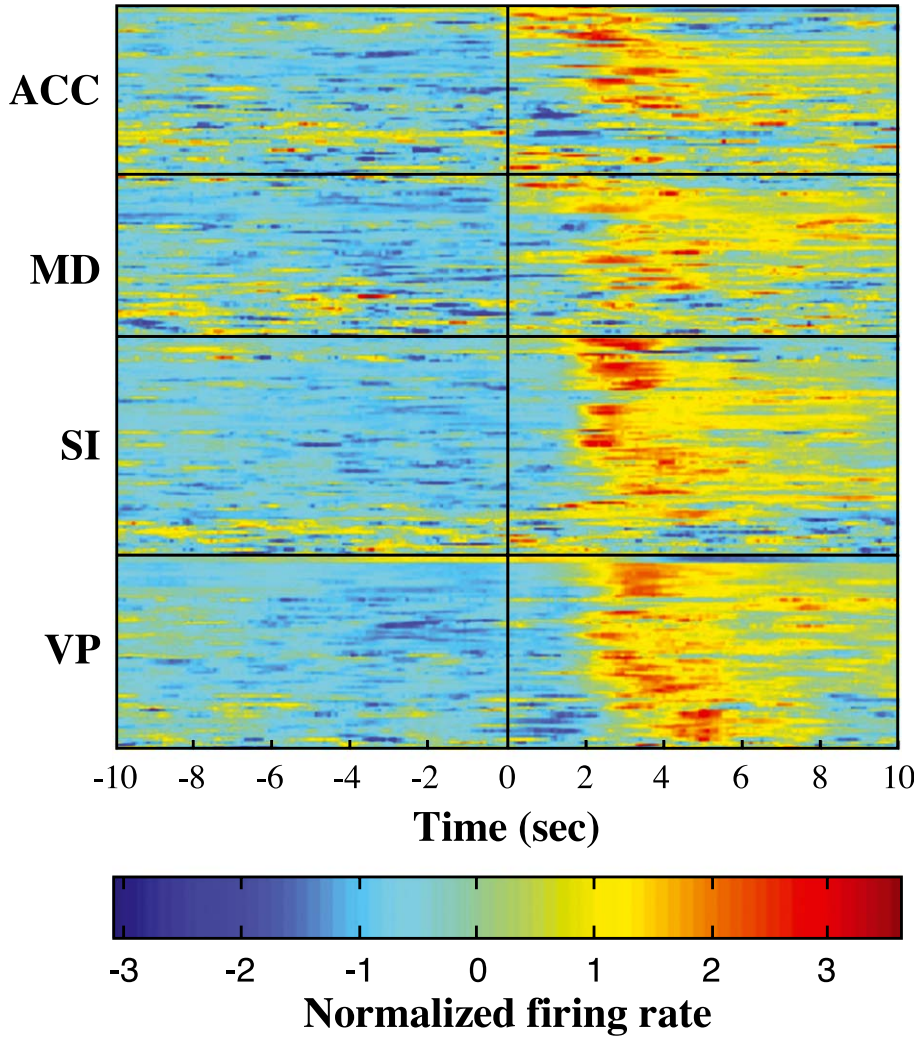

Fig. 2. Cluster plot depicted the temporal distribution patterns of neural activity in ACC, MD, SI, and VP. The firing rate was normalized to the average of 0 and standard deviation of 1 (dark red for the highest frequency and dark blue for lowest); time = 0 on the axis corresponded to the time of stimulation start. Each line of the image represents normalized activity of one neuron. Both ACC and MD neurons showed less intense spike activity; more importantly, a small portion of them presented early responses at the start of painful stimuli; in contrast, neurons in SI and VP were activated more strongly and responded to pain stimuli with a latency of 2–4 s.

negative natural logarithm of the statistical p values, i.e., -ln p, and is used to plot the averaged ensemble significance of neuronal responses over time. This was initially introduced by Aertsen et al. [1] to express the significance across time for joint peristimulation time histogram. This logarithmic transformation serves to expand the scale in the interesting region in which the probability density has low values (i.e., for p values smaller than 0.05). Moreover, it allows a more sensible comparison of different values of significance. The 'p values' produced by the aforementioned sliding-window method were converted into *surprise* to highlight the significance of the responses distributed over a time period.

2.5. Histology

After the termination of the experiment, rats received an overdose of ketamine. Recording sites were marked by electrophoretically deposited iron (10–20 μA DC current, 10–20 s duration, anode at the electrode) at the tips of selected wires. Animals were then perfused with 4% paraformaldehyde. The brains were post-fixed in a solution of 5% potassium ferricyanide/4% paraformaldehyde for several days. Coronal sections (40 μm) were cut through the SI, ACC, and thalamus. Recording sites were determined under a light microscope. The iron deposits were easily identified as blue dots.

3. Results

3.1. Pain-related behaviors

When noxious radiant heat was applied to the hind paw, rats promptly lifted their feet with an average latency of 3.2 ± 0.1 s; this was followed by aversive behaviors such as licking of the stimulated paw, accompanied occasionally by gentle biting. The latencies on each side of the foot were compared with paired t-test. No statistically significant difference was noted between left and right hind paws ($p = 0.7181$). During the sham stimulation, rats usually sat silently without any visible movement or other behavioral responses.

3.2. Pain-evoked neural activity

Data included in this study were from eight male Sprague–Dawley rats, with ACC and MD from six of the rats while SI and VP from five. A total of 256 neurons were recorded during pain stimulation (74 SI, 59 ACC, 68 VP, and 55 MD). Table 1 summarized the location of microelectrode arrays and the number of units recorded from each rat. The mean firing rates of ACC, SI, VP, and MD neurons were 3.8 ± 0.4, 4.4 ± 0.4, 5.8 ± 0.7, and 6.6 ± 0.7 spikes/s (mean $\pm$ S.E.), respectively.

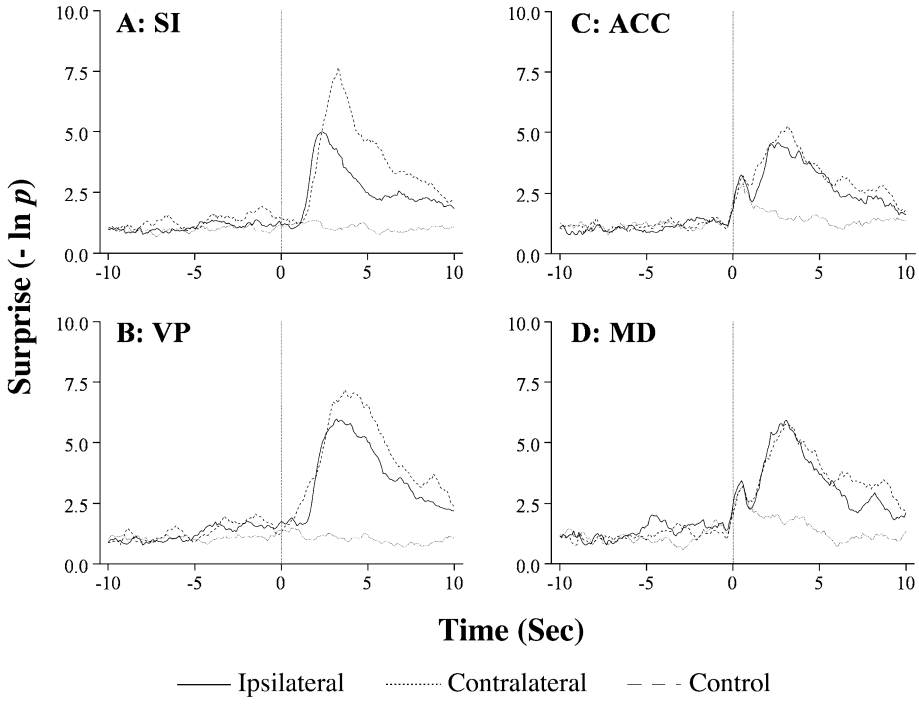

Fig. 3. *Surprise* plot indicating an overall bilateral response to unilateral painful stimulation. Time = 0 on the x-axis corresponded to the time of stimulation start. The y-axis represented the negative logarithm of the probability (-ln p). As shown here, SI had significant contralateral bias (A); VP had a slightly less biased response (B) compared to SI. By contrast, ACC (C) and MD (D) increased their neural activity bilaterally without contralateral bias. Both ACC and MD showed an initial peak within 1 s near the stimulation start, suggesting an anticipatory response regarding pain stimuli.

3.2.1. General neuronal responses

The single units could be classified into two categories, i.e., excitatory or inhibitory, according to their responses to pain. The overall neuronal responses in the 256 neurons were summarized in Table 2.

In ACC and MD, the most common response was excitatory, although occasional units with inhibitory response were encountered. Of 59 units recorded from the ACC, 32 (54%) showed significant excitatory responses to pain stimulation, whereas 9 (15%) displayed significant inhibitory responses. In the MD thalamus, 27 of 55 (49%) units were excitatory and 4 of 55 (7%) were inhibitory. In contrast, the response observed in SI and VP was exclusively excitatory during noxious stimulation. As indicated in Table 2, 73% of units in SI displayed increased alterations in firing rate. In addition, a higher proportion of 91% of units increased the spike activity in VP thalamus. No units showed biphasic responses in each of the areas during the entire recording sessions. Rasters and perievent histograms depicted the average firing rate and typical excitatory response in the four recording areas, as illustrated in Fig. 1. Note the difference in neural spike activity among the different areas. The neuronal activity in ACC and MD slowly increased and lasted longer, compared with the sharp increase in SI and VP.

3.2.2. Temporal coding patterns

Fig. 2 shows the neuronal responses of the cortex and thalamus arranged in clusters according to its temporal sequence. The firing rate for each neuron (indicated with a line in the image) was normalized to an average of 0 Hz and a standard deviation of 1 to display relative changes (red for the highest frequency and blue for lowest). Time = 0 on the transverse axis corresponded to the time of stimulation start. As depicted in Fig. 2, both ACC and MD neurons showed relatively moderate changes of spike activity. More impor-

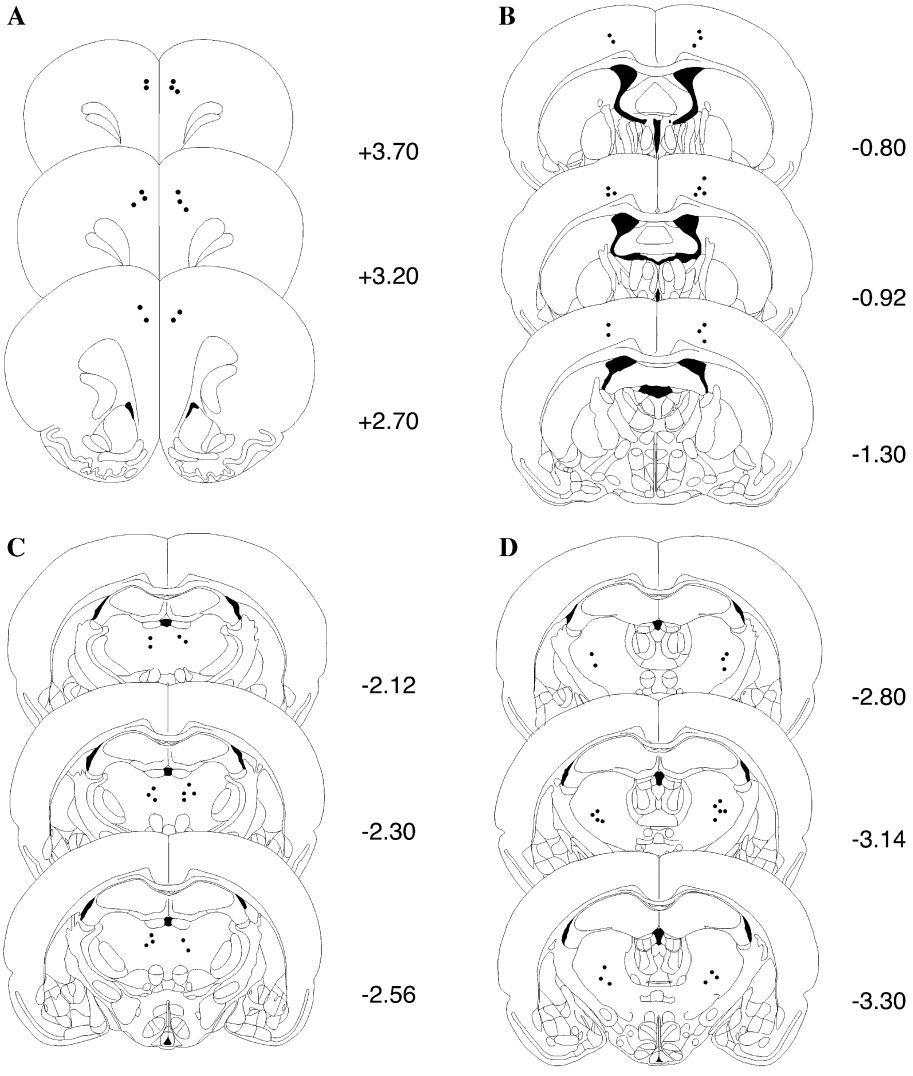

Fig. 4. A schematic drawing indicating the location of recording sites in ACC (A), SI (B), MD (C) and VP (D). The black dots labeled the position of iron deposits at the tips of selected microwires.

tantly, a small portion of them presented early responses to pain stimulation. In contrast, neurons in SI and VP were activated more strongly and responded to pain stimuli with a latency of 2–4 s. The relative response magnitude of SI and VP was notably higher (darker red) than that of ACC and MD. This result revealed that ACC and MD might be functionally associated in the coding of pain. Such was the case for SI and VP.

3.2.3. Spatial coding patterns

The *surprise* plot of $-\ln p$ indicated an overall bilateral response to unilateral painful stimuli, with significant contralateral bias in SI and a less evident contralateral bias in VP (Fig. 3A and B). By contrast, ACC and MD increased their neural activity bilaterally without contralateral bias (Fig. 3C and D). It is interesting to see that both ACC and MD showed an initial peak within 1 s near the stimulation start (including sham stimulation), suggesting an anticipatory response mediated by the medial pain pathway.

3.3. Histology

The location of microwires as revealed by the iron deposits at the tips of selected microwires was depicted in Fig. 4, in which the black dots labeled the recording sites. As indicated in the figure, in the cingulate cortex, most of the iron deposits were found in the anterior areas; in the somatosensory cortex, most of the recording tips were in the hind limb region; in MD, tips were mainly found in the mediodorsal part; whereas in VP, the tips were primarily located in ventroposterior part.

4. Discussion

This study provides the first report characterizing the simultaneously recorded single-neuron response patterns of SI, ACC, and lateral and medial thalamus to painful stimuli. With the many-neuron microwire array recording technique, our results reveal a fundamental difference in the temporal coding patterns of both pain systems. The data support the idea that SI and lateral thalamus are mainly engaged in pain sensation whereas ACC and medial thalamus may mediate pain affect. In addition, we infer that SI may play a role in integrating nociceptive information from both contralateral and ipsilateral hind-paws, based on the findings that SI showed bilateral neural activity despite the contralateral bias in response to unilateral painful stimuli.

4.1. Methodological considerations

The many-neuron microwire array recording technique allows for simultaneous measurement of the spike activity of dozens of individual neurons in behavior animals [8,22]. The procedure was developed originally to provide a real-time window onto neuronal function so that the investigator may better understand the relationship between neuronal activity and behavior. Here, we first introduce this method to study pain-evoked neural responses in distributed neural circuits. This will eventually allow study of how neural ensembles encode the nociceptive information. The fine spatial and temporal resolutions of this technique will contribute toward defining pain-related brain regions with greater precision.

In the present study, we have used noxious radiant heat as a means of evoking painful sensation without a major tactile component. This procedure minimized the possibility that spatial information of pain signal comes from tactile input, which is a major advantage over electric or mechanical noxious stimulation.

4.2. Primary somatosensory cortex and lateral thalamic nuclei

The potential role of SI in pain processing so far has been difficult to clarify. One reason is that functional neuroimaging studies do not consistently reveal pain-related activation of SI [26]. Several factors may contribute to the failure to detect SI activation in pain processing. These include, cognitive factors, imprecise tactile components of pain stimuli, inhibitory effects within SI as well as the low temporal resolution of imaging techniques [3,5,25]. Our result indicated that SI may have an essential role in the sensory-discriminative aspects of pain. First, the perievent histograms showed a strong but brief increase of firing rate in SI. This may be related closely with ‘first pain’, the early component of pain perception, because first pain is characterized by a short duration, with sharp and precise location. This is in accordance with the MEG study of Ploner et al. [28] who proposed that transient SI activation may mediate first pain. Results from our current study indicated that SI is involved in coding the short-term temporal element of pain. Second, SI activity was revealed as contralaterally biased neural activity in response to unilateral painful stimulation, reflecting a role of SI in coding the stimulus location. This was consistent with the result of Bingel et al. [4], who used a laser stimulus as noxious stimulation and found significant contralateral preference in SI. Previous electrophysiological evidence in animals also demonstrated that the nociceptive SI neurons had restricted receptive fields [9,18–20], in agreement with the notion that SI is responsible for the stimulus location.

Ventral posterior thalamus (VP), a lateral thalamic nucleus, had a response pattern very similar to that for SI, which could be seen in Figs. 1, 2 and 3. Anatomic studies revealed nociceptive projections from the lateral thalamic nuclei, particularly from the ventral posterior lateral nucleus (VPL), to SI [14]. So, it is possible that lateral thalamus shares with SI in the processing of pain.

An interesting feature of our result was that SI was frequently activated bilaterally during pain stimulation

(Fig. 3), despite the contralateral predominance. This may be attributed to the bilateral interactions in SI during the processing of painful stimulation via connections between hemispheres. These pathways make it possible for SI to integrate information from both contralateral and ipsilateral hind-paws. The function of transcallosal activity remains primarily unknown, but one might presume that the information could be used to influence appropriate motor responses. Shuler et al. [35] also found that SI neurons respond to both contralateral and ipsilateral whisker stimuli. They interpret this as evidence of cortical integration of bilateral whisker stimuli. Their findings and our current result present a challenge to the conventional notion that the cortices simply process contralateral aspects of unilateral stimuli.

4.3. Anterior cingulate cortex and medial thalamic nuclei

Data about the involvement of ACC in the affective dimension of pain comes mostly from neuroimaging studies [17,26,30]. Electrophysiological recordings in the rabbits and rats demonstrated that nociceptive neurons in ACC had large and bilateral receptive fields [36,40,42], a property that was consistent with a role in the affective or motivational processing. Our results provide further evidence for the participation of ACC in coding the affective-motivational aspects of pain. First, in the present study, the neuronal responses in ACC were not as strong as SI but with longer-lasting duration, reflecting that ACC is not involved primarily in precise pain discrimination. Second, we also found ACC showed an anticipatory response at the very onset of the light leading to the painful stimulation (Figs. 2 and 3), which does not occur in SI and VP. This could also be seen during sham stimulation, when rats usually sit silently without any visible movement or other behavioral responses. Since this is the first pain-testing session for these rats, and sham stimulation was randomly inserted, it should not be considered as a model of conditioning. On the other hand, since pain is a strong unpleasant feeling, rats might quickly learn to notice the stimulation that was once associated with pain. Thus, the observed early responses in MD and ACC might better be interpreted as anticipatory or motivational response to these pain-related environmental changes. This suggests a specific role of ACC in associative processes related to the affective-motivational component of pain. Third, we confirmed that ACC neurons had bilateral receptive fields, according with its role in coding consequences of the pain affect.

Anatomical studies provide direct evidence to the projection from medial thalamus to ACC [32,41]. Neurons in medial thalamus typically had large bilateral receptive fields, similar to that of ACC neurons. Our finding of the same response patterns in MD as that in ACC strongly suggested a close functional association between MD and ACC in pain perception. They may work together as components of a distributed system to subserve the affective-motivational rather than sensory-discriminative aspects of pain.

Price [29] supports the idea that pain sensation is in series with and is a cause of pain unpleasantness. However, our results show that brain areas composed of medial and lateral pain system respond concurrently to peripheral pain stimulation. This seems to be in favor of the conventional view of Melzack and Casey [21] that pain sensation and affect may be processed in parallel. Sikes and Vogt [36] also point out that complete disconnection of ACC from somatosensory cortex in rabbits does not alter the percentage of units driven by noxious stimuli nor response latency within ACC. Thus, it is possible that ACC receives nociceptive inputs in parallel with somatosensory cortex. Nevertheless, the radiant heat stimulation employed in the current study is not fully suitable to address this question in that the skin temperature is gradually increased instead of abruptly; hence, the response latency may not be accurate enough to disclose the activation sequence. Further investigation will be necessary to answer this question.

In summary, our results begin to reveal the distributed activity patterns evoked by noxious heat stimulation within SI, VP, ACC, and MD. Brain areas belonging to the medial pain system revealed bilateral, earlier, and more moderate responses, in accordance with the coding of affective responses to pain. On the other hand, areas of the lateral pain system displayed more contralateral, longer latency, and transient responses, suggesting a role in the coding of sensory-discriminative aspect of pain.

Acknowledgements

This study was supported by National Natural Science Foundation of China (30170307), a grant from the 211 project, and a startup grant for young scientists from the 985 project of Peking University to F.L., NIH grants EB002092 and AA10980 to D.J.W., and NS-43441 and TW06144 to J.-Y.C.

References

[1] A.M. Aertsen, G.L. Gerstein, M.K. Habib, G. Palm, Dynamics of neuronal firing correlation: modulation of "effective connectivity", J. Neurophysiol. 61 (1989) 900–917.

[2] D. Albe-Fessard, K.J. Berkley, L. Kruger, H.J. Ralston, W.D. Willis Jr., Diencephalic mechanisms of pain sensation, Brain Res. 356 (1985) 217–296.

[3] A.V. Apkarian, Functional imaging of pain: new insights regarding the role of the cerebral cortex in human pain perception, Semin. Neurosci. 7 (1995) 279–293.

[4] U. Bingel, M. Quante, R. Knab, B. Bromm, C. Weiller, C. Buchel, Single trial fMRI reveals significant contralateral bias in responses to laser pain within thalamus and somatosensory cortices, Neuroimage 18 (2003) 740–748.

[5] M.C. Bushnell, G.H. Duncan, R.K. Hofbauer, B. Ha, J.I. Chen, B. Carrier, Pain perception: is there a role for primary somatosensory cortex? Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 7705–7709.

[6] K.L. Casey, S. Minoshima, K.L. Berger, R.A. Koeppe, T.J. Morrow, K.A. Frey, Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli, J. Neurophysiol. 71 (1994) 802–807.
[7] C. Chang, B.C. Shyu, A fMRI study of brain activations during non-noxious and noxious electrical stimulation of the sciatic nerve of rats, Brain Res. 897 (2001) 71–81.
[8] J.Y. Chang, L. Chen, F. Luo, L.H. Shi, D.J. Woodward, Neuronal responses in the frontal cortico-basal ganglia system during delayed matching-to-sample task: ensemble recording in freely moving rats, Exp. Brain Res. 142 (2002) 67–80.
[9] E.H. Chudler, F. Anton, R. Dubner, D.R. Kenshalo Jr., Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval, J. Neurophysiol. 63 (1990) 559–569.
[10] R.C. Coghill, J.D. Talbot, A.C. Evans, E. Meyer, A. Gjedde, M.C. Bushnell, G.H. Duncan, Distributed processing of pain and vibration by the human brain, J. Neurosci. 14 (1994) 4095–4108.
[11] R.C. Coghill, C.N. Sang, J.M. Maisog, M.J. Iadarola, Pain intensity processing within the human brain: a bilateral, distributed mechanism, J. Neurophysiol. 82 (1999) 1934–1943.
[12] D.P. Friedman, E.A. Murray, Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque, J. Comp. Neurol. 252 (1986) 348–373.
[13] J.D. Greenspan, R.R. Lee, F.A. Lenz, Pain sensitivity alterations as a function of lesion location in the parasylvian cortex, Pain 81 (1999) 273–282.
[14] S.I. Gingold, J.D. Greenspan, A.V. Apkarian, Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys, J. Comp. Neurol. 308 (1991) 467–490.
[15] R.K. Hofbauer, P. Rainville, G.H. Duncan, M.C. Bushnell, Cortical representation of the sensory dimension of pain, J. Neurophysiol. 86 (2001) 402–411.
[16] A.J. Hudson, Pain perception and response: central nervous system mechanisms, Can. J. Neurol. Sci. 27 (2000) 2–16.
[17] A.K. Jones, W.D. Brown, K.J. Friston, L.Y. Qi, R.S. Frackowiak, Cortical and subcortical localization of response to pain in man using positron emission tomography, Proc. R. Soc. Lond., B Biol. Sci. 244 (1991) 39–44.
[18] D.R. Kenshalo Jr., O. Isensee, Responses of primate SI cortical neurons to noxious stimuli, J. Neurophysiol. 50 (1983) 1479–1496.
[19] D.R. Kenshalo Jr., E.H. Chudler, F. Anton, R. Dubner, SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation, Brain Res. 454 (1988) 378–382.
[20] Y. Lamour, J.C. Willer, G. Guilbaud, Rat somatosensory (SmI) cortex: I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non- noxious stimulation, Exp. Brain Res. 49 (1983) 35–45.
[21] R. Melzack, K.L. Casey, Sensory, motivational and central control determinants of pain: a new conceptual model, in: D.R. Kenshalo (Ed.), The Skin Senses, Thomas, Springfield, 1968, pp. 423–443.
[22] M.A. Nicolelis, L.A. Baccala, R.C. Lin, J.K. Chapin, Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system, Science 268 (1995) 1353–1358.
[23] M.A. Nicolelis, A.A. Ghazanfar, B.M. Faggin, S. Votaw, L.M. Oliveira, Reconstructing the engram: simultaneous, multisite, many single neuron recordings, Neuron 18 (1997) 529–537.
[24] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, Academic Press, New York, 1998.
[25] R. Peyron, L. Garcia-Larrea, M.C. Gregoire, N. Costes, P. Convers, F. Lavenne, F. Mauguiere, D. Michel, B. Laurent, Haemodynamic brain responses to acute pain in humans: sensory and attentional networks, Brain 122 (Pt 9) (1999) 1765–1780.
[26] R. Peyron, B. Laurent, L. Garcia-Larrea, Functional imaging of brain responses to pain. A review and meta-analysis, Neurophysiol. Clin. 30 (2000) 263–288.
[27] M. Ploner, H.J. Freund, A. Schnitzler, Pain affect without pain sensation in a patient with a postcentral lesion, Pain 81 (1999) 211–214.
[28] M. Ploner, J. Gross, L. Timmermann, A. Schnitzler, Cortical representation of first and second pain sensation in humans, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 12444–12448.
[29] D.D. Price, Psychological and neural mechanisms of the affective dimension of pain, Science 288 (2000) 1769–1772.
[30] P. Rainville, Brain mechanisms of pain affect and pain modulation, Curr. Opin. Neurobiol. 12 (2002) 195–204.
[31] P. Rainville, G.H. Duncan, D.D. Price, B. Carrier, M.C. Bushnell, Pain affect encoded in human anterior cingulate but not somatosensory cortex, Science 277 (1997) 968–971.
[32] R.T. Robertson, S.S. Kaitz, Thalamic connections with limbic cortex: I. Thalamocortical projections, J. Comp. Neurol. 195 (1981) 501–525.
[33] A. Schnitzler, M. Ploner, Neurophysiology and functional neuroanatomy of pain perception, J. Clin. Neurophysiol. 17 (2000) 592–603.
[34] W. Schultz, R. Romo, Role of primate basal ganglia and frontal cortex in the internal generation of movements, Exp. Brain Res. 91 (1992) 363–384.
[35] M.G. Shuler, D.J. Krupa, M.A. Nicolelis, Bilateral integration of whisker information in the primary somatosensory cortex of rats, J. Neurosci. 21 (2001) 5251–5261.
[36] R.W. Sikes, B.A. Vogt, Nociceptive neurons in area 24 of rabbit cingulate cortex, J. Neurophysiol. 68 (1992) 1720–1732.
[37] R.T. Stevens, S.M. London, A.V. Apkarian, Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey, Brain Res. 631 (1993) 241–246.
[38] J.D. Talbot, S. Marrett, A.C. Evans, E. Meyer, M.C. Bushnell, G.H. Duncan, Multiple representations of pain in human cerebral cortex, Science 251 (1991) 1355–1358.
[39] R.D. Treede, D.R. Kenshalo, R.H. Gracely, A.K. Jones, The cortical representation of pain, Pain 79 (1999) 105–111.
[40] B.A. Vogt, R.W. Sikes, The medial pain system, cingulate cortex, and parallel processing of nociceptive information, Prog. Brain Res. 122 (2000) 223–235.
[41] B.A. Vogt, D.N. Pandya, D.L. Rosene, Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents, J. Comp. Neurol. 262 (1987) 256–270.
[42] H. Yamamura, K. Iwata, Y. Tsuboi, K. Toda, K. Kitajima, N. Shimizu, H. Nomura, J. Hibiya, S. Fujita, R. Sumino, Morphological and electrophysiological properties of ACCx nociceptive neurons in rats, Brain Res. 735 (1996) 83–92.