

Corticothalamic Influences on Thalamic Neurons During Nociceptive Transmission in Awake Rats

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ABSTRACT Pain is a multidimensional phenomenon and processed in a neural network. The supraspinal, brain mechanisms are increasingly recognized in playing a major role in the representation and modulation of pain. The aim of the current study is to investigate the functional interactions between cortex and thalamus during nociceptive processing, by observing the pain-related information flow and neuronal correlations within thalamo-cortical pathways. Pain-evoked, single-neuron activity was recorded in awake Sprague-Dawley rats with a Magnet system. Eight-wire microarrays were implanted into four different brain regions, i.e., the primary somatosensory (SI) and anterior cingulate cortex (ACC), as well as ventral posterior (VP) and medial dorsal thalamus (MD). Noxious radiant heat was delivered to the rat hind paws on the side contralateral to the recording regions. A large number of responsive neurons were recorded in the four brain areas. Directed coherence analysis revealed that the amount of information flow was significantly increased from SI cortex to VP thalamus following noxious stimuli, suggesting that SI cortex has descending influence on thalamic neurons during pain processing. Moreover, more correlated neuronal activities indicated by crosscorrelation histograms were found between cortical and thalamic neurons, with cortical neurons firing ahead of thalamic units. On basis of the above findings, we propose that nociceptive responses are modulated by corticothalamic feedback during nociceptive transmission, which may be tight in the lateral pathway, while loose in the medial pathway. **Synapse 61:335–342, 2007.** © 2007 Wiley-Liss, Inc.

INTRODUCTION

Sensory processing in general has been recognized as a network activity in central nervous system, where computations depend on large-scale feedback loops (Ahissar and Kleinfeld, 2003; Crabtree, 1999; Ghazanfar et al., 2000). It is now widely accepted that pain experience is a consequence of an integration of cognitive, sensory, and affective processes (Melzack and Casey, 1968). The perception of pain requires the activation of multiple neurons across the pain system and the interactions between the thalamus and cortex, as well as limbic system (Almeida et al., 2004; Apkarian et al., 2005; Brooks and Tracey, 2005; Peyron et al., 1999; Price, 2000, 2002; Treede et al., 1999). Neuroimaging studies have identified a

network consisting of somatosensory (SI), limbic, and associative structures that can be subdivided into a lateral and a medial system, based on the projection sites from medial or lateral thalamic structures to the

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cortex (Bushnell et al., 1999; Casey et al., 1994; Craig et al., 1996, 2000; Jones et al., 1992; Porro et al., 1998; Rainville et al., 1997, 1999; Talbot et al., 1991). The lateral system is primarily thought to have a role in processing the sensory-discriminative aspects of pain, while the medial system is involved in the affective-motivational component of pain (Schnitzler and Ploner, 2000; Treede et al., 1999; Vogt and Sikes, 2000; Wang et al., 2003).

Extensive data support the anatomical connections between cortex and thalamus, making it possible to investigate the functional interactions among SI systems (Arnold et al., 2001; Bernardo and Woolsey, 1987; Chmielowska et al., 1989; Jensen and Killackey, 1987; Jones, 1985). Experiments on the coding of vibrissae sensation has shown that there exists tightly related functional neural ensembles in the SI pathway to code tactile stimulus location (Ghazanfar et al., 2000). Examination of the amount and direction of information flow within thalamocortical pathways suggested that the frequency-specific coding of peripheral electrical stimulation depends on the reciprocal interaction among brain structures (Yang et al., 2005). On the other hand, the cortex is not merely a receiver for coding sensory perception. Anatomical and physiological evidence suggests that the cortical feedback on primary thalamic relays has multiple influences on their response properties, for example, receptive fields (Ghazanfar et al., 2001; Kim et al., 2003; Price and Webster, 1972; Sherman and Guillery, 1996, 1998). Research on the coding of whisker twitching behavior in rats revealed a highly synchronous 7–12 Hz oscillatory neural activity among SI (cortex) and ventroposterior medial (VPM) thalamic cells, which appeared first in the SI and later in the VPM thalamus. This means SI exerts a powerful rhythmic influence on VPM neurons (Fanselow et al., 2001; Nicolelis et al., 1995).

Although there is good evidence that the brain stem, e.g., PAG, has descending control on the spinal cord nociceptive activity (Budai and Fields, 1998; Tracey et al., 2002), less well established is the idea that modulation can also occur at the cortical level to alter thalamic activity during the processing of nociceptive information. This may be better understood by clarifying the signal transmissions and neuronal correlations within the pain pathways.

The present study was aimed at investigating the dynamic interactions of neurons between cortices and thalamus during nociceptive processing, by recording the pain-evoked single-unit response in rat SI, ACC, mediodorsal (MD) and ventroposterior (VP) thalamus. By using partial directed coherence (PDC) and cross-correlation analysis of neuronal activity, we sought to disclose how nociceptive information flows, both in magnitude and direction within the thalamo-cortical loops during painful stimuli. Our results indicate that

SI cortical feedback may have a significant influence on the pain-related activity of thalamic neurons.

MATERIALS AND METHODS

Animals

Nineteen-male Sprague-Dawley rats (300–350 g) were housed individually in cages under a 12–12 h dark–light cycle (light phase started from 7:30 a.m.). Food and water were available ad libitum until surgery day. All experiments were approved by the Animal Care and Use Committee at the Chinese Academy of Sciences and are in accordance with the IASP guidelines for animal study. Every effort was made to minimize both animal suffering and the number of animals used.

Surgery

Rats were anesthetized with ketamine (100 mg/kg, i.p.) and mounted on a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). Four microarrays, each consisting of eight stainless-steel Teflon-insulated wires (50- μ m diameter, Biographics, Winston Salem, NC), were implanted into the following target areas: (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 MD, –2.3 A, 0.8 L, and 5.5 V; (4) for VP, –3.0 A, 3.0 L, and 6.0 V, positioned according to Paxinos and Watson (1998). All animals were implanted in the four regions unilaterally. The details of surgery procedure are described elsewhere (Wang et al., 2003). Rats received penicillin injection before surgery to prevent infection, and housed individually after surgery for a full week before exposing to any experiment.

Noxious heat stimulation

Nociceptive responses were evoked by radiant heat stimuli applied to the plantar surface of the hindpaw contralateral to the microelectrode implantation. Each rat was placed in a plastic chamber (44 \times 44 \times 44 cm³) on a glass floor under which a radiant heat apparatus (12.5-W projector bulb included) located. A beam of light through a hole (4 mm diameter) in the apparatus was aimed at the hindpaw through the glass plate. The light beam was turned off when the rat lifted the paw. The time length between the lighting onset and paw lift was defined as paw-withdrawal latency. Time stamps (resolution, 1 ms) marking stimulation start and end were recorded and synchronized with the neural spike recording. Each trial was repeated at intervals of no less than 20 s during the whole recording session (1.5–2.0 h). Because the stimulus was delivered only when animal was quiet and showed no voluntary motor activity, each session generally consisted of about 40 trials. Sham stimuli

(i.e., turning the light on and off to mimic the real stimulation without focusing on the paw) were randomly inserted among real painful stimulation as control.

Electrophysiological recording

Neural activity from multiple microwires were simultaneously recorded through the light-weight cables connecting the headset to a rotating commutator, filtered between 0.5 and 5 kHz (6 dB cut-off), sampled at 50 Hz, and then sent to a multichannel spike sorting device (Biographics). Signals from each two microwires were subtracted from each other before digitized to eliminate possible noises from cardiac and skeletal muscle movements. Waveforms were picked up by setting proper parameter pairs for amplitude and duration through a spike sorting system and recorded into a database file with a PC-based software Magnet (Biographics). The identity of clearly sorted single neurons was verified by graphical capture of waveforms (see Fig. 1 for an example) and interspike interval histograms (ISI). Data were then analyzed with commercially available PC-based programs STRANGER (Biographics) and Nex (Plexon).

Statistical analysis

Peri-stimulus time histograms (PSTH) were generated with Nex with a bin of 100 ms and a Gaussian filter of three bins. Only when a change of firing rates from the baseline exceeds the limit of $P < 0.005$ for more than three consecutive steps in a moving-window comparison were the neuron taken as responsive to the stimulation (Chang et al., 2002; Schultz and Romo, 1992; Wang et al., 2003, 2004).

Crosscorrelation histograms were created by the same computer analysis software. One neuron was selected as the reference neuron and the other neurons recorded within the same session were defined as partner neurons for the crosscorrelograms. The firing time of the reference neuron was set at 0 s, and the partner neuron's peri-spike histogram was calculated within the time range of -0.5 to 0.5 s around the reference neuron's spike, with a 5-ms bin size and a 3-bin Gaussian smooth. The relative temporal sequence of firing was indicated by the time lag, i.e., 'plus' represented the partner neuron fired 'after' the reference neuron and 'minus' represented 'before'. The significance level of the crosscorrelograms was tested using 95% confidence interval for at least five successive bins (i.e., 25 ms).

The MatLab (The MathWorks) platform was used for partial directed coherence (PDC) analysis. The methodology of PDC has been described in detail elsewhere (Baccalá and Sameshima, 2001; Fanselow et al., 2001; Sameshima and Baccalá, 1999). Briefly, PDC is a frequency domain representation of the key

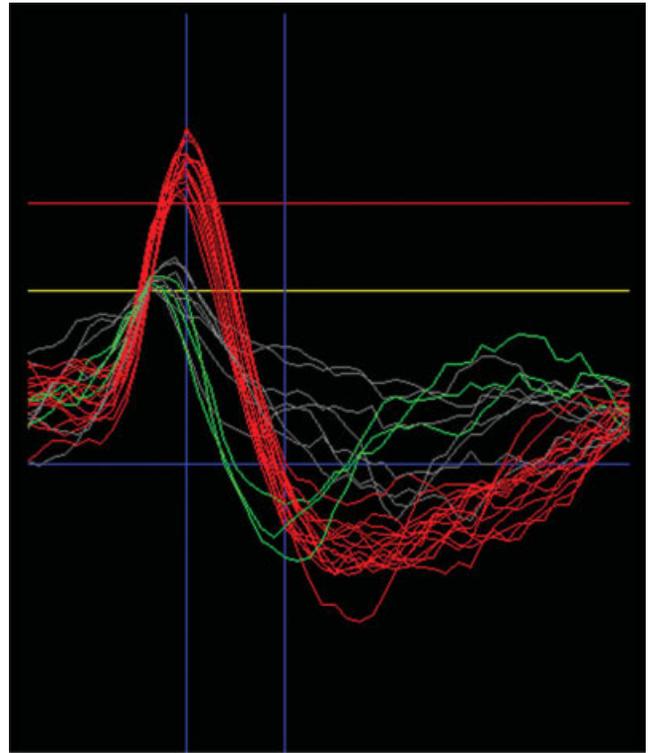


Fig. 1. An example of signal sorting with Magnet system. Waveforms were picked up by setting proper parameters for amplitude and duration. Spike activities from a given DSP channel were clustered into two single-units (marked as red and green respectively) according to their peak values and declining slopes. The unselected signals were shown in gray.

concept of Granger causality. If knowledge of $x(n)$'s past significantly improves prediction of $y(n)$, we could then state that an observed time-series $x(n)$ Granger-causes series $y(n)$. This relation between time-series is by no means reciprocal. Absence of PDC between two structures at a given frequency means the lack of a direct link between them. Thus, PDC allows the detection of coactivations among simultaneous neuronal activities by highlighting one neuronal group that possibly drives another.

For PDC analysis, principal component analyses (PCA) throughout the recording session for neurons in each brain area were first performed in Nex. Then the first principal component (PC1) of a given brain area that has the largest pain response were exported into MatLab, and the value of PDC across 1–50 Hz for each 2.5-s analysis time window (with 96% overlap) were calculated. These values were then averaged around the stimulation events. The results were normalized to Z scores relative to baseline (before stimulation) PDC.

Two-tail Student's t test and ANOVAs were performed where appropriate to compare results. When post-hoc tests were indicated, Duncan's post-test was used.

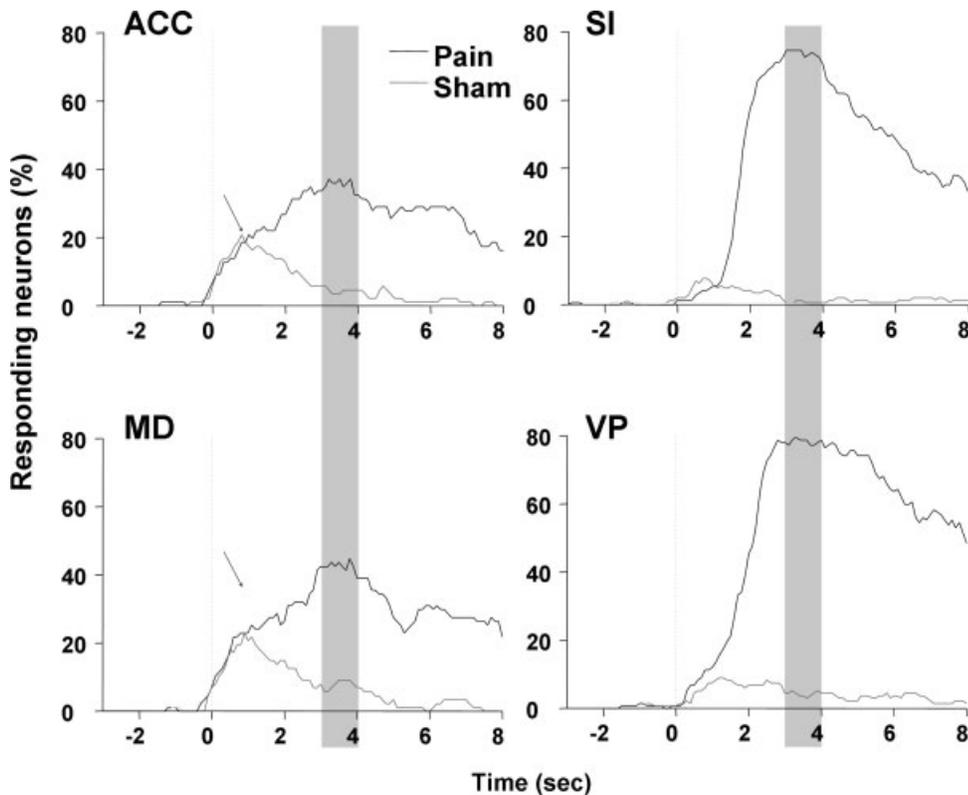


Fig. 2. Temporal distribution of percentage of neurons significantly activated by noxious stimulation. Time = 0 indicates the onset of stimulation. As highlighted with the gray bar, the maximal percentage of neurons responding to noxious heat was 70–80% within SI and VP (lateral pain pathway); in contrast, that for ACC and MD (medial pain pathway) was approximately half of SI and VP. Around 20% of ACC and MD neurons showed anticipatory responses to noxious or sham stimulation, as the arrows indicated.

Histology

After the termination of the experiment, rats received an overdose of ketamine. Microwire tracks and tip positions were marked by iron electrophoretic deposit (10–20 μ A DC current, 10–20 s duration, anode at the electrode) at the tip of selected wires. Animals were then perfused with 4% paraformaldehyde. The brains were postfixed in a solution of 5% potassium ferricyanide/4% paraformaldehyde for 48 h. Coronal sections (40 μ m) were cut through the SI, ACC, and thalamus. Microwire tracks and tip positions were determined using a light microscope. The iron deposits were easily identified as blue dots.

RESULTS

We successfully positioned microarrays in SI and VP in 18 cases, and in ACC and MD in 12 cases, according to the histological results. A total of 445 neurons were recorded, including 140 SI, 86 ACC, 132 VP, and 87 MD.

Pain-evoked behavioral and single-unit response

Noxious stimulus induced quick and obvious paw lift with an average latency of 3.11 ± 0.08 s (mean \pm SEM). In contrast, sham stimulation did not cause any visible paw movement or other behavioral responses.

Pain-evoked neuronal response can be seen in every recorded area. The number of responsive neurons increased over time (Fig. 2). The maximum percentage of responsive neurons was 37.2, 44.8, 74.6, and 79.5% for ACC, MD, SI, and VP, respectively. The preliminary analysis results of part of these data have been published elsewhere (Wang et al., 2003).

Information flow within thalamo-cortical loops

We used PDC analysis to determine the amount and direction of information flow between thalamus and cortex during the presentation of noxious heat, thus to explore the reciprocal influence between thalamic and cortical neural ensembles. Figure 3 illustrated the result of PDC analysis between two simultaneously recorded brain areas. As can be seen, the amount of directed coherence from SI to VP at all frequencies significantly increased 0.5 s after the presentation of stimulation and lasted for at least 7 s (Fig. 3A, top), compared to the prestimulation level. In contrast, those from VP to SI presented more complex pattern at different frequency during the poststimulation period (Fig. 3A, bottom). For this animal, the matrix comprising normalized PDC across 1–50 Hz and 0–7 s poststimulus in each trial was averaged into a single value. Then a two-way ANOVA was performed to quantitatively measure the difference in the amount of PDC between pain and sham conditions. The result showed that during pain stimula-

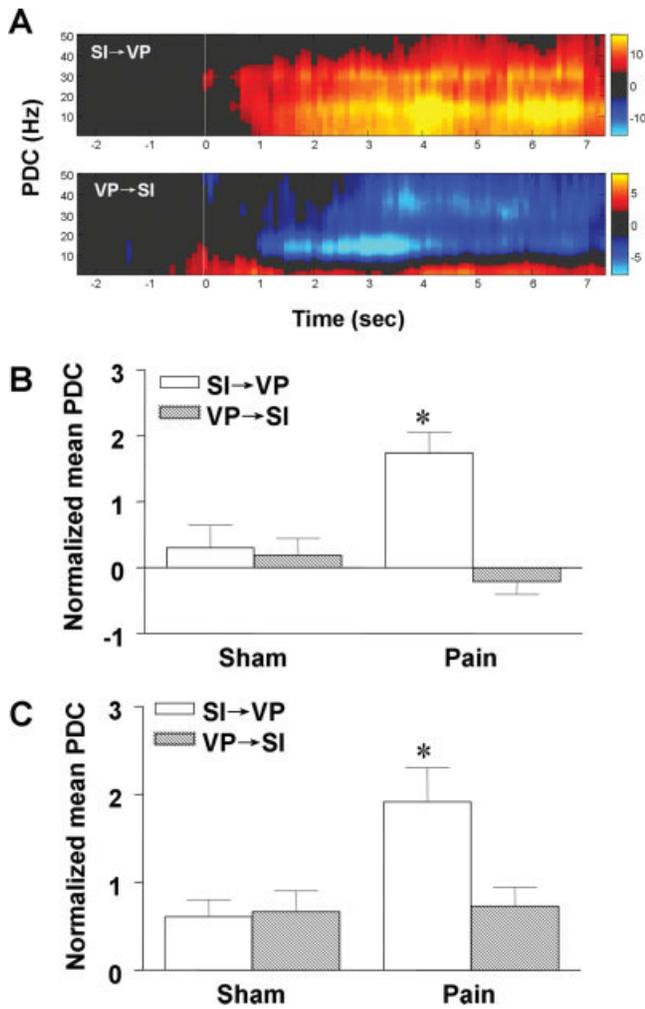


Fig. 3. Result of partial directed coherence analysis between SI and VP. **A**: PDCs from SI to VP (top) and from VP to SI (bottom). These PDC values were normalized to z -scores relative to the mean and variance of baseline PDC (i.e., before stimulation). The normalized PDCs exceeding 95% confident interval of the baseline were displayed in pseudo color. Warm and cool colors indicate the increase and decrease in PDC, respectively. **B**: Comparison of PDC between pain and sham conditions in this animal using two-way ANOVA analysis. **C**: Comparison of PDC from animal populations ($n = 18$). * $P < 0.05$, compared with sham.

tion, the amount of directed coherence from SI to VP was significantly higher than sham (Bonferroni's posttest, $P < 0.01$, see Fig. 3B). In contrast, there was no statistically significant difference in PDC from VP to SI compared with the control. A comparison of PDC averaged among animal populations was illustrated in Figure 3C, which is consistent with that in individual animal (Fig. 3B).

Similar analysis was also performed for ACC and MD neurons (Fig. 4). As shown in Figure 4A, a brief increase of directed coherence from ACC to MD occurred after the stimulus application (Fig. 4A, top). In contrast, those from MD to ACC showed a predominant decrease (Fig. 4A, bottom) during the poststimu-

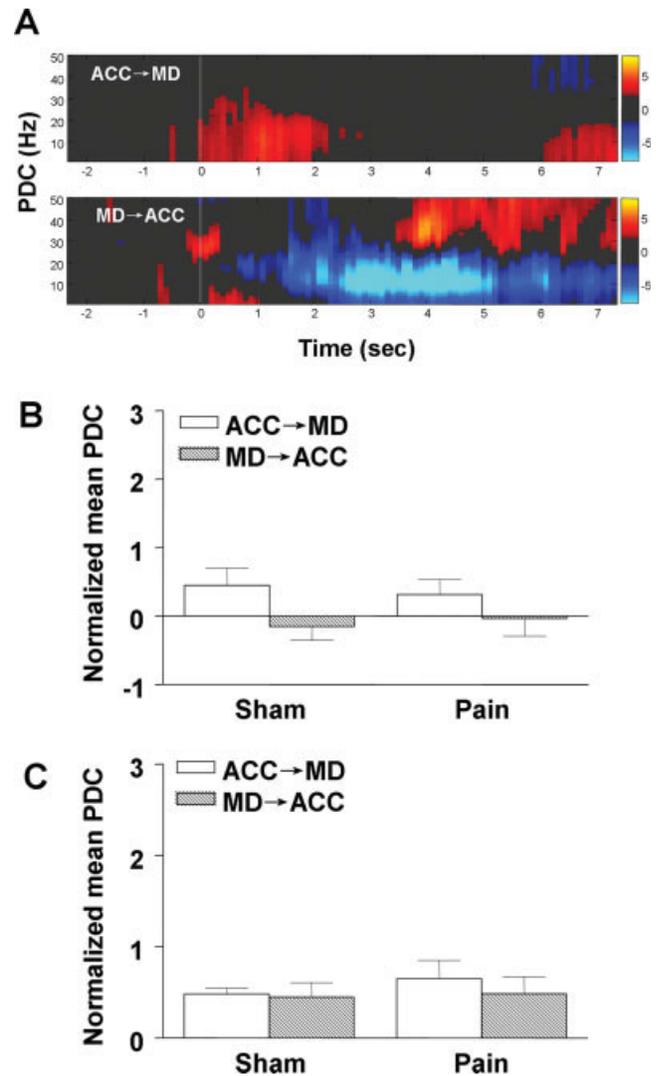


Fig. 4. Result of partial directed coherence analysis between ACC and MD. **A**: PDCs from ACC to MD (top) and from MD to ACC (bottom). **B**: Comparison of PDC in this animal using two-way ANOVA analysis. **C**: Comparison of PDC from animal populations ($n = 12$).

lation period. As for the comparison of averaged PDC between pain and sham in individual animal (Fig. 4B) or animal populations (Fig. 4C), no significant difference was observed in PDC in either direction.

Crosscorrelation and temporal relationship between thalamic and cortical neurons

Pairwise crosscorrelograms were created for all simultaneously recorded neurons. Correlated activity was found between neurons in the following categories: (1) intraregional crosscorrelations (between neurons within the same region: ACC, $n = 775$ pairs, the significantly correlated neuronal pairs account for 7.5 and 7.1% for pain and sham, respectively; MD, $n =$

TABLE I. Correlated neuronal activity and time lag under pain and control conditions

Reference-partner	Number of neuronal pairs			Time-lag (ms)	
	Total	Control (%)	Pain (%)	Control	Pain
ACC-ACC	775	55 (7.1)	70 (9.0)	18 ± 9	9 ± 11
ACC-SI	1210	38 (3.1)	42 (3.5)	-73 ± 44	31 ± 38 ^{##}
SI-SI	599	208 (34.7)	255 (42.6) ^{**}	2 ± 4	-4 ± 4
MD-MD	478	116 (24.3)	116 (24.3)	4 ± 6	6 ± 8
MD-VP	731	55 (7.5)	50 (3.8)	-15 ± 26	-50 ± 22
VP-VP	599	202 (33.7)	236 (39.4) [*]	4 ± 5	2 ± 6
ACC-MD	1065	16 (1.5)	13 (1.2)	-65 ± 60	-142 ± 76 ^{##}
ACC-VP	1252	44 (3.5)	65 (5.2) [*]	-31 ± 33	-5 ± 33
SI-MD	697	33 (4.7)	77 (11.0) ^{**}	-32 ± 20	-20 ± 21
SI-VP	1300	163 (12.5)	268 (20.6) ^{**}	5 ± 17	-62 ± 13 [#]

ACC, anterior cingulate cortex; MD, medial dorsal nucleus of thalamus; SI, primary somatosensory cortex; VP, ventral posterior nucleus of thalamus.

* $P < 0.05$, ** $P < 0.01$, Fisher's exact test; # $P < 0.05$, ## $P < 0.01$, two-way ANOVA followed by Duncan's post-hoc test. All compared with values under control condition.

478, 24.3% vs. 24.3%; SI, $n = 599$, 42.6% vs. 34.7%; VP, $n = 599$, 39.4% vs. 33.7%); (2) interregional cross-correlations (between neurons within different regions: ACC-MD, $n = 1065$, 1.2% vs. 1.5%; SI-VP, $n = 1300$, 20.6% vs. 12.5%; ACC-SI, $n = 1210$, 3.5% vs. 3.1%; MD-VP, $n = 731$, 6.8% vs. 7.5%; ACC-VP, $n = 1252$, 5.2% vs. 3.5%; SI-MD, $n = 697$, 11.0% vs. 4.7%). The correlated activity under the pain condition was significantly higher than the control between neurons from ACC-VP, SI-MD, and SI-VP, as well as within SI or VP (χ^2 test, $P < 0.05$; see Table I), which indicated the increased functional connection between or within these areas following noxious stimulation.

The temporal relationship between correlated neurons was investigated by the time lag of the peak activity from the reference point in the crosscorrelogram. For SI-VP correlations, the mean time lag of peak correlated activity in pain session (-62 ± 13 ms) was significantly longer than that in control session (5 ± 17 ms). The firing of SI units tend to precede that of VP during the nociceptive transmission, suggesting that the nociceptive inputs gave rise to enhanced descending controls in the somatosensory pathway that may in turn affect the ascending processing.

DISCUSSION

The present study examined the interactions between cortices and thalamus in the rat pain systems using PDC and crosscorrelation analysis. A major finding of this article is that the SI cortex has enhanced descending influence on thalamic neurons during pain processing. This result provides the first evidence at the level of neural assemblies that top-down modulation exists in suprathermal nociceptive circuits.

A considerable amount of anatomical and physiological data support the idea that corticothalamic inputs have a significant effect on mechanisms of sensory information processing (Ghazanfar et al., 2001; Hupe et al., 1998; Mignard and Malpeli, 1991; Nicoletis, 2005; Roelfsema et al., 1998). Recent studies on the

coding of vibrissae sensation in rats revealed that a large amount of information flows from SI to ventroposterior medial (VPM) thalamus during the whisker twitching period (Fanselow et al., 2001), suggesting an active descending modulation in the sensory processing circuit. In the present study, the result of PDC analysis showed that noxious stimulation induced an increased PDC from SI cortex to VP thalamus. This is consistent with our previous study on tonic pain in which significant information flow directed from cortex to thalamus in the first hour following subcutaneous injection of formalin (Huang et al., 2006). Furthermore, crosscorrelation analysis in this study also demonstrated that SI neurons had larger chance to fire ahead of VP thalamic neurons during radiant heat stimulation. It is widely believed that pain is a unique sensation and the perception of pain has large-scale modulation. The descending pain regulatory system involves many regions at different levels of the brain neuroaxis from brainstem to telencephalon, which could exert suppressive or facilitative influence on nociceptive inputs (Brooks and Tracey, 2005; Ohara et al., 2005). It is therefore likely that the preceding cortical discharge observed in the present study reflects a feedback modulation from SI cortex to VP thalamus.

In this study, we interpret the corticofugal influence in the pain pathways as a facilitative effect based on the following reasons. Previous study have shown that inactivation of the SI cortex with lidocaine in both awake and anesthetized rats could reduce the responses of ventrobasal thalamic neurons to repetitive electrical stimuli (Yuan et al., 1985, 1986). Similarly, using cooling to suppress SI and/or SII cortex, Ghosh et al. (1994) also have found that 10 out of 32 cat ventroposterolateral (VPL) neurons displayed a reduction in response level to tactile stimulation. In a recent study, Ghazanfar et al. (2001) reported that SI cortex has a dual influence on its primary thalamic relay in rats, by showing that a large number of thalamic neurons showed a reduction in response magnitude while others showed enhancement follow-

ing SI inactivation. Therefore, these studies supported the notion that SI corticofugal activity could facilitate SI transmission mediated by ventrobasal thalamic neurons. On the other hand, it is possible that the cortical feedback observed here may have a facilitative effect on thalamic activity on the consideration of the protective role played by acute pain. By fastening the nociceptive signal transmission, the pain system can efficiently detect the threat of damage and thus avoid the possibility of permanent injury. This is the vital function of pain sensation.

Additional result in this study was that the pain-related increase of PDC in the descending direction only occurred in the lateral pathway but not the medial. Although both pathways need descending feedback modulation in order to correctly convey necessary information, the required speeds are probably different. For the lateral pathway, the precise and monosynaptic projection of ascending fibers permits the quick formation of sensory perception. A fast and tight feedback connection is also needed to finish the job. However, in the case of medial pathway, the ascending projection is diffuse and multisynaptic, and the development of emotional feelings is time-consuming. Thus, the time scale of feedback might possibly be large and the connection of feedback circuit be slow and loose. That is why we could see the change of time lags in crosscorrelation analysis, but no change of PDC could be observed.

Crosscorrelation analysis is a method to detect the tendency that two neurons fire with a fixed time lag. The correlated activity between the two neurons means that they might have direct connection or a third neuron might drive them simultaneously. In the present study, correlated neuronal activities were observed between neurons in the same and different areas. It is noteworthy that a significant difference in both the number of correlated neuronal pairs and the time lags was observed between pain and control sessions for SI-VP correlations. Anatomically, there exist associational connections between VP and SI (Arnold et al., 2001; Bernardo and Woolsey 1987; Bourassa et al., 1995; Chmielowska et al., 1989; Jensen and Killackey, 1987; Jones, 1985; Kharazia and Weinberg, 1993), and MD and ACC (Andree et al., 1983; Beckstead, 1979; Gigg et al., 1992; Krettek and Price, 1977; Wang and Shyu, 2004). The coding theory of synfire chains does not even require a direct connection between the fired neurons (Ikegaya et al., 2004). Thus the precise firing sequence observed in our study will be easily recognized as some connective circuits.

In summary, our results suggest that there exist feedback descending control within thalamo-cortical pathways for radiant heat pain coding. The nature of this feedback is different in the two pain pathways. The feedback may be tighter in the lateral pathway,

as revealed by positive result of both crosscorrelation and PDC analysis; while it may be looser in the medial pathway, where only crosscorrelation may find some cue of it.

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