Properties of heat-sensitive neurons in the premotor cortex of conscious monkeys

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Abstract: To investigate neuronal activity involved in responses to noxious stimuli in conscious monkeys, the animals were subjected to a task that required them to detect a small change in facial skin temperature or light (second temperature: T2, second light: V2) relative to an initial condition (T1 or V1), and to detect changes in V2 along with a heat task. Recordings were obtained from 57 neurons in the ventral premotor cortex (PMv) during the heat or light detection task. T1 neurons and T2 neurons showed increased activity only during T1 or T2, and T1/T2 neurons were activated by both T1 and T2 stimuli. T1/T2 neurons showed an increase in firing at higher T1 temperatures, whereas T1 neurons did not. About half of the non-light/heat-sensitive T1/T2 neurons showed increased firing at higher T2 temperatures, whereas T2 neurons showed no such increase. The heat responses of heat-sensitive PMv neurons were significantly suppressed when monkeys shifted their attention from heat to light. The present findings suggest that heat-sensitive PMv neurons may be involved in motor responses to noxious heat, whereas light/heat-PMv neurons may be involved in emotional and motivational aspects of pain and inappropriate motor responses to allow escape from noxious stimuli.

Keywords: attention, heat-sensitive neuron, monkey, ventral premotor cortex

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Introduction

The premotor cortex (PM) is a critical area involved in the execution of complex body movements [1-4]. The PM is connected with many other cortical regions such as the prefrontal, cingulate or parietal cortices involved in higher brain functions and receives extensive sensory information from these regions [5,6]. The PM is involved in the integration of complex motor events, such as preparation for a series of body movements or planned movements [3,4,6]. The arm, neck, face, and oral regions have motor representations in the caudal part of the ventral PM (PMv). Long-train electrical stimulation of the PMv evokes complex motor movements [7,8]. Many PMv neurons respond to tactile stimulation of the body surface, and receptive fields (RFs) of PMv neurons are somatotopically organized, allowing involvement in sensorimotor transformation for guiding orofacial and arm movements [9]. Somatosensory inputs to the PMv provide information necessary for the execution of precise body movements such as hand-reaching to a specific target or for deciding the correct direction for achieving a given goal.

A subset of PMv neurons receive visual inputs; these visuomotor neurons are involved in the control of arm movements under visual guidance [10,11]. Another class of PMv neurons are mirror neurons that fire during the execution of hand movements or observations of similar actions by others [12]. Collectively, these findings demonstrate that somatosensory and visual inputs to the PMv contribute to precise control of the movements of the arms and other body parts.

A previous study of somatosensory-evoked potentials (SEPs) in human subjects demonstrated that electrical stimulation of the upper limbs evoked large SEPs with short and long latencies in the PMv region [13]. SEPs with different latencies originated from different types of primary afferent fibers, both myelinated and unmyelinated. In this regard, long-latency SEPs are likely evoked by stimulation of small-diameter Aβ or C-fibers, whereas short-latency SEPs are of Aδ fiber origin. The majority of small-diameter Aβ and C-fibers convey nociceptive input, whereas large-diameter Aδ fibers provide non-noxious somatosensory inputs [14-16]. Furthermore, fMRI studies in humans have shown that nocuous stimuli produce robust activation of the PM [17-20]. These data suggest that nociceptive and non-nociceptive somatosensory inputs modulate PMv neuronal activity. To understand the mechanisms underlying pain processing by PMv neurons, it is necessary to determine whether PMv neurons receive noxious inputs and how various noxious stimuli such as heat modulate nociceptive neurons. For this purpose, the present study was conducted to examine whether PMv neurons receive nociceptive heat inputs and to analyze the performance-related response properties of heat-sensitive PMv neurons during changes in temperature and light intensity in conscious monkeys. The effect of attentional shift from heat to light on the activity of heat-sensitive PMv neurons was also studied. To this end, monkeys were subjected to heat and light detection tasks and trained to detect small changes in temperature applied to the facial skin and small changes in light intensity. The activity of single neurons was recorded from the PMv during the performance of these heat and light detection tasks.

Materials and Methods

Ethics statement

The Animal Experimentation Committee of Nihon University approved this study (AP14D017). All surgical procedures and animal care were conducted according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals, the guidelines for Institutional Animal Care, and the guidelines of the International Association for the Study of Pain [21].

Animal preparation

Two male Japanese macaques (Macaca fuscata, both 5 years old) weighing 5.4-6.2 kg were used for this study. The monkeys were anesthetized initially with ketamine hydrochloride (10 mg/kg, i.m., Sankyo, Tokyo, Japan), and anesthesia was subsequently maintained with a mixture of isoflurane (3-5%, Mylan, Canonsburg, PA, USA) and oxygen. Each monkey was then placed in a stereotaxic frame. A head holder for chronic experiments and a recording chamber were implanted on the skull. Enamel-coated stainless wire electrodes were chronically implanted into the oribucularis oris muscle beneath the facial skin for EMG recording. The recording chamber was placed over the PM (15-20 mm from the ear bar). During surgery, body temperature was maintained at 37-38°C with a heating pad. Heart rate was continually monitored by ECG recording. Expired CO2 concentration was also controlled and maintained at a level between 4.0 and 5.0%.
Behavioral tasks

After completion of the surgical procedures, the monkeys were routinely sedated with a small dose of ketamine (2-3 mg/kg, i.m.) and given penicillin (10,000 units/kg, i.m., Meiji Seika, Tokyo, Japan) and subcutaneous saline (40-50 mL of a 5% glucose solution in 0.18% NaCl). Furthermore, the analgesic Ketoprofen (5 mg/kg, i.m., Kissi Pharma, Tokyo, Japan) was administered daily for postoperative analgesia for 3-4 days. Beginning seven days later, the monkeys were trained daily until they were able to discriminate changes in the intensity of light illumination (>90% correct responses). They were then trained for 2-3 months to perform heat as well as light detection tasks. During daily training, access to water was restricted to 300 mL per day. The training took place daily until the performance criteria (see below) were reached, upon which single-neuron recording in PMv was conducted.

Figure 1 shows a schematic illustration of the behavioral tasks used in the present study, which were modified from a previously described protocol [22]. The monkeys were seated quietly in a primate chair for 2-3 hours. A thermal probe with the baseline temperature set at 35°C was placed on the right whisker pad skin. A red light signal on a panel placed in front of the monkey prompted the animal to press a button to initiate a trial. When the monkey pressed the button, three different types of task were presented randomly. The first task was the “heat detection task” (Fig. 1A). For this, the monkey pressed the button, and a T1 temperature shift was applied to the face after the button press; the T1 stimulus was 45, 46, or 47°C for 4 s; then at 6 to 10 s after the onset of the T1 temperature stimulus, a T2 temperature shift (+0.8°C) was applied to the face (Fig. 1A). If the monkey released the button within 3 s after onset of the T2 stimulus, it was given 3 mL of orange juice as a reward. The second task was the “light detection task” (Fig. 1B). For this, the monkey pressed the V1 light button (V1: application of 2.2 V to the bulb) on the front panel; 6 to 10 s after the V1 light illumination, a V2 light (V2: +0.3 V) intensity shift was applied. If the monkey detected the V2 light within 3 s, signaled by releasing the button, it received a reward of orange juice. The third task was the “light detection + heat task”. When the monkey pressed the button, a T1 temperature shift and V1 light (2.2 V) were presented simultaneously (Fig. 1C). However, a T2 temperature shift was not presented. After a period of 6-10 s, the light stimulus intensity increased above the baseline stimulation (2.2 V + 0.3 V). If the monkey detected the change in V2 light intensity within 3 s by releasing the button, it received a reward. In this task, monkeys needed to shift its attention from heat to light. The escape response was defined as that whereby the monkey released the button before the onset of the T2 or V2 stimulus, whereas a correct response was when the monkey released the button during the T2 or V2 stimulus. If the monkey did not release the button after cessation of the T2 temperature or V2 light, a low-pitch sound was presented to the monkey to indicate an inappropriate response, and a time-out period was inflicted. The appearance of lip motor activity during the task was also monitored by recording orbicularis oris muscle EMG activity via a bipolar enamel-coated electrode chronically implanted into the muscle and observing the mechanical lip responses elicited (Fig. 1D).

Statistical analysis

Spike firing frequencies of neuronal responses during the four periods were statistically tested using the Mann-Whitney U-test. Correlations between detection times and firing rates using the following formula: NORM = RATE/MAX × 100, where NORM is the normalized spike frequency, RATE is the spike frequency in each trial, and MAX is the maximum spike frequency at each T1 temperature for each neuron. Spike firing frequencies were analyzed for 3 periods as follows: The control period (4 s before T1 stimulus onset). The T1 period (4 s starting from 2 s after T1 stimulus onset). The T2 period (period between T2 stimulus onset and the averaged detection time). Based on the monkey’s behavior, the average detection time was determined as 600 ms for trials with a T1 temperature of 47°C, 700 ms for 46°C, and 1,000 ms for 45°C. Based on the statistical analysis, neurons were classified into three types as follows: When the response during the T1 period was significantly higher than that in the control period and the response during the T2 period was not, then the neuron was defined as a T1 neuron. When the T2-period response was significantly greater than that of the control period response and the T1-period response was not, then the neuron was designated as a T2 neuron. When the spike responses during the T1 and T2 periods were both significantly larger than those in the control period, then the neuron was identified as a T1/T2 neuron.

Results

Recordings were obtained from single neurons in the PMv during the heat detection, light detection, and light detection + heat tasks performed by conscious monkeys that had been trained to detect small changes in temperature applied to the facial skin and also to detect small changes in light
intensity. A total of 459 neurons were recorded from 143 penetrations into the PMv (cytoarchitectonic area F5a) of three hemispheres, and the activity of 57 of these neurons was found to be modulated during the heat and/or light detection tasks.

Classification of PMv neurons

The neurons detected in the PMv included heat-sensitive neurons, light-sensitive neurons responding only to light stimuli, and mechanosensitive neurons. Since the main focus of study was the heat sensitivity of PMv neurons, only the activity of heat-sensitive neurons was analyzed. Heat-sensitive PMv neurons were divided into heat-sensitive and light/heat-sensitive neurons according to their responses to heat and light stimuli. Each heat-sensitive or light/heat-sensitive PMv neuron had a cutaneous RF on the face and/or other body surfaces, and responded to non-noxious mechanical stimulation (brushing) of the RF. There was no clear somatotopic arrangement of the RFs in the PMv. Heat-sensitive and light/heat-sensitive PMv neurons were intermingled in area F5a at the posterior portion of the arcuate sulcus (Fig. 2B). Heat-sensitive and light/heat-sensitive PMv neurons were classified as T1 neurons, T2 neurons, and T1/T2 neurons according to their responsiveness to T1 and/or T2 stimuli, as outlined in the next section.

Responses of PMv neurons to T1 and T2 stimuli

Twelve heat-sensitive neurons recorded from the PMv were classified as T1 neurons since they responded to T1 but not T2 stimuli; an example is shown in Fig. 3A. No dynamic responses to heat stimuli were observed in T1 neurons, and their firing frequency increased gradually during the T1 stimulus (Fig. 3A). Furthermore, T1 neurons did not increase their firing frequency when higher T1 temperatures (46°C, 47°C) were used (e.g. Fig. 3B) and they did not respond to light stimuli (e.g. Fig. 3C). The neurons responded to gentle brushing of the facial skin and had a mechanosensitive RF located in a large area of the face bilaterally (Fig. 3D).

Thirty-five heat-sensitive PMv neurons were classified as T2 neurons since they increased their firing following a small change in the T2 stimulus temperature, but they did not respond to the T1 stimulus (e.g. Fig. 4A). T2 neurons were sub-classified as heat-sensitive \( (n = 13) \) and light/heat-sensitive \( (n = 22) \) neurons. Many heat-sensitive T2 neurons \( (10/13) \) tended to increase their firing frequency when higher T1 temperatures were applied (upper panel in Fig. 4B). Conversely, light/heat-sensitive T2 neurons showed no change in firing frequency at the higher T1 temperatures (lower panel in Fig. 4B). These neurons did not alter their firing following light presentation (Fig. 4C). Eighty-nine percent of T2 neurons had RFs in the face, and for the remaining neurons, the RFs were located in the face and body, as exemplified in Fig. 4D.

Ten T1/T2 neurons responsive to both T1 and T2 heat stimuli were identified in the PMv (Fig. 5). A typical example of a T1/T2 neuron responsive to both T1 and T2 stimuli is shown in Fig. 5A. These neurons did not show obvious dynamic responses and gradually increased their firing during the heat stimulus, and increased their firing at higher T1 temperatures (Fig. 5A). These were sub-classified as heat-sensitive \( (n = 4) \) and...
The correlation coefficients for most light/heat-sensitive T2 PMv neurons showed a significant correlation with V2 detection time (Fig. 6D). T2 neurons detected small changes in light or heat stimulus intensities. As illustrated in Fig. 6A, B, and C, there was no significant correlation between detection of small changes in light or heat stimulus intensities. The relationship between normalized spike rate and detection time. (A) Heat-sensitive T1/T2 neurons. (B) Heat-sensitive T2 neurons. (C) Light/heat-sensitive T1/T2 neurons. (D) Light/heat-sensitive T2 neurons. (E) Distribution histogram of correlation coefficients of T1/T2 neurons. (F) Distribution histogram of correlation coefficient of T2 neurons. Red bars: heat-sensitive neurons. Black bars: light/heat-sensitive neurons. *P < 0.05.

The relationship between escape occurrences and firing rate of heat-sensitive neurons. (A) Escape latency and escape frequency histograms. (B) Firing frequencies of heat-sensitive ventral premotor cortex (PMv) neurons during escape from different T1 temperatures. Escape task indicates that monkeys released the button before the T2 stimulus. Correct response task indicates that monkeys detected the change in T2 temperature shift and released the button during the T2 stimulus. *P < 0.05.

Light/heat-sensitive (n = 6) neurons. An example of a neuron responsive to the V2 light stimulus and classified as a light/heat-sensitive T1/T2 neuron is depicted in Fig. 5C. The mechanosensitive RF of this neuron was located in the whisker pad skin; gentle brushing of the whisker pad around the thermal probe produced robust activation of this neuron (Fig. 5D). Ninety percent of T1/T2 neurons had RFs in the face, and for the rest of them, the RFs were located in the face and body as exemplified in Fig. 5D.

Detection time and neuronal activity

The relationship between light or heat stimulus detection time and spike rate was analyzed in T1/T2 and T2 PMv neurons (Fig. 6). Shorter detection times and higher spike rates indicated that the PMv neurons had faster detection of small changes in light or heat stimulus intensities. As illustrated in Fig. 6A, B, and C, there was no significant correlation between detection time and spike rate in heat-sensitive and light/heat-sensitive T1/T2 neurons.

In contrast, the spike rate of heat-sensitive and light/heat-sensitive T2 neurons showed a significant correlation with V2 detection time (Fig. 6D). The correlation coefficients for most light/heat-sensitive T2 PMv neurons and heat-sensitive T2 neurons were negative (light/heat: 74%, heat: 70%), indicating that high spike rate responses occurred in these neurons with shorter detection times. The remaining heat-sensitive and light/heat-sensitive T1/T2 and T2 neurons did not show a significant negative correlation (Fig. 6E, F).

Modulation of PMv neuronal activity during escape and attentional shift

Escape responses from stimuli were then examined for any modulation of PMv neuronal activity. As illustrated in Fig. 7A, when higher T1 temperatures (46°C, 47°C) were applied to the face, escape latency decreased in comparison to that at 46°C and escape frequency was more significant. There were no significant differences in firing rates at each of the three T1 stimulus temperatures between correct response tasks and escape tasks (Fig. 7B), suggesting that PMv neurons were not involved in escape performance from noxious heat. The effect of attentional shift from heat to light on PMv neuronal activity was also examined (Fig. 8). PMv neuronal activity was decreased during light+heat detection tasks compared with that during heat detection tasks (Fig. 8A). The average firing frequency of heat-sensitive PMv neurons was significantly suppressed when monkeys shifted their attention from heat to light (Fig. 8B).

Discussion

This is the first documented report to indicate that PMv neurons in conscious monkeys respond to tactile stimulation of the face and/or body. A subset of these neurons also respond to heat stimulation of the face and light stimulation. Heat-sensitive PMv neurons were classified as T1, T2, or T1/T2 neurons according to the properties of their responses to heating of the face. The present findings suggest that PMv neuronal responses to noxious heat stimulation of the face may contribute to the execution of sequential motor responses to heat in conscious monkeys, and that light/heat-sensitive PMV neurons may contribute to the modulation of motor performance and may also be involved in attentional, emotional and motivational aspects of pain that elicit escape from the stimulus, irrespective of modality.

The PM is cytoarchitectonically classified into several subcortical areas according to their cellular organization [2]. All heat-sensitive neurons were located in cytoarchitectonic area F5a. Many neurons in this area are involved in motor and visuomotor functions related to hand-reaching and mouth movements. Area F5a is involved in decision making for various motor sequences associated with sensory discrimination, suggesting that sensory inputs to this area are crucial for precise motor performance [2]. Area F5a does not receive somatosensory inputs from the somatosensory thalamus, but rather from other cortical regions via cortico-cortical connections [2,5,23]. The present study revealed that many PMv neurons received somatosensory inputs from the face and other parts of the body,
and that some responded to noxious heat and non-noxious tactile stimuli. Together with previous studies, the present data suggest that PMv neurons are involved in the processing of non-noxious and noxious somatic information and the modulation of motor commands.

Three types of heat-sensitive neurons in the PMv area were recorded. T1 and T1/T2 neurons responded to heating of the facial skin with a gradual increase in firing frequency during T1 heat stimulation; they had no dynamic response and did not increase their firing above that in response to a 45°C stimulus when higher temperatures (46°C and 47°C) were applied to the facial skin. These patterns of response to heat stimulation of the facial skin are different from those observed in primary somatosensory cortical (SI) neurons in anesthetized and conscious monkeys [24,25]. Most SI heat-sensitive neurons increase their firing frequency following an increase in stimulus temperature. Furthermore, many SI 3b nociceptive neurons appear to show dynamic responses and increase in a transient increase in firing rate at the onset of heat stimuli applied to the skin and an increase in dynamic firing following an increase in stimulus intensity. This transient increase in dynamic responses is thought to be involved in the discrimination of heat stimulus intensity [26,27].

On the other hand, SI 3a nociceptive neurons gradually increase their firing during heating of the RF [27]. A gradual increase in firing during heating of the skin similar to that of the T1 and T1/T2 neurons recorded in PMv in the present study has also been observed in nociceptive neurons in the limbic cortices [22,28]. Furthermore, most nociceptive neurons in the face area of SI have restricted RFs in the face contralateral to the stimulus. These nociceptive neurons are thought to be involved in spatial discrimination of pain [29]. In contrast, the present study has revealed that most PMv neurons have large RFs in the face bilaterally and/or occasionally in the face and other parts of the body, suggesting that heat-sensitive and light/heat-sensitive PMv neurons may not be involved in spatial discrimination of pain, unlike SI nociceptive neurons.

It has been suggested that nociceptive neurons with a large RF and a gradual increase in firing during heating of the RF are involved in emotional and motivational aspects of pain [22]. Thus, the present findings suggest that T1 responses in heat-sensitive PMv neurons may contribute to emotion-related motor behaviors such as pain-relieving behavior. When compared to T1 responses, T2 responses were transient and dynamic when monkeys detected small changes in T2 temperature. Such transient firing patterns are thought to be inappropriate for modulating complex movements [30]. Nonetheless, T2 transient responses of heat-sensitive and light/heat-sensitive T2 neurons may be involved in triggering movement sequences related to the detection of small changes in T2 temperature.

Escape behavior from noxious heat stimuli is known to increase neuronal activity in the anterior cingulate cortex (ACC) of conscious monkeys [22], suggesting that ACC nociceptive neurons are involved in escape behavior from noxious stimuli. Although it was anticipated that PMv neuronal activity would be enhanced in relation to the expectation of escape from noxious heat stimuli, the present study revealed no significant correlation between escape action and spike activities of PMv neurons. Together with previous results [28], the present findings suggest that T1 activity of heat-sensitive PMv neurons may not be essential for escape from noxious stimuli.

Attention affects pain sensation and various sensory functions [31]. It was previously reported that noxious heat-evoked responses in ACC neurons were significantly suppressed following a shift of attention from heat to light in conscious monkeys [22]. In a present study, a similar suppressive effect on T1 and T2 heat-evoked responses in heat-sensitive PMv neurons was observed when monkeys shifted their attention away from the heat to light stimuli. Such attention-related suppression of PMv neuronal activity may contribute to the modulation of PMv neuronal activity during motor functions. Furthermore, suppression of T1 heat responses following an attentional shift to light may allow for an appropriate sequence of motor performance, whereas suppression of T2 responses may contribute to the initiation of motor performance.

In conclusion, the present study of conscious monkeys has demonstrated that some PMv neurons responded to heat stimulation of the facial skin, modulated the heat stimulus intensity, and increased their firing when monkeys detected a small change in heat stimulus intensity. These findings suggest that nociceptive facial information is sent to the PM and contributes to the modulation of PMv neuronal activity. This modulation may be involved in the alteration of motor-related PMv neuronal activity, facilitating precise and appropriate sequences of motor performance, and may also be involved in attentional, emotional and motivational aspects of pain.

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Conflict of interest

The authors have no conflict of interest to declare.

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