Primary Somatosensory Cortical Neuronal Activity During Monkey’s Detection of Perceived Change in Tooth-Pulp Stimulus Intensity

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Iwata, Koichi, Yoshiyuki Tsuboi, and Rhyuji Sumino. Primary somatosensory cortical neuronal activity during monkey’s detection of perceived change in tooth-pulp stimulus intensity. J. Neurophysiol. 79: 1717–1725, 1998. To elucidate the functional properties of primary somatosensory cortical neurons for the perception of tooth-pulp sensation, neuronal activity was recorded from the primary somatosensory cortex (SI) in awake behaving monkeys. Monkeys were trained to detect changes in tooth-pulp stimulus intensity applied to the upper canine or incisor tooth pulp. Stimulus intensities applied to the tooth pulp were multiples of the threshold intensity for the jaw opening reflex (1.0 T) elicited by tooth-pulp stimulation. When monkeys pressed a button, baseline electrical pulses (V1: 0.5 T, 1.0 T, 2.0 T, or 3.0 T) were applied to the tooth pulp. After 4–8 s, a V2 stimulus (0.3 T, 0.5 T, 1.0 T, or 2.0 T) was added to V1. Percent escapes at V1 stimulus intensity of 0.5 T and 1.0 T were ~10%, 22% at 2.0 T, and 40% at 3.0 T (total of 1,997 trials). A total of 862 single units were recorded from the SI. Thirty-seven SI neurons responded to electrical stimulation of the tooth pulp (tooth-pulp–driven neurons; TPNs), 139 SI neurons responded to tactile stimulation of the lateral face area, whereas 351 SI neurons were not responsive to tactile stimulation of the oro-facial regions. Thirty of 37 TPNs were recorded long enough to test with V1 stimuli ranging from 0.5 T to 3.0 T. Eleven of 30 TPNs linearly increased their firing frequency following increases in stimulus intensity (encoding TPNs), whereas 19 did not (nonencoding TPNs). Mean first spike latency of encoding TPNs was 24.8 ± 1.7 ms (n = 11), that of nonencoding TPNs was 23.6 ± 1.5 ms (n = 19), and that of unclassified TPNs was 24.7 ± 3.7 ms (n = 7). TPNs were distributed in the areas 1–2, 3a, and 3b within the oral projection area and the transition zone between the face and oral projection areas of the SI. All of them received inputs from the intraoral structures, facial skin, or both. The firing frequency of eight encoding and nonencoding TPNs was correlated with detection latency at stimulus intensities of 0.5 and 1.0 T. On the other hand, when the baseline stimulus was increased to 2.0 T and 3.0 T, the discharge of most TPNs did not increase in firing frequency with the reduction in detection latency. These results indicate that the discharge rates of some SI TPNs are correlated with detection latency at near-noxious threshold and noxious stimulus intensities. These findings suggest that some TPNs are involved in the sensory-discriminative aspect of tooth-pulp sensation in the near-pain threshold and pain ranges.

INTRODUCTION

It is well-known that somatosensory information is represented in the primary somatosensory cortex (SI) with somatotopic organization (Darian-Smith et al. 1966; Felleman et al. 1983; Kaas et al. 1979; Landgren and Olsson 1980; Lund and Sessle 1974). Jaw and orofacial sensory inputs project to the lateral part of the SI, and other body parts are represented in the medial portion in several species, such as monkeys (Kaas et al. 1979; Ogawa et al. 1989), cats (Darian-Smith et al. 1966; Felleman et al. 1983; Landgren and Olsson 1980; Lund and Sessle 1974), and rats (Armstrong-James and Fox 1987; Chapin and Lin 1984; Welker 1971). Most of the SI neurons receive noxious cutaneous input, whereas some of them also receive proprioceptive or noxious inputs. It is believed that the major function of SI neurons is to process the spatiotemporal perception of the whole body surface. It is likely that the perception of body parts is processed by low-threshold mechanoreceptive (LTM) neurons that respond to noxious mechanical stimulation of their receptive fields. Those LTM neurons are somatotopically arranged in the SI.

Several lines of evidence reveal that some SI neurons respond to noxious heat and/or mechanical stimulation of the body surface (Chudler et al. 1986, 1990; Kenshalo and Isensee 1983; Kenshalo et al. 1988; Lamour et al. 1982). It has also been reported that SI neurons responding to noxious thermal stimulation are located in areas 1, 2, and 3 of the SI (Kenshalo et al. 1983, 1988). Most of these nociceptive neurons were classified as wide dynamic range (WDR) neurons that responded to both noxious and noxious stimuli and increased their firing frequency following increases in stimulus intensity (Chudler et al. 1990; Kenshalo et al. 1983, 1988). A minority of the nociceptive neurons were classified as nociceptive specific (NS) neurons that responded exclusively to noxious thermal and/or mechanical stimulation (Chudler et al. 1990; Iwata et al. 1990; Kenshalo et al. 1983).

It has also been reported that some of the WDR, NS, and/or LTM SI neurons receive inputs from the tooth pulp (tooth-pulp–driven neurons: TPNs) (Biedenbach et al. 1979; Iwata et al. 1986, 1987, 1990, 1994; Lund and Sessle 1974; Mason et al. 1985; Matsumoto et al. 1987, 1989). These TPNs are distributed within laminae III–V of areas 3a and 3b of the orofacial area of the SI in cats (Haslster and Muhs-Clement 1964; Iwata et al. 1986, 1987, 1990, 1994; Matsumoto et al. 1989). Most TPNs receive inputs from the intraoral structures, facial cutaneous tissues, or both. Furthermore, many of them exhibit an increase in their firing frequency following increases in stimulus intensity (Iwata et al. 1990; Matsumoto et al. 1987). These observations suggest that TPNs in SI are possibly involved in the perception of tooth pulp, cutaneous, mucosal, and periodontal inputs.
However, because previous studies were performed in anesthetized animals, it is not known whether animals perceived the tooth-pulp stimulation. To clarify the functional role of the SI for the perception of tooth-pulp sensation, it is necessary to study awake, behaving animals. Chudler et al. (1986) recorded large field potentials from the oral projection area of SI and the secondary somatosensory cortex (SII) of awake monkeys after electrical stimulation of the tooth pulp. These potentials were elicited at nonnoxious stimulus intensities (i.e., they did not induce escape behavior). Furthermore, the SI field potentials became larger after increases in stimulus intensity. When a noxious stimulus was applied to the tooth pulp, the large field potentials were recorded from SII as well. Kenshalo et al. (1988), also using awake behaving monkeys, reported that the firing frequency of SI nociceptive neurons increased following graded heat stimulation and correlated well with the speed with which the monkeys perceived a change in noxious thermal stimuli. These findings suggest that nociceptive neurons in SI have a role in the perception of sensations produced by noxious stimuli applied to the facial skin.

To clarify the functional role of TPNs for the perception of the sensation produced by electrical stimulation of the tooth pulp, awake behaving monkeys were trained to detect changes in the intensity of a stimulus applied to the tooth pulp. The goal of this study was to elucidate the relationship between the firing frequency of TPNs in the SI and the detection latencies at which the monkeys perceived the changes in stimulus intensity. A part of this study was published in abstract form (Nomura et al. 1996).

METHODS

This study was approved by the Animal Experimentation Committee at Nihon University School of Dentistry, and the treatment of the animals conformed to the guidelines of the International Association for the Study of Pain (Zimmerman 1983).

Animal preparation

Two Japanese Macaca monkeys weighing 6.5–9.2 kg (M. fascata, 4–5 yr old) were used for the present study. Before starting training, the monkey’s water was restricted to 150 ml/day for 1 wk. Monkeys were trained to sit in the chair for 2–3 h and also to detect changes in the intensity of a light. They were seated facing an illuminated button and, at head height, a white electric light. In daily sessions they were trained to hold down the button and to release it when the light intensity was increased. The criterion performance was when the monkeys could hold the button down for between 4 and 8 s (the times were selected at random) and to release it within 3 s of the change in light intensity with >80% accuracy. Correct behavior was rewarded with 0.3 ml of orange juice. The training took place daily until criterion performance was reached. At this time, initial surgery was performed.

The monkeys were anesthetized initially with ketamine hydrochloride (10 mg/kg ip). Anesthesia was subsequently maintained with a mixture of halothane (2–3%), nitrous oxide (60%), and oxygen. Monkeys were placed in a stereotaxic frame. A head holder for chronic experiments was implanted onto the surface of the skull and stabilized using stainless steel screws and dental acrylic resin. During the initial surgery, body temperature was maintained at 37–38°C with a heating pad, and heart rate was continually monitored by electrocardiographic recording. Expired CO₂ concentration was also...
SI TOOTH-PULP-DRIVEN NEURONS DURING DETECTION TASK

...and JOR threshold were measured everyday before training the monkeys (tooth-pulp impedance: 90.7 ± 33.2 (SD) MΩ ranging from 46.7 to 162.3 MΩ; JOR threshold: 83.5 ± 21.5 µA ranging from 40 to 200 µA). Stimulus intensity was randomized as multiples of the threshold intensity for the JOR (1.0 T). The monkeys were seated quietly in the monkey chair, and an illuminated button was placed in front of them. When the cue light was illuminated, the monkeys pressed a button that caused electrical pulses (500 µs duration, 1 Hz) to be applied to the tooth pulp at an intensity of 0.5, 1.0, 2.0, or 3.0 T stronger than that that elicited a JOR. After a randomly determined period, ranging from 4 to 8 s, the stimulus intensity increased above the baseline stimulus (V2: 0.3, 0.5, 1.0, or 2.0 T). When the monkeys detected the change in stimulus intensity, they released the button within 3 s and received a reward (0.3 ml orange juice). In the present study, the monkeys could stop the tooth-pulp stimulation at any time by releasing the button. However, this behavior was not rewarded when monkeys released the button before the V2 stimulus came on.

Recording procedure

When the monkeys recovered from surgery and its ability to discriminate change in intensity of tooth-pulp stimulation was restored, the behavioral testing was carried out while simultaneously recording activity of units in the contralateral SI. Recordings were made daily from SI neurons whose activity was evoked by electrical stimulation of the tooth pulp during the detection task, using

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**Behavioral task**

A schematic illustration of the task used in the study reported here is shown in Fig. 1. Tooth-pulp impedance (mean ± SD) monitored and maintained at a level between 3.0 and 4.0%. After the initial surgery, the monkeys were tested daily until the ability to discriminate the change in intensity of the light illumination had been reestablished. After that, they were reanesthetized with ketamine and halothane (2–3%), nitrous oxide (60%), and oxygen for implantation of the tooth-pulp electrodes. Upper canine or incisor teeth were prepared for implantation of wire electrodes. Two small holes were drilled into the dentine on the lingual and labial sides of the tooth, and bipolar platinum wire electrodes were embedded using amalgam, and sealed with acrylic resin. Bipolar Teflon-coated stainless steel wire electrodes were also embedded into the ipsilateral digastric muscles to monitor the jaw-opening reflex (JOR). The monkeys were trained to detect the change in stimulus intensity applied to the tooth pulp. After completion of training on this detection task, the monkeys were reanesthetized using the same anesthetic procedure as used for the initial surgery, and a metal chamber was installed over the orofacial projection area of the SI.

After completing each surgical procedure, the monkeys were routinely sedated with a small amount of ketamine (2–3 mg/kg im) and given penicillin (10,000 U/kg im) and glucose-saline (40–50 ml of a 5% glucose solution in 0.18% NaCl, sc). Mefenamic acid (10 mg/kg, Pontal) dissolved in 200 ml orange juice was given daily after surgery for 3–4 days.

**Recording procedure**

When the monkeys recovered from surgery and its ability to discriminate change in intensity of tooth-pulp stimulation was restored, the behavioral testing was carried out while simultaneously recording activity of units in the contralateral SI. Recordings were made daily from SI neurons whose activity was evoked by electrical stimulation of the tooth pulp during the detection task, using
removed. Fifty-micrometer-thick serial sections were cut along the path of the electrode penetrations. Every section was then counterstained with cresyl violet, and the locations of recording sites were subsequently analyzed using a light microscope.

**Statistical analysis**

Statistical analysis was performed by using analysis of variance (ANOVA) followed by post hoc Fisher’s protected least significant difference (PLSD) or Scheffe’s tests where appropriate. Differences were considered significant at $P < 0.05$.

**RESULTS**

Monkeys were trained to detect the change in stimulus intensity applied to the tooth pulp. Monkeys were used for recording experiments when >80% correct responses to detect the change in stimulus intensity applied to the tooth pulp were achieved. Monkeys were able to release the button before the stimulus intensity was increased (at the V2 stimu-
neurons, and 90 responded to upper lip stimulation, 9 to lower lip stimulation, 44 to tongue stimulation, and 102 to periodontal membrane stimulation. Three hundred fifty-one neurons did not have any identified receptive fields on the face or intraoral structures to mechanical stimuli. Figure 3 shows sample poststimulus time histograms (PSTHs) of a TPN following application of different intensities of V1 (0.5, 1.0, 2.0, and 3.0 T). When the stimulus intensity of 0.5 T was applied, a small number of spikes were elicited just after the onset of the stimulus (indicated by the arrows in Fig. 3A). When stimulus intensities were increased from 1.0 to 3.0 T, firing frequency increased with increases in stimulus intensity.

On the other hand, a TPN illustrated in Fig. 3B did not increase firing frequency following increases in stimulus intensity. When the V1 stimulus intensity was 2.0 or 3.0 T, neuronal activity was frequently depressed for 50 ms just after peak firing was reached. Regression analysis of the V1 stimulus-response functions of each TPN revealed two groups of TPNs classified according to their $r^2$ values; encoding TPNs whose $r^2$ values were $>0.6$ and nonencoding TPNs (monkey R: 433 neurons; monkey A: 429 neurons) were isolated from the orofacial projection areas of the SI. Thirty-seven of them responded to electrical stimulation of the tooth pulp (16 TPNs from monkey R and 21 TPNs from monkey A). Tactile stimulation of the lateral face produced responses in 139 neurons. Although $>80\%$ correct responses were observed, the percent of escape responses was greater at stimulus intensities of 2.0 and 3.0 T (Fig. 2).

Responses to the baseline (V1) stimulus

Eight hundred sixty-two single neurons (monkey R: 433 neurons; monkey A: 429 neurons) were isolated from the orofacial projection areas of the SI. Thirty-seven of them responded to electrical stimulation of the tooth pulp (16 TPNs from monkey R and 21 TPNs from monkey A). Tactile stimulation of the lateral face produced responses in 139 neurons. Although $>80\%$ correct responses were observed, the percent of escape responses was greater at stimulus intensities of 2.0 and 3.0 T (Fig. 2).

FIG. 6. Latency histogram of TPNs. First spike latencies following tooth-pulp stimulation were plotted. ■, encoding TPNs; □, nonencoding TPNs; ●, TPNs that could not be classified as encoding or nonencoding TPNs.

FIG. 7. Electrode penetration tracks were plotted on the SI of one monkey’s hemisphere. Note that tracks where encoding and nonencoding TPNs were encountered were intermingled with each other. CS, central sulcus.

FIG. 8. Intracortical distribution of TPNs in one hemisphere. ●, encoding TPNs; ○, nonencoding TPNs. Top trace is from the most medial section and the bottom is the lateral. CS, central sulcus; IPS, intraparietal sulcus.
TPNs) and 19 did not grade firing frequencies following increases in stimulus intensities (Fig. 5B: nonencoding TPNs, \( r^2 < 0.6 \)). Figure 6 illustrates the histogram of first spike latencies of TPNs after V1 tooth-pulp stimulation \( (V1 = 1.0) \). Most of the TPNs responded with first spike latencies of 20–30 ms after tooth-pulp stimulation \( (SE: \text{encoding} = 24.8 \pm 1.7 \text{ ms}; \text{nonencoding} = 23.6 \pm 1.5 \text{ ms}) \). There were no significant differences in latencies between encoding and nonencoding TPNs.

**Cortical distribution of TPNs**

Figure 7 illustrates the cortical distribution of electrode penetration tracks where TPNs were encountered in one hemisphere. Most TPNs were distributed in the oral projection area, and some were in the intermediate zone between oral and facial projection areas of the SI. Encoding (●) and nonencoding TPNs (○) were intermingled. All TPNs received input from both tooth pulp and orofacial structures. This distribution pattern was observed within the SI cortex as well. Sample intracortical distribution of the TPNs from one hemisphere is illustrated in Fig. 8. TPNs were distributed in the areas 1−2, 3a, and 3b of the SI near the central sulcus. No distribution differences of encoding and nonencoding TPNs were observed in the SI. Receptive fields were mainly located in the intraoral structures, such as periodontal tissues, and some of them were in the face area as shown in Fig. 9. Furthermore, receptive fields of encoding TPNs were restricted to the intraoral structures as illustrated on the left sides of the bottom panels in Fig. 9. On the other hand, receptive fields of nonencoding TPNs were located in both intraoral structures and facial skin.

**Relation between firing frequency and detection latency**

Figure 10 shows the sample recordings of PSTHs after V2 stimulation at different V1 stimulus intensities. Phasic responses were observed after the V2 stimulus. V2 stimulus onset is indicated by the arrows in each histogram. Firing frequencies increased following increases in V2 stimulus intensity at all of the V1 stimulus intensities. When the...
stimulus intensity was high (V1 = 3.0 T, V2 = 2.0 T), depression of the spike potentials was observed just after the peak frequency, as previously shown in Fig. 3, for responses to V1 stimulus intensities.

Regression analysis was applied to the relationship between firing frequency and detection latencies to the V2 stimulus. It has been shown in human psychophysical studies that 0.5 and 1.0 T stimuli do not produce pain sensation, whereas 2.0 and 3.0 T produce pain (McGrath et al. 1981, 1983; Mumford and Stanley 1981). Thus in this study, stimulus intensities of 0.5 to 1.0 T and 2.0 to 3.0 T were categorized as near-noxious threshold and noxious stimuli, respectively. According to the above-mentioned categories, r² values at 0.5 to 1.0 T stimuli and 2.0 to 3.0 T stimuli are plotted in the histograms in Fig. 11, A and B, respectively. A sample scatter plot between firing frequency and detection latency is shown in Fig. 11Aa. When the V1 values were 0.5 and 1.0 T, for 8 of 30 TPNs there was a significant correlation between firing frequency and detection latency (P < 0.05). On the other hand, when the stimulus intensities were high (2.0 and 3.0 T), firing frequencies of only 3 of 30 TPNs were significantly correlated with detection latency (P < 0.05) as illustrated in Fig. 11Bb.

**DISCUSSION**

It is known from human psychophysical experiments that electrical stimulation of the tooth pulp elicits both pain and nonpain (prepain) sensations (Brown et al. 1985; Byers 1984; McGrath et al. 1981, 1983; Mumford and Bowsher 1988; Mumford and Stanley 1981; Shimizu 1964). Anatomic and electrophysiological studies using anesthetized animals have shown the existence of many large myelinated nerve fibers in the tooth pulp (Beasley and Holland 1978; Cadden et al. 1983; Dong et al. 1993; Holland 1978; Holland and Robinson 1983; Lisney 1978; Sessle 1987). Recently, Dong et al. (1993) provided direct evidence of the existence of intra-pulpal Aβ nerve fibers using a single-unit recording technique. These results suggest that the prepain sensation produced by weak electrical stimulation of the tooth pulp in humans may be elicited by intra-pulpal Aβ nerve fibers. High-intensity electrical stimulation of the tooth pulp has been known to activate small diameter nerve fibers. It has been also reported that there is a high correlation between stimulus intensity and primary afferent responses in the tooth pulp following graded electrical stimulation (Boissonade and Matthews 1993; Byers 1984; Mason et al. 1985). Although electrical stimulation is not the most accurate procedure for activating only C or Aδ nerve fibers in the tooth pulp, it is convenient to use this technique for analyzing the relationship between stimulus intensity and neuronal activity in a quantitative manner. Furthermore, natural tooth-pulp stimuli such as thermal or chemical stimulation is difficult to apply in awake behaving animals. Thus electrical stimulation of the tooth pulp is a suitable method for quantitatively activating pulpal small and large diameter nerve fibers. Therefore awake behaving monkeys were studied to analyze the relationship between cortical neuronal activity and the perceived intensity of electrical tooth-pulp stimulation.

The tooth-pulp stimulus intensity was defined relative to the threshold intensity for the JOR to normalize the stimulus intensities in different animals. The relationship between the detection latencies of changes in tooth-pulp stimulus intensities and neuronal responses from SI neurons were analyzed precisely. In human pain reports, it has been shown that when the stimulus intensity was increased to >2.0 T, a pain sensation occurred (McGrath et al. 1981, 1983; Mumford and Bowsher 1988; Mumford and Stanley 1981). In this study, when the stimulus intensity was lower than the JOR threshold, escape occurred on ~10% of the trials, whereas when the stimulus intensity was at 2.0 and 3.0 T, escape frequencies increased to 20–40%. These findings suggest that stimulus intensities of 0.5 and 1.0 T for the JOR are near-noxious, whereas 2.0 and 3.0 T are noxious for monkeys.

It is well-known that SI neurons are somatotopically arranged such that each SI neuron receives somatosensory

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**FIG. 11.** Histograms of r² values following V2 stimulus at different V1 stimulus intensities. A: histogram of r² values when V1 values are 0.5 T and 1.0 T. B: histogram of r² values when V1 values are 2.0 T and 3.0 T. Sample scatter plots of monkey’s detection latency and firing frequency of TPNs are illustrated in Aa and Bb. Spikes/100 ms after stimulus are plotted against as the detection latency. Solid lines in each scatter plot represent the linear regression of the equation fit to the scatter plots. ■, encoding TPNs; □, nonencoding TPNs.
information from a restricted region of the body (Darian-Smith et al. 1966; Felleman et al. 1983; Kaas et al. 1979; Landgren and Olsson 1980; Taira 1987). It has been reported that hindlimb regions in monkeys are represented in the medial portion of the posterior part of the central sulcus and intraoral structures are in the most lateral part (Kaas et al. 1979; Ogawa et al. 1989). Most of the neurons in SI responded to mechanical stimulation of the receptive fields, and some of them also received nociceptive inputs (Chudler et al. 1990; Kenshalo et al. 1983; Lamour et al. 1982). Furthermore, it has been also reported that a large number of SI neurons responded to electrical, chemical, or thermal stimulation of the tooth pulp in the orofacial projection area in the SI (Iwata et al. 1986, 1987, 1990, 1994; Lund and Sessle 1974; Matsumoto 1984; Matsumoto et al. 1987, 1989). Most of the TPNs were located in the oral projection area of SI, and they were located in areas 1–2 and 3 cytoarchitectonically. In previous studies, it has been reported that TPNs were located in the areas 3a and 3b of the orofacial projection area in cats (Iwata et al. 1986, 1987, 1990, 1994; Lund and Sessle 1974; Matsumoto 1984; Matsumoto et al. 1987, 1989). These cytoarchitectonic differences of TPN distribution between previous results are likely related to species differences.

It has been reported that many TPNs receive inputs from the intraoral structures, facial skin, or both (Iwata et al. 1986, 1987, 1990, 1994; Lund and Sessle 1974; Matsumoto 1984; Matsumoto et al. 1987, 1989). Based on receptive-field properties, TPNs were classified as (1) TPNs that responded exclusively to innocuous mechanical stimulation of the receptive field, (2) WDR neurons that responded to both innocuous and noxious stimulation of the receptive fields and increased their firing frequency following increases in stimulus intensity, or (3) NS neurons that exclusively responded to noxious mechanical or thermal stimulation of the receptive fields (Iwata et al. 1990). The previous findings revealed that most of the TPNs were activated by both tooth pulp and cutaneous noxious and/or nonnoxious stimulation, suggesting that TPNs in SI are involved in processing innocuous and noxious sensory information from cutaneous, mucosal, and/or periodontal inputs as well as from the tooth pulp. In the present study, we did not use any noxious natural stimuli, such as pinching or squeezing of the skin. Thus WDR and NS TPNs could not be distinguished. The data from the present study describe similar convergence properties of TPNs, in which all TPNs receive inputs from the intraoral mucous membrane, facial skin, or periodontal structures. The convergence of peripheral sensory inputs on TPNs suggests that these neurons may be involved in signaling spatial localization and referred pain. We also found that encoding TPNs had receptive fields restricted to the intraoral structures, whereas nonencoding TPNs had receptive fields on the facial skin and/or intraoral structures, and some of the nonencoding TPNs had larger receptive fields than those of the encoding neurons. This may suggest that TPNs with restricted receptive fields in the intraoral structures are involved in the sensory encoding process related to tooth-pulp sensation. Many TPNs increase their firing frequency following increases in stimulus intensity (Iwata et al. 1990; Matsumoto et al. 1987). In the present study, many TPNs increased


