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Coding of peripheral electrical stimulation frequency in thalamocortical pathways

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Abstract

Frequency information of the environment is an important feature for sensory perception. It has been demonstrated that cortical and thalamic neurons exhibited frequency-specific responses to peripheral stimulation. In the present study, we investigated the effects of 1–100 Hz peripheral electrical stimulations on various thalamic and cortical areas in awake rats. We used chronically implanted microelectrode arrays to record neural activities from the anterior cingulate cortex, primary somatosensory cortex, and medial dorsal and ventral posterior thalamus. The results revealed that cortical and thalamic neurons exhibited frequency-specific responses at both single-neuron and ensemble levels. Clusters of neurons responded to different frequency ranges with changes of both the peak firing rates and the phases of the peak responses in a stimulation cycle. Partial directed coherence analysis showed that information flowing between these recorded areas is also enhanced or inhibited in some frequency-specific pattern during stimulation. These evidences suggest that central nervous system may code environmental frequency information mainly with the activation of selected neural circuits according to their own intrinsic electrical properties. These properties, in turn, may facilitate or inhibit their responses when stimulation with specific frequency information arrives.

Keywords: Frequency perception; Frequency-specific response; Anterior cingulate cortex; Primary somatosensory cortex; Thalamus; Partial directed coherence; Transcutaneous electric nerve stimulation; Analgesia

Introduction

Perception of frequency information in the environment is an important function of the sensory system. As two examples, visual and auditory systems specifically develop to distinguish frequencies of electromagnetic waves and sound waves, respectively. Recent studies have revealed that peripheral somatosensory stimulation in certain frequency ranges can induce specific neural responses in the cortex and thalamus. By stimulating vibrissae at frequencies from 1 to 40 Hz, Garabedian et al. (2003) observed that neurons in primary somatosensory cortex (SI) exhibited the highest total spiking rate to repetitive stimuli between 5 and 10 Hz. Such frequency-dependent processing was found throughout the vibrissa sensory system. For instance, ventral posterior thalamus (VP) and SI neurons showed a wide variety of frequency-dependent filter characteristics, including 'low pass', 'high pass', and 'band-pass' (Ahissar et al., 2000; Fanselow and Nicolelis, 1999; Moore, 2004). These evidences suggest that thalamocortical pathways may have the ability to code frequency information in this range of stimuli.

Studies on the effect of peripheral electrical stimulation revealed that specific frequencies applied to certain body sites may have specific effect on the central nervous system. For example, peripheral stimulation of 2 Hz produces a significant increase in the release of enkephalin, whereas 100 Hz increases the release of dynorphin in the spinal cord level (Fei et al., 1986; Han and Sun, 1990; Han, 2003; Ulett et al., 1998). Also, it has been clinically demonstrated that only high-frequency deep brain stimulation is effective in the treatment of Parkinson's disease and other movement

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disorders (Lozano, 2001; Tarsy, 2001). Recent development of the Brain-Computer Interconnection (BCI) technique also showed that there exists frequency-dependent neural response to flicker stimulations (Gao et al., 2003; Kalcher et al., 1996; Pfurtscheller et al., 1995–96, 2000; Pregenzer and Pfurtscheller, 1999). In short, the effects of peripheral stimulation were often frequency-specific. These evidences also suggest that the central nervous system must have specific approaches to code environmental frequency information. Thus, it will be very interesting to investigate systemically how neurons in these pathways code peripheral stimulation of different frequencies.

Efforts have been made to clarify the central mechanism of frequency coding. Studies demonstrated that analgesia induced by different frequencies of peripheral electrical stimulation was organized in different brain areas. Specifically, the arcuate nucleus of the hypothalamus and the parabrachial nucleus of the pons play crucial roles in low- and high-frequency peripheral electrical stimulation-induced analgesia, respectively (Wang et al., 1990a,b, 1991). Histological study of c-*fos* expression suggested that overlapped but distinct neuronal networks were activated by these two frequencies (Guo et al., 1996). It has also been hypothesized that distinct low- and high-frequency processing modes exist in SI, and more generally the vibrissa sensory system (Moore, 2004).

However, no research has been conducted on the ensemble responses of the thalamocortical pathway neurons to peripheral electrical stimulation of a wide frequency range. How these neurons detect stimulation frequencies and 'control' the frequency-specific responses has yet to be determined. The present study was conducted to investigate the ensemble neuronal response of VP and SI, the somatosensory projection pathway, as well as medial dorsal thalamus (MD) and anterior cingulate cortex (ACC), the more subconscious sensory pathway, to peripheral electrical stimulation of 1 to 100 Hz in awake rats. The multichannel singe-unit recording technique was employed, which has been proved to be suitable for the study of ensemble neuronal activities (Fanselow et al., 2001; Ghazanfar et al., 2000; Katz et al., 2001; Nicolelis et al., 1993, 1995, 1997, 1998; Nicolelis and Chapin, 1994; Wang et al., 2003, 2004; Williams et al., 1999). Our working hypothesis is that the intrinsic electrical property of neural circuits might render them sensitive to stimulation of specific frequencies. Hence, the frequency-dependent neuronal responses should be at neural circuit, or cell assembly level. If this hypothesis is true, we should expect scattered frequency-specific responses across different brain areas.

Materials and methods

Subjects

The experiment was performed on eight male Sprague–Dawley rats weighing 300–350 g. The rats were provided by the Animal Service Center of Peking University Health Science Center. Animals were housed individually, with ad lib access to food and water, on a reverse light–dark schedule with the light phase started at 7:00 p.m. All experiments were carried out in accordance with the standards for use of laboratory animals established by the Institute of Laboratory Animal Resources, U.S. National Academy of Sciences, and with the Institutional Animal Care and Use Guideline of Peking University. All efforts have been made to minimize animal suffering and to reduce the number of animals used.

Implantation of recording electrodes

Rats were administered penicillin (16,000 U, i.m.) before surgery to prevent infection. Neural activity was recorded from the anterior cingulate cortex (ACC), primary somatosensory cortex (SI), medial dorsal thalamus (MD), and ventral posterior thalamus (VP). With each animal under ketamine anesthesia, four small craniotomies were made for microelectrode array implantation, as described by Nicolelis et al. (1997) and Wang et al. (2003). Coordinates for the craniotomies were according to the atlas of Paxinos and Watson 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 MD, −2.3 A, 0.8 L, and 5.6 V; (4) for VP, −3.0 A, 3.2 L, and 6.0 V. Four arrays of 8 Teflon-insulated stainless steel microwires were slowly lowered into the target areas. When the electrodes were in the correct locations, they were cemented to the skull with dental acrylic. Rats were allowed to recover for a week before recording sessions began.

Recording procedures

Neural electric 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 time resolution for data collection was 50 kHz. The signals were band-pass filtered between 0.5 and 5 kHz (6 dB cutoff) before being sent to a spike-sorting device. Spike activities were monitored on a computer. Waveforms were picked up by setting proper parameter pairs for amplitude and duration, and recorded into a database file with a PC-based software *Magnet* (Biographics, Inc. USA). The identity of clearly sorted single neurons was verified by graphical capture of waveforms. Data were then analyzed with commercially available PC-based programs *STRANGER* (Biographics, Inc. USA) and *Nex* (Plexon, Inc. USA). The animals' behaviors during the stimulation session were videotaped using a video camera (Vigour, VG-2012, China) recording 30 frames per second.

Stimulation protocol

During the recording session, rats were awake and slightly restricted in a hanging-up waistcoat with their