Hearing Research 259 (2010) 107–116

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Research paper

Neural substrate of sound duration discrimination during an auditory sequence in the guinea pig primary auditory cortex

Shuntaro Okazaki [a], Shin'ichiro Kanoh [b], Minoru Tsukada [c], Kotaro Oka [d,*]

[a] Department of Rehabilitation for Sensory Functions, Research Institute, National Rehabilitation Center for Persons with Disabilities, Saitama, Japan
[b] Department of Electronic Engineering, Graduate School of Engineering, Tohoku University, Miyagi, Japan
[c] Faculty of Engineering, Tamagawa University, Tokyo, Japan
[d] School of Fundamental Science and Technology, Graduate School of Science and Technology, Keio University, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 3 March 2009
Received in revised form 19 October 2009
Accepted 21 October 2009
Available online 24 October 2009

Keywords:
Sound duration
Change detection
Mismatch negativity
Unit recording
Guinea pig

ABSTRACT

Mismatch negativity (MMN) is a negative component of event-related brain potentials elicited by stimulus transitions. Stimulus duration transition also elicits MMN (duration MMN), with a magnitude that is related to the degree of duration change and the discrimination ability. The neural substrates of duration MMN have not yet been investigated. We therefore studied how duration transitions in an auditory stimulus train are represented in neurons in the primary auditory cortex of anesthetized guinea pigs. Two types of neuronal responses to the context of changes in stimulus duration were found. One was a reduced response as the duration of the preceding stimulus was increased. Second was an enhancement of the late components of the response including sustained and offset responses at the duration transition. The former may be explained by the previously proposed two-tone suppression, which is dependent on the preceding stimulus duration. The latter is likely to be caused by stimulus-specific adaptation that could be a possible neural generator of duration MMN.

1. Introduction

Environmental sounds are often presented successively and are perceptible as an auditory sequence with altering features of frequency, intensity, and duration. Discrimination of sound features is contextually modulated by preceding stimuli (Bartlett and Wang, 2005). Two-tone stimuli have been widely used to investigate suppression (or facilitation) of auditory neuron activity by a preceding or conditioner stimulus (Abbas and Sachs, 1976; Harris and Dallos, 1979; Calford and Semple, 1995; Brosch and Schreiner, 1997; Brosch et al., 1999; Reale and Brugge, 2000; Bartlett and Wang, 2005; Brimijoin and O'Neill, 2005; Nakamoto et al., 2006). Conditioner stimuli whose sound features are most similar to those of the probe stimuli were found to produce the strongest suppression. This stimulus-specific effect is thought to contribute to the detection of sound feature transitions. However, there is so far no evidence for a stimulus-specific effect affecting the perception of sound duration. It is generally held that response suppression of the probe stimulus response is strengthened when the duration of the conditioner stimulus is increased (Harris and Dallos, 1979; Bartlett and Wang, 2005), however this duration-dependent aspect on two-tone suppression seems not to contribute to the discrimination of sound duration.

There have been many studies on the mechanisms that permit detection of changes in an auditory sequence containing variable sound features (e.g. Näätänen et al., 1978, 1989; Jacobsen and Schröger, 2003; Ulanovsky et al., 2003). Most studies have focused on mismatch negativity (MMN), a change in brain activity in response to a discriminable change in auditory input that can be detected by electroencephalography or by recordings from micro electrodes. This response is usually interpreted as being generated by an "automatic" cortical change-detection process based on differences between the current input and the representation of the regular aspects of the conditioner auditory input (Näätänen et al., 2005). MMN has been observed in non-human animals even when they are anesthetized (Ruusuvirta et al., 1998; Umbricht et al., 2005; Astikainen et al., 2006; Okazaki et al., 2006). Working on the primary auditory cortex (AI) of anesthetized cats, Ulanovsky et al. (2003) investigated the neural substrate of the MMN elicited by transitions of sound frequency and intensity. Although MMN can also be elicited by duration transition (duration MMN) in human (e.g. Jacobsen and Schröger, 2003) and in anesthetized

---

Abbreviations: AI, primary auditory cortex; ANOVA, analysis of variance; ε_{GG}, Greenhouse–Geisser epsilon; MMN, mismatch negativity; N_2O, dinitrogen monoxide; OSD, onset of the stimulus difference; PSTH, peri-stimulus time histogram; SI, index of the stimulus-specific adaptation; SOA, stimulus onset asynchrony

* Corresponding author. Address: School of Fundamental Science and Technology, Graduate School of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan.
E-mail address: oka@bio.keio.ac.jp (K. Oka).

0378-5955/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.heares.2009.10.011

animals (Umbricht et al., 2005; Okazaki et al., 2006), the neural substrates of duration MMN have not yet been investigated. Since the duration MMN as well as frequency MMN are shown to be indices of discrimination ability (Troche et al., 2009), the neural substrate will provide an important information for the duration discrimination.

Some subcortical neurons are known to show selectively larger responses to acoustic stimuli containing specific sound features of frequency, intensity, and duration (termed the "characteristic" frequency, intensity and duration). These feature-selective neurons show the strongest adaptation to repetitive stimuli containing characteristic features, but fail to respond to stimuli with non-characteristic features. Cortical neurons appear to recover from adaptation by a process of feature transition. Szymanski et al. (2009) proposed a possibility that cortical integration of the adaptation of feature-selective neurons might result in a neural representation where AI neurons respond more strongly to a rarely presented "deviant" stimulus than to the same stimulus when it is common, or "standard". This phenomenon, termed "stimulus-specific adaptation", has been proposed as a possible single-neuron generator of MMN (Ulanovsky et al., 2003, 2004).

If an AI neuron shows stimulus-specific adaptation for sound duration, then neurons projecting to the AI neuron may be expected to display duration selectivity. There is extensive evidence that some subcortical and cortical neural circuits are selective for sound duration (e.g. Casseday et al., 1994; Ehrlich et al., 1997; Galazyuk and Feng, 1997; He et al., 1997; Brand et al., 2000; Takahashi et al., 2004; Fremouw et al., 2005; Jen and Wu, 2006; Pérez-González et al., 2006). It is plausible to suggest that AI neurons may show stimulus-specific adaptation for sound duration and thereby contribute to the generation of duration MMN.

The guinea pig is a well-established animal model for investigating neuronal representations of sound duration in subcortical areas (Yu et al., 2004; Wang et al., 2006; Yin et al., 2008). In previous investigations on the animal model of duration MMN, we demonstrated that duration MMN can be recorded in anesthetized guinea pigs and discussed the relationship between duration MMN and the discrimination process for the change in stimulus duration (Okazaki et al., 2006). To extend our previous study we have now examined how AI neurons represent the transition of stimulus duration during an auditory sequence and have investigated the neural substrates of duration MMN and duration discrimination processing.

2. Materials and methods

All experiments were performed in accordance with the Society for Neuroscience Policies on the Use of Animals and Humans in Neuroscience Research and were approved by the Animal Experimentation Committees of Tamagawa University and Keio University.

2.1. Animal preparation

Eight female guinea pigs (3–5 weeks old) weighing 250–350 g were used in this study. Body temperature was maintained at 37 ± 1 °C throughout the experimental procedure. Operation was performed under ketamine (40 mg/kg, i.m.) and xylazine (20 mg/kg, i.m.) anesthesia. Tracheotomy was performed for artificial respiration with dinitrogen monoxide (N_2O) and sevoflurane anesthesia. Bone and dura overlying the left auditory cortex (3.0 mm posterior bregma, 10.0 mm lateral midline, 5 mm × 5 mm) (Smith and Kraus, 1988) were removed for single-unit recording. A silver wire reference electrode was attached to the dura under the occipital bone (1 mm caudal from lambda). After the operation, the animal was moved to a sound-proof chamber and fixed with a steel anchor attached to the frontal bone. N_2O (60–70%), sevoflurane (0.5–2%), and oxygen (30–40%) were introduced via artificial respiration (GENEQ SAR-830 ventilator, Canada) after spontaneous respiration was eliminated by pancuronium bromide (0.2 mg/kg); the absence of apnea was maintained by pancuronium bromide (0.2 mg/kg/3 h) during observation and recording.

2.2. Acoustic stimulation

MMN is generally elicited by repetitive stimuli with rare intervening stimuli that deviate in sound features (termed "oddball" stimuli). MMN can be estimated by comparing event-related brain potentials evoked by the rarely intervening stimuli (deviant stimuli) with those evoked by the frequently repetitive stimuli (standard stimuli). However, it was recently suggested that there are some problems for this typical definition of duration MMN (e.g. Jacobsen and Schröger, 2003). We therefore adopted more appropriate stimuli that are also known to induce MMN (Sams et al., 1983; Haenschel et al., 2005); the protocol for measuring duration MMN is presented below (see also Section 4).

The stimuli used in this study consisted of successive trains that pseudo-randomly changed in duration train-by-train (Fig. 1A); the successive trains were repeated over 50 times. Each stimulus in the train was broadband noise of 4 durations (50, 75, 150, and 200 ms) with a 5 ms rise/fall. These durations were selected in the range corresponding to guinea pig's vocalization (Harper, 1976; Suta et al., 2003) and were designed such that all combinations of durations had equally spaced duration differences of 25 ms (25–150 ms) at the duration transition. Each noise stimulus commenced with an identical signal so that spectro-temporal characteristics of the noise stimuli may not affect the duration discrimination (e.g. 50-ms signal of earlier part of 200-ms stimulus and 50-ms stimulus are identical). Acoustic stimuli were delivered to the entrance of the right ear through an attenuator, a speaker driver, and a tweeter with a conical tube (PA5, ED1, and ES1, respectively; Tucker–Davis Technologies, Alachua, FL, USA). The sound pressure level of all stimuli was 76 dB SPL at the tube tip.

Each stimulus was presented repeatedly 7–13 times in a train with an interval of 510 ms from onset to onset (stimulus onset asynchrony or SOA). The number of stimuli repetitions was pseudo-randomly aligned such that the occurrence of the duration transition was 10%. The first and seventh stimuli in the repetition were defined as "deviant" and "standard" stimuli, respectively, (c.f. Haenschel et al., 2005).

2.3. Unit recording

Platinum/tungsten electrodes coated with quartz glass and with tip diameters of 25 μm (impedance: 3–5 MΩ, ESI2ec; Thomas Recording, Giessen, Germany) were inserted perpendicular to the cortical surface of the left AI. Responses of a few neurons enduring approximately 1 h acquisition time were obtained for each penetration at a depth of 200–1400 μm from the surface. Response signals were amplified using pre-amplifiers (20×, EM112/R; Thomas Recording) and amplifier modules (2000×, MEG-6116; Nihon Koden, Tokyo, Japan) and then filtered by 500 Hz high-pass and 10 kHz low-pass filters (MEG-6116; Nihon Koden). The responses were digitized at 20 kHz. Neuron spikes were isolated from the responses by using appropriate threshold levels and were recorded with an acquisition window of 1.6 ms using an acquisition program (Discovery; DataWave Technologies, Longmont, CO, USA). Multiunit responses were decomposed to single-unit responses by a clustering method using add-on software (Autocut; DataWave Technologies). Waveforms of spikes were confirmed by comparison to a template waveform of initial several spikes on a MATLAB