Neuroscience 318 (2016) 58–83

AN ANALYSIS OF NONLINEAR DYNAMICS UNDERLYING NEURAL ACTIVITY RELATED TO AUDITORY INDUCTION IN THE RAT AUDITORY CORTEX

M. NOTO, [a] **J. NISHIKAWA** [a] **AND T. TATENO** [a,b]*

[a] *Bioengineering and Bioinformatics, Graduate School of Information Science and Technology, Hokkaido University, Kita 14, Nishi 9, Kita-ku, Sapporo 060-0814, Japan*

[b] *Special Research Promotion Group, Graduate School of Frontier Biosciences, Osaka University, 1-3 Yamadaoka, Suita, Osaka, Japan*

Abstract—A sound interrupted by silence is perceived as discontinuous. However, when high-intensity noise is inserted during the silence, the missing sound may be perceptually restored and be heard as uninterrupted. This illusory phenomenon is called auditory induction. Recent electrophysiological studies have revealed that auditory induction is associated with the primary auditory cortex (A1). Although experimental evidence has been accumulating, the neural mechanisms underlying auditory induction in A1 neurons are poorly understood. To elucidate this, we used both experimental and computational approaches. First, using an optical imaging method, we characterized population responses across auditory cortical fields to sound and identified five subfields in rats. Next, we examined neural population activity related to auditory induction with high temporal and spatial resolution in the rat auditory cortex (AC), including the A1 and several other AC subfields. Our imaging results showed that tone-burst stimuli interrupted by a silent gap elicited early phasic responses to the first tone and similar or smaller responses to the second tone following the gap. In contrast, tone stimuli interrupted by broadband noise (BN), considered to cause auditory induction, considerably suppressed or eliminated responses to the tone following the noise. Additionally, tone-burst stimuli that were interrupted by notched noise centered at the tone frequency, which is considered to decrease the strength of auditory induction, partially restored the second responses from the suppression caused by BN. To phenomenologically mimic the neural population activity in the A1 and thus investigate the mechanisms underlying auditory induction, we constructed a computational model from the periphery through the AC, including a nonlinear dynamical system. The computational model successively reproduced some of the above-mentioned experimental results. Therefore, our results suggest that a nonlinear, self-exciting system is a key element for qualitatively reproducing A1 population activity and to understand the underlying mechanisms.

Key words: auditory subfields, computational model, nonlinear dynamics, optical imaging, synaptic depression.

INTRODUCTION

In sound perception, sensitivity to expected signals may be enhanced under certain noisy circumstances, and robustness against background noise can be ensured. For example, a sound is perceived as interrupted or discontinuous when part of the sound is replaced by a gap of silence. However, when the gap is replaced by a noise burst with a louder sound level, the interrupted sound is heard as continuous throughout the noise. This illusory phenomenon is known as auditory (or temporal) induction (Warren et al., 1972; Bashford and Warren, 1987), and it illustrates one example of the constructive nature of sound perception. Furthermore, recent electrophysiological studies have revealed that the primary auditory cortex (A1) is related to auditory induction and the neural correlates of auditory induction have been studied for several classes of sounds in many species, such as birds (Braaten and Leary, 1999), gerbils (Kobayasi et al., 2012), guinea pigs (Kubota et al., 2012), cats (Sugita, 1997), monkeys (Miller et al., 2001; Petkov et al., 2003, 2007), and humans (Repp and Lin, 1991; Warren and Bashford, 1999; Micheyl et al., 2003; Riecke et al., 2007). To the best of our knowledge, no such studies have been conducted in rats, one of most commonly used organisms. Although experimental evidence has been accumulating, the neural mechanisms underlying auditory induction in A1 neurons are poorly understood.

In the central auditory pathway, the responses of neurons to complex natural sound are not necessarily predictable from simple sound stimuli such as sound

*Correspondence to: T. Tateno, Bioengineering and Bioinformatics, Graduate School of Information Science and Technology, Hokkaido University, Kita 14, Nishi 9, Kita-ku, Sapporo 060-0814, Japan. Tel: +81-11-706-6763.
E-mail address: tateno@ist.hokudai.ac.jp (T. Tateno).

Abbreviations: AAF, anterior auditory field; AC, auditory cortex; A1, primary auditory cortex; AVAF, anterior ventral auditory field; BF, best frequency; BN, broadband noise; CF, characteristic frequency; ERB, equivalent rectangular bandwidth; FHN, FitzHugh–Nagumo; GF, gammatone filter; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; LA, locally evoked activity; MGB, medial geniculate body; NA, no activation; NN, notched noise; PA, propagating activity; PAF, posterior auditory field; PBP, pure-tone burst, broadband noise, and pure-tone burst; PGP, pure-tone burst, gap, and pure-tone burst; PNP, pure-tone burst, notched noise, and pure-tone burst; PT, pure tone; VAF, ventral auditory field; vMGB, ventral nucleus of the medial geniculate body.

http://dx.doi.org/10.1016/j.neuroscience.2015.12.060

impulses (or clicks), pure tones (PTs) over the audible frequency range, or broadband noise (BN), all of which are often used to identify linear dynamical systems (Calabrese et al., 2011; for a review, Theunissen and Elie, 2014). Because the auditory system is intrinsically a complex and highly nonlinear dynamical system, it is natural to suppose that nonlinear dynamical properties may determine perception and functions in the auditory system. Furthermore, nonlinear phenomena can also be exhibited by neurons in the auditory cortex (AC) in response to both simple and complex sound stimulation. For instance, a linear dynamical system using spectro-temporal receptive fields of AC neurons can poorly predict their responses to complex and/or natural sound stimuli (Calabrese et al., 2011). In addition, simple nonlinear mechanisms such as adaptation, compression, and rectification, which are often also found in the peripheral auditory pathways, are insufficient to explain the nonlinearities found in AC neurons (Christianson et al., 2008; de la Rocha et al., 2008; Sharpee et al., 2008). Therefore, to elucidate the responses to such sound stimuli, a nonlinear dynamical system is a key element for understanding signal processing and modeling responses in AC neurons (Wrigley and Brown, 2004; Hoshino, 2007; Curto et al., 2009; Sharpee, 2013).

In this study, therefore, to understand the neural mechanisms underlying auditory induction in AC neurons, we used both experimental and computational approaches: i.e., (i) optical imaging of rat A1 and (ii) computational modeling of the neural pathway from the periphery to the A1. First, to characterize population responses across rat auditory cortical subfields to sound, we identified five subfields, using optical imaging methods. In understanding dynamics of A1, the subfield identification was critically important to distinguish A1 from other subfields. Next, we examined neural population activity related to auditory induction with high temporal and spatial resolution in the rat AC, including the A1 and several other AC subfields. In addition, we developed a computational A1 model that included a nonlinear dynamical system; this model, which phenomenologically mimicked the neural population activity in the A1 from the periphery through the subcortical regions, was used to investigate the mechanism underlying auditory induction. Regarding this mechanism, we focused particularly on the nonlinear dynamics of A1 population activity that were influenced by sound history-dependent thalamocortical and intracortical synaptic input and the resultant recurrent A1 activity. Our results suggested that a nonlinear, self-exciting system is important for qualitatively reproducing the A1 population activity related to auditory induction and understanding the underlying mechanism.

EXPERIMENTAL PROCEDURES

All experiments were carried out in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals, and with approval of the Institutional Animal Care and Use Committee of Hokkaido University.

Surgical procedures

Eight male rats (Wistar/ST, 6–12 weeks old, 163–331 g, Japan SLC, Japan) with normal Preyer's reflex were used for the experiments. The rats were anesthetized with a mixture of midazolam (10 mg/kg, i.p.; Astells Pharma, Japan) and xylazine (12 mg/kg, i.p.; Bayer AG, Germany) in saline as the initial dose (Inaoka et al., 2011; Tateno et al., 2013). The adequacy of anesthesia was confirmed by the absence of toe-pinch reflexes. Supplemental doses were administered every 1 h with half the initial dose (midazolam, 5 mg/kg, i.m. and xylazine, 6 mg/kg i.m.) to maintain anesthesia. Dexamethasone (0.5 mg/kg i.m.; Kobayashi Kako, Japan) was also administered to suppress cerebral edema. During the experiment, rectal temperature was maintained at 34 ± 1 °C using a heat pad. This temperature is slightly lower than normal, but it was the best condition for stable recording in our setup, as described in a previous study (Song et al., 2006). As increasing the animals' body temperature in the experiment, we observed that the areas from which the evoked activity was initiated were not profoundly shifted, but tended to be enlarged slightly. A custom-made metal adapter was attached to the skull with dental cement, and was used to hold the animal's head during recording. A local anesthetic (xylocaine gel; AstraZeneca K.K., Japan) was applied to all incision sites. To prevent visual interference from the excitation light used for voltage-sensitive dyes, both eyes were kept closed. After resection of the temporal muscle, a hole (approximately 7 mm in the rostrocaudal direction and approximately 5 mm in the dorsoventral direction) was drilled in the temporal bone, and the left AC was exposed (Fig. 1Aa). The dura mater was removed and the cortex was stained twice with a voltage-sensitive dye RH-1691 (1 mg/ml; Optical Imaging, Israel) in an artificial cerebrospinal fluid (ACSF) solution (135 NaCl, 5 KCl, 5 HEPES, 1.8 $CaCl_2$, and 1 $MgCl_2$ in mM) for 30 min (1 h in total). After staining, the cortex was covered with 2% agarose in saline and sealed with a glass coverslip to reduce pulsation.

Optical recording

The principles of optical recording with voltage-sensitive dyes have been described in the literature (Song et al., 2006; Kubota et al., 2008). We used an imaging system with a high-speed and high-resolution CMOS camera system (MiCAM02, Brainvision, Japan) to detect optical signals. The CMOS camera was mounted on a tandem-lens fluorescence microscope (THT, Brainvision). Light from a 150-W halogen lamp (HL-151, Brainvision) was projected through an excitation filter (wavelength $\lambda = 632 \pm 11$ nm) and reflected by a dichroic mirror ($\lambda = 550$–640 nm) to activate voltage-sensitive dye at the cortical surface. Fluorescence signals were then collected through the dichroic mirror, projected through an absorption filter ($\lambda > 665$ nm), and detected with the CMOS camera. The microscope was focused at a depth of 300 μm below the cortical surface to minimize the interference from blood vessels and to concentrate on the activities in cortical layer II/III (Fig. 1Ab). Although this