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Frequency-Dependent Stimulus-Specific Adaptation and Regularity Sensitivity in the Rat Auditory Thalamus

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Abstract—Recent electrophysiological studies in animals using oddball stimuli have demonstrated that neurons along the auditory pathway from the inferior colliculus to the auditory cortex (AC) have a strong response to rarely presented stimuli. This phenomenon is termed stimulus-specific adaptation (SSA), which is regarded as novelty detection. However, in the medial geniculate body (MGB), it is not clear whether SSA is frequency dependent or if neurons in the MGB are sensitive to the regularity of the stimuli. In this present study, we analyzed the relationship between stimulus frequency and SSA, as well as explored regularity sensitivity using extracellular recordings in the MGBs of rats with regular and irregular oddball stimuli. It was found MGB neurons exhibited strong SSA when the pure-tone stimulus of the oddball stimulus deviated far from the characteristic frequency, even in the ventral region of the MGB, suggesting that the MGB may contribute to SSA in the primary AC. Moreover, we found the neuronal population in the MGB was sensitive to high-order sound structure, where deviant responses were smaller and standard responses were stronger for irregular oddball stimuli. We conclude that regularity detection occurs in the MGB, but in a manner distinct from the AC.

Key words: stimulus-specific adaptation, medial geniculate body, auditory response, novelty detection, regularity.

INTRODUCTION

Despite the auditory environment being continuously filled with concurrent auditory stimuli, humans can easily isolate and attend to stimuli that are novel and/or salient. An essential task for the brain is to discern novel information from irrelevant background. On a neuronal level, the ability to adapt to repeated sounds while maintaining responsiveness to deviant sounds is known as stimulus-specific adaptation (SSA) and is one of the mechanisms underlying detection of novelty and change (Ulanovsky et al., 2003; Yu et al., 2009b). SSA has been widely described along the auditory pathway with oddball stimuli, including AC (Ulanovsky et al., 2003; Szymanski et al., 2009; Von Der Behrens et al., 2009; Antunes et al., 2010; Farley et al., 2010; Taaseh et al., 2011; Fishman and Steinschneider, 2012; Nieto-Diego and Malmierca, 2016), MGB (Anderson et al., 2009; Yu et al., 2009b; Antunes et al., 2010; Bäuerle et al., 2011; Richardson et al., 2013; Antunes and Malmierca, 2014; Duque et al., 2014), and inferior colliculus (IC) (Malmierca et al., 2009; Zhao et al., 2011; Ayala and Malmierca Dr, 2012; Ayala et al., 2012; Pérez-González et al., 2012; Anderson and Malmierca, 2013; Duque et al., 2016). These studies used two tones with frequencies close to neuronal characteristic frequencies (CFs) or best frequencies and demonstrated a functional pathway for SSA from the midbrain to the AC (see Malmierca et al., 2014; Khouri and Nelken, 2015, for review). In general, SSA is weaker for the lemniscal pathway than the non-lemniscal pathway. The primary AC (A1) is the first station in the lemniscal pathway that undergoes SSA, while there is little or no SSA in the ven-

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Abbreviations: AC, auditory cortex; CF, characteristic frequency; CSI, common stimulus-specific index; FRA, frequency-responding area; IC, inferior colliculus; ISI, interstimulus interval; MGB, medial geniculate body; MGd, dorsal region of medial geniculate body; MGm, medial region of medial geniculate body; MGv, ventral region of medial geniculate body; PSTH, peristimulus time histogram; SI_i, stimulus-specific index; SPL, sound pressure level; SSA, stimulus-specific adaptation; TRN, thalamic reticular nucleus.

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tral MGB (MGv) (Malmierca et al., 2014; Khouri and Nelken, 2015).

The MGB is a strategic gateway to the AC, which receives ascending and massive descending inputs from the IC (Winer et al., 1996; Bartlett and Smith, 1999; Bartlett et al., 2000; Ito and Oliver, 2012) and AC (Ojima, 1994; Sherman and Guillery, 1996; Winer et al., 1999), respectively. Recently, Duque et al demonstrated SSA in the IC is frequency dependent, where high-frequency oddball stimuli usually elicit strong SSA (Duque et al., 2012). It is unknown whether SSA in the MGB is frequency dependent. This is an important issue for two reasons. First, SSA variation across the frequency responding area (FRA) may shed light on underlying neuronal mechanisms, where homogeneous SSA would suggest a larger contribution from intrinsic properties (Abolafia et al., 2011; Duque et al., 2012). Second, SSA variation across the FRA may also shed light on the auditory pathway origin of SSA. For example, if neurons in the MGv exhibit strong SSA in some bands of the FRA, the MGv could potentially contribute to SSA in the AC.

Two types of oddball stimuli, regular oddball (RO) and irregular oddball (IRO), have been used in previous SSA studies. For RO stimuli, the deviant stimuli occur after exactly the same number of standard stimuli. For IRO stimuli, the deviant stimuli occur randomly. RO stimuli reflect both regularity and rarity, while IRO stimuli only reflect rarity. Regularity is abundant in nature (Nelken et al., 1999) and may help animals predict future stimuli. Yaron and colleagues first compared responses to both types of oddball stimuli and found the AC is sensitive to regularity (Yaron et al., 2012). Given the strong reciprocal connections between the AC and MGB (Ojima, 1994; Sherman and Guillery, 1996; Winer et al., 1999), it would be of interest to explore a potential thalamic origin for cortical sensitivity to regularity.

In this present study, we recorded from neurons throughout the rat MGB using oddball paradigms similar to those previously used to study the AC (Yaron et al., 2012) and IC (Duque et al., 2012). We aimed to characterize SSA and regularity detection across the FRA in the main subdivisions of the MGB. It was found that SSA is stronger in the non-CF region of the FRA and neurons in the MGv may undergo strong SSA. Furthermore, although responses to RO and IRO stimuli are very similar, the MGB neuronal population is sensitive to high-order sound structure with deviant responses being weaker and standard responses being stronger for IRO stimuli.

EXPERIMENTAL PROCEDURES

Animals

Male and female Wistar rats (280–360 g) with clean external ears were used in the present study. All animal procedures were approved by the Animal Subjects Ethics Committee of Zhejiang University. Anesthesia was induced using 1.35 g/kg urethane (20% solution, intraperitoneal, Sinopharm Chemical Reagent Co., Shanghai). The level of anesthesia was monitored based on hind paw and corneal reflexes and kept stable with supplementary doses of urethane (0.5 g/kg/h) as needed. In order to suppress tracheal secretion, atropine sulfate (0.05 mg/kg, subcutaneous) was administered 15 minutes prior to the anesthesia and a local anesthetic (2% xylocaine) was liberally applied to the wound. Animals were surgically prepared as described previously (Yu et al., 2009a; Yu et al., 2011; Xu et al., 2017). Briefly, rats were mounted in a stereotaxic device and a midline incision was made in the scalp. A craniotomy was performed to vertically access the MGB and the dura mater was removed. Following implantation of a metal head restraint, the rat was removed from the stereotaxic device and held via the head post in a manner that exposed the rat to a free-field acoustic environment. During the experiment, rats were kept on a heating blanket and body temperature was maintained at 37–38 °C.

Recording

Tungsten microelectrodes with impedances of 5–7 M (Frederick Haer & Co., Bowdoinham, ME) were stereotaxically implanted into rat MGB based on a rat brain atlas from the top of the brain (Paxinos and Watson, 2005). The vertical coordinate of the electrode array was measured from a point slightly above the cortical surface. For recording, electrodes were positioned with a stepping-motor microdrive, which was controlled outside the soundproof room. The signal recorded by the microelectrode was amplified and stored using TDT software (OpenEX, TDT).

Acoustic stimuli

Acoustic stimuli were digitally generated using the computer-controlled Auditory Workstation (Tucker-Davis Technologies, TDT, Alachua, FL) and delivered to the ear via coupled magnetic speakers (MF1, TDT) mounted on a probe. The sound pressure was calibrated and set to 60-dB SPL at the semicircle midpoint with a ¼″ condenser microphone (Brüel & Kjær 4954, Nærum, Denmark) and a PHOTON/RT analyzer (Brüel & Kjær). All stimuli were presented contralateral to the recording side. Upon isolation of a single MGB neuron, the following stimuli were applied:

1) Frequency screening procedure: Tones (100 ms; 5-ms rise-fall time) with multiple combinations of frequencies and intensities were presented to determine the FRAs. Tones were presented randomly with 5 repetitions at each frequency (0.5–48 KHZ in 26 logarithmic steps) and intensity (0–70 dB SPL in 10 dB steps) and interstimulus intervals (ISIs) of 300 ms. We used the FRAs to determine the CF and the high-frequency (HF) and low-frequency (LF) edges.
2) Frequency-dependent oddball stimulation: During the oddball stimulus experiments, three types of frequency combinations were presented to analyze the relationship between SSA and tone frequency (Fig. 1A). We first selected two frequencies, f_1 and f_2, that bordered a central frequency $(f_1 \times f_2)^{1/2}$ close to the CF with a 0.53 octave separation. Then,

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