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Research report

CS-specific modifications of auditory evoked potentials in the behaviorally conditioned rat

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ABSTRACT

The current report provides a detailed analysis of the changes in the first two components of the auditory evoked potential (AEP) that accompany associative learning. AEPs were recorded from the primary auditory cortex before and after training sessions. Experimental subjects underwent one (n = 5) or two (n = 7) days of conditioning in which a tone, serving as a conditioned stimulus (CS), was paired with mild foot shock. Control subjects received one (n = 5) or two (n = 7) days of exposure to the same stimuli delivered randomly. Only animals receiving paired CS-US training developed a conditioned tachycardia response to the tone. Our analyses demonstrated that both early components of the AEP recorded from the granular layer of the cortex undergo CS-specific associative changes: (1) the first, negative component (occurring ~21 ms following tone onset) was significantly augmented after one and two days of training while maintaining its latency, and (2) the second, positive component (occurring ~50 ms following tone onset) was augmented after two days of training, and showed a significant reduction in latency after one and two days of training. We view these changes as evidence of increased cortical synchronization, thereby lending new insight into the temporal dynamics of neural network activity related to auditory learning.

1. Introduction

Numerous studies reveal that the primary auditory cortex (area A1) undergoes modifications that parallel the animal's emotional experiences with sound (Diamond and Weinberger, 1986; Bakin and Weinberger, 1990; Edeline and Weinberger, 1993; Gao and Suga, 2000; Kisley and Gerstein, 2001; Tzounopoulos and Leão, 2012; McGann, 2016). If conditioned responding develops to a tone stimulus that has become a reliable predictor of a rewarding or punishing event, an alteration in the tonotopic map may ensue, as the area of cortex devoted to processing the tone's frequency undergoes expansion (Recanzone et al., 1993; Morris et al., 1998; Rutkowski and Weinberger, 2005; Reed et al., 2011; Bieszczad and Weinberger, 2012, also see Weinberger, 2015, for a review). Other forms of plasticity may emerge following auditory learning, such as a reduction in neural thresholds, or a decrease in tuning bandwidth (sharpening of tuning) for frequencies deemed relevant to an animal (Froemke et al., 2013; Voss et al., 2015), as well as a reduction in cortical synaptic inhibition (Sarro et al., 2015). Additionally, auditory neurons may exhibit shorter response latencies or an increase in temporal synchronization after sounds take on new significance (Börgers et al., 2005, 2008; Headley and Weinberger, 2011, 2013; Leon et al., 2008). Finally, simply exposing an animal to an enriched auditory environment, in the absence of any experimentally-imposed behavioral contingencies, has been shown to improve the signal-to-noise ratio of A1 neuronal responses (van Praag et al., 2000; Engineer et al., 2004; Percaccio et al., 2007). All these findings offer a stark contradiction to the notion of neurons in primary auditory cortex operating as low level sensory analyzers, having no role in the encoding of learned aspects of sound. On the contrary, A1 neurons appear to be intimately involved in the representation of acquired knowledge about sounds, their relation to stimulus outcomes, behavioral responses, and the response-outcome contingencies that determine the conditions for reinforcement.

The majority of recent findings regarding learning-induced plasticity have been confirmed on the basis of recordings made from individual or small groups (2–3) of auditory cortical neurons acquired usually from a very narrow (5–30 ms from stimulus onset) response epoch (Voss et al., 2015). This approach allows for the neurobiological study of learning and memory at a high level of spatial and temporal resolution (Polley et al., 2004, 2006; Rutkowski and Weinberger, 2005; Bieszczad and Weinberger, 2012; Reed et al., 2011). One drawback of such an approach, how-

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ever, is that neural recordings with high-impedance electrodes can become unstable over a matter of days (Headley and Weinberger, 2011, 2013), making it difficult to study modifications in neural activity that require longer periods to develop. An alternative approach is to record the local field potential, which is the derivation of extracellular synaptic potentials summated across a much larger region of cerebral cortex (Galván et al., 2002; Kluge et al., 2011; Wehr and Metherate, 2011; Farley and Noreña, 2015). These potentials lack the spatial resolution of single and multi-unit recordings (Gaucher et al., 2012; Cheveigné et al., 2013; Liu et al., 2015), however, they tend to remain stable over many days, and are well suited for studies in which the goal is to observe the temporal evolution of learning-induced neural plasticity. Moreover, because the local field potential is derived from the combined activity of hundreds or thousands of neurons, in some instances this signal may bring to light aspects of sensory processing that are not readily apparent at the level of the single neuron (Wehr and Metherate, 2011).

Upon presentation of an appropriate sound stimulus (e.g., a click or simple tone), the cortically-recorded field potential displays a distinctive early biphasic waveform referred to as the auditory evoked potential (AEP; see Fig.1b). The two earliest peaks of the AEP, termed the N1 and P2 (when recorded from the middle cortical layers) to signify their polarity and precedence over later oscillations that follow, are considered to represent the earliest stages of cortical processing. Their spatiotemporal distribution has been extensively studied. Both the N1 and P2 component are believed to arise from the asynchronous activation of two separate populations of vertically-oriented pyramidal neurons that receive input from thalamocortical fiber tracts (Barth and Di, 1990; Szymanski et al., 2011; Fishman and Steinschneider, 2012).

The mid-layer N1 auditory evoked component originates primarily from thalamic activation of pyramidal neurons located within the supragranular/granular layers (Shaw, 1988; Barth et al., 1993; Huang and Winer, 2000; Lee and Winer, 2008), with the largest current sink centered at the border of layers III/IV (Shiramatsu et al., 2016). According to Schaefer et al., (2015), who classify this current sink as, “s1,” it has a median onset latency of 14.6 ms and is elicited by the lemniscal thalamocortical inputs from MGv. It is accompanied by another early sink (“s2”, median onset latency = 11.4 ms) found in layer VI (Schaefer et al., 2015), which is elicited by the non-lemniscal thalamocortical inputs from MGm. The major current source for the epoch representing the mid-layer N1 is located at layers II/upper layer III (Shiramatsu et al., 2016), or in layers I/II (Schaefer et al., 2015). Schaefer et al. (2015) also identify two more, weaker current sources, in the middle of layers V and VI.

The origins of the mid-layer P2 component are quite different (Lakatos et al., 2007; Happel et al., 2010; Kajikawa and Schroeder, 2011; Intskirveli et al., 2016). The two earliest secondary current sinks are found within layer VI (“s3”, median onset latency = 50.8 ms) and layer V (“s5”; Kaur et al., 2005;

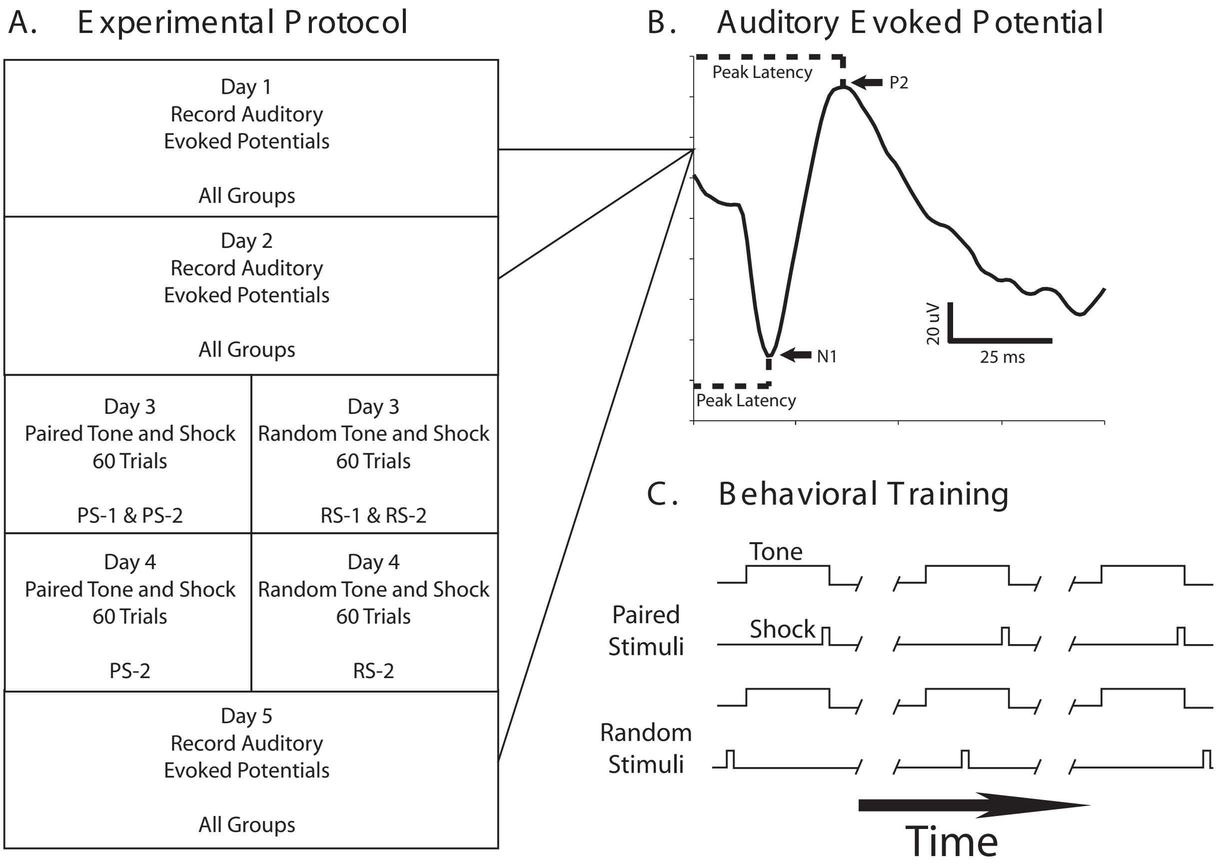

Fig. 1. Experimental procedures and AEP response measures. (A) Chronological breakdown of experimental protocol. All animals underwent procedures for recording auditory evoked potentials (AEPs) on days 1 and 2. The physiological data obtained on day 2 was designated as “pre-training” data. On day 3 PS-1 and PS-2 groups underwent paired tone – shock training, while RS-1 and RS-2 groups underwent randomly presented tone – shock training. On day 4 PS-2 and RS-2 groups received an additional training session. On day 5 all groups underwent procedures for recording AEPs (“post-training” data). (B) Representative auditory evoked potential averaged across twenty trials in which a 5.7 kHz 50 dB SPL tone stimulus was presented. Arrows identify the peaks of N1 and P2 components. Calibration bars: 25 ms (X-axis) and 20 μV (Y-axis). (C) Trials used for behavioral training. PS-1 and PS-2 rats received “paired-stimuli” trials, in which a 6 s tone co-terminated with 0.5 s shock. RS-1 and RS-2 rats received “random-stimuli” trials in which shocks and tones were randomly presented. For illustrative purposes, three sample random trial types are shown. In reality, however, tone and shock stimuli were often separated by several (up to 30) seconds.