



Research report

Baseline theta activities in medial prefrontal cortex and deep cerebellar nuclei are associated with the extinction of trace conditioned eyeblink responses in guinea pigs



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HIGHLIGHTS

- We assessed the impact of baseline theta activity on the extinction of TEBC.
- Stronger baseline mPFC theta activity predicted faster extinction of the trace CRs.
- Likewise, greater pre-CS DCN theta activity predicted faster CR extinction.
- The pre-CS-onset theta power in the mPFC and the DCN were correlated.

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ABSTRACT

It has been shown that both the medial prefrontal cortex (mPFC) and the cerebellum are involved in the extinction of trace conditioned eyeblink responses (CR). However, the neural mechanisms underlying the extinction are still relatively unclear. Theta oscillation in either the mPFC or the cerebellum has been revealed to correlate with the performance of trace CRs during the asymptotic acquisition. Therefore, we sought to further evaluate the impacts of pre-conditioned stimulus (CS) spontaneous theta (5.0–10.0 Hz) oscillations in the mPFC and the deep cerebellar nuclei (DCN) on the extinction of trace CRs. Albino guinea pigs were given acquisition training for ten daily sessions followed by seven daily sessions of extinction. Local field potential (LFP) signals in the mPFC and the DCN were recorded when the animals received the CS-alone extinction training. It was found that higher mPFC relative theta ratios [$\theta/(\delta + \beta)$] during the baseline period (850-ms prior to the CS onset) were predictive of fewer CR incidences rather than more adaptive CR performance (i.e., higher CR magnitude and later CR peak/onset latencies). Likewise, the pre-CS DCN theta activity was associated with the faster CR extinction. Furthermore, it was revealed that the power of pre-CS theta activities in the mPFC and the DCN were correlated until the extinction training day 2. Collectively, these results suggest that the mPFC and the DCN may interact with each other, and the brain oscillation state in which baseline theta activities in both areas are present contributes to the subsequent extinction of trace CRs.

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1. Introduction

Trace eyeblink conditioning (TEBC) is one of the most useful behavioral models for investigating the neural mechanisms underlying motor learning [1–3]. This paradigm of experiment typically involves paired presentations of a conditioned stimulus (i.e., a pure tone) with an aversive unconditioned stimulus (i.e., a corneal air-puff or electrical shock), which are separated by a trace interval. After conditioning, the organisms are able to associate the CS with the US and to perform a defensive conditioned eyeblink response

(CR) before the onset of the US. It is well established that the acquisition and expression of trace CRs are cerebellum-dependent tasks [4–12]. Nevertheless, to retain the memory trace during the trace interval, the forebrain structures such as the hippocampus [13–17] and the medial prefrontal cortex (mPFC) [18–22] are recruited to support the learning process.

Of the forebrain areas, the mPFC is implicated since electrophysiological recording studies have demonstrated that the CS is capable to evoke persistent firing activity in the mPFC neurons when executing the TEBC task [23–27]. Importantly, researches using the neuronal tract-tracing techniques have shown that neurons in the mPFC are anatomically connected with neurons in the cerebellum via the pontine nuclei [25,28–33]. As a result, the output signals carried by the persistent firing of the mPFC neurons are currently speculated to engage in sustaining the CS-related neuronal activity in the cerebellum, providing a possible mechanism for bridging the trace interval [2,3,34]. In support of this speculation, presenting the cerebellum with basilar pontine nuclei mossy fiber inputs, whose temporal patterns mimic the persistently active neurons in the mPFC, is necessary for the expression of trace CR-like responses in rabbits [11]. Moreover, we have recently shown evidence that direct persistent inputs from the mPFC to the cerebellum are sufficient for the acquisition and expression of trace CR-like responses in guinea pigs [35], providing additional support to the preceding speculation.

In addition to the acquisition, the mPFC is involved in the extinction of TEBC when the CS was no longer reinforced by the US. This notion is supported by the evidence that lesions made on the rostral part of mPFC severely impaired the extinction of acquired trace CRs in the rabbits [19]. However, it remains unclear how the mPFC engages in the extinction of aversive motor memory. Theta-band (5.0–10.0 Hz) oscillation is one of the important ways for the mPFC to participate in learning and memory including TEBC [36]. For instance, it was showed that the phase of CS-induced theta oscillations in the mPFC coupled with the amplitude of local gamma oscillations, which might result in stronger prefrontal cortical responses to the CSs during TEBC [37]. Moreover, the CS-evoked theta oscillations in the mPFC were demonstrated to synchronize with those in the entorhinal cortex, which might contribute to the consolidation of trace CRs [38]. Intriguingly, we have found that the pre-CS-onset spontaneous mPFC theta oscillations are indicative of adaptive performance of the trace CRs, relying on whether the mPFC is necessary for the learning process [39]. Considering that the extinction of trace CRs have been proposed to be an active learning process as the acquisition [40] which requires the involvement of mPFC [19], the current study thus aimed to further evaluate the impacts of spontaneous mPFC theta activity during the baseline period on the extinction of trace CRs. Because the cerebellum is also implicated in the extinction process of trace CRs [41], together with correlation of the cerebellar theta oscillations with the CR performance [42], we sought to assess the effect of baseline cerebellar theta activity on the subsequent extinction of trace CRs.

2. Materials and methods

2.1. Subjects

A total of twenty adult male albino Dunkin-Hartley guinea pigs (3–4 months old) were used as subjects in this experiment. The animals were individually housed and had free access to food and water in their home cages. The weight of the animals was maintained between 450 and 550 g before the surgery. All the surgical, recording, and behavioral procedures were approved by the Animal Care Committee of the Third Military Medical

University and were performed in accordance with the principles outlined in the NIH Guide for the Care and Use of Laboratory Animals. Efforts were made to minimize the suffering and the use of animals.

2.2. Surgery and electrode implantation

The detailed electrode implantation procedures have been recently described by Chen et al. [39,42]. Briefly, each animal was chronically implanted with two monopolar stainless steel electrodes (bare diameter: 254.0 μm , No. 792300, A-M systems, Carlsberg, WA, USA). Each electrode was mounted in a 28-G stainless steel cannula. The electrodes then were attached to a pin connector. According to the brain atlas of guinea pig [43], one electrode was implanted into the right mPFC (1.0 mm lateral, 2.0 mm ventral, and 1.5–2.5 mm anterior to Bregma), and the other electrode was implanted into the region adjacent to the left deep cerebellar nuclei (DCN; 2.5 mm lateral, 5.0 mm ventral, and 15.0–16.0 mm posterior to Bregma). Four stainless steel screws were positioned on the surface of skull (2.5 mm posterior, ± 5.0 mm lateral to Bregma; 8.5 mm posterior, ± 5.0 mm lateral to Bregma), and were connected to serve as reference. The whole electrode construction was cemented in place with dental acrylic. Each animal was fitted with a headstage and a loop attached to the apex of the left upper eyelid. This loop was utilized to attach the left upper eyelid to a high-resolution movement-measuring apparatus (JZ-101, XH, Beijing, China). At last, the animals were allowed one week to recover from the surgery.

2.3. Behavioral training

To habituate the experimental situation, the animals were placed in a Plexiglas containing box located in a sound- and light-attenuating chamber without any stimulus for 2 days, 30 min per day. A lightweight cable was connected to the connector pins secured on the animal's head. The CS was a tone (2 kHz, 85 dB, 350 ms, and 5 ms rise/fall time), and it was delivered by a speaker placed above the containing box. The US was an airpuff (100 ms, 3.0 psi measured at the source), and it was applied by a thin pipe directed to the left corneal.

Phase I: During the acquisition, the CS was paired with the US, with the CS offset separated by a 500-ms trace interval from the US onset. Conditioning training consisted of 5 blocks of 10 CS-US pairings trials for a total of 50 trials per session per day. The intertrial interval varied from 20 to 40 s, resulting in a mean of 30 s, and the animals were consecutively trained for 10 days (days 1–10). The animals were required to meet the >70% CR level criterion.

Phase II: After the acquisition, the animals received consecutively 7 daily session (days 11–17) of CS-alone extinction training until the CR levels dropped to 25% or less.

Phase III: The animals received the CS re-pairing with the US for 2 consecutive training days (days 18–19) to test the re-acquisition of trace CRs.

2.4. Data acquisition

The LFP signals were measured as the voltage difference between the monopolar recording electrode and the reference screws, and were amplified by 1000 times and filtered between 0.5 and 30 Hz. The LFP, eyelid movement mechanogram and markers of the applied stimuli were digitized at a sample rate of 10 kHz by a data acquisition system (Powerlab 8/35, ADInstruments, Australia) and were acquired using the software Chart (*v.* 7.0). A

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