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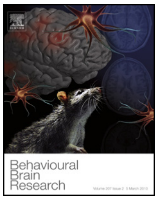

Research report

The decline in rat hippocampal theta activity during response inhibition for the compound stimulus of negative patterning and simultaneous feature-negative tasks

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HIGHLIGHTS

- We examined the relationship between the decline of theta activity and learning task.
- The decline of theta activity was observed during non-RFT of simultaneous feature negative task.
- This study showed the relationship between the decline of theta activity and inhibition response.

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ABSTRACT

In experiment 1 of this study, we compared hippocampal theta activity between negative patterning and simple discrimination tasks. Our results demonstrated a transient decline in theta activity during response inhibition for a compound stimulus in the negative patterning task. In experiment 2 of this study, we compared hippocampal theta activity among simultaneous feature-negative, compound stimulus discrimination, and simple discrimination tasks in order to determine the cause of the decline in hippocampal theta activity during negative patterning tasks. Our results revealed that the decline in hippocampal theta activity occurred during the response inhibition for a compound stimulus in the simultaneous feature-negative task but not during the compound stimulus discrimination or simple discrimination tasks. Thus, we conclude that the transient decline in hippocampal theta activity is related to the inhibition in response to a compound stimulus that has an element that overlaps with a single stimulus.

1. Introduction

Theta activity recorded from the hippocampal CA1 region in rodents [1,2] is generated by synchronous electric activity of cells in the entire hippocampal formation [3–6], and several studies have examined theta activity in this brain area as it relates to hippocampal-dependent learning tasks (for example, place learning [7–9], contextual fear conditioning [10], delayed non-matching to sample [11], and configural tasks [12–14]).

Over a decade ago, Gray and McNaughton [15] proposed the conflict resolution model, which suggested that the hippocampus was important for providing the inhibition of a response to a stimulus that presented a conflict of goals, specifically playing a role in increasing the weight of negative information [15]. Recently, Chan et al. [16] and Davidson and Jarrard [17] expanded on this theory by proposing that, in associative learning, inhibition of a response to a conflicting stimulus occurs when a stimulus comprises of simple inhibitory associations between events embedded in concurrently simple excitatory associations. Additionally, they suggested that the hippocampus plays a role in the formation of these associations. They described that a negative patterning task was a typical inhibitory learning task that required the formation of a simple association, whereas a simple discrimination task was described as a typical non-inhibitory learning task. During a negative patterning task (A+, B+, AB−) [14], a rat's lever press response for a single stimulus (A or B) is rewarded during the reinforcement trial (RFT), but a rat's lever press response for a compound stimulus (AB) is not rewarded during the non-reinforcement trial (non-RFT). In a simple discrimination task (A+, B−), animals are rewarded when presented with a stimulus (A+), but not when a stimulus B is presented (B−). Although some studies have made an argument in favor of the hippocampus's role in learning the negative patterning task [18–20], other studies have argued that the loss

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of hippocampal function does not impair an animal's performance on this task [21,22]. Therefore, the present agreement on the hippocampal contribution to the negative patterning task is that this brain area is involved in, but not critical for, learning this type of task [15–17,23,24].

2. Experiment 1

Recently, we revealed changes in hippocampal theta activity with acquisition of the negative patterning task. Specifically, we demonstrated that hippocampal theta activity transiently declines during the response inhibition of a compound stimulus, and that this transient decline is not observed during the simple discrimination task [14]. Interestingly, this reduction in hippocampal theta activity also does not extend over the retention period [12]. We think that this inconsistency was due to a difference in the resolution time and methods used for calculating hippocampal theta power. In a previously conducted study [12], we calculated the change in hippocampal theta power over every 500-ms period and the indicator of this change was calculated using a theta-delta ratio (theta-delta ratio = power of theta band (6–12 Hz)/power of delta band (2–4 Hz)). In another study conducted by our group [14], the change in hippocampal theta power was calculated over each 250-ms period and the indicator of that power used only the strength of the theta band.

In the current study, we reanalyzed the data of the first Sakimoto study mentioned [12] to examine whether the transient decline in hippocampal theta activity was observed during the presentation of the compound stimulus in the retention period of the negative patterning task. Hippocampal theta power was calculated using the strength of the theta band only in order to replicate the analysis method used in our second Sakimoto et al. study [14]. We also calculated theta power using a 100-ms time period in order to examine the change in activity during presentation of the stimulus in both negative patterning and simple discrimination tasks in greater detail.

2.1. Materials and methods

2.1.1. Subjects

This experiment used data collected from the negative patterning task group ($n = 12$) in experiment 1 of the previous study [12] and data from the simple discrimination task group ($n = 11$) in experiment 2 of the previous study [12].

2.1.2. Apparatus, surgery and history

This information has been described in our previous study (see [12]).

2.1.3. Procedure

The procedure of the current experiment had been used in our previous study (see [12]). Briefly, rats were given one 30-min habituation session to the operant box, and were then trained to press a lever. Following the acquisition of this response, rats were given 2 days of continuous reinforcement training (100 reinforcements/day), followed by 3 days of training at variable intervals of 20 s (VI20; 40 reinforcements/day). Next, rats were randomly split into a negative patterning task ($n = 12$) group and a simple discrimination task group ($n = 11$), and were trained on each task accordingly. Following task training, electrodes for EEG recording were implanted into each rat, and following a 1-week recovery period, recording sessions were conducted during the retraining of each group to their respective tasks.

2.1.4. Learning tasks

2.1.4.1. Negative patterning task. The negative patterning task protocol has been published in our previous study (see [12]). After the VI20 schedule, rats were trained to a negative patterning task where rats' lever press responses were rewarded when a tone (2000 Hz, 75 dB) or light (5 light-emitting diodes: 41 lux) stimulus was presented only (T+, L+) but not when a compound stimulus of both tone and light was presented (TL−). Each session consisted of 120 trials made up of 60 RFTs and 60 non-RFTs. All stimuli remained on until either 10 s had elapsed or until the rat pressed the lever, and each trial was separated by variable inter-trial intervals (20–40 s). Stimuli sequences were randomly determined, but no more than 4 trials of the same type occurred in succession. Task criteria were met when the RFT response rate reached at least 90%, and the non-RFT response rate was no more than 50%. Learning was considered complete when the criteria were met for 3 consecutive days or a total of 5 days.

2.1.4.2. Simple discrimination task. The simple discrimination task protocol has been used in our previous study (see [12]). After, the VI20 schedule, rats were trained on the simple discrimination task where they were taught to discriminate 2 individually presented stimuli (tone or light). They were then randomly assigned to 1 of 2 simple discrimination task groups. For 1 group (T+, L−), their lever press responses were rewarded when the tone stimulus was presented (T+) but not when the light stimulus was presented (L−). For the other group, the stimuli were reversed (L+, T−).

2.1.5. Analysis

2.1.5.1. Electroencephalogram recording and analysis. EEG waveforms were amplified (System 360; NEC Sanei, Tokyo, Japan) and digitized at a sampling rate of 1000 Hz using a time constant of 3 s. All EEG analyses were done using MATLAB version R2007b (The Mathworks Inc., Natick, MA, USA) and focused on the last 3 sessions before the rats completely learned each of the tasks. The recording period was from 4000 ms before stimulus onset to 10,000 ms after stimulus onset, while the analysis period spanned from 500 ms before stimulus onset to 4000 ms after stimulus onset. Hippocampal theta power was computed by wavelet analysis using a 2-ms point size. Wavelet analysis employed the Morlet basis function provided within the MATLAB wavelet toolbox to determine the power of theta oscillatory activity [12]. The analysis period was divided into 45 sub-periods of 100 ms each. Each epoch contained wavelet analysis data from 50 points, and mean hippocampal theta power was computed for each period. The mean hippocampal theta power from 500 to 400 ms (−400-ms period) before stimulus onset was counted as the baseline (no stimuli were present during this period), and the relative theta power calculated for each period was normalized to that during the −400-ms period (relative theta power of each period = theta power of each period/theta power at the −400-ms period). We then analyzed the 6- to 12-Hz frequency band of hippocampal theta waves. The analysis of hippocampal EEGs included counting the number of correct responses for both RFTs and non-RFTs. A go response for the reinforced stimulus was defined as the correct response for RFTs and a no-go response for the non-reinforced stimulus was defined as the correct response for non-RFTs in both tasks. Trials with artifacts were eliminated from wavelet analyses.

2.1.6. Statistical analysis

The change of hippocampal theta activity over time (from −400 ms to 4000 ms, with each lasting 100 ms) was compared between the 2 groups (negative patterning and simple discrimination task groups) as between-subjects factors on each trial type: