



Research report

Baseline hippocampal theta oscillation speeds correlate with rate of operant task acquisition

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ABSTRACT

Many lines of evidence indicate that theta rhythm, a prominent neural oscillatory mode found in the mammalian hippocampus, plays a key role in the acquisition, processing, and retrieval of memories. However, a predictive neurophysiological feature of the baseline theta rhythm that correlates with the learning rate across different animals has yet to be identified. Here we show that the mean theta rhythm speed observed during baseline periods of immobility has a strong positive correlation with the rate at which rats learn an operant task. This relationship is observed across rats, during both quiet waking ($r=0.82$; $p<0.01$) and paradoxical sleep ($r=0.83$; $p<0.01$), suggesting that the basal theta frequency relates to basic neurological processes that are important in the acquisition of operant behavior.

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1. Introduction

Hippocampal theta oscillations (HTOs) are strongly synchronized electroencephalograms generated by the brain, and occur in the 4–11 Hz frequency range [1,2]. Previous research has provided clear evidence that HTOs are triggered by novel stimulation [3], and several types of learning such as operant conditioning [4,5]. While HTOs during waking (WK) are typically accompanied by increased alertness [1,6,7], they are also a typical marker of paradoxical sleep (PS; also known as rapid eye movement sleep). Several lines of evidence suggest that HTOs play a prominent role in the acquisition and processing of new memories. Theta oscillations are always present across hippocampus when animals explore a novel environment [3,8]. Additionally, neuronal populations across hippocampus and prefrontal cortex involved in spatial memory formation, and local field potentials across amygdala involved in fear conditioning and the formation of emotional memories, phase-lock to HTOs [9,10]. Furthermore, septal lesions which abolish HTOs are associated with profound antero-

grade amnesia [11]. Together these findings implicate this form of neural oscillation as an important modulator of learning processes.

Despite the compelling evidence supporting HTOs as a critical modulator of information storage, the exact nature of the relationship between this oscillatory neural mode and behavioral learning rates has yet to be determined. Several studies using concurrent electrophysiological recordings have shown that HTO power increases with task difficulty [12] and decreases as learning progresses [13]. Moreover, one classical study utilizing electrophysiological data recorded immediately prior to task performance showed that HTO power predicts learning rates across animals [14]. Unfortunately, these studies did not temporally dissociate their electrophysiological recordings from periods of behavioral task performance. Given that both HTO power and learning rates vary with attention state [15,16], additional study is necessary in order to elucidate the relationship between basal HTO properties and learning rates. Here we demonstrate that the mean frequency of HTOs during baseline periods positively correlates with learning rates across rodents performing a long-term operant conditioning learning task. Moreover, this relationship is observed during both quiet waking and PS. Thus, our findings provide the first experimental evidence correlating the mean frequency of hippocampal theta oscillations with learning rates across different animals.

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2. Materials and methods

2.1. Animal care and use

All experimental procedures were designed to avoid discomfort of the animals, and were in strict accordance with Brazilian Federal Animal Welfare of Health Guidelines and the University of Sao Paulo Animal Care and Use Committee on animal well being. *Male Whistar rats* ($n=9$) weighing a mean of 380 g were used for all experiments presented. Rats were housed in individual cages at 20–25 °C, in a 12/12 h light/dark cycle. Food restriction was initiated 5 days before training; animals were fed 20 g of standard rodent show per day, so as to maintain 85% of the free feeding body weight. Water was provided ad libitum. Following adequate dietary restriction, animals were subjected to a standard operant conditioning task where they learned to respond to a light by pressing a lever that caused reward delivery (sucrose solution droplet). Tests were carried out inside a Standard Modular Operant Test Chamber for rats (ENV-008, MED Associates Inc., USA) equipped with a response lever, a white light to signal reward availability, and a liquid cup receptacle for reward delivery. The stages of the learning task were as follows:

- (1) *Shaping*: Rats learned to press the lever to receive one droplet of a 10% sucrose solution. If 30 s elapsed without lever pressing, animals were also rewarded. Session ended when rats reached 100 lever pressings, or when 120 reward droplets were delivered (session duration of approximately 1 h). Animals were subjected to two step-1 sessions in consecutive days.
- (2) *Continuous reinforcement (CRF)*: Rats were rewarded only upon pressing the lever. Sessions ended when animals reached 80 lever pressings or after 1 h, whichever came first. Animals were subjected to two step-2 sessions in consecutive days.
- (3) *Variable interval schedule (VI30)*: In this training step, reward was available on average at every 30 s, as signaled by the switching on of the white light. Animals were subjected to 10 1-h sessions on consecutive days.
- (4) *Discrimination training (DT)*: This final training step was used to compute the learning curve slopes presented in this study. In this step, the white light was activated randomly, so that the total time with light on was 50% of the 1-h session. Lever-pressing responses during light-on intervals (S^D) were randomly rewarded on a VI-30 s schedule (R). No responses were rewarded if light was off (extinction = S^A). Learning was considered satisfactory when the discrimination index was ≥ 90 , where $DI = (S^D / (S^A + S^D)) \times 100$. In a typical session $S^A = 51$, $S^D = 576$, with R delivered 47 times. In this session $DI = 91.9$, and the ratio between S^D and R was 12.2. Animals were subjected to 15 1-h sessions on consecutive days.

2.2. Surgical electrode implantation

One day following the completion of the learning task, rats were anesthetized with ketamine (30 mg/kg i.p.). Subsequently, rats were placed on a standard stereotaxic apparatus. The dorsal surface of the skull was exposed, cleaned, and two holes were drilled into the skull to receive bipolar tungsten electrodes. Electrodes were made of pairs of SML-insulated tungsten wires (100- μ m dia., each wire, California Wires Company) that were separated by 200 μ m and glued together. Electrodes were implanted in the left hemisphere at the following coordinates in millimeter antero-posterior (AP) from bregma [17]: CA1 subfield = 2.8, 1.5, and 3.0; CA3 subfield = 2.8, 2.5, and 3.7. To hold the implant, three stainless steel screws were driven bilaterally into the skull overlying the frontal (AP +2.0, L 2.0 with reference to the bregma), parietal (AP -2.0, L 5.0), and occipital (AP -6.0, L 2.0) lobes. A ground screw electrode (Silver wire A-M Systems Inc. 782500, California Wires Company) was implanted 2 mm caudal to lambda. Additionally, tungsten electromyographic electrodes (the same type of wire used to brain activity recording) were implanted in the trapezius, rostrum, and epicantus lateral muscles. The entire implant was secured with dental acrylic.

2.3. LFP and EMG recordings

After the post-operative period (around 5–6 days), animals were placed within an acrylic 20 cm $\times$ 40 cm box with food and water available ad libitum. LFP and EMG data were then recorded through the wake-sleep cycle for 2–5 consecutive days using a 21-channel Neuronfax EEG System (Nihon-Kohden Corporation, Japan). LFP signals were pre-amplified ($1000\times$) and filtered (0.5–40.0 Hz). Signals were then fed to the computer acquisition system through an A/D converter card (CAD12/32, Lynx Tecnologia, São Paulo, Brazil) and digitized at 256 Hz. EMG signals were sampled at 1024 Hz. LFP and EMG were stored in a computer for off-line analysis.

2.4. Data analysis and statistics

Two analytical approaches, complex demodulation and ANOVA [18,19], were used to automate the process of determining continuous fluctuations of hippocampal LFP frequencies recorded from CA1 or CA3 subfields. These methods allowed us to determine the instantaneous frequency from a short data segment with high accuracy. In order to determine the overall mean frequency, we averaged the mean frequency measured across 100 segments of 30 s per animal (50 for WK, 50 for PS).

2.5. Histology

At the conclusion of recordings, a small marking was made at the tip of each electrode through electrolytic lesions (5 mA for 10 s). Rats were then euthanized with a pentobarbital overdose (200 mg/kg, i.p.) and perfused transcardially with phosphate buffered saline (PBS) followed by a 4% paraformaldehyde (PFA) solution in 0.1 M PBS. Brains were post-fixed in 4% PFA, dehydrated in a 20% sucrose solution, frozen in dry ice, and sectioned on a microtome at 30 μ m intervals. We used Nissl staining to visualize the location of the electrode tips. Visual examination of Nissl stained frontal sections confirmed that electrode tips were located in that CA1 and CA3 field of hippocampus as described in Paxinos and Watson [17].

3. Results

Nine *male Whistar rats* were subjected to an operant behavioral learning task across 15 days. As expected, learning occurred in a stepwise manner over several daily 1-h sessions, with considerable variation among animals. For example, the fastest learner reached $>90\%$ of correct performance in as little as 9 days, while the slowest learner failed to reach the same criterion even after 15 days of continuous training (Fig. 1). The slope of the learning curve was determined by linear regression and used as an estimate of learning rate. High elevation slopes indicated fast learners and low elevation slopes indicated slow learners (see Fig. 1, inset).

After completing the behavioral learning task, animals were implanted with local field potential electrodes in the CA1 and CA3 subfields of dorsal hippocampus, and electromyographic recording electrodes in the trapezius, rostrum, and epicantus lateral muscles. Following a 1-week recovery period, electrophysiological recordings were conducted for 2–5 days/animal (Fig. 2). Behavioral states were scored using LFP and EMG data, and visual inspection. Consistent with previous reports [2], theta frequency changes were constant across all channels recorded, though theta power varied. The mean theta frequency observed during waking and PS was ~ 7 Hz (Fig. 1, bottom panels); however, theta frequency values varied dramatically depending on the animal's muscle activity behavior. For instance, higher theta frequencies are observed in

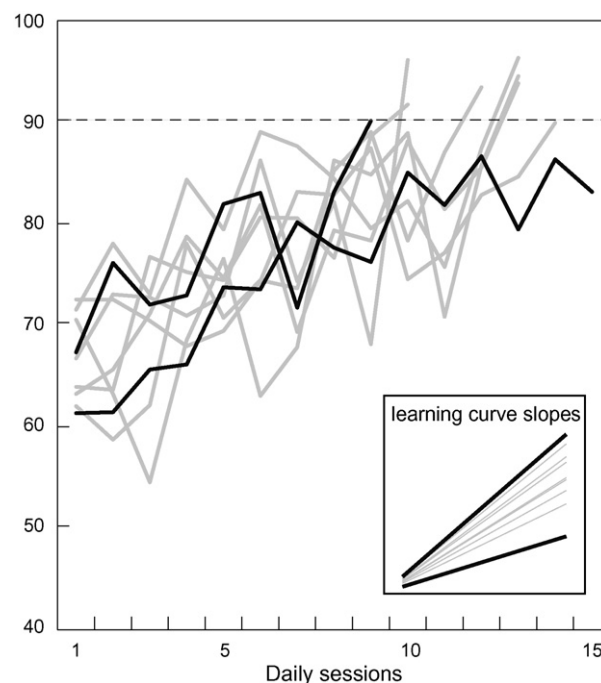


Fig. 1. Operant task learning rates. Temporal evolution of performance in an operant conditioning task ($n=9$ rats). The fastest and slowest learning curves are indicated in black; intermediate speed learning curves are displayed in grey. Dashed line indicates performance criterion. Learning rates were estimated as the slopes of the learning curves (inset; same color scheme).

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