Sustained hippocampal theta-oscillations reflect experience-dependent learning in backward temporal order memory retrieval

Hongjie Jiang‡, Jing Cai‡, Diogo Santos-Pata‡, Lei Shi, Xuanlong Zhu, Jiaona Tong, Yudian Cai, Chenyang Li, Rui Wang, Jia Yin, Shaomin Zhang# and Sze Chai Kwok#

浙江大学医学院附属第二医院
The Second Affiliated Hospital Zhejiang University School of Medicine

昆山杜克大学
DUKE KUNSHAN UNIVERSITY

Abstract

Navigating within our neighborhood, learning a set of concepts, or memorizing a story, requires remembering the relationship between individual items that are presented sequentially. Theta activity in the mammalian hippocampus has been related to the encoding and recall of relational structures embedding episodic memories. However, how theta oscillations are involved in retrieving temporal order information in opposing directionality (forward vs backward) has not been characterized. Here, using intracranial recordings from 10 human epileptic patients of both genders with hippocampal electrodes, we tested the patients with a temporal order memory task in which they learned the spatial relationship among individual items arranged along a circular track and were tested on both forward-cued and backward-cued retrieval conditions. We found that sustained high-power oscillatory events in the hippocampal theta (2-8 Hz) band, as quantified by $P_{episode}$ rate, were higher for the backward conditions during the later stage but not in the earlier stage. The theta $P_{episode}$ results are consistent with the behavioral memory performance. In contrast, we observed a stronger effect of forward than backward retrieval for the gamma (30-70 Hz) $P_{episode}$ rate irrespective of stages. Our results revealed differential roles of theta vs. gamma oscillations in the retrieval of temporal order and how theta oscillations are specifically implicated in the learning process for efficient retrieval of temporal order memories under opposing directionality.

Materials and Methods

In the current study, we recorded hippocampal local field potential activity via intracranial EEG in 10 epileptic patients while they performed a temporal order memory test (Figure 1C). Participants viewed through a circular track in virtual reality and then made a relative order memory judgment between two items with respect to a sample (Figure 1A). We manipulated the extent of how participants experienced the virtual reality environment by dividing the experiment into three stages and compared cued judgments of temporal order for forward versus backward sequences (Figure 1B).

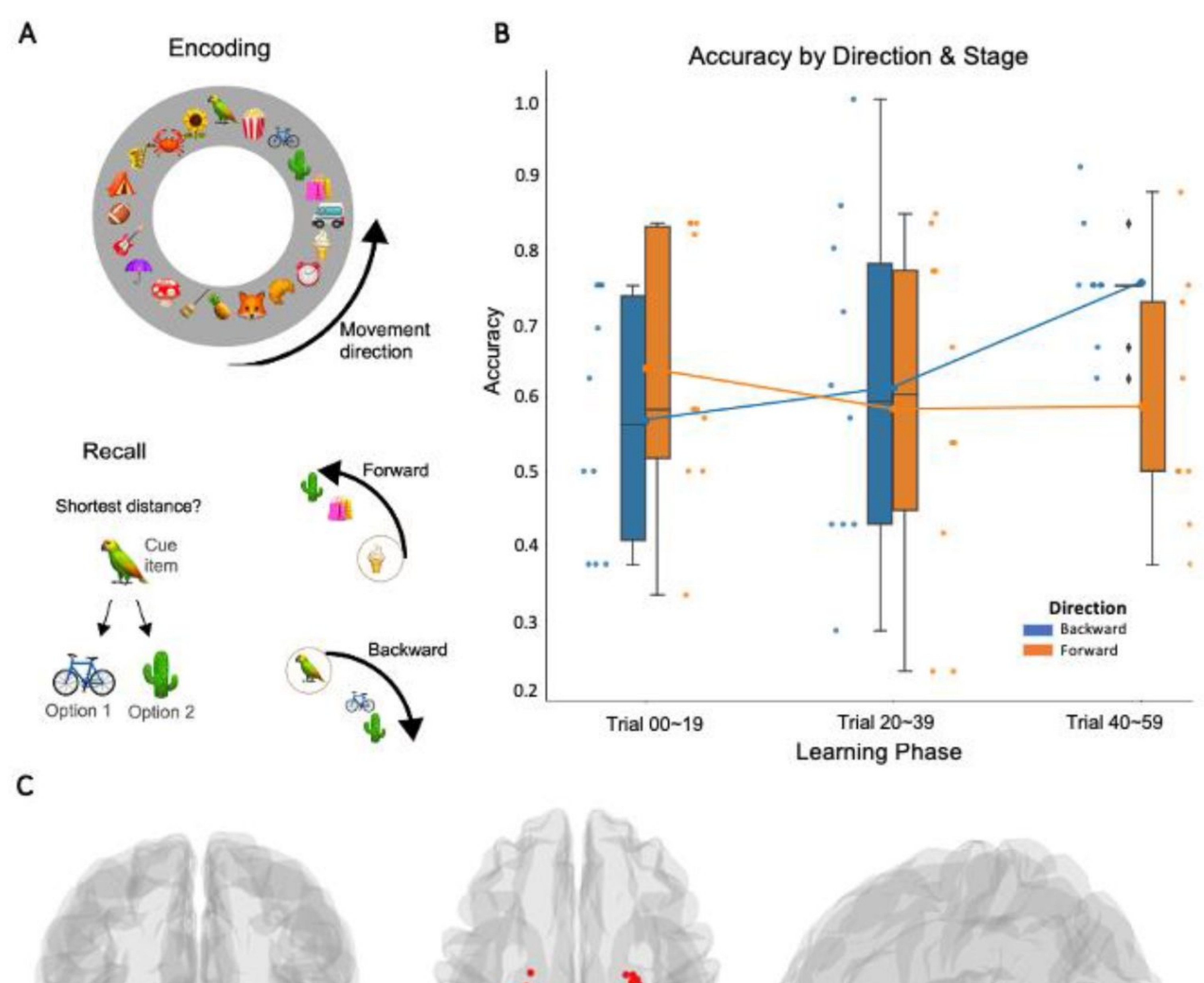
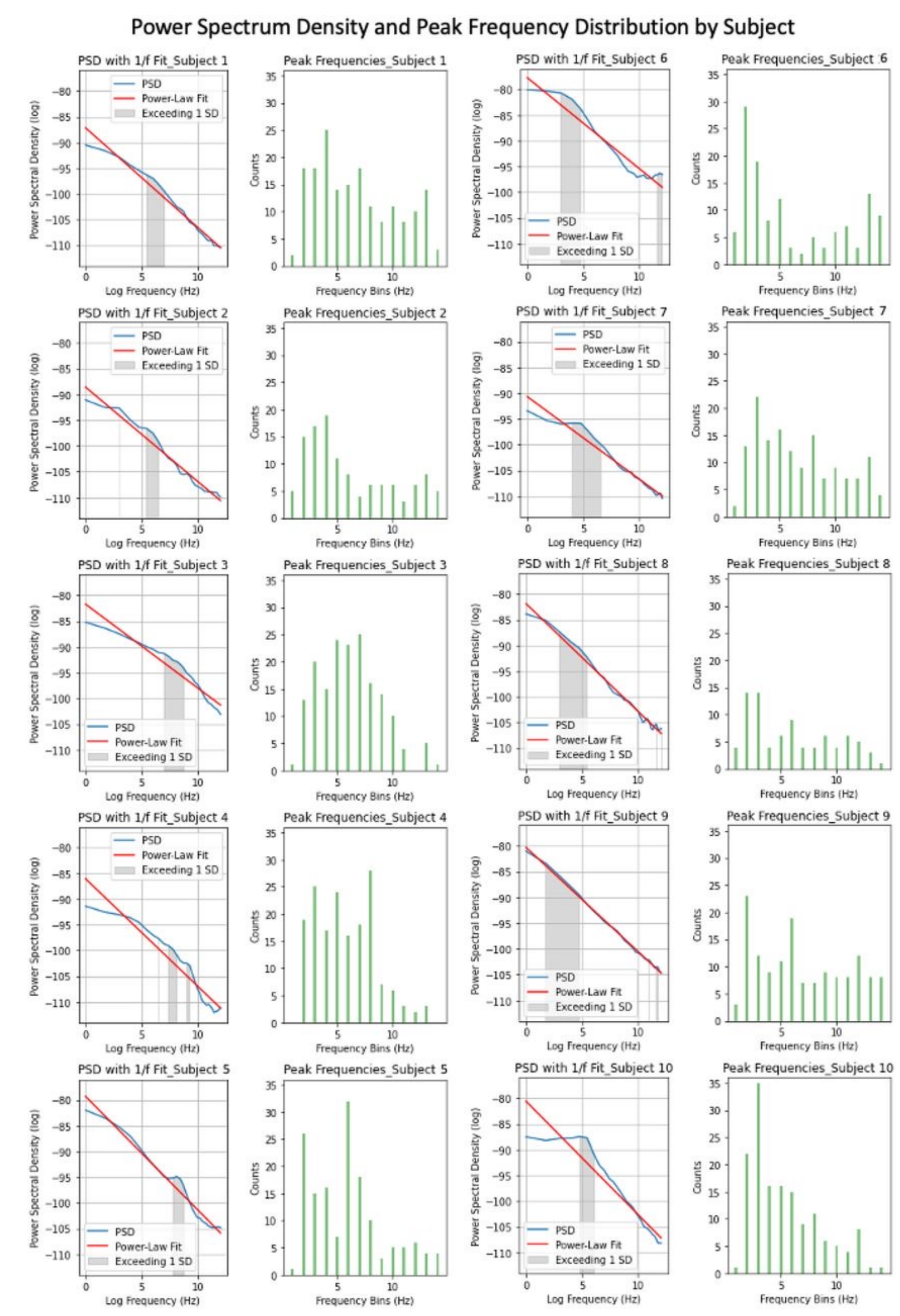


Fig 1. A: Illustration of the virtual navigation task paradigm. B: Memory task accuracy, each dot represents a single participant's performance at early, middle or late stage of the task, under forward or backward condition. C: Electrode locations in the hippocampus from individual patients (n=10) in MNI space coordinates by front, top, and lateral views.

Results



Firstly, we demonstrated the frequency dependence of the recall task across subjects. By fitting the power spectrum density to the 1/f background spectrum in a log-log space, we identified the frequency bands where oscillatory power exceeded 1 standard deviation over the 1/f background (Figure 2 left, gray regions). Moreover, we calculated the number of oscillatory activities and detected subject-specific dominant frequencies (Figure 2 right, histograms). Both measures consistently revealed prominent oscillations during recall at theta band and low gamma band, which gave us an understanding of the frequency dependence for the task. After taking into account each subject's variation, this result guided us to choose the frequency band of 2 - 8Hz (theta) and 30 - 70Hz (gamma) for the $P_{episode}$ analysis.

Fig 2. Power Spectrum Density for each subject in a log-log space, fitting to the 1/f background spectrum

In line with memory accuracy, a significant interaction effect (*F (df=2) = 6.90, p = .032*) was revealed where the rates of theta $P_{episode}$ during forward trials (EM = 0.374, 95%CI = [0.266, 0.482]) was higher than during backward trials (EM = 0.310, 95%CI = [0.200, 0.421]) at the early stage of the task, followed by a reversed pattern at the late stage of the task when the rates of theta $P_{episode}$ became higher for backward trials (EM = 0.418, 95%CI = [0.308, 0.527]) than during forward trials (EM = 0.369, 95%CI = [0.258, 0.480]) (Figure 3A). For comparison, we performed a corresponding set of p-episodes analysis on the gamma band (30 - 70 Hz). We found no significant fixed effect of task stage or interaction but only a fixed effect on recall directionality $P_{episode}$ (*F (df=1) = 5.59, p = .018*), where $P_{episode}$ was higher for forward trials (EM = 0.595, 95%CI = [0.362, 0.828]) than backward trials (EM = 0.538, 95%CI = [0.304, 0.771]) (Figure 3B).

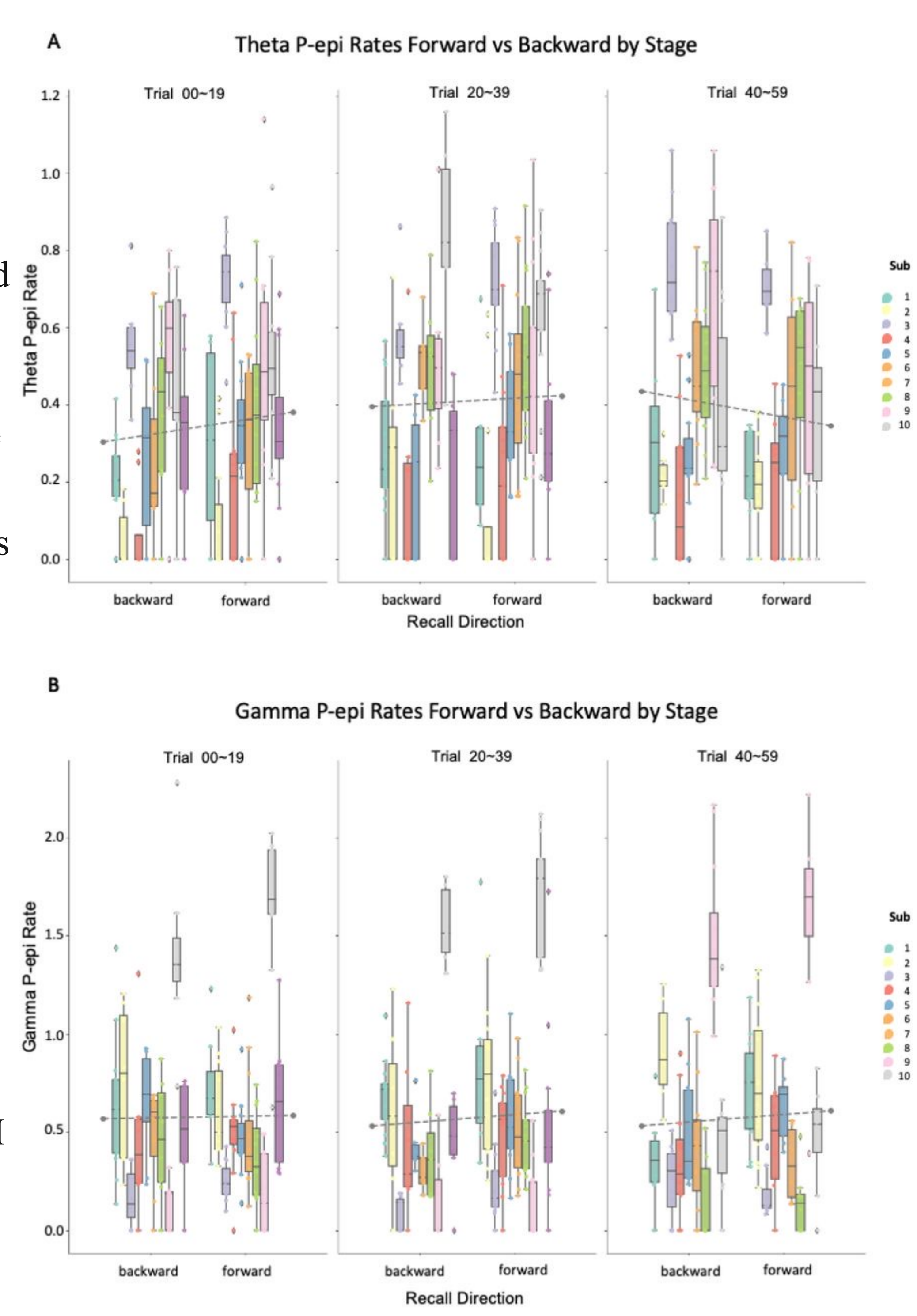


Fig 3. A: Theta $P_{episode}$ rates organized by directionality and stage conditions. There is a directionality by stage interaction. B: Gamma $P_{episode}$ rates organized by directionality and stage conditions. There is a main effect of directionality irrespective of stage.

Conclusions

All in all, we showed that hippocampal theta and gamma activity are respectively involved in the retrieval of relational structures embedding temporal order memories. Specifically, the sustained theta oscillations reflect the learning processes obtained from repeated experiences. This study helps elucidate part of the electrophysiological mechanisms underlying the interplay between learning and spatiotemporal sequence memories upon retrieval in the hippocampus.

Acknowledgements

The research results of this publication are sponsored by the Kunshan Municipal Government research funding Project Number: **23KKSGR017**.
For a full-text pre-print, please see https://www.biorxiv.org/content/10.1101/2023.07.10.548388v1. For more information about the lab, please visit http://www.kwoklab.org.