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High-gamma activity in the human hippocampus and parahippocampus during inter-trial rest periods of a virtual navigation task

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ABSTRACT

In rodents, hippocampal cell assemblies formed during learning of a navigation task are observed to re-emerge during resting (offline) periods, accompanied by high-frequency oscillations (HFOs). This phenomenon is believed to reflect mechanisms for strengthening newly-formed memory traces. Using magnetoencephalography recordings and a beamforming source location algorithm (synthetic aperture magnetometry), we investigated high-gamma (80–140 Hz) oscillations in the hippocampal region in 18 human participants during inter-trial rest periods in a virtual navigation task. We found right hippocampal gamma oscillations mirrored the pattern of theta power in the same region during navigation, varying as a function of environmental novelty. Gamma power during inter-trial rest periods was positively correlated with theta power during navigation in the first task set when the environment was new and predicted greater performance improvement in the subsequent task set two where the environment became familiar. These findings provide evidence for human hippocampal reactivation accompanied by high-gamma activities immediately after learning and establish a link between hippocampal high-gamma activities and subsequent memory performance.

Introduction

The formation of spatial memories is proposed to proceed in two stages (Buzsaki, 1989, 2015). In the encoding phase, during active exploration of an environment, a transient change of synaptic strengths in the hippocampus is formed accompanied by theta-band neuronal oscillations. Subsequently, during 'offline' states, including slow-wave sleep and quiet wakefulness, the newly formed synaptic network re-emerges, accompanied by high frequency oscillations (HFOs), operating to potentiate and strengthen the synaptic changes and thereby consolidate the otherwise labile memory traces.

Rodent studies have shown that the sequential activation of place cells during navigation reoccurs ("replays") when the animal is asleep or in a state of awake immobility after exploration, and this replay is accompanied by HFOs (O'Neill et al., 2010). Disruption of hippocampal HFOs impairs spatial learning (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009; Jadhav et al., 2012), suggesting a causal relationship between HFOs and memory formation. Replay is sensitive to environmental novelty (Carr et al., 2011): After navigating in a new environment, the strength of place cell replay is stronger (Diba and Buzsaki, 2007; O'Neill et al., 2008) and the probability of the occurrence of HFOs and the firing rates of place cells are significantly higher (Cheng and Frank, 2008) than that following navigation in a familiar environment.

The two-stage model has been intensively investigated in animal models. Are comparable neurophysiological learning mechanisms used in the human hippocampus? Currently, there is very limited, but highly suggestive evidence that this is the case. fMRI studies (Deuker et al., 2013; Gruber et al., 2016; Staresina et al., 2013; Tambini and Davachi, 2013; Tambini et al., 2010) have reported that brain regions that are active during learning, are reactivated during sleep or rest periods after learning. For instance, using multivariate pattern classification analysis, Deuker et al. (2013) found stimulus-specific patterns during encoding reoccurred spontaneously during postlearning resting periods and sleep. Importantly, these studies showed that the strength of the spontaneous

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reactivation could predict the subsequent memory performance.

To date, there is only limited electrophysiological evidence pertaining to the two-stage model. Direct evidence about hippocampal replay came from a recent MEG study. Using decoding methods, Kurth-Nelson et al. (2016) trained the classifier on the MEG evoked response elicited by the presentation of objects and tested the classifiers on the spontaneous brain activity when no object was presented. They found during object-free periods after learning, the brain spontaneously replayed the representations of four objects learned in the learning period in a reverse order lasting on an order of 120 ms. Using a similar MEG decoding approach, Jafarpour et al. (2014) reported that recollection of images depicting faces and scenes is also associated with a replay of neural representations that are formed at very early (180 ms) stages of encoding. This study reveals that the replay mechanism might be a crucial neural computation in human brain. However, these results were on the MEG sensor level and which source brain regions and neuronal oscillations are related to the replay phenomenon is unclear. To address this question, from intracranial recordings in human patients, Axmacher et al. (2008) investigated the role of high-gamma in the hippocampus and rhinal cortex in memory consolidation. They detected robust high-gamma rhythms (80–140 Hz) during the post-learning sleep period in the two brain structures, and documented that high-gamma in the rhinal cortex was positively correlated with subsequent memory performance. In another study using noninvasive MEG measurements, Cornwell et al. (2014) found that post-learning high-gamma power was positively correlated with subsequent spatial learning performance after the rest period. But in the two studies, there was no control condition, it is therefore uncertain whether the high-gamma activities reported are learning-specific or only a general trait marker related to general cognitive processing speed.

In the present study, we leveraged the high time resolution of MEG to investigate the temporal dynamics of human hippocampal "reactivation" during the ITI immediately after learning trials. MEG was recorded while participants performed two task sets of a virtual Morris water maze task. Each set included a *hidden platform* condition (task: finding the hidden platform) and a *random swimming* condition (task: aimlessly swimming in a pool without platforms). Environment layouts of each condition in the two task sets were the same. In a previous report on data from the same experiment (Pu et al., 2017), we studied the role of low frequency theta oscillations (4–8 Hz) in spatial encoding during navigation. We found that there was significantly greater theta power in right hippocampus and parahippocampus in the first compared to the second task set, which was associated with environment encoding; and there was significantly more left hippocampal and parahippocampal theta in the *hidden platform* condition than in the *random swimming* condition, which was associated with encoding of the hidden platform location.

Here we asked first, whether high-gamma power during the ITI in the hippocampal and parahippocampal region used for encoding would mirror the patterning of hippocampal and parahippocampal theta power change during navigation. We reasoned that during the rest period after hippocampus dependent learning, the region used for encoding accompanied by theta oscillations would be spontaneously reactivated but accompanied by high frequency oscillations for memory consolidation (Axmacher et al., 2008); second whether the power of high-gamma was correlated with the theta power, since reactivation is proportional to the previous learning (Sutherland and McNaughton, 2000, see Buzsaki, 2015 for a review); third, we asked whether high-gamma power after navigating in the new environment (first task set) was associated with learning improvement in the familiar environment (second task set), since adequate consolidation of the newly-encoded environment representation to form a cognitive map of the space should facilitate learning to flexibly navigate to new locations in the same environment (Wolbers and Hegarty, 2010).

Materials and methods

Participants. Eighteen male participants (mean age = 29 years; range = 18–39 years, right handed) participated in the study. Two additional participants were excluded from the final data analyses because of the excessive head movement (>4 mm from the initial head position). The study was approved by Macquarie University's human subjects ethics committee. All participants gave written informed consent. Analysis of data during active navigation was previously reported in Pu et al. (2017). The current analysis investigated high-gamma during the ITI of the experiment when participants rested quietly following each trial of spatial navigation.

Experiment design. A detailed description of the experimental paradigm is in Pu et al. (2017). In brief, naive participants performed two task sets of a virtual Morris water maze task. In each task set of the task, there were two conditions. In the hidden platform condition, participants needed to find a hidden platform submerged in opaque water by using the visual cues on the walls surrounding the virtual pool. In the random swimming condition where no cues were attached on the wall, participants were instructed just to move aimlessly and there was no platform in this condition. The purpose of removing the cues from the random swimming condition was to examine whether the link between right hippocampal and parahippocampal theta and environmental encoding was dependent on the complexity of the environment (cue rich vs. cue poor) (see Pu et al., 2017 for more details). For all the conditions, participants were instructed to look at the screen all the time and keep moving non-stop. The environment of each condition in the two task sets was the same, thus the environment in the first task set was defined as new environment and that in the second one as familiar environment. The platform location was the same in each task set but different across the two task sets. The distance to the boundary of the two platform locations in the two task sets was the same. Therefore, the difference between the two task sets allowed us to measure *learning of the environment* (Pu et al., 2017), and the difference between the *hidden platform* condition and the *random swimming* condition provided an index of *goal-directed spatial navigation* (Cornwell et al., 2008). To avoid the possibility that environment learning was confounded with learning a specific location, the location of the hidden platform was changed and counterbalanced between the task sets. Moreover, the starting positions of the participants in each block of fours trials were different and pseudo-randomised but were consistent across blocks. Thus the ideal path lengths in each block were the same.

In each task set, there were 40 trials including 20 hidden platform and 20 random swimming trials respectively, presented in alternating blocks of four trials. Between each trial, there was a 4.5–5.5 s ITI (Fig. 1), during which a grey screen was presented and participants rested quietly without movement.

Behavioral measures. The length of the path taken from the starting position to the hidden platform in each trial was recorded. Performance improvement was computed as the average path length of the first block minus that of the last one, divided by the number of blocks.

MEG recordings. Recordings were made in a magnetically shielded room (Fujihara Co. Ltd., Tokyo, Japan) with a 160-channel KIT system (Model PQ1160R-N2, Kanazawa, Japan) with superconducting quantum interference device (SQUID)-based first-order axial gradiometers (50-mm baseline; Kado et al., 1999; Uehara et al., 2003). Neuromagnetic signals were digitized continuously at a sampling rate of 1000 Hz filtered at 0.03 and 200 Hz. Before recordings, the locations of the five marker coils and three fiducial markers, and the participant's head shape were digitized with a pen digitizer (Polhemus Fastrack, Colchester, VT, USA). The five marker coils were energized before and after each task set to determine head movement and position within the MEG dewar.

MRI scans. High-resolution T1-weighted anatomical magnetic resonance images (MRIs) were acquired in a separate session at Macquarie University Hospital, using a 3 T Siemens Magnetom Verio scanner with a 12-channel head coil. Images were obtained using 3D GR\IR scanning sequence with the following parameters: repetition time, 2000 ms; echo time, 3.94 ms; flip angle, 9°; slice thickness, 0.93 mm; field of view, 240 mm; image dimensions, 512 × 512 × 208.