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Research report

Spontaneous fast gamma activity in the septal hippocampal region correlates with spatial learning in humans

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HIGHLIGHTS

- Spontaneous hippocampal region gamma correlates with spatial learning in humans.
- Gamma in the septal hippocampal subregion is associated with superior learning.
- Fast gamma between 80 and 140 Hz is especially linked to spatial performance.

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ABSTRACT

Hippocampal neuronal populations exhibit multiple kinds of activity patterns, from the dominant theta rhythm during active exploration to high-frequency ripple-like activity during periods of relative inactivity. In animals, evidence is rapidly accruing that these high-frequency ripple activity patterns subserve retention of spatial learning performance. In a translational effort to address the possible function of offline hippocampal processes in humans, we measured spontaneous gamma activity during an awake rest period within a virtual spatial learning context. Whole-head magnetoencephalographic (MEG) recordings were taken while healthy participants ($N = 24$) quietly rested (eyes open) between encoding and retrieval phases of a hippocampal-dependent virtual Morris water maze task. Results are that fast gamma activity (80–140 Hz) in the septal or posterior region of the hippocampus (bilaterally) was positively correlated across participants with subsequent within-session spatial learning rate. Fast gamma did not predict initial retrieval performance following rest, failing to provide evidence of a direct link between spontaneous high-frequency activity patterns during awake rest and consolidation of previous spatial memories. The findings nevertheless are consistent with a prospective role for offline human hippocampal processes in spatial learning and indicate that higher spontaneous gamma activity in the septal hippocampal region is related to faster updating of spatial knowledge in familiar virtual surroundings.
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1. Introduction

Hippocampal neuronal populations exhibit multiple kinds of coherent activity that support learning and memory. The most studied network pattern is the theta rhythm, which takes the form of sinusoidal-like 4–10 Hz oscillations that are prevalent during exploratory behavior [1]. Elegant empirical and computational studies have provided key insights into theta (reviewed in [2]), including its potential role in regulating place cell firing [3,4] as well as its link to spatial memory performance in animals [5] and humans [6–9]. In addition to theta, the hippocampus also exhibits rhythmic gamma oscillations (>30 Hz) and irregular sharp-wave activity (i.e., ripples) containing high frequency components (>80 Hz), particularly during non-exploratory behavioral states such as consummation, quiet rest and sleep [10,11]. These high-frequency activity patterns have garnered significant interest for their possible role in 'offline' signaling between the hippocampus and neocortex, a candidate mechanism for long term memory consolidation [10,12,13].

Growing evidence indicates that offline high-frequency ripples are critical for learning [14]. Single-unit recordings have revealed that the same hippocampal neuronal populations that are active during spatial exploration show reactivation or 'replay' during ripple events after spatial exploration. Replay is thought to strengthen patterned activity and potentially drive hippocampal-neocortical signaling as a mechanism of memory consolidation [12]. Indeed, disrupting ripple activity leads to impaired memory performance [15–17]. Originally associated with sleep [18,19], recent studies have confirmed that ripple-associated neuronal replay also occurs

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during awake rest periods [20]. Comparatively little is known about the functional relevance of these offline activity patterns for human learning [21]. Initial findings in epileptic patients are consistent with a role for ripple activity in verbal memory performance [22]. In that study, the number of rhinal cortical ripples, rather than hippocampal ripples, during awake rest was positively associated with subsequent item retrieval. No evidence in humans, however, has been reported in a spatial learning context. This is the ideal starting point for translating findings from animal research to the human hippocampus given that the former traditionally uses spatial learning paradigms to study hippocampal functioning.

We noninvasively studied dynamical brain activity during an awake rest period situated between encoding and retrieval phases of a hippocampal-dependent virtual reality Morris water maze task [23,24]. For these healthy participants, a positive association was previously reported between navigation-related hippocampal theta and task performance [8]. Magnetoencephalographic (MEG) recordings of participants' quietly resting were used to reconstruct spontaneous hippocampal activity by adaptive beamforming [25,26], which was correlated with spatial performance. We targeted spontaneous 80–140 Hz activity ('fast gamma') to match that used by Axmacher and colleagues [22] for quantifying hippocampal and rhinal cortical ripples from intracranial recordings in humans. We predicted that the overall magnitude of hippocampal region fast-gamma power measured during awake rest would positively correlate with subsequent spatial performance, indicating a possible contribution of offline hippocampal region high frequency activity in human spatial learning.

2. Material and methods

2.1. Participants

Twenty-five healthy, right-handed adults completed the study and were paid for participation, as previously described [8]. One participant from the original sample was removed from the present analyses because of excessive head movement during the awake rest recording, leaving an $N = 24$ (12 women; age, mean ± SD = 29 ± 6 y). All participants gave informed consent in writing prior to participation. The study was approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health.

2.2. Task procedure

Participants performed a virtual Morris water maze task, which is also described in Cornwell et al. [8]. Briefly, participants navigated two virtual pools to an escape platform. In one pool, participants were at risk of receiving electric shocks before reaching the platform (threat). In the other pool, they were completely safe from shocks (safe). Participants alternated between pools, performing four trials during each alternation from one of four starting positions (N, S, E, W), randomized without replacement. Other than the distal cues on the surrounding walls that can be used as landmarks for navigation, the pools were structurally identical. The threat manipulation was designed to reveal contributions of navigation-related hippocampal theta (2–8 Hz) to spatial cognition and anxiety [8], but was not relevant to the current goal of linking offline hippocampal gamma activity to subsequent spatial learning performance. Accordingly, navigation data were averaged between the two pool contexts.

Two tasks runs were administered. The first consisted of visible platform trials (encoding phase), with the platform's position fixed. There were 20 visible platform trials completed per pool followed by one probe trial per pool at the end of the run. During the probe trials the platform was removed unbeknownst to the participants. The second task run consisted of 20 hidden platform trials per pool (retrieval phase), with the platform fixed in the same position as during the first task run. During these trials, the platform was initially hidden but became visible after 15 s if it was not found beforehand. Participants were informed that the platform location in each pool context was fixed throughout the task. They were instructed to navigate as quickly and directly as possible to the platform on each trial regardless of whether it was visible or hidden.

In between the two task runs, a single MEG recording was collected while participants relaxed with their eyes open for 5 m. During the awake rest recording, participants were closely monitored by video camera to ensure that they remained awake during this period. They were not given any additional instructions other than to hold still, keep their eyes open and not sleep.

2.3. MEG acquisition

Neuromagnetic activity was measured by a 275-channel whole-head magnetometer (VSM MedTech, Inc., British Columbia, Canada) in a magnetically-shielded room using 3rd-gradient balancing for active noise cancellation. For the awake rest recording, data were collected at 1200 Hz for 5 m with a 0–300 Hz bandpass. Fiducial coils placed at the nasion and preauricular sites were energized during the run to record head position continuously and used for offline coregistration with each participant's anatomical magnetic resonance images (MRI) that were acquired in a separate session. MEG data from the task runs are presented elsewhere [8].

2.4. Resting-state source analyses

A minimum-variance adaptive beamformer algorithm was utilized to estimate regional oscillatory power during rest ([25,26]; for a similar resting-state analytic approach, see Rutter et al. [27]). Signal covariance across the sensor array was computed from a single 280 s epoch (after removing the first and last 10 s of the 5 m recording). This was done separately for data bandpass filtered in the slow gamma (30–80 Hz) and fast gamma (80–140 Hz) frequency bands. A multi-sphere source space model generated from participants' MRIs was used for source power estimation (5-mm spatial sampling grid). Band-specific source power at each grid point or voxel was integrated over the entire 280-s epoch and divided by a constant noise estimate, which was derived from the same covariance matrices for each frequency band, to correct for depth biases in beamformer power estimates (pseudo-Z metric). Using Analysis of Functional NeuroImages (AFNI, [28]) individual subject source volumes were within-volume normalized, co-registered to their anatomical MRIs and spatially warped to a Talairach template for group analyses.

Based on our a priori hypothesis, we performed a targeted analysis of bilateral hippocampus. We used the same anatomical masks as in Cornwell et al. [8], which were created with the automated Talairach Atlas Daemon [29] and resampled to the 5-mm grid of the source imaging data. Spontaneous oscillatory power estimates were averaged for voxels in septal (posterior, $-45 < y < -29$ mm in Talairach space) and temporal (anterior, $-9 > y > -20$ mm) thirds of the left and right hippocampus and extracted for analyses in SPSS 18. The intermediate third of the hippocampus was not included in our analyses in order to maximize independent septal and temporal hippocampal source power estimates [8]. Fig. 1 shows short segments from the entire time courses of fast gamma activity reconstructed from sample voxels located within septal and temporal hippocampal subregions.

Although the standardized atlas-based masks are centered at the left and right hippocampus, we do not make the strong claim that the source power estimates are exclusively measuring activity