



## Slow-theta power decreases during item-place encoding predict spatial accuracy of subsequent context recall

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### ABSTRACT

Human hippocampal theta oscillations play a key role in accurate spatial coding. Associative encoding involves similar hippocampal networks but, paradoxically, is also characterized by theta power decreases. Here, we investigated how theta activity relates to associative encoding of place contexts resulting in accurate navigation. Using MEG, we found that slow-theta (2–5 Hz) power negatively correlated with subsequent spatial accuracy for virtual contextual locations in posterior hippocampus and other cortical structures involved in spatial cognition. A rare opportunity to simultaneously record MEG and intracranial EEG in an epilepsy patient provided crucial insights: during power decreases, slow-theta in right anterior hippocampus and left inferior frontal gyrus phased the left temporal cortex and predicted spatial accuracy. Our findings indicate that decreased slow-theta activity reflects local and long-range neural mechanisms that encode accurate spatial contexts, and strengthens the view that local suppression of low-frequency activity is essential for more efficient processing of detailed information.

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### 1. Introduction

A major goal of human memory research is to elucidate the neural mechanisms underlying memory formation. Explorations of the subsequent memory effect (SME), initially examined by contrasting hemodynamic responses during the encoding of later-remembered events with those of later-forgotten events, have identified many of the neural correlates of successful encoding (Schacter and Wagner, 1999). Applying this contrast to electrophysiological activity has additionally revealed that SMEs are associated with specific frequency bands, helping to delineate how encoding processes are regulated by oscillatory activity. Among these frequencies, the 4–8 Hz band received special attention in humans because it resembles the theta rhythm of small mammals, which has extensively shown memory-related properties (Buzsáki and Moser, 2013; Hasselmo, 2005). For example, in rabbits, hippocampal theta activity predicts the learning rate of classical conditioning, whereas its loss impairs spatial memory in rats (Winson, 1978). In addition to these observations, it was found that theta bursts can induce long-term potentiation (LTP) of synapses in hippocampus (Larson et al., 1986; Larson and Munkácsy,

2015), suggesting a physiological mechanism by which theta oscillations could mediate memory storage processes.

In agreement with animal literature, human EEG/MEG studies have often found that theta power during encoding is positively correlated with subsequent memory (Atienza et al., 2011; Crespo-García et al., 2012; Friese et al., 2013; Hanslmayr et al., 2009; Klimesch et al., 1996; Osipova et al., 2006; Summerfield and Mangels, 2005). These positive SMEs were usually seen over frontal and temporal regions and corroborated by intracranial EEG (iEEG) recordings (Lega et al., 2012; Sederberg et al., 2003). It has been proposed that theta power increases during successful encoding might reflect the recruitment of cortical regions (Sederberg et al., 2003), where theta oscillations could be induced via hippocampal-cortical feedback loops (Klimesch et al., 1996). In this way, human theta oscillations could modulate synaptic plasticity across hippocampus and cortex via a phase-dependent mechanism (Crespo-García et al., 2010; Osipova et al., 2006; Sederberg et al., 2003) similar to the one demonstrated in the rat hippocampus (Hölscher et al., 1997; Pavlides et al., 1988).

However, other studies have reported negative SMEs in the broad theta band (Burke et al., 2013; Guderian et al., 2009; Long et al., 2014; Sederberg et al., 2007). These theta power decreases are seen during the successful encoding of single items and inter-item associations

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(Greenberg et al., 2015) and are widely detected with surface sensors or iEEG contacts targeting medial temporal lobe (MTL) and fronto-temporal structures (Greenberg et al., 2015; Long et al., 2014). Since negative SMEs manifest in key regions for successful encoding (e.g., hippocampus and left prefrontal cortex), the traditional vision that increased theta activity is necessary for memory formation faces a challenge. To explain these findings, Greenberg and collaborators (Greenberg et al., 2015) proposed that theta power decreases may reflect reduced neuronal correlations across the cortex and MTL. Such a mechanism would be beneficial for episodic memory encoding because it means that the network is able to process and store more information.

Although these contrary theta patterns are not fully understood, some experiments have shown that SMEs can be dissociated by specific task manipulations or other oscillatory properties. Positive or negative SMEs manifest when study and test contexts match or mismatch, respectively, which constitutes evidence that theta power plays a crucial role in context-item binding (Staudigl and Hanslmayr, 2013). SMEs also vary across brain regions, time-windows and frequency ranges (e.g., early narrow-band frontal power increases vs. late broad-band hippocampal power decreases; Long et al., 2014) and seem to reflect different phase-synchronization patterns (Burke et al., 2013). Besides these parameters, opposite SMEs can coexist in hippocampus at distinct frequency components (positive SMEs at ~3 Hz vs. negative SMEs at ~8 Hz; Lega et al., 2012), suggesting the existence of functionally dissociable theta bands (for more details, see discussion in Lega et al., 2012). Indeed, growing evidence indicates that slow-theta activity (peaking at ~3 Hz) in the human hippocampus may be the functional equivalent to the hippocampal theta rhythm of rodents (Jacobs, 2014; Watrous et al., 2013). For example, when previous findings in rats (Vanderwolf, 1969) were replicated in neurosurgical patients with depth recordings in hippocampus, it was observed that activity in slower frequencies (1–4 Hz) increased with movement in virtual navigation (Clemens et al., 2013; Ekstrom et al., 2005; Watrous et al., 2011). In addition, MEG studies have shown that better navigation performance is related to increased hippocampal activity at slow theta frequencies (Cornwell et al., 2008; Kaplan et al., 2012).

Together, these findings suggest that human hippocampal slow-theta activity may be involved in the formation of accurate contextual spatial locations supporting spatial navigation. To investigate this hypothesis and the sign of the relationship, we directly focused on theta activity time-locked to the encoding of item-place associations, and correlated it with spatial accuracy for contextual locations in a subsequent memory test. We designed a spatial navigation video game to implement a SME experiment. The game was set in a computer-simulated grass arena, with distal cues comprising a mountain landscape and clouds. The arena was populated with different pictures of buildings at given locations that participants were instructed to remember. In a later session, participants were prompted with specific building pictures, and asked to either orient themselves in the direction of the building or navigate to the remembered location. The successful performance of the task partly relied on the formation of associations between the pictures and distal visual cues, as well as accurate spatial information derived from path integration mechanisms, two processes in which hippocampus is known to be involved (O'Keefe and Nadel, 1978). Theta SMEs were evaluated by performing correlation analysis between theta activity measured during the encoding of picture-context associations and subsequent spatial memory accuracy. In order to validate MEG effects found in healthy participants, we additionally acquired iEEG recordings while epilepsy surgery patients performed the task. We also had the exceptional opportunity of recording MEG and iEEG simultaneously in a patient with implanted depth electrodes in cortical regions of the left hemisphere. With this dataset, we were able to investigate how SMEs manifesting in local hippocampal activity were related to hippocampal-cortical phase interactions.

## 2. Materials and methods

### 2.1. Participants and data acquisition

A sample of 13 healthy participants (8 females, mean  $\pm$  SD age:  $23 \pm 3.7$  years; all right-handed) were considered in the present study. MEG was recorded using a whole-head system with 148-magnetometers (Magnes 2500 WH, 4D-Neuroimaging, San Diego, CA, USA). Data were acquired at a sampling rate of 1017 Hz and on-line band-pass filtered between 0.1 and 400 Hz. All participants had normal or corrected-to-normal vision and reported no history of neurological or psychiatric diseases.

Patients with drug-resistant epilepsy were recruited over a period of 2 years, while undergoing iEEG monitoring at the University Hospital of Erlangen, Germany. A final sample of 12 patients (4 females, mean  $\pm$  SD age:  $30.9 \pm 8.6$  years; all right-handed) participated in the present study. These patients were implanted with a total of 866 iEEG contacts (diameter: 1.1 mm; spacing: 4.5/5 mm), distributed in 18 subdural (grids and strips) and 81 depth electrodes imbedded in silicon sheets (Fig. 1). Seven of the patients had depth electrodes targeting mediotemporal regions, containing contacts labeled as hippocampus (24) or entorhinal cortex (7). Out of the total, 10 patients performed the task on a bedside laptop, while iEEG was continuously sampled at 1024 Hz and referenced to white matter. Two patients participated in a simultaneous MEG and iEEG recording. Unfortunately, the head of one patient could not be positioned close to the MEG sensors, and only the iEEG data was analyzed. MEG was recorded using a whole-head system with 248 magnetometers (Magnes 3600 WH, 4D-Neuroimaging, San Diego, CA) housed in a magnetically-shielded room at the same University Hospital. Data were acquired at a sampling rate of 2034 Hz and iEEG were average referenced. A successful simultaneous recording was obtained from a 43-year-old patient (right-handed female) implanted with 9 platinum strip electrodes. Contacts targeted lateral and mesial structures from parietal, temporal and frontal lobes of the left hemisphere. This patient suffered from a left temporo-basal tumor (astrocytoma WHO grade II) that was completely resected 30 years before the iEEG monitoring. Presumably, the epileptic seizures were originated from the border of the resection. The clinical invasive recording revealed that seizure onset was medial to the resected region, detected by two electrode contacts (MNI coordinates [ $-34 -17 -30$ ] and [ $-39 -17 -29$ ]). All healthy participants and patients gave informed consent before the experiment and performed the task in seated position.

### 2.2. Task and stimuli

The spatial navigation task was implemented as a video game using Unity3D ([www.unity3d.com](http://www.unity3d.com)). The virtual environment depicted a circular field of grass surrounded by a wall, with distal cues consisting of mountains and a sky dotted with clouds. To navigate through this field, participants operated thumb-controlled devices: either a joystick compatible with MEG (Celeritas Fiber Optic Response System) or a gamepad for recordings in the ward. Participants were instructed to observe pictures of buildings (shop facades and houses) at different locations within this field and remember the location in which each picture appeared. Each run of the task consisted of an encoding phase and a memory test (Fig. 2). An encoding trial started with a 3-s fixation period, after which the participant's point of view was situated at the center of the field, facing the sun (starting point). Participants had to find a 3D-house model cueing a particular location and navigate to it. Navigation was divided in two steps: first, left and right turns were enabled until facing the cue; then, only forward (radial) movements. At the location, a picture was presented superimposed on the environment for 3 s. The trial ended with a 1.5-s period where blinks were allowed. At test, each studied picture was presented on a black background after a fixation period. Participants were immediately placed in the field, at

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