

Human Hippocampal Theta Oscillations during Movement without Visual Cues

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The hippocampus exhibits theta oscillations when animals navigate. Vass et al. (2016) discovered that theta oscillations are also present when humans are moved through a virtual environment without sensory feedback, indicating that theta oscillations have a general role in spatial cognition beyond sensorimotor processing.

The hippocampus has long been a confounding brain structure. From lesion and anatomical studies in the past 50 years, we know that the hippocampus has a vital role coordinating brain-wide networks to support high-level behaviors, including spatial navigation (Morris et al., 1982) and memory (Scoville and Milner, 1957). However, we do not understand the specific computational process that the hippocampus performs to support such complex behaviors. One method for probing the hippocampus is examining its theta oscillation, a large-scale electrical rhythm that is easily visible in extracellular recordings at ~4–10 Hz in rodents (Buzsáki, 2002) and ~1–7 Hz in humans (Jacobs, 2014; Watrous et al., 2013). Theta oscillations are seemingly present whenever the hippocampus is active (Buzsáki, 2002). Therefore, one tactic for understanding the computational role of the hippocampus is to characterize the behaviors that activate theta oscillations or alter their properties.

In rodents, hippocampal theta oscillations are most commonly associated with spatial navigation because theta appears when an animal runs through an environment and because its power increases with the animal's movement speed (McFarland et al., 1975). Studies in humans have found increases in theta prevalence associated with various aspects of behavior in virtual reality, including movement speed (Watrous et al., 2013). Despite these findings, the precise functional role of theta still is not understood (Buzsáki, 2002), in part because navigation is a rich, multifaceted behavior. One possibility is that theta oscillations are most closely coupled to the

sensory and motor processes that are used for navigation, such as viewing spatial landmarks and locomoting (Bland and Oddie, 2001). A second possibility is that theta is more closely related to the higher-level cognitive process of an animal keeping track of its current spatial location during navigation (O'Keefe and Recce, 1993).

The study by Vass et al. (2016) in the current issue of *Neuron* incorporated an innovative experimental design that makes it possible to distinguish between these possibilities in humans. In this study participants performed a computer virtual-reality navigation experiment, in which they had to navigate to particular destinations in a cross-shaped environment. The participants performing this task were neurosurgical patients who had electrodes implanted in their hippocampus. During the task patients usually used a joystick to control their movement across the environment, as in a video game. However, the task also included a special feature allowing them to “teleport” across an environment, as if in a science-fiction movie. The patients were eager to use the teleporter accurately because it served as a “short cut” that allowed them to navigate across the environment more rapidly.

Entering any of the four teleporters in the environment caused the screen to go blank, and after a delay, the patient reappeared at a location close to the center of the environment. Given that participants in this type of virtual-reality task rely on vision to navigate, the absence of visual information during teleportation allowed Vass et al. to identify the brain

activity associated solely with internal updating of spatial location without interference from sensorimotor processing. It should be noted that the ability to perform this manipulation is an advantage of studying navigation with virtual reality, as it is hard to dissociate spatial and sensorimotor processing during real navigation.

It is known that hippocampal theta oscillations are active during movement in a virtual reality environment in humans (Watrous et al., 2013). Vass et al. expanded our knowledge of theta's functional role by examining how teleportation modulated the power and phase of these signals. Their hypothesis was that if theta oscillations were indeed being driven by sensory input, there would be an attenuation of hippocampal theta during teleportation. Instead, Vass et al. found no effect of teleportation on theta oscillations: entering the teleporter did not decrease the power or the prevalence of the theta oscillations that had been present during active navigation (Figure 1). They also found no indication of theta phase reset at the onset of transportation, which indicates that the theta oscillations that arose during navigation continued unencumbered into the teleportation period. A critical control finding was that theta power decreased significantly when patients simply viewed a blank screen without teleportation or spatial processing of any kind. The absence of theta in this blank-screen control condition is important because it indicates that the theta oscillations observed in this study were related to navigation rather than just being present continuously and unrelated to task performance.

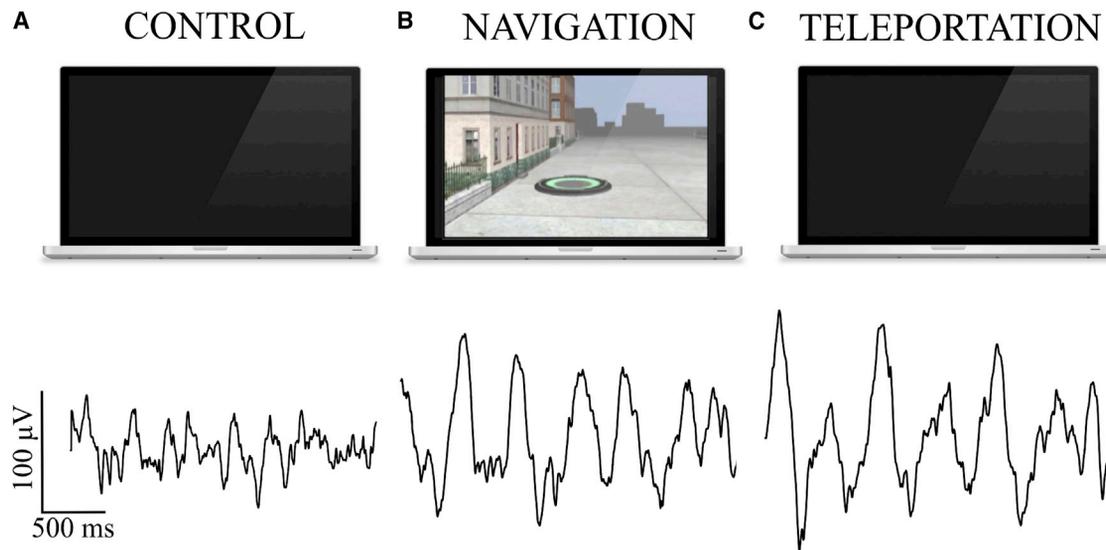


Figure 1. Illustration of the Experimental Conditions in Vass et al.

(A) Top, blank screen viewed by patients during control condition. Bottom, example of hippocampal theta oscillation recorded during control condition. (B) Top, screenshot of the virtual environment as viewed by patient during active navigation, prior to stepping into teleporter (seen as the circle in front of the patient). Bottom, example hippocampal theta oscillation recorded during active navigation. (C) Top, blank screen viewed by patients during teleportation. Bottom, example of hippocampal theta LFP recorded during teleportation. Hippocampal recordings courtesy of L. Vass and A. Ekstrom.

Theta oscillations are considered to be important computationally in the hippocampus for various reasons, including the fact that they may support location tracking during navigation (O'Keefe and Recce, 1993). Vass and colleagues' discovery of theta oscillations during teleportation indicates that the human hippocampus can compute spatial information even in the absence of any kind of sensory input. This is the clearest evidence yet that human hippocampal theta oscillations have a broader functional role such that they exist without any simultaneous sensorimotor processing.

A limitation of this study is that, due to the nature of human intracortical recordings, only three patients were included in this dataset. In particular, one patient contributed over half the electrodes analyzed. Vass et al. addressed this limitation through a careful task design that dissociates spatial and sensory information at the level of individual electrodes. Furthermore, the authors' data analyses indicate that the findings are robust because they did not find significant differences in the nature of teleportation-related theta signals between the vast majority of the electrodes. Nonetheless, given the substantial theoretical impor-

tance of this work, it will be of interest to characterize this pattern in a larger cohort of patients.

Vass et al.'s main finding is that during teleportation with a blank screen, the human hippocampus generates similar theta oscillations compared to periods of normal navigation when patients received sensory information. This finding represents a fundamental difference from many results in rodent navigation, where animals exhibit diminished hippocampal theta when they do not receive certain sensorimotor information (Chen et al., 2011).

What explains these differences? Expanding upon prior work, these findings indicate that the human hippocampus exhibits theta-band oscillations in a larger range of behavioral settings than has typically been observed in rodents. To the extent that theta oscillations can be viewed as a proxy for overall hippocampal activation (Buzsáki, 2002), these findings indicate that the hippocampus is relevant for a broad and general class of behavioral functions in humans, especially when viewed in comparison to our current knowledge of rodent electrophysiology. Previous work in humans showed that hippocampal theta oscillations are impli-

cated in other types of behaviors beyond spatial coding, including working memory maintenance (Axmacher et al., 2010) and episodic memory encoding (Lega et al., 2012). By showing that human theta oscillations can also be driven by internal brain processes even in the absence of external stimuli, Vass et al.'s work further demonstrates the widespread functional role of the human hippocampus.

Although examining this issue is challenging in simple animals, there is some evidence that theta oscillations play a role in higher-order behavioral processes in rodents beyond movement and sensorimotor processing. For example, Johnson and Redish examined the hippocampal mechanisms that allowed rats to compute future movement through space (Johnson and Redish, 2007). The authors reported the presence of theta oscillations when rats were at the "choice points" of a maze, where the rat has to make a decision about the next direction to move. The presence of theta oscillations when the animal paused to think about potential future routes is reminiscent of theta during teleportation, because both periods require the internal generation of spatial information without active sensory information. This supports

the notion that theta may generally be involved in a broad range of internal computations, and future work will need to be done to determine whether this differs between humans and rodents.

By demonstrating that theta oscillations are involved in behavior beyond sensorimotor processing, Vass and colleagues' findings suggest that theta oscillations may also be bound to other behaviors that have been associated with the hippocampus in other areas of work (Buzsáki, 2002), such as the neural representation of time (Eichenbaum, 2014) and memory retrieval (Miller et al., 2013). As the basic principles of the hippocampal and entorhinal systems become more developed and extend beyond navigation, closer examination of the pervasive theta oscillation may help explain the general nature

of the neural computations performed by the hippocampus and surrounding structures in various behaviors.

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A Cool Approach to Probing Speech Cortex

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In this issue of *Neuron*, Long et al. (2016) employ a novel technique of intraoperative cortical cooling in humans during speech production. They demonstrate that cooling Broca's area interferes with speech timing but not speech quality.

A critical issue neurosurgeons face is delineating the extent of cortical tissue that can be safely resected. If you remove too little tissue, one may not get the desired clinical results. On the other hand, if you remove too much tissue you risk impairing motor and language function postoperatively. In the 1930s, Wilder Penfield and colleagues applied electrical stimulation directly to motor and somatosensory cortex during neurosurgical procedures. Their findings provided a systematic mapping of motor function and culminated in the famous cortical homunculus diagram (Penfield and Boldrey, 1937). Over the next 20 years, Penfield devised protocols for awake language mapping (motor cortex can be mapped under anesthesia)

that remain largely unchanged to this day (Penfield and Roberts, 1959).

In addition to providing an invaluable tool for neurosurgeons, electrical stimulation mapping (ESM) is a unique technique for probing function in a causal manner. During a typical language mapping procedure, the patient is awoken from anesthesia while cortex is still exposed and is asked to perform the same tasks Penfield first employed over 80 years ago: counting and picture naming. While the patient engages in counting or naming, different cortical sites are repeatedly stimulated. If the applied electrical current reliably disrupts the patient's speech output, or causes naming errors with intact speech output, the cortical site is deemed to be

critical for language and is spared from resection. Even though counting and picture naming tasks tap into a relatively small subset of language functions, sparing of sites identified by ESM dramatically reduces postoperative deficits and the procedure remains the gold standard in the field (Chang et al., 2015; Sanai et al., 2008).

A large current is necessary (the actual threshold varies by patient but is on the order of 10 mA) to achieve a reliable behavioral deficit during stimulation. Applying such a stimulating current repeatedly can cause neuronal afterdischarges, which can develop into a seizure in either diseased or healthy tissue. Historically, intravenous pharmacological agents were