Functionally distinct high and low theta oscillations in the human hippocampus

Abhinav Goyal[1], Jonathan Miller[2], Salman Qasim[2], Andrew J. Watrous[3], Joel M. Stein[4], Cory S. Inman[5], Robert E. Gross[5], Jon T. Willie[5], Bradley Lega[6], Jui-Jui Lin[6], Ashwini Sharan[7], Chengyuan Wu[7], Michael R. Sperling[8], Sameer A. Sheth[9], Guy M. McKhann[10], Elliot H. Smith[11], Catherine Schevon[12], and Joshua Jacobs*[2]

[1]Department of Neurologic Surgery, Mayo Clinic, Rochester MN, 55905
[1]Mayo Clinic College of Medicine, Mayo Clinic, Rochester MN, 55905
[2]Department of Biomedical Engineering, Columbia University, New York, NY 10027
[3]Department of Neurology, University of Texas, Austin
[4]Department of Radiology, University of Pennsylvania, Philadelphia, PA 19104
[5]Department of Neurological Surgery, Emory University, Atlanta, GA 30322
[6]Department of Neurological Surgery, University of Texas Southwestern, Dallas, TX 75390
[7]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, PA 19107
[8]Department of Neurology, Thomas Jefferson University, Philadelphia, PA 19107
[9]Department of Neurological Surgery, Baylor College of Medicine, Houston, TX, 77030
[10]Department of Neurosurgery, Columbia University Medical Center, New York, NY 10032
[11]Department of Neurosurgery, University of Utah, Utah
[12]Department of Neurology, Columbia University Medical Center, New York, NY 10032

December 14, 2018

*Correspondence: joshua.jacobs@columbia.edu, 351 Engineering Terrace, Mail Code 8904, 1210 Amsterdam Avenue, New York, NY 10027, 212-854-2445

Abstract

Based on rodent models, researchers have theorized that the hippocampus supports episodic memory and navigation via the theta oscillation, a ∼4–10-Hz rhythm that coordinates brain-wide neural activity. However, recordings from humans indicated that hippocampal theta oscillations are lower in frequency and less prevalent than in rodents, suggesting interspecies differences in theta's function. To characterize human hippocampal theta, we examined the properties of theta oscillations throughout the anterior–posterior length of the hippocampus as neurosurgical patients performed a virtual navigation task. During virtual movement, we observed hippocampal oscillations at multiple frequencies from 2 to 10 Hz. The posterior hippocampus prominently displayed oscillations at ∼8-Hz and the precise frequency of these oscillations correlated with the speed of movement, implicating these signals in spatial navigation. We also observed slower ∼3-Hz oscillations, but these signals were more prevalent in the anterior hippocampus and their frequency did not vary with movement speed. In conjunction with other recent findings, our results suggest an updated view of human hippocampal electrophysiology: Rather than one hippocampal theta oscillation with a single general role, high and low theta oscillations, respectively, may reflect spatial and non-spatial cognitive processes.

Introduction

The theta oscillation is a large-scale network rhythm that appears at ∼4–10 Hz in rodents and is hypothesized to play a universal role in mammalian spatial navigation and memory (Kahana et al., 2001; Buzsáki, 2005). However, in humans, there is mixed evidence regarding the relevance and properties of hippocampal theta. Some studies in humans show hippocampal oscillations at 1–5 Hz that have similar functional properties as the theta oscillations seen in rodents (e.g., Arnolds et al., 1980; Jacobs et al., 2007; Vass et al., 2016; Watrous et al., 2011; Watrous, Lee, et al., 2013; J. F. Miller et al., 2018). There is also evidence that human movement-related hippocampal theta oscillations vary substantially in frequency according to whether a subject in a physical or virtual environment (Aghajan et al., 2016; Bohbot et al., 2017; Yassa, 2018). Together, these studies have been interpreted to suggest that the human hippocampus does show a signal analogous to theta oscillations observed in rodents but that this oscillation is more variable and slower in frequency (Jacobs, 2014). These apparent discrepancies in the frequency of theta between species and behaviors shed doubt on the notion that theta represents a general neurocomputational phenomenon that coordinates brain-wide neural activity consistently across species and tasks.

Our study aimed to resolve these discrepancies by characterizing the properties of human hippocampal oscillations in spatial cognition. We analyzed intracranial electroencephalographic (iEEG) recordings from the hippocampi of fourteen neurosurgical patients performing a virtual-reality (VR) navigation task. Our study had two differentiating factors compared to previous work. First, our behavioral task had a distinctive design that required subjects to closely attend to their current location throughout movement, which, we hypothesized, would more clearly show the properties of human hippocampal oscillations specifically related to navigation. Second, we recorded signals at various positions along the anterior–posterior axis of the hippocampus, which allowed us to probe the anatomical organization of these oscillations.

Given the anatomical differences in the hippocampus between rodents and humans (Strange et al., 2014), we hypothesized in particular that understanding the spatial organization of human theta could help explain the apparent interspecies differences that were reported previously. Therefore, we analyzed the spectral and functional features of human hippocampal oscillations and tested their consistency along the length of the hippocampus. In contrast to earlier work that generally emphasized a single theta oscillation for a given behavior, we instead found that the hippocampus showed multiple oscillations at distinct frequencies (often at ∼3 Hz and ∼8 Hz), even in a single subject. Further, ∼8-Hz oscillations in the posterior (but not anterior) hippocampus often correlated with spatial processing. By demonstrating multiple patterns of hippocampal oscillations with different anatomical and functional properties, our findings suggest that human hippocampal theta-band oscillations at different frequencies are generated by separate anatomical networks to support distinct functions.

Results

Fourteen neurosurgical patients performed our virtual-reality (VR) spatial memory task as we recorded neural activity from iEEG electrodes implanted in their hippocampi. The task required that subjects press a button to indicate when they were located at the position of a specified hidden object as they were moved at a randomly varying speed in one direction along a linear track (Fig. 1). We performed spectral analyses of the iEEG signals during movement phases of the task for all hippocampal recording sites and used a peak-picking procedure (Manning et al., 2009; Zhang et al., 2018) to identify prominent narrowband oscillations (see *Methods*). Overall, we observed hippocampal narrowband oscillations at frequencies in the range of 2 to 10 Hz (Fig. 2A), consistent with earlier findings (Ekstrom et al., 2005;

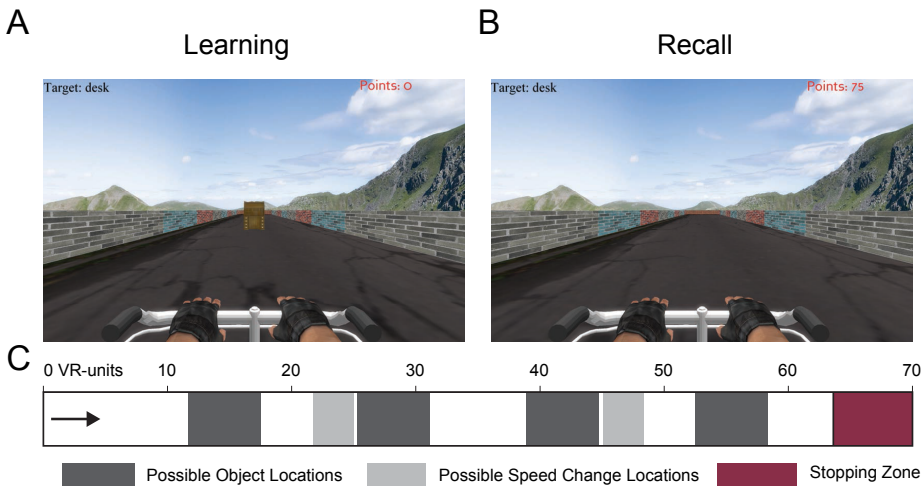

Figure 1: Spatial memory task. A. Task screen image during a learning trial, where the object is visible as the subject travels down the track. **B.** Task image during a recall trial, in which the object is invisible and the subject must recall the object location. **C.** Task schematic, showing possible object and speed change locations.

Jacobs et al., 2007; Watrous et al., 2011; Bush et al., 2017), with oscillations being most prevalent at ∼3 Hz and ∼8 Hz. For convenience, we refer to these hippocampal oscillations as low theta (2–4 Hz) and high theta (4–10 Hz) although we acknowledge that some other studies have used the terms "delta" and "alpha" to refer to parts of these frequency ranges.

Anatomical organization of hippocampal high- and low-theta oscillations. We next examined the characteristics of the oscillations we identified with regard to the location of each recording site along the hippocampus' anterior–posterior axis. Many previous electrophysiological studies in rodents generally focused on hippocampal oscillations in the dorsal area (analogous to the posterior hippocampus of humans; Strange et al., 2014) or those that are consistent across the length of the hippocampus (Lubenov & Siapas, 2009). However, a different line of work in humans (Maguire et al., 1997; Greicius et al., 2002; Kumaran et al., 2009; Poppenk et al., 2013; Lin et al., 2018) and animals (Moser & Moser, 1998; Royer et al., 2010; Fanselow & Dong, 2010; Hinman et al., 2011) showed that there are functional variations along the length of the hippocampus. This suggested to us that oscillations at different anterior–posterior positions could have distinct spectral and functional properties.

We measured the anterior–posterior location of each hippocampal electrode in a subject-specific manner, defined as the relative distance between the anterior and posterior extent of the hippocampus (see *Methods*). In this scheme, positions of 0% and 100% would correspond to electrodes at the anterior and posterior tips of the hippocampus, respectively. As seen in Figure 2B&C, within individual subjects, we observed narrowband oscillations at various frequencies. Individual electrodes displayed oscillations at either one or two distinct frequency ranges during the task—we refer to these electrodes as "single oscillators" and "dual oscillators." Qualitatively, in many individuals we observed that the frequency of the oscillations at a given electrode correlated with its anterior–posterior location. Electrodes at posterior sites (labeled orange in Fig. 2) generally showed oscillations at ∼8 Hz. More anterior sites (labeled green and blue) had oscillations at lower frequencies and more often showed two distinct oscillatory peaks.

We verified these observations quantitatively by analyzing oscillation mean frequencies across our

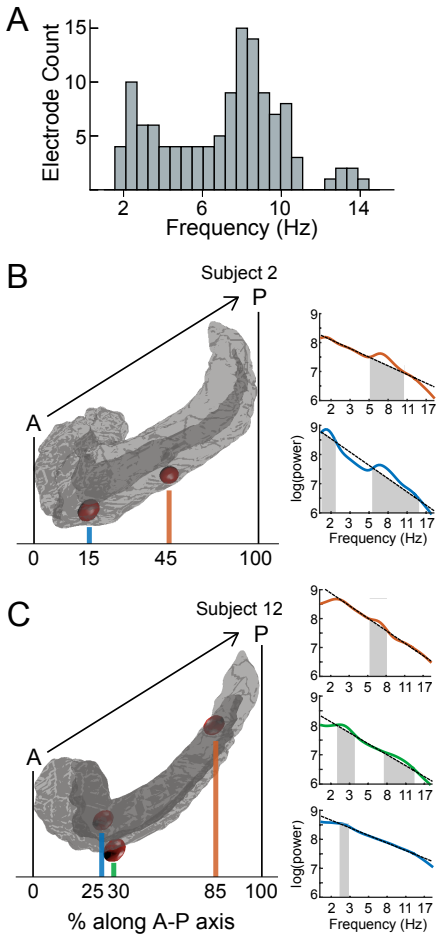

Figure 2: Power spectra of electrodes at different positions along the anterior–posterior axis of the hippocampus. A. The distribution of detected oscillations across all hippocampal electrodes in our dataset. **B.** Rendering of Subject 2's left hippocampus (left) and the power spectra (right) for electrodes implanted in this area. Shading in the power spectrum indicates detected narrowband oscillations. **C.** Rendering of Subject 12's left hippocampus and power spectra for the implanted electrodes.

complete dataset, combining across subjects. Although individual subjects generally were implanted with only a small number of hippocampal contacts, in aggregate our dataset sampled 80% of the anterior–posterior length of the hippocampus (Fig. 3A). Every hippocampal electrode showed at least one narrowband oscillation within 2–10 Hz (Fig. 3B). 60% (54 of 90) of electrodes showed a single oscillatory peak, which was usually (94%) in the high-theta (4–10 Hz) band (Fig. 3C). The remaining 40% (36 of 90) of electrodes had two oscillatory peaks (Fig. 3D). In the posterior hippocampus, 75% of electrodes had only a single oscillatory peak; whereas in the anterior hippocampus approximately equal numbers of electrodes showed single and dual peaks (Fig. 3B).

We next examined how the properties of these oscillations varied with electrode location. Among the single oscillators, there was a correlation between oscillation frequency and anterior–posterior position, such that the electrodes that showed oscillations at higher frequencies were more prevalent in posterior regions ($r = 0.31$, $p = 0.02$; Fig. 3C). Dual oscillators did not show a significant correlation between frequency and location for either their lower or higher oscillatory bands ($|r| < 0.2$, p's> 0.25; Fig. 3D).

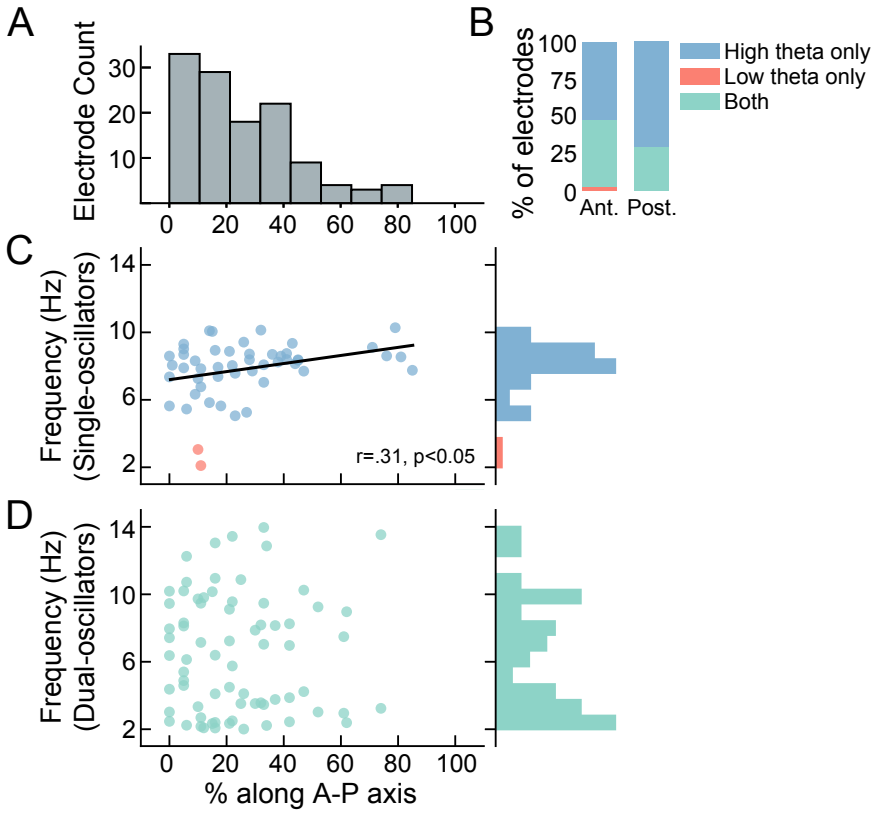

Figure 3: Oscillation properties across frequency and space. A. Distribution of electrode locations along the hippocampus anterior–posterior axis. **B.** Proportions of dual oscillators and single oscillators for anterior and posterior hippocampus. **C.** Frequencies and hippocampal localizations of single oscillators across subjects. Fitted line indicates the correlation between frequency and anterior–posterior position. **D.** Frequency and localization of dual oscillators.

Additional analyses of theta properties. We considered the possibility that there was a relationship between the particular frequencies of the oscillations that appeared at individual dual oscillator electrodes. This could be the case, for example, if one electrode with two apparent oscillations was actually demonstrating an oscillation and its faster harmonic. However, we did not find a significant correlation between the frequencies of the high and low oscillations at individual dual oscillator electrodes ($p = 0.85$, permutation procedure), indicating that our dual oscillator results are not driven by harmonics.

We also compared the properties of these oscillations between hemispheres, given that our dataset included both left and right coverage (52 and 38 electrodes, respectively). Overall trends were consistent across both hemispheres, with both left and right hemispheres displaying low-and high-theta oscillations. Among the high-theta single oscillators, mean frequencies were significantly higher on the right hemisphere than the left ($t_{50} = 2.65$, $p = 0.01$, unpaired t-test). The electrodes that were dual oscillators did not show significant differences in frequency between the two hemispheres ($t_{34} = 0.91$, $p = 0.65$, unpaired t-test).

Earlier studies showed that theta oscillations in both humans and monkeys appeared in transient bouts (Ekstrom et al., 2005; Watrous, Lee, et al., 2013; Jutras et al., 2013), which were shorter in duration compared to rodent theta oscillations that often persisted for many seconds (Buzsáki, 2005). To compare our results with signals in rodents, we measured the durations of oscillatory bouts from individual electrodes in the low- and high-theta bands and for single- and dual-oscillator electrodes (Fig.

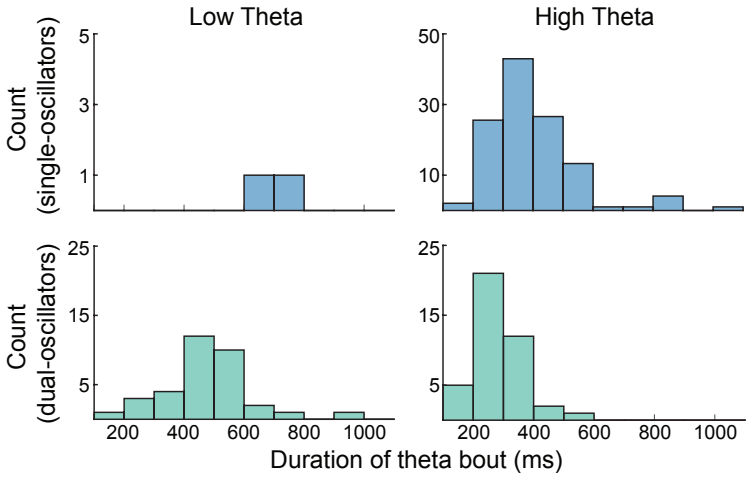

Figure 4: Analysis of the duration of individual theta oscillation bouts. Histograms showing the distributions of mean durations of the bouts of theta oscillations from individual electrodes. Individual plots show these distributions separately for low- and high-theta rhythms from from single and dual oscillator electrodes.

4). Individual electrodes showed a range of mean theta-bout durations. The mean bout duration was longer for low- than for high-theta oscillations ($t_{191} = 4.96$, $p < 10^{-5}$, unpaired t-test). Within the high- theta band, we observed longer theta bouts at single-oscillator than dual-oscillator electrodes (399 vs 285 ms, respectively; $t_{154} = 4.79$, $p < 10^{-5}$, unpaired t-test). The longer durations of high-theta bouts at single oscillators suggests that these signals may reflect a different kind of oscillatory pattern that is relatively more similar to rodent oscillations compared to the dual oscillator network.

The frequency of high-theta oscillations correlates with movement speed. In rodents, the instantaneous frequency of the hippocampal theta oscillation correlates with the speed of running (McFarland et al., 1975; Geisler et al., 2007; Bender et al., 2015) and in both humans and rodents theta power correlates with speed (McFarland et al., 1975; Watrous et al., 2011). These results were taken to indicate that theta oscillations are important for path integration (Burgess et al., 2007; Jeewajee et al., 2008; Korotkova et al., 2017). We tested for correlations between movement speed and theta frequency to identify an additional potential functional role for hippocampal oscillations in spatial processing. To do this, at each electrode we measured the precise frequency of the oscillations in each movement epoch, when the subject was moved at a particular fixed speed along the virtual track (see *Methods*). Then, for each electrode, we computed the correlation across epochs between the speed of movement and the oscillation frequency.

Many electrodes with high-theta oscillations showed positive correlations between frequency and movement speed. Figure 5A–B illustrates this pattern of results for five example electrodes. We found that the mean correlation between movement speed and oscillatory frequency was reliably positive for high-theta oscillations (Fig. 5C, right), both for single and dual oscillators (both p's$< 10^{-5}$). The mean speed–frequency correlation was significantly larger for single- than dual-oscillators ($t_{86} = 6.3$, $p < 10^{-7}$). Also, many electrodes showed significant speed–frequency correlations individually. Of 52 high-theta single oscillators, 35 (67%) showed a significant ($p < 0.05$) speed–frequency correlation, which was more than expected by chance ($p < 0.001$, binomial test). Similarly, of 36 dual oscillators, 10 (28%) showed a significant high-theta speed–frequency correlation ($p < 0.05$, binomial test).

The speed–frequency correlation was specific to the high-theta band. Of 31 electrodes with narrowband low-theta oscillatory peaks, including both single and dual oscillators, none individually

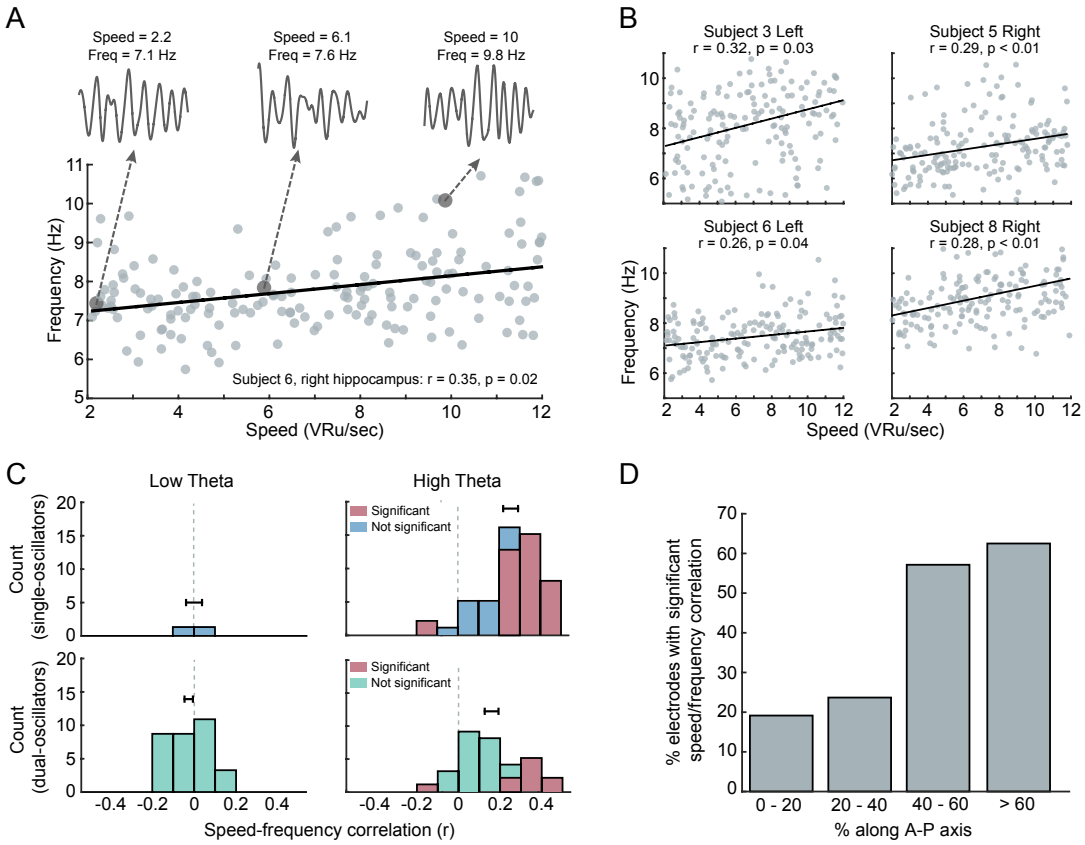

Figure 5: Analyses of the relation between theta frequency and movement speed. A. An example electrode with a positive high theta frequency–speed correlation. 2-s trace of filtered hippocampal oscillations during slow, medium, and fast speeds. **B.** Example electrodes from both left and right hippocampus that display significantly positive high theta speed–frequency correlations. **C.** Histogram of correlation coefficients for single and dual oscillators, separately aggregated for low- and high-theta bands. Significant correlations indicated in red. Error bars are SEM. **D.** Percentage of electrodes with high theta oscillations in each hippocampal region with a significant positive correlation between movement speed and frequency.

showed a significant speed–frequency correlation, consistent with earlier work on low theta in the human hippocampus (Arnolds et al., 1980). Further, the distribution of low-theta speed–frequency correlation coefficients was not significantly different positive ($p > 0.05$; Fig. 5C, left).

We next examined how the strength of high-theta speed–frequency correlations varied along the length of the hippocampus. We performed a two-way ANOVA comparing the speed–frequency correlation coefficients of electrodes with high-theta peaks according to whether they were in the anterior or posterior hippocampus and whether they were single or dual oscillators. This analysis showed that the mean correlation between speed and oscillation frequency was significantly greater in the posterior hippocampus ($F_{1,106} = 11.75$, $p = 0.0009$; Fig. 5D) with no effect of single vs. dual oscillators. This result supports the idea that high-theta oscillations in the posterior hippocampus are preferentially involved in spatial processing (Kumaran et al., 2009; Lin et al., 2018).

Discussion

Our most novel finding is showing the existence of high (∼8 Hz) theta oscillations in the human posterior hippocampus that relate to movement during virtual spatial navigation. Similar to theta oscillations measured in rodents (Royer et al., 2010; Korotkova et al., 2017), the frequency of these human high-theta oscillations correlated with both movement speed and with distance of the recording electrode from the anterior extent of the hippocampus. Further, we found that human high-theta oscillations have distinct functional and anatomical properties compared to the slower theta oscillations that were measured in the same task. In conjunction with earlier work showing human low theta related to memory (Lega et al., 2012; J. F. Miller et al., 2018), this suggests that high and low theta oscillations represent distinct functional network states. Our findings therefore support the view that the human medial temporal lobe and hippocampus have distinct oscillatory states to support different behaviors (Watrous, Tandon, et al., 2013), rather than having a single stationary oscillation to support all behaviors. Because the prevalence of high and low theta oscillations differed along the anterior–posterior length of the hippocampus, it suggests that human high-theta oscillations index functional processes involved in spatial processing that are primarily supported by posterior areas. Further, by humans showing theta frequency variations along the the hippocampus, it demonstrates a potential difference compared to rodents, which usually are described as showing a constant theta frequency along the hippocampus (Lubenov & Siapas, 2009; Long, Bunce, & Chrobak, 2015; but see Schmidt et al., 2013).

Previous work on human hippocampal oscillations emphasized the potential functional role of rhythms at ∼1–5-Hz in memory and navigation because lower frequencies often appeared more prevalent overall in mnay datasets (for review, see Jacobs, 2014). Our study has several distinctive methodological features that could explain why we observed a greater prevalence of hippocampal oscillations at faster oscillations compared to these earlier studies. Although not all studies precisely report the locations of their recording electrodes, it seems that most previous datasets more extensively sampled electrodes in relatively anterior areas of the hippocampus (e.g. Watrous et al., 2011; Watrous, Lee, et al., 2013). By contrast, our study measured each electrode's anterior–posterior location and included greater electrode coverage in middle and posterior sections of the hippocampus, which were the regions that more specifically showed high theta. This increased posterior sampling is the result of evolution in clinical procedures. In recent years, stereotactic electroencephalographic (sEEG) methods have become more common, which has led to increased posterior hippocampal coverage in standard clinical epilepsy mapping (e.g., Lin et al., 2018).

An additional differentiating factor of our study was the design of our spatial VR task. Rather than allowing the subject to control their own movement with a fixed top speed as in earlier studies, here subjects' speeds changed randomly. Given these random speed changes, to perform the task well subjects could not predict their location based on timing and instead had to carefully attend to their view of the spatial environment throughout each trial. We hypothesized that this increased spatial attention would increase the prevalence in our data of neural patterns related to spatial processing. Accordingly, the relatively high prevalence of high-theta oscillations is consistent with the idea that this signal is particularly important for spatial processing, similar to theta observed in rodents (Burgess, 2008; Korotkova et al., 2017). Thus, our data indicate that human high theta is functionally analogous to the "Type 1" theta rhythm commonly measured in navigating rodents (Bland, 1986).

A conclusion from much earlier work was that the human hippocampus primarily showed a single theta oscillation, but that this signal had a lower frequency than in rodents (Jacobs, 2014). Instead, our findings indicate that the human hippocampus exhibits multiple theta oscillations and that the properties of these signals vary according to task demands (Montgomery et al., 2009; Watrous et

al., 2011). This now raises the question of the functional role of the human low theta rhythm. One possible explanation is that the low theta oscillation, which we often found in the anterior hippocampus, is related to the "Type 2" theta oscillations that had been characterized previously in rodents. In rodents, Type 2 theta oscillations appear most strongly when animals are stationary and are often linked to anxiety (Bland, 1986). In contrast, current data from humans link oscillations in this low-theta band to memory processing (Lega et al., 2012; Lin et al., 2018; J. F. Miller et al., 2018). Therefore, one possibility is that the low-theta oscillations we observed are an analog of the Type 2 theta oscillations found in rodents, with these signals in humans having a broader functional role beyond anxiety, perhaps including episodic memory and other types of cognitive processes that involve the anterior hippocampus (Bannerman et al., 2004; Mitchell et al., 2008). This interpretation is bolstered by the finding that Type 2 theta oscillations in rodents are generated by a distinct network of cells in the ventral hippocampus (Mikulovic et al., 2018), which is homologous to the human anterior hippocampus (Strange et al., 2014).

One contribution of our work is showing definitively that high-theta oscillations appear in the human hippocampus during movement in virtual reality. Two recent studies measured human hippocampal oscillations from people walking in the physical world and reported high theta oscillations (Bohbot et al., 2017; Aghajan et al., 2016; but see Meisenhelter et al., 2018). These results were interpreted to suggest that virtual navigation relies on a fundamentally different, higher-frequency oscillatory network state compared to real-world navigation (Yassa, 2018). By showing high-theta hippocampal oscillations during VR, our results suggest a different view. We propose that theta oscillations at various frequencies can be prevalent in both virtual and real spatial environments, with the particular dominant oscillatory frequency that appears at a given moment reflecting a trade-off between spatial and non-spatial attention as well as other cognitive and task demands. The fixed-speed motion of previous VR paradigms (e.g., Ekstrom et al., 2003; Jacobs et al., 2007, 2013; J. F. Miller et al., 2018) may have required less spatial attention compared to real-world navigation and compared to our paradigm with its randomized movement speed. It is possible that some earlier VR studies showed relatively less high theta because they required less spatial attention. Finally, it should be noted that at least one of the studies that previously showed high-theta oscillations in real-world navigation showed examples of these patterns at relatively posterior locations (Bohbot et al., 2017). With our findings, it suggests that the human anterior and posterior hippocampus, respectively, are implicated in low and high theta oscillations with different behavioral properties (Fanselow & Dong, 2010; Strange et al., 2014).

Our finding of relatively higher theta frequencies towards the posterior part of the human hippocampus is also consistent with our understanding of the spatial propagation of these oscillations. Hippocampal theta oscillations in both humans and rodents are often traveling waves (Lubenov & Siapas, 2009; Zhang & Jacobs, 2015) that propagate in a posterior-to-anterior (in humans) or dorsal-to-ventral (rodent) direction. One potential mechanism for neural traveling waves is a network of weakly coupled oscillators (Ermentrout & Kleinfeld, 2001). If a hippocampal network of weakly coupled oscillators had higher mean oscillation frequencies at posterior locations, as we found here, it would produce posterior-to-anterior traveling waves (Zhang et al., 2018). Thus, our finding of higher frequencies in posterior sites provides general support for the coupled oscillator model of hippocampal traveling waves (Zhang & Jacobs, 2015; Lubenov & Siapas, 2009).

One reason why theta oscillations are thought to be important functionally is by coordinating brain-wide networks to synchronize cortical–hippocampal interactions in learning and memory (Sirota et al., 2008). Therefore, given that we showed that the human hippocampus exhibits two separate theta oscillations in a single task, an important area of future work will be to understand the potential relation of each of these signals to brain-wide neocortical dynamics (von Stein et al., 1999). In particular, it is

notable that the properties of the anterior and posterior hippocampal oscillations resemble the theta and alpha rhythms that are prominent in the overlying frontal and occipital lobes (Voytek et al., 2010; Zhang et al., 2018), especially including the "midfrontal" theta often found in scalp recordings (Mitchell et al., 2008). Given the predominent involvement of the frontal and occipital lobes in high-level and sensory processing, respectively, this suggests that low and high theta oscillations may reflect different types of hippocampal–neocortical interactions that underlie distinct functional processes (R. Miller, 1991; Watrous, Tandon, et al., 2013). This multiplicity of human theta patterns could allow the human hippocampus to coordinate a diverse set of brain-wide neural assemblies to support various types of behaviors including both spatial navigation as well as memory and other cognitive processes (Buzsaki & Moser, 2013; Eichenbaum & Cohen, 2014).

Methods

Participants. Fourteen participants undergoing treatment for medication-resistant epilepsy participated in our study. Neurosurgeons implanted these patients with clinical depth electrodes for functional mapping and the localization of seizure foci. Implantation sites were determined solely by clinical teams, though electrodes were often placed in medial temporal lobe regions that are of interest experimentally. Research protocols were approved by the institutional review boards at each participating hospital, and informed consent was obtained from all patients.

Task. The participants in our study performed a new spatial task, which we specifically designed to encourage patients to pay attention to their location in the virtual environment. We hypothesized that this task design had potential for eliciting more reliable hippocampal activity related to spatial processing than previous studies of human navigation (Qasim et al., 2018). Because the subjects in our study were undergoing continuous monitoring for epileptiform activity, we were limited to studying virtual navigation as subjects remained in their hospital bed throughout testing. Therefore, to encourage subjects to pay attention to their virtual spatial location, we asked patients to press a button on their game controller when they were at the location of a hidden object, while simultaneously manipulating speed of movement.

In the 3D virtual spatial memory game (Qasim et al., 2018), patients were moved along the length of a virtual reality (VR) track, which we defined as having a length of 70 virtual reality units. The ground was textured to mimic asphalt, and the track was surrounded by stone walls (See Fig. 1). On each trial, patients were placed at the beginning of the track and they began each trial by pressing a button on a game controller. Next, a four second long countdown was displayed. After the countdown, patients were moved forward along the track. Within each third of the track, patients were moved at a constant speed, chosen randomly from a uniform distribution between 2 and 12 VR-units/second. Locations where speed changes began are indicated by the light gray shading in the schematic shown in Figure 1C. When speed changes occurred, acceleration occurred gradually over the course of one second to avoid jarring transitions.

While moving, the patients' goal was to learn the location of a hidden object. The first two times that the patient traveled down the track, the object's location was visible (Fig. 1A). On subsequent trials, the object was invisible, and patients were instructed to press the button on the controller when they believed they were at the correct location (Fig. 1B). The closer the patient pressed the button to the correct location, the more points they received (as indicated in the top right of the display), thus encouraging careful attention to current location in the environment. Patients were also required to press the button when they approached the end of the track where the ground was colored red. Possible object locations are indicated by the dark gray shading in Figure 1C.

Each trial consisted of the subject traveling a single time down the track, either encoding or retrieving object location. Within each trial, the task would automatically change the subject's speed twice at certain possible speed change locations (Fig. 1C), such that the subject's path down the track consisted of three constant speed regions.

Electrophysiological Recordings We recorded patients' intracranial electroencephalographic (iEEG) data from implanted depth electrodes via the clinical or research recording systems present at the participating hospitals (Nihon Kohden; XLTEK; Neuralynx; Blackrock). Data were recorded at a sampling rate of either 1000 or 2000 Hz. iEEG signals were initially referenced to common intracanial or scalp contact, and were subsequently re-referenced using an anatomically weighted referencing scheme prior to analysis. Data were notch filtered at 60 Hz using a zero-phase-distortion Butterworth filter to remove line noise prior to subsequent analyses. iEEG recordings were aligned to the behavioral task laptop via synchronization pulses sent to the recording system.

Electrode Localization We localized depth electrodes for each subjects using an established semi-automated image processing pipeline (Jacobs et al., 2016). To delineate the hippocampus, we applied the Automatic Segmentation of Hippocampal Subfields multi atlas segmentation method to pre-implantation high-resolution hippocampal coronal T2-weighted and whole brain 3D T1-weighted scans. Electrode contact coordinates derived form post-implantation CT scans were then co-registered to the segmented MRI scans using Advanced Normalization Tools (Avants et al., 2008) and anatomic locations were automatically generated. A neuroradiologist reviewed and confirmed contact locations based on the co-registered source images and the processed data. Contacts were given normalized locations along the hippocampal axis by determining the coronal slice containing the center of the contact as well as the first and last slice containing the hippocampus. For specific subjects, a neuroradiologist generated transparent 3D surface renderings of the subjects hippocampal segmentation and corresponding co-registered electrode contacts.

To determine each contact's anterior–posterior (A–P) localization within the hipocampus, we obtained virtual slices along the hippocampal long axis, and determined the slice on which the contact was located. The A–P localization was determined as the slice number along the axis divided by the total slice number. When we wished to make a designation between anterior and posterior hippocampus in our analyses, we used 40% along the anterior–posterior axis as the midpoint, as our electrodes were located between 0% and 80% along the anterior–posterior axis. If two neighboring electrodes in one subject were located on the same slice and exhibited the same oscillation frequencies during movement, to avoid double counting, one of the electrodes was randomly dropped for data analysis.

Spectral Analysis In order to identify oscillatory frequencies with a high frequency resolution, we followed the MODAL algorithm for adaptive characterization of neural oscillations (Watrous et al., 2018). In short, this algorithm operates by first excluding epochs of the data that could potentially result from epileptic activity (Gelinas et al., 2016). Then, the algorithm defines relevant frequency bands as those frequencies exceeding one standard deviation above the background $1/f$ spectrum. MODAL then computes the instantaneous frequency and phase for each frequency band, but only when the local power spectrum (computed in 10 second, non-overlapping windows) indicated a local increase in power for that band.

We called electrodes that only exhibited a single oscillation throughout the task "single oscillators" while we called those that exhibited two oscillations "dual oscillators." For an electrode to be designated as a dual oscillator, the two frequency bands detected by MODAL had to be at least 0.5 Hz apart. Each trial consisted of three intervals that each had a constant speed of movement.

We computed the particular oscillation frequency corresponding to each movement interval and band by following the following procedure. First, throughout each interval we used MODAL to measure the instantaneous frequency of the iEEG signal at each timepoint. Then, we computed a histogram of the distribution of frequencies (0.1-Hz bins), identified the single most-often occurring frequency (i.e., the mode), and used this value to summarize the oscillatory activity in that interval.

Competing Financial Interests. The authors declare no competing financial interests.

Acknowledgements. This work was supported by the National Institutes of Health (R01-MH104606, S10-OD018211), and the National Science Foundation (Graduate Research Fellowship DGE 16-44869). We thank Shachar Maidenbaum for providing thoughtful comments on the manuscript.

References

Aghajan, Z. M., Schuette, P., Fields, T., Tran, M., Siddiqui, S., Hasulak, N., ... others (2016). Theta oscillations in the human medial temporal lobe during real world ambulatory movement. *Current Biology*, *27*(24), 3743-3751.

Arnolds, D. E. A. T., Lopes Da Silva, F. H., Aitink, J. W., Kamp, A., & Boeijinga, P. (1980). The spectral properties of hippocampal EEG related to behaviour in man. *Electroencephalography and Clinical Neurophysiology*, *50*, 324–328.

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis*, *12*(1), 26–41.

Bannerman, D., Rawlins, J., McHugh, S., Deacon, R., Yee, B., Bast, T., ... Feldon, J. (2004). Regional dissociations within the hippocampus–memory and anxiety. *Neuroscience & Biobehavioral Reviews*, *28*(3), 273–283.

Bender, F., Gorbati, M., Cadavieco, M. C., Denisova, N., Gao, X., Holman, C., ... Ponomarenko, A. (2015). Theta oscillations regulate the speed of locomotion via a hippocampus to lateral septum pathway. *Nature communications*, *6*.

Bland, B. H. (1986). The physiology and pharmacology of hippocampal formation theta rhythms. *Prog. Neurobiol.*, *26*, 1–54.

Bohbot, V. D., Copara, M. S., Gotman, J., & Ekstrom, A. D. (2017). Low-frequency theta oscillations in the human hippocampus during real-world and virtual navigation. *Nature Communications*, *8*, 14415.

Burgess, N. (2008). Grid cells and theta as oscillatory interference: Theory and predictions. *Hippocampus*, *18*, 1157-1174.

Burgess, N., Barry, C., O'Keefe, J., & London, U. (2007). An oscillatory interference model of grid cell firing. *Hippocampus*, *17*(9), 801–12.

Bush, D., Bisby, J. A., Bird, C. M., Gollwitzer, S., Rodionov, R., Diehl, B., ... Burgess, N. (2017). Human hippocampal theta power indicates movement onset and distance travelled. *Proceedings of the National Academy of Science USA*, *114*(46), 12297-12302.

Buzsáki, G. (2005). Theta rhythm of navigation: Link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus*, *15*, 827–840.

Buzsaki, G., & Moser, E. (2013). Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nature Neuroscience*, *16*(2), 130–138.

Eichenbaum, H., & Cohen, N. J. (2014). Can we reconcile the declarative memory and spatial navigation views on hippocampal function? *Neuron*, *83*(4), 764–770.

Ekstrom, A. D., Caplan, J., Ho, E., Shattuck, K., Fried, I., & Kahana, M. (2005). Human hippocampal theta activity during virtual navigation. *Hippocampus*, *15*, 881–889.

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature*, *425*, 184–187.

Ermentrout, G., & Kleinfeld, D. (2001). Traveling Electrical Waves in Cortex Insights from Phase Dynamics and Speculation on a Computational Role. *Neuron*, *29*(1), 33–44.

Fanselow, M. S., & Dong, H.-W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, *65*(1), 7-19.

Geisler, C., Robbe, D., Zugaro, M., Sirota, A., & Buzsaki, G. (2007). Hippocampal place cell assemblies are speed-controlled oscillators. *Proceedings of the National Academy of Sciences, USA*, *104*(19), 8149.

Gelinas, J. N., Khodagholy, D., Thesen, T., Devinsky, O., & Buzsáki, G. (2016). Interictal epileptiform discharges induce hippocampal–cortical coupling in temporal lobe epilepsy. *Nature medicine*, *22*(6), 641.

Greicius, M. D., Krasnow, B., Boyett-Anderson, J. M., Eliez, S., Schatzberg, A. F., Reiss, A. L., & Menon, V. (2002). Regional analysis of hippocampal activation during memory encoding and retrieval: fmri study regional analysis of hippocampal activation during memory encoding and retrieval: an fmri study. *Hippocampus*, *13*(1), 164-174.

Hinman, J. R., Penley, S. C., Long, L. L., Escabi, M. A., & Chrobak, J. J. (2011). Septotemporal variation in dynamics of theta: speed and habituation. *Journal of Neurophysiology*.

Jacobs, J. (2014). Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1635), 20130304.

Jacobs, J., Kahana, M. J., Ekstrom, A. D., & Fried, I. (2007). Brain oscillations control timing of single-neuron activity in humans. *Journal of Neuroscience*, *27*(14), 3839–3844.

Jacobs, J., Miller, J., Lee, S. A., Coffey, T., Watrous, A. J., Sperling, M. R., ... Rizzuto, D. S. (2016, December). Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. *Neuron*, *92*(5), 1–8.

Jacobs, J., Weidemann, C. T., Miller, J. F., Solway, A., Burke, J. F., Wei, X., ... Kahana, M. J. (2013). Direct recordings of grid-like neuronal activity in human spatial navigation. *Nature Neuroscience*, *16*(9), 1188–1190. doi: 10.1038/nn.3466

Jeewajee, A., Barry, C., O'Keefe, J., & Burgess, N. (2008). Grid cells and theta as oscillatory interference: electrophysiological data from freely moving rats. *Hippocampus*, *18*(12), 1175–1185.

Jutras, M. J., Fries, P., & Buffalo, E. A. (2013). Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. *Proceedings of the National Academy of Sciences, USA*.

Kahana, M. J., Seelig, D., & Madsen, J. R. (2001). Theta returns. *Current Opinion in Neurobiology*, *11*, 739–744.

Korotkova, T., Ponomarenko, A., Monaghan, C. K., Poulter, S. L., Cacucci, F., Wills, T., ... Lever, C. (2017). Reconciling the different faces of hippocampal theta: the role of theta oscillations in cognitive, emotional and innate behaviors. *Neuroscience & Biobehavioral Reviews*.

Kumaran, D., Summerfield, J. J., Hassabis, D., & Maguire, E. A. (2009). Tracking the emergence of conceptual knowledge during human decision making. *Neuron*, *63*(6), 889-901.

Lega, B., Jacobs, J., & Kahana, M. (2012). Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus*, *22*(4), 748–761.

Lin, J.-J., Umbach, G., Rugg, M. D., & Lega, B. (2018). Gamma oscillations during episodic memory processing provide evidence for functional specialization in the longitudinal axis of the human hippocampus. *Hippocampus*.

Long, L. L., Bunce, J. G., & Chrobak, J. J. (2015). Theta variation and spatiotemporal scaling along the septotemporal axis of the hippocampus. *Frontiers in systems neuroscience*, *9*, 37.

Lubenov, E. V., & Siapas, A. G. (2009). Hippocampal theta oscillations are travelling waves. *Nature*, *459*(7246), 534–539.

Maguire, E., Frackowiak, S. J., & Frith, C. D. (1997). Recalling routes around london: activation of the right hippocampus in taxi drivers. *Journal of Neuroscience*, *17*, 7103-7110.

Manning, J. R., Jacobs, J., Fried, I., & Kahana, M. J. (2009). Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *Journal of Neuroscience*, *29*(43), 13613–13620.

McFarland, W. L., Teitelbaum, H., & Hedges, E. K. (1975). Relationship between hippocampal theta activity and running speed in the rat. *Journal of comparative and physiological psychology*, *88*(1), 324.

Meisenhelter, S., Testorf, M. E., Gorenstein, M. A., Hasulak, N. R., Tcheng, T. K., Aronson, J. P., & Jobst, B. C. (2018). Cognitive tasks and human ambulatory electrocorticography using the rns system. *Journal of neuroscience methods*.

Mikulovic, S., Restrepo, C. E., Siwani, S., Bauer, P., Pupe, S., Tort, A. B., ... Leao, R. N. (2018). Ventral hippocampal olm cells control type 2 theta oscillations and response to predator odor. *Nature Communications*.

Miller, J. F., Watrous, A. J., Tsitsiklis, M., Lee, S. A., Sheth, S. A., Schevon, C. A., ... Jacobs, J. (2018). Lateralized hippocampal oscillations underlie distinct aspects of human spatial memory and navigation. *Nature communications*, *9*(1), 2423.

Miller, R. (1991). *Cortico-hippocampal interplay and the representation of contexts in the brain*. Springer-Verlag.

Mitchell, D., McNaughton, N., Flanagan, D., & Kirk, I. (2008). Frontal-midline theta from the perspective of hippocampal theta. *Progress in neurobiology*, *86*(3), 156.

Montgomery, S., Betancur, M., & Buzsaki, G. (2009). Behavior-dependent coordination of multiple theta dipoles in the hippocampus. *Journal of Neuroscience*, *29*(5), 1381.

Moser, M., & Moser, E. (1998). Functional differentiation in the hippocampus. *Hippocampus*, *8*(6), 608–619.

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Science*, *17*(5), 230-240.

Qasim, S., Miller, J., Inman, C., Gross, R., Willie, J., Lega, B., ... others (2018). Single neurons in the human entorhinal cortex remap to distinguish individual spatial memories.

Royer, S., Sirota, A., Patel, J., & Buzsáki, G. (2010). Distinct representations and theta dynamics in dorsal and ventral hippocampus. *The Journal of neuroscience*, *30*(5), 1777–1787.

Schmidt, B., Hinman, J. R., Jacobson, T. K., Szkudlarek, E., Argraves, M., Escabí, M. A., & Markus, E. J. (2013). Dissociation between dorsal and ventral hippocampal theta oscillations during decision-making. *Journal of Neuroscience*, *33*(14), 6212–6224.

Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., & Buzsáki, G. (2008). Entrainment of Neocortical Neurons and Gamma Oscillations by the Hippocampal Theta Rhythm. *Neuron*, *60*(4), 683–697.

Strange, B. A., Witter, M. P., Lein, E. S., & Moser, E. I. (2014). Functional organization of the hippocampal longitudinal axis. *Nature Reviews Neuroscience*, *15*(10), 655–669.

Vass, L. K., Copara, M. S., Seyal, M., Shahlaie, K., Farias, S. T., Shen, P. Y., & Ekstrom, A. D. (2016). Oscillations go the distance: Low-frequency human hippocampal oscillations code spatial distance in the absence of sensory cues during teleportation. *Neuron*, *89*(6), 1180–1186.

von Stein, A., Rappelsberger, P., Sarnthein, J., & Petsche, H. (1999). Synchronization between temporal and parietal cortex during multimodal object processing in man. *Cerebral Cortex*, *9*(2), 137-150.

Voytek, B., Canolty, R., Shestyuk, A., Crone, N., Parvizi, J., & Knight, R. (2010). Shifts in gamma phase–amplitude coupling frequency from theta to alpha over posterior cortex during visual tasks. *Frontiers in Human Neuroscience*, *4*.

Watrous, A. J., Fried, I., & Ekstrom, A. D. (2011). Behavioral correlates of human hippocampal delta and theta oscillations during navigation. *Journal of Neurophysiology*, *105*(4), 1747–1755.

Watrous, A. J., Lee, D. J., Izadi, A., Gurkoff, G. G., Shahlaie, K., & Ekstrom, A. D. (2013). A comparative study of human and rat hippocampal low-frequency oscillations during spatial

navigation. *Hippocampus*.

Watrous, A. J., Miller, J., Qasim, S. E., Fried, I., & Jacobs, J. (2018). Phase-tuned neuronal firing encodes human contextual representations for navigational goals. *eLife*, *7*, e32554.

Watrous, A. J., Tandon, N., Conner, C. R., Pieters, T., & Ekstrom, A. D. (2013). Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. *Nature Neuroscience*, *16*(3), 349–356.

Yassa, M. A. (2018). Brain rhythms: higher-frequency theta oscillations make sense in moving humans. *Current Biology*, *28*(2), R70–R72.

Zhang, H., & Jacobs, J. (2015). Traveling theta waves in the human hippocampus. *The Journal of Neuroscience*, *35*(36), 12477–12487.

Zhang, H., Watrous, A. J., Patel, A., & Jacobs, J. (2018). Theta and alpha oscillations are traveling waves in the human neocortex. *Neuron*, *98*(6), 1269 - 1281.e4.