

Traveling theta waves in the human hippocampus

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Abstract

The hippocampal theta oscillation is strongly correlated with behaviors like memory and spatial navigation, but we do not understand its specific functional role. One hint of theta's function came from the discovery in rodents that theta oscillations are traveling waves that allow parts of hippocampus to simultaneously exhibit separate oscillatory phases. Because hippocampal theta oscillations in humans have different properties compared to rodents, we examined these signals directly using multielectrode recordings from neurosurgical patients. Our findings confirm that human hippocampal theta oscillations are traveling waves but show that these oscillations appear at a broader range of frequencies compared to rodents. Human traveling waves showed a distinctive pattern of spatial propagation such that there is a consistent phase spread across the hippocampus irrespective of the oscillations' frequency. This suggests that traveling theta oscillations are important functionally in humans because they coordinate phase coding throughout the hippocampus in a consistent manner.

Significance Statement

We show for the first time in humans that hippocampal theta oscillations are traveling waves, moving along the length of the hippocampus in a posterior-to-anterior direction. The existence of these traveling theta waves is important for understanding hippocampal neural coding because they cause neurons at separate positions in the hippocampus to experience different theta phases simultaneously. The theta phase that a neuron measures is a key factor in how that cell represents behavioral information. Therefore, the existence of travelling theta waves indicates that to fully understand how a hippocampal neuron represents information it is vital to also account for that cell's location in addition to conventional measures of neural activity.

Introduction

The hippocampal theta oscillation is a key brain signal that underlies various aspects of cognition and behavior including memory and spatial navigation (Winson, 1978; Seager et al., 2002). Theta has been implicated in many critical aspects of neuronal processing, as it increases in amplitude during hippocampally dependent behaviors (Vanderwolf, 1969), modulates synaptic plasticity (Pavlides et al., 1988; Huerta & Lisman, 1993) and coordinates brain-wide neuronal networks (R. Miller, 1991; Buzsáki, 1996; Siapas et al., 2005; Sirota et al., 2008). For these reasons, characterizing hippocampal theta is important for understanding how the brain supports a range of behaviors.

Traditionally the theta rhythm was thought to indicate when the hippocampus as a whole transitions between processing states (Pavlides et al., 1988; Stewart & Fox, 1990; R. Miller, 1991; Hasselmo et al., 2002). However, recent studies suggested a new view of theta's function by showing that separate segments of the hippocampus simultaneously exhibit different theta phases, with the wave traveling continuously along the septal–temporal axis (Lubenov & Siapas, 2009; Patel et al., 2012). One theory suggests that hippocampal neurons signal future or past events by activating at late or early theta phases (Dragoi & Buzsáki, 2006; Lubenov & Siapas, 2009). Thus, the existence of phase variations across the hippocampus indicates that neurons at different positions simultaneously represent information about events at different times. This intriguing idea suggests that to fully understand hippocampal coding it not only is sufficient to examine the rate and timing of each cell's spiking (Jensen & Lisman, 2000; Huxter et al., 2003; Dragoi & Buzsáki, 2006), but that we also must take into account each cell's location relative to theta traveling waves (Lubenov & Siapas, 2009).

Despite the fact that theta oscillations are central to many general neural models of behavior, there is uncertainty about whether theta oscillations are present in all species. Early work suggested that the human hippocampus does not exhibit theta (Halgren et al., 1978; Arnolds et al., 1980). Later work showed evidence of task-related theta in human hippocampus (Ekstrom et al., 2005; Lega et al., 2012; Watrous et al., 2011), but with key differences compared to rodents including decreases in amplitude, duration, and frequency (Watrous, Lee, et al., 2013; Jacobs, 2014). Our primary goal is to test whether the rodent finding of theta as a traveling wave persists in humans

despite these interspecies differences.

We examined the spatial properties of human hippocampal theta oscillations by recording from epilepsy patients that were implanted with depth electrodes for seizure monitoring. These patients had depth electrodes implanted along the longitudinal (septal–temporal or anterior–posterior) axis of their hippocampus. Each probe had multiple contacts, which provided multiple measurements of individual theta waves. We used spatial and spectral methods to analyze these recordings and characterize theta's frequency and propagation speed. Our findings indicate that human hippocampal theta waves do behave as traveling waves, moving along the hippocampus from septal to temporal structures, but they have distinctive spectral properties compared to rodents, which are informative regarding the mechanisms underlying theta's generation and propagation.

Materials and Methods

Patients and electrophysiology. We recorded brain activity from 14 epilepsy patients who had electrodes implanted to map the extent of their seizures for subsequent resective surgery. Seven of the patients are male and seven are female. These patients had depth electrodes targeting their hippocampus with a posterior approach. During recording patients performed a working-memory task on a bedside laptop computer. Data from these patients were reported previously (Jacobs & Kahana, 2009; van Gerven et al., 2013), but the analyses described here are novel. We analyzed data from this task's encoding trials, which ranged between 530 and 1280 observations per patient. Each observation for our data analyses corresponded to a 1-s period when the patient encoded one item into memory. These periods each extended from 200 ms before each item presentation to 800 ms afterward.

Electrode locations were identified by inspecting post-implant computed tomography (CT) scans, which were then aligned with MRI scans from before electrode implantation. We computed each electrode location in three-dimensional space using Talairach coordinates and distinguished electrodes that were located outside of the hippocampus (Talairach & Tournoux, 1988; Insanedi & Amaral, 2004). We computed the absolute value of the Talairach X coordinate to analyze depth electrode angles while combining across left and right hemispheres. Individual patients' MRI and CT scans were inspected to verify and occasionally correct the automatic localizations.

As described below, our data analyses consisted of three steps to characterize traveling theta oscillations: (1) Identifying clusters of electrodes that exhibited theta oscillations at the same frequency, (2) testing whether the electrodes in these theta clusters exhibited instantaneous phase synchrony, and (3) examining spatial gradients of theta phase to identify traveling waves.

Identifying groups of electrodes with theta oscillations. First, we downsampled the data to 250 Hz and rereferenced each electrode's raw signal, as in other studies on traveling brain oscillations waves in human intracranial and scalp recordings (Bahramisharif et al., 2013; Massimini et al., 2004; van der Meij et al., 2012; De Munck et al., 2007; Patten et al., 2012; Alexander et al., 2013). We used average referencing because it seemed to reveal larger theta signals and because it provided one more electrode for data analysis rather than requiring the removal of a single reference electrode. Nonetheless, we performed these analyses with multiple referencing methods and found that the traveling wave patterns generally remained consistent regardless the referencing method used, consistent with previous findings (van der Meij et al., 2012; Patten et al., 2012). In one version of our analyses we measured the signal's kurtosis to exclude atypical neural traces (Sederberg, Schulze-Bonhage, Madsen, Bromfield, Litt, et al., 2007), with thresholds of 4 and 6 excluding 26% and 6% of trials, respectively.

We then used Morlet wavelets to measure the instantaneous power and phase at each electrode for 33 frequencies logarithmically spaced from 2 to 32 Hz (wave number = 6). Here we refer to human hippocampal oscillations at 2 to 10 Hz as "theta" because previous work showed that these signals have similar functional properties as the ~8-Hz "theta" oscillations in rodents (e.g., Lega et al., 2012; Watrous et al., 2011; Jacobs et al., 2007). We prefer this naming scheme because it emphasizes the functional link between human hippocampal oscillations and rodent theta, rather than reinforcing the notion that brain oscillations should be solely defined on the basis of fixed frequency ranges (for expanded discussion see Jacobs, 2014).

Our next objective was to identify narrowband oscillatory peaks that surpassed each electrode's background power spectrum, which generally is distributed as $1/f$ (K. J. Miller et al., 2007; Manning et al., 2009; Freeman, 2004; Hughes et al., 2012). To detect significant narrowband oscillations, we first fit each electrode's background $1/f$ using a robust regression in log-log coordinates. Then we subtracted away this background signal to reveal a corrected power spectrum that emphasizes

the presence of narrowband peaks (e.g., Fig. 1). To identify narrowband peaks, we set a threshold of the mean of the corrected power spectrum plus one standard deviation. We then designated significant narrowband peaks as local maxima exceeding this threshold.

We used a sliding window to identify narrowband oscillations that appear simultaneously at multiple electrodes in each depth probe. We moved a 2-Hz window in 0.5-Hz increments across the frequency spectrum, each time counting the number of electrodes that show oscillatory peaks within that range. We defined a cluster to be four or more electrodes that showed a peak within the window. We included only the peak window in cases where consecutive windows exceed this threshold. The central frequency of each cluster was assigned as the mean of the peak frequencies from the individual electrodes that comprise the cluster.

Detecting theta traveling waves. For each cluster's central frequency, at each electrode we compute the instantaneous phase at each timepoint using the Hilbert transform (Freeman, 2004, 2007). We compute a single reference phase for each timepoint as the circular mean (Fisher, 1993) of the phases from individual electrodes. We then measure each electrode's phase shift as the circular difference compared to the cluster reference. Each electrode's phase shift thus indicates whether, at any given moment, a particular electrode's oscillation is ahead of or behind the cluster's mean phase (negative or positive phase shifts, respectively).

We used circular statistics to test whether there were consistent theta phase patterns within these oscillatory clusters (Fisher, 1993). For each cluster, we computed each electrode's mean phase shift and then assessed the distribution of phase shifts across trials. A non-uniform distribution of phase shifts indicates that a consistent phase pattern is present across trials at a given electrode. We assessed each electrode's stability within the cluster by measuring the mean circular vector length of its phase differences \bar{r} . We included a given electrode in a cluster if it exhibited significant phase coupling with the other cluster members at the level of individual trials using a Rayleigh test ($p < 10^{-20}$ or $\bar{r} > 0.6$).

We characterized traveling waves by examining the spatial distribution of phase shifts across the electrodes in each cluster. We used a permutation procedure to assess the statistical significance of the traveling wave in each individual theta cluster. This procedure used a customized shuffling approach to test for a relation between electrode location and the relative theta phase it measures.

For both the true and shuffled data, we used a regression to model the relation between phase shift and electrode position, with the resultant r^2 indicating the magnitude of the traveling wave pattern. Our shuffling procedure randomly permuted the locations of the electrodes 10,000 times. We then assessed the statistical significance of the traveling wave pattern in the real data by comparing the real r^2 with the distribution of r^2 values from the shuffled data. Significant waves had a r^2 exceeding the 95th percentile of the shuffled data's r^2 , which corresponds to a threshold of $p < 0.05$.

Because the model is calculated to fit the relation between phase (in °) and electrode position (in mm), the slope of the regression line reveals the cluster's rate of theta phase change across space (Fig. 4D). This number is the cluster's wave number, k , which we compute in units of °/mm. We use k to indicate the cluster's propagation speed s , in units of meters per second, with the formula $s = \frac{\omega}{k}$, where ω is the cluster's temporal frequency. We also compute the wavelength λ of each theta traveling wave as $\lambda = \frac{2\pi}{k}$.

Spatial dynamics of theta phase. The first method we used to examine the range of phase shifts within individual theta clusters involves examining phase differences across all pairwise combinations of electrodes within a cluster. A cluster with n electrodes has $\frac{n(n-1)}{2}$ electrode pairs. For each pair we compute two differences: a phase difference and spatial distance between the two electrodes' Talairach coordinates. We then pool these differences across patients to perform an across-electrode measurement of the rate of phase change across space. To estimate the range of theta phase that is expressed across the entire hippocampus, we pooled data across subjects by aligning each subject's data to a single fixed reference point (Talairach X = ±24, Y = -8, Z = -20; Talairach & Tournoux, 1988). We then readjusted each electrode's phase shift so that it was measured relative to this fixed reference point and plotted it together (Fig. 5B).

Results

To characterize the spatial dynamics of human hippocampal theta oscillations, we recorded signals from epilepsy patients who had one or more multi-contact depth electrodes surgically implanted along the long axis of their hippocampus for seizure mapping (Fig. 1A,B). Each depth electrode contained multiple recording contacts spaced at an interval of 5 mm along the "long" axis of the

hippocampus, which extends in a temporal-septal or posterior-anterior direction and is structurally analogous to the dorsal-ventral axis in rodents (Lubenov & Siapas, 2009; Patel et al., 2012). We analyzed recordings from periods between clinical procedures when patients were awake and performing the encoding phase of a memory task on a laptop computer (Jacobs & Kahana, 2009, 2010).

Our initial observations provided evidence of signals propagating along the length of the hippocampus (Fig. 1). Fig. 1C illustrates this phenomenon in recordings from six neighboring contacts in one patient. We observed theta-band signals on multiple contacts. The timepoints of theta peaks systematically shifted later in time in relation to the electrode's position along the long axis of the hippocampus, with greater delays corresponding to increasingly anterior locations (Fig. 1D). Figure 1E reveals this pattern using spectral analysis, plotting the phase of this signal as a function of space and time. This plot displays diagonal bands, which are evidence of a traveling oscillation by showing that the phase systematically shifts with position. Following these initial observations, we designed follow-up analyses to fully characterize traveling waves across the complete dataset.

Characterizing simultaneous multi-site recordings of human hippocampal theta. A prerequisite for studying traveling oscillations is to record a single oscillation from multiple locations. This is a challenge in the human hippocampus where theta signals can be unreliable. Some researchers have reported the inability to identify even a single electrode with a reliable theta oscillation (Halgren et al., 1978; Arnolds et al., 1980). There are several challenges to measuring hippocampal theta oscillations in epilepsy patients, including the variable positions of clinically implanted electrodes (O'Keefe & Burgess, 1999), and human hippocampal theta's lower amplitude and slower frequency (Jacobs, 2014).

We addressed these issues by designing a signal-processing procedure that is optimized to identify groups of electrodes that simultaneously measure a single oscillation (see *Materials & Methods*). This procedure targets electrodes with strong narrow-band oscillations at a single shared frequency, minimizing potential errors from electrodes with weaker signals. In this procedure, we compute each electrode's power spectrum using wavelets and then identify electrodes with narrowband oscillations that are visible above the $1/f$ background power spectrum (K. J. Miller

et al., 2007; Manning et al., 2009; Lega et al., 2012). Then we identify clusters of four or more electrodes with oscillations at the same frequency.

We used this approach to identify groups of electrodes that oscillated together at frequencies from 2 to 10 Hz. Consistent with previous findings in the human hippocampus (Jacobs, 2014), we observed oscillatory clusters at the broader theta range of 2 to 4 Hz in addition to the conventional “theta” band of 4–8 Hz. All of the 14 patients had at least one depth electrode that exhibited a theta-band peak. This consisted of 106 (66%) of 160 total depth electrode contacts. 63 of these electrodes fell into clusters of at least four electrodes (spanning 11 clusters in 10 patients, as one patient had two depth probes). The next step of our analyses examines the spatial phase dynamics across these theta clusters to identify traveling waves.

Characterizing the spatial characteristics of hippocampal traveling waves. We compared the theta phase between electrodes within each cluster to assess whether there is a consistent inter-electrode phase pattern. A consistent phase pattern is a requirement for observing a traveling wave but there has been evidence that human theta oscillations exhibit independent phases between neighboring cortical areas (Raghavachari et al., 2006). We characterized phase consistency by measuring each electrode’s instantaneous theta phase and then computing whether each site had a consistent phase shift relative to the cluster overall (see Methods). All the theta clusters we observed exhibited electrodes with significant phase synchrony. Across all clusters 81% of electrodes (51 of the 63 electrodes) exhibited significant phase consistency with the cluster mean. This indicates that our methods reliably identify clusters of hippocampal electrodes that have consistent theta phase relations. Our next step was to test whether these synchronized cluster phase patterns exhibit traveling waves.

We measured the spatial progression of phase across each cluster by using a linear regression to model the relation between theta phase lag and electrode location. This identified electrode clusters that exhibited significant traveling theta waves and measured three key properties of these signals: direction, propagation speed, and spatial wavelength. For example, Figure 2D,E depicts a cluster of six electrodes where the relative phase lag systematically varies along a depth electrode across a range of 18° , from 6° at the most posterior site to -12° at the most anterior electrode. In this measurement scheme, the entire cluster has a mean phase of 0° and the wave moves in a

posterior-to-anterior direction from locations with positive phase lags to those with negative ones.

We identified traveling waves by testing for a significant relation between theta phase and electrode position using a permutation procedure at $p < 0.05$ (see *Materials & Methods*). Of 11 theta hippocampal electrode clusters, six exhibited a traveling wave. All six of the traveling waves propagated in a posterior-to-anterior direction, which was a consistent unidirectional pattern that was unlikely to have occurred by chance ($p < 0.02$, $df=1$, binomial test). This indicates that posterior-to-anterior movement is a significant characteristic feature of human hippocampal theta oscillations. This posterior-to-anterior movement is consistent with the dorsal-to-ventral direction of theta propagation found in rodents (Lubenov & Siapas, 2009; Patel et al., 2012), given the rotation of the hippocampus that occurred during evolution (Strange et al., 2014). These traveling-wave patterns were not related to the presence of epileptiform activity. We determined this by re-running our statistical framework after excluding periods of data that have high kurtosis, which is a marker of abnormal neural signals (see Methods; Sederberg, Schulze-Bonhage, Madsen, Bromfield, Litt, et al., 2007).

Frequency analyses of travelling waves. The neural mechanism of hippocampal traveling waves remain unknown (Lubenov & Siapas, 2009; Patel et al., 2012). We hypothesized that characterizing the properties of human theta traveling waves could provide a key interspecies datapoint to explain how these waves propagate. Two properties are especially important for characterizing a traveling wave: temporal frequency and propagation speed. Temporal frequency measures the rate of phase change over time at a single electrode and is measured in cycles per second (Hz). Propagation speed measures the rate at which an oscillation moves across space and is measured in meters per second. Figure 4A depicts the (temporal) frequencies of the clusters where we observed traveling theta waves, which span a range of frequencies from 2 to 8 Hz. Figure 4B reveals the wave propagation speeds that we observed, which span 1–5 m/s.

Two models for the propagation of hippocampal traveling waves are time-delayed excitation from a single oscillator (SO) and a series of weakly coupled oscillators (CO) (Ermentrout & Kleinfeld, 2001; Lubenov & Siapas, 2009; Patel et al., 2012). Because our dataset contained theta oscillations at a range of temporal frequencies (Fig. 4A), we hypothesized that comparing how different waves propagated could distinguish the model that best explained these waves' propa-

gation. The CO model predicts a correlation between temporal frequency and propagation speed. The SO model predicts no such relation. Previous work in rodents did not have the ability to distinguish between these models because the theta oscillations they measured had only a narrow range of temporal frequencies. We thus tested for a correlation between frequency and speed by aggregating across data from patients with theta oscillations at various temporal frequencies. As shown in Figure 4C, we observed a significant positive correlation between temporal frequency and propagation speed ($r(4) = 0.84, p < 0.05$). The result supports the CO model by showing that waves with faster temporal frequencies move more rapidly through the hippocampus (see *Discussion*).

An implication of the CO model is that there is a consistent spatial distribution of phase across the theta oscillations that appear throughout the hippocampus. This implies that a useful way of measuring theta propagation is by computing the spatial frequency or wave number k , which is the rate of phase change per unit space. Our analyses indicate that human theta traveling waves have a mean spatial frequency of $\sim 7.2^\circ/\text{cm}$ (Fig. 4D).

Progression of theta phase through the hippocampus. The existence of traveling theta oscillations implies that hippocampal neurons at different locations simultaneously experience different theta phases. Individual hippocampal subregions project to separate cortical regions (Cenquizca & Swanson, 2007; Patel et al., 2012). Thus, to understand how the hippocampus coordinates brain-wide computations it is important to map the range of theta phases that are expressed simultaneously. This issue is of particular importance because previous studies on this topic reported conflicting phase ranges of 360° (Lubenov & Siapas, 2009) and 180° (Patel et al., 2012).

We used two approaches to examine the range of theta phases that is expressed simultaneously across the hippocampus. First, we examined theta phase differences between pairs of electrodes within individual traveling theta waves (Fig. 5A). Pairs of electrodes within an individual patient exhibited theta phase differences of up to 23° . The magnitude of these differences correlated with interelectrode distance ($r(47) = -0.71, p < 0.01$) and provided an estimated spatial frequency of $6.8^\circ/\text{cm}$, similar to the measure reported above. However, because each individual patient's electrodes only cover a subset of the hippocampus, this measure did not show the full range of theta phase that appeared simultaneously.

To more fully examine theta phase across the hippocampus, we conducted a separate analysis that pooled data across patients with electrodes at different locations. First, we identified the theta phase lag for each electrode, as in the above analyses. We then adjusted each electrode's phase lag relative to a fixed anatomical reference point (coordinate X=±24, Y=-8, Z=-20; Talairach & Tournoux, 1988). Figure 5B reveals the results of this analysis, showing that we observed a total theta phase range of 28° by examining a range of electrodes across 40 mm ($r(25) = -0.82, p < 0.01$). The human hippocampus has been estimated to have a length between ~40–45 mm (Insausti & Amaral, 2004; Duvernoy, 2005) and 70 mm (Rao et al., 2012), depending on whether it is measured by counting coronal brain slices or along its curved shape, respectively. Extrapolating from these measurements, our findings suggest that the range of theta phase that is expressed simultaneously across the whole human hippocampus is ~28–49°.

In rodents, theta phase shifts through the layers of the hippocampus (Brankačk et al., 1993; Lubenov & Siapas, 2009). It is possible that these layer-wise phase shifts could cause the appearance of travelling waves in a depth electrode that was angled so that successive contacts sampled different layers. We examined this issue by testing whether the depth electrodes with travelling theta waves were positioned distinctively. Angles and Talairach coordinates did not significantly differ between the depth electrodes that did or did not measure travelling waves (t tests in X, Y, and Z directions, p 's > 0.15, uncorrected). There was also no relation between electrode position and travelling-wave spatial or temporal frequency (p 's > 0.4, Pearson's correlation). By demonstrating that there were no significant differences in the positioning of the electrodes with traveling waves, it suggests that our findings are not driven by layer-wise phase shifts within the hippocampus. This view is further supported by the hint in our data that some travelling waves extended outside the hippocampus proper, where they would not be affected by intrahippocampal layer differences (see Figures 2 & 3).

Theta power variations. A key characteristic of human theta oscillations is that they vary in amplitude during behavior (Sederberg, Schulze-Bonhage, Madsen, Bromfield, McCarthy, et al., 2007; Lega et al., 2012; Jacobs, 2014), in contrast to theta in rodents, which has a consistently high amplitude throughout sustained periods of behavior (Buzsáki, 2002). To examine how the variability of human theta amplitude could affect traveling waves, we compared the properties of

traveling waves between epochs of high or low theta power.

We used a median split to separate our dataset into periods of high and low theta power. We compared the temporal and spatial frequencies of theta between periods of high and low theta power but did not observe significant changes between these two periods (p 's>0.2). All six traveling waves exhibited increased phase consistency when theta power was elevated ($t(5) = 4.6$, $p < 0.01$). This suggests that theta power could indicate how reliable neighboring sites in the hippocampus exhibit a specific phase relationship.

Discussion

Our observation of traveling waves in the human hippocampus indicates an important interspecies link in the properties of theta oscillations and may be informative about mechanisms underlying theta's spatial propagation. Whereas hippocampal theta oscillations have been demonstrated in many rodent studies, in many cases human data did not provide clear evidence for such signals. This discrepancy was problematic for neural models in which hippocampal theta oscillations have a critical role in supporting navigation, memory, and brain-wide network processing (R. Miller, 1991; Buzsáki, 2005). Our observation that human theta oscillations are traveling waves supports the general approach of studying the hippocampus of animals to make insights into the neural basis of human memory and navigation. Furthermore, aspects of our findings appear to go beyond animal studies by showing that travelling hippocampal theta waves propagate in a spatially consistent manner that is optimal for phase coding.

Because our work used data from clinical depth electrodes, we were not able to measure theta phase across the layers of the hippocampus with the precision of the microelectrodes used in animal studies (Brankačk et al., 1993; Lubenov & Siapas, 2009; Patel et al., 2012). Thus, despite our best efforts to rule out the effects of intrahippocampal location on travelling waves (see *Results*), there is nonetheless a possibility that aspects of our findings were affected by layer-specific phase shifts. Further probing the electrophysiology of the human hippocampus with more precise recordings is an important area of future work that could improve our understanding of these patterns.

Unlike hippocampal theta in rodents, which appears at ~8 Hz, a distinctive feature of human theta oscillations is that they are present at a broad range of frequencies from approximately 1 to

10 Hz (Jacobs, 2014). This variation allowed us to measure the relation between theta's frequency and its other attributes. We found a positive correlation between theta frequency and propagation speed (Fig. 4), which supports the coupled oscillator (CO) model of traveling wave propagation (Ermentrout & Kleinfeld, 2001; Lubenov & Siapas, 2009). The CO model suggests that there are a series of local theta oscillators along the length of the hippocampus. We hypothesize that theta oscillations begin at the septal end of the hippocampus (posterior in humans, dorsal in rodents) and travel in a temporal (anterior in humans, ventral in rodents) direction because of weak phase coupling between the local oscillators arranged along the length of the hippocampus (Fig. 6B). Because the propagation in this model is driven by phase differences rather than time delays, this causes oscillations to propagate through space at a rate that correlates with oscillation's temporal frequency (Fig. 6D,F). The main alternative model of theta traveling waves is the single oscillator (SO), which relies on a single source oscillator at the medial septum that connects to sites along the length of the hippocampus via a series of axons with fixed conduction delays (Fig. 6A). Because these conduction delays are fixed, SO wave propagation speeds would be constant regardless of frequency (Fig. 6C,E). Our findings support the CO model because we found that propagation speed was frequency dependent rather than constant.

The CO model is not only important for understanding how theta oscillations propagate, but it also has implications for explaining how hippocampal neurons encode information. The existence of traveling waves indicates that parts of the hippocampus simultaneously represent different theta phases. The propagation of these waves based on COs indicates that phase differences across the hippocampus are precisely coordinated. There are constant phase between the oscillations that appear at particular positions along the hippocampus (Fig. 7, right panels). This pattern means that an individual neuron can maintain synchrony with cells at other positions along the length of the hippocampus while monitoring only its local theta phase. Many models of hippocampal processing are based on the synchronous activation of assemblies of neurons (e.g., Harris et al., 2003). Spatial phase patterns from CO traveling waves could provide a straightforward mechanism for these assemblies to be synchronized. SO models of traveling waves could not support such patterns because they do not provide a consistent spatial phase distribution across different frequencies (Fig. 7, left panels).

A number of studies pointed out the potential importance of theta oscillations for facilitating

phase-based encoding of behavioral information. Place cells use theta-phase coding to represent an animal's spatial location in a manner that extends beyond rate-based coding (O'Keefe & Recce, 1993; Jensen & Lisman, 2000; Huxter et al., 2003). Later studies suggested that theta oscillations also underlie a possibly related phenomenon, in which hippocampal neurons use theta phase coding to signal the *timing* of events (Jensen & Lisman, 1996; Dragoi & Buzsáki, 2006; Lubenov & Siapas, 2009). In this theory (Lubenov & Siapas, 2009), when a theta wave propagates along the length of the hippocampus, it causes individual neurons to experience a sequence of theta phases. Given the hypothesized link between theta phase and the neural representation of time, the continuous progression of phase at each location causes individual neurons to sequentially represent information related to future, present, and past events. Following this idea, it suggests that a spatially distributed assembly of neurons could represent the relations between events at different times by each individual cell spiking at separate local theta phases.

The septal–temporal axis of the hippocampus is important because it explains variation in how individual neurons encode information. As one moves along the hippocampus in the septal-to-temporal direction, there is a continuous increase in the size of a place cell's place field (Jung et al., 1994; Kjelstrup et al., 2008). This variation in neuronal coding is likely to interact with traveling waves. Specifically, traveling waves will cause place cells to activate in order of increasing field size: septal cells with small place fields activate first, followed by temporal place cells with larger place fields. This suggests that the hippocampus first represents specific information about the current location and later, as theta moves through space, it represents coarser spatial information. This temporal variation in the precision of hippocampal representation could be important more broadly beyond place cells because hippocampal neurons are known to exhibit a range of behavioral information (Eichenbaum, 1996; Quiroga et al., 2005; Komorowski et al., 2013). Thus, one open question is whether the hippocampal cells that represent non-spatial information also exhibit other analogous septal-to-temporal variations in information coding, which could interact with traveling waves.

Compared to rodents, human hippocampal theta oscillations are challenging to measure because they are smaller in amplitude, slower in frequency, and more variable (Vanderwolf, 1969; Halgren et al., 1978; Watrous et al., 2011; Jacobs, 2014). These factors may have contributed to our not observing theta traveling waves in every patient. Nonetheless, we believe that two features of

our analyses made it possible for us to identify reliable human theta oscillations in many patients that were akin to signals in rodents. First, we used a peak-picking method where we only analyzed signals at frequencies with peaks above the $1/f$ background spectrum. Second, we focused on oscillations that appeared on multiple electrodes. This targeted approach allowed us to focus on the strongest theta signals, which exhibited traveling waves as in rodents. A further complication is that the amplitude of human theta oscillations varies dramatically with ongoing behavioral events (Sederberg, Schulze-Bonhage, Madsen, Bromfield, McCarthy, et al., 2007; Watrous, Tandon, et al., 2013). A further possibility is that at any moment the human hippocampus could simultaneously exhibit multiple patterns of theta oscillations from separate sources that are phase shifted (Agarwal et al., 2014) or independent (Raghavachari et al., 2006; Sirota et al., 2008). These multiple theta oscillations could be difficult to observe from the clinical macroelectrodes used in epilepsy patients, which only measure the single theta oscillation that is visible in the aggregate local field potential.

Perhaps the most intriguing aspect of the theta oscillation is that it is thought to coordinate brain-wide neuronal assemblies, linking hippocampus and neocortex (R. Miller, 1991; Buzsáki, 2006; Sirota et al., 2008). The fact that theta oscillations are traveling waves has key implications for understanding how this linking occurs. Connectivity to the neocortex varies along the length of the hippocampus (Cenquizca & Swanson, 2007). As theta propagates, the greatest level of neuronal excitation appears at the position in the hippocampus that exhibits the theta trough (Buzsáki, 2005; Lubenov & Siapas, 2009). These factors indicate that at any given moment the hippocampus is preferentially sensitive to a particular neocortical input. Thus, traveling theta waves may provide a sort of neural “searchlight” that allows the hippocampus to separately consider different neocortical inputs in sequence. In this way, traveling theta waves could explain how the hippocampus organizes information from a broad range of neocortical networks. To understand theta’s role in aggregating brain-wide signals, one important next step is to elucidate the relation between neuronal activity in neocortical networks relative to the hippocampal theta wave. In humans there is evidence that hippocampal theta oscillations have a different frequency compared to neocortex (Jacobs et al., 2007), which suggests there may not be a straightforward pattern of one-to-one phase coupling between neocortex and hippocampus. Uncoupling the cortical correlates of hippocampal traveling waves is a challenging but critical next step towards

understanding the role of the hippocampus in modulating brain-wide networks.

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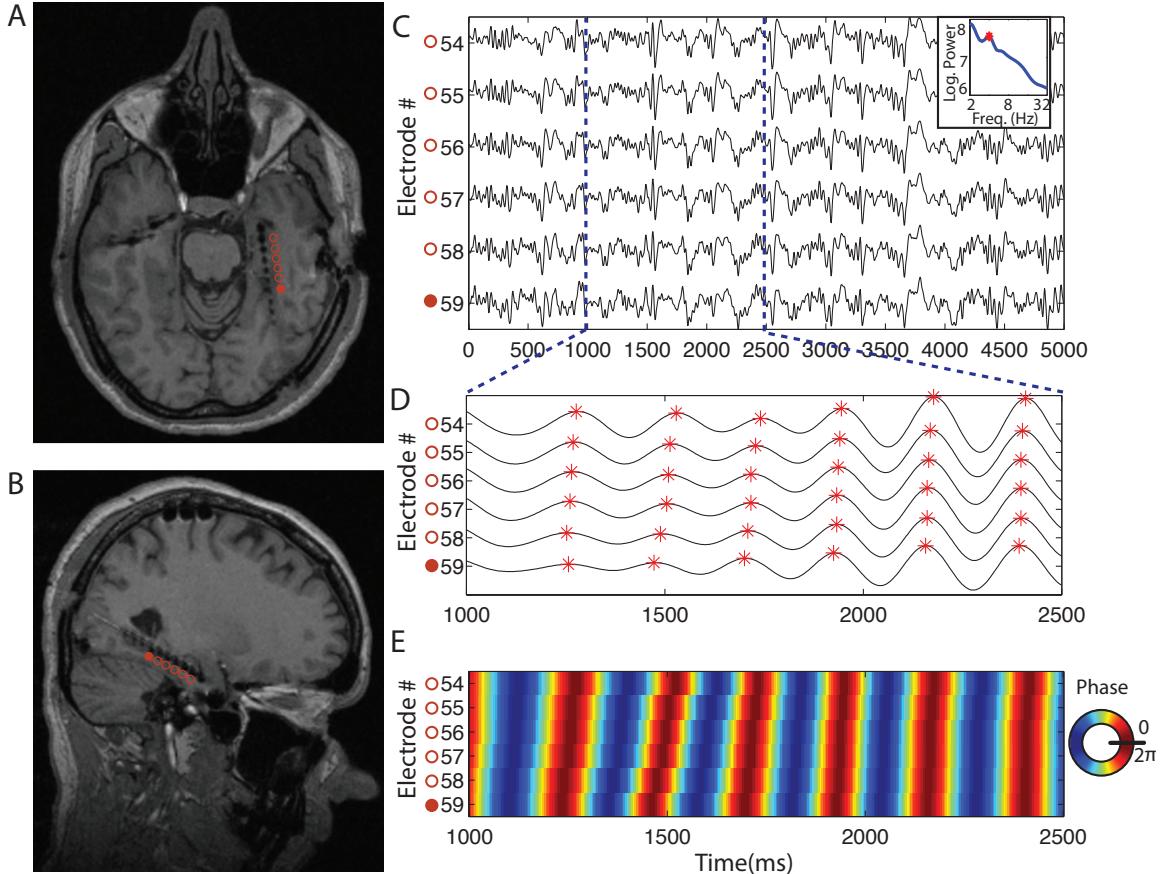


Figure 1: An example hippocampal traveling wave. **A.** Axial MRI of a patient who had electrodes implanted along the length of the hippocampus. Electrode locations are denoted by the black imaging artifacts. Colored circles are labels indicating correspondence between electrodes in Panels A & C. **B.** A sagittal MRI from this same patient. **C.** The raw EEG theta waveform signal that was recorded for 5 s from six consecutive depth electrodes. The electrodes are ordered from anterior (top of plot) to posterior (bottom). **D.** A bandpass filtered (3–5 Hz) version of the EEG trace from Panel C. Red asterisks denote the peaks of individual theta cycles. **E.** Colormap plotting the filtered theta traces from panel D. Red denotes the peak of the oscillation and blue denotes troughs.

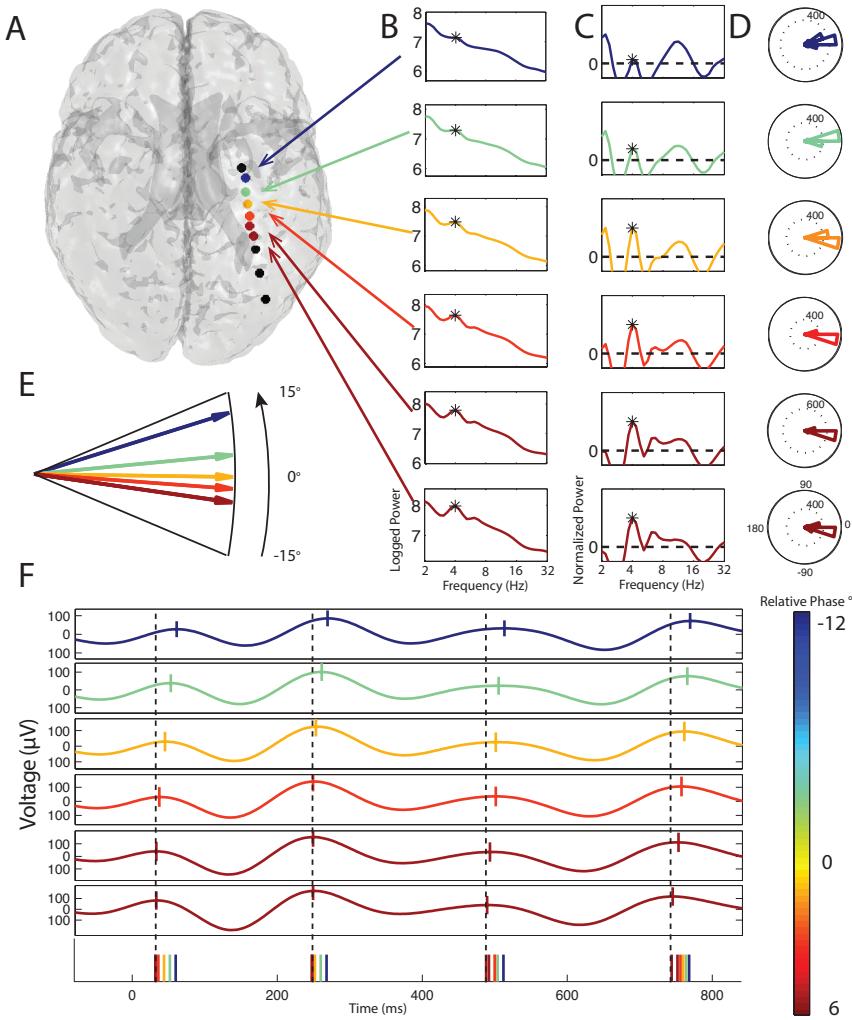


Figure 2: Example hippocampal ~4-Hz traveling theta waves. **A:** Brain image depicting the locations of the depth electrodes implanted in patient 3. Electrodes denoted as colored circles. For each electrode in a theta cluster (see Methods), color indicates the relative phase of the oscillation at that electrode (see color bar in bottom right). Black denotes electrodes where theta was not observed. From top to bottom, electrodes 1, 2, 3 and 4 were manually localized to the hippocampus. **B.** Power spectra at electrodes where significant theta-band oscillations were observed. Black asterisk denotes the frequency with significant theta narrowband oscillations. **C.** Normalized power spectra, computed by removing the $1/f$ background signal from the power spectra in Panel B. **D.** Histogram of the relative phases of theta oscillations measured from each electrode across trials. Phase moves in a clockwise direction in these plots, so each theta cycle is first encountered at the electrode at the bottom of the plot (positive relative phase), and last reaches the electrode at the top of the plot (negative relative phase). **E.** Phase detail plot indicating the relative phase of each electrode's theta oscillation. Colored arrows indicating an orderly progression of phase from the most posterior (blue) to the most anterior electrode. **F.** Example EEG traces from each electrode. Vertical ticks denote the peak phase. Black dotted line is a reference indicating the timepoint of the phase of the bottom (most posterior) electrode. Bottom row of the plot illustrates the timepoints when each electrode reached its peak phase. The ordering of the colored ticks indicates the relative timepoints when each electrode exhibited a theta peak.

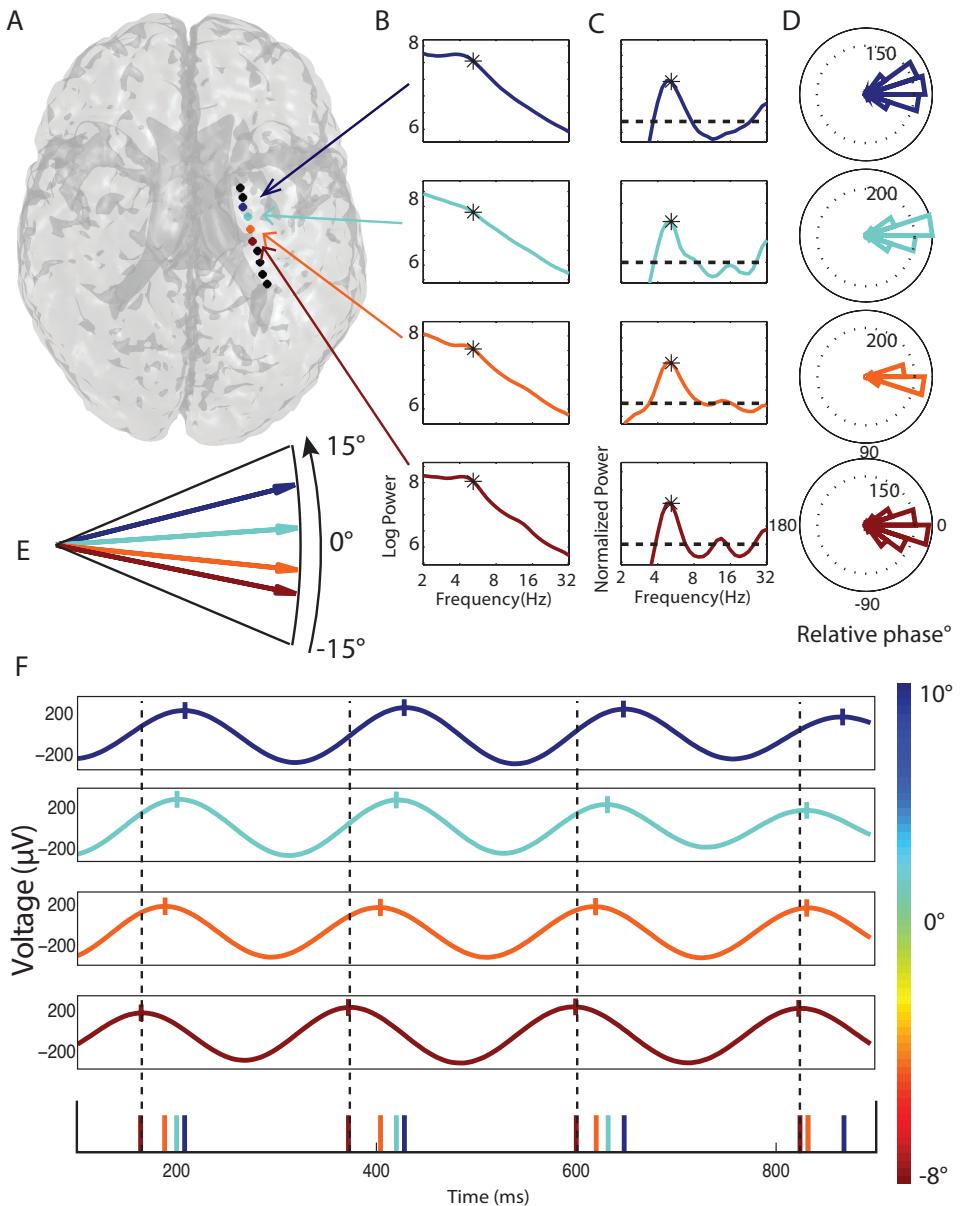


Figure 3: Example hippocampal traveling theta waves at ~ 5.2 Hz. A–F: Plots indicate a hippocampal traveling wave observed in one patient's right hippocampus. Format for individual panels follow the caption of Figure 2. From top to bottom, electrodes 3, 4, 5 and 6 were manually localized to the hippocampus.

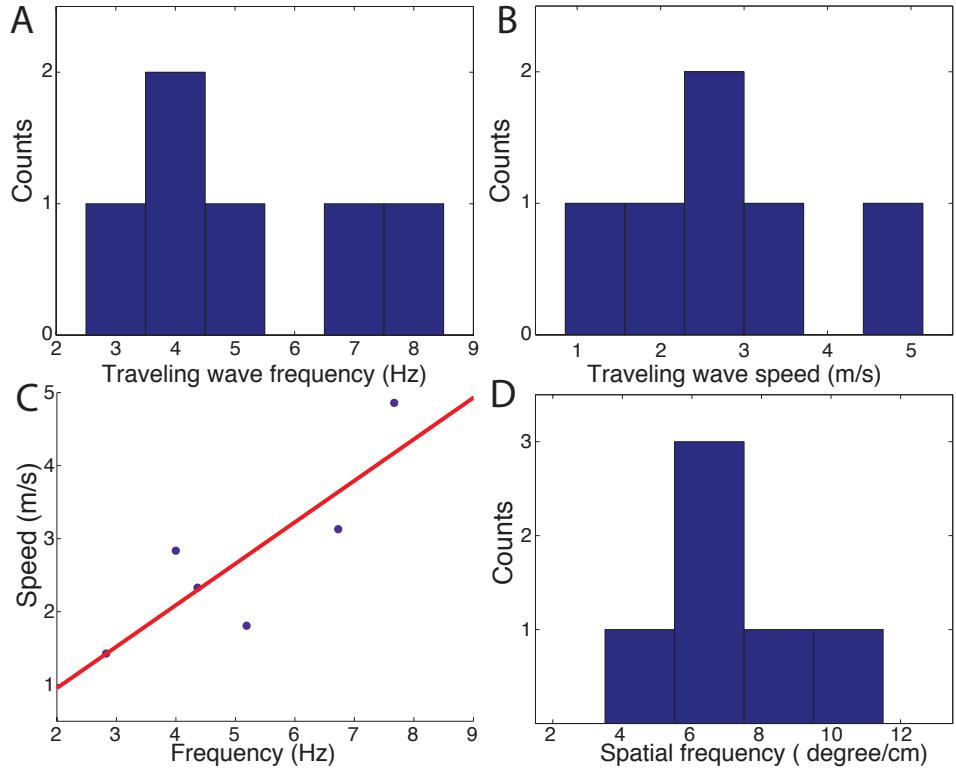


Figure 4: Population analysis of hippocampal traveling waves. **A.** Histogram of the frequency of each traveling theta wave. **B.** The speeds of traveling theta waves moving through the hippocampus. All waves travelled in a posterior-to-anterior direction. **C.** Scatter plot indicating the relation between traveling-wave frequency and speed. Red line indicates a best-fit regression line. **D.** Histogram of the spatial frequencies of hippocampal traveling theta waves.

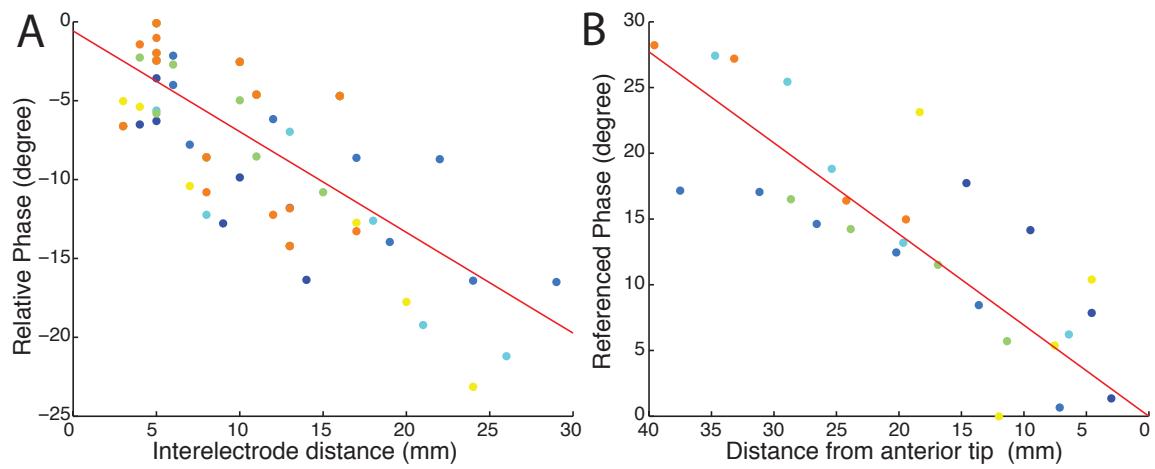


Figure 5: Analysis of relative theta phase across the hippocampus. **A.** Theta phase differences across all pairs of electrodes within each theta traveling wave. Each point depicts a single electrode pair, with color distinguishing electrodes from separate patients. The horizontal coordinate indicates the distance between the electrodes in the pair. The vertical coordinate indicates the phase differences observed for the theta oscillations at each electrode. Negative phases denote that theta phase progresses in a posterior-to-anterior direction. Red line denotes the best fit regression line. **B.** The normalized theta phase at each electrode where a traveling hippocampal theta wave was observed. Each point denotes one electrode. The horizontal coordinate indicates the electrode's distance to the anterior tip of hippocampus in Talairach space. The vertical coordinate indicates the electrode's estimated phase difference relative to the tip of the hippocampus (see *Materials & Methods*). Red line denotes the best fit regression line.

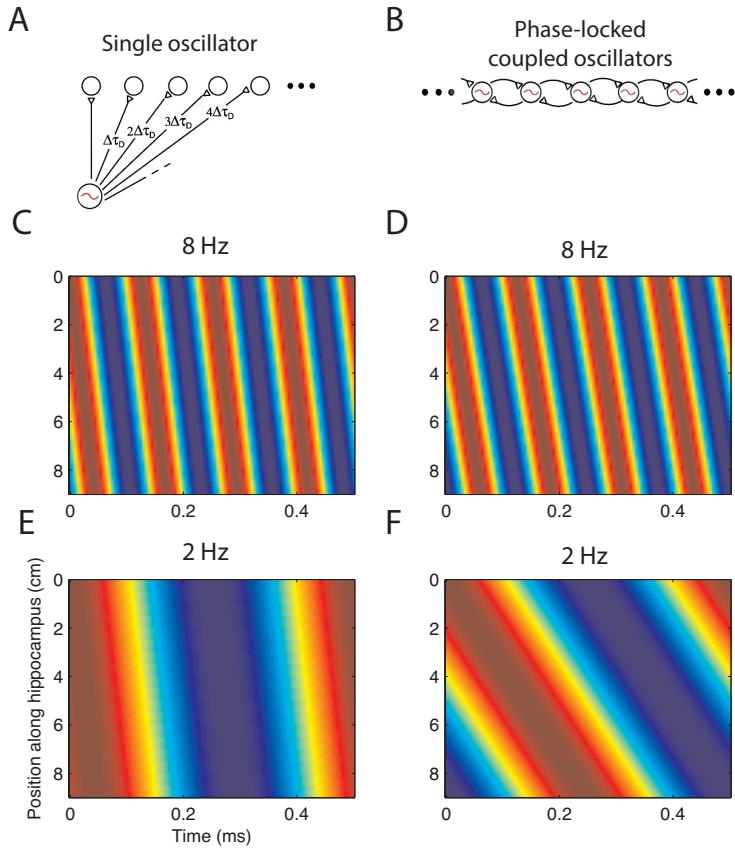


Figure 6: Models of traveling theta waves. **A.** Illustration of a single-oscillator model of theta traveling waves. According to this theory there is a single theta oscillator in the medial septum, which has projections along the length of the hippocampus. Each projection's synaptic delay ($x\Delta\tau_D$) is proportional to its length x , which produces the appearance of a traveling theta wave. **B.** Coupled oscillator model of theta propagation. According to this model there are a series of weakly coupled theta oscillators along the length of the hippocampus. Each oscillator has a particular connection weight and an intrinsic frequency. This model predicts that traveling waves appear in the hippocampus when an oscillation begins in the medial septum and gradually propagates through the hippocampus via a series of coupled oscillators. Figures from Panels A & B were obtained and modified with permission from Ermentrout and Kleinfeld (2001). **C.** Spatial propagation of a traveling theta wave at 8 Hz following a single oscillator model. Plot indicates theta phase as a color, plotted as a function of position along hippocampus and time. **D.** Spatial propagation of a traveling theta wave at 8 Hz following the coupled oscillator model. **E.** Spatial propagation of a 2-Hz traveling theta wave following the single-oscillator model. Here the speed of propagation (slope of colored lines) is the same as Panel C, demonstrating that speed is not frequency dependent. **F.** Spatial propagation of a 2-Hz traveling theta wave following the coupled oscillator model. Slope changes compared to Panel D demonstrates a change in the speed of theta's propagation.

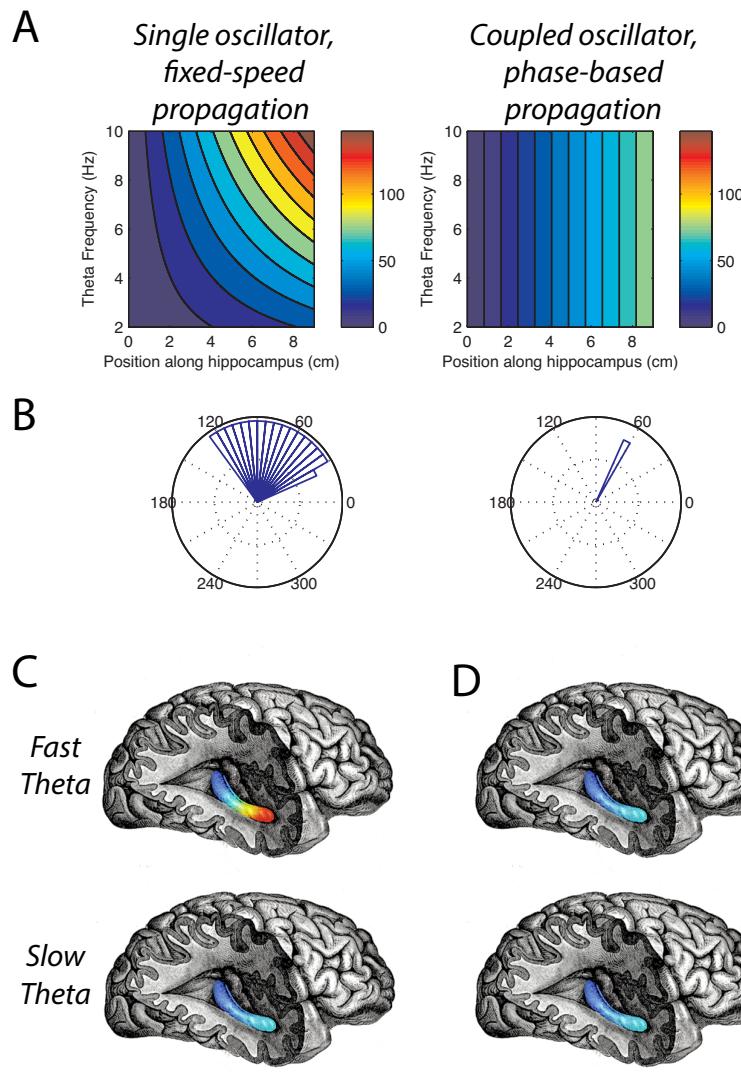


Figure 7: Models of hippocampal traveling waves predict different patterns of phase propagation. **A:** Depiction of how theta phase varies through the hippocampus as a function of position (horizontal axis) and theta's temporal frequency (vertical axis). Left panel depicts theta phase propagation under a single oscillator (SO) model, in which oscillations move at a fixed speed. Right panel depicts theta phase propagation based on a series of coupled oscillators (CO), in which the wave propagates based on phase delays. **B.** Circular histograms indicating the relative phase differences between two locations along the length of the hippocampus for theta oscillations with various temporal frequencies. Relative phase differences remain constant irrespective of theta frequency for the CO model (right panel) but not the SO model (left panel). **C.** Graphical illustration of theta phase across the hippocampus for the SO model. Color indicates the oscillation's instantaneous phase at each location for fast (top) and slow (bottom) theta oscillations. By comparing these plots across fast and slow theta it shows that the phase spread under the SO model is frequency dependent. **D.** Theta phase spread under the CO model for fast and slow theta oscillations, showing a constant rate of phase spread.