Gamma Oscillations in Rat Hippocampal Subregions Dentate Gyrus, CA3, CA1, and Subiculum Underlie Associative Memory Encoding

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Gamma Oscillations in Rat Hippocampal Subregions Dentate Gyrus, CA3, CA1, and Subiculum Underlie Associative Memory Encoding

Highlights

- Slow gamma activity characterized hippocampal LFPs when rats explored objects
- Slow gamma increase could not be explained by cessation of locomotion
- Slow gamma during familiar object exploration correlated with novelty
- Slow gamma during novel object exploration related to subsequent associative memory

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In Brief

Hippocampal local field potentials are modulated by both memory and behavior. Trimper et al. describe how these factors interact to influence the hippocampal network state and demonstrate that slow gamma activity in particular correlates with associative memory encoding.

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INTRODUCTION

Neuronal oscillations reflect rhythmic fluctuations of transmembrane ion currents summed across neurons (Buzsáki et al., 2012). This rhythmicity modulates the timing—and thus the efficacy—of synaptic transmission and synaptic plasticity (Huerta and Lisman, 1995; Hyman et al., 2003; Orr et al., 2001; Zarnadze et al., 2016), shaping interactions between populations of neurons within and across brain regions (Engel et al., 2001; Singer, 1999; Varela et al., 2001). Depending on the brain region, oscillatory activity often correlates with overt behaviors, such as reaching or locomotion (Ahmed and Mehta, 2012; MacKay and Mendonça, 1995), or with covert cognition, such as attention (Tiitinen et al., 1993; Tallon-Baudry et al., 1997; Fries et al., 2001; Jensen et al., 2007) or memory (Igarashi et al., 2014; Montgomery and Buzsáki, 2007; Jutras et al., 2009, 2013; Shirvalkar et al., 2010; Trimper et al., 2014). Much progress has been made in understanding how neuronal oscillations in sensory (Brovelli et al., 2004; Nicolelis et al., 1995), motor (Engel and Fries, 2010; MacKay and Mendonça, 1995), and cognitive (Herzmann et al., 2004; Colgin, 2016) systems relate to the respective functions of these systems by mediating well-timed interactions within and across neuronal networks. A major remaining challenge is to understand how multiple neuronal oscillations with differing cognitive and behavioral correlates can interact to determine the oscillatory network state of a brain region.

One brain region exhibiting oscillatory activity correlated with both cognition and overt behavior is the hippocampus. In particular, neuronal oscillations in the hippocampus relate closely to both memory and movement (Colgin, 2016, for review). For example, in the rodent hippocampus, local field potential (LFP) oscillations in the theta (6–10 Hz), slow gamma (30–55 Hz), and fast gamma (65–90 Hz) frequency ranges relate not only to memory performance but also to running speed outside of explicit memory tasks (Kemere et al., 2013; Siawiriska and Kasicki, 1998; Trimper et al., 2014; Winson, 1978; Zheng et al., 2016). Despite our good understanding of the relationship between hippocampal oscillations and locomotion, other important behaviors are underexplored. In semi-naturalistic settings, rats explore their environment in sporadic bursts of running, punctuated by frequent stops during which they often explore their surroundings, including the objects they would ordinarily encounter in real-world settings (Golani et al., 1993; Renner and Seltzer, 1991; Whishaw et al., 2006). However, little is known about the patterns of hippocampal oscillations during these moments of spontaneous exploration. This gap in knowledge about hippocampal oscillations during object exploration contrasts with the increasing use of spontaneous object recognition memory tasks in rodent studies (Clark and Squire, 2010) and with the widely held view of the mammalian hippocampus as being central to associating nonspatial items, such as objects, with spatial information, such as locations (e.g., Davachi, 2006; Knierim et al., 2006; Manns and Eichenbaum, 2006; Witter et al., 2000). Thus, an important question is how the patterns of oscillations in the hippocampus distinguish object exploration from other behaviors during spatial navigation and whether these oscillatory patterns relate to encoding object-location associative memories or more narrowly reflect the act of exploration.

SUMMARY

Neuronal oscillations in the rat hippocampus relate to both memory and locomotion, raising the question of how these cognitive and behavioral correlates interact to determine the oscillatory network state of this region. Here, rats freely locomoted while performing an object-location task designed to test hippocampus-dependent spatial associative memory. Rhythmic activity in theta, beta, slow gamma, and fast gamma frequency ranges were observed in both action potentials and local field potentials (LFPs) across four main hippocampal subregions. Several patterns of LFP oscillations corresponded to overt behavior (e.g., increased dentate gyrus-CA3 beta coherence during stationary moments and CA1-subiculum theta coherence during locomotion). In comparison, slow gamma (~40 Hz) oscillations throughout the hippocampus related most specifically to object-location associative memory encoding rather than overt behavior. The results help to untangle how hippocampal oscillations relate to both memory and motion and single out slow gamma oscillations as a distinguishing correlate of spatial associative memory.

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To address this broad question, we recorded neuronal activity from the hippocampus as rats were tested for object-location associative memory while freely locomoting on a circular track. The specific questions were (1) whether patterns of hippocampal oscillations during exploration of objects would reflect more than the cessation of locomotion, and if so, (2) the extent to which these oscillations would correspond to memory for the object encounters rather than simply reflecting the act of exploration. We recorded spiking and LFPs from the principal cell layers of four major subregions of the hippocampus: dentate gyrus (DG), CA3, CA1, and subiculum. The goal in recording from all four regions simultaneously was to measure the functional dynamics of the local circuitry and assess potential heterogeneity across regions in terms of correlates with cognition and behavior. For example, by one view, dentate gyrus and CA3 are hypothesized to be particularly important for associative memory encoding, whereas CA1 and subiculum may be of greater importance for resolving discrepancies between internal and external representations in service of environmental navigation (Kesner and Rolls, 2015).

The results showed that the pattern of oscillatory activity across these four subregions clearly distinguished overt behaviors, differing prominently among moments of object exploration, stationary moments, and periods of locomotion. Moreover, when the pattern of oscillatory activity was contrasted across memory conditions during the single behavioral state of object exploration, slow gamma power and region-region coherence distinguished between exploring novel, repeated, and repositioned objects and, during exploration of novel objects, related to whether the rat would subsequently show good object-location associative memory. The results highlight the intersection of memory and locomotion in determining the oscillatory network state of the hippocampus and offer insights as to how oscillatory signatures of both behavior and cognition interact within a single brain region. The results also reveal that slow gamma oscillations across the major hippocampal subregions mark an oscillatory network state of effective associative memory encoding.

RESULTS

To ask how hippocampal network activity related to both memory and overt behavior, action potentials and LFPs were recorded simultaneously from DG, CA3, CA1, and subiculum in six rats as the animals performed a novel object recognition memory task that probed the rats’ memory for objects and objects’ locations. Figure 1 shows LFP recording sites in each of the four subregions in six rats, as well as example LFPs recorded from each of these four subregions during the approach and exploration of novel objects. The intra-hippocampal connectivity among DG, CA3, CA1, and subiculum is serial (Amaral and Witter, 1989); thus, a key initial question was how the oscillatory amplitude and synchrony between LFPs of connected subregions changed as rats engaged in object exploration behavior. Accordingly, Figure 1 also shows power and coherence during object approach and exploration (mean number of object encounters ± SEM across rats = 50.8 ± 8.6 events) across a range of frequencies between LFPs from connected regions (DG-CA3, CA3-CA1, and CA1-subiculum). Large increases in slow gamma coherence between DG and CA3 and between CA3 and CA1 were apparent during novel object exploration. Increases in slow gamma power during object exploration relative to the pre-exploration approach period were also visible in these regions. A main question of the present study was the extent to which this pattern of intra-hippocampal oscillatory synchrony reflected memory for the object encounters or simply the act of object exploration. However, because hippocampal activity was well known to be modulated by voluntary locomotion (Whishaw and Vanderwolf, 1973), a preliminary question was whether the pattern of oscillatory interactions observed reflected object exploration or just the cessation of locomotion.

Novel Object Exploration Elicited a Distinct Hippocampal Oscillatory State

As shown in Figure S1 for DG, CA3, CA1, and subiculum (and in previous reports for subsets of these subregions, e.g., Ahmed and Mehta, 2012; Kemere et al., 2013; Zheng et al., 2015), the frequency and amplitude of hippocampal LFPs—in theta, slow gamma, and fast gamma ranges—were strongly influenced by rats’ speed of locomotion. Slow gamma power was at its relative highest across movement speeds in DG, CA3, and CA1 when rats were stationary. Thus, a possible explanation for the slow gamma coherence increase observed between DG and CA3 and between CA3 and CA1 (as well as power increases within those regions) during object exploration was that the rats stopped locomoting.

To assess this possibility, power and coherence were calculated for hippocampal LFPs during novel object exploration events (mean number of events ± SEM across rats = 50.8 ± 8.6), stationary moments when the rat was not exploring objects (78.7 ± 26.5), locomotion as a rat approached novel objects (50.8 ± 8.6), and locomotion not close in time to object exploration (168.2 ± 18.9) (see Experimental Procedures for details on how these epochs were defined, and see Figure S1 for confirmation that average speed of movement differed across these four behavioral states). Figure 2 shows subregional power and coherence across the four behavioral conditions (approach, exploration, stationary, and running). The results are also shown after subtracting the grand mean across behavioral conditions to highlight better the similarities and dissimilarities between conditions in a manner that paralleled the statistical testing. Specifically, differences in spectral measures between conditions were evaluated by an ANOVA-based statistical approach that tested whether data from at least one condition differed from the grand mean. Table S1 provides the accompanying statistics for each significant frequency range (frequency cluster) derived from a cluster-based random permutation approach (see Experimental Procedures for details of analyses). Figure S2 reproduces the data displayed in Figure 2 but includes only frequencies below 20 Hz to enhance visualization of differences in this lower frequency range. The results show that hippocampal oscillatory activity during object exploration differed markedly from hippocampal activity during locomotion and, importantly, from hippocampal activity during stationary moments. This latter finding indicates that the hippocampal oscillatory network state during object exploration...
could not be accounted for merely as a reduction in locomotive speed, instead supporting the idea that hippocampal subregions were engaged in a unique pattern of oscillatory activity that was specific to object exploration.

In particular, object exploration was distinguished from the other behavioral conditions by especially prominent slow gamma (30–55 Hz) and fast gamma (65–90 Hz) power in DG, CA3, and CA1, consistent with a previous report (Trimper et al., 2014). Stationary moments were distinguished by relatively high beta (13–25 Hz) power in DG and CA3, as well as relative decreases in fast gamma power in CA1 and subiculum and in theta power in all four subregions. The oscillatory patterns associated with stationary moments were consistent with previous studies that reported changes associated with cessation of locomotion (Ahmed and Mehta, 2012; Kemere et al., 2013; Zheng et al., 2015), though Rangel et al. (2015) observed increases in DG beta only when cessation of locomotion occurred at behaviorally relevant loca-

Figure 1. Slow Gamma Coherence Increased while Rats Explored Novel Objects

(A) Illustration of the serial connections of the hippocampal subregions (DG, CA3, CA1, and SUB [subiculum]), as well as its connections with the entorhinal cortex (EC).

(B) Coronal hippocampal section showing LFP recording locations (circles) for each rat (different colors) in each of the four targeted subregions.

(C) Example LFP data as a rat approached (<0 s) and explored (>0 s) a novel object.

(D) Moving window spectrograms for each hippocampal subregion time-locked to the initiation of novel object exploration (0 s). Minimum and maximum power values in decibels are noted on each spectrogram.

(E) Moving window coherograms for each pair of directly connected hippocampal subregions time-locked to the initiation of novel object exploration (0 s). Minimum and maximum coherence values are noted on each coherogram. Increased coherence and power in the slow gamma range were apparent for DG/CA3 and CA3/CA1 during exploration relative to approach.

The two conditions involving locomotion (i.e., approaching an object or running on a track with no object present) were similar to each other and were distinguished from the other conditions by lower levels of (and perhaps somewhat lower-frequency) slow gamma power (relative to object exploration), particularly in DG and CA3, and by high levels of theta power, particularly in CA1 and subiculum. In addition to power, LFP synchrony between connected hippocampal regions, as measured with coherence, also distinguished object exploration from the other behavioral conditions. Object exploration was associated primarily with large relative increases in slow gamma coherence between DG and CA3 and between CA3 and CA1. Stationary moments were associated with relatively high beta coherence between DG and CA3. Theta coherence between CA1 and subiculum was similarly high for both locomotive states relative to the other two behavioral conditions. Thus, distinct overt behaviors were associated with markedly different patterns of oscillatory activity throughout the hippocampal subregions, and the pattern of activity observed during object exploration—namely, prominent slow gamma in DG and CA3, and CA1—could not be accounted for merely as the product of locomotive speed.

Theta, slow gamma, and fast gamma oscillations were prominent in the hippocampal LFPs recorded in the present study, and prior studies of hippocampal oscillations have observed that the amplitude of gamma oscillations can be modulated by the phase of theta oscillations (e.g., Tort et al., 2009; Trimper et al., 2014). We therefore next asked whether the magnitude of the theta-phase modulation of slow gamma or fast gamma
Figure 2. Object Exploration Was Accompanied by a Distinct Spectral Profile

(A) Illustration of the four behavioral states analyzed.
(B) Top: spectral power for each hippocampal subregion (and averaged across subregions) for each behavioral state. Bottom: spectral power plotted as the difference from average across behavioral states.
(C) Top: coherence for each directly connected pair of hippocampal subregions (and averaged across subregion pairs). Bottom: coherence plotted as the difference from average across behavioral states.

Throughout the figure, gray rectangles mark frequency ranges exhibiting significant interactions between behavioral state and subregion. Black horizontal lines bookended by dagger symbols (†) indicate frequency ranges differing significantly (p < 0.05) across behavioral states, and those bookended by asterisks indicate significant differences after Bonferroni correction for multiple comparisons (here, 5 for power and 4 for coherence). Colored lines indicate mean (darker shading) ± SEM (lighter shading). See also Figures S1–S3.
amplitude differed between behavioral conditions in DG, CA3, CA1, or subiculum. The magnitude theta-phase modulation was calculated separately for slow gamma and fast gamma as a modulation index based on the LFP in each region as described previously (e.g., Tort et al., 2009). Figure S3 shows the results as mean modulation indices across rats for each region and for each behavioral condition. The amplitudes of both slow gamma and fast gamma were modulated by the phase of theta oscillations in DG, CA3, CA1, and subiculum, but the modulation indices in each region were similar across behavioral conditions (exploration, stationary, run, and approach). Specifically, one-way ANOVAs for slow gamma and for fast gamma within each region observed no main effects of behavioral condition differences in average locomotion speed. When rats stopped to explore objects compared to when rats simply stopped, gamma power and coherence, particularly slow gamma in DG and CA3, were markedly and significantly higher (see Table S2 for detailed statistics). The amount of head movement during object exploration was somewhat greater than during stationary moments (Figure 3A), further indicating that the increased slow gamma power and coherence during exploration were not simply related to the negative correlation between movement speed and slow gamma power (e.g., Figure S1). Fast gamma power in all subregions and fast gamma coherence between CA3 and CA1 were also revealed to increase significantly during object exploration. However, these fast gamma differences could
potentially be accounted for by locomotive speed differences. Altogether, these results indicate that the pattern of hippocampal LFP activity during object exploration represents a distinct network state and demonstrate that the high levels of slow gamma oscillations reflect more than the cessation of locomotion.

**Hippocampal Spike Timing Was Modulated by Oscillations**

An important component of oscillatory analyses is the demonstration of spiking modulation by rhythmic LFP activity, which would indicate that oscillations in LFPs were attributable to local circuits and could not instead be attributed to volume conduction from distal sources (Buzsáki et al., 2012). Therefore, to assess the extent to which oscillations in hippocampal LFPs modulated spike timing within and between subregions, action potentials from principal neurons in each subregion were compared to simultaneously recorded LFPs in each region (e.g., DG spikes and DG LFPs), as well as to simultaneously recorded LFPs in downstream connected regions (e.g., DG spikes and CA3 LFPs). Across the entire recording session, regardless of behavioral state, the overall trend was that spike timing for a substantial portion of neurons in all four subregions (Table S3) was significantly phase aligned to multiple oscillatory ranges (theta, beta, slow gamma, and/or fast gamma), both in the same subregion (Figure 4) and in the immediate downstream region (Figure S4). Only neurons firing at least 50 action potentials when oscillatory power was strong were considered to address the possibility that spike-phase relationships could be obscured by including spikes in the analyses when oscillations were not prominent. The analysis was conducted separately for each frequency range (theta, beta, slow gamma, and fast gamma). The results indicated that the timing of action potentials of principal neurons of the hippocampus were modulated by oscillations in each frequency range but that the extent of modulation depended on the specific range and hippocampal subregion. In addition, the phase at which spiking tended to align with the oscillations varied across different subregions and frequency bands.
occur relative to oscillations in the LFP depended on the specific frequency range and hippocampal subregion (Figures 4 and S4). In particular, action potentials of significantly phase-modulated principal cells in DG and CA3 were both more likely to be aligned to the peak of local slow gamma oscillations yet both more likely to be aligned to the trough of local fast gamma oscillations (Watson-Williams F test of phases for slow gamma versus fast gamma; DG: F(1,47) = 76.35, p < 0.0001; CA3: F(1,137) = 318.5, p < 0.0001). More broadly, the findings suggest that the LFP oscillations reflect physiologically relevant signals in the hippocampus.

In comparison to LFP oscillations, hippocampal spiking activity as measured by either firing rates (Figure S5) or spike-phase timing (Figures 4 and S4) only modestly distinguished behavioral states, perhaps reflecting an advantage for LFPs in summing activity across many neurons to assess network states (Buzsáki et al., 2012). In particular, a significant difference in firing rate across behaviors, after Bonferroni alpha correction for four subregions, was revealed in CA1 (n = 266, F(3,795) = 18.65, p = 0.0001, partial eta2 = 0.066) and DG (n = 40, F(3,117) = 4.356, p = 0.006, partial eta2 = 0.066), but not in CA3 (n = 124, F(3,369) = 2.63, p = 0.081, partial eta2 = 0.0181) or subiculum (n = 39, F(3,114) = 0.721, p = 0.542, partial eta2 = 0.019). Modestly higher CA1 pyramidal neuron firing rates were associated with locomotion, consistent with previous reports (e.g., Ahmed and Mehta, 2012; Zheng et al., 2015), whereas putative DG granule cells preferably fired during exploration relative to other behavioral states.

In terms of spike-phase timing, low hippocampal firing rates overall (mean hertz ± SEM: DG = 0.79 ± 0.12, CA3 = 0.63 ± 0.07, CA1 = 0.87 ± 0.45, subiculum [SUB] = 1.09 ± 0.12) prevented analyses regarding differences in spike timing across behavioral conditions for ranges other than the theta range, because spike-phase modulation by transient or nonstationary rhythms can be assessed only when spikes are present and oscillatory bouts are pre-selected to be strong to avoid spurious results (Colgin et al., 2009). These analyses of spike to theta phase modulation by behavioral state (Figure S5) revealed no significant differences in terms of the number of significantly phase-modulated neurons across states, at least not after Bonferroni correction for four subregions (DG: χ2(3) = 5.946; CA3: χ2(3) = 8.682, p = 0.035; CA1(3): χ2(3) = 0.316, p = 0.345; SUB: χ2(3) = 4.110, p = 0.250), but did show a significant increase in the strength of theta phase alignment (i.e., pairwise phase consistency) (Vincik et al., 2010) for locomotive relative to nonlocomotive states for DG (F(3,53) = 7.02, p < 0.001, partial eta2 = 0.397). Thus, spiking in all hippocampal regions was modulated by oscillations in all four oscillatory ranges (Figure 4), but analytical constraints permitted assessment of spike-phase differences between behavioral conditions for only the theta range. As a result, subsequent analyses focused on whether oscillations in LFPs across subregions of the hippocampus during object exploration reflected memory for the encounters or just the behavioral state of exploration, an approach that revealed marked oscillatory differences during object exploration (Figures 1, 2, and 3) and that was not limited by the analytical constraints that pertained to spiking.

### Hippocampal Slow Gamma Oscillations during Object Exploration Distinguished Memory Conditions in an Object-Location Associative Memory Task

A main question of the present study was whether patterns of hippocampal oscillations would correspond to associative memory for the object encounters. Figure 5 shows a schematic of and behavior results from the object-location recognition memory task, which involved up to 24 trials per session of rats completing triplets of clockwise laps on a circle track and spontaneously exploring novel objects, objects repeated in the same location, and objects repeated in swapped locations. Rats exhibit a well-known preference for novelty (Ennaceur and Delacour, 1988); thus, a reduction in exploration time across successive encounters with a stimulus can be interpreted as rats remembering the stimulus. Rats showed a large and significant reduction in exploration duration (t(5) = 4.50, p = 0.006, Cohen’s d = 1.836) when novel objects from lap 1 were encountered again in the same locations on lap 2 (mean number of events ± SEM across rats = 87.0 ± 10.1), which indicated memory for at least the object identities. To ask whether the rats also remembered the specific locations of the objects, on some trials, the objects were repeated again in swapped locations on lap 3. Rats explored these swapped objects (mean number of events ± SEM across rats = 80.7 ± 5.6) for a different amount of time than repeated (20.3 ± 1.4 events) or novel objects (n = 20.3 ± 1.4 events) in control conditions (F(2,10) = 10.93, p = 0.003, partial eta2 = 0.686). Specifically, rats explored swapped objects for a longer duration than objects repeated in the same location (t(5) = 3.45, p = 0.018, d = 1.41) but less than novel objects on lap 3 (t(5) = 3.20, p = 0.024, d = 1.30), indicating that rats had memory for the prior locations of objects, similar to previous reports (e.g., Save et al., 1992).

To ask whether hippocampal oscillations might differ by memory condition, power and coherence across subregions were calculated during the first second of lap 3 object exploration of repeated, novel, and swapped objects lasting at least 1 s, when overt movement was similar (Figure S1). A window of 1 s, rather than a longer duration (e.g., 2 s), was selected to permit inclusion of a number of events from each condition in the analyses (mean number of events ± SEM across rats = 10.0 ± 1.1, 4.2 ± 0.9, and 27.8 ± 4.9 for novel objects, repeated objects, and swapped objects on lap 3, respectively). Figure 6 shows the results across frequency ranges as differences from the grand mean across conditions to highlight the comparisons of interest (see Table S4 for detailed statistics; see Figure S6 for figures that include individual data points for each rat). Slow gamma power in DG and CA3 differed markedly across the three memory conditions, in both cases being at its relative highest during exploration of novel objects, its relative lowest during exploration of repeated objects, and at an intermediate level during exploration of swapped objects. Based on the overall prominence of hippocampal gamma oscillations during object exploration (e.g., Figure 2), power in each subregion was also averaged and plotted separately in the slow gamma range and fast gamma range as normalized differences across the three memory conditions. Statistically significant linear trends (novel > swap > repeat) were observed for overall average hippocampal slow gamma power (F(1,5) = 15.60, p = 0.011,
partial $\eta^2 = 0.757$) and specifically for DG slow gamma power ($F(1,5) = 28.46$, $p = 0.003$, partial $\eta^2 = 0.851$) and CA3 slow gamma power ($F(1,5) = 16.80$, $p = 0.009$, partial $\eta^2 = 0.771$), whereas no significant differences were observed for any contrast in the fast gamma range (see Figure 6 and Table S5 for statistical details).

Compared to the results for power, coherence between connected hippocampal subregions showed relatively small differences across memory conditions, at least when plotted across a range of frequencies (Figure 6). However, when coherence between subregions was averaged across the slow gamma range, statistically significant linear trends (novel > swap > repeat) were observed for overall hippocampal slow gamma coherence ($F(1,5) = 11.85$, $p = 0.018$, partial $\eta^2 = 0.703$), as well as specifically for the slow gamma coherence between CA1 and subiculum ($F(1,5) = 6.70$, $p = 0.046$, partial $\eta^2 = 0.583$). To ask whether these results for coherence could be explained by simultaneous but undirected increases in slow gamma power (e.g. because of volume conduction) the non-normalized directed transfer function (DTF) was calculated and plotted for oscillatory interactions between hippocampal subregions for the three memory conditions. DTF is a directional autoregressive metric (similar to Granger causality in the frequency domain) that discounts zero-lag phase relationships and instead reflects the predictiveness of oscillations in one region for oscillations of the same frequency in another region (Kaminski and Blinowska, 1991). Statistically significant linear trends (novel > swap > repeat) were observed for overall hippocampal slow gamma DTF ($F(1,5) = 19.01$, $p = 0.007$, partial $\eta^2 = 0.795$), as well as specifically for the DTF between DG and CA3 ($F(1,5) = 8.01$, $p = 0.037$, partial $\eta^2 = 0.616$). No significant differences between memory conditions were observed in the fast gamma range for power, coherence, or DTF (zero of thirteen linear contrasts in Figures 6C–6E; see Table S5 for detailed statistics). In contrast, seven of the thirteen linear contrasts for slow gamma power, coherence, and DTF (Figures 6C–6E) were statistically significant, a proportion higher than one would expect by chance with an alpha level of 0.05 (see Figure 6 for clarification of alpha corrections for multiple comparisons).

Thus, the results demonstrated increased slow gamma activity in a subset of hippocampal subregions correlated with the
degree of novelty associated with the lap 3 object presentations. In particular, novel objects were associated with the largest slow gamma amplitude, synchrony, and predictiveness. In comparison, repeated objects in novel locations were associated with the second-highest levels, and repeated objects in repeated locations were associated with the lowest levels. These results support a role for hippocampal slow gamma oscillations in the encoding of novel associative recognition memories for objects and their locations.

Hippocampal Slow Gamma Oscillations during Exploration of Novel Objects Related to Subsequent Memory for Objects and Locations

The pattern of slow gamma differences observed during the lap 3 test of object-location associative memory (novel > swap > repeat) suggested that the degree of slow gamma might have been inversely related to the amount of information repeated from the initial object presentation and thus perhaps positively related to the amount of new encoding at the time of the test. To ask more directly whether hippocampal oscillations would reflect memory encoding, LFPs recorded during lap 1 novel object exploration were split into three subsequent memory conditions based on whether, on laps 2 and 3, the rats showed good memory for both the object and its location (object+location); good memory for the object, but not its location (object); or poor memory for both aspects of the initial encounter (poor). Figure 5 illustrates how the memory conditions were defined and shows performance split by the three subsequent memory conditions. Rats did not decrease their exploration times from lap 1 to lap 2 for the poor memory condition (t(5) = 0.296, p = 0.779, d = 0.121) but decreased their exploration times from lap 1 to lap 2 similarly for object+location (83% reduction; t(5) = 21.857, p < 0.0001, d = 8.923) and object (85% reduction; t(5) = 51.627, p < 0.0001, d = 21.08) memory conditions. On lap 3, rats significantly increased their exploration times for the object+location condition (lap 2 to lap 3 percentage increase = 341%; t(5) = -3.425, p = 0.019, d = 1.398) but did not do so for the object memory condition (lap 2 to lap 3 percentage increase = 152%; t(5) = 1.193, p = 0.278, d = 0.778).
decrease = 5%; \( t(5) = 0.304, p = 0.773, d = 0.124 \). Thus, the behavioral results validated the partitioning of the events into poor, object, and object+location conditions.

Figure 7 shows differences during the initial 1.5 s of novel object exploration between subsequent memory conditions for power, coherence, and DTF across hippocampal subregions (see Tables S6 and S7 for detailed statistics; see Figure S7 for figures that include individual data points for each rat). A 1.5 s window was used rather than a 2 s window to permit inclusion of enough events in each memory condition (mean number of events ± SEM across rats = 8.5 ± 1.6, 21.5 ± 3.7, and 8.8 ± 2.1 for object+location, object, and poor memory conditions, respectively). Similar to the results for the lap 3 memory test, the subsequent memory contrasts highlighted the slow gamma range. More specifically, average power in the slow gamma range in DG and CA3 differed mark-

edly and statistically significantly across the three memory conditions. For both subregions, slow gamma power was at its relative highest during exploration of novel objects for which both the object and the location were subsequently remembered, its relative lowest during exploration of novel object encounters that were poorly remembered, and at an intermediate level during exploration of novel objects for which the object identity, but not the location, was remembered (linear trend; DG: \( F(1,5) = 11.64, p = 0.019, \) partial \( \eta^2 = 0.699 \); CA3: \( F(1,5) = 6.835, p = 0.047, \) partial \( \eta^2 = 0.578 \); overall hippocampus mean: \( F(1,5) = 6.835, p = 0.047 \)). This same pattern (object+location > object > poor) was also present in DG-CA3 coherence (\( F(1,5) = 40.294, p = 0.001, \) partial \( \eta^2 = 0.762 \)) and overall hippocampal coherence (\( F(1,5) = 14.410, p = 0.013, \) partial \( \eta^2 = 0.742 \)). The pattern was similar for DTF, although in this case the differences did not reach statistical significance (all ps > 0.142). In comparison, for the fast gamma range, the trends for power, coherence, and DTF were less consistent and were statistically significant for only CA3-CA1 coherence (\( F(1,5) = 15.981, p = 0.010, \) partial \( \eta^2 = 0.762 \)). Altogether, five of the thirteen linear contrasts for slow gamma power, coherence, and DTF were statistically significant.
significant, a proportion higher than one would expect by chance with an alpha level of 0.05 (Figures 7C–7E).

Thus, combined with the previous results from the lap 3 memory test, the results from lap 1 novel object exploration indicated that the patterns of oscillations in the hippocampus, particularly in the slow gamma range, clearly distinguished moments when the rats were similarly engaged in the behavior of object exploration based on inferred differences in subsequent memory content and quality. In particular, the amount or success of memory encoding during an object-location associative memory task appeared to be reflected in the general prominence of intra-hippocampal slow gamma oscillatory interactions.

DISCUSSION

In the present work, we asked whether the patterns of hippocampal oscillations during object exploration in an object-location associative memory task corresponded best to (1) cessation of locomotion, (2) the act of object exploration, or (3) memory for the object encounters. Results indicated that the overall pattern of hippocampal theta, beta, slow gamma, and fast gamma oscillations across DG, CA3, CA1, and subiculum were influenced by all three variables. However, during object exploration, slow gamma oscillations in particular related most specifically to associative memory for the object encounters. Hippocampal LFPs during object exploration were marked by prominent slow gamma oscillations, for which the strength and degree of intra-hippocampal synchrony related to subsequent spatial associative memory for the objects and, likewise, differentiated among bouts of exploring novel, repeated, and relocated objects. These patterns of slow gamma oscillations differed starkly from those observed during both locomotion and stationary moments. The memory effects on slow gamma oscillations were not limited to oscillatory power in a single hippocampal subregion or to coherence in any one region-region interaction but instead appeared to reflect an increased prevalence of slow gamma oscillations throughout the hippocampus (although not uniformly) during associative memory encoding. Thus, the overall pattern of oscillatory activity in the hippocampus distinguished object exploration as a unique network state, and the specific pattern of hippocampal slow gamma oscillations reflected associative memory for the encounters rather than solely the act of exploration.

One interpretation of the current results is that slow gamma oscillations related specifically to associative encoding of object-location memory in the hippocampus, whereas the other patterns of oscillations, particularly theta, reflected more global interactions between the hippocampus and other brain regions in support of integrating nonmemory processes. Previous studies have highlighted slow gamma oscillations in the hippocampus as an indicator of intra-hippocampal synchrony (Colgin et al., 2009; Colgin and Moser, 2010), and a number of studies have highlighted the importance of the hippocampus for spatial associative memory (e.g., Eichenbaum et al., 1999; Komorowski et al., 2009; Tort et al., 2009). In line with these results, prominent intra-hippocampal slow gamma oscillations during exploration of novel objects related to good subsequent memory for both the object and its location and, at test, correlated with the degree of object or location novelty. Oscillations in other frequency ranges were better explained by differences in overt behavior. Theta oscillations are believed to emerge from, and in turn support, interactions between the hippocampus and many other brain regions (Buzsáki, 2002; Colgin, 2016), and theta rhythms within the hippocampal formation are well known to be strongly modulated by locomotive speed (Bender et al., 2015; King et al., 1998; Stawinska and Kasicki, 1998; Whishaw and Vanderwolf, 1973).

The idea offered here is not that theta and slow gamma oscillations in the hippocampus relate narrowly or universally, for example, to locomotion and associative memory encoding, respectively. Numerous past studies have linked hippocampal theta oscillations and memory performance, for example, during spatial navigation (Belchior et al., 2014; McNaughton et al., 2006; Siegle and Wilson, 2014; Wang et al., 2015; Winson, 1978), and in the current report, we replicate a clear (inverse) relationship between locomotion and slow gamma oscillations in the rat hippocampus. Furthermore, others have previously made the case that slow gamma oscillations in the hippocampus correspond to memory retrieval processes rather than encoding processes (Colgin et al., 2009; Colgin and Moser, 2010). Instead, the view advanced here is that memory states intersect with behavioral states to shape the oscillatory dynamics of the hippocampus. By this view, during encounters with novel objects—and against the backdrop of oscillations corresponding to that behavioral state—slow gamma oscillations could coordinate spike timing and synaptic plasticity between subregions of the hippocampus in support of associating those objects in memory with the location in which it was encountered as the rats navigated and explored the entire testing apparatus.

More broadly, the current findings highlight the importance of considering object exploration as something more than the cessation of locomotion and how memory for this behavior would be supported by the hippocampus. Many have emphasized the confluence of spatial and nonspatial inputs in the mammalian hippocampus (Knierim et al., 2006; Mano and Eichenbaum, 2006; Witter et al., 2000) and have suggested that it may be particularly important for remembering nonspatial items in a spatial context, such as remembering an object encountered in a particular location (Burgess et al., 2002; Kesner et al., 2004; Jarrard, 1993; Malkova and Mishkin, 2003). Moving forward, additional work will be needed to understand how oscillatory interactions between the hippocampus and other brain regions mediate local and global neural processes needed to negotiate bilaterally between making memories during action and acting on retrieved memories. In this avenue, study of oscillations in the hippocampus can reveal more broadly how action and cognition can combine to shape network dynamics in the brain.

EXPERIMENTAL PROCEDURES

Subjects

Subjects were six male Long-Evans rats aged 6 to 12 months, individually housed (12 hr light/dark cycle, testing during light phase) with free access to water. Rats were placed on a restricted diet such that the animals maintained at least 90% of their free-feeding weight (~400 g). All procedures involving rats were approved by the Institutional Animal Care and Use Committee at Emory.
University. The Supplemental Experimental Procedures contain additional details for procedures described here.

Behavioral Task and Analyses
Figure 5 shows a schematic of the behavioral task. Each trial consisted of a single lap around the track with no objects present followed by three laps with objects present in the 10 o’clock and 2 o’clock positions, relative to the inner stem of the track at 6 o’clock. On the first object lap (lap 1), rats encountered two novel objects. On lap 2, rats encountered duplicates of the same objects from lap 1 in the same positions. On lap 3, rats encountered one of two new object configurations. Either one object was replaced with a duplicate in the same location (repeat) while the other was replaced with a novel object (novel), or the two objects were repeated again but in swapped locations (swap). Rats performed up to 72 trials across up to 5 days of testing, with up to 24 trials on a single day. Sessions were recorded using a digital video camera (30 frames/s), and the rat’s head location was recorded for each frame. This frame-by-frame location information was combined with manual coding of object exploration events to define epochs of exploration, stationary moments, and periods of locomotion across a range of movement speeds.

The behavioral data were also used to partition lap 1 exploration events by subsequent memory (Figure 5). Specifically, lap 1 object encounters lasting at least 1.5 s were sorted into memory conditions by subsequent exploration times on laps 2 and 3. Objects for which rats reduced their exploration duration from lap 1 to lap 2 by less than 50% were assigned to the poor memory condition. Objects for which rats reduced their exploration from lap 1 to lap 2 by at least 50% and then explored that object more than repeated objects on lap 3 when it swapped locations were assigned to the object+location memory condition. If rats reduced their exploration of an object from lap 1 to lap 2 by at least 50%, but then explored the object on lap 3 less than their average exploration time for repeat objects, the object was assigned to the object memory condition. Lap 3 exploration was compared to the average exploration duration for repeat objects based on the idea that the lap 3 repeat exploration duration would, on average, represent a combination of object+location memories and object memories.

Surgical Implantation of Tetrodes and Data Acquisition
Sterile-tip surgery was conducted under isoflurane anesthesia to implant chronic recording tetrodes, which were subsequently positioned in the principal cell layers of DG, CA3, CA1, and subiculum subregions of the dorsal hippocampus in one hemisphere. LFPs were recorded continuously (sampling rate = 1,500 Hz, bandpass filter = 1–400 Hz). Spiking data were recorded (sampling rate = 50,000 Hz, bandpass = 600–6,000 Hz) for putative action potentials that surpassed a user-defined amplitude threshold. Action potentials recorded on the same tetrode were later manually separated into distinct units by plotting several waveform characteristics across the four wires (e.g., peak spike amplitude, waveform shape as reflected in principal-component analysis) using Offline Sorter (Plexon).

Neural Data Analyses
LFP Analyses
Spectral analyses implemented a multitaper fast Fourier transform method for calculating coherence and power (Bokil et al., 2010). Evaluation of statistically significant differences across conditions and subregions or subregion pairs in spectral measures by frequency was performed using a cluster-based permutation approach similar to that described previously (Maris and Oostenveld, 2007) but adapted here to calculate F statistics (ANOVA) for more than a single independent variable and more than two levels of each variable. Nonnormalized directed transfer function, also referred to as the transfer matrix (H), was calculated as the inverse of the fast Fourier-transformed multivariate autoregressive coefficient matrix (Kaminski and Blinowska, 1991).

Spiking Analyses
For all spiking analyses, only putative pyramidal neurons (n = 448, 424, and 59 for CA3, CA1, and subiculum, respectively) or granule neurons (n = 104 for DG) emitting at least 50 spikes across conditions were considered. Spike-LFP phase analyses were based on procedures in prior reports (Colgin et al., 2009; Mizuseki et al., 2012). In addition, strength of phase modulation was assessed with pairwise phase consistency (Vinck et al., 2010), which quantifies the consistency of angular phase preference for each possible pair of action potentials, thus avoiding the bias associated with mean resultant length.

SUPPLEMENTAL INFORMATION
Supplemental information includes Supplemental Experimental Procedures, seven figures, and seven tables and can be found with this article online at https://doi.org/10.1016/j.celrep.2017.10.123.

AUTHOR CONTRIBUTIONS
J.B.T. and J.R.M. designed experiments and analyses. J.B.T. conducted experiments and analyses. C.R.G. and K.M. assisted with data collection. A.C.J. and K.M. assisted with data processing. J.B.T. and J.R.M. wrote the manuscript.

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REFERENCES
Ahmed, O.J., and Mehta, M.R. (2012). Running speed alters the frequency of hippocampal gamma oscillations. J. Neurosci. 32, 7373–7383.
Amaral, D.G., and Witter, M.P. (1989). The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience 31, 571–591.
Belchior, H., Lopes-Dos-Santos, V., Tort, A.B., and Ribeiro, S. (2014). Increase in hippocampal theta oscillations during spatial decision making. Hippocampus 24, 693–702.
Bender, F., Gorbati, M., Cadaveico, M.C., Denisova, N., Gao, X., Holman, C., Korotkova, T., and Poromarenko, A. (2015). Theta oscillations regulate the speed of locomotion via a hippocampus to lateral septum pathway. Nat. Commun. 6, 8521.
Bokil, H., Andrews, P., Kulkarni, J.E., Mehta, S., and Mitra, P.P. (2010). Chronox: a platform for analyzing neural signals. J. Neurosci. Methods 192, 146–151.
Brovelli, A., Ding, M., Ledberg, A., Chen, Y., Nakamura, R., and Bressler, S.L. (2004). Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. Proc. Natl. Acad. Sci. USA 101, 9849–9854.
Burgess, N., Maguire, E.A., and O’Keefe, J. (2002). The human hippocampus and spatial and episodic memory. Neuron 35, 625–641.
Buzsáki, G. (2002). Theta oscillations in the hippocampus. Neuron 33, 325–340.
Buzsáki, G., Anastassiou, C.A., and Koch, C. (2012). The origin of extracellular fields and currents—ECoG, LFP and spikes. Nat. Rev. Neurosci. 13, 407–420.
Clark, R.E., and Squire, L.R. (2010). An animal model of recognition memory and medial temporal lobe amnesia: history and current issues. Neuropsychologia 48, 2234–2244.
Colgin, L.L. (2016). Rhythms of the hippocampal network. Nat. Rev. Neurosci. 17, 239–249.
Colgin, L.L., and Moser, E.I. (2010). Gamma oscillations in the hippocampus. Physiology (Bethesda) 25, 319–329.
Colgin, L.L., Denninger, T., Fyn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.B., and Moser, E.I. (2009). Frequency of gamma oscillations routes flow of information in the hippocampus. Nature 462, 353–357.
Davachi, L. (2006). Item, context and relational episodic encoding in humans. Curr. Opin. Neurobiol. 16, 693–700.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M., and Tanila, H. (1999). The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 23, 209–226.

Engel, A.K., and Fries, P. (2010). Beta-band oscillations—signalling the status quo? Curr. Opin. Neurobiol. 20, 156–165.

Engel, A.K., Fries, P., and Singer, W. (2001). Dynamic predictions: oscillations and synchrony in top-down processing. Nat. Rev. Neurosci. 2, 704–716.

Ennaceur, A., and Delacour, J. (1988). A new one-trial test for neurobiological studies of memory in rats: 1: behavioral data. Behav. Brain Res. 31, 47–59.

Fries, P. (2015). Rhythms for cognition: communication through coherence. Neuron 88, 220–235.

Fries, P., Reynolds, J.H., Rorie, A.E., and Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291, 1560–1563.

Golani, I., Benjamini, Y., and Eilam, D. (1993). Stopping behavior: constraints on exploration in rats (Rattus norvegicus). Behav. Brain Res. 53, 21–33.

Herrmann, C.S., Munk, M.H., and Engel, A.K. (2004). Cognitive functions of gamma-band activity: memory match and utilization. Trends Cogn. Sci. 8, 347–355.

Huerta, P.T., and Lisman, J.E. (1995). Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 15, 1053–1063.

Hyman, J.M., Wyble, B.P., Goyal, V., Rossi, C.A., and Hasselmo, M.E. (2003). Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J. Neurosci. 23, 11725–11731.

Igarashi, K.M., Lu, L., Colgin, L.L., Moser, M.B., and Moser, E.I. (2014). Coordination of entorhinal-hippocampal ensemble activity during associative learning. Nature 510, 143–147.

Jarrard, L.E. (1993). On the role of the hippocampus in learning and memory in the rat. Behav. Neural Biol. 60, 9–26.

Jensen, O., Kaiser, J., and Lachaux, J.P. (2007). Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci. 30, 317–324.

Jutras, M.J., Fries, P., and Buffalo, E.A. (2009). Gamma-band synchronization in the macaque hippocampus and memory formation. J. Neurosci. 29, 12521–12531.

Jutras, M.J., Fries, P., and Buffalo, E.A. (2013). Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. Proc. Natl. Acad. Sci. USA 110, 13144–13149.

Kamiński, M.J., and Blinowska, K.J. (1991). A new method of the description of the information flow in the brain structures. Biol. Cybern. 65, 203–210.

Kemere, C., Carr, M.F., Karlsson, M.P., and Frank, L.M. (2013). Rapid and continuous modulation of hippocampal network state during exploration of new places. PLoS ONE 8, e73114.

Kesner, R.P., and Rolls, E.T. (2015). A computational theory of hippocampal functions and tests of the theory: new developments. Neurosci. Biobehav. Rev. 48, 92–147.

Kesner, R.P., Lee, I., and Gilbert, P. (2004). A behavioral assessment of hippocampal function based on a subregional analysis. Rev. Neurosci. 15, 333–351.

King, C., Recce, M., and O’Keefe, J. (1998). The rhythmicity of cells of the medial septum/diagonal band of Broca in the awake freely moving rat: relationships with behaviour and hippocampal theta. Eur. J. Neurosci. 10, 464–477.

Kneirim, J.J., Lee, I., and Hargreaves, E.L. (2006). Hippocampal place cells: parallel input streams, subregional processing, and implications for episodic memory. Hippocampus 16, 755–764.

Komorowski, R.W., Manns, J.R., and Eichenbaum, H. (2009). Robust conjunctive item-place coding by hippocampal neurons parallels learning what happens where. J. Neurosci. 29, 9918–9929.

MacKay, W.A., and Mendonça, A.J. (1995). Field potential oscillatory bursts in parietal cortex before and during reach. Brain Res. 704, 167–174.

Malkova, L., and Mishkin, M. (2003). One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. J. Neurosci. 23, 1956–1965.

Manns, J.R., and Eichenbaum, H. (2006). Evolution of declarative memory. Hippocampus 16, 795–808.

Maris, E., and Oostenveld, R. (2007). Nonparametric statistical testing of EEG and MEG data. J. Neurosci. Methods 164, 177–190.

McNaughton, N., Ruan, M., and Woodnort, M.A. (2006). Restoring theta-like rhythmicity in rats restores initial learning in the Morris water maze. Hippocampus 16, 1102–1110.

Mizuseki, K., Royer, S., Diba, K., and Buzsáki, G. (2012). Activity dynamics and behavioral correlates of CA3 and CA1 hippocampal pyramidal neurons. Hippocampus 22, 1659–1680.

Montgomery, S.M., and Buzsáki, G. (2007). Gamma oscillations dynamically couple hippocampal CA3 and CA1 regions during memory task performance. Proc. Natl. Acad. Sci. USA 104, 14495–14500.

Nicolesis, M.A., Baccala, L.A., Lin, R.C., and Chapin, J.K. (1995). Sensorimotor encoding by synchronous neural ensemble activity at multiple levels of the somatosensory system. Science 268, 1353–1358.

Orr, G., Rao, G., Houston, F.P., McNaughton, B.L., and Barnes, C.A. (2001). Hippocampal synaptic plasticity is modulated by theta rhythm in the fascia dentata of adult and aged freely behaving rats. Hippocampus 11, 647–654.

Rangel, L.M., Chiba, A.A., and Quinn, L.K. (2015). Theta and beta oscillatory dynamics in the dentate gyrus reveal a shift in network processing state during cue encounters. Front. Syst. Neurosci. 9, 96.

Renner, M.J., and Seltzer, C.P. (1991). Molar characteristics of exploratory and investigatory behavior in the rat (Rattus norvegicus). J. Comp. Psychol. 105, 326–339.

Save, E., Poucet, B., Foreman, N., and Buhot, M.C. (1992). Object exploration and reactions to spatial and nonspatial changes in hooded rats following damage to parietal cortex or hippocampal formation. Behav. Neurosci. 106, 447–456.

Shirvalkar, P.R., Rapp, P.R., and Shapiro, M.L. (2010). Bidirectional changes to theta-gamma coupling during state transitions induced by theta burst stimulation. J. Neurosci. 30, 704–716.

Siegle, J.H., and Wilson, M.A. (2014). Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. eLife 3, e03061.

Singer, W. (1999). Neuronal synchrony: a versatile code for the definition of relations? Neuron 24, 49–65, 111–125.

Stawiniski, U., and Kasicki, S. (1998). The frequency of rat’s hippocampal theta rhythm is related to the speed of locomotion. Brain Res. 796, 327–331.

Tallon-Baudry, C., Bertrand, O., Delpeuch, C., and Perrier, J. (1997). Oscillatory γ-band (30–70 Hz) activity induced by a visual search task in humans. J. Neurosci. 17, 722–734.

Tittinen, H., Sinkkonen, J., Reinkainen, K., Aho, K., Lavikainen, J., and Näättänen, R. (1993). Selective attention enhances the auditory 40-Hz transient response in humans. Nature 364, 59–60.

Tort, A.B., Komorowski, R.W., Manns, J.R., Kopell, N.J., and Eichenbaum, H. (2009). Theta-gamma coupling increases during the learning of item-context associations. Proc. Natl. Acad. Sci. USA 106, 20942–20947.

Trimmer, J.B., Stefanscucu, R.A., and Manns, J.R. (2014). Recognition memory and theta-gamma interactions in the hippocampus. Hippocampus 24, 341–353.

Varela, F., Lachaux, J.P., Rodríguez, E., and Martinerie, J. (2001). The brainwave: phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229–239.

Vinck, M., van Wingerden, M., Womelsdorf, T., Fries, P., and Pennartz, C.M. (2010). The pairwise phase consistency: a bias-free measure of rhythmic neuronal synchronization. Neuroimage 51, 112–122.
Theta sequences are essential for internally generated hippocampal firing fields. Nat. Neurosci. 18, 282–288.

Whishaw, I.Q., and Vanderwolf, C.H. (1973). Hippocampal EEG and behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learned movement patterns in rats and cats. Behav. Biol. 8, 461–484.

Whishaw, I.Q., Gharbawie, O.A., Clark, B.J., and Lehmann, H. (2006). The exploratory behavior of rats in an open environment optimizes security. Behav. Brain Res. 171, 230–239.

Winson, J. (1978). Loss of hippocampal theta rhythm results in spatial memory deficit in the rat. Science 201, 160–163.

Witter, M.P., Wouterlood, F.G., Naber, P.A., and Van Haeften, T. (2000). Anatomical organization of the parahippocampal-hippocampal network. Ann. N Y Acad. Sci. 911, 1–24.

Zarnadze, S., Bäuerle, P., Santos-Torres, J., Böhm, C., Schmitz, D., Geiger, J.R.P., Dugladze, T., and Gloveli, T. (2016). Cell-specific synaptic plasticity induced by network oscillations. eLife 5, e14912.

Zheng, C., Bieri, K.W., Trettel, S.G., and Colgin, L.L. (2015). The relationship between gamma frequency and running speed differs for slow and fast gamma rhythms in freely behaving rats. Hippocampus 25, 924–938.

Zheng, C., Bieri, K.W., Hwaun, E., and Colgin, L.L. (2016). Fast gamma rhythms in the hippocampus promote encoding of novel object-place pairings. eNeuro 3, 1–19.