

Phase precession in the human hippocampus and entorhinal cortex

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Keywords:

Hippocampus, phase precession, entorhinal cortex, theta oscillation, place cells.

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Abstract

1 Knowing where we are, where we have been, and where we are going is critical to many behaviors, including
2 navigation and memory. One potential neuronal mechanism underlying this ability is phase precession, in which
3 spatially tuned neurons represent sequences of positions by activating at progressively earlier phases of local
4 network theta (~5–10 Hz) oscillations. Phase precession may be a general neural pattern for representing sequential
5 events for learning and memory. However, phase precession has never been observed in humans. By recording
6 human single-neuron activity during spatial navigation, we show that spatially tuned neurons in the human
7 hippocampus and entorhinal cortex exhibit phase precession. Furthermore, beyond the neural representation
8 of locations, we show evidence for phase precession related to specific goal-states. Our findings thus extend
9 theta phase precession to humans and suggest that this phenomenon has a broad functional role for the neural
10 representation of both spatial and non-spatial information.

11 Introduction

12 Our brain's ability to link related experiences is critical to everyday life, and to our memory for past experiences.
13 One crucial example is spatial navigation, which requires awareness of individual locations and the association
14 between multiple locations, such as those on the same path. Similarly, episodic memory requires the encoding of
15 individual events and the association between sequential events. The hippocampal formation is important for both
16 spatial cognition and episodic memory¹⁻⁴. Therefore, neural activity in this region might play a key role in linking
17 sequential locations and events.

18 Specifically, theories of how the brain represents sequential experiences rely on the idea that the timing of neuronal
19 spiking is critical for learning associations⁵⁻¹⁰. Spike timing, in turn, is thought to be coordinated across networks
20 by fluctuations in the large-scale network activity that can be estimated via the local field potential (LFP)¹¹⁻¹⁶. This
21 suggests that a coordinated relationship between network oscillations and single-cell spiking may play a mechanistic
22 role in complex behaviors or aspects of cognition, such as memory^{17,18}, that require the association of sequential
23 events. A prominent potential mechanism for the binding and compressing of sequential events is hippocampal phase
24 precession, extensively observed in rodents, during which active neurons rhythmically spike in coordination with the
25 local theta frequency (5–10 Hz) oscillation. Phase precession is readily observable in many hippocampal place cells¹⁹
26 and entorhinal grid cells^{20,21}. Because these neurons spike slightly faster than the theta oscillation as the rodent runs
27 through specific locations, phase precession results in sequences of locations being encoded at different phases of
28 theta oscillations. As such, phase precession may compress spatial trajectories on the scale of behavior into the brief
29 timescale of the theta cycle that is conducive to synaptic plasticity²²⁻²⁴.

30 There is evidence that phase precession's utility for binding and compressing sequential events may be used
31 by the brain to represent non-spatial features of experience as well. While phase precession is often described in
32 hippocampal place cells or entorhinal grid cells, it has also been observed in a diverse range of brain areas such
33 as ventral striatum²⁵, subiculum²⁶, basal forebrain²⁷, and medial prefrontal cortex²⁸. Critically, a slew of recent
34 work has directly observed phase precession independent of location within a place or grid field, encoding elapsed
35 time during REM sleep²⁹, wheel-running³⁰, jumping³¹, fixation³², presentation of task-relevant stimuli³³⁻³⁵, and task
36 epoch²⁷. The widespread prevalence of phase precession suggests that this phenomenon has a more general role
37 beyond representing the current spatial location, and that it could be relevant for building neural representations in
38 many regions to support diverse aspects of cognition, learning, and memory.

39 Despite its prevalence in rodents, and the many theories suggesting a fundamental role for phase precession
40 in neural coding^{19,36-38}, phase precession has not been observed in humans. To examine this issue, we analyzed
41 simultaneous single-neuron and LFP activity from neurosurgical patients as they performed a virtual spatial memory
42 task and examined the patterns of spike–LFP interaction. Here, we describe spatial phase precession in humans
43 analogous to that observed in navigating rodents. We also describe evidence for phase precession related to the coding
44 of non-spatial variables, in which neurons transiently spike faster than the theta oscillation during trajectories to
45 specific goals. Overall, our findings extend precession to humans and demonstrate its potential use for encoding both
46 spatial and non-spatial features of experience.

47 Results

48 **Spatial phase precession in hippocampus and entorhinal cortex during navigation.** We analyzed recordings
49 of neuronal spiking from 1,074 neurons in the hippocampus, entorhinal cortex, parahippocampal gyrus, anterior
50 cingulate cortex, and amygdala of 13 neurosurgical patients undergoing clinical treatment for drug-resistant epilepsy.
51 During recordings, subjects performed a goal-directed navigation task in a 2D virtual environment on a laptop
52 computer^{39,40} (Supplementary Fig. 1; see *Methods*). The virtual environment contained six goal stores surrounding
53 the perimeter of a square track, with the center of the environment obstructed by buildings. Subjects were able to
54 travel around the track in either clockwise or counterclockwise directions (Fig. 1A).

55 Given our interest in phase coding, we first characterized the prevalence of theta oscillations in the human
56 hippocampus and compared their properties to those seen in rodents, leveraging a publicly-available dataset⁴².

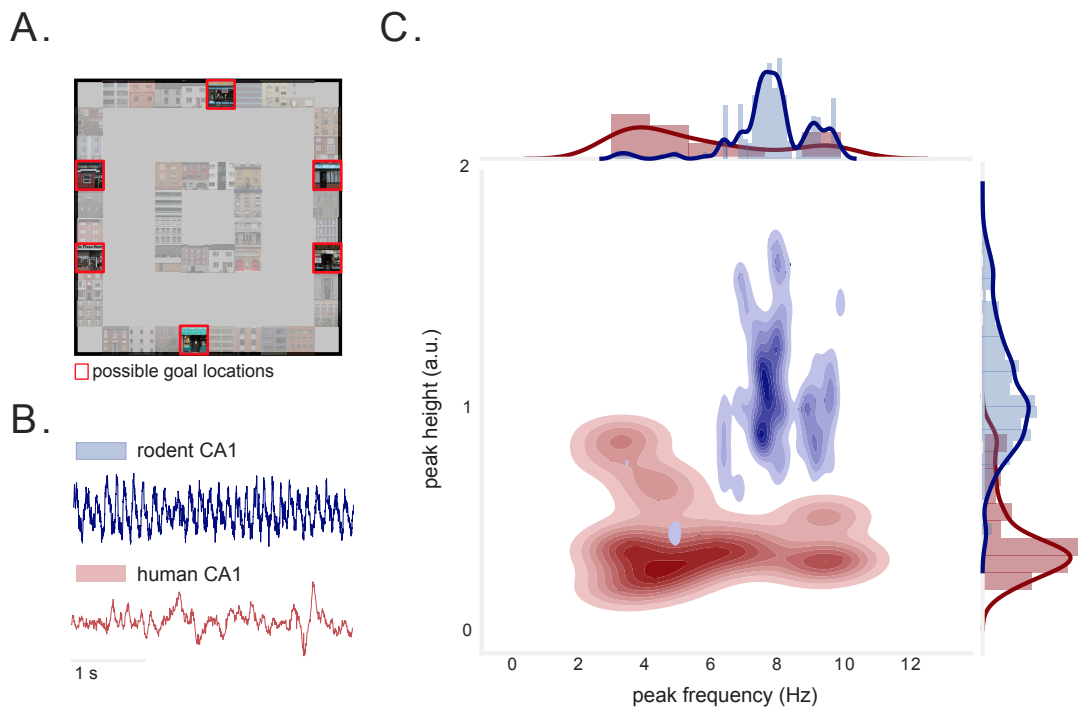


Figure 1: Virtual environment and hippocampal theta oscillations during task. A) Overhead view of task environment. Red squares denote locations of possible goal locations. B) Examples of raw LFP data from rodent (publicly available dataset⁴¹) and human hippocampus. C) Joint distribution of peak frequency and peak height of LFP power spectral density (PSD) from rodent (blue) and human (red) hippocampus. Rodent hippocampal recordings exhibit highly stereotyped peaks. Human hippocampal recordings exhibit significantly smaller peak heights, and peaks are at significantly lower frequencies (p 's $< 2 \times 10^{-34}$, Wilcoxon rank-sum tests).

57 Compared to rodents, human hippocampal theta spanned a significantly broader range of frequencies ($p < 4 \times 10^{-4}$,
58 Levene test), with significantly smaller, lower-frequency peaks in the power spectrum (p 's $< 3 \times 10^{-8}$, Wilcoxon
59 rank-sum tests; Figs. 1B-C, S2). Because human theta appears to span both low and high frequencies⁴³, we assessed
60 phase precession with respect to oscillations at a broad range of LFP theta frequencies (2–10 Hz) (Fig. 1C). To assess
61 phase precession we first identified each neuron whose firing was modulated by the subject's position in the virtual
62 environment. We labelled the clockwise (CW) and counter-clockwise (CCW) movement periods and then used a
63 shuffle-corrected ANOVA to identify 292 spatially modulated neurons that fired significantly more when subjects
64 moved through particular locations during one or both of these movement conditions⁴⁴, after correcting for multiple
65 comparisons (see *Methods*). Because phase precession in rodents is most predominant near the place-field center⁴⁵
66 and on short trajectories⁴⁶, we tested for phase precession during short trajectories through the field center, defined as
67 the peak firing location for each neuron (Fig. 2A).

68 We observed that some of the spatially tuned neurons showed spiking at progressively earlier phases of the theta
69 oscillation during individual trajectories through their firing field (Supplementary Fig. 3). To assess if this was a
70 consistent pattern across trajectories, we leveraged the fact that during phase precession, spikes at later positions in
71 the trajectory should occur at earlier phases, manifesting as a negative correlation between spike-phase and position¹⁹.
72 In this way, spiking at different phases of the LFP would correspond to different relative positions along the path to a
73 neuron's firing field center (Fig. 2B,C). We tested for this pattern by measuring the correlation⁴⁷ between spike-phase
74 and position using circular statistics⁴⁸ and a shuffle-based permutation procedure (see *Methods*).

75 By performing this procedure across all of the spatially-tuned neurons we identified, we report the first evidence
76 of phase precession in humans. Figure 2D shows three examples of single neurons recorded in the hippocampus
77 and entorhinal cortex that exhibited significant phase precession during navigation at particular spatial locations (see
78 Supplementary Fig. 4 for additional examples). Each of these neurons increased their firing in a specific region of
79 the environment (Fig. 2D, left). As a person approached the center of that region, the neuron initially spiked at late

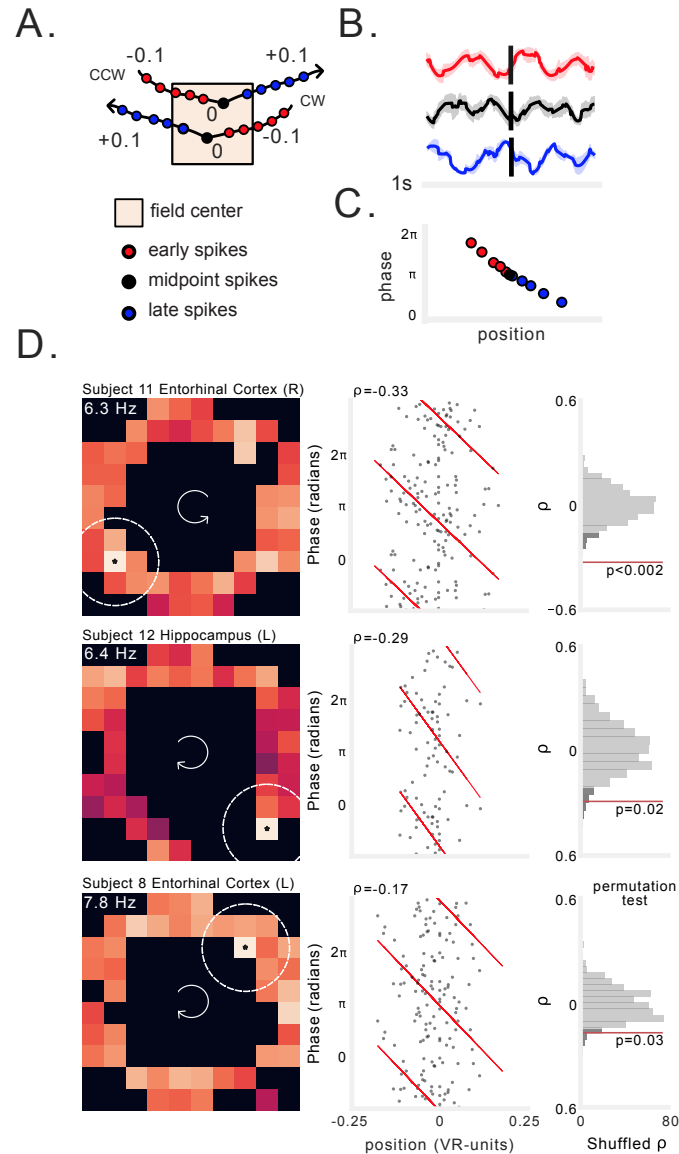


Figure 2: Examples of spatial phase precession in human hippocampus and entorhinal cortex. A) Schematic illustrating our method for selecting spikes near peak firing bin (*see Methods*). For each spatially modulated cell we analyzed phase precession using spikes that occurred early (red), at the midpoint (black), and late (blue) in trajectories through the center of the firing field. B) Spike-triggered average (STA) LFP (reconstructed from phase) for early, midpoint, and late trajectory spikes from one neuron. C) Schematic of spike phase as a function of distance from center spike during a trajectory through the field, showing phase precession as a negative progression of phase-by-position. D) Three examples of spatial phase precession. Each row shows an individual neuron. Left: firing rate heat map. Text label indicates average firing rate in peak firing bin, which is noted with an asterisk. Brighter colors denote higher firing rates. Dotted lines indicate maximum radius around field in which spiking was assessed. Arrows in the center of the heatmap indicate the movement direction. Middle: spike phase as a function of location relative to the field center. Spike phases are duplicated vertically to enable visualization of circular-linear regression. Rho indicates circular-linear regression coefficient. Right: statistical assessment of circular-linear regression rho using surrogate distribution of circular-linear regression rho values generated by permutation of spike phases. Red line indicates value of real data. Dark gray shading indicates 95th percentile of surrogate distribution.

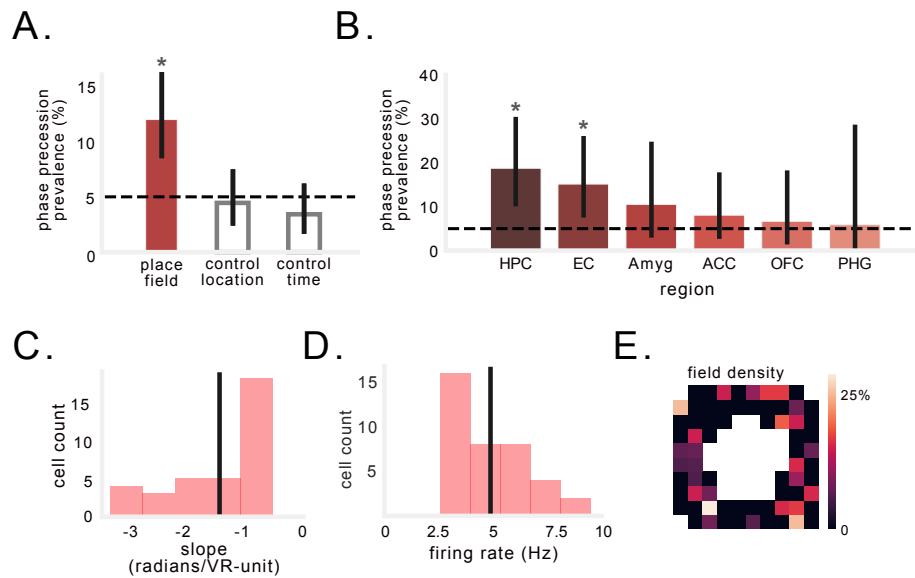


Figure 3: Prevalence and characteristics of spatial phase precession in humans. A) Percentage of spatially modulated cells that exhibit phase precession during trajectories through the firing field (filled bar). Grey bars show control analyses of precession relative to alternative locations, or as a function of time, not position, during spiking episodes (see Supplementary Fig. 5). Black dotted line denotes chance. Solid black line indicates 95% binomial confidence interval. Asterisk indicates significant proportion of spatially modulated cells exhibiting phase precession during trajectories through the firing field ($p < 3 \times 10^{-6}$, binomial test). B) Percentage of spatially modulated cells across regions. Asterisk indicates significant proportion of cells exhibit phase precession ($p < 0.002$, binomial test). C) Distribution of circular-linear regression slopes identified for neurons exhibiting significant phase precession. Black line indicates mean. D) Distribution of average firing rate of peak firing bins in which phase precession was observed. E) Prevalence of phase precession across the environment. Colors indicate percentage of firing fields in each bin that exhibited precession.

80 phases of the 2–10 Hz LFP, but as they continued their trajectory through the center and past it, spikes occurred at
 81 progressively earlier phases (Fig. 2D, middle). This change in spike phases between early positions and late positions
 82 is characterized by significant negative phase–position correlations (Fig. 2D, right).

83 After testing the spatially-tuned neurons in our dataset for phase precession with our permutation procedure, we
 84 found that precession was widespread, with 12% (35/292) of neurons exhibiting this phenomenon, which is well
 85 above what would be observed by chance ($p < 3 \times 10^{-6}$, binomial test; Fig. 3A). Of these 35 neurons, 22 neurons
 86 exhibited uni-directional spatial tuning and precession and 10 neurons exhibited bi-directional spatial tuning and
 87 precession. The remaining 3 neurons exhibited uni-directional precession in one location and bi-directional precession
 88 in another. Notably, we specifically observed significant proportions of spatially modulated cells exhibiting spatial
 89 phase precession in the hippocampus and entorhinal cortex (p 's < 0.002, binomial test; Fig. 3B). Phase precessing
 90 neurons exhibited an average circular–linear correlation coefficient of -0.26 ± 0.09 , an average slope of -1.36 ± 0.8
 91 radians/VR-units (Fig. 3C), and an average in-field firing rate of 4.9 ± 1.7 Hz (Fig. 3D). Phase precessing neurons had
 92 spatial firing fields throughout the environment (Fig. 3E). To test whether spatial phase precession was consistent
 93 across an entire behavioral session, we separately computed the circular–linear correlation coefficient for the first
 94 and second halves of the session and found no difference between halves ($p = 0.4$, paired t-test), with significantly
 95 negative correlation coefficients in each half (p 's < 0.002, one-sample t-test). We found evidence for spatial phase
 96 precession in 11/12 of the subjects with spatially modulated neurons. These results thus demonstrate the existence
 97 of phase precession as a neural code for spatial position in humans during virtual navigation. The theta-frequency
 98 (2–10 Hz) and regions involved (hippocampus, entorhinal cortex) suggest that the phase precession we observed is
 99 largely analogous to that documented in rodent place and grid cells.

100 To be sure that our findings of precession indicated a spatial phase code relative to space, we tested two alternative
 101 explanations for our results: that precession was equally prevalent at randomly selected spatial locations (in which the
 102 neuron was sufficiently active), or that precession was actually measuring the advance of spike phase according to

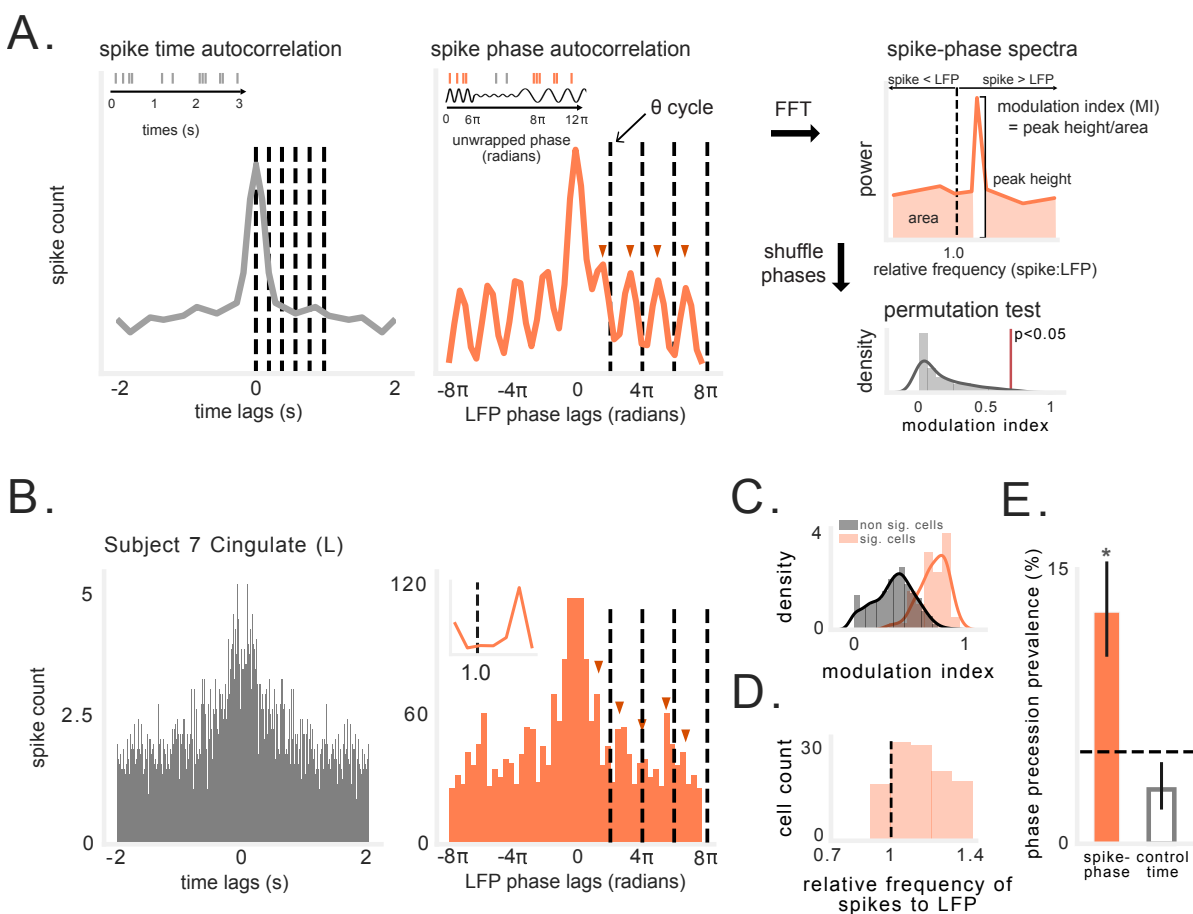


Figure 4: Spike-phase spectra reveals precession-like pattern in non-spatially tuned neurons. A) Schematic illustrating analysis of rhythmic spiking frequency relative to LFP oscillation (*see Methods*). Left: Autocorrelation of spike times (gray), with dotted lines at 200 ms intervals. Middle: Autocorrelation of unwrapped spike phases. Dotted lines indicate one cycle of ongoing LFP in 2–10 Hz band. Red arrows indicate peaks in autocorrelation, which occur progressively earlier than cycles of ongoing LFP. Fast Right: Fourier transform (FFT) of autocorrelation function yields power spectral density (PSD) showing cell spiking frequency relative to ongoing LFP frequency. The modulation index (MI) is visualized here as the ratio of the spectral peak height to power at all other relative frequencies. This value is compared to a null distribution of MI values generated by shuffling spike phases in each cycle. B) Left: Spike time autocorrelation showing little evidence of theta modulation. Right: Spike phase autocorrelation (orange) showing cell oscillating slightly faster than ongoing LFP (cycles of 2–10 Hz LFP indicated by dotted line). Inset shows spike-phase spectra. C) Modulation index (MI) of spike-phase spectral peaks for significant vs. non-significant neurons. D) Distribution of relative frequencies for neurons exhibiting significant MI. Values to the right of the black line indicate that the rhythmic spiking frequency slightly exceeded the LFP frequency. E) Percentage of non-spatial cells that exhibit precession-like spiking relative to LFP phase, compared to cell's exhibiting precession relative to time in a spiking episode. Black dotted line denotes chance level. Solid black line indicates 95% binomial confidence interval. Asterisk indicates significant proportion of cells ($p < 7 \times 10^{-18}$, binomial test).

103 elapsed time (see *Methods*; Supplementary Fig. 5A, C). Neither alternative model identified significant proportions of
104 phase-precessing cells, and these models resulted in the identification of a smaller number of cells as compared to our
105 primary analyses ($\chi^2 = 20.6$, $p < 4 \times 10^{-5}$, chi-squared test; Fig. 3A; see also Supplementary Fig. 5B, D). These
106 results indicate that human phase precession occurs more strongly at locations that show the highest firing rates, and
107 that phase precession in spatially tuned neurons is more closely tied to location than elapsed time during movement.

108 **Evidence for phase precession without spatial coding.** While phase precession has been observed most readily
109 relative to specific spatial locations, there is also evidence for precession with respect to non-spatial behaviors
110 and stimuli^{27,29–31,33}, and in regions outside the hippocampal formation^{25,28}. These findings suggest that phase
111 precession could be a more general phenomenon that the brain uses to represent diverse types of consecutive, relevant
112 stimuli/states using different phases of an oscillation. To examine this possibility, we used a broader analytical method
113 to test whether the non-spatially tuned neurons exhibited phase precession without reference to position. To do this,
114 we measured each neuron's rhythmic frequency of spiking in comparison to the local theta oscillation^{49,50}. Identifying
115 a consistent pattern of faster-than-LFP rhythmic spiking would indicate the presence of a precession-like pattern of
116 LFP-coordinated spiking that could bind and compress sequential, non-spatial features of the task — just as spatial
117 phase precession is theorized to do for locations^{24,51}.

118 We identified neurons that showed rhythmic spiking at a frequency faster than the theta oscillation by using a
119 method that has identified this pattern in animals with very stereotyped, 8 Hz theta such as rats^{26,42,52} and mice^{53,54},
120 as well as animals with human-like theta that appears at a range of frequencies, such as bats⁵⁵. In brief, in this method
121 we first measured the theta phase estimate for each spike from the concurrent 2–10 Hz LFP and “unwrapped” the
122 phase time series so that it increased linearly, like elapsed time. We then measured the spike-phase spectrum, which
123 we defined as the power spectral density of the time series of unwrapped spike phases (see *Methods*). In contrast
124 to conventional spectral analysis that measures the frequency of a signal relative to absolute time, the spike-phase
125 spectra reflects the relative frequency of rhythmic spiking compared to the frequency of concurrent LFP oscillations.
126 If a spike-phase spectra showed a peak at a relative frequency > 1.0 it would indicate that a neuron's rhythmic spiking
127 was faster than the concurrent oscillations in the LFP, and thus this neuron's spiking exhibited precession relative
128 to the LFP (Fig. 4A). This method ensures that a consistent relationship between the spiking frequency and LFP
129 frequency can be identified even if the LFP shifts in frequency or amplitude, and even though neuronal spike times
130 alone may not show a clear oscillation (Supplementary Fig. 6), as is the case in humans and bats⁵⁵. We validated this
131 method by applying it to data from rodent CA1 and identifying a consistent > 1.0 relative frequency (Supplementary
132 Fig. 7), consistent with the spatial phase precession observed in these neurons⁴².

133 To assess whether precession-like rhythmic spiking was evident for non-spatially tuned cells, we applied this
134 method to the 744 neurons that were active during the task but did not exhibit significant spatial tuning. Figure 4B
135 depicts an example neuron that we identified with this method that showed significant precession. This analysis found
136 that the rhythmicity of this cell's spiking frequency occurred at a frequency that reliably exceeded the frequency of
137 the LFP (right panel), although no consistent rhythm is apparent from the spike timing alone (left panel). Using
138 this method we found that 12% of non-spatially tuned neurons (90/744) showed a significant relationship between
139 neuronal spiking frequency and LFP frequency (Fig. 4C), at a range of relative frequencies > 1.0 (Fig. 4D). The
140 number of neurons that showed this phenomenon was significantly more than we expected by chance ($p < 7 \times 10^{-18}$,
141 binomial test; Fig. 4E).

142 We performed a control analysis (Supplementary Fig. 5C) to rule out the possibility that these effects could be
143 explained by the absolute spike timing, though this was unlikely given the relative lack of intrinsic rhythmicity in the
144 spike timing (see Supplementary Fig. 6). This analysis confirmed that most of these neurons show phase precession
145 only when spiking is measured relative to the instantaneous ongoing oscillation rather than absolute time⁵⁶ (Fig.
146 4E). These results illustrate how the frequency variability of human hippocampal theta⁴³ may diminish traditional
147 measures of phase precession, and demonstrate the potential for phase precession in neurons that are not spatially
148 tuned. We next sought to test whether this new non-spatial precession pattern might vary behaviorally in relation to
149 non-spatial, higher level features of the task, such as prospective goals.

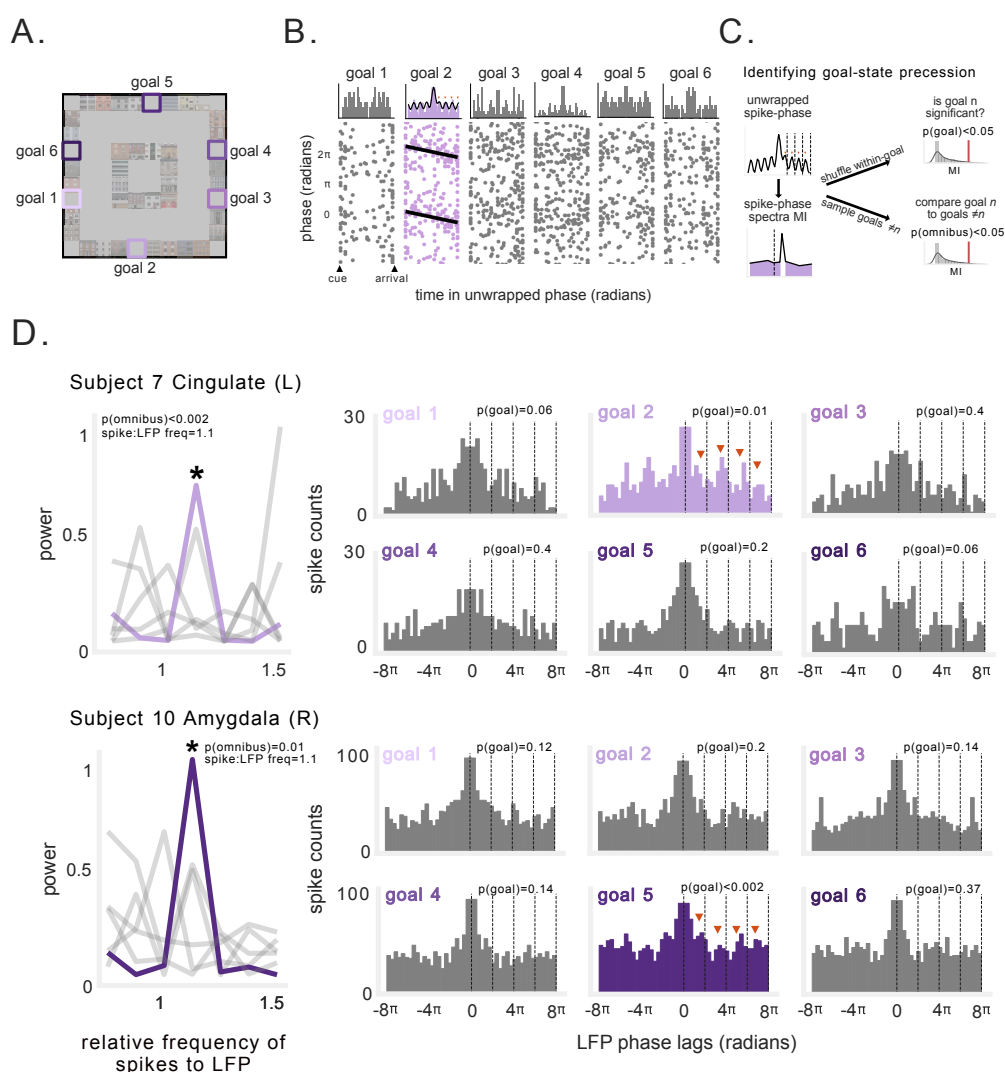


Figure 5: Goal-state phase precession. A) Schematic of task environment. Labels indicate goal locations. B) Spike-phases during navigation to different goals for example neuron. Top: unwrapped spike-phase autocorrelograms for each goal. Black line indicates fit of decaying-oscillation function. Spiking frequency transiently exceeded LFP frequency only during navigation to goal 2. Bottom: Spike-phase as a function of duration within each goal epoch. Black line indicates circular-linear regression fit. C) Schematic of method for assessing goal-state phase precession. If a neuron exhibited a significant spike-phase spectral peak at relative frequency exceeding 1 (following multiple comparisons correction), and this effect was significantly stronger than that observed during trajectories to other goals, then this neuron was classified as exhibiting goal-state precession (*see Methods*). D) Example neurons exhibiting phase precession during navigation to specific goals. Left: Spike-phase spectra depicting frequency of neuronal spiking relative to ongoing LFP. Asterisk denotes spectral peaks that were significant and significantly different from other spike-phase spectra for other goals. Gray lines denote non-significant goals. Right: Spike-phase autocorrelograms during navigation to each goal (significant goal epochs depicted in color). Text indicates the p-value for significance tests described in C).

150 **Evidence for phase precession during trajectories to specific goals.** Having shown that non-spatially tuned
151 neurons can exhibit phase precession, we next tested whether this was a tonic pattern⁵⁰ or, alternatively, one that
152 emerged selectively to code for specific stimuli or states. Specifically, recent work has shown that human hippocampal-
153 cortical networks represent goals and their intermediate locations⁵⁷; furthermore we found previously that this task
154 elicits distinctive patterns of rate- and phase- coding for goals⁵⁸. Therefore, we assessed whether phase precession
155 emerged selectively during trajectories to specific goals in service of binding those trajectories for learning and
156 memory.

157 During each trial of this task, the subject was cued to travel to a randomly selected goal location (Fig. 5A). We
158 found that some neurons specifically showed phase precession only during travel to particular goals. Figure 5B
159 shows an example of a neuron whose spiking shows phase precession during navigation to goal 2, but not the other
160 goals. This effect is evident in the spike-phase autocorrelogram for that goal, which shows that during travel to goal 2
161 rhythmic spiking occurs at a frequency that is slightly faster than the ongoing 2–10 Hz LFP. To systematically test for
162 goal-state phase precession, we measured the spike-phase spectrum during trajectories to each goal and compared
163 these spectra between goals, using a permutation procedure and correcting for multiple comparison across goals (Fig.
164 5C, see *Methods*). Figure 5D depicts two example neurons from the hippocampus and amygdala of two different
165 subjects (see Supplementary Fig. 8 for additional examples). These neurons exhibited rhythmic spiking at faster
166 frequencies than the ongoing LFP while the subjects were en route to specific goals. Critically, this rhythmic spiking
167 was goal-specific and did not appear during trajectories to other goals. These patterns were thus examples of phase
168 precession for a particular goal-state, similar to phase precession in a place field.

169 We applied this method to the 448 non-spatially tuned neurons that were sufficiently active during each goal,
170 and found a population of neurons exhibiting a significant pattern of faster-than-LFP rhythmic spiking during at
171 least one goal (Fig. 6A), across a range of relative frequencies (Fig. 6B). Overall, 11% of these neurons (49/448)
172 exhibited significant goal-state precession. We found at least one neuron exhibiting goal-state phase precession in
173 10/13 subjects. Of the neurons exhibiting goal-state precession, almost all did so for only one of the six goals (Fig. 6C).
174 This effect was present at significant levels in anterior cingulate, orbitofrontal cortex, amygdala, and hippocampus,
175 but not parahippocampal gyrus or entorhinal cortex (p 's < 0.02, binomial test; Fig. 6D).

176 We performed a series of control analyses that rules out the possibility that our observation of precession for
177 specific goal states was confounded by between-goal differences in LFP power or neuronal firing rate (Fig. 6E).
178 Indeed, neither example neuron in Figure 5 exhibited increased firing rates during goals that showed precession,
179 suggesting that goal-state precession was independent of goal-specific firing rate increases⁵⁸. Overall, only 17 of
180 the 49 neurons that showed goal-state precession also showed increased goal-specific firing rate increases (ps < 0.05,
181 one-way ANOVA), and only 2 of 17 of these neurons showed precession and a firing rate increase for the same goal³⁵
182 (Fig. 6F). Next, we tested whether subject performance on different goals might be responsible for our results, i.e.,
183 whether precession might occur when subjects perform more efficient navigation. We measured subject's performance
184 on each goal (see *Methods*) and found no significant difference in navigational performance between goals that elicited
185 precession and those that did not (Supplementary Fig. 9A, B). Because differences in theta power, firing rate, and
186 behavior did not account for our results, our findings indicate that non-spatial phase precession selectively occurs
187 during trajectories to specific goals and may also support the representation of non-spatial, sequential features of
188 behavior.

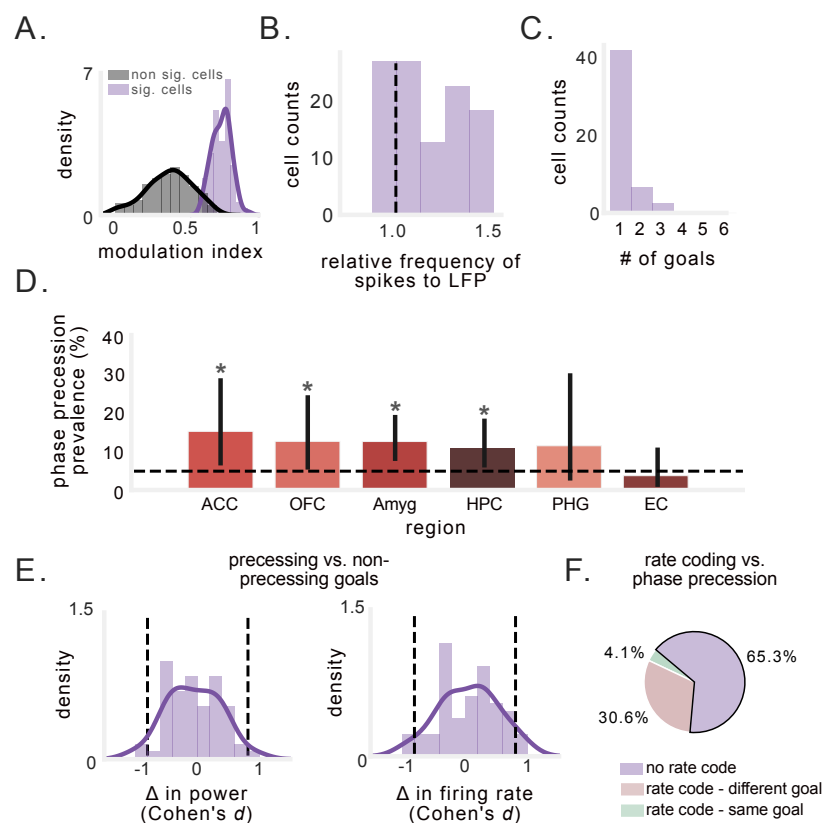


Figure 6: Prevalence and characteristics of goal-state phase precession in neurons that are not spatially tuned. A) Modulation index (MI) of spike-phase spectral peaks for significant vs. non-significant goals. B) Peak spike-phase PSD frequency for all goals for which a neuron exhibited a significant MI in the spike-phase spectra. Values to the right of the black line indicate that the neuronal frequency slightly exceeded the LFP frequency, indicating precession. C) Number of goals per neuron for which precession was observed. Most neurons exhibited precession during only one goal. D) Percentage of non-spatial cells in each region that exhibited goal-state phase precession. Asterisks indicate significant proportion of cells ($p < 0.02$, binomial test). E) Distribution of Cohen's d for the difference in 2–10 Hz power (left) and firing rate (right) between trajectories to goals showing precession vs. those that did not. Black dotted line indicate effect size of ± 0.8 . F) Analysis of overlap between goal-state phase precession and rate coding for goals.

189 Discussion

190 The nature of the neural code is a fundamental question in neuroscience. Our findings show the first evidence that
 191 neurons in the human brain spike in rhythm with local network oscillations to represent spatial position and non-spatial
 192 events, in addition to the well-established code based on firing rate. Specifically, we demonstrate the existence of
 193 phase precession in humans during a virtual spatial memory task. We provide evidence for rodent-like spatial phase
 194 precession in human hippocampus and entorhinal cortex, in which spatially tuned neurons spike at earlier phases of
 195 theta (2–10 Hz) LFP oscillations as subjects moved through the putative place field center. We also provide evidence
 196 for the existence of non-spatial, goal-state phase precession which occurs transiently during trajectories to specific
 197 goals. These findings thus extend phase precession beyond rodents, and beyond spatial location, highlighting its
 198 potential as a more widespread neuronal mechanism for coordinating spike timing during behavior and cognition.

199 The spatial phase precession we observed bears important similarities to phase precession in rodents. We found
 200 spatial phase precession most predominantly in hippocampus and entorhinal cortex, where place and grid cells,
 201 respectively, are canonically found^{2,59–61}. This suggests that the spatial phase precession we observed may be driven
 202 primarily by place- and grid- cells, as it is in rodents. One potential reason why phase precession has not previously
 203 been observed in humans is because human theta oscillations often appear at a slower and broader range of frequencies
 204 compared to those seen in rodents^{43,62,63}. We specifically assessed phase precession relative to the broader range of
 205 theta frequency (2–10 Hz) fluctuations of the LFP, in line with the recent discoveries of phase precession in bats⁵⁵

206 and marmosets⁶⁴ — two animals with similarly heterogeneous theta oscillations. Our findings are also consistent
207 with findings from rodents, who continue to show phase precession even when LFP theta power and theta-modulated
208 spiking are reduced^{25,65,66}. Furthermore, phase coding may not depend on regular, high amplitude rhythmicity in
209 neural activity⁵¹. Instead, shifting LFP frequency can modulate spike-time intervals for synaptic plasticity without
210 affecting the spike-phase⁵¹. Recent work in rodents has indeed demonstrated that the theta phase code is robust to
211 changes in theta frequency, even as temporal lags between spikes are altered⁵⁶. It is thus likely that the spatial phase
212 precession we observed is analogous to that described in rodents, despite differences in theta range and rhythmicity.

213 Phase precession has predominantly been observed during place- or grid- cell spiking⁶⁷. However, recent work has
214 discovered the presence of phase precession relative to sound^{33,34}, odor³⁴, time in an episode^{29–31}, task progression²⁷,
215 and REM sleep²⁹. These findings highlight the potential generalizability of phase precession to non-spatial domains.
216 In these instances, phase precession may enable the encoding of any successive stimuli or state, with the progression of
217 phases binding a myriad of non-spatial sequences together for learning. By leveraging the idea that any variable may
218 be encoded in spike phase if the frequency of spike rhythmicity exceeds the frequency of the local LFP oscillation^{42,51},
219 we showed that phase precession also occurs with respect to behavioral states other than inhabiting a specific physical
220 location—in this case, exclusively during trajectories to specific goals. The fact that this result is so specific, only
221 showing up for a subset of goals for each neuron, might suggest an ensemble temporal code responsible for encoding
222 all of the goals in the task^{68,69}.

223 The goal-state phase precession we observed was largely independent of rate coding for goals, which has been
224 described previously in human studies^{58,60,70}. That the presence of rate and phase coding for goals is statistically
225 independent is consistent with observations in rodents that showed that phase precession can appear for specific
226 behavioral states even in the absence of concurrent firing-rate changes³⁵. These findings support the theory that phase
227 precession is used by the brain to signal behavioral states independent of firing-rate changes^{71,72}. A challenge for
228 future work is to understand the specific features of this phenomenon, such as the role of different phases within
229 goal-state precession. One hypothesis is that goal-state precession may help track a person’s “episodic” position
230 within a goal-seeking event. This would align with work in rodents showing phase-precession in “episode” or “time”
231 cells when a rodent runs on a treadmill with a goal³⁰ but not without a goal⁷³, as well as evidence from human imaging
232 showing that hippocampal and entorhinal cortex population activity correlates with distance to goal⁷⁴. Furthermore,
233 goal-state phase precession may relate to the phase precession observed in ventral striatum “ramp cells”²⁵, and medial
234 prefrontal cortex neurons in rodents²⁸. The former exhibited precession as rodents approached reward locations, and
235 the latter exhibited precession that was clearest when rodents approached the decision point in a maze²⁸. Given that
236 we found goal-state phase precession across various brain regions, including frontal cortex, these prior works further
237 support the hypothesis that precession may represent “episodic” position within top-down behavioral states.

238 It is important to understand the prevalence of phase precession due to its likely theoretical relevance as neuronal
239 mechanism for binding and compressing sequential events. In brief, phase precession organizes spiking at time
240 intervals below the deactivation time constant of NMDA receptors, facilitating synaptic plasticity between neurons that
241 encode events at behavioral time-scales^{7,10,24,75–77}. Strengthening associations between consecutively active neurons
242 may be a widely useful mechanism for learning associations. Our findings extend phase precession to the human
243 brain and demonstrate that precession does not necessarily depend on physiological constraints, such as a stationary
244 ~8 Hz theta oscillations^{25,51,55,65,66}. Furthermore, our results show that a consistent difference between spiking and
245 LFP frequency extends beyond place- or grid- field activity and may represent non-spatial mental sequences related to
246 a memory task. This consistent spike–LFP frequency difference has been characterized by oscillatory-interference
247 models as a function of spatial inputs, such as velocity, but may include non-spatial inputs if they increase spiking
248 frequency above the network oscillation^{78,79}. Therefore, our findings demonstrate the potential utility for phase
249 precession in humans, across diverse brain regions, as a general, domain-free mechanism for temporal compression of
250 specific experiences.

251 In summary, we have provided evidence for spatial phase precession in the human hippocampus and entorhinal
252 cortex during virtual navigation and shown that it exhibits features similar to those seen in rodents. Further, we also
253 demonstrated the existence of phase precession that is specific to trajectories to particular goals. These findings suggest
254 that phase precession is a general mechanism for temporal coding in the human brain, despite the heterogeneity in

255 theta rhythmicity in human MTL. Furthermore, the discovery of goal-state phase precession extends the potential for
256 phase coding to be physiologically relevant for an array of experiential features, even when the neurons do not show
257 concurrent firing rate changes for those features. Overall, our results suggest that phase precession is an important
258 neural code across species and brain regions, not only for spatial cognition and memory but also for non-spatial
259 features of experience.

260 Methods

261 **Data recording and participants.** The thirteen participants in our study were epilepsy patients who had Behnke–Fried
262 microelectrodes⁸⁰ (Ad-Tech Medical) surgically implanted in the course of clinical seizure mapping at the University
263 of California, Los Angeles. The Medical Institutional Review Board at the University of California-Los Angeles
264 approved this study (IRB 10–000973), and patients provided informed consent to participate in research. Microwire
265 signals were recorded at 28–32 kHz, and we used Combinato for spike detection and sorting⁸¹. Manual sorting
266 identified single- versus multi-unit activity versus noise on the basis of previously determined criteria^{82,83}. The local
267 field potential for each neuron was recorded from the local microelectrodes and was downsampled to 250 Hz for
268 spectral analysis. For comparison with rodent data we used a publicly available dataset (CRCNS hc-2, hc-3)^{41,42,84}.

269 **Task.** This behavioral task is described in several previous studies^{39,40,58,85}. Subjects first learned the navigational
270 controls during a 4-delivery training session in a large, wide-open arena. After the practice session, subjects performed
271 the main task, in which they were instructed to drive passengers to one of 6 goal stores in the virtual environment.
272 Upon arrival, on-screen text displayed the name of the next randomly selected destination store. The task was
273 self-paced in order to accommodate patient testing needs and therefore subjects performed at ceiling. The size of
274 the virtual environment was 10×10 VR units, the width of the road was 2.5 VR units, and the obstructed area in
275 the center of the road was 5×5 VR units. During navigation, subjects had a 60° field of view, a maximum forward
276 speed of 1.25 VR units/s, a maximum backward speed was 0.5 VR units/s, and maximum angular velocity of 40° /s.
277 To encourage subjects to take the shortest route to each destination, subjects received 50 points for each successful
278 delivery and had one point deducted for each second that they spent navigating. Points were constantly displayed
279 on-screen. Patients performed an average of 73 ± 11 deliveries in each session. To assess performance on this task,
280 we measured subjects' excess path length (EPL) on each trajectory, defined as ratio of the actual path length to the
281 ideal path length. We computed ideal path length on each trial using the A-star search algorithm to identify the most
282 computationally efficient path between goals in the environment⁸⁶.

283 **Statistical analysis and software.** All statistical analyses were carried out in Python, primarily using the SciPy⁸⁷
284 and statsmodels⁸⁸ libraries. For comparisons between two groups, we primarily utilized the Wilcoxon rank-sum test
285 unless otherwise specified. For omnibus testing, we used ANOVAs, determining the p-value by comparing the real
286 test-statistic to those from empirically derived null distributions generated by shuffling the true data. All figures were
287 made using the Matplotlib⁸⁹ and Seaborn libraries.

288 **Characterizing place-cell activity.** To assess how neuronal activity related to the subject's virtual spatial location,
289 first, we binned the environment into a 10×10 spatial grid. We computed the firing rate map for each neuron by
290 dividing the number of spikes by the amount of time spent in each spatial bin. We then used an ANOVA to assess
291 whether the interaction of X and Y spatial bin (and thus 2D position) significantly modulated firing rate. To assess the
292 significance of the ANOVA we circularly shuffled the firing rate and generated 500 surrogate test-statistics, and used
293 this null distribution to determine the shuffle-corrected p-value of the ANOVA using the real data. These p-values
294 were then FDR-corrected for multiple comparisons between the three movement types (CW, CCW, bi-directional).

295 Only neurons with critical statistics exceeding 99% of the shuffled data ($p < 0.01$) were considered to be spatially
296 modulated. We considered spatially-modulated neurons to be analogous to place- and grid- cells, because the firing
297 rate in at least one spatial bin deviated significantly from the others. We identified the spatial bin with the highest
298 firing rate (analogous to the center of a place- or grid- field). We only included a spatial bin if the person passed
299 through it at least 3 times, and occupied it for at least 4 seconds.

300 **Spectral analysis of LFP and spike time.** To assess the prevalence and frequency of theta oscillations in the human
301 and rodent LFP, we computed the continuous Morlet wavelet transform (wave number 6) at 20 logarithmically spaced
302 frequencies between 1 and 32 Hz. Then, to identify theta-like oscillations, we utilized an iterative algorithm to subtract

303 the aperiodic background and fit a Gaussian to putative peaks⁹⁰. For this fitting procedure, we restricted the maximum
304 number of peaks to 2, and the maximum peak width to 4 Hz. We only assessed the peak height (parameterized as the
305 height of the Gaussian's peak relative to the aperiodic background) and the peak frequency (parameterized as the
306 center frequency at which the Gaussian reaches its peak) for the largest peak in the PSD. To assess the prevalence and
307 frequency of theta oscillations in human and rodent spiking, we computed the autocorrelation of spike times, and
308 performed a fast Fourier transform (FFT), yielding the PSD of the spike train.

309 **Phase estimation.** We estimated the instantaneous phase of LFPs in the theta frequency range. Theta oscillations
310 in human hippocampal formation are often bursty and non-stationary, and vary from low (2–5 Hz) to high (5–
311 10 Hz) frequencies^{43,62,63} - similar patterns are observed in bats⁹¹ and non-human primates^{92,93}. In order to analyze
312 fluctuations in the LFP analogous to rodent theta, we estimated 2–10 Hz phase by identifying peaks, troughs, and
313 midpoints in the lowpass-filtered LFP, and linearly interpolated between these points. This phase-interpolation method
314 has been used previously to effectively estimate theta phase in bats⁵⁵, as well as in rodents^{94,95}. To ensure that phase
315 estimates were not based on an unreliable low amplitude signal, we computed the instantaneous power of the LFP
316 and discarded those time-points in which the power fell below a 25th percentile threshold⁵⁵.

317 **Spatial phase precession.** To identify phase precession in this dataset, for each spatially modulated cell we first
318 identified every trajectory through the cell's peak firing location. Following the methods used in some recent studies
319 for measuring phase precession^{55,96,97}, first for each such trajectory, we identified the spike closest to the center of
320 the bin as the center spike (our reference point for the center of the bin on each trajectory)^{55,96,97}. We limited our
321 analysis to spikes in close spatial proximity to the center of the peak firing bin. To do so, we only analyzed the 11
322 closest spikes to the center of the peak firing bin. To ensure that these 11 spikes did not occur too distant from the
323 peak firing bin, we set a diameter threshold of 40% of the environmental width, meaning that we did not analyze
324 spikes that occurred further than 2 VR-units from the center of the peak firing bin. We re-ran our analyses while
325 varying the inclusion criterion for the number of spikes (9, 11, & 13) and the radius (40% & 60%) and found that the
326 parameters we selected did not significantly affect the proportion of cells exhibiting spatial phase precession ($\chi^2 =$
327 5.25, $p = 0.5$, chi-squared test).

328 We next tested for phase precession using circular statistics. Specifically, for each cell we measured the relation
329 between spike phase and the subject's position by computing the circular-linear correlation coefficient⁴⁷. To assess
330 statistical significance, we used a shuffling procedure. For each cell we computed a surrogate distribution for this
331 correlation coefficient by assigning random phases to each spike from the distribution of all the spike phases for that
332 neuron, and re-computing the correlation 500 times. This null distribution effectively scrambled the relationship
333 between spike position and spike phase and controlled for any effect of spurious phase estimates. A circular-linear
334 correlation was considered significant only if it exceeded the 95th percentile of this surrogate distribution.

335 **Control analyses for spatial phase precession.** We performed two control analyses for alternative explanations
336 for the spatial phase precession we observed. The first analysis tested whether the peak firing bin, our analogue to the
337 place-field center, was important to observing precession. To do so, we selected control locations for each cell and
338 assessed the strength and prevalence in these control bins. Control bins were chosen as to not overlap with the peak
339 firing bin (at least 30 % of the map width away) and also had to be traversed a minimum of 3 times with a minimum
340 firing rate of 0.5 Hz. Furthermore, because we only analyzed the 11 spikes in the immediate vicinity of the peak firing
341 bin, control bins matched the peak firing bin in sample size of spikes per trajectory, ensuring that effects were not
342 confounded by firing rate differences.

343 Another possible alternative explanation for our findings is that the phase precession we observed here is actually
344 encoding time to peak firing, independent of spatial position, with particular spike phases occurring at specific
345 time-intervals within any epoch of elevated firing rate⁹⁸. To control for this possibility, we identified epochs of
346 elevated firing rate in the time domain without any information about position, which we refer to as "firing rate
347 motifs"⁹⁸. We identified the spike that occurred closest in time to the peak firing of each motif field, and used the 11

348 spikes in the immediate temporal vicinity (within 2 seconds before or after) to compute a circular-linear correlation
349 between spike phase and spike time relative to the motif field peak, matching our spatial phase precession analysis.

350 **Non-spatial phase precession** To measure non-spatial phase precession without reference to place fields, we
351 compared the spiking frequency of each neuron to the frequency of the local LFP, with relatively faster rhythmic
352 spiking classified as phase precession^{42,49}. However, detecting oscillations in spike times alone is difficult in humans
353 (Supplementary Fig. 6) and bats⁵⁵, potentially due to the transient, non-stationary nature of theta observed in these
354 species^{55,63}. Instead, we applied a method introduced by Mizuseki et al.⁴² which measures spiking frequency relative
355 to the ongoing LFP. This is a particularly useful method when the ongoing LFP is non-stationary but may still be
356 an important reference “clock” for neuronal spiking. To perform this procedure, we computed the autocorrelation
357 histogram of each neuron based on the timescale determined by the phase of the reference LFP, rather than the
358 conventional method of using absolute time. We computed this autocorrelation using 60°-bins with window-length
359 of 4 cycles⁵⁵. We then computed the Fourier transform of the autocorrelation histogram to yield the power spectral
360 density (PSD) of the frequency of spiking relative to the LFP. Here, a peak relative frequency greater than 1.0 indicates
361 that the cell is oscillating at a faster frequency than the reference LFP. We excluded neurons that exhibited both a
362 peak near 1.0 as and significant phase-locking ($p < 0.05$, Rayleigh test) to ensure that we did not mistakenly identify
363 phase-locked neurons⁸⁵ as exhibiting phase precession. To measure the strength of this effect we measured the
364 amplitude of the PSD, normalized by the total amplitude across all other relative frequencies²⁶, which we refer to as
365 the “modulation index” (MI) (Fig. 4A).

366 In order to ensure that our results did not arise from poor phase estimates due to low LFP amplitude, we discarded
367 spikes that occurred during the lowest 25th percentile of LFP power in the oscillation of interest^{26,55}. In order to
368 ensure that low spike counts did not confound our estimates we only analyzed cells with more than 100 valid spike-
369 phase estimates for the autocorrelation. We compared the modulation index to the null distribution of modulation
370 indices for the peak frequency generated by circularly-shuffling the phases within each cycle of theta. This rigorous,
371 within-cell shuffling ensured that cross-cycle dynamics (such as precession) were disrupted while maintaining slower
372 and more rapid spiking dynamics^{26,55}. The modulation index was considered significant if it exceeded the 95th
373 percentile of this surrogate distribution. Finally, we excluded cells that exhibited significant phase-locking during the
374 entire session (Rayleigh test) in order to ensure that peaks close to 1.0 did not result from phase-locked spiking.

375 **Goal-state phase precession** To measure goal-state phase precession, we separately applied our analysis of non-
376 spatial precession to spiking during each of the six goal trials. We only included neurons for which we observed at
377 least 100 spikes per goal, to allow us to analyze non-spatial precession for each goal. We established two tests to
378 characterize significant goal-state phase precession. First, just as we did with session-wide non-spatial precession,
379 the magnitude of detected phase precession (as indicated by a peak in the spike-phase spectra exceeding 1.0) had
380 to be greater than the 95th percentile of the shuffled distribution. Because we conducted this test for all six goals
381 separately, we used the False Discovery Rate procedure⁹⁹ to correct the resulting p-values for multiple corrections
382 across goals. If a goal exhibited significant non-spatial precession, we then compared the goal-specific modulation
383 index to a surrogate distribution of modulation indices generated by selecting 500 random spike-trains from across
384 the entire session. Each null spike-train was generated to match the number of spikes recorded during the significant
385 goal to ensure that firing rate differences did not account for our results. A significant p-value indicated goal-state
386 precession that was significantly stronger for the goal in question than for the session as a whole.

387 Acknowledgements

388 We are grateful to the patients for participating in our study. This work was supported by the National Institute
389 of Mental Health (R01-MH104606) and the National Science Foundation (to J.J.), and NSF Graduate Research
390 Fellowship DGE 16-44869 (to S.E.Q.). We thank Kamran Diba, Sam McKenzie, Jonathan Miller, Andrew Watrous,
391 and Melina Tsitsiklis for helpful comments and suggestions.

392 **Author Contributions**

393 Conceptualization, J.J. and S.E.Q.; Methodology, J.J. and S.E.Q.; Investigation, I.F. and J.J.; Software, S.E.Q.;
394 Formal Analysis, S.E.Q.; Writing – Original Draft, S.E.Q.; Writing – Review Editing, S.E.Q., J.J., and I.F.; Funding
395 Acquisition, I.F., J.J., and S.E.Q.; Resources, I.F. and J.J.; Visualization, S.E.Q. and J.J.; Supervision, J.J.

396 **Declaration of Interests**

397 The authors declare no competing interests.

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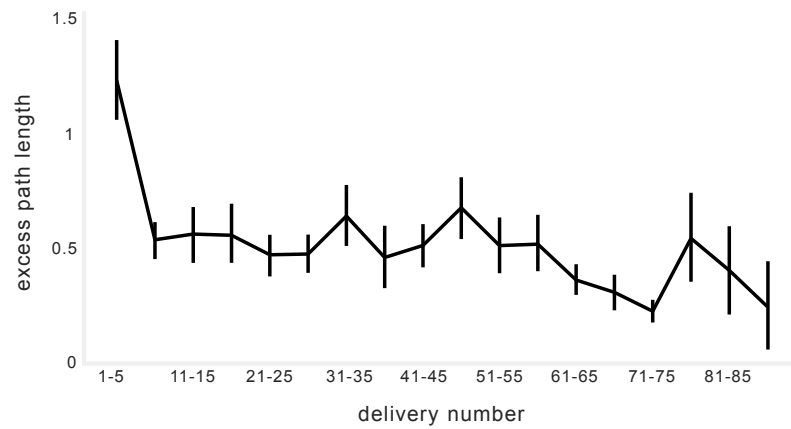
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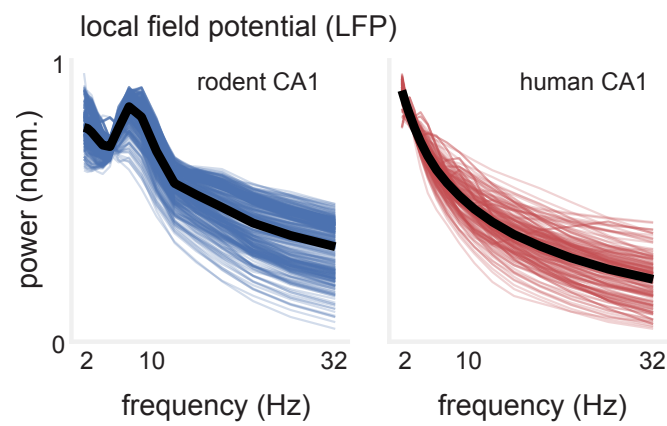
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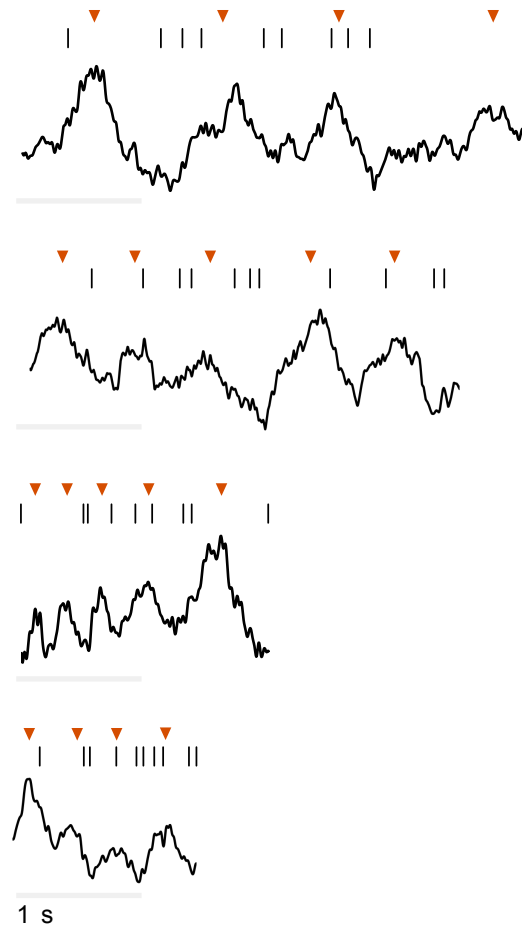
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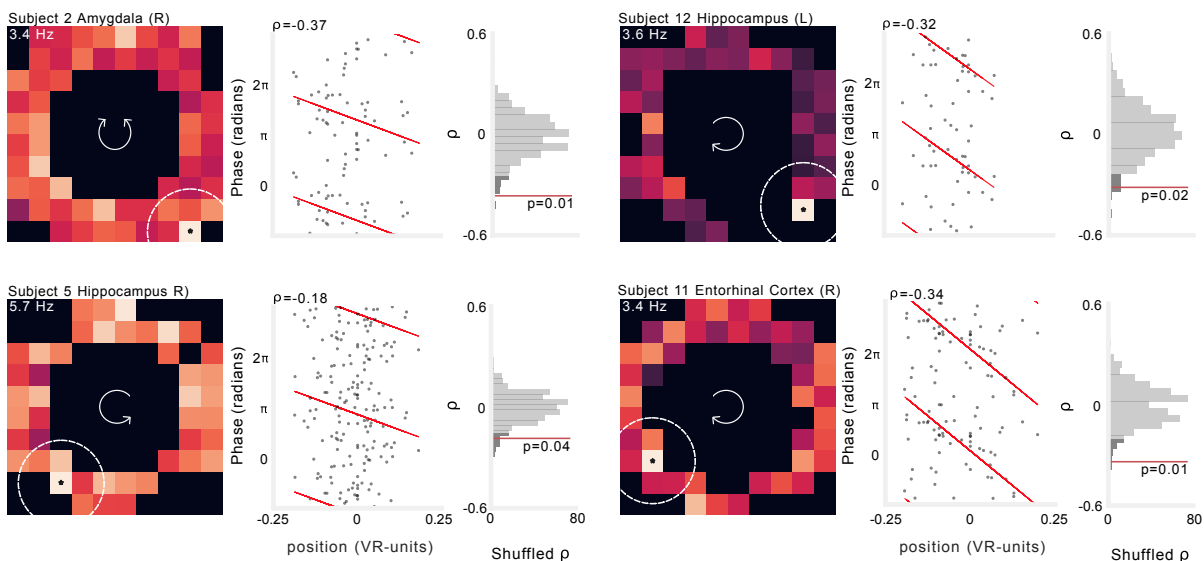
Supplemental Figure 1: Behavioral performance in the task. Plot indicates the mean excess path length across all sessions as a function of trial number.



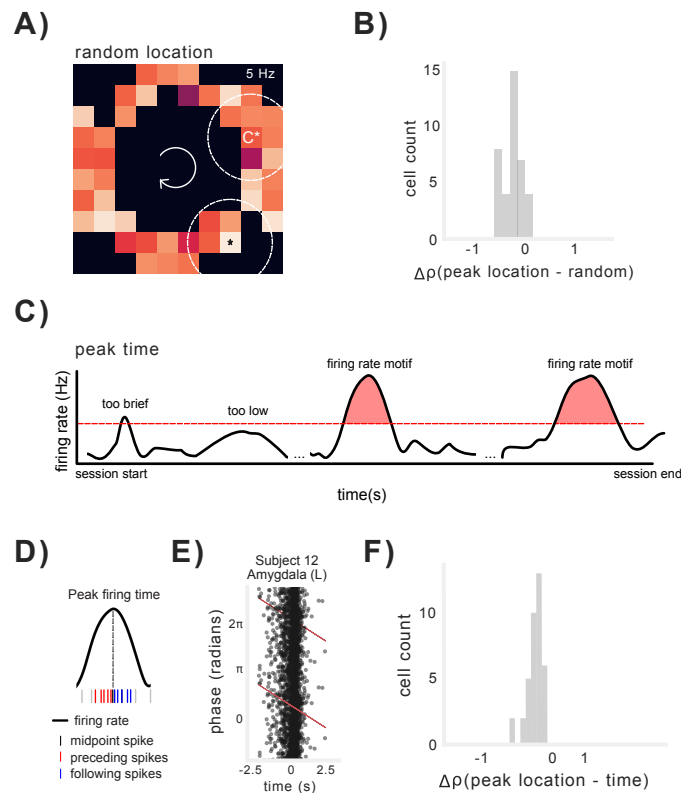
Supplemental Figure 2: Differences in rodent and human hippocampal theta oscillations. PSD of hippocampal LFPs recorded in navigating rodents (blue) and humans (red). Black line denotes average across channels. Rodent hippocampal LFP shows a clear peak in the 5-10 Hz range in almost all channels, while the human LFP does not.



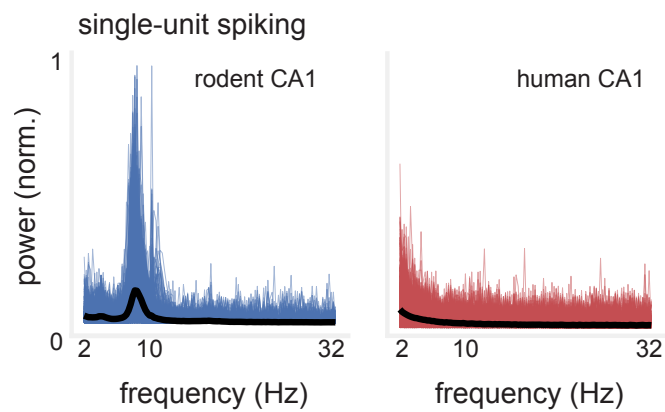
Supplemental Figure 3: Examples of spatial phase precession during individual passes through a field. Spike times and 1–30-Hz filtered LFP data during individual passes through peak firing bins for four neurons that exhibited significant spatial phase precession. Red arrows denote peaks of individual theta cycles.



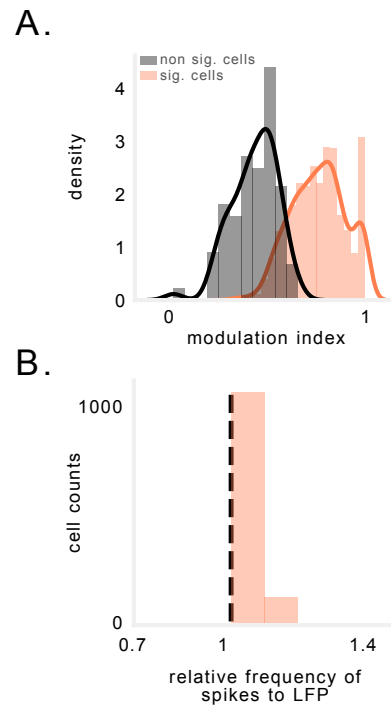
Supplemental Figure 4: Additional examples of spatial phase precession. The activity of four neurons that show significant spatial phase precession. Left: firing rate heat map. Brighter colors denote higher firing rates. Text label indicates the color scale for the plot with the mean firing rate of the peak firing bin, which is noted with an asterisk. Dotted lines indicate maximum radius around field in which spiking was assessed. Arrows in the center of the heatmap indicate the movement direction for which this plot was computed. Middle: spike phase as a function of location relative to the field center. Spike phases are duplicated vertically to enable visualization of circular-linear regression (red). Text indicates circular-linear regression coefficient (ρ). Right: surrogate distribution of circular-linear regression ρ -values generated by permutation of spike phases. Red line indicates value of real data. Dark gray shading indicates 95th percentile of surrogate distribution.



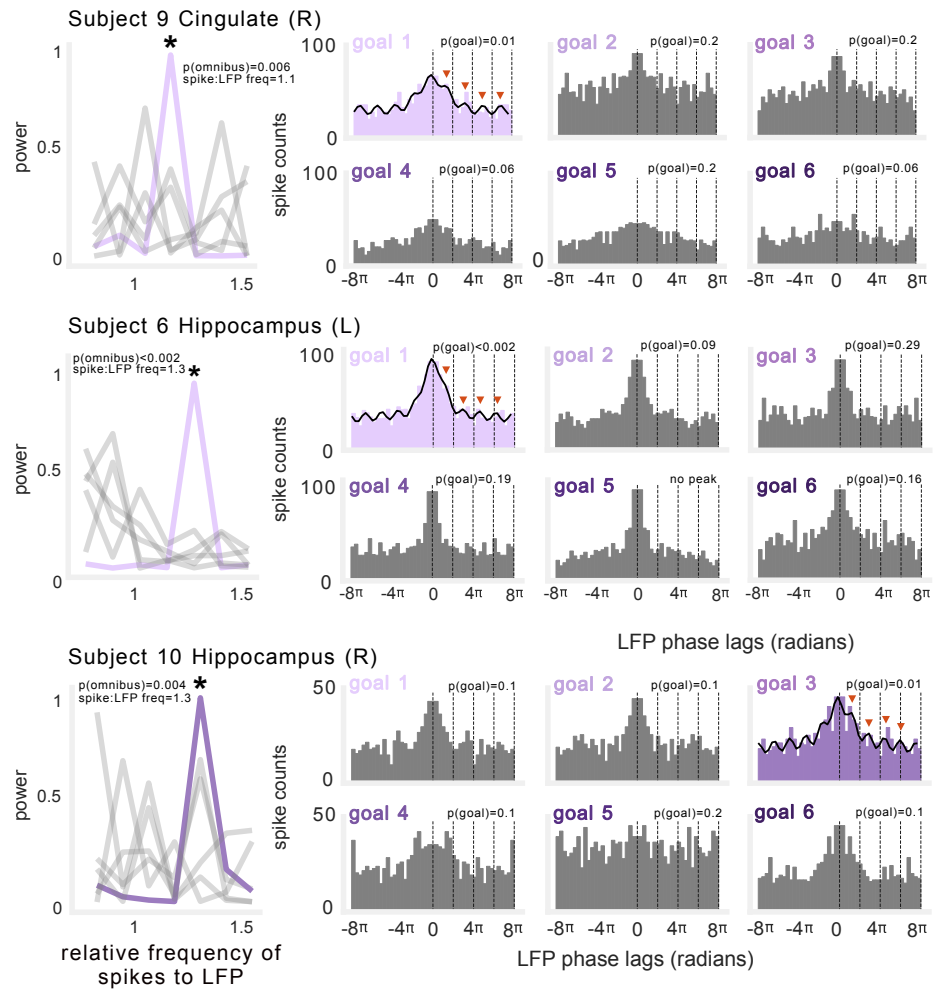
Supplemental Figure 5: Location- and time- control analyses for spatial phase precession. A) Example of alternate location selected to test whether peak firing bins exhibited significantly greater phase precession than randomly selected locations. B) Distribution of differences in circular-linear correlation coefficients for precession observed in peak firing bin vs. randomly selected location. C) Schematic of method for identifying elevated firing rate. Firing rate had to exceed a firing rate threshold of 1.5 Hz for at least 250 ms in order to be classified as a firing rate "motif". D) Schematic of method for time-based phase precession within motifs of elevated firing rate. E) Example neuron exhibiting significant phase precession relative to elapsed time within a firing rate motif. F) Distribution of differences in circular-linear correlation coefficients for precession observed in peak firing bin vs. time in firing motifs.



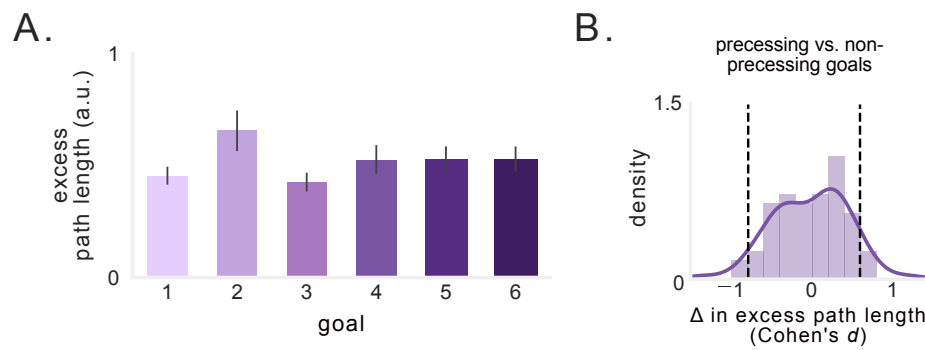
Supplemental Figure 6: Differences in rodent and human hippocampal neuronal spiking. Power spectral density from single-unit discharge from rodent (blue) and human (red) hippocampus. Solid black line indicates average across neurons. Rodent spiking shows clear theta modulation of spike timing while human spiking does not.



Supplemental Figure 7: Phase precession in rodent CA1 without reference to position. A) Modulation index (MI) of spike-phase spectral peaks for significant vs. non-significant neurons recorded in rodent CA1. B) Distribution of relative frequencies for neurons exhibiting significant MI in the spike-phase spectra. Values to the right of the black line indicate that the neuronal frequency slightly exceeded the LFP frequency.



Supplemental Figure 8: Additional examples of goal-specific phase precession. Three example neurons exhibiting phase precession during navigation to specific goals. Left: Power spectral density depicting frequency of neuronal spiking relative to ongoing LFP. Asterisk denotes peaks that were significant and significantly different from other goals. Gray lines denote spike-phase spectra for non-significant goals. Right: Spike-phase autocorelograms during navigation to each goal (significant goal epochs depicted in color). Text indicates the p-value for both significance tests described in Figure 5C), and relative frequency of spiking to LFP. Black line indicates fit of decaying-oscillation function added to significant examples shows oscillation in spike-phase autocorelogram.



Supplemental Figure 9: Goal-specific phase precession is not a function of a differences in navigation performance. A) Excess path length as a function of goal. B) Distribution of Cohen's d comparing excess path length during trajectories to goals that showed precession vs. those that did not. Black dotted line indicates effect size of ± 0.8 .