Supplementary Materials for

**Goal discrimination in hippocampal non-place cells when place information is ambiguous**

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The supplementary materials include:

- Supplementary methods
- Figs. S1 to S19
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Supplementary methods

Animals
In total 14 male mice (11-14 months old) were involved in this study including six WT and eight 5XFAD mice on a C57Bl/6 background. All animals were either obtained from the Jackson laboratory or bred in the animal facilities at Georgia Institute of Technology. Mice were housed on a reverse 12-hour light/12-hour dark cycle, and all electrophysiology and behavioral experiments were performed during the dark cycle. All animal work was approved by the National Institutes of Health guidelines on animal care and use at Georgia Institute of Technology. Biological replicates were defined as electrodes, experimental sessions, neurons, or animals as indicated in different analyses.

Surgical procedures
Mice were anesthetized with isoflurane before headplate implant surgery. A custom stainless steel headplate was fixed to the skull using dental cement (C&B Metabond, Parkell) and the target craniotomy site for LFP recordings was marked on the skull (in mm, from bregma: −2.0 anterior/posterior, +/-1.8 medial/lateral for CA1). Craniotomies were later performed before electrophysiology recording sessions. These craniotomies (200-500um diameter) were made by using a dental drill to thin the skull and then opening up a small hole in the skull with a 27-gauge needle. When not performing recording experiments, the craniotomies were sealed with a sterile silicon elastomer (Kwik-Sil WPI).

Behavioral training and analysis
The virtual-reality annular track environment was designed using ViRMEN open-source software and displayed on a cylindrical screen using an HD projector system reflected by several mirrors (1). To begin the behavioral task, head-fixed animals ran on a spherical treadmill composed of an 8-inch Styrofoam ball floating on air (Fig. S1A). Animals either immediately began behavioral training in the virtual reality environment the first time they were head-fixed on the treadmill (n = 11) or were given 1-3 days of habituation to the treadmill without the virtual-reality projector system turned on (n = 3). Animals ran on the ball and their translational and rotational velocities were tracked via an optical mouse and converted into movement through the virtual reality environment. In the first phase of behavioral training, animals navigated around the annular track environment and received a sweetened condensed milk reward (1:2 water dilution) when they entered either of the two reward zones. These locations were indicated with visual cues, and the reward location was the second instance of a patterned visual cue on each lap around the circular track (Fig. S1A). Once animals began demonstrating anticipatory licking before the reward zone, the animals were transitioned to the second phase of the behavioral task. In the second phase of behavioral training, animals had to lick in the reward zone in order to receive a reward (Figure S1BC). The second phase of behavioral training was the same environment and used the same visual cues as the first phase of training. Licks were detected using a photo-interrupter placed in front of the animal’s mouth around the reward spout, with signals of least 2V from 0V baseline were considered as a lick. Recording commenced after animals learned to lick in order to receive the reward. All of the behavioral analysis was performed on data from recording sessions. Raw behavioral data tracking translational and rotational velocity, licks, position, and time were analyzed using Matlab®. Position and velocity data were smoothed using a moving average and all data was segmented into trials in which each
trial was one full lap (360 degrees) around the annular track in which the animal passed through two reward zones. Only sessions and trials in which animals licked routinely were included to ensure animals were motivated and engaged in the task. Trials with at least 2 licks were considered motivated running trials. Only sessions with at least 10 motivated trials and 5 rewards were included in further analysis (Table S1). If the animal licked at least once in the reward zone, the trial was considered correct. We quantified lick rate and velocity as licks per second and degrees traveled in the track per second, respectively.

**Electrophysiology recordings**

Recordings were performed during the virtual-reality task described above. Animals were head-fixed on the treadmill for a maximum of 5 hours per recording session, with one recording session per day (number of sessions ranged from 1-4 per animal, Table S1). A 32-channel, single shank probe (NeuroNexus) was placed in a slightly different location within the craniotomy at the beginning of each recording session and advanced vertically to the CA1 pyramidal layer of hippocampus identified via electrophysiological characteristics: large theta waves, sharp-wave ripples, and 150+μV spikes on multiple channels. Recording sites (250μm between farthest sites) spanned the layer. Recordings consisted of interleaved periods of behavioral task performance, when animals navigated through the virtual reality environment, and no-task periods, during which no virtual-reality environment was displayed on the screen. Data were acquired with a sampling rate of 20 kHz using an Intan RHD2000 Evaluation System using a ground pellet as reference. LFP was obtained by downsampling raw traces to 2kHz and bandpass filtering between 1-300Hz.

**Classification of putative pyramidal cells and interneurons**

Spike detection and sorting were performed using MountainSort automated spike sorting and automated curation, followed by manual curation guided by visual inspection of waveforms and cross-correlograms (Fig. S19A)(2). Prior to manual curation, automatic curation was performed by applying quality thresholds to include units with a peak signal to noise ratio (SNR) greater than or equal to 1, less than 10% overlap with noise, and greater than 95% isolation against other units (Fig. S19B) (2). These three metrics were used to quantify the clustering results in MountainSort (2). SNR was defined as the peak absolute amplitude of the average waveform divided by the standard deviation of the aligned waveforms for each sampling time. The overlap with noise was the fraction of “noise events” in a cluster. The isolation metric measured how well separated the cluster is from other clusters. To account for periods of instability in the recordings during which single units were lost, stability criteria were applied such that only stable periods (no sudden loss of a single unit’s firing rate) would be considered in analysis. Firing rate (FR) for each unit was computed over the course of the recording session. Firing rate was clustered into two distributions, low FR and high FR, using k-means clustering. A stable period was defined as the longest length of time that the FR was 2 standard deviations above the low FR mean. If the firing rate of the unit never dropped below 10% of the high FR mean, the stable period was defined as the whole recording session. Stable periods (which last over minutes to hours) were used to identify which cells should be included or excluded in calculations of spatial firing maps and related analyses. For example, a cell was included in recording epoch 1 (30-60 minutes) but excluded from recording epoch 2 on the same day if the cell was unstable in the second epoch (3). Cell types were classified into putative pyramidal cells and putative interneurons based on the spike width and the first moment of the autocorrelogram (Fig. S19C).
These measurements are well-established metrics used for cell-type classification (4–8). Spike width was calculated as the length in milliseconds from the negative peak of the spike to the positive trough, where the trough was defined as the first instance when the differential of the waveform was equal to 0. The first moment of the autocorrelogram was calculated as the center of mass along the time-axis of an autocorrelogram calculated with lags of 0 to 50 ms. Single units were excluded if the autocorrelograms had a peak spike count less than 10. The mean firing rate was computed for each single unit and only stable periods for each unit contributed to the mean FR calculation (described above). The three parameters (spike width, firing rate, autocorrelogram moment) were then plotted for all single units, and these plots revealed two clear clusters that could be isolated using the spike width and autocorrelogram moment parameters. Putative pyramidal cells were defined as units that had a spike width greater than 0.5 ms and a first moment of the autocorrelogram less than 5 ms. Overall these thresholds for spike width and first moment of the autocorrelogram are similar to previously reported classification criteria, although the autocorrelogram function is dependent on the window it is measured within (4, 6, 8). For each unit, the cell’s recording depth was measured as the relative distance from the channel with largest waveform amplitude for that unit to the channel with highest ripple power (root mean square of filtered LFPs in 150-250 Hz) (Fig. S19DE).

LFP channels for obtaining stable theta phase

In brief, theta episodes were detected based on the LFP power ratio in theta (5–10 Hz) and delta (2–4 Hz) bands. A theta period was defined as a period during which this theta (5-12 Hz) to delta (2-4 Hz) ratio was 2 standard deviations above the mean for at least 6 seconds. Theta periods were manually inspected to ensure that the criteria used accurately included theta periods. To isolate CA1 recorded signals from the pyramidal layer center, we computed the highest ripple power (root mean square of filtered LFPs in 150-250 Hz) among all recording channels within the same probe (Fig. S10AB). This pyramidal layer channel was used for analysis and denoted as “within the pyramidal layer” or “pyr LFP channel” (Fig. S10EG). To obtain stable theta phases to measure theta-gamma states we used LFP recorded above the pyr LFP channel. We identified a theta channel for each recording that had similar theta-phase relationships to the pyramidal layer. To do this, we calculated the time lag of theta troughs (negative peaks of filtered LFP in 4-12 Hz) of all 32 channels relative to the top (most dorsal towards stratum oriens) channel (Fig. S10CD). The time lag was small and stable for more dorsal recording sites (closer to the top channel). To identify a theta channel, we used a generalized logistic function (GLF) to characterize the relationship between recording position (ReP.) and the theta time lag (Fig. S10D).

\[ \text{Lag} = b + \frac{a}{1 + e^{-c(\text{ReP.} - d)}} \]

where a, b, c, d were parameters of the GLF, a is the amplitude and b is the baseline (highest time lag). The channel closest to the 90% amplitude was identified (90%Amp-Ch.) and the channel positions 25 µm higher than the 90%Amp-Ch were evaluated as candidate theta channels. Among the candidate theta channels, the channel closest to the pyramidal layer was selected as the theta channel in order to use a recording site as close as possible to the pyramidal layer while still obtaining a stable theta phase (Fig. S10D). Recordings were included in theta-gamma clustering only if they satisfied two criteria. First, recorded signals had to have a phase-depth relationship as reported previously and indicated by good GLF fit and root mean square error of GLF lower than four (9). Second, the selected theta channel must be dorsal to the pyr LFP channel. After this quality control, 9 out of 36 recording sessions were excluded from the
theta-gamma coupling analyses based on these criteria. The total number of recording sessions included in theta-gamma coupling was 14 for WT and 13 for 5XFAD mice. We found similar results even if these sessions were included. Power spectral density of LFP was calculated using Welch’s method, with 50% overlapping Hamming windows of 512-ms length.

Wavelet spectrum normalized by theta phase
To decompose each theta cycle into its time-frequency decomposition, LFPs were first downsampled to 1000 Hz for faster subsequent calculations. Morse wavelets were then applied to the LFP using the Morse wavelet transform Ψ_β,γ(ω) = U(ω)a_β,γω^β e^{-ωγ} in the Fourier-domain form (25-150 Hz with 2.5 Hz step), where U(ω) is the Heaviside step function with U(ω) = 1 for ω > 0 and U(ω) = 0 elsewhere. a_β,γ = 2(γβ)^β/γ is the normalization constant.

The implementation of Morse wavelet is based on the jLab toolbox (http://www.jmlilly.net/software), which is also used as the default wavelet in the Matlab Wavelet Toolbox (Mathworks, Natick, MA). We use γ = 3 for maximizing frequency domain symmetry, time-frequency concentration, and similarity to a Gaussian (10). With a fixed γ, increasing β would increase the number of oscillations in the wavelet function thus improving the frequency resolution while decreasing the time resolution in the wavelet spectrum. Because there are usually more than 2.5 gamma cycles within a theta period, we use the default setting (γ = 3, β = 20) in the Matlab Wavelet Toolbox such that there are almost two and half (√γβ/π ≈ 2.5) completed periods in the wavelet before it decays in the time domain. We selected these parameters to ensure the wavelet spectrum represents more properties of the analyzed signals than that of wavelet itself, since the wavelet spectrum is essentially an interaction between the signal and the wavelet. We used Morse wavelets because the widely used Morlet wavelets were approximately analytic, exhibiting leakage onto the negative frequency axis in high time resolution settings. As a result, amplitude or phase estimation of signals using Morlet would be badly biased (10). While the Morse wavelet (γ = 3, β = 20) here was strictly analytic, it captured the essential idea of Morlet wavelets while avoiding its deficiencies and therefore was preferable for cross-frequency coupling analysis in the brain (11, 12).

To produce a time-frequency representation of LFP power, the wavelet power spectrum was z-scored across time for a given frequency. Instantaneous theta phase θ(t) was computed by linearly interpolating values between troughs (phase -π and π), zero-crossings (ascending zero with phase -π/2 and descending zero phase with π/2), and peaks (phase 0) of filtered LFP in 1-60 Hz board theta band (Fig. S10EG) (13). We then extracted a time-frequency decomposition matrix for each theta cycle A_k = {a_{t,f} = WS(t, f), t = T_k, T_k + 1, ..., T_k+T_k}, where A_k is the kth theta period detected such that θ(T_k) = 0° or -π, θ(T_k+1) = 360° or π.

θ(T_k + p) < θ(T_k + q), for any p < q and T_k + q ≤ T_k+1

Because the duration of the theta cycle varies, we separated each theta cycle into 20 phase bins, thus A_k was normalized into a 51 (Frequency) × 20 (theta phase) power matrix, also denoted as A_k(f, θ). This produced a frequency and theta phase power matrix (FPP). Twenty phase bins were chosen for the theta phase analysis as this was sufficient to robustly extract phase features of the three gammas with acceptable computational demands.

Clustering power in the wide gamma band across theta cycles
To separate theta cycles into different theta-gamma coupling states, K-means clustering was used because it was computationally more efficient than community clustering and it more reliably
extracted medium gamma oscillations in the deep pyramidal layer of CA1 (14). For clustering, the FPP for each theta cycle was considered as a set of points in 1020-dimensional space (51 frequencies × 20 phases). K-means clustering assigns the n power samples \( A_i \) in the frequency-phase domain to exactly one of \( k \) clusters defined by centroids, where \( k \) is chosen before clustering (15). A distance matrix \( D \) is used for clustering and we used Pearson correlation distance \( D = 1 - C \), where \( D_{ij} \) quantifies the distance between any pair of theta cycles \( A_i \) and \( A_j \). The Pearson correlation (C) is a standard similarity measure (cf. distance if 1-C) in image processing especially because it is invariant to power (16). For an optimal \( k \), we first checked the clustering quality using several standard measures including Silhouette Index, Dunn Index, and Davies-Bouldin Index. The clustering quality decreased in general with increasing \( k \). We chose \( k = 3 \), based on multiple reports of three gammas in CA1 (17–21). Indeed, we extracted the S-gamma (30-60Hz), M-gamma (60-100Hz), and F-gammas (100-160Hz) in both genotypes (Fig. S10EFGH). In using Pearson correlation as a distance measure for k-means, we are treating the FPP as a normalized image, and clustering based on notions of image similarity. In our analysis phase wrapping does not affect the results because the correlation is computed from the same points or bins (in frequency and phase) between one image (FPP) and another. Therefore, the geometrical relationship between bins does not matter: the correlation is not affected by whether adjacent bins have similar values or those values are on opposite sides of the image. Here we applied the k-means++ algorithm implemented in Matlab Statistics and Machine Learning Toolbox (Mathworks, Natick, MA).

Gamma fields were defined as fields above a threshold of 95% of the peak of the average FPP within one cluster. The gravity frequency and theta phase for the center of gravity of each gamma field were extracted. Thus, the feature of a specific cluster could be represented by the gravity frequency and gravity theta phase of its gamma field. Gravity frequency was defined as the weighted average of frequencies (y coordinates) of all points within the gamma field, while gravity phase was the weighted average (circularly) of phases (x coordinates) of all points within the gamma field (Fig. S10FH). The weight of each point in the gamma field was defined by the power value at that point in the FPP. S-, M- and F-gamma clusters correspond to the gravity frequencies from low to high frequencies (Fig. S10FH).

**Pairwise phase consistency for spike-field analysis**

To quantify spike-field phase synchronization, we calculated the pairwise phase consistency (PPC) between LFP and spikes. PPC is unbiased by the number of trials and less affected by the number of recorded spikes than conventional phase-locking analysis (22). In short, PPC for a given frequency band \( f \) is calculated with the following equation (for details refer to Vinck et al., 2012):

\[
PPC(f) = \frac{1}{|M|(|M| - 1)} \sum_{m \in M,l \in M,l \neq m} \sum_{k=1}^{N_m} \sum_{j=1}^{N_l} \frac{\sum_{k=1}^{N_m} \sum_{j=1}^{N_l} U_{k,m}(f) \cdot U_{j,l}(f)}{N_m N_l}
\]

in which \( |M| \) is the number of trials in total, \( U_{k,m} \) is the instantaneous phase of filtered LFP at frequency \( f \) when the \( k \)th spike occurs during trial \( m \). \( N_m \) and \( N_l \) are the number of spikes in trial \( m \) and \( l \) respectively. The instantaneous phase of filtered LFP was calculated using the Hilbert transform. For PPC analyses, we aimed to systemically assess spike-field coupling across frequencies including theta, gamma, and frequencies in between. Therefore, we segregated frequencies into 20Hz bands across 20-160Hz. Thus, PPC was calculated for delta (1-5Hz), theta (5-12Hz), beta (12-20Hz), and non-overlapping 20Hz wide frequency bands from 20 to 160 Hz.
(10 frequency bands in total). Neurons included in the spike field analysis had to satisfy the following two criteria: (1) neurons fired at least five spikes in each of the six spatial bins in the task on both correct and incorrect trials and (2) firing rates were higher than 1Hz and neurons were classified as putative pyramidal cells (n = 311) to ensure that enough spikes were available for analysis (Table S2).

**Place cell identification and spatial information quantification**

The animal’s position was smoothed through locally-weighted scatter plot smoothing (Lowess) with an 11-sample window (0.22s) (23). To quantify place cells, we calculated an occupancy-normalized firing rate map of putative pyramidal cells as a function of position on the annular track, using 2-degree bins and Gaussian smoothing of spike counts and time spent in each bin. Firing rate maps were calculated only using the cell’s stable times (described above) during running periods (speed ≥ 1 degree/s). Spatial information for pyramidal cells was then calculated using the firing rate maps by applying the following equation:

$$\text{Spatial Information} = \sum_i p_i \frac{\lambda_i}{\lambda} \log_2 \frac{\lambda_i}{\lambda}$$

Where $p_i$ was the probability the animal was in the $i$th bin, $\lambda$ was the mean firing rate of the cell, and $\lambda_i$ was the firing rate of the cell in the $i$th bin (24, 25). Place cells were pyramidal cells that met the following criteria: (1) a peak firing rate greater than 1 Hz, (2) an average firing rate less than 10 Hz (to exclude potential interneurons), and (3) spatial information content in the 95th percentile or above compared to the shuffled spike train data. Non-place cells were those that did not reach place cell criteria. In order to control for biases due to low-firing in place or non-place cells, only cells that fired at greater than 0.5 Hz were included in further analysis (Table S2). To quantify spatial coding across the entire environment, spatial information significance (SpaInfo Sig.) was defined as the spatial information (SpaInfo) normalized by spatial information from the randomly resampled distribution (SpaInfoRe) of the same cell (24, 26).

$$\text{SpaInfo Sig.} = \frac{\text{SpaInfo} - \text{mean}(\text{SpaInfoRe})}{\text{std}(\text{SpaInfoRe})}$$

where std referred to standard deviation. Because the shuffled data is usually not symmetrically distributed around the mean, $z > 2$ does not necessarily mean that the raw spatial information is higher than the 95th percentile of the shuffled data, the criteria which defined place cells.

**Goal discrimination index**

The circular track was divided into two halves, each ending at a reward zone, and further divided into quarters. Similarity scores between normalized firing rate maps for halves or quarters of the track were computed using Pearson correlation coefficients in which speed was controlled as a covariate. Goal Discrimination Index (GDI) was defined as

$$\text{GDI} = \frac{(\text{SimiQtr}_{2-4} - \text{SimiQtr}_{1-3}) / (|\text{SimiQtr}_{2-4}| + |\text{SimiQtr}_{1-3}|)}{\frac{1}{2} \ln \left( \frac{1 + r}{1 - r} \right)}$$

$\text{SimiQtr}_{1-3}$ was the Fisher z-transform of similarity scores between the normalized firing maps for the first and third quarters of the track (false goal similarity, sub-path leads to the false goal); while $\text{SimiQtr}_{2-4}$ was the same for the second and fourth quarters of the track (true goal similarity, sub-path leads to the true goal). Fisher z-transform of correlation coefficients $r$ was applied in order to make the distribution of correlation values approximately normal.

GDI, defined based on sub-paths or parts of the path leading to the false goal or the true goal, is calculated to test how well the cell discriminated between the two sub-paths in cells that code for
distance to goal. Cells that do not code for distance to goal may have low correlations between the two sub-paths leading to each goal or the two sub-paths leading to each false goal (e.g., negative correlation values for true and false goal similarity). Yet a relatively higher true goal similarity than false goal similarity in this cell would lead to positive GDI even though both similarity scores are low. Therefore, GDI in cells that do not code for distance to goal may result in spurious high values. Thus, we segregated the population based on cells’ goal similarity, which is a measure of the cells’ coding for distance to goal at the single cell level. Cells with extremely high goal-similarity (driven by both high true and false goal similarity values) may have GDI approaching zero if the cell fired similarly on both sub-paths to the true and false goals. Indeed we observed GDI approaches zero in cells with higher goal similarity (Fig. 1D left panel; GDI for cells with goal similarity ≥ 0.3).

Partial correlation was used to reduce the impact of speed on spatial similarity (Fig. S2BCDE, left). To quantify distance to goal coding, the partial correlation between firing rates as a function of position was performed between segments of the track with the same distance to reward but distinct cues, e.g. between the first half and second half of the track (goal similarity). In order to check whether partial correlation controlled for speed modulation, we compared raw correlations and partial correlations between the first half and the second half of the track while including or excluding the reward zone, which has the largest changes in speed (Fig. S2A). We expected speed to have a larger impact on raw correlations when the reward zone was included than excluded and therefore lead to higher correlations when the reward zone was included. If partial correlations control for this effect of speed, we would expect that partial correlation values would be much more similar than raw correlation values when the reward zone was included or excluded. Indeed, goal similarity was significantly higher when calculated using raw correlations with the reward zones included versus excluded (Fig. S2BCDE, middle). Differences between correlations when the goal zone was included or excluded dramatically decreased when using partial correlation to compute goal similarity (Fig. S2BCDE, right). In summary, partial correlations controlled for speed modulation effects on the similarity of neuronal firing between different spatial segments. We used a similar approach to control for both speed and lick rate. Because licking is not a continuous variable and occurred mainly close to or within true or false goal zones, we used the non-parametric correlation coefficient Spearman’s $\rho$ instead of Pearson’s $r$ correlation. Using this approach, we found that speed and lick rate did not noticeably alter GDI (Fig. S3). Spearman’s $\rho$ was also used to quantify the correlation between GDI and the success rate to receive reward in each session (Fig. S15). To prevent poor estimates of spatial similarity due to very low firing rates, only cells that fired ≥ 0.5 Hz were included in this analysis (Table S2).

To assess the relationship between licking behavior and spiking of non-place cells, peri-stimulus time histograms (PSTHs) around licks were calculated separately at the false goal zone (P3) and true goal zone (P6). Licks occurring 10 degrees before entering the zones were also included as they indicated anticipatory licking (Fig. S6). For P6, only licks before the reward was triggered were included and therefore licking was anticipatory not consumptive. Only cells that met the following criteria for significant lick-related activity were included: peak Z value ≥ 3 with at least one neighboring bin to the peak bin ≥ 0 and at least 100 spike counts in the raw PSTH.

**Bayesian decoding of current position**
Estimates of current position were decoded from populations of single unit spiking activity using a Bayesian decoder \(^{(27, 28)}\). Trials for each recording session were randomly divided into training and testing trials (5-fold cross validation). Training trials were used to calculate occupancy-normalized firing rate maps for each included cell using 5-degree spatial bins. To test the decoder, spikes from each cell during test trials were binned into temporal blocks of 500ms (mice typically cover around 2-7 degrees of the 360 degree track in 500ms). For each temporal block with active cells, the spatial probability distribution was calculated as follows\(^{(29)}\):

\[
P(\theta|S_i^N) = \frac{1}{C} \prod_{i=1}^{N} \left( \frac{\tau f_i(\theta)}{S_i^1} \right)^{S_i} \exp \left( -\tau \sum_{i=1}^{N} f_i(\theta) \right)
\]

where \(N\) is the number of included cells, \(\tau\) is the time window to be decoded, \(\theta\) is position, \(S_i\) is the spiking activity of cell \(i\) in the time window, \(f_i(\theta)\) is the occupancy-normalized firing rate for cell \(i\) over position \(\theta\), and \(C\) is a constant used to normalize \(P(\theta|S_i^N)\) to sum to 1. The decoding result was validated using 5-fold cross validation and the output was averaged. When place cells or non-place cells were deleted from the population used to decode position, the same number (determined by 30% of the pyramidal cells recorded; Table SS3) of place or non-place cells were randomly deleted from each recording session. This deletion process was repeated 100 times and the results of each iteration were averaged and smoothed with a 2D Gaussian kernel (\(\sigma = 5\) degrees). If the number of place or non-place cells was less than 30% of pyramidal cells in one recording session, all cells of that type were deleted. For each session, decoding was performed over the entire track (0-360 degrees, global position) and over the position along the path to the goal, collapsing both halves of the track together (0-180 degrees). The decoding probability distribution was normalized to chance levels (divided by a uniform distribution), thus the normalized probability of 1 represents the chance level when all positions are decoded equally \(^{(30)}\). The probability of decoding the goal zone was defined as the peak values of the goal zone (150-180 degrees) in the decoded position and was calculated as a function of the actual position for each 10-degree bin. To ensure acceptable baseline levels of decoding for actual position before excluding any cells, only sessions with a normalized probability of decoding the actual global position above 1.5 were included in these decoding analyses. In total six sessions in WT animals and six sessions in 5XFAD animals were included in decoding analyses. Results were similar for deleting 20% or 40% of pyramidal cells and deleting more cells slightly increased the significance (Fig S7; Table S3).

**Statistics**

ANOVA for repeated measures and mixed model ANOVAs for repeated measures were performed in R to evaluate the effects of within-subject and between-subject factors for all categorized factors including location (30 degree spatial bins, or three locations groups including true goal zone, false goal zone, and other zones), performance (correct vs. incorrect), cell type, and genotype on neuronal activity including firing rate, pair-wise phase consistency, and theta-gamma state transition types (occurrences of the three theta gamma states, and their 9 types of transitions). However, an ANOVA was not suitable to address non-categorical factors such as speed and licking. As a result, linear mixed-effects modeling (LME) was performed instead when evaluating the effects of location (categorical variable), speed (continuous variable), and licking behaviors (continuous variable) on neuronal firing or PPC. In the LME, location, speed, and licking modulation effects on neural activity were considered as explanatory variables or
fixed effects. To control for variation due to individual cell differences, we used intercepts for each cell as random effects for repeated measurements. The LME was fitted to the data using the lme4 package in R (31). Statistical significance was generated for fixed-effect terms with Satterthwaite methods for denominator degrees of freedom for F-tests using the lmerTest package in R (32). Statistical significance values were presented similarly as for a classic ANOVA, except that the degrees of freedom in F tests could be non-integer numbers. T tests between subgroups were performed as post-hoc analysis. False discovery rate (FDR) correction (q < 0.1) was applied to correct for multiple comparisons, and the number of comparisons were further described in Table S4. Many comparisons were paired, e.g. between correct and incorrect trials, and were indicated as such.

In behavioral analyses, to control for the potential effects of differences in session numbers (days) between individual subjects, we used a hierarchical bootstrapping approach for post-hoc analysis (33, 34). In bootstrapping, N subsamples of the data are resampled with replacement from the original data and then the metric of interest is calculated for each subsample. For each genotype (5XFAD and WT), we resampled with replacement from animals in each group, then for each resampled animal, we resampled with replacement from the sessions. We performed the hierarchical bootstrapping as described above, then calculated the mean of this resampled population of values, and then repeated the bootstrapping 10^4 times. We thus produced a distribution of resampled means for each genotype and each locations of interests. These resampled distributions were used to compute whether the metric of interest was significantly different between genotypes or locations. Since animals were used as the first level of the resampling process, each animal contributed equally to the final resampling distributions. Thus, our results were reported as direct probabilities of location difference being greater or less than 0 for paired comparisons within each genotype; and direct probabilities of the WT population being greater or less than the 5XFAD population for unpaired genotype comparisons (33). For example, when we performed paired comparisons of speed between the true goal zone and the false goal zone within WT mice, the significance level was defined as P_{boot} = 2 \times \text{Min} \{P_1, 1-P_1\}, where the direct posterior probability P_1 = \text{probability} (\text{Speed}_{\text{true goal zone}} - \text{Speed}_{\text{false goal zone}} \geq 0). False discovery rate (FDR) correction (q < 0.1) was applied to correct for multiple comparisons.
**Fig. S1. Navigation task with false goal zones to assess neural codes for place, cues, and rewards.**

**A.** Left, schematic of virtual-reality experimental set-up. Right, annular track spatial navigation task with wall cues shown on the annulus. Each wall cue is repeated twice. **B.** Example of one animal’s position as a function of time in the annular track during the task. The time and location of each lick is represented by a black dot. Reward is delivered only if the animal licks in the reward zone, indicated by green triangles, and is a correct trial. On incorrect trials, animals do not lick in the reward zone, indicated by red crosses. **C.** Averaged lick rate (top) and speed (bottom) as a function of position across wild-type, WT (grey), and 5XFAD (red) animals. The track featured false goal wall cues that were identical to those in the true goal zone. The true goal zone could be distinguished by the overall sequence of wall cues across the trial (e.g. that it was the second identical cue) and by distal cues. Mean +/- SEM. WT: n = 17 sessions; 5XFAD: n = 19 sessions. **D.** Same as C except averaged across mice instead of sessions, meaning the sessions for each mouse were averaged together so that each mouse was considered as a sample. WT: n = 6 mice; 5XFAD: n = 8 mice.
Fig. S2. Spatial firing similarity using partial correlation to assess the effects of speed. A. Schematic of repeated wall patterns in the environment. The similarity of spatial firing was calculated between yellow and orange segments and was performed two ways: one including the entire track and goal zone (All) and the other including the track before the goal zone (Pre-goal zone, Pre). Both pair-wise correlation (Raw) and partial correlation regressing out speed (R.S.) were calculated to examine the partial correlation approach to control for the effects of speed on the spatial similarity measurement. We examined correlations with and without the goal zone because animals consistently slowed down to lick in both reward zones which caused common speed variation within goal zones. The raw correlation tended to be higher than the partial correlation, and raw correlations of the total track (All) were higher than the track without goal zones (Pre). This result revealed that speed increased the raw correlation values and this increase was largely driven by speed changes at the goal zone. No significant differences were found between partial correlations with (All) or without the goal zone (Pre), indicating that the partial correlation approach controlled for these speed differences. B. Left, Scatter plot (top) of partial correlation (Y-axis) versus raw correlation (X-axis) and histogram of differentiation indices (bottom) with mean value (solid green vertical line) and p-value of t test shown (p=3.21e-07, t_{216}=5.276) for place cells in WT mice. Dashed lines indicate identity line. Middle, same as left for the raw correlation comparison between goal zone included (All) and goal zone excluded (Pre, p=0.015, t_{216}=2.457). Right, same as left for the partial correlation comparison between goal zone included and goal zone excluded (p=0.044, t_{216}=2.028). C. As in B for non-place pyramidal cells.
in WT mice. Statistics are listed from left to right (p=0.176, t_{104}=1.361; p=0.032, t_{104}=2.180; p=0.057, t_{104}=1.922). D. As in B for place cells in 5XFAD mice; statistics are listed from left to right (p=5.71e-06, t_{275}=4.627; p=0.038, t_{275}=2.080; p=0.552, t_{275}=-0.595). E. As in D for non-place pyramidal cells in 5XFAD mice; statistics are listed from left to right (p=2.14e-4, t_{146}=3.798; p=1.66e-05, t_{146}=4.455; p=0.192, t_{146}=1.310). Pyr.: pyramidal cells.
Fig. S3. Goal discriminability in CA1 pyramidal cells using partial correlation to assess effects of speed and licking. A. Top: Schematic of repeated wall patterns in the environment. Bottom: Example of partial correlation technique to control for the effects of speed and licking.
rate on goal similarity. True goal similarity and false goal similarity were calculated in the same way. Scatter plot (top row) of partial correlation (Y-axis) versus raw correlation (X-axis) and the histogram of differentiation indices (bottom row) with mean value (solid green vertical line) and p-value of the t test shown for place cells and non-place cells in WT and 5XFAD mice from left to right. Raw correlation was significantly higher than partial correlation (Statistics from left to right are p=3.82e-09, t_{216}=6.144; p=0.025, t_{104}=2.282; p=2.51e-07, t_{275}=5.289; p=0.028, t_{146}=2.215; un-paired t test, q < 0.1, FDR correction of 4 comparisons). **B.** Comparisons of Goal Discrimination index (GDI, defined as (True goal similarity - False goal similarity)/(|True goal similarity|+|False goal similarity|), see Supplementary Methods for details) using raw correlation values without considering speed and licking as covariates. Data shown for both place cells and non-place cells as a function of the goal similarity (left panel) and spatial information significance (SpaInfo Sig., right panel), respectively for WT (top) and 5XFAD (bottom) mice. * indicates significant differences (un-paired t test, q < 0.1, FDR correction of 20 comparisons = 10 cells group segregations × 2 genotypes); black arrowhead denotes less strict statistics (p < 0.05, un-paired t test with no FDR correction). **C.** As in B but using partial correlation to control for speed and licking.
Fig. S4. Two components of goal similarity in CA1 pyramidal cells in WT and 5XFAD mice.  
A. Top. Schematic of the two similarity values (correlation coefficients) that were computed between the segments of the track indicated with yellow and orange arrows. One sub-path leads to the false goal (Simi F.) and the other sub-path leads to the true goal (Simi T.). Simi F. and Simi T. were compared within (2 paired t test) and between (2 un-paired t test) place cells and non-place cells. Cells were grouped by goal similarity score into five groups (Goal similarity > -1, 0, 0.1, 0.2, and 0.3) shown in the five columns respectively. WT (top) and 5XFAD (bottom) mice are shown in the rows.  
B. As in A, but segregating cells by spatial information significance. * indicates significant differences (un-paired t test for cell type comparisons and paired test for similarity type comparisons, q < 0.1, FDR correction of 80 comparisons = 2 similarities × 2 cell types × 10 cells group segregations × 2 genotypes), and black arrowhead denotes less strict statistics (p < 0.05, t test with no FDR correction).
Fig. S5. No significant impact of firing rate on goal discrimination index in non-place cells of WT animals. Non-place cells were separated into four groups based on overall firing rate and spatial information significance (low firing and low spatial-tuning, open grey square; low firing and high spatial-tuning, open black square; high firing and low spatial-tuning, filled grey square; high firing and high spatial-tuning, filled black square), using thresholds of firing rate above or below 1 Hz and SpaInfo Sig. above or below 2). The corresponding two-way ANOVA is shown below. Neither firing rate nor interaction effects were observed (p > 0.6, F test for all 3 comparisons listed at the bottom). No significant differences were found between low firing and high firing in the high spatial tuning group (black unfilled vs black filled squares; p = 0.503, t_{88} = -0.672, unpaired t test).
Fig. S6. Lick associated firing activity in WT mice. A. Peristimulus time histograms (PSTHs) around licks were used to quantify lick-related firing. Two example significant lick-related cells (peak Z value ≥ 3 and at least one bin neighboring the peak bin ≥ 0) are shown on top, blue and red indicating peak firing before and after licking, respectively. Two units without significant lick-related firing are shown below. B. Pie charts show the percentage of the pyramidal cell population with significant lick-related activity before (blue) or after (red) licking or with no significant lick-related activity (grey).
Figure S7. Decoding analysis excluding 20% and 40% of pyramidal cells in WT mice.

A. Decoding analysis excluding 20% of pyramidal cells (n = 6 sessions, Table S3). Left: Normalized probability of decoding actual position over the entire track including all cells (purple circles), excluding a subset of place cells (gray diamonds), or excluding a subset of non-place cells (black squares). Each line indicates one recording session; circle, diamond, and square markers indicate mean; error bars indicate standard error of the mean. * indicates significant differences (paired t test, q < 0.1, FDR correction of 6 comparisons = 3 cells group × 2 genotype). Center: Normalized probability of decoding actual position relative to the goal over the entire track including all cells (purple circle), excluding a subset of place cells (gray diamond), or excluding a subset of non-place cells (black square). * indicates significant differences (paired t test, q < 0.1, FDR correction of 150 comparisons = 6 whole track comparisons [3 cells group × 2 genotype] + 144 comparisons [18 positions × 3 cells group × 2 genotype over chance level, and cell type comparisons of 18 positions × 2 genotype]). Right: Changes in the decoded probability after excluding a subset of place cells (gray diamond), or a subset of non-place cells (black square) compared to including all cells (purple line). Regions inaccurately decoded as the goal are highlighted in orange. Red * indicates significant differences higher than the chance (one sample t test, q < 0.1, FDR correction of 150 comparisons). Red arrowhead denotes less strict statistics (p < 0.05, paired t test with no FDR correction). Black * indicates significant cell type differences between excluding a subset of place cells versus a subset of non-place cells (paired t test, q < 0.1, FDR correction of 150 comparisons). B. As in A but excluding 40% of pyramidal cells.
Fig. S8. Spatial firing rate and speed differences between correct trials and incorrect trials. 
A. Schematic of the track with the false goal cue at P3 (yellow). F: false goal; T: true goal. B. Left, firing rate over position on correct (green) and incorrect (grey) trials of place (top) and non-place pyramidal cells (bottom) in WT mice (place cells: $p = 2.7 \times 10^{-6}$, $F_{5,975}$ (performance × location) = 6.85, two-way repeated measures ANOVA; non-place cells: $p = 7.0 \times 10^{-5}$, $F_{5,850}$ (performance × location) = 5.38, two-way repeated measures ANOVA) and in 5XFAD mice (place cells: $p = 0.61$, $F_{5,1235}$ (performance × location) = 0.715, two-way repeated measures ANOVA; non-place cells: $p = 2.0 \times 10^{-4}$, $F_{5,995}$ (performance × location) = 4.86, two-way repeated measures ANOVA). * indicates significant differences between correct and incorrect trials (paired-t test, $q < 0.1$, FDR correction of 24 comparisons = 2 cell types × 2 genotypes along 6
locations), and black arrowhead denotes less strict statistics ($p < 0.05$, paired t test with no FDR correction). C. Speed over position on correct and incorrect trials for WT (left) and 5XFAD (right) mice (n = 16 sessions, WT: $p = 2.6e-15$, $F_{5,75}$ (performance × location) = 26.47, two-way repeated measures ANOVA; n = 19 sessions, 5XFAD: $p = 2.0e-16$, $F_{5,90}$ (performance × location) = 33.38, two-way repeated measures ANOVA). One session with no incorrect trials was excluded from WT data here, compared to n = 17 in Figure 1C. * indicates significant differences between correct and incorrect trials (paired-t test, $q < 0.1$, FDR correction of 24 comparisons = 2 behavior metrics × 2 genotypes along 6 locations), and black arrowhead denotes less strict statistics ($p < 0.05$, paired t test with no FDR correction). D. As in C for lick rates (WT: $p = 2e-16$, $F_{5,75}$ (performance × location) = 73.68, two-way repeated measures ANOVA; 5XFAD: $p = 2.0e-16$, $F_{5,90}$ (performance × location) = 54.11, two-way repeated measures ANOVA).
**Fig. S9. LFP power in both WT and 5XFAD animals.**

**A.** LFP power in WT (black, n = 14 sessions) and 5XFAD (red, n = 13 sessions) mice for 6 spatial bins (with one graph per bin) for both correct (top) and incorrect trials (bottom). P values are shown on the top of each panel (unpaired t test). Blue arrows indicate robust genotype differences across all locations.

**B.** LFP power on correct (green) and incorrect (black) trials for 6 spatial bins (graphs 1-6) for both WT (top) and 5XFAD mice (bottom). P values are shown on the top of each panel (paired t test), and blue arrows indicate frequency bands with significant differences (p < 0.05).
Fig. S10. **Identification of pyramidal and theta channels.** A. Recording sites on a NeuroNexus A32 probe where each dot represents one channel, dot size represents the average ripple power and * denotes the highest ripple power channel and the center of pyramidal layer in this example recording. B. Example LFP traces recorded on each channel in A during ripple events. s.r.: stratum radiatum, s.o.: stratum oriens. C. Example LFP traces recorded on each channel in A during theta oscillations. T denotes the channel used to measure theta phase (theta channel) to normalize the
wavelet spectrum in the time domain for each single theta cycle. \textbf{D.} Time lag of theta trough across all channels compared to the top channel as function of recording depth. A sigma function was used to fit the curve (solid line). The channel closest to the 90\% amplitude (dash vertical line) of the time lag curve was identified (90\%Amp-Ch.) and the lowest channel 25 \textmu m higher than the 90\%Amp-Ch was chosen as the theta channel. \textbf{E.} Two simultaneously recorded LFP traces with eleven successive theta cycles from CA1 in a WT mouse (M8, S180214) showing the theta channel for theta phase estimation (top trace) and pyr. channel (bottom trace, see Supplementary Methods for details). Raw traces (grey) were filtered for broadband theta (red, 1-60 Hz) to estimate the instantaneous theta phase. Troughs marked the start and end of each theta cycle (dashed vertical line). Frequency-phase power (FPP) of the pyramidal layer LFP for each theta cycle is shown below each theta cycle (3\textsuperscript{rd} row). Each theta cycle was assigned to one of the three clusters based on the FPP (blue for slow gamma or S-gamma, purple for medium gamma or M-gamma, and turquoise for fast gamma or F-gamma). \textbf{F.} Average FPPs across theta cycles within the three TG states (\textit{top:} S-gamma, \textit{n} = 11828; \textit{middle:} M-gamma, \textit{n} = 12775; and \textit{bottom:} F-gamma, \textit{n} = 11585 theta cycles) from the same animal as in \textbf{E}. Triangles indicate the center of gravity (see Supplementary Methods). \textbf{G.} As in \textbf{E} for a 5XFAD mouse (M13, S180716). \textbf{H.} As in \textbf{F} for the 5XFAD mouse in \textbf{C} (\textit{top:} S-gamma, \textit{n} = 26221 theta cycles; \textit{middle:} M-gamma, \textit{n} = 26982 theta cycles; and \textit{bottom:} F-gamma, \textit{n} = 26623 theta cycles).
**Fig. S11.** Theta-gamma state occurrence and transitions before entering the goal zone and as functions of positions. A. Slow (blue circle, left), medium (purple circle, center), and fast (dark green circle, right) theta-gamma state occurrence probability for incorrect and correct trials over the whole track except the goal zone for WT (left side of graphs, n = 14 sessions) and 5XFAD mice (right side of graphs, n = 13 sessions). Each line indicates one session, blue lines indicate sessions with lower occurrence on correct trials and red lines indicate sessions with higher occurrence probability.
occurrence on correct trials. Comparisons were made across correct trials (C) and incorrect trials (I) for WT (p = 9.31e-6, F_{11,143} (theta-gamma transition type (TG-trans.) × performance) = 4.45, two-way repeated measures ANOVA) and 5XFAD mice (p = 1.42e-5, F_{11,132} (TG-trans. × performance) = 4.368, two-way repeated measures ANOVA). In total 48 comparisons = 12 [3 × 3 transitions + 3 occurrences] × 2 genotype × 2 performance were made and corrected via FDR (24 paired t tests between correct and incorrect trials, and 24 non paired t tests between genotypes). **B.** Transition probabilities between slow (blue circle), medium (purple circle), and fast (dark green circle) theta-gamma states for incorrect and correct trials over the whole track except the goal zone for WT and 5XFAD mice. Circles and arrows at the top of each graph indicate transitions from one state to another, e.g. an arrow from a blue circle to a purple circle indicates the probability of a slow theta-gamma cycle followed by a medium theta-gamma cycle. * denotes significant differences with FDR corrections for the 48 comparisons (q < 0.1); black arrowhead denotes less strict statistics (p < 0.05, paired t test with no FDR correction; p = 1.42e-5, F_{11,275} (TG-trans. × performance) = 8.078, three-way mixed ANOVA). **C.** Directed graph summarizing theta-gamma coupling state occurrences and transitions between correct and incorrect trials shown in A and B for WT animals, with red indicating higher probability and blue indicating lower probability on correct versus incorrect trials. Only significant changes from correct and incorrect trials (paired t test, q < 0.1, FDR correction from 48 comparisons) are highlighted, less strict statistics are highlighted by a dashed line for p < 0.05, paired t test. **D.** As in C for 5XFAD mice. **E.** Top: schematic of track cues with the false goal (P3) highlighted in yellow and the true goal (P6). **Bottom:** Slow (blue circle, left), medium (purple circle, center), and fast (dark green circle, right) theta-gamma state occurrence probability for incorrect (grey) and correct (light green) trials as a function of position for WT (left 3 graphs) and 5XFAD mice (right 3 graphs). **F.** Transition probabilities between slow (blue circle), medium (purple circle), and fast (dark green circle) theta-gamma states for incorrect (grey) and correct (light green) trials as a function of position for WT (left 3 graphs) and 5XFAD mice (right 3 graphs). Circles and arrows at the top of each graph indicate the probability of a transition from one state to another. * denotes significant differences, q < 0.1, FDR corrections for the 144 comparisons = 6 locations × 2 genotypes × 12 [3 × 3 transitions + 3 occurrence]; black arrowhead denotes less strict statistics (p < 0.05, paired t test with no FDR correction; p = 1.76e-8, F_{55,712} (TG-trans. × location × performance) = 2.57, three-way repeated measures ANOVA for WT; p = 2.6e-11, F_{55,660} (TG-trans. × location × performance) = 3.02, three-way repeated measures ANOVA for 5XFAD).
Fig. S12. Comparison of behaviors and neural activity between early and late trials in WT animals. A. Speed (top) and lick rate (bottom) for early (black circle) and late (black triangles) trials at the true goal zones (True G., P6), false goal zones (False G., P3), and other zones (Others, P1, P2, P4, P5). n = 17 sessions (Table S1). B. As in A but comparing correct and incorrect trials in the false goal zone (left) and other zones (right). * indicates significant differences (paired-t test, q < 0.1, FDR correction of 22 comparisons = 11 [3 all trial comparisons + 2 performance × 2 locations × 2 halves session] × 2 metrics [speed and lick rate]), and black arrowhead denotes less
strict statistics (p < 0.05, paired t test with no FDR correction). C. GDI of early (circle) and late trials (triangles) for place cells (gray) and non-place cells (black) as a function of goal similarity (left panel) and spatial information significance (SpaInfo Sig., right panel). No significant differences were found (p > 0.05, paired t test for all 20 comparisons = 10 cells group segregations × 2 cell types). D. PPC of early (circle) and late trials (triangles) for place cells (gray) and non-place cells (black) at the false goal zone during correct trials. Neurons included in the analysis met the following two criteria: (1) neurons fired at least five spikes in the false goal zone during correct trials of both early and late sessions and (2) firing rates were higher than 1Hz. No significant differences were found (un-paired t test, q > 0.1, FDR correction of 20 comparisons = 2 cell types × 10 frequency bands); black arrowhead denotes less strict statistics (p < 0.05, un-paired t test with no FDR correction). E. Slow (blue), medium (purple), and fast (green) theta-gamma state occurrences over the track before the reward zone (P1 to P5) for incorrect and correct trials before entering the reward zones in both early (circle) and late (triangle) trials. No significant differences were found between early-late comparisons for correct and incorrect trials, or correct-incorrect comparisons in early and late sessions (paired t test, q > 0.1, FDR correction of 12 comparisons = 2 performance × 2 halves session × 3 TG states). Black arrowhead denotes less strict statistics (p < 0.05, paired t test with no FDR correction).
Fig. S13. Genotype comparisons of animal behaviors. A. Time on task (top), motivated trial counts (center), and success rates (bottom) for WT and 5XFAD mice (From top to bottom: time spent on task, \( p = 0.228, t_{34} = -1.228 \) using un-paired t test, \( p = 0.671 \) using hierarchical bootstrap test; motivated trial numbers, \( p = 0.115, t_{34} = -1.618 \) using un-paired t test, \( p = 0.422 \) using hierarchical bootstrap test; and success rate of getting reward, \( p = 0.570, t_{34} = -0.574 \) using un-paired t test, \( p = 0.790 \) using hierarchical bootstrap test). B. Lick rate (top), speed (center), and occupancy (bottom) at the true goal zone, false goal zone, and other zones in WT and 5XFAD animals. (Licking rate, \( p = 0, F_{2,68}(Location)=107.652; p = 0.330, F_{1,34}(Genotype)=0.979; p = 0.062, F_{2,68}(Location \times Genotype)=2.892, \) two-way mixed ANOVA. Speed (middle), \( p = 1.52e^{-14}, F_{2,68}(Location)=52.677; p = 0.101, F_{1,34}(Genotype)=2.850; p=4.32e^{-4}, F_{2,68}(Location \times Genotype)=8.702, \) two-way mixed ANOVA. Occupancy (bottom), \( p=1.11e^{-16}, F_{2,68}(Location)=66.118; p = 0.002, F_{1,34}(Genotype)=11.655; p = 7.63e^{-05}, F_{2,68}(Location \times Genotype)=10.934 \) two-way mixed ANOVA.) Black and orange * indicates significant differences for t test (black) and hierarchical bootstrap test (orange), \( q < 0.1, \) FDR correction of 54 comparisons = 2 tests \([t \text{ test and hierarchical bootstrap methods}] \times 9 \text{ comparisons} \times 2 \text{ genotypes} + \text{un-paired genotype comparisons across the 3 locations}] \times 3 \text{ behavioral metrics [lick rate, speed, and occupancy time}]).
Fig. S14. Goal discriminability in CA1 pyramidal cells in 5XFAD mice. A. Schematic of repeated wall patterns in the environment (top). Normalized firing rates as a function of position for all place (left, n = 276) and non-place pyramidal (right, n = 147) cells organized by their peak firing position. B. Firing rate as a function of position for three place (left) and three non-place
(center) cells. The peak firing rate for each cell is shown at the top right. Spatial information (right) was compared between place cells and non-place cells (p = 5.64e-21, Wilcoxon rank-sum test). C. Three similarity scores (correlation coefficients) were computed between firing rate maps covering the segments of the track indicated with yellow and orange arrows: goal similarity score (Goal similarity, left), false goal similarity score (False goal similarity, middle) and true goal similarity score (True goal similarity, right). Normalized firing rates for 40 place cells (top) and non-place cells (bottom) with the highest similarity scores were organized by peak firing position. D. Comparisons of Goal Discrimination index (GDI, defined as (True goal similarity - False goal similarity)/(|True goal similarity|+|False goal similarity|), see Supplementary Methods for details) between place cells and non-place cells were made with two different inclusion criteria based on the goal similarity (left panel) and spatial information significance (SpaInfo Sig., right panel). * indicates significant differences (un-paired t test, q < 0.1, FDR correction of 20 comparisons = 10 cells group segregations × 2 genotypes); black arrowhead denotes less strict statistics (p < 0.05, un-paired t test with no FDR correction).
Fig. S15. Association of neural activities with success rate to get reward. Scatter plots of GDI versus success rate pooling cells from all animals (left, n = 493 for place cells and n = 252 for non-place cells) and separating WT (center, n = 217 for place cells and n = 105 non-place cells) and 5XFAD mice (right, n = 276 for place cells and n = 147 non-place cells) for place cells (gray diamonds, top) and non-place cells (black squares, bottom). Correlation coefficients and p values (Spearman’s ρ) were shown on the top of each panel. Significant positive and negative correlations (p < 0.05) are indicated with regression lines in red, respectively, (p < 0.05). We pooled cells from all animals together and observed a positive correlation between GDI and success rate in non-place cells (r = 0.173, p =0.005, Spearman’s ρ test). When we separated animals by genotype, we find GDI and success rate are positively correlated in 5XFAD (r = 0.201, p =0.014, Spearman’s ρ test) but not WT mice (r = 0.074, p =0.450, Spearman’s ρ test), perhaps due to the larger number of sessions in 5XFAD mice.
Fig. S16. Decoding of goal zone across positions for all cells and excluding a subset of place or non-place cells in 5XFAD mice. Top: Normalized probability of decoding the goal zone along the whole path to the goal (purple) in 10 degrees bins (n = 6 sessions, Table S3). Bottom: Change in the decoded probability after excluding a subset of place cells (gray diamond) or a subset of non-place cells (black square) compared to including all cells (purple line). Red * indicates significant differences higher than chance level (one sample t test, q < 0.1, FDR correction of 150 comparisons = 6 whole track comparisons [3 cells group × 2 genotype] + 144 comparisons [18 positions × 3 cells group × 2 genotype over chance level, and cell type comparisons of 18 positions × 2 genotype]). Red arrowhead denotes less strict statistics (p < 0.05, paired t test with no FDR correction). No significant cell type differences were found when excluding subsets of place cells and excluding subsets of non-place cells (p > 0.05, paired t test; p = 0.591, F_{1,5} (cell type) = 0.330; p = 9.44e-9, F_{17,85} (location) = 5.956; p = 0.125, F_{17,85} (location × cell type) = 1.473, two-way repeated measures ANOVA). Markers indicate mean, error bars indicate standard error of the mean. F: false goal; T: true goal.
Fig. S17. Comparison of place and non-place pyramidal cell properties between WT and 5XFAD animals. A. Goal similarity (Fisher transform of Pearson r), spatial information significance, mean firing rate, peak firing rate in the spatial map, and spatial information from left to right for both place cells (n = 217) and non-place pyr. cells (n = 105) for WT (black) and 5XFAD (red) mice (place cells, n = 276; non-place cells, n = 147). B. Place field mean firing rate, out of field firing rate, number of place fields, place field peak firing rate, and place field size (from left to right) for place cells in WT and 5XFAD mice. * indicates significant differences (Wilcoxon rank-sum test, q < 0.1, FDR correction of 25 comparisons in total from A to B). Simi G.: similarity scores between each half of the track.
**Fig. S18. Spike field phase synchrony of place cells and non-place cells in 5XFAD mice.**

**A.** Top: Schematic of cues in the track with the false goal cue at P3, yellow. Each half of the track is shown as a separate row. 

**B.** PPC of place cells (top) and non-place pyramidal cells (bottom) for ten frequency bands: delta (1-5Hz), theta (5-12Hz), beta (12-20Hz), and non-overlapping 20Hz wide frequency bands from 20 to 160 Hz across positions for all incorrect (gray) or correct (green) trials (mean ± sem, n = 114 place cells, 70 non-place pyramidal cells). * indicates significant differences between correct and incorrect trials (paired t test, q < 0.1, FDR correction from 480 comparisons = 8 comparisons [performance comparisons across 2 cell types and 2 genotypes + genotype comparisons across 2 performance and 2 cell types] over 10 frequency bands along 6 locations; p = 2e-16, F$_{9, 1017}$ (frequency × performance) = 16.79, three-way repeated measures ANOVA for place cells; p = 2e-16, F$_{9, 621}$ (frequency × performance) = 20.44, three-way repeated measures ANOVA for non-place cells).
Fig. S19. Spike sorting metrics, classification of putative pyramidal cells and interneurons, and cell type distributions across recording locations. A. Schematic diagram of the spike sorting process. In total 5269 single units were sorted using the automated spike detection and sorting algorithm of MountainSort (2). 1939 units were excluded (black) and 3330 were included (orange) after applying the following quality control criteria: peak signal to noise ratio (SNR) greater than or equal to 1, less than 10% overlap with noise, and greater than 95% isolation.
against other units. Manual curation was then performed by visual inspection of waveforms and spike train cross-correlograms with other putative units, finally extracting 2427 units for further analysis (light blue). **B.** Distribution of all units on quality control metrics: SNR, overlap with noise, and isolation against other units. Units that did not meet quality control criteria (grey) or pass manual inspection were excluded, while units that met all criteria and inspection (light blue) were classified as single units and included in further analysis. Dashed lines indicate the quality control criteria thresholds. **C. Left:** Distributions of spike width and mean of the autocorrelogram for all recorded single units with putative pyramidal cells in green (n = 1245), putative interneurons in blue (n = 320), and unidentified cells in gray (n = 792). Each circle is a single unit. Distributions of putative pyramidal cells (green) and putative interneurons are also shown in histograms. **Right:** Average waveforms (thick line) with standard deviation (shaded) of classified putative pyramidal cells and interneurons. **D.** Average sharp-wave ripple power (150-250 Hz) for all recording channels across recording depths (linearized probe channels), centered on the channel with highest sharp-wave ripple power and therefore the center of the pyramidal layer in 5XFAD (dark red) and WT (black) mice, mean ± SEM. **E.** Proportion of place cells (n = 253), non-place cells (n = 284), and interneurons (n = 133) in WT (left), and 5XFAD (right; n = 325, 383 and 187 for place cells, non-place cells, and interneurons respectively) animals. Recording depths were 11.86 ± 2.40 µm (n=253, place cells in WT, mean ± SEM), 21.35 ± 2.58 µm (n=284, non-place cells in WT), 9.12 ± 3.31 µm (place cell in 5XFAD, n=325) and 11.26 ± 3.09 µm (non-place cell in 5XFAD, n=383) below the peak ripple power channel respectively. Non-place cells were slightly but significantly more towards the radiatum layer (larger positive value in our measure) than those of place cells in WT animals (p=0.008, t535=2.676, unpaired t test), and non-place cells in 5XFAD animals (p=0.017, t665=-2.393, unpaired t test). This is in line with a previous study that pyramidal cells located towards pyramidal oriens are more likely to have place fields than those towards radiatum (called deep and superficial, respectively (35)). There is no difference between place cell and non-place cell depths in 5XFAD animals (p=0.636, t706=0.474, unpaired t test), and no genotype differences between place cell depths (p=0.524, t576=-0.637, unpaired t test). It is important to note that the differences between the mean depth in place cells and non-place cells (9.49 µm for WT, 2.14 µm for 5XFAD) were less than the minimal spatial scale of the probe (12.5 µm) and thus we may miss smaller variations in cell locations. SEM: standard error of mean. Pyr: pyramidal cells; Int: interneurons; AMP: amplitude.
| Animal | Genotype | Recording duration (min) | Total units recorded | Int. | Pyr. | Place cells | Non-place pyr. cells |
|--------|----------|--------------------------|----------------------|------|------|-------------|---------------------|
| 1      | 5XFAD    | 174.96                   | 83                   | 2    | 71   | 19          | 52                  |
| 1      | 5XFAD    | 166.81                   | 85                   | 12   | 55   | 24          | 31                  |
| 1      | 5XFAD    | 30.77                    | 24                   | 5    | 9    | 2           | 7                   |
| 1      | 5XFAD    | 80.65                    | 85                   | 5    | 58   | 11          | 47                  |
| 7      | 5XFAD    | 61.29                    | 71                   | 25   | 6    | 3           | 3                   |
| 7      | 5XFAD    | 22.68                    | 61                   | 26   | 11   | 5           | 6                   |
| 8      | WT       | 89.18                    | 7                    | 0    | 3    | 1           | 2                   |
| 8      | WT       | 67.08                    | 119                  | 7    | 71   | 40          | 31                  |
| 8      | WT       | 41.23                    | 12                   | 7    | 5    | 2           | 3                   |
| 9      | WT       | 60.15                    | 33                   | 0    | 22   | 10          | 12                  |
| 9      | WT       | 69.20                    | 58                   | 8    | 41   | 32          | 9                   |
| 9      | WT       | 51.78                    | 43                   | 3    | 38   | 20          | 18                  |
| 9      | WT       | 30.04                    | 92                   | 22   | 45   | 22          | 23                  |
| 10     | 5XFAD    | 7.66                     | 99                   | 13   | 54   | 17          | 37                  |
| 10     | 5XFAD    | 102.11                   | 89                   | 17   | 58   | 38          | 20                  |
| 10     | 5XFAD    | 41.58                    | 53                   | 8    | 38   | 17          | 21                  |
| 10     | 5XFAD    | 30.00                    | 122                  | 16   | 30   | 14          | 16                  |
| 11     | 5XFAD    | 68.49                    | 92                   | 12   | 46   | 28          | 18                  |
| 11     | 5XFAD    | 110.96                   | 81                   | 8    | 39   | 19          | 20                  |
| 11     | 5XFAD    | 90.63                    | 86                   | 10   | 60   | 37          | 23                  |
| 12     | WT       | 71.97                    | 110                  | 18   | 36   | 24          | 12                  |
| 12     | WT       | 36.28                    | 87                   | 11   | 44   | 13          | 31                  |
| 12     | WT       | 34.57                    | 30                   | 3    | 18   | 6           | 12                  |
| 13     | 5XFAD    | 85.78                    | 57                   | 8    | 33   | 13          | 20                  |
| 13     | 5XFAD    | 93.24                    | 58                   | 3    | 38   | 21          | 17                  |
| 14     | WT       | 50.76                    | 141                  | 13   | 65   | 31          | 34                  |
| 14     | WT       | 85.55                    | 84                   | 10   | 55   | 27          | 28                  |
| 14     | WT       | 30.08                    | 53                   | 5    | 29   | 7           | 22                  |
| 15     | WT       | 105.08                   | 14                   | 3    | 11   | 0           | 11                  |
| 16     | 5XFAD    | 121.05                   | 90                   | 7    | 44   | 25          | 19                  |
| 16     | 5XFAD    | 54.83                    | 85                   | 0    | 42   | 22          | 20                  |
| 18     | 5XFAD    | 38.78                    | 12                   | 3    | 6    | 2           | 4                   |
| 19     | 5XFAD    | 63.37                    | 30                   | 7    | 10   | 8           | 2                   |
| 20     | WT       | 65.96                    | 56                   | 15   | 23   | 0           | 23                  |
| 20     | WT       | 69.33                    | 24                   | 8    | 13   | 7           | 6                   |
| 20     | WT       | 23.40                    | 31                   | 0    | 18   | 11          | 7                   |

WT: wild-type; min: minutes; Int. Interneuron; Pyr.: Pyramidal.
Table S2. Number of cells and recordings per animal included in single cell spatial analysis.

| Animal ID | Genotype | Recording Days | All recorded pyr. cells | Spatial analysis (≥ 0.5 Hz) | Spatial spike-field analysis |
|-----------|----------|----------------|-------------------------|-----------------------------|-----------------------------|
|           |          |                | Place cells             | Non-place pyr. cells        | Place cells                 | Non-place pyr. cells        |
| 8         | WT       | 3              | 43                      | 36                          | 32                          | 29                          | 13                          | 12                          |
| 9         | WT       | 4              | 84                      | 62                          | 78                          | 34                          | 17                          | 14                          |
| 12        | WT       | 3              | 43                      | 55                          | 34                          | 5                           | 3                           | 3                           |
| 14        | WT       | 3              | 65                      | 84                          | 56                          | 33                          | 29                          | 16                          |
| 15        | WT       | 1              | 0                       | 11                          | 0                           | 0                           | 0                           | 7                           |
| 20        | WT       | 3              | 18                      | 36                          | 17                          | 4                           | 3                           | 10                          |
| Total WT  |          | 17             | 253                     | 284                         | 217                         | 105                         | 65                          | 62                          |
| 1         | 5XFAD    | 4              | 56                      | 137                         | 50                          | 84                          | 21                          | 35                          |
| 7         | 5XFAD    | 2              | 8                       | 9                           | 8                           | 4                           | 8                           | 6                           |
| 10        | 5XFAD    | 4              | 86                      | 94                          | 70                          | 22                          | 29                          | 3                           |
| 11        | 5XFAD    | 3              | 84                      | 61                          | 70                          | 11                          | 25                          | 6                           |
| 13        | 5XFAD    | 2              | 34                      | 37                          | 30                          | 6                           | 10                          | 8                           |
| 16        | 5XFAD    | 2              | 47                      | 39                          | 40                          | 19                          | 21                          | 12                          |
| 18        | 5XFAD    | 1              | 2                       | 4                           | 2                           | 1                           | 0                           | 0                           |
| 19        | 5XFAD    | 1              | 8                       | 2                           | 6                           | 0                           | 0                           | 0                           |
| Total 5XFAD |        | 19             | 325                     | 383                         | 276                         | 147                         | 114                         | 70                          |

See Supplementary Methods for inclusion criteria. WT: wild-type, ID: identifier, Pyr.: Pyramidal.
Table S3. Number of cells and recordings per animal included in decoding analysis.

| Animal ID | Genotype | Session ID | All recorded cells | Place cells | Non-place cells | Percentage of pyr. cells deleted |
|-----------|----------|-----------|--------------------|------------|----------------|---------------------------------|
|           |          |           |                    |            |                | 20% | 30% | 40% |
| 8         | WT       | 180214    | 119                | 40         | 31             | 14  | 21  | 28  |
| 9         | WT       | 180511    | 33                 | 10         | 12             | 4   | 7   | 9   |
| 9         | WT       | 180516    | 58                 | 32         | 9              | 8   | 9   | 9   |
| 9         | WT       | 180518    | 92                 | 22         | 23             | 9   | 14  | 18  |
| 14        | WT       | 180727    | 53                 | 7          | 22             | 6   | 7   | 7   |
| 20        | WT       | 200203    | 31                 | 11         | 7              | 4   | 5   | 7   |
| 7         | 5XFAD    | 180327    | 71                 | 3          | 3              | 1   | 2   | 2   |
| 10        | 5XFAD    | 180522    | 89                 | 38         | 20             | 12  | 17  | 20  |
| 10        | 5XFAD    | 180523    | 53                 | 17         | 21             | 8   | 11  | 15  |
| 11        | 5XFAD    | 180611    | 86                 | 37         | 23             | 12  | 18  | 23  |
| 16        | 5XFAD    | 191106    | 90                 | 25         | 19             | 9   | 13  | 18  |
| 19        | 5XFAD    | 200122    | 30                 | 8          | 2              | 2   | 2   | 2   |

WT: wild-type, ID: identifier, Pyr.: Pyramidal. 30% of pyramidal cells were used to determine the number of cells excluded in the main analysis.
Table S4. Number of multiple comparisons for false discover rate corrections.

| Results section                                                                 | Metrics for analysis | Details about number of comparisons                                                                 | Related figures          |
|---------------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------------------------------|--------------------------|
| 1. Animals perform virtual reality navigation task with false goal cues         | Behavior             | 54 comparisons = 2 tests [t test and hierarchical bootstrap methods] × 9 comparisons [6 paired comparisons across the 3 locations: goal zones, false goal zones, and other zones for 2 genotypes + un-paired genotype comparisons across the 3 locations] × 3 behavioral metrics [lick rate, speed, and occupancy time] | Fig. S13                 |
| 2. Non-place cells discriminate between real and false goals better than place cells | Goal discriminability index (GDI) | 20 comparisons = 10 cell group segregations × 2 genotypes | Fig. 1D Fig. S14D        |
| 3. Non-place cells improve task-relevant codes including position, distance to goals, and false goal discrimination | Bayesian decoding of current position over chance level | 8 chance level comparisons = 2 [current, and noncurrent decoding] × 2 frames [global position, and distance to goal] × 2 genotypes | NA                      |
|                                                                                  | Bayesian decoding of current position across cells types and genotypes | 6 comparisons = 3 cell groups [All, excluding place cells, and excluding non-place cells] × 2 genotypes | Fig. 2B                  |
|                                                                                  | Distance to goal decoding | 150 comparisons = 6 whole track comparisons [3 cells group × 2 genotype] + 144 comparisons [18 positions × 3 cells group × 2 genotype over chance level, and cell type comparisons of 18 positions × 2 genotype] | Fig. 2EG Fig. S16       |
| 4. Non-place cell firing differs between correct and incorrect performance      | Firing rate          | 24 comparisons = 2 cell types × 2 genotypes along 6 locations | Fig. S8B                 |
|                                                                                  | Pairwise phase consistency | 480 comparisons = 8 comparisons [performance comparisons across 2 cell types and 2 genotypes + genotype comparisons across 2 performance and 2 cell types] over 10 frequency bands along 6 locations | Fig. 3C Fig. 4B Fig. S18 |
|                                                                                  | Power spectrum density of LFP | 1488 comparisons = 4 group comparisons [correct, incorrect performance and WT, 5xFAD] over 62 frequency bands along 6 locations | Fig. S9                  |
|                                                                                  | Theta-gamma state transitions in non-goal zones | 48 comparisons = 12 [3 × 3 transitions + 3 occurrence] × 2 genotype × 2 performance | Fig. 3E Fig. 4D Fig. S11ABCD |
|                                                                                  | Behavior between 1st and 2nd halves of session | 22 comparisons = 11 [3 all trial comparisons + 2 performance × 2 locations × 2 halves session] × 2 metrics [speed and lick rate] | Fig. S12AB               |
| 5. Deficits in non-place cell goal discrimination and gamma modulation in a mouse model of Alzheimer’s disease | Firing metrics of single units | 25 comparisons = 2 genotypes × 2 cell types × 5 metrics + 5 place cell metrics | Fig. S17                 |
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