A diversity of interneurons and Hebbian plasticity facilitate rapid compressible learning in the hippocampus

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The hippocampus is able to rapidly learn incoming information, even if that information is only observed once. Furthermore, this information can be replayed in a compressed format in either forward or reverse modes during sharp wave–ripples (SPW–Rs). We leveraged state-of-the-art techniques in training recurrent spiking networks to demonstrate how primarily interneuron networks can achieve the following: (1) generate internal theta sequences to bind externally elicited spikes in the presence of inhibition from the medial septum; (2) compress learned spike sequences in the form of a SPW–R when septal inhibition is removed; (3) generate and refine high-frequency assemblies during SPW–R-mediated compression; and (4) regulate the inter-SPW interval timing between SPW–Rs in ripple clusters. From the fast timescale of neurons to the slow timescale of behaviors, interneuron networks serve as the scaffolding for one-shot learning by replaying, reversing, refining, and regulating spike sequences.

Shortly after watching a movie, we can recall many scenes in detail and remember long stretches of dialog. However, as time passes, our memories may only preserve some aspects of the plot and a few memorable lines. This example illustrates how memories operate on separate timescales. On the short timescale, we clearly remember recent events after only a single viewing, while memories operate on separate timescales. On the short timescale, the plot and a few memorable lines. This example illustrates how

This observation, among others, led to the two-stage model of memory formation. In the initial stage, a labile form of the memory is imprinted onto the hippocampus. This initial acquisition is accompanied by a theta oscillation in the hippocampal local field potential (LFP). The second stage of memory formation occurs during consummatory behaviors such as sleeping or eating. In this stage, strongly correlated activity is initiated in the hippocampus as a SPW–R complex. The spike sequence elicited by the stimulus during waking is replayed in compressed time during SPW–Rs. The SPW–R propagates out of the hippocampus, presumably for long-term memory consolidation in the cortex.

This two-stage model requires some mechanism for forming the initial memory. This initial mechanism should handle the fact that we often only see a stimulus once. Furthermore, this hypothesized fast-learning mechanism should allow for compressible spiking, as observed in SPW–Rs. Finally, this mechanism should allow for the reversal of spike sequences. Spike sequences can be compressed in reverse order, even for mice navigating novel mazes in the initial lap.

What known hippocampal dynamics allows for learning subject to these constraints? Narrowing our focus to episodic memory formation yields one possible candidate: the internally generated theta sequence (IGTS). First reported in the CA1, these cells partition time during episodic memory tasks. The IGTSs are dependent on the medial septum (MS) and hippocampal theta oscillations for normal functioning. Here, we explore the hypothesis that IGTSs may serve as a compressible backbone to bind information during single-trial learning.

Leveraging recent advances in training spiking neural networks, we construct networks of phase precessing IGTSs using a dual oscillator model. Unlike previous dual oscillator models, we consider a novel implementation: one oscillator corresponds to inhibition from the MS, while another oscillator corresponds to the interneuron control of spike times during SPW–Rs. In effect, the interference between these oscillators serves to dilate spike sequences during SPW–Rs to create IGTSs. The IGTSs bind new, stimulus-evoked sequences in a single trial to form memory engrams that can be compressed and reversed in time. Our results provide evidence of a single interneuron mechanism for gating, controlling, transforming, and refining spike sequences for rapid learning.

**Results**

**Internally generated theta assemblies with network-based dual oscillators.** The network model consists of the following three layers, which we constructed and analyzed incrementally: the inputs, the septal–hippocampal–oscillatory–theta (SHOT) network, and the readout layer. The inputs serve as one of the oscillators. The next layer, the SHOT network, is the critical nucleus of the circuit that creates IGTSs and SPW sequences. The SHOT network contains the second oscillator. The final layer is the readout layer, whereby sequences must be learned in a single trial. These to-be-learned sequences are elicited by an externally applied supervisor.

Thus, given the architecture of this network model, we interpreted the input, SHOT network, and read outlayer to correspond to the MS (INP-MS), the hippocampal area CA3 (SHOT-CA3), and the CA1 region (RO-CA1), respectively. Finally, we interpreted the supervisor, which elicits spiking in the RO-CA1 layer, to be the entorhinal cortex (SUP-EC). The interference pattern or ‘beat’ between the SHOT-CA3 network oscillator and the INP-MS oscillator creates IGTSs, while removal of the INP-MS creates compressed sequences (SPWs).

This is our interpretation of an inherently abstract model, which we implemented in a spiking network. However, this implementation is not unique. For example, the sources of these oscillations could be entirely intrahippocampal. Additionally, given that only inhibitory connections are required for sequence generation in the SHOT network, it may be contained in the CA1.
To model the oscillatory and inhibitory nature of the MS, the SHOT-CA3 interneurons (SHOT-CA3I) receive the INP-MS signal as follows:

\[ I_{\text{MS}}(t) = i^{\text{GABA}}(\kappa + \cos(2\pi\theta_{\text{MS}}t)) \quad (1) \]

The parameter \( \theta_{\text{MS}} \) is the theta oscillation frequency of the INP-MS, \( \kappa \geq 1 \) controls the baseline inhibition levels, and \( F^{\text{GABA}} < 0 \) controls the amplitude of this oscillation (and scales the baseline inhibition).

It has been reported that IGTSs can generate sequential firing fields on a behavioral timescale, while neurons oscillate at a theta frequency inside the field\(^6\). The spiking rate within a field is slightly faster than the LFP theta frequency, an effect that is termed phase precession\(^6,10\). Unlike previous works\(^11–13\), we take the perspective of the faster than the LFP theta frequency, an effect that is termed phase frequency of \( \theta \) and is defined as follows:

\[ \psi(t) = \cos(2\pi\theta_{\text{INT}}t + \psi) \quad (2) \]

where \( \psi \) denotes the phase preference of a neuron with respect to the \( \theta_{\text{INT}} \) oscillator. The phase preference dictates the firing order of a neuron in the compressed SPW sequence. When the INP-MS is on, the current is as follows:

\[ z(t) = \cos(2\pi\theta_{\text{MS}}t) + \cos(2\pi\theta_{\text{INT}}t + \psi) \quad (3) \]

\[ z(t) = 2\cos\left(2\pi\frac{\theta_{\text{INT}} + \theta_{\text{MS}}}{2} + \frac{\psi}{2}\right) \times \cos\left(2\pi\frac{\theta_{\text{INT}} - \theta_{\text{MS}}}{2} + \frac{\psi}{2}\right) \quad (4) \]

The sum becomes a product of a carrier (\( C(t) \)) and envelope (\( E(t) \)) function. Note, again, that the currents are dimensionless and lack amplitude terms (for example, \( F^{\text{GABA}} \)). The envelope oscillates on a long timescale (\( \int（t - \theta_{\text{INT}})^{-1} \)) and controls the IGTS firing fields. The envelope inherits an identical order of firing from the \( \theta_{\text{INT}} \) oscillator through its phase, \( \xi \) when \( \theta_{\text{INT}} > \theta_{\text{MS}} \). This allows for SPW–R-like compression of the IGTS by removing the INP-MS (Supplementary Fig. 2).

To determine how the SHOT-CA3I control spike sequences, we analyzed the currents that the neurons receive (Fig. 1I). The total current to the SHOT-CA3E displayed characteristics of an interference pattern, as expected. However, the SHOT-CA3I current did not. The current was dominated by a single oscillation, \( \theta_{\text{INT}} \). This was surprising as the SHOT-CA3I directly receive INP-MS and generate the \( \theta_{\text{INT}} \) oscillation, unlike the excitatory neurons.

We investigated this aspect further by decomposing the total current into all sources: the background current, the SHOT-CA3I synaptic current, and the INP-MS (Fig. 1g). For both populations, the inhibitory synaptic currents displayed an interference pattern. One oscillator was \( \theta_{\text{INT}} \). The second oscillator, however, did not correspond to the INP-MS directly, but instead to a \( \pi \)-shifted or vertically flipped version of the INP-MS. As the SHOT-CA3I also receive INP-MS directly, the INP-MS destructively interferes with its phase-shifted counterpart, allowing SHOT-CA3I to oscillate at \( \theta_{\text{INT}} \).
Next, we investigated the structure of the FORCE-trained weight matrices. At first, the weights appeared to be random (Supplementary Fig. 3a,b). However, after sorting neurons according to their phase preferences in \( \theta_{\text{INT}} \), a spatial structure emerged. We observed recurring light and dark bands in the weight matrix, in addition to random phase-independent inhibitory connections. The
random connections sampled from the entire SHOT-CA3I. Thus, by receiving these connections, a neuron can detect the population-level oscillation in \( \theta_{\text{MS}} \) for destructive interference (Methods). The banding structure, however, implies that interneurons preferentially inhibit interneurons that already fired in \( \theta_{\text{INT}} \), thus advancing the \( \theta_{\text{INT}} \) oscillation forward. This band reappeared in multiple trials of FORCE training (Supplementary Fig. 3c–f).

Finally, by using either the INP-MS oscillation (not shown) or population activity (Fig. 1b,f) as a reference theta oscillation, both excitatory neurons and interneurons precess in phase. This is a classical result of dual oscillator models, as the carrier, \( \theta_{\text{INT}} \), behaves like a linear oscillator for the \( \theta_{\text{INT}} \) oscillations of the INP-MS amplitude but robust against \( \theta_{\text{INT}} \) variations.

**Firing-field generation is robust.** For the IGTSs to serve as a compressible backbone for learning, the interference mechanism should be robust. To that end, we retrained the network using the following different conditions: (1) smaller integration time steps (Supplementary Fig. 4); (2) parameter heterogeneity (Supplementary Fig. 5); (3) larger networks (Supplementary Fig. 6c); (4) different SHOT-CA3E/SHOT-CA3I ratios (Supplementary Fig. 6a,b,d,e); and (5) synaptic failure (Supplementary Fig. 7). In all cases, the network generated ordered IGTSs that compressed when the INP-MS was removed and a weight matrix banding structure (Supplementary Figs. 5 and 6).

Next, we considered how the trained network (Fig. 1) would extrapolate to varied \( \theta_{\text{AS}} \) frequencies. If the SHOT-CA3 is operating as a linear oscillator, we expect that the firing-field periodicity scales like \( [\theta_{\text{AS}} - \theta_{\text{INT}}]^{-1} \) near \( \theta_{\text{INT}} \), while population activity has a period of \( \theta_{\text{AS}}^{-1} \). Furthermore, our model predicts that the IGTS order reverses when \( \theta_{\text{AS}} > \theta_{\text{INT}} \) (Methods). This regime should also induce phase recession. Finally, we also predict that firing fields emerge near the harmonics of \( \theta_{\text{INT}} \). To test this hypothesis, we slowly swept \( \theta_{\text{AS}} \) (2 Hz to 12 Hz; Supplementary Fig. 8). We found that the SHOT-CA3 behaves like a linear oscillator for the \( \theta_{\text{AS}} \) values tested. This surprising ability to extrapolate to new inputs is due to the ability of the SHOT-CA3I to create destructive interference of any input to maintain the \( \theta_{\text{INT}} \) oscillator. The firing fields also reversed near the harmonics of \( \theta_{\text{INT}} \). Thus, \( \theta_{\text{AS}} \) directly determines the frequency of population activity, as predicted from a dual oscillator model.

Finally, although ramping the background current to the interneurons had no effect on the frequency of population activity, there was a small yet significant effect on the period of the interference pattern (Supplementary Fig. 9). However, a stronger reduction in the background current destroyed \( \theta_{\text{INT}} \) and caused SHOT-CA3I to lock onto INP-MS (not shown). This phenomenon mirrors recent results, whereby optogenetic suppression of interneurons reduces phase precession rates but increases intracellular theta amplitude\(^{17}\). Rampng the INP-MS oscillation amplitude (\( F_{\text{AABA}} \)) produced a large and significant effect on the periodicity of the IGTSs and a small yet significant effect on the frequency of population activity (Supplementary Fig. 9). Thus, the network is sensitive to large modulations of the INP-MS amplitude but robust against \( \theta_{\text{AS}} \) variations.

**SPWs can be initiated stochastically.** So far, the SPWs induced in our model (when the INP-MS is deactivated) are periodic and must be activated by an externally applied current, as the INP-MS inhibits the SHOT-CA3E. We investigated whether SPWs could be initiated stochastically when the INP-MS is turned off by adding recurrent excitation to the SHOT-CA3E. Once again, we performed this incrementally to mechanistically understand how ordered SPWs are generated in the SHOT-CA3 network.

First, in lieu of a constant background current, we injected the SHOT-CA3 neurons with white noise (Fig. 2a–d). All inhibitory connections were identical as before (as in Fig. 1). A current pulse to the INP-MS produced a SPW in the SHOT-CA3 network. The oscillation rate of the SPW increased with the amplitude of the current pulse (Fig. 2e,f). However, the amplitude of the SPW decreased with the frequency of the current pulse. The amplitude of the SPW also increased with the duration of the current pulse (Fig. 2g). The amplitude of the SPW decreased with the number of current pulses (Fig. 2h). The amplitude of the SPW also increased with the number of current pulses (Fig. 2i).

**Table 1 | Parameters used for SHOT-CA3 neurons, reversion interneurons, and RO-CA1 excitatory and inhibitory populations**

| Parameter value | SHOT-CA3I | SHOT-CA3E | REV | RO-CA1E | RO-CA1I |
|-----------------|-----------|-----------|-----|---------|---------|
| N               | 2,000     | 2,000     | 2,000 | 2,000 (1,000; Fig. 4f) | 2,000   |
| \( \tau_{\text{ms}} \) | 2 ms | 2 ms | 2 ms | 2 ms | 2 ms |
| \( \tau_{\text{ms}} \) | 10 ms | 10 ms | 10 ms | 10 ms | 10 ms |
| \( \mu \) | 10 pA | -5 pA | -40 pA | -40 pA | -37.5 pA |
| \( \sigma_{\text{max}} \) | -65 mV | -65 mV | -65 mV | -65 mV | -65 mV |
| \( \sigma_{\text{threshold}} \) | -40 mV | -40 mV | -40 mV | -40 mV | -40 mV |
| \( \gamma \) | 20 ms | 20 ms | 20 ms | 20 ms | 5 ms |
| \( \gamma \) | 2 ms | 2 ms | 2 ms | 2 ms | 2 ms |
| \( g \) (FORCE) | 0.1 | 0.1 | NA | NA | NA |
| \( q \) (FORCE) | 15 | 15 | NA | NA | NA |
| \( C_{\gamma} \) (FORCE) | 200 | 200 | NA | NA | NA |
| \( C_{\gamma} \) (FORCE) | 200 | 200 | NA | NA | NA |
| \( \Delta_{\gamma} \) (FORCE) | 0.5 ms | 0.5 ms | NA | NA | NA |
| \( \mu^{-1} \) (FORCE) | 0.0025 ms | 0.0025 ms | NA | NA | NA |
| \( \theta_{\text{INT}} \) | 5.5 Hz | NA | NA | NA | NA |
| \( \theta_{\text{AS}} \) | 2–12 Hz | NA | NA | NA | NA |
| \( \kappa \) | 1–15 (varies) | NA | NA | NA | NA |
| \( \mu_{\text{GABA}} \) | -10 pA | 0 pA | 0 pA | 0 pA | 0 pA |
| FORCE training time | 19 s | 19 s | NA | NA | NA |

For all networks, we used an integration time step of \( dt = 0.05 \) ms and Euler integration. Some of the parameters are not applicable (NA). Also note that the background current to neurons can vary depending on the presence or absence of the INP-MS. See the Methods and figures for more details.
SHOT-CA3I transiently activated the \( \theta_{\text{INT}} \) oscillator. In the absence of this current, the \( \theta_{\text{INT}} \) oscillator was destroyed by the noise, as the oscillator was no longer detected in FORCE oscillator components (Fig. 2b), voltage traces (Fig. 2c), or voltage autocorrelations (Fig. 2d). However, the spikes were still biased toward a particular order, as noise percolated through the inhibitory weight structure for both populations (Fig. 2b).

Next, we investigated the potential mechanisms that could initiate and terminate a SPW in lieu of externally applied currents (as in Fig. 2b). To initiate a SPW, we densely coupled a subset of 50 SHOT-CA3E (the initiators). The initiators projected to the rest of the excitatory population. To terminate SPWs, all excitatory neurons had spike frequency adaptation currents. As noise induces spiking throughout the network, a random subset of initiators were stimulated to spike (Fig. 2e–g). This triggered a positive-feedback loop through recurrent excitation, which caused a synchronized burst throughout SHOT-CA3E. However, this triggered the accumulation of adaptation currents, which terminated the burst. It induced a refractory period whereby SHOT-CA3E could not spike until the adaptation current had decayed. As the \( \theta_{\text{INT}} \) oscillator had not been activated, the spikes in the bursts did not have sequential ordering and were pathologically synchronized (Fig. 2g).

Finally, we added SHOT-CA3E to SHOT-CA3I connections (Fig. 2h). The SHOT-CA3E self-activated through recurrent excitation and now also activated the \( \theta_{\text{INT}} \) oscillator (Fig. 2i,j). The \( \theta_{\text{INT}} \) oscillator protracted the recruitment of SHOT-CA3E into the burst, thereby creating an ordered sequence during the SPW rather than synchronized bursts. The adaptation variable then terminated the burst. The
Fig. 3 | Two mechanisms of reverse compression. a, Top: SHOT-CA3 network schematic of reverse compression when the INP-MS frequency is faster than the recurrent oscillation (\(\theta_{\text{INP}} > \theta_{\text{INT}}\)). Bottom: schematic of the mathematical mechanism for mirror reversion. b, The filtered spike trains \(\langle r(t) \rangle, t_i = 20\, \text{ms}, \tau_i = 2\, \text{ms}\) fired by the SHOT-CA3E. The overline denotes the presence (first 10s) or absence (last 1s) of the INP-MS. c, The zoomed-in 500 ms segment of the black boxed region in b. The bursts occur in reverse order relative to the firing fields from b. d, A zoomed-in segment of activity from the black boxed region in b. e, Both excitatory and interneurons recess in phase relative to population activity (average inhibitory recession rate of 0.72 s\(^{-1}\), s.d. of 0.37 s\(^{-1}\), \(n = 100\); average excitatory rate of 0.4 s\(^{-1}\), s.d. of 0.1 s\(^{-1}\), \(n = 100\)). f, Top: network schematic of interneuron reversion, a reverse compression mechanism using a dedicated population of interneurons to trigger reverse compression. Bottom: the mathematical mechanism that allows for this compression. The reversion interneurons fires bursts of inhibition locked in time to \(\theta_{\text{INT}}\), with the burst rate varying as a function of the phase preference for the excitatory SHOT-CA3 neuron. g, The firing fields are now in the same order as in Fig. 1d. As in Fig. 2b, the INP-MS is on for the first 10s and deactivated for the final 1s. The reversion interneurons are brought online when the INP-MS is off. The overlines denote periods when the INP-MS is present, absent, and when the reversion (REV) interneurons are turned on. h, A zoomed-in, 500 ms segment of reverse compression. The excitatory neurons fire bursts in reverse order relative to the firing fields. i, The population activity for SHOT-CA3I, SHOT-CA3E, and the reversion interneurons for 500 ms before and 500 ms after the INP-MS is removed. j, Both excitatory (red circles, spike times) and interneurons (blue circles, spike times) precess in phase relative to the network theta oscillation (gray) when the reversion interneurons are off. Phase precession rates are identical to Fig. 1 (population activity using \(N = N_{\text{CA3}} + N_{\text{CA1}} = 4,000, \) gray).
reversion and mirror reversion) are based on manipulations to the INP-MS frequency to reverse the order during the IGTS. The third mechanism utilizes a secondary population of interneurons (interneuron reversion) to reverse the order of spiking in SHOT-CA3E during the SPW.

In mirror reversion, the frequencies satisfy $\theta_{MS} > \theta_{INT}$, which reverts the IGTS order (Fig. 3a–c), as the envelope, $E(t)$, now inherits $-\psi$ from the $\theta_{INT}$ oscillation. Removing the INP-MS reverses the burst order during compressed replay (Fig. 3c). However, this is not a plausible mechanism, as this results in phase reversion (Fig. 3e) and reversed theta sequences (Fig. 3d), an event that is seldom observed experimentally\(^{1,2}\). Harmonic reversion is possible when $\theta_{INT}$ is near the harmonics of $\theta_{INT}$, at which the IGTS order also reverses (Supplementary Fig. 8). However, memories encoded onto the IGTS under mirror or harmonic reversion only display reverse replays as the SPW sequence order is fixed, while both forward and reverse sequences are observed in SPWs\(^{3,4}\).

However, a more plausible mechanism for reverse compression utilizes another population of interneurons. During SPWs, excitatory neurons receive the non-dimensionalized currents $z^{FOR}(t)$ where $\theta_{INT}$ oscillates, as follows:

$$z^{FOR}(t) = \cos(2\pi \theta_{INT} + \psi) \tag{5}$$

The phase preference, $\psi$, orders the neurons in a sequence. Thus, a reverse replay is equivalent to replacing $\psi$ with $-\psi$.

To perform this transform, we utilized another interneuron current (the reversion current), whereby the total current during reverse replay is now

$$z^{REV}(t) = \cos(2\pi \theta_{INT} - \psi) = z^{FOR}(t) + 2 \sin(\psi) \sin(2\pi \theta_{INT}) \tag{6}$$

The reversion current we add to equation (5) is a synchronized pulse of the $\theta_{INT}$ oscillator. However, each neuron receives more or less of this pulse through the amplitude term $2 \sin(\psi)$. Thus, we implemented the reversion current as another population of interneurons that receives SHOT-CA3I (Fig. 3f–i). This reverses the excitatory SHOT-CA3 sequences when the INP-MS is removed (Fig. 3b; Methods). The pulse amplitude $2 \sin(\psi)$ does not need to be exact (Supplementary Fig. 11) and is robust to heterogeneity in the weight amplitude. The reversion interneurons may also receive INP-MS to prevent their firing during theta states (Supplementary Fig. 11). Furthermore, phase reversion is not observed in interneuron reversion (Fig. 3i). Thus, interneurons with selective connectivity can reverse the timing of spike-timing during SPWs in a plausible way.

### Online and immediate learning using a theta backbone

Compressible theta sequences are one component of fast learning in this model. The other component is a mechanism to write new information onto these sequences. Reading out information falls to a layer of readout (RO-CA1) neurons, which we interpret to be CA1 pyramidal neurons (Fig. 4a).

We derived a local learning rule that allowed us to store new sequences in the RO-CA1 onto the IGTSs in the SHOT-CA3 with only one presentation of the to-be-learned RO-CA1 sequences. The learning rule governing the excitatory weight ($a_{CA1e}^{PRE}^{CA3}$) from a SHOT-CA3E to a RO-CA1 neuron is given by the following equation:

$$a_{CA1e}^{PRE}^{CA3} = \lambda \cdot r_{CA1e}^{PRE}(t) r_{CA3e}^{PRE}(t) - \lambda \cdot r_{CA1e}^{PRE}(t) r_{CA3e}^{PRE}(t - \tau) \tag{7}$$

This learning rule is Hebbian ($\lambda \cdot r_{CASE}^{CA3}(t) r_{CASE}^{CA1}(t)$), with a forgetting term $\lambda \cdot r_{CASE}^{CA3}(t) r_{CASE}^{CA1}(t - \tau)$, where $\lambda$ dictates the learning rate and $r_{CASE}^{CA3}(t)$ are the synaptically filtered spikes. The variable $\tau$ denotes the period of the IGTS. The learned weights are interpreted to be Schaffer collateral connections. We call this the local Fourier rule based on its origins in function approximation theory (Supplementary Fig. 12; Supplementary Note). Like other rules, this rule is phenomenological\(^{21,22}\).

To test the local Fourier rule, we triggered to-be-learned sequences in the RO-CA1 while simultaneously presenting the INP-MS (Fig. 4b,c) to the SHOT-CA3 (equation (7)). We interpreted the external activity that caused the to-be-learned sequences to come from the supervisor from the entorhinal cortex (SUP-EC).

Critically, the $a_{CA1e}^{PRE}^{PRE}$ weights are too weak to trigger spikes in the presence of the INP-MS and do not interfere with SUP-EC-triggered spikes. However, removal of the INP-MS led to the RO-CA1 sequences replaying in compressed sequential order after a single trial of learning (Fig. 4d).

Surprisingly, this compression did not capture all spikes in the RO-CA1. In fact, the local Fourier rule combined with IGTSs created high-frequency assemblies in the RO-CA1 during compressed replay (Fig. 4d,f). This is due to the Hebbian learning rule, as only RO-CA1 neurons that fired in phase with SHOT-CA3E were remembered. The frequency of assembly firing is $\Gamma = \theta_{INT} + \frac{\bar{t}_{MS}}{\theta_{INT} - \theta_{INT}}$ (Methods). For the parameters we had chosen, this yielded $\Gamma = 136\text{ Hz}$. Lower frequency ranges, including within the gamma range, were possible with smaller values of $\theta_{INT}$ for a fixed $\theta_{SUP}$.

Our result implies that theta oscillations and Hebbian plasticity can induce the formation of high-frequency assemblies,
which appear during SPWs. Unlike other mechanisms of high-frequency oscillations\textsuperscript{21-25}, the assemblies here are learned through Hebbian plasticity operating on phase precessing IGTSs rather than recurrence, or through different populations serving as separate gamma and theta oscillators\textsuperscript{26}. Stimulating the reversion interneurons triggered a reverse replay of these assemblies (Fig. 4e). More complicated spiking patterns were also learned (Fig. 4g).

Finally, the local Fourier rule was shown to be robust against synchronized supervisors (Supplementary Fig. 13), non-uniform phase distributions in the SHOT-CA3 (Supplementary Fig. 5a–c), heterogeneity in the SHOT-CA3 (Supplementary Fig. 5d–f),
different E/I balances in the SHOT-CA3 (Supplementary Fig. 6), and synaptic failure in the SHOT-CA3 (Supplementary Fig. 7). Our model implies that MS inhibition in conjunction with Hebbian plasticity can simultaneously regulate spike timing on the short (gamma and higher), intermediate (theta), and long (behavioral) timescales.

**Triggering SPW–Rs.** With the network layers constructed and analyzed, we added the final component to the model: interneurons in the RO-CA1. The RO-CA1 excitatory neurons (RO-CA1E) excite RO-CA1 interneurons (RO-CAI1), while RO-CAI1 inhibit RO-CA1E\(^{36,24}\) (Fig. 5a).

The RO-CAI1E were (as in Fig. 4) stimulated to spike in a to-be-learned sequence by the SUP-EC (Fig. 5c). The local Fourier rule constructed a memory engraving in a single trial. The INP-MS was removed and triggered a compressed replay of the now-learned sequence (Fig. 5b–d). The population activity (Fig. 5f) in the RO-CA1 displayed ripple-like high-frequency oscillations during compression. Activity in the SHOT-CA3, however, demonstrated a sharp increase when the INP-MS was removed (Fig. 5g). This is a combined effect of removing the INP-MS from SHOT-CA3I and applying a super-threshold current to SHOT-CA3E. Compression resulted in high-frequency assembly formation in RO-CA1E (Fig. 5c,d), while RO-CAI1 fired high-frequency synchronous volleys (Fig. 5e). The number of RO-CA1E assemblies was lower than the number of bursts triggered in the RO-CA1I (eight versus ten).

The majority of the activity was due to RO-CA1I, which were locked to population activity ripples (Fig. 5h). If we regard population activity as a proxy (albeit a poor one) for the LFP, then our results mirror parvalbumin basket cells locking to LFP ripples\(^{27,28}\). The RO-CA1E assemblies also displayed some locking to the ripples (Fig. 5i). However, the assemblies preceded the ripple peaks, as RO-CA1E synapses onto RO-CAI1 triggered the synchronized ripples. This effect is similar to the pyramidal interneuron network gamma mechanism\(^{23,24}\).

As the SHOT-CA3 and reversion interneurons coordinated spike timing, we investigated whether RO-CAI1 performed a similar function. To test this hypothesis, we disabled RO-CA1I post-learning while triggering a compressed replay (Fig. 5i) by removing the INP-MS. The assemblies in RO-CA1E were no longer segregated to discrete moments in time but extensively overlapped. In fact, the first assembly overlapped with the last assembly during replay. This implies that RO-CAI1 may be refining the duration of learned pyramidal assemblies and segregating them to discrete intervals of time (Fig. 5), with strong, synchronized pulses of inhibition. Indeed, in vivo, it appears that pulses of inhibition dominate during ripples in the CA1 over excitation\(^{30}\). This may help to transmit information reliably out of the hippocampus. It is possible to manually separate these assemblies, for example, as shown in Fig. 4d. However, adding interneurons to the RO-CA1 in these cases will still further refine assembly segregation (as in Fig. 5d,i). As with the SHOT-CA3 and reversion interneurons, our results support the idea that interneurons in the CA1 also regulate spike-timing by refining the width of learned assemblies in the CA1 via a procedure like the pyramidal interneuron network gamma mechanism\(^{23,24}\).

**High-frequency assemblies nest on a theta oscillation.** Assembly discretization occurred during SPW–Rs in our model. Gamma oscillations (of varying frequency) are often nested with theta oscillations and are implicated in memory tasks\(^{20,24}\). These gamma oscillations are also found during SPW–Rs\(^{13,25,26}\). Thus, we investigated whether high-frequency assemblies would persist in theta states (Supplementary Fig. 14).

Providing a stronger background current to SHOT-CA3E resulted in RO-CA1E firing as phase precessing assemblies nested on theta. This occurred after learning with the local Fourier rule (as in Fig. 5). Thus, theta phase segregation and Hebbian learning rules can generate theta-nested assemblies. This is similar to the operations of a working memory buffer (as suggested in ref. 19). Here, the number of assemblies or items in this buffer is as follows:

\[
N_{\text{items}} \leq \frac{\theta_{\text{INT}}}{\theta_{\text{INT}} - \theta_{\text{MS}}}
\]

The period of the INP-MS oscillation \((\theta_{\text{MS}})^{-1}\) acts as the temporal resolution of the buffer, while the IGTS period \((\theta_{\text{INT}} - \theta_{\text{MS}})^{-1}\) determines the capacity of the buffer (Methods). Our model parameters yield a maximum of 16 items in the buffer.

**Ripple clusters minimize the fragmentation of memories.** Finally, we investigated how stochastic SPW–R initiation would alter replays\(^{25,30}\).

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Fig. 5 | Single-trial learning in the hippocampus. a. Network schematic of the SHOT-CA3 receiving INP-MS and a downstream RO-CA1 network. Inputs from the SUP-EC trigger the to-be-learned sequence in the RO-CA1. Left: in the learning phase, the SUP-EC inputs trigger sequential firing in the RO-CA1E. The local Fourier rule binds the RO-CA1 spiking activity to the firing fields in the SHOT-CA3E. Right: compressed replay can be triggered after learning by turning off the INP-MS, I, inhibitory, E, excitatory. b. Spike raster plot of SHOT-CA3E. The outlines denote the presence or absence of the INP-MS and the activation of the local Fourier rule. c. Spike raster plot of RO-CA1E. The purple overline denotes the presence of inputs from the SUP-EC. RO-CA1E are stimulated to fire bursts (see inset for a zoomed-in view) by SUP-EC inputs during \(t \in [1, 2]\). The INP-MS is turned off during \([4.03, 4.13]\) to trigger a compressed replay. d. Zoomed-in segment of the blue boxed region of c of compressed assembly replay triggered when the INP-MS is off. e. Spike raster plot of the RO-CA1I during SPW–R (time aligned with d). f. The total population activity for the RO-CA1I (gray; time aligned with b and c) and the bandpass-filtered (150–250 Hz) population activity (burgundy). g. The total population activity in the SHOT-CA3. h. A zoomed-in segment of the total RO-CA1 population activity, RO-CA1I population activity, RO-CA1E population activity, and the filtered ripple band during SPW–R. Note that population activities have been normalized such that maximum activity is set to unity, and they are not to scale. High-frequency oscillations are triggered by the excitatory population. RO-CA1E high-frequency assemblies trigger the interneuron network to fire at a high frequency. i. Compressed replay triggered by removing the INP-MS while disabling the RO-CAI1. This causes the learned assemblies to overlap. j. Schematic of SPW–R mechanism and function, detailing formation and high-frequency-assembly refinement. The SHOT-CA3E trigger ordered but overlapping assembly spiking in RO-CA1E through their excitatory postsynaptic potentials (EPSPs). When interneurons are included, the excitatory assemblies trigger the RO-CA1E to fire. The SHOT-CA3 EPSPs are refined in width by RO-CA1 inhibitory post synaptic potentials (IPSPs). k. The INP-MS is kept off and SPW–Rs are initiated by stochastically turning on an extra current with a constant probability per unit time (Methods). The learned connections from the SHOT-CA3 to RO-CA1E are identical to those in b. Some replays are correct, while other replays are fragmented and/or distorted. One of the FORCE-decoded \(\theta_{\text{INT}}\) oscillators (light blue) demonstrates that correct replays are locked to the ascending component of the \(\theta_{\text{INT}}\) oscillation while fragmented replays are locked to the descending phase of the \(\theta_{\text{INT}}\) oscillation (highlighted by broken lines). We term this type of error ‘phase distortion’. l. Phase distortion may be minimized by locking the probability of ripple initiation to the underlying \(\theta_{\text{INT}}\) oscillation in the SHOT-CA3E. The inter-ripple interval distribution (estimated after 3,000 s of simulation) is a good qualitative match for the multimodal distribution from a previous study\(^{25}\) (top inset; adapted from ref. 19. Cell Press.), which has peaks at the harmonics of a theta oscillation period of 110 ms, although there are some quantitative errors as we used a slower \(\theta_{\text{INT}}\) of \(\theta_{\text{INT}} = 150\) ms.
Here, we considered a more controlled and phenomenological model of stochastic SPW–R activation, rather than recurrent excitation (considered in Fig. 2). We disabled the INP-MS post-learning and stochastically turned on extra excitation to initiate SPW–Rs (Fig. 5k). This phenomenological model of SPW–R initiation caused random replays of the learned memory (Fig. 5k). We found
that depending on when the SPW–R was initiated, replays could display an error, which we term ‘phase distortion’. In phase distortion, the replay is fragmented into disordered pieces. Phase distortion occurred when SPW–Rs were initiated in the wrong phase of $\theta_{\text{INT}}$ (Fig. 5k). To reduce phase distortions, SHOT-CA3I can bias the probability of SPW initiation to the correct phase range of $\theta_{\text{INT}}$. We considered the probability $p(t)$ of initiating a SPW–R as follows:

$$p(t) = p_0 \cos(2\pi \theta_{\text{INT}} + \psi)$$  \hspace{1cm} (9)

where $\psi$ is the phase that minimizes phase distortion. The parameter $p_0$ serves as the background SPW activation rate and $p_i$ determines how strong the SPW generation probability oscillates. This oscillatory component, $\cos(2\pi \theta_{\text{INT}} + \psi)$, was decoded from SHOT-CA3I (Methods). A relative refractory period was also incorporated (Methods). This strategy for minimizing phase distortions had an observable effect on inter-SPW–R interval distributions. The inter-SPW–R intervals now displayed a strong $\theta_{\text{INT}}$ modulation (Fig. 5i). This is qualitatively similar to previously reported distributions\(^{36}\), which are multimodal with peaks at 110 ms, 220 ms, 330 ms, and 440 ms. The inter-SPW–R intervals from that study\(^{36}\) imply that there is some theta modulation in SPW–R initiation, with a potential $\theta_{\text{INT}}$ value of ~9.1 Hz. Thus, our results support the idea that inhibition can also influence SPW–R initiation and inter-SPW–R interval distributions to minimize replay fragmentation.

Discussion

Our memory systems have to handle multiple simultaneous constraints to record, store, and catalog important events. One constraint is that stimuli are often presented only once. Thus, we investigated whether single-trial learning was possible utilizing background spiking activity as a backbone for learning. The background spiking activity took the form of the IGTS\(^{6,7}\), generated via a dual oscillator model. We interpreted one oscillator as intrahippocampal, controlling spike-timing during SPWs. The second oscillator was externally applied and interpreted as the medial septum (MS). We found that this approach was sufficient to create stable firing fields in pyramidal neurons, but not interneurons. Removal of the INP-MS oscillator triggered compression of the firing fields as ordered bursts. A dedicated population of interneurons also induced reverse replays.

We derived a local learning rule that could successfully bind to-be-learned sequences that were generated by external inputs in RO-CA1 onto the IGTS. Forward or reverse replays could be induced by removing the INP-MS. Surprisingly, through a combination of the local Fourier rule and theta oscillations during learning, high-frequency assemblies emerged during replays. These assemblies also persisted in the presence of MS inhibition, where they nested on the theta oscillation. These assemblies triggered ripple-like oscillations in the RO-CA1. The RO-CA1 were the dominant component of population activity and displayed phase-locking to the ripples in this population activity. The ripples served to segregate learned assemblies and prevented assembly overlap. Finally, we demonstrated that SHOT-CA3I can prevent memory fragmentation due to phase distortions during replay by modulating the probability of SPW–R initiation. We predicted that this would have an observable effect on inter-SPW–R interval distributions, which has been observed experimentally\(^{36}\). Our results support the role of interneurons in generating, compressing, reversing, and refining spike sequences for stable learning.

A link between theta-phase compression and SWR–R compression. Our results suggest that the mechanism for SPW–R compression and SWR–R compression within a theta cycle may be one and the same. The timing of spikes during both events can be coordinated by a single population of interneurons, operating in two modes, which are delineated by the presence of MS inhibition. When the INP-MS was present, the sequence compression within a theta cycle was due to $\theta_{\text{INT}}$, the oscillator that was regulating sequence compression during SPW-Rs.

The hypothesis that these compression mechanisms are related is supported by two lines of experimental evidence. First, the SPW–R compression ratio is only slightly larger (30%) than theta-phase compression\(^{1,2}\). Second, in extended replay, SPW–Rs often occur in clusters containing multiple SPW–Rs\(^{36,38}\). The individual SPW–Rs within a cluster have a 100–150-ms gap, or a theta period, between them\(^{36,38}\). Strikingly, in a previous study\(^{36}\), the authors found theta harmonics in the inter-SPW–R interval as peaks in the distribution at 110 ms, 220 ms, 330 ms, and 440 ms. It is important to note that SPW–R clusters also form due to phase-locking in 7–10 Hz sleep spindles\(^{36}\). However, SPW–R clusters are reliably evoked during quiet awake scenarios, when an animal is exploring longer mazes\(^{36,38}\).

Experimental predictions from our model. We suggest a novel experiment to assess whether dual oscillators support IGTSs. First, employing the left/right alternation task, as in a previous study\(^{4}\), should yield stable firing fields during wheel running\(^{6,7}\) (Fig. 6, left). We suggest using a closed-loop feedback system\(^{40–42}\) to optogenetically drive the MS to oscillate at different frequencies during wheel running (Fig. 6, right). For a sufficiently large driving frequency, $\theta_0 > \theta_{\text{INT}}$, interference theory predicts sequence reversal in the IGTS and phase recession (Fig. 6, right). For additional model predictions, see the Supplementary Note and Table 2.
Limitations of the model. While our model displays many of the intrinsic rhythms and behaviors of the hippocampus, like all models, it is a simplification. Here, we consider discrepancies between our model and the experimental data. We list the following four limitations: (1) interneurons display limited or no phase precession; (2) the presence of attractor network dynamics in the CA3; (3) the gamma and high-frequency oscillation that we predict due to the CA3 is faster than observed; and (4) the aperiodicity of observed IGTSs. We discuss the limitations of our model in more detail in the Supplementary Note and Table 2.

While pyramidal cells precess in phase under a variety of conditions\textsuperscript{6,10}, interneuron phase precession is less clear. Some interneurons in the CA1 display phase precession due to strong, monosynaptic connectivity with a phase precessing pyramidal neuron\textsuperscript{43}. Other measurements of interneuron phase precession demonstrate a greater variability in phase precession slopes\textsuperscript{19,43}, with some interneurons even displaying bouts of phase recession (see figures 3 and 4 in ref. 19). Interestingly, it has been noted\textsuperscript{19} that interneurons fire wider bursts, which might make phase precession more difficult to assess. However, as the leaky integrate-and-fire model has limitations in producing the rich dynamics of real neurons, interneuron phase precession in our network model may be eliminated by considering other neuron models.

Our model does not use recurrent excitatory connectivity to create sequences. The recurrent activity is used only to activate interneuron networks. Both phase precessing and SPW spike sequences are internally created in our model by inhibitory weights. While interneuron spike sequences have been documented\textsuperscript{44}, both experimental
work\(^{1,2,3}\) and theoretical modeling\(^{1,12,13}\) have demonstrated that excitatory connectivity is an important factor for sequence generation and compression. It would be interesting to combine our model with attractor-like dynamics in the future.

Other models of replay and theta sequences. Dual oscillator models have been suggested as a mechanism for phase precession long before this study\(^{10}\). Other studies have considered somato-dendritic interference as a source of phase precession\(^{11,12}\). Recent studies have demonstrated how multiple intrahippocampal oscillators with uniform phase clustering at discrete values can yield a slower oscillation in global population activity\(^{1,2}\). This mirrors our result with the continuous uniform distribution endowing INP-MS control over population activities. Here, we consider the novel hypothesis that phase precession arises from the need to dilate pre-existing SPW sequences for single-trial learning of new sequences.

Multiple-oscillator models were also considered as a mechanism of grid cell firing\(^{5}\). In these models, the theta frequency is linked to animal velocity in velocity-controlled oscillators. By using three velocity-controlled oscillators with phase shifts separated by \(\frac{\pi}{3}\), hexagonal grid patterns emerge in space. However, recent experiments have cast doubt on this mechanism, as grid cells still occur in bats, which do not exhibit theta oscillations\(^{15}\). Furthermore, in vivo patch recordings have demonstrated that an underlying ramp of depolarization encodes significantly more spatial information than the theta envelope\(^{16,17}\). Here, we consider the following alternative hypothesis: the interference arises between an oscillator controlling the spike times during SPWs and the MS. This creates a compressible IGTS for single-trial learning.

Finally, other models have either linked theta sequences to SPW–Rs\(^{19}\) or considered the problem of fast learning in the hippocampus. We summarize these in the Supplementary Note.

Conclusions. A long-standing hypothesis is that interneurons control spike-timing. Here, we demonstrated how populations of interneurons can achieve the following: (1) generate theta oscillations in the hippocampus through recurrent and septal inhibition; (2) create phase precessing theta sequences; (3) trigger compressed replay of these sequences in forward and reversed modes; (4) facilitate single-trial learning of spike trains as high-frequency assemblies; (6) refine said assemblies by minimizing their overlap in time; (7) nest these assemblies on a theta oscillation after learning; and, finally, (8) modulate the inter-SPW–R intervals to prevent replay fragmentation. This intricate control over spiking in our model was facilitated with little more than a pair of oscillators, interneuron–pyramidal reciprocal connectivity, and Hebbian plasticity.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of code and data availability and associated accession codes are available at https://doi.org/10.1038/s41593-019-0415-2.

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Methods

Leaky integrate-and-fire network. The SHOT-CA3 network for Figs. 1 and 3–5 consists of coupled leaky integrate-and-fire neurons, as follows:

$$\tau_m v_m^C = -v_m^C + R m_j^C + R \sum_{j=1}^{N_{CA3}} \theta_j^C \delta(t - t_j),$$

$$\tau_m v_m^A = -v_m^A + R m_j^A + R \sum_{j=1}^{N_{CA3}} \theta_j^A \delta(t - t_j),$$

$$\tau_m v_m^E = -v_m^E + R m_j^E + \sum_{j=1}^{N_{CA3}} \theta_j^E \delta(t - t_j),$$

where \(CA3\) and \(CAI\) denote the excitory and inhibitory populations, respectively, of the SHOT-CA3, while \(REV\) denotes the reversion interneurons (see the section "Reversion interneuron population" below). The neurons receive a constant background current \(I^b\) for \(\alpha = CA3, CAI, REV\). The SHOT-CA3 current is set at or above the threshold, while the SHOT-CA3, REV currents vary depending on the condition (INP-MS On vs Off; see Table 1 and figure captions for parameters). The parameter \(R = 1 \times 10^5 \Omega\) serves as the resistance. When the voltage reaches a threshold value, \(v_{threshold}\), they are immediately reset to \(v_{reset}\) followed by an absolute refractory period, \(\tau_m\), during which the neuronal dynamics are quenched at the reset value. The membrane time constant is \(\tau_m\). The spikes themselves are filtered by the double exponential synapse as follows:

$$r_m = r_m^{in} - r_m^{out} + h_{m}^{out},$$

$$h_{m}^{out} = h_{m}^{in} + \frac{1}{\tau_m} \frac{pA \cdot ms^2}{V} \sum_{j=1}^{N_{CA3}} \delta(t - t_j),$$

where \(r_m\) is the synaptic rise time, and \(t_j\) is the decay time and \(t_j\) is the \(j\)th spike fired by the \(j\)th neuron. The SHOT-CA3 all receive INP-MS where \(\theta_j\) is the input frequency, and \(\kappa^2 = 1\) determines the tonic level of the inhibitory drive. The INP-MS has the amplitude \(F^{in}\) as \(-10^5\) for \(i = 1, 2, \ldots, N_c\). The excitatory neurons do not receive INP-MS. The reversion interneurons do not receive INP-MS (Figs. 3 and 4), but our results still hold when the reversion interneurons receive INP-MS (Supplementary Fig. 11). The network consisted of \(N_{CA3} = 2,000\) spiking neurons. However, the hippocampus is a circuit consisting of \(O(10^3)\) neurons (in rat), and our network model of \(CA3\) is not to scale. Thus, our results may not reflect the full behavior of a much larger circuit.

The weight matrices \(\omega^{CA3CAI}\) and \(\omega^{CAICA3}\) are described in further detail in the section "FORCE training internal sequences". All weight matrices that we considered are unities, with the units of current (\(pA\)) carried by the synaptically filtered spike trains \(r(t)\) (see equation (14)). The SHOT-CA3 also receive a current from the reversion interneuron population (Figs. 3 and 4). \(I_{syn}^{CAI}\), \(I_{syn}^{CA3}\), which is described in greater detail in the section "Reversion interneuron population". In all cases, when we refer to the filtered spike train, we mean \(r(t)\) as given by equation (13). However, the filtering time constants differ for different figures and different populations of neurons (see Table 1 for parameters).

As shown in Fig. 4, the RO-CA1 layer was included in the simulation as follows:

$$\tau_m v_m^C = -v_m^C + R m_j^C + \sum_{j=1}^{N_{CA3}} \theta_j^C \delta(t - t_j),$$

$$\tau_m v_m^A = -v_m^A + R m_j^A + \sum_{j=1}^{N_{CA3}} \theta_j^A \delta(t - t_j),$$

$$\tau_m v_m^E = -v_m^E + R m_j^E + \sum_{j=1}^{N_{CA3}} \theta_j^E \delta(t - t_j),$$

where \(CA3\) and \(CAI\) were trained using the local Fourier rule. A series of external input currents (SUP-EC) \(I_{sup}^{CA3E}\) and \(I_{sup}^{CA3I}\) were trained using recursive least squares (RLS), an online learning scheme described in further detail in the section "RLS technique". The network approximant of the intended dynamics is given by the following:

$$\hat{x}(t) = \hat{\phi}^{CA3E},$$

where \(\phi\) determines the amount of learned recurrence the network receives and \(\phi^a\) and \(\phi^b\) are referred to as the neural encoders and decoders, respectively. The encoder\/decoder help determine the tuning preferences of the neurons. The decoders were trained using recursive least squares (RLS), an online \(L_2\) minimization scheme described in further detail in the section "FORCE training a balanced \(L_2\) network" below. We include this section for completeness.

FORCE training inhibitory connections in a balanced \(E/I\) network. Here we discuss trained \(E/I\) connectivity balanced \(E/I\) network for completion alone. The network we trained was a balanced \(L_2\) network, which is described in further detail in the section "FORCE training a balanced \(L_2\) network" below. The \(L_2\) network is given as follows:

$$S^{local} = \begin{cases} \frac{T \cdot g}{\lVert \theta \rVert^2} & \beta = CA3, C \neq CA3I, C \neq CA3E, \theta = \hat{\phi}^a, \phi^b = \hat{\phi}^b > 0 \\ -\frac{g}{\lVert \theta \rVert^2} & \beta = CA3, \theta = \hat{\phi}^b, \phi^a = \hat{\phi}^a < 0 \\ 0 & \text{otherwise} \end{cases}$$

With \(N_{CA3}\) excitatory neurons and \(N_{CAI}\) inhibitory neurons, each neuron received precisely \(C_{CA3} = pN_{CA3}\) excitatory connections and \(C_{CAI} = pN_{CAI}\) inhibitory connections from the rest of the network, where \(p\) is the degree of sparsity in the network. The \(N_{CA3}\) neuron \(j\) was considered to be present between neuron \(i\) in population \(\beta\) (presynaptic) and neuron \(i\) in population \(\alpha\) (postsynaptic), and \(\delta\) otherwise. The variable \(N_{CA3}\) controls the coupling strength while \(g = \sqrt{C_{CA3} \cdot C_{CAI}}\). Here, however, we did not train a balanced \(E/I\) network, but rather a balanced \(L_2\) network (see the section "FORCE training a balanced \(L_2\) network" below). We include this section for completeness.

In normal FORCE training, the learned term is given by the following:

$$L^{\beta} = g (\eta^{\beta} \cdot \phi^a),$$

where \(\eta\) determines the amount of learned recurrence the network receives and \(\eta^a\) and \(\eta^b\) are referred to as the neural encoders and decoders, respectively. The encoder\/decoder help determine the tuning preferences of the neurons. The decoders were trained using recursive least squares (RLS), an online \(L_2\) minimization scheme described in further detail in the section "RLS technique". The network approximant of the intended dynamics is given by the following:

$$\hat{x}(t) = \hat{\phi}^{CA3E},$$

where \(\phi\) determines the amount of learned recurrence the network receives and \(\phi^a\) and \(\phi^b\) are referred to as the neural encoders and decoders, respectively. The encoder\/decoder help determine the tuning preferences of the neurons. The decoders were trained using recursive least squares (RLS), an online \(L_2\) minimization scheme described in further detail in the section "FORCE training a balanced \(L_2\) network" below. We include this section for completeness.
where the operation (s) sets s to 0 if its negative (positive) and retains its value otherwise.

First, we decomposed the decoders and encoders as follows:

\[
\eta - \Phi = ((\eta(s) + (\eta(s))_+ \cdot ((\phi(s))_+ + (\phi(s))_-)
= \eta(s) + (\eta(s))_+ \cdot (\phi(s))_-
= \eta(s) + (\eta(s))_+ \cdot (\phi(s))_-
= \eta(s) + (\eta(s))_+ \cdot (\phi(s))_-
\]

(23)

Thus, we can consider the following weights:

\[
I_{\eta}^{\Phi} = \begin{cases} 
(\eta(s) + (\eta(s))_+ \cdot (\phi(s))_+ \cdot (\phi(s))_-) \beta = \text{CA3E} \\
(\eta(s) + (\eta(s))_+ \cdot (\phi(s))_+ \cdot (\phi(s))_-) \beta = \text{CA3I}
\end{cases}
\]

(24)

which implements an alternate boundary condition to equation (21). Furthermore, implementing equation (24) only required O(N) computations, as only encoders and decoders are bounded by their signs. This derivation, among other results, is originally from a previous publication.

**RLS technique.** The decoders were determined dynamically to minimize the squared error between the approximant and intended dynamics, \( e(t) = \dot{x}(t) - x(t) \). The RLS technique updates the decoders accordingly:

\[
\Phi(t) = \Phi(t - \Delta t) \frac{P(t - \Delta t) e(t) + e(t) P(t - \Delta t) e(t)}{1 + \rho(t) \Psi(t - \Delta t) e(t)}
\]

(25)

\[
P(t) = P(t - \Delta t) \frac{P(t - \Delta t) e(t) e(t) P(t - \Delta t)}{1 + \rho(t) \Psi(t - \Delta t) e(t)}
\]

(26)

and \( e(t) = f(x(t), \dot{x}(t)) \). RLS and FORC training was described in greater detail in other studies. The network is initialized with \( \Phi(0) = 0, P(0) = I \mu, \) where \( I \) is an N-dimensional identity matrix, and \( \mu \) controls the learning rate of RLS.

**FORCE training a balanced I network.** In addition to the procedure described above, a balanced network can be generated with recurrent inhibition alone. In particular, we considered the same network equations as before with the following constraints:

\[
S_{\eta} = \text{CASE, CASE} = 0, S_{\phi} = \text{CASE, CASE} = 0, \]

\[
P = \text{I threshold + O(m m Dimensional)), F = \text{I threshold + O(m m Dimensional)}
\]

where the interneuron network receives a super-threshold \( F = \text{I threshold} = -40 \text{ pA} \) background current that is being balanced by the recurrent inhibition. The excitatory neurons in the population also received inhibitory connections and thus have a super-threshold background current after FORCE training is concluded. However, during FORCE training, the current \( F = \text{I threshold} \) was clamped below the threshold \( F = \text{I threshold} \) to prevent firing in the excitatory neurons, thereby eliminating both EE and IE weights. This occurs through the dependence of equation (25) on \( \Phi(t) \), and \( x(t) = 0 \).

**IGTs.** To construct a SHOT-CA3 network with a recurrently generated theta sequence of firing, we FORCE trained the network to learn the following supervisor:

\[
x(t) = \cos(2\pi t) + \chi, \quad i = 1, 2, ..., m
\]

(27)

Here, \( \chi \) is the frequency of the oscillation that is embedded in the recurrent weights of the network and \( \chi \) is a phase shift for the m components of the supervisor. The m components of the supervisor yielded an \( N \times m \) dimensional matrix of encoders and decoders with \( m = 100 \) components. For each neuron, exactly one encoder element was non-zero and set to 1. The phase shift was randomly selected and uniformly distributed over [0, 2\( \pi \)]. When trained in this fashion, the inhibitory currents and the INP-MS combined to generate an interface pattern in the excitatory neurons (Supplementary Figs. 1 and 2):

\[
z(t) \approx \cos(2\pi t) + \cos(2\pi t) + \psi, \quad i = 1, 2, ..., \text{CASE}
\]

(28)

We interpreted \( z(t) \) to be the fluctuating, dimensionless, component of the current an excitatory SHOT-CA3 neuron receives. Note that we have written \( \psi \) as opposed to \( \chi \), as the phases of the excitatory neurons are only indirectly related to the phases in the supervisor (equation (27)). This is due to the operations applied in equation (24).

**Interference-based control of population activity by the INP-MS.** With the currents arriving at each neuron given by equation (28), we considered the conditions under which the INP-MS influences population activity of the SHOT-CA3. In particular, we set out to provide sufficient conditions under which population activity \( p(t) \) was a periodic function in time with period \( \theta_{\text{MS}} \).

Proceeding generally, we assumed that a network transforms its currents via some unspecified differentiable nonlinearity \( F(z) \), where \( F(z) \geq 0 \) into spike rates. This implies that population activity is given by the following:

\[
\rho(t) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \rho_{\text{str}}(\psi) F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi
\]

(29)

The function \( \rho(t) \) is the population activity for a network of neurons with identical tuning curves \( F(z) \) receiving heterogeneous currents, \( z(t) \). The heterogeneity is in the phases of the currents, \( z(t) \), through the variable \( \psi \). We assumed that this parameter comes from a static distribution with density function \( \rho_{\text{str}}(\psi) \). Next, we considered \( \rho(t) + \theta_{\text{MS}} \):

\[
\rho(t + \theta_{\text{MS}}) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \rho_{\text{str}}(\psi) F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi
\]

(30)

\[
\rho(t + \theta_{\text{MS}}) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \rho_{\text{str}}(\psi) F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi
\]

(31)

\[
\rho(t + \theta_{\text{MS}}) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \rho_{\text{str}}(\psi) F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi
\]

(32)

If the phase distribution is uniform \( \rho_{\text{str}}(\psi) = \frac{1}{2\pi} \) then:

\[
\rho(t + \theta_{\text{MS}}) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \frac{1}{2\pi} F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi
\]

(33)

\[
\rho(t + \theta_{\text{MS}}) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \frac{1}{2\pi} F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi
\]

(34)

\[
\rho(t) = \rho(t)
\]

(35)

where line (34) is justified by the fact that \( G(\omega, t) = \int F(x(2\theta_{\text{MS}}t + \psi) + \cos(2\theta_{\text{MS}}t)) d\psi \) is periodic in \( \omega \) with period \( 2\pi \), and phase shifts \( (2\theta_{\text{MS}}t) \) in line (33) do not alter integrals of periodic functions. This implies that a uniform distribution is a sufficient condition for \( \theta_{\text{MS}} \) control of population activities. Finally, we considered \( \rho(t) \) when INP-MS is removed:

\[
\rho(t) = \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} \rho_{\text{str}}(\psi) F(x(2\theta_{\text{MS}}t + \psi)) d\psi
\]

(36)

Thus, \( \rho(t) \) is a constant and given by \( \rho(t) = \frac{1}{2\pi} \int_{-2\theta_{\text{MS}}}^{2\theta_{\text{MS}}} F(\psi) d\psi \). Consequently, for uniformly distributed phase preferences, population activity is constant in the absence of INP-MS despite the fact that all the neurons are oscillating.

**Interference-based SPW–R and theta-phase compression of spike sequences.** Multiple-oscillator models are well studied in the literature. Here we demonstrate that SPW–R compression is also well explained by interference theory, and that the phase precession–based compression and SPW-based compression share the same mechanism in interference theory. Considering the current arriving at the SHOT-CA3, \( z(t) \), again,

\[
z(t) = \cos(2\pi t) + \cos(2\pi t) + \psi \]

(36)
Equation (37) implies that the firing field order is controlled by the envelope \( \cos \left( 2\pi \left( \frac{\theta_{\text{INT}} - \theta_{\text{MS}}}{2} \right) + \psi \right) \) in particular the phases \( \psi \). If the phase distribution of \( \psi \) is uniform, then the firing fields are uniformly distributed in time. If \( \theta_{\text{INT}} < \theta_{\text{MS}} \), then the envelopes have phases \( \psi_i/2 \), whereas if \( \theta_{\text{INT}} > \theta_{\text{MS}} \), the phases become reversed with \(-\psi_i/2\). The end effect of this transformation is to either preserve or reverse the order of the firing fields (the envelope).

Reverse compressed replay with dual oscillator-based mechanisms. If INP-MS is removed, the interference pattern collapses and the neurons receive the input \( z_i^{\text{REV}}(t) = \cos(2\pi \theta_{\text{INT}} t + \psi) \) (38)

where FOR is short for forward compression. Removal of the INP-MS triggers a compression provided that the neurons also receive an additional super-threshold constant current. Thus, the default compression mode is a forward compression, whereby bursts occur in the same order as the firing fields when the INP-MS is present. This compression can be reversed in two ways: (1) reverse the order of the firing fields \( z_i(t) \) and maintain \( z_i^{\text{REV}}(t) \) or (2) reverse \( z_i^{\text{REV}}(t) \) and maintain the order of firing fields.

In mirror inversion, the INP-MS is present and satisfies the frequency relationship \( \theta_{\text{INT}} > \theta_{\text{MS}} \). The firing fields are reversed in order relative to the compression phase. However, this is not a valid mechanism for reverse compression, as \( \theta_{\text{INT}} > \theta_{\text{MS}} \), both excitatory and interneuron populations recess in phase. To our knowledge, phase recession has only been observed once26. In harmonic reversion, the firing fields reverse near the harmonics of \( \theta_{\text{INT}} \) (Supplementary Fig. 8). For \( \theta_{\text{INT}} \) just slightly larger than \( \theta_{\text{MS}} \), the firing fields reverse.

Finally, directly reversing \( z_i^{\text{REV}}(t) \) also triggered a reverse compressed replay. An additional population of interneurons, the reversion interneurons, was sufficient for this type of reversion. Reverse compression corresponded to SHOT-CA3I receiving the current, as follows:

\[
z_i^{\text{REV}}(t) = \cos(2\pi \theta_{\text{INT}} t - \psi)
\]

Thus, reversion interneurons should be inhibited by SHOT-CA3I (through \( \sin(2\pi \theta_{\text{INT}} t) \)) while subsequently inhibiting the excitatory neurons. The amount of inhibition an excitatory neuron in SHOT-CA3 receives from the reversion population is controlled by the amplitude function \( \sin(\psi) = 2\sin(\psi) \).

Reversion interneuron population. The reversion population is a population of \( N_{\text{MS}} \) interneurons with leaky integrate-and-fire dynamics and receive inhibition from SHOT-CA3I. For simplicity, we took \( N_{\text{INT}} = N_{\text{MS}} \) and \( \theta_{\text{INT,CA3}} = \theta_{\text{INT,CA3}} \) where \( I_{\text{INT,CA3}} \) is the \( I_{\text{INT,CA3}} \times I_{\text{INT,CA3}} \) identity matrix and \( \theta_{\text{INT,CA3}}^{\text{REV}} \) is a scalar quantity with \( \theta_{\text{INT,CA3}}^{\text{REV}} > 1 \) that determines the amount of inhibition the reversion population receives. The only parameter difference between the reversion population and the other neurons is the background current, \( I_{\text{REV}} \), which varies when the INP-MS is present or absent (Figs. 3 and 4). From the preceding section, we required the reversion population to transmit the signal \( 2 \sin(\psi) \sin(2\pi \theta_{\text{INT}} t) \) in a biologically plausible manner. First, the reversion interneurons must be locked into the internally generated theta oscillation through the term \( \sin(2\pi \theta_{\text{INT}} t) \). Thus, we trained a decoder \( \phi_{\text{REV}} \) that can decode \( \sin(2\pi \theta_{\text{INT}} t) \) from the activity of the reversion population, as follows:

\[
\lambda(t) = \langle \phi_{\text{REV}} \rangle = \langle \phi_{\text{REV}} \rangle^T \rho_{\text{REV}}(t) \approx \sin(2\pi \theta_{\text{INT}} t) = s(t)
\]

where \( \phi_{\text{REV}}^{\text{INT,CA3}} \) was trained using the decoded internal oscillators of the SHOT-CA3 network as a supervisor. The training is not performed online as in RLS, but is learned immediately through \( L_{\text{RMS}} \) optimization as follows:

\[
\phi_{\text{REV}}^{\text{INT,CA3}} = \left( \int_0^T \rho_{\text{REV}}^T(t) \rho_{\text{REV}}(t) + I_{\text{REV}}^2 \right)^{-1} \left( \int_0^T \rho_{\text{REV}}(t) s(t) \right) dt
\]

where \( \delta = 50 \) acts as a regularization parameter and \( T = 25 \) was used to compute \( \rho_{\text{REV}}^{\text{INT,CA3}} \). Finally, note that the current \( i_{\text{REV}}^{\text{CA3,REV}}(t) \) is strictly inhibitory and performs the necessary reversion in the excitatory neurons. The parameter \( A_{\text{REV}} \) was used to scale the current upward so that the SHOT-CA3 interneuron and reversion interneuron currents were of similar magnitude \( (A_{\text{REV}} = 10 \text{ pA}) \). As the excitatory neurons receive an extra source of inhibition, they required a larger excitatory drive when the INP-MS is deactivated.

Furthermore, as the current \( i_{\text{REV}}^{\text{CA3,REV}}(t) \) is strictly negative, a set of weights \( \omega_{\text{CA3,REV}} \) was found via a constrained optimization problem

\[
\text{argmin}_{\omega_{\text{CA3,REV}}} \langle \omega_{\text{CA3,REV}} \rangle^T \langle \rho_{\text{CA3,REV}} \rangle, \quad \omega_{\text{CA3,REV}} \leq 0, \quad \forall i, j
\]

This problem can be solved numerically, for example, with the MATLAB function lsqnonneg. However, for simplicity, we did not take this approach and simply applied the negative current, equation (42), to the SHOT-CA3E.
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Software and code

Policy information about availability of computer code

Data collection

The code for this modeling study was coded by Wilten Nicola using the MATLAB 2018a programming environment.

Data analysis

All analysis was performed using the default MATLAB 2018a statistical analysis function suite.

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Sample size
This was a modelling study with primarily deterministic neural networks. Sample sizes only factored in some of the linear regression analysis performed in this paper. No statistical methods were used to predetermine sample sizes. As the network is deterministic, very few discrete points are required to interpolate a trend in behaviours as a response to inputs. The \(O(10^3)\) theta cycles or \(O(10^2)\) firing fields were sufficient to infer trends over the parameter distributions we considered. With a deterministic network, significantly less discrete simulations could have been performed to determine the same trends with a continuous parameter sweep.

Data exclusions
The only data excluded was in Figure 1I, when estimating the phase precession slopes (only the central linear bulk of points was included, not the discontinuous phase densities around 0, 2\(\pi\), as the phase is a discontinuous variable). This data is excluded as it is an artifact of the discontinuity of the phase variable.

Supplementary Figure S8 I also had data excluded where the points for sufficiently high INP-MS amplitudes exhibited wild discontinuities with the rest of the linear trend. In these parameter regimes, the network fails to perform its task. Including these points would corrupt the analysis of the preceding points, where the network remains functional.

Replication
The results were replicated by retraining the spiking neural network 10 times (included in Supplementary Figure S3) at the nominal parameters used in the manuscript, and under other parameter sets (increased network size, heterogeneity, noise in the neurons) to ensure that the resultant weight matrices had similar banding structures, and the network dynamics/function was preserved.

Randomization
Randomization was not relevant to this study. This is a modelling study without subjects or groups.

Blinding
Blinding was not relevant to this study. This is a modelling study, without subjects or groups.

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