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Spike phase precession persists after transient intrahippocampal perturbation

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Oscillatory spike timing in the hippocampus is regarded as a temporal coding mechanism for space, but the underlying mechanisms are poorly understood. To contrast the predictions of the different models of phase precession, we transiently turned off neuronal discharges for up to 250 ms and reset the phase of theta oscillations by stimulating the commissural pathway in rats. After recovery from silence, phase precession continued. The phase of spikes for the first theta cycle after the perturbation was more advanced than the phase of spikes for the last theta cycle just before the perturbation. These findings indicate that phase advancement that emerges within hippocampal circuitry may be updated at the beginning of each theta cycle by extrahippocampal inputs.

The timing of neuronal spikes in oscillatory networks is under the combined influence of external inputs and the internal self-organizing dynamics of the network. A robust example of this is the firing patterns of hippocampal pyramidal cells. Pyramidal cells discharge selectively when the rat is in specific locations in its environment[1], yet the timing of their spikes is influenced by the endogenous theta oscillation. As the rat walks through the firing field of a place cell, which takes five to ten theta cycles, the cell fires at progressively earlier phases on successive cycles of the ongoing theta oscillation[2]. This relationship allows for the prediction of the future center of the field from the phase advancement of the action potentials across successive theta cycles[3–6]. Furthermore, neuronal assemblies that represent successive places along the trajectory of the rat have a predictable temporal relationship within each theta cycle[3,7,8]. This mechanism is potentially useful for encoding sequence information and for preparing the animal for what is to come next[9,10].

Although numerous computational models have attempted to account for the mechanisms that underlie the spike 'phase-precession' observation[2,9,11–21], direct experimental exploration of the phenomenon is limited[3–6,13,22,23]. Here we test and contrast the predictions of different classes of models by transiently perturbing firing patterns of place cells and resetting the phase of theta oscillations by stimulating the ventral hippocampal commissure. We found preservation of the spatial dependence of theta phases of individual spikes after transient perturbation, indicating that spatial information in intrahippocampal networks may be updated by cortical inputs at every theta cycle.

RESULTS

Single-pulse stimulation of the intrahippocampal pathways reset the theta phase and reliably silenced all recorded hippocampal pyramidal cells and interneurons for a period of one or two theta cycles (**Fig. 1a**). Under anesthesia, single-pulse stimulation, by synchronously discharging large ensembles of pyramidal cells and interneurons, triggers a combination of GABA receptor–mediated inhibition, Ca^{2+}-mediated K^+ conductance increase and disfacilitation. As a result, all pyramidal cells, granule cells and interneurons are silenced for 50–250 ms, depending on the strength of simulation[24–26]. In the present experiments, stronger stimulation synchronized theta more reliably ($P < 0.01$; F-test) and produced longer silent periods ($P < 0.01$; t-test). Recovery of population firing after the stimulation was fast, and after 200–250 ms, both firing rate and theta amplitude fully recovered, even after the strong stimulus. Significantly increased phase coherency of the local field potentials across individual laps could be observed for about 1 s (seven to eight theta cycles) after the stimulation (**Fig. 1b**). Single-pulse stimulation of the perforant-path input can also reset theta and transiently silence place-related activity (E.I. Moser *et al.*, *Soc. Neurosci. Abstr.* **33**, 519.12, 2003). Neurons in the entorhinal cortex, when strongly synchronized by the CA1 output, produce a detectable population spike in the granule cell layer[27]. Evoked reverberating activity was never observed here (data not shown), even at stronger stimulus intensity, indicating that the major effect of stimulation was confined to the hippocampus[28]. The stimulation produced no overt behavioral effects and did not affect the running velocity of the rat (control, 0.26 ± 0.02 m/s; weak stimulation, 0.24 ± 0.01 m/s; strong stimulation, 0.23 ± 0.02 m/s; not significant, t-test).

We recorded from 162 well-isolated CA1 place cells in five rats. Thirty-five units had firing fields in the start area of the maze where stimulation was delivered, and these units were used to examine the effects of stimulation on phase precession (number of cells/sessions for the five rats: 2/1, 3/2, 5/3, 17/3, 8/3). As expected from the suppression of population firing, single-pulse stimulation transiently silenced in-field firing for at least one or two theta cycles. During stimulation trials, despite the theta phase reset and transient interruption of firing, spike phases were still correlated with the spatial position of the animal immediately after recovery, similar to control trials (**Fig. 2a**). To quantify this effect,

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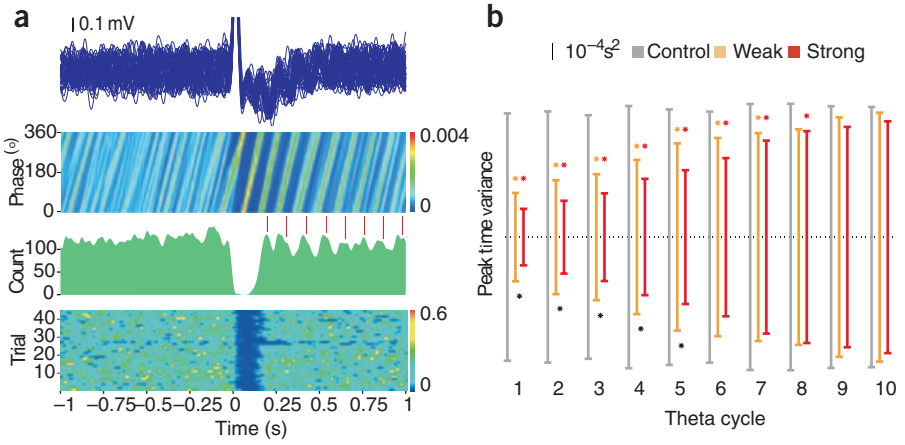

Figure 1 Single-pulse stimulation of intrahippocampal afferents resets theta and silences spiking activity. (**a**) First (upper) panel: superimposed field activity recorded during successive runs in a typical recording session, before and after weak stimulation (time zero). Second panel: instantaneous distribution of phases across successive runs as a function of time. Vertical lines indicate troughs of averaged field activity (data not shown). Third panel: peri-event histogram of three simultaneously recorded interneurons. Fourth (bottom) panel: combined peri-event spiking activity of pyramidal cells ($n = 20$) and interneurons ($n = 3$). Color calibration, spikes per bin (fourth panel), probability (second panel). Note transient silence (<200 ms) and full recovery of global firing rate after stimulation. (**b**) Theta reset after single-pulse stimulation ($n = 5$ rats). Variance of theta peak occurrence times (vertical bars) in successive cycles after stimulation compared with the control condition after crossing of the photobeam. A smaller variance corresponds to higher phase coherence: $^*P < 0.01$, *F*-test; colored asterisk indicates significant difference when compared with control; black asterisk indicates significant difference between strong and weak stimulation.

we determined the mean theta phase for the early, middle and late portions of the firing field for all neurons[6]. This analysis showed no effect of stimulation on spike phase precession (**Fig. 2b**; not significant, circular analysis of variance (ANOVA)). Furthermore, neither peak firing rate nor mean phase at the center of the field was affected by the stimulation (not significant, linear ANOVA and circular ANOVA, respectively). The small but nonsignificant decrease in peak firing rate (**Fig. 2b**) is probably due to the missing spikes after the stimulation.

To examine possible transient effects that were not detected by the previous analysis, we measured the difference between the average spike phase in the last theta cycle before stimulation and the average spike phase in the first theta cycle upon recovery for each lap. We compared this resulting phase difference to the phase advancement of similarly spaced theta cycles in control trials. Assuming an average-sized firing field, the phase of place cell spikes is expected to advance about 40–60° during the time period of two theta cycles[2]. After both weak and strong stimulation, the phase advanced by approximately 40° (**Fig. 3**), which is significantly larger than the zero change expected if phase precession resumed from the same point upon recovery (**Fig. 3c**). The mean phase shift after the perturbations was less than that during control laps (~70°), but the magnitude of the phase shift did not differ significantly across the groups (as indicated by overlapping 95% confidence intervals in **Fig. 3c**).

The final analysis examined whether single-pulse stimulation had an impact on population coding. Within each theta cycle, place cells with overlapping fields discharge in the same order as their fields are traversed; moreover, the closer their firing fields are in space, the closer their respective firings occur in time[3,7]. Thus, the behavioral sequence (traversal of the first and then the second field), which may take on the order of a second, is reflected in the fine-timescale physiological activity (activation of the first and then the second place cell within a given theta cycle), which lasts on the order of a few dozen milliseconds. This results in a time-compressed

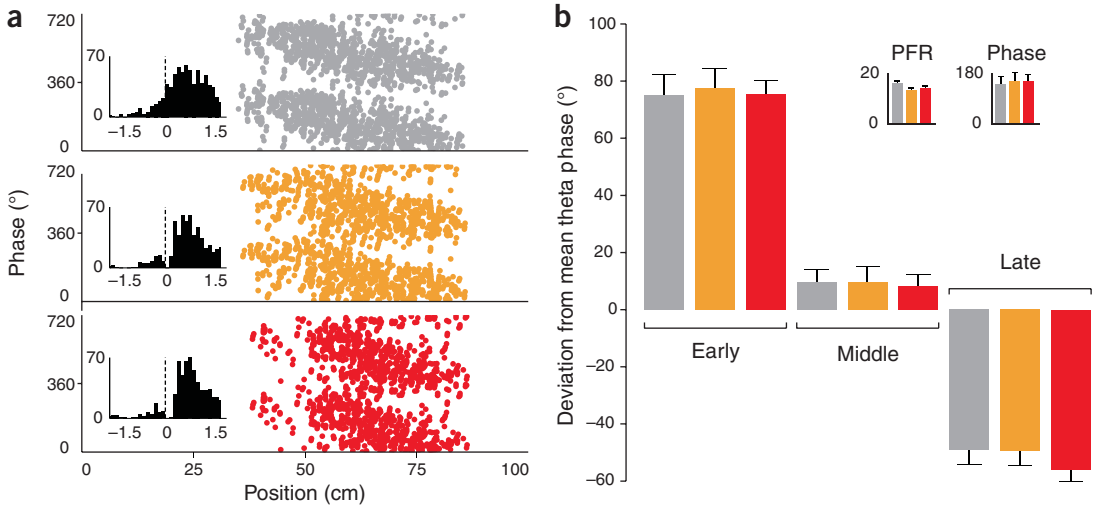

Figure 2 Phase precession is preserved after stimulation-induced perturbation. (**a**) Phase precession for a place cell during control, weak and strong stimulation runs. Note overall similarity of plots across conditions. Insets: peri-stimulus histograms of spikes (*x* axis, counts per bin; *y* axis, time in seconds). (**b**) For overall group statistics, theta phases were determined separately for each of the early, middle and late subfields and were expressed as deviations from the overall mean phase. Error bars, 95% confidence intervals. Insets: Peak firing rates (PFR) and theta phases (Phase) at peak firing rate locations. Color code for experimental conditions as in **Figure 1**.

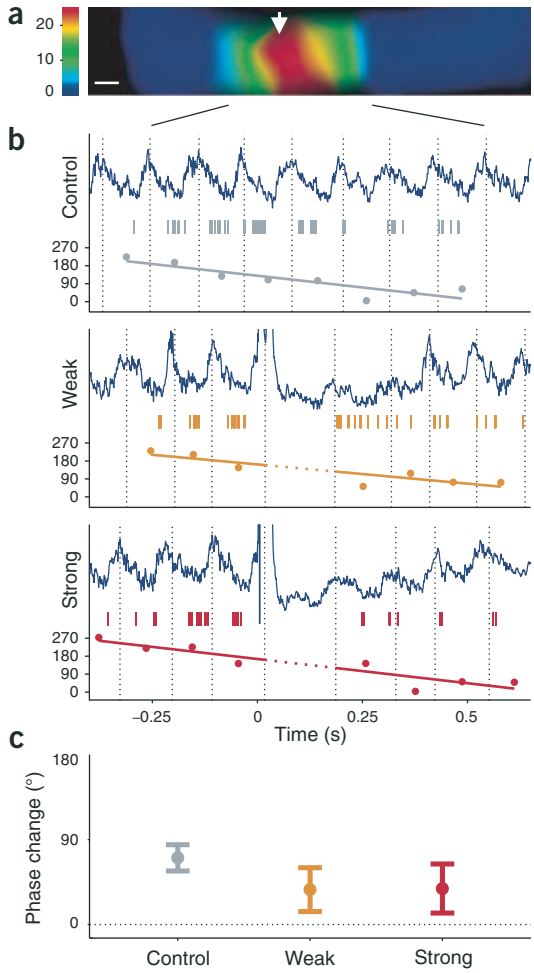

Figure 3 Phase precession is preserved after stimulation-induced perturbation. (**a**) Firing field during control trials. Color calibration, spikes per second; white bar, 5 cm; arrow, stimulation site. (**b**) Field theta rhythm, place cell firing (ticks) and average spike phase per theta cycle (in degrees; closed circles) from representative single runs under each condition. Note similar slope of phase advancement in each trial, despite transient disruption of spiking and theta oscillation after stimulation. (**c**) Group data for 35 neurons. Mean phase difference between the last theta cycle before stimulation and the first theta cycle after stimulation. For the control, the last theta cycle before crossing the photobeam and the theta cycle closest in time to the recovery cycle in stimulation trials were analyzed. Vertical bars, 95% confidence intervals. Under all three conditions, the theta phase advanced significantly ($P < 0.05$). Control and stimulation conditions did not differ significantly.

representation of spatial information. To test how this property was affected by hippocampal perturbation, we first selected all place cell pairs with overlapping fields for which at least one of the neurons overlapped with the position of stimulation ($n = 99$). We then plotted for all cell pairs the peaks of their time cross-correlograms (**Fig. 4a**) as a function of the spatial distance between the centers of their firing fields[7]. The five diagonal dot clouds (**Fig. 4b**) reflect time-compressed representation of spatial information[3,7] in five subsequent theta cycles. The great degree of similarity between the three conditions indicates that fine-timescale properties of spike sequences within place-coding cell assemblies are preserved despite perturbation of hippocampal dynamics.

DISCUSSION

Single-pulse stimulation of the intrahippocampal associational and commissural afferents reset theta phase and transiently inactivated hippocampal network activity. Despite these perturbations, the phase of the spikes after recovery was similarly correlated with the spatial position of the animal as it was in control laps. Although the behavioral variable in our experiments was the position of the rat, the physiological mechanisms that underlie phase precession are also relevant for a broad range of behaviors[4,29].

Several computational models have been proposed to account for the phase precession phenomenon. These models differ in their assumptions and predictions. One class of models assumes interactions between two oscillators with slightly different frequencies, whereby the cycles of the faster oscillator occur progressively earlier relative to those of the slower oscillator (that is, it precesses in phase). These models predict that if one or both oscillators are reset, the resuming spike-phase relationship should be strongly altered by the perturbation. Thus, a simple two-oscillator model in which at least one oscillator is within the hippocampus[2,14–16,18] (as opposed to the entorhinal cortex[17,21], for example) cannot account for the present observations. Yet our findings do not invalidate all versions of coupled oscillators. More-complex models that take into account the history-dependent activity of neuronal population activity[30] may be compatible with the present observations.

A second class of models base phase precession on single-cell membrane properties[4,5,13,19,23]. In this view, the amount of excitation determines the phase at which a cell fires: the more the membrane is depolarized, the earlier the cell discharges relative to theta. As the animal traverses the firing field of a place cell, this cell receives increasing amounts of excitation at each theta cycle; therefore, the combined dendritic excitation and somatic inhibition reach firing threshold earlier and earlier—resulting in phase precession. These models predict that transient interruption of hippocampal firings should be followed by resumption of phase precession, commensurate with the resumed level of excitation. In principle, these single-cell models can account for our findings with the additional assumption that continued excitation is provided by extrahippocampal inputs. Silencing the network should abolish spike history–dependent

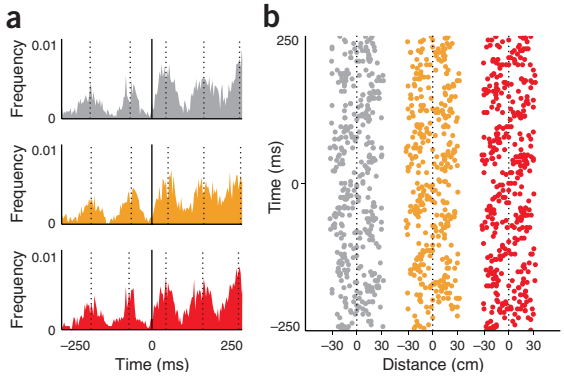

Figure 4 Assembly coding is maintained after transient perturbation. (**a**) Cross-correlograms of two place cells with partially overlapping firing fields (distance between centers, 22 cm). Notice theta rhythm modulation of cross-correlograms. Successive peak occurrence times (vertical dotted lines) were determined for all overlapping pairs ($n = 99$) for group statistics. (**b**) Cross-correlation between peak occurrence times and distance between firing fields of neuron pairs[7]. Color code for experimental conditions as in **Figure 1**.

effects in single cells[4], and thus the contribution of spiking history in place cells does not seem to be critical.

The simplest, but rather unlikely, explanation of our findings is that the timing of each spike in the CA1 hippocampal region is under the exquisite control of extrahippocampal inputs that themselves code for position. Alternatively, external inputs are combined with self-organization of hippocampal cell assemblies. Models in this group[9,11,12] assume that phase precession reflects some internally generated sequence-predicting mechanism, as is the case during hippocampal sharp waves[31–33]. In these models, the cell assembly that codes for the current position of the rat strongly discharges at the trough of the theta cycle in both CA1 and CA3 pyramidal cells. In the recurrently connected hippocampal CA3 network, this group in turn is assumed to excite (by unidirectional connections) the cell assembly that represents the next position of the animal along the predicted trajectory[34,35]. Because of synaptic and propagation delays, cells with firing fields that occur later in the sequence fire later during the theta cycle. As a result, as the rat moves toward the firing field of a cell, that cell discharges at progressively earlier phases, that is, it precesses relative to the theta 'clock' signal. This continuous propagation of activity within the CA3 network is interrupted by the next inhibitory phase of theta oscillation[36]. The initiation of assembly sequence reactivation during the next theta cycle is triggered by inputs from structures upstream of the hippocampus. In our experiments, the average spike phase during the first theta cycle on recovery was smaller than the average spike phase during the last theta cycle before commissural stimulation. This is consistent with the hypothesis that extrahippocampal inputs update the network at each theta cycle. Alternatively, other internal mechanisms, operating at a timescale that is slower than the theta cycle, may be responsible for the advancement of phase after transient silencing of the hippocampal network.

In summary, our findings indicate that intrahippocampal cell assemblies may self-organize their sequences cycle by cycle[3,7] and that extrahippocampal information, which conveys updated environmental, movement-generated feedback and other influences operating at a slower timescale, is incorporated in each new theta cycle.

METHODS

Rats and stimulation protocol. Five adult male Long-Evans rats (250–300 g) were implanted with eight independently movable tetrodes (groups of four twisted 13-μm nichrome wires) in the hippocampus (3–4 mm posterior to bregma, 1.5–3.5 mm from the midline) and with a bipolar stimulation electrode (diameter, 60 μm) in the contralateral hippocampal commissure (1.3 mm from the midline), following National Institutes of Health guidelines. The protocol was approved by the Institutional Animal Care and Use Committee of Rutgers University. After the animals had recovered, evoked responses were triggered by single-pulse (0.1 ms) stimulation at two current levels. 'Weak' and 'strong' stimuli corresponded to population spike threshold and to approximately 50% of maximal population spike, respectively.

Behavioral task. The experimental setup consisted of a computer-controlled U-shaped maze in which the water-deprived rats were trained to shuttle back and forth between two water cups. Water was withheld for 24 h before the first training session. The experiments were run every day until the rat was fully satiated. During weekends they were given water *ad libitum*. Droplets of water were automatically delivered for a period of about 2 s after the rat crossed a photodetector near the cup. For stimulation trials, the rats received single electric pulses (0.1 ms; current range, 60–400 μA; weak or strong stimulus) when crossing a photodetector as they departed from a water cup on their way to the other water cup. On average, the rats ran approximately 60 laps before reaching satiation, yielding 20 laps for each of the control, weak-stimulation and strong-stimulation conditions. A recording session typically consisted of blocks of five laps for each experimental condition, intermingled in a pseudorandom order.

Data acquisition and analysis. During the recording sessions, electrode signals were acquired at 20 kHz on a 64-channel DataMax system (16-bit resolution; RC Electronics Inc.). For offline spike sorting, the wide-band signals were digitally high-pass filtered (0.8–5 kHz). Units were then identified and isolated by a semiautomatic 'cluster cutting' algorithm[37,38], followed by computing auto- and cross-correlations. To track the position of the animals in the maze, two small light-emitting diodes (10-cm separation) mounted above the headstage were filmed by a digital video camera. Their moment-to-moment positions were later extracted and resampled (at 40 Hz) for analysis. All behavioral events (including arrival at and departure from water cups, opening and closing of a solenoid valve controlling water delivery and brain stimulation) were monitored, triggered and stored on disk by custom-written software running in LabView (National Instruments). Neurophysiological and behavioral data were explored using NeuroScope (http://neuroscope.sourceforge.net, L. Hazan, Center for Molecular and Behavioral Neuroscience, Rutgers University; G. Buzsáki *et al.*, *Soc. Neurosci. Abstr.* **33**, 768.2, 2004). Spike sorting was performed in two steps, first automatically using KlustaKwik (http://klustawik.sourceforge.net, K. Harris, Center for Molecular and Behavioral Neuroscience, Rutgers University) and then manually using Klusters (L. Hazan, http://klusters.sourceforge.net; L. Hazan *et al.*, *Soc. Neurosci. Abstr.* **33**, 768.3, 2004]). Firing maps were computed using a kernel-based method[39]. The firing rate at a point, x, was estimated by

$$f(x)dt = \frac{\sum n_t w(|x - x_t|)}{\sum w(|x - x_t|)}$$

where n_t is the number of action potentials emitted in a given time bin, x_t is the position of the rat in that time bin and dt is the time bin size. The kernel function w is a Gaussian of width 2.5 cm. Firing fields were defined as the ensemble of contiguous bins containing the location of maximal firing rate, for which the firing rates were >20% of the peak firing rate[6].

Phase reset was assessed by measuring the time stamps of successive theta peaks (defined as midpoints between zero crossings of the theta wave) after stimulation, and then comparing stimulation against control laps using F-tests.

To estimate the duration of silence induced by the stimulation, poststimulus time histograms (duration, 500 ms; bin width, 10 ms) were constructed, and the transition point was determined using a maximum likelihood estimator[40]. The two levels of stimulation were compared to the control with t-tests.

To compare phase precession plots across experimental conditions, firing fields were first divided into early (first third), middle (second third) and late (last third) subfields. Because the phase precession for different neurons spans slightly different ranges, the phase for each spike was first recentered on the overall mean phase in the firing field. The resulting relative phases in each subfield were then compared between experimental conditions using circular ANOVAs. This analysis would not, however, detect an overall shift in the phase precession plot toward higher or lower phases (a vertical translation that maintained an identical slope) in the different experimental conditions. Thus, a second approach was also used. For each subfield, the average theta phase was measured across experimental conditions (using all spikes fired in that subfield under all three conditions). Then, for each spike the angular deviation from the average phase was computed. Deviations were then compared between experimental conditions using circular ANOVAs.

Peak firing rates were compared using ANOVAs, and theta phases at peak locations were compared using circular ANOVAs. To control for different running velocities, the time taken for each rat to walk through a small area around the location of the stimulation (from 10 cm before to 20 cm after) was measured during the three experimental conditions.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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