



Decoding septohippocampal theta cells during exploration reveals unbiased environmental cues in firing phase

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Spatial theta cells in competitive burst synchronization networks: Reference frames from phase codes
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Introduction

How can environmental cues reset a neural code for space? Path integration is the idiothetic process, analogous to angular integration for head direction [1,2], that guides the neural code for position using egocentric motion signals. Interacting with external sensory cues is critical for path integration to remain calibrated within a fixed spatial reference frame [3,4]. Rather than abrupt resets, the calibration of the spatial metric reflected by grid cells may be predominantly mediated by boundaries [5] in a way that reflects continuous gating between extrinsic and intrinsic information streams [6,7]. It is unclear whether some form of place-to-grid feedback could support continuous spatial calibration.

Which pathway could place-to-grid feedback take? The hippocampus forms bidirectional loops with subcortical structures that regulate the septal-hippocampal theta rhythm (6–10 Hz) [8,9]. Theta-rhythmic activity propagates through the circuits of the septum, mammillary bodies, and anterior thalamus via excitatory burst synchronization [10–12]. Here we study the hypothesis that theta bursting and spatial inputs create a spatial phase code that supports flexible learning of spatial synchronization patterns. We recorded theta cells from a constellation of hippocampal and subcortical areas in freely exploring rats to look for spatial phase information and rate-phase correlations. Recordings took place in an 80-cm cylindrical arena with an orienting visual cue and lasted multiple hours to allow adequate sampling of spikes ($n=8$ rats, mean 15.5 spikes/s) given spatial biases in exploratory behavior. To establish that spatial modulation was not due to behavioral biases, we trained generalized linear models (GLMs) to predict spikes based on spatial and trajectory-based factors. To demonstrate spatial synchronization patterns, we modeled intrinsic theta bursting in oscillatory neuronal network models trained with path-integrating phase codes (cf. [13,14]).

ID phase-coding synchronization

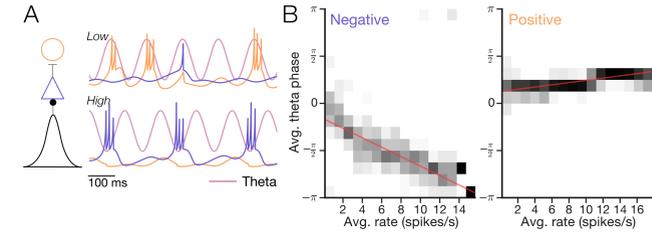


Fig. 1. A motivating theory for spatial phase codes expressed as correlations between firing rate and phase. (A) Spatial input (black) drives a theta cell with theta-rhythmic inhibition (blue) which suppresses a theta cell with theta-rhythmic excitation (orange). Model bursting neurons change rate and theta phase with low vs. high spatial inputs. (B) This simple connectivity scheme creates strong negative correlations between rate and phase and weaker positive correlations.

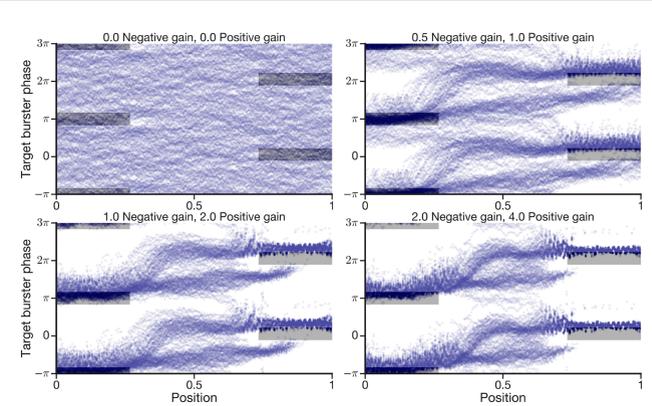


Fig. 1 (cont'd). Competitive learning of weights from negative/positive phase-coding cells with distributed spatial tuning allows synchronization to a 1D spatial phase code (gray rectangles). We simulated an intrinsic theta-bursting neuron model with competitive spatial-phase coding weights as a spatial trajectory moved back-and-forth between 0 and 1. Blue dots represent individual bursts from this target bursting neuron for 1-hour simulations with various synchronization gains: from none (top left) to strong feedback (bottom right).

Spatial theta cells: Firing rate vs. phase

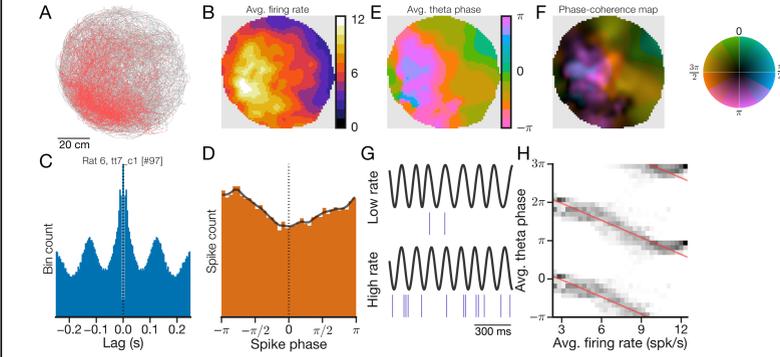


Fig. 2. We recorded subcortical theta cells in rats exploring an 80-cm cylindrical arena. Spikes from an example cell in lateral septum (A) were strongly modulated by space (B) while showing strong theta-rhythmic correlations (C) and a preference for anti-phase firing (D). The average phase of firing across space (E) reveals stronger phase coherence (F) near the arena center. Activity switches from in-phase single spikes (G, top) to anti-phase bursts (G, bottom) during periods of low and high spatial modulation, as reflected in the negative rate-phase correlation (H).

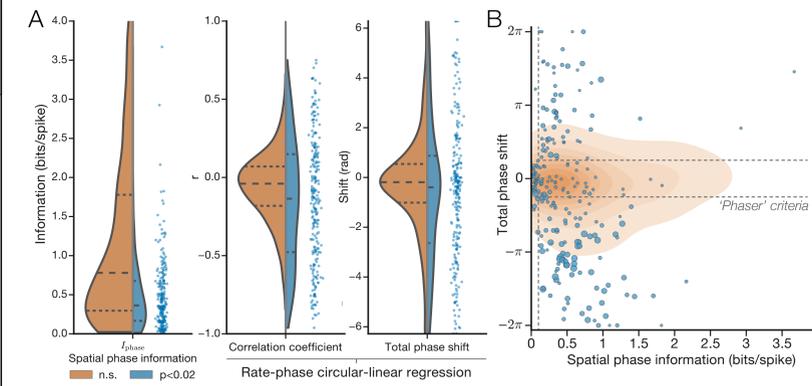


Fig. 3. Calculating the mutual information between space and phase reveals broadly distributed rate-phase correlations. (A) 233/840 theta cell recordings had significant spatial phase information (blue, left). Significant spatial cells showed heavier tails for correlation coefficient (middle) and total regressed phase shift (right). (B) Higher spatial phase information (x-axis) corresponds to larger regressed negative and positive phase shifts (y-axis) in spatial cells (blue circles, size indicates correlation strength). Nonsignificant cells (contours) were distributed around zero shift.

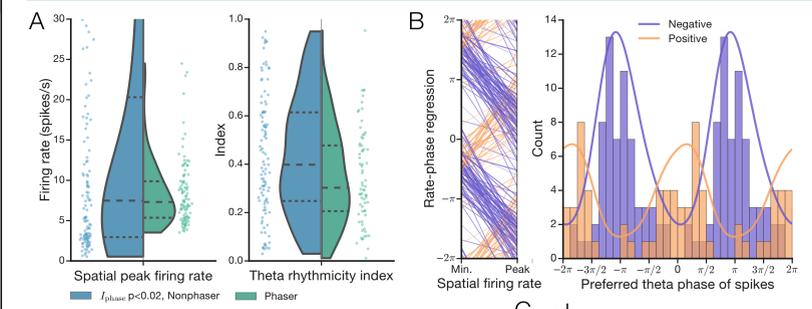


Fig. 4. 'Phaser' cells are selected (101/233 spatial recordings) based on spatial phase information and phase shift criteria (Fig. 3B). (A) Phasers have a restricted range of peak firing rates (left) and slightly weaker theta rhythmicity (right) compared to spatial nonphasers. (B) Negative (blue) and positive (orange) phasers take opposing phase trajectories across firing rates (left) and segregate across the theta cycle on the basis of preferred firing phase (right). (C) Phaser cells were predominantly found in the septum and primarily lateral septum, constituting 13.2% of septal recordings.

Rate/phase coding subtypes

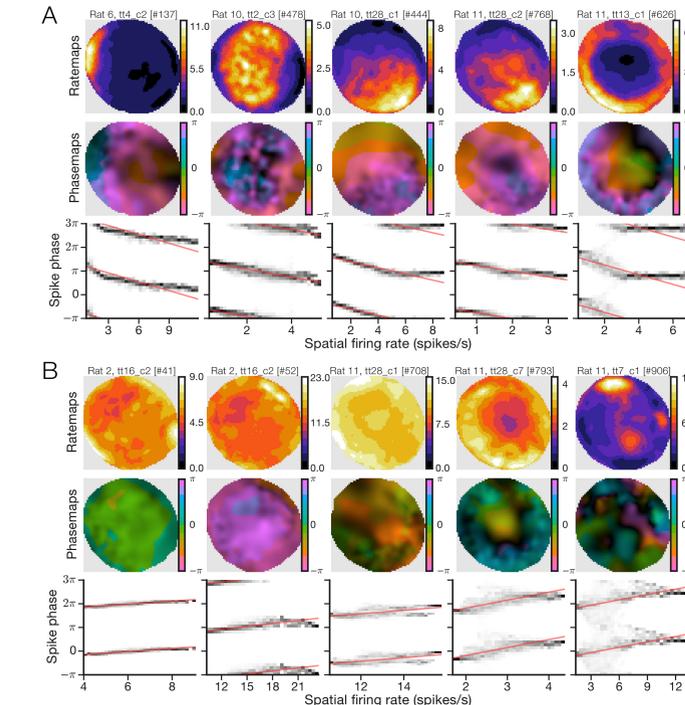


Fig. 5. Spatial phase-coding 'phaser' cells divide into 'negative' (A) and 'positive' (B) subtypes based on the direction of rate modulation of firing phase. (A,B) Example cells have firing ratemaps (top), phase-coherence maps (middle), and spatial rate/phase regressions (bottom). Negative phasers have stronger spatial modulation than positive.

Space/trajectory directional GLM

To participate in a path integration system, phase modulation must either be nondirectional or uniformly directional across space. To reveal whether spatial activity reflected behaviorally and directionally unbiased environmental cues, we trained a generalized linear model (GLM) to predict spike counts on the basis of spatial (L/Q, linear/quadratic; W, wall proximity) and trajectory-based (S, speed; D, direction) variables:

$$\hat{Y}_i = \hat{\beta}_0 + \hat{\beta}_L L_i + \hat{\beta}_Q Q_i + \hat{\beta}_W W_i + \hat{\beta}_S S_i + \hat{\beta}_D D_i$$

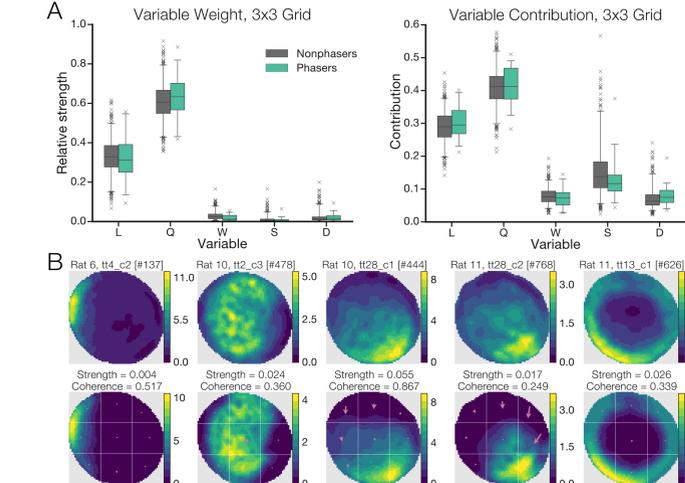


Fig. 6. The GLM was trained on a 3 x 3 grid that evenly partitioned the arena to expose possible directional inhomogeneities reflecting behavioral biases. (A) Model weight (left) was dominated by linear/quadratic (L, Q) functions of space. Maximal contributions of variables showed reduced trajectory-dependence in phasers relative to nonphaser cells. (B) GLM-predicted reconstructions of ratemaps from Fig. 5A.

Burst synchronization model with GLM inputs

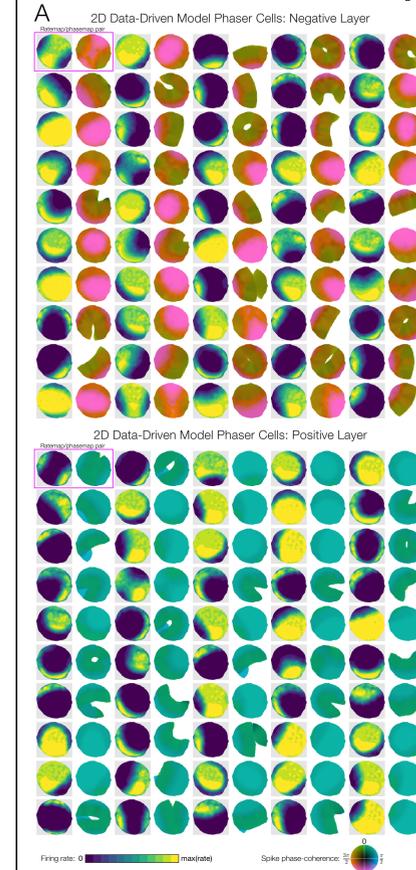


Fig. 7. A low-dimensional spatial model of phaser cell inputs was derived from the GLM (Fig. 6). (A) Generative spatial inputs drove simulations of negative and positive phaser cells (left, 50 example ratemap/phasemap pairs shown out of 1,000). (videos) Intrinsic theta-bursting neurons were the target of the synchronizing input from the phaser populations. With competitive learning, 64 targets simultaneously learned a spectrum of path-integrating spatial phase codes across spatial offsets and preferred directions. (B) The target cell (left) learns phase codes (middle columns) to create spatial synchronization patterns (right).

We presented network and statistical models that outlined a novel mechanism for anchoring spatial representations in continuous regions of neural synchrony. We recorded theta cells from hippocampal and subcortical areas in exploring rats and found spatial responses, comprising strong negative (phase precession) and weaker positive (phase processing) rate-phase correlations. A space/trajectory GLM showed that trajectory dependence and potential behavioral biases were dominated by pure spatial factors in these cells. Biological phasers were found in hippocampus and lateral septum, but not thalamic sites. Lateral septal cells are well-placed to combine theta oscillations and spatial inputs as required for the phaser mechanism. While our data-driven simulations of 2D phasers showed constrained spatial tuning, training with path-integrating phase codes flexibly produced border-aligned regions of phase synchronization that could contribute to the role of border visits in correcting (or distorting) [5] the spatial metric carried by grid cells. Our results reveal a possible role for spatial theta cells in anchoring the hippocampo-entorhinal spatial metric, but analogous rate-to-phase conversion mechanisms may subservise other brain systems with externally-referenced intrinsic neural codes.

Acknowledgments

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