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Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences

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Abstract

Cell assembly sequences during learning are “replayed” during hippocampal ripples and contribute to the consolidation of episodic memories. However, neuronal sequences may also reflect preexisting dynamics. We report that sequences of place-cell firing in a novel environment are formed from a combination of the contributions of a rigid, predominantly fast-firing subset of pyramidal neurons with low spatial specificity and limited change across sleep-experience-sleep and a slow-firing plastic subset. Slow-firing cells, rather than fast-firing cells, gained high place specificity during exploration, elevated their association with ripples, and showed increased bursting and temporal coactivation during postexperience sleep. Thus, slow- and fast-firing neurons, although forming a continuous distribution, have different coding and plastic properties.

The restructuring of hippocampal networks through synaptic plasticity is necessary for the formation of new episodic memories. Replay of hippocampal place-cell (1) sequences during sharp wave ripples (SPW-Rs) of waking immobility (2–5) and non-rapid eye movement sleep (6–13) after learning has been proposed to support memory consolidation (10–13). Replay is conceptualized and typically studied as a phenomenon with higher-order interactions within populations of neurons taken to have similar properties (10–14). However, networks built from similar neurons are unstable (15), and recent findings demonstrate that biophysical properties of cortical pyramidal neurons are highly diverse and characterized by lognormal distributions of synaptic weights, long-term firing rates, and spike bursts (16). Furthermore, temporal correlations of hippocampal neurons are largely preserved across brain states and environmental situations, suggesting that learning-induced changes are constrained within a dynamically stable network (16–17). An example of a preexisting bias between place-cell sequences in a novel environment and sleep before the novel experience (preplay) has been described (18–20), although its computational relevance has been questioned recently (14). To clarify the relationship between preexisting

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S22

References (28–36)

biophysical properties of neurons and their contribution to learning, characterization of individual neurons is necessary. We performed such analyses during sleep in rats before and after they explored a novel environment.

Simultaneous recordings of well-isolated CA1 pyramidal single units were performed in four rats. Several methods were used to assess the relationship between firing patterns during exploration of one of two linear or a circular track (MAZE) in rooms B, C and D, respectively, and candidate SPW-R sequences during preexperience sleep (PRE) and postexperience sleep (POST) in the home cage in room A (fig. S1) (21). First, a spatial Bayesian decoder (2), constructed from the firing-rate vectors of place cells ($n = 491$ cells) during track running (eight novel exploration sessions), was applied to all candidate ripple events (21) (figs. S2 to S4) of PRE, MAZE, and POST immobility epochs to estimate the posterior probabilities of position in forward (2, 5, 9) or reverse virtual traversals of the track (3, 4) (Fig. 1, A and B). These virtual traversals were measured as weighted correlations over the Bayesian derived posteriors for place across all 20-ms bins in each ripple event (21) and normalized as Z scores [rZ (sequence score) (21)] (figs. S5 to S8).

To determine each place cell's contribution to PRE and POST sequences [per cell contribution (PCC)], a PCC score was defined as the neuron's mean contribution across all PRE and POST putative events as determined by a cell-specific shuffling technique (21). Neurons that showed significant PCC scores in either PRE or POST were considered to be strongly contributing to sequence formation ($n = 216$ neurons (Fig. 2B) (21). Importantly, the majority of neurons strongly contributing to PRE (73%) also contributed to POST sequences (Fig. 2C and fig. S19), suggesting that these neurons represent rigid network elements. Strongly contributing neurons < 50 percentile of that session's PRE to POST sleep PCC change (PCC) were classified as rigid cells (blue x's in Fig. 2B), whereas those > 50 percentile as plastic cells (red x's in Fig. 2A and figs. S9 to 11). Rigid and plastic neurons were similarly distributed along the track (fig. S2). The contribution of individual neurons to the overall population POST-PRE score (POST rZ – PRE rZ) was assessed by either shuffling or excluding neurons with increasing or decreasing PCC scores from the analysis (Fig. 2C and fig. S12) (21). Replay (POST > PRE) was eliminated after shuffling or removal of the top 10 to 20% of cells with the highest PCC scores, whereas it remained after shuffling or removal of the bottom 75% (Figs. 2, C and D, and fig. S12). These results suggest that from the PRE to the POST sleep, plastic neurons are added to a preexisting backbone structure, leading to an increase in maze-related sequential activity (replay) associated with learning (Fig. 2C)

Although both rigid and plastic neurons contributed to replay sequences, the nature of their representation was different. Plastic neurons had higher place-specific indices and fewer place fields compared with rigid cells (Fig. 3A), and plastic but not rigid neurons increased their spatial specificity steadily during learning (Fig. 3B and fig. S13). Neither overall firing-rate changes (figs. S14 and S15) nor potential errors in neuronal clustering or neuron classification (figs. S2 and S11) could account for the above differences. These findings suggest that precision in spatial coding is a property developed during maze running by a small plastic subset of cells.

Next, we asked whether rigid and plastic neurons have different biophysical and network properties. Session-wide firing rates of rigid neurons were significantly higher compared with plastic neurons (Fig. 4, A and B, and figs. S14 and S15). Ripple-related spiking, bursting, and pair-wise coactivation were higher in plastic versus rigid neurons (Fig. 4A and figs. S14 to S16). In PRE sleep, coactivity was dominated by fast-firing neurons, and these correlations remained unchanged into POST sleep. In contrast, slow-firing neurons showed the strongest increases in coactivation from PRE to POST sleep (Fig. 4B). Pair-wise coactivity and temporal bias patterns were stable from PRE to POST for pairs of rigid cells, whereas plastic cell pair interactions were modified by experience on the novel maze (10) (figs. S16 and S17).

Because the above analyses indicated that overall firing rates and ripple-related activity of neurons predicted their coding and plastic features, in our final analysis we divided place cells into equal subgroups by either “off-line” sleep-firing rate or ripple-rate gain and repeated the Bayesian place decoding analysis for each group. Low-rate neurons (median, 0.39 Hz) contributed more spatial information per spike on the maze and displayed increased within-ripple firing-rate gains from PRE to POST sleep than high-rate cells (median, 1.12 Hz) (fig. S16). Slow-firing, but not fast-firing, neurons increased their contribution to neuronal sequences from PRE to POST sleep (Fig. 4D). Conversely, PRE to POST increases in sequence content were limited to cells that showed a high degree of ripple-specific recruitment (gain) (Fig. 4E and figs. S20 to S22), suggesting that ripples are privileged windows for learning-related changes in excitability. Similar results were obtained using several Bayesian and non-Bayesian replay methods (figs. S19 to S22).

Using several established and newly developed methods, we demonstrate that sequences of place cells in a novel environment are formed from a combination of relatively fast-firing group of pyramidal neurons with relatively unchanging temporal dynamics and a slow-firing plastic subset of neurons (22). Firing properties of neurons predicted their rigid (18–19) and plastic (10) features. Slow-firing neurons gained high place specificity during maze exploration (23–24) and showed increased ripple-related recruitment during POST-experience sleep. In contrast, fast-firing neurons had low selectivity (16–25), have been shown previously to project to multiple targets (26) and to form an interactive subnetwork responsible for global stability, thus allowing plasticity to take place in the remaining majority of slow-firing cells (16–17). Fast-firing neurons may generalize across situations, whereas slow-firing neurons may differentiate among them (27). Because replay sequence-forming neurons are drawn from the wide span of a continuous log-rate distribution (16) with varying coding, biophysical, circuit, and plasticity properties, these events can forward a synthesis of preexisting and new information to downstream observer neurons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1. PRE and POST maze sequence events

(A) Simultaneous recording of 77 place cells (rightward runs) used to generate a sequence template. (B) Representative forward and reverse sequences during PRE maze sleep, immobility in the novel MAZE, and POST-learning sleep. (C) Cumulative distribution of rZ for PRE, MAZE, and POST events, and 95% confidence intervals. Vertical dashed lines, medians. Inset, mean $\pm$ SE of sequence scores in each condition. * $P < 0.05$; ** $P < 0.005$; *** $P < 0.0005$ (Kruskal-Wallis test, followed by post hoc Tukey-Kramer tests). Sign-rank tests were used for within-condition significance testing. (D) As inset in (C), but events with forward and reverse sequences are shown separately (within epoch comparisons, ranked-sum test).

Fig. 2. A small fraction of neurons show experience-induced plasticity

(A) Cumulative distributions ($\pm$ 95% confidence intervals) of PCC (21) to ripple sequence content (inset shows mean $\pm$ SE). (B) Relationship between each neuron's contribution to PRE and POST sequence content. Gray line, least-squared regression between all PRE and POST PCC scores. Neurons strongly contributing to either PRE or POST (21) are marked with X; others are marked with dots. Strongly contributing neurons in the lower 50th percentile of that session's PRE versus POST change (PCC) were considered rigid cells and those in the upper 50th percentile as plastic cells. (C) Raster and local field potential (LFP) plots of example ripple events from the PRE, MAZE, and POST epochs (diamonds show within-ripple spike-time center of mass). These six events correspond to the top row of Fig. 1B. Rigid and plastic cell spikes are shown in blue and red, respectively. Although rigid cells tend to predominate in the PRE epoch, the marked increase in sequence content observed in the MAZE and POST epochs is driven by the recruitment of plastic cells. (D) To assess the contribution of neurons with differing PCC scores to the change in virtual travel content from the PRE to the POST epoch, the replay analysis was repeated using templates in which an increasing percentage (x axis) of neuron's place fields were shuffled either beginning with those that showed the lowest PCC values (blue line) (shaded area shows bootstrapped 95% confidence interval) or beginning with neurons with the highest PCC scores (red line). (E) Effect on sequence content of removal of rigid (black) or plastic (gray) neurons. The PRE to POST increase in sequence content is attributable to only a small number of plastic cells.

Fig. 3. Properties of rigid and plastic neurons differ on the novel maze

(A) Differences in spatial coding properties (top panels, log-mean $\pm$ log-SE; bottom panels, mean $\pm$ SE, rank-sum tests). (B) Within-session improvement of plastic neurons' infield versus outside field firing ratios. Plastic cells improved spatial coding overlaps on the maze; left panel shows the within-session changes of place field representation for rigid (blue) or plastic (red) neurons (shaded region shows bootstrapped 95% confidence interval). Right panel, per cell summary of within-field firing specificity changes (mean $\pm$ SE) (21).

Fig. 4. Low-firing-rate, high-ripple-recruitment neurons show high learning-related plasticity (A) Summary of excitability and synchrony profiles of rigid and plastic cells. Each panel shows the cumulative distributions of the two groups; dashed lines show medians (P values, rank-sum tests). (B) To examine the relationship between firing rates and learning-related changes in pair-wise coactivation (Pearson's correlation of firing rates in 100-ms bins), neurons in PRE, MAZE, and POST were sorted by their overall session (SESS) firing rates [(B), left panel]. (C) Coactivation was assessed across overlapping groups each containing 20% of place cells with similar firing rates (step size, 1% of cells). Although fast-firing cells dominated the coactivation structure during the PRE (left panel), it was the slow-firing cells that showed the highest increase in coactivation from PRE to POST (middle two panels). Moreover, it was the slow-firing cells that showed the greatest replay (partial correlation across coactivation values between RUN and POST, accounting for PRE). (D and E) An additional replay analysis restricted to place cells with either low or high firing rates (D) or within-ripple firing-rate gains [(E), annotation same as in Fig. 2D] confirms the findings obtained using the PCC method.