Firing rates of hippocampal neurons are preserved during subsequent sleep episodes and modified by novel awake experience

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What determines the firing rate of cortical neurons in the absence of external sensory input or motor behavior, such as during sleep? Here we report that, in a familiar environment, the discharge frequency of simultaneously recorded individual CA1 pyramidal neurons and the coactivation of cell pairs remain highly correlated across sleep–wake–sleep sequences. However, both measures were affected when new sets of neurons were activated in a novel environment. Nevertheless, the grand mean firing rate of the whole pyramidal cell population remained constant across behavioral states and testing conditions. The findings suggest that long-term firing patterns of single cells can be modified by experience. We hypothesize that increased firing rates of recently used neurons are associated with a concomitant decrease in the discharge activity of the remaining population, leaving the mean excitability of the hippocampal network unaltered.

Information in neuronal networks is believed to be represented in part by the firing rates of neurons. In the awake brain, firing-rate changes of cortical neurons can be brought about by various external inputs or reafferentation from movement-associated signals. During sleep, these signals are largely absent and neuronal discharges are driven by the internal dynamics of the networks. Can the internal dynamics of cortical networks be modified by experience? If so, the functional modification of the circuitry should be reflected by the long-term firing rates of the participating neurons in various network states (1).

The hippocampus is believed to play a critical role in the acquisition and consolidation of episodic-declarative memories (2–3). It has been suggested that experience modifies ensemble discharge patterns in hippocampal networks. Specifically, the new patterns acquired during exploration are repeatedly reactivated during consummatory behaviors, immobility, and slow-wave sleep (SWS), thus consolidating the learned neuronal representations (4–6). Acquisition of novel ensemble patterns and their endogenous reactivation are correlated with two fundamentally different network states: θ-field oscillation and irregular sharp waves (7–10). An early investigation sought support for these ideas by recording from pairs of CA1 pyramidal neurons during exploration-sleep cycles. One cell of the pair was a place cell (11), and the rat was confined physically to the cell's place field to ensure prolonged activation of the neuron. The main finding was that the neuron with sustained activity during exploration continued to fire at a higher rate during subsequent sleep, relative to the control cell. Subsequent experiments, using large-scale recordings, could not confirm the suggested correlation between firing rates in the awake and sleeping animal (12). On the other hand, these studies reported that pyramidal cells with overlapping place fields preserved their pairwise temporal correlations during subsequent sleep but were not correlated with coactivated cell pairs recorded from a sleep episode preceding the awake session (13, 14). Some aspects of these experiments have been criticized on both technical (15, 16) and experimental grounds (17). To elucidate the conditions that may be responsible for the short- and long-term changes of firing patterns of hippocampal neurons, we examined the consequences of sustained discharge rates and coactivation of CA1 pyramidal cells on their endogenous discharge patterns during sleep, using parallel recordings of multiple single-unit activity.

Methods

Twenty-one male rats of the Long–Evans strain (300–500 g) were implanted with 8 individually movable tetrodes (18). Recording in nine rats took place in their home cage. Before implantation, seven rats were trained to run continuously in a running wheel (29.5 cm in diameter) for water reinforcement available in an adjacent box (30 cm $\times$ 40 cm $\times$ 35 cm) (19). Electrophysiological parameters were recorded first in the home cage ("sleep before"; 15 min), followed by testing in the running-wheel apparatus ("familiar"; 15 min) and again in the home cage ("sleep after"; 15 min). The remaining five animals were placed in a large rectangular plywood box (1.2 m $\times$ 1.2 m, 0.5 m high) during the day for 4–7 days. Repeated exploration of the box was facilitated by randomly dispersing chocolate pieces on the floor (20). In these rats, all recordings, including sleep sessions, were taken in the box. Water and food were available. Activation of new sets of cells was tested by either moving the animal to a carton box or by the addition of various objects (running wheel, wall partitions, cardboard boxes) placed in the apparatus after the rat awoke spontaneously from a sleep episode ($n = 5$ rats) (10, 20, 21). An infrared light-emitting diode was attached to the head stage to track the position of the animal (19). The spatial displacement of the diode permitted the assessment of motor activity of the rat with 1-cm resolution. After amplification ($\times$10,000) and band-pass filtering (1 Hz-5 kHz), field potentials and extracellular action potentials were digitized continuously at a 20 kHz-rate with a DataMax system (16-bit resolution; RC Electronics, Santa Barbara, CA). Interneurons and pyramidal cells were separated by a multidimensional clustering method, using the principal components of the detected spikes (13, 14, 18). Only units with clear refractory periods, well defined cluster boundaries, and firing rates (>0.02 Hz) were included in the present analysis (2–6 cells per tetrode; ref. 22). The stability of unit isolation was assessed by displaying the first principal component for each of the four tetrode-recording sites over the entire recording session. Units with gradual drifts or sudden jumps in the first principal component were excluded. In addition, the stability of fast-firing putative interneuron clusters in the multidimensional space was regarded as evidence that the physical location of the tetrode in the brain remained the same. Approximately 30% of the tetrodes recorded at least one

Abbreviations: SWS, slow-wave sleep; REM, rapid eye movement.

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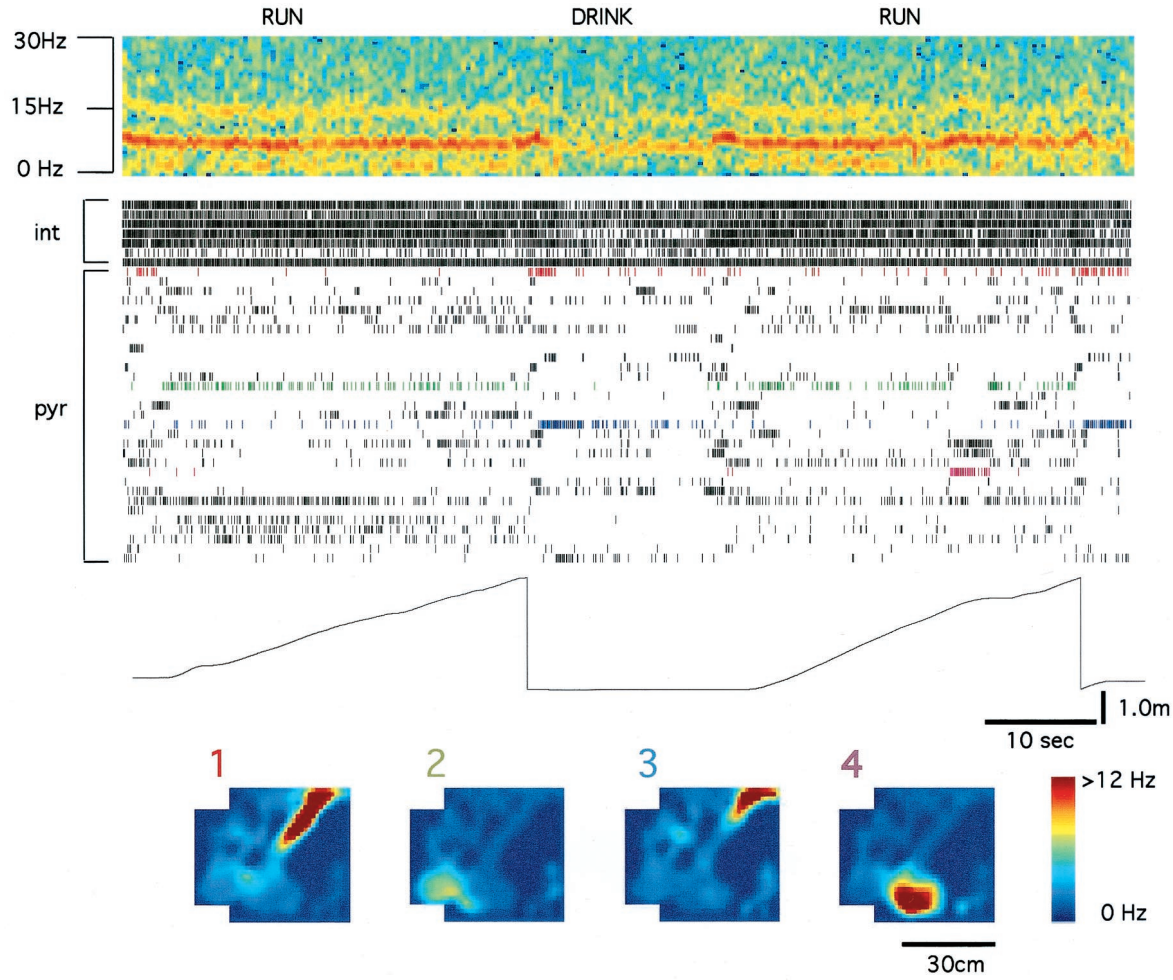

Fig. 1. Ensemble activity of CA1 pyramidal cells (pyr; $n = 30$) and putative interneurons (int; $n = 7$) in the running-wheel task. Other recorded neurons with <0.1-Hz firing rates are not shown. (*Top*) Continuous display of spectral power during run–drink–run transitions. Note high theta power (7 Hz) during running (red band). (*Middle*) Spike times of individual cells and the output of the odometer. Continuous slope reflects steady running. Neurons with in-wheel firing-rate ratios >2 were termed ''wheel'' cells (e.g., neuron 2; green). (*Bottom*) The rectangle portion on the left part of the firing map represents the wheel and the large square represents the box area. Three more neurons with place fields in the box area (red, blue, and magenta) are also shown. Neurons 1 and 3 illustrate overlapping place fields while the rat was approaching the water spout, whereas neurons 3 and 4 illustrate nonoverlapping fields (13). Several other pyramidal cells showed place fields in either the wheel or the box area (not shown).

putative interneuron. About half of all well isolated units was not included in the analysis as a result of these strict criteria.

Theta activity was detected by calculating the ratio of the Fourier components of the theta (5–10 Hz) and delta (2–4 Hz) frequency bands (18). A ratio of >6 identified theta epochs, and epochs with <3 theta/delta ratios identified non-theta epochs. Non-theta epochs with sleep posture were classified as SWS. Sleep posture with closed eyes associated with theta activity for >10 sec, and occasional muscle twitches identified rapid eye movement (REM) sleep. To quantify the degree of coactivation of two neurons, their cross-correlation was computed (12). The firing-rate function of two neurons $[F_1(t),F_2(t)]$ was calculated with 100-ms bins. The cross-correlation of the firing-rate functions was calculated by normalizing the covariance of the firing-rate functions by the standard deviations, thereby calculating the correlation coefficient between the firing-rate functions at each time bin:

$$C_{F_1F_2}(\tau) = \frac{E([F_1(t+\tau) - \bar{F}_1][F_2(t) - \bar{F}_2])}{\sigma_{F_1}\sigma_{F_2}}. \qquad [1]$$

For the scatter plots, we plotted $C_{F_1F_2}(0)$, i.e., the r value for ± 50 ms. After completion of the experiments, the rats were deeply anesthetized and perfused. The brains were sectioned and stained with cresyl violet method to verify electrode placements.

Results

We examined the discharge relationship of pyramidal cells in awake and sleep states in two different paradigms. In the first experiment, the rat was trained to perform a stereotypic task (''familiar'' environment). The goal of these experiments was to repeatedly activate the same set of cells daily. In the second experiment, the rat was tested in a novel environment to ascertain that at least one subset of neurons active during the exploration will be different from in the previous waking state (20).

We first examined whether behaviorally induced selective activation of hippocampal pyramidal neurons can produce short- (<30 min) and/or long-term (>30 min) changes in firing patterns. Discharge patterns in the awake rat were determined while the animal performed a wheel-running task (19). After a predetermined number of wheel turns, a sound alert signaled the

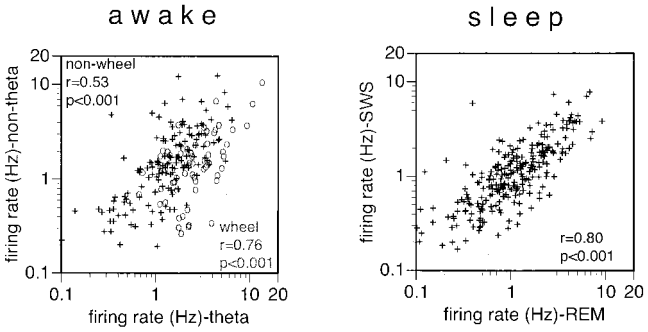

Fig. 2. Short-term (<30 min) comparison of discharge frequency of individual pyramidal cells during different behavioral states. (*Left*) Relationship between firing rates of wheel cells and non-wheel cells during running in wheel and walking in box (theta behaviors) and drinking/immobility (non-theta). (*Right*) Relationship between firing rates during REM and SWS. The high correlation of firing rates across different stages of sleep indicates that similar cell assemblies are being activated in both SWS and REM sleep.

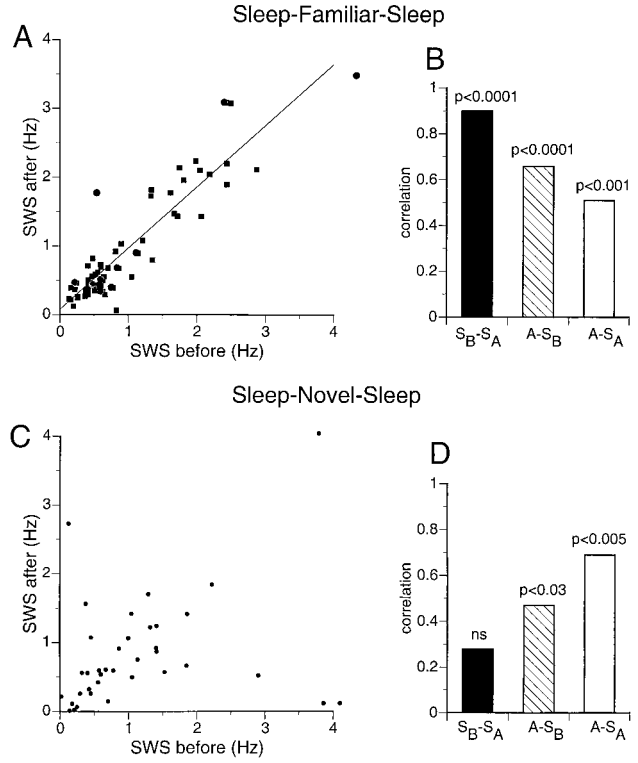

Fig. 3. Comparison of discharge frequency of pyramidal cells in two successive SWS episodes, interrupted by either a wheel-running session (*A*, familiar) or novel exploration (*C*, novel). Wheel cells (filled gray circles) are shown separately in *A*. (*B* and *D*) Mean correlation values for sleep before vs. sleep after (S_B-S_A), awake vs. sleep before (A-S_B), and awake vs. sleep after (A-S_A) sessions in the well trained running-wheel task (*B*) and in the novel environment (*D*). Note high and low correlations between successive sleep sessions in the familiar and novel environments, respectively.

availability of water reward, and the rat ran directly to the waterspout in the box part of the apparatus. The return path was also quite stereotypic. Consequently, subsets of place-related neurons (19, 23) were consistently activated in the wheel ["wheel cells" (19) and/or the box area (Fig. 1]. The mean firing rate for each neuron was calculated by dividing all spikes emitted during theta-associated running and walking in the entire session (520 ± 241 sec; mean duration ± SD). Non-theta behaviors included cumulative drinking and immobility epochs (452 ± 247 sec; ref. 18) .

Fig. 2 shows the relationship of firing rates between theta and non-theta behaviors. We found a significant positive correlation between firing rates in the two awake network states for both wheel cells and other cells that were active in the box area ($P < 0.001$; $n = 6$ rats). Similar to the observation in the awake animal, firing rates of pyramidal neurons during sleep-associated theta (REM) and non-theta (SWS) states, recorded in the home cage, were positively correlated (Fig. 2; $P < 0.001$; $n = 9$ rats).

After observing a reliable preservation of firing rates between different behavioral states on a short time scale (<30 min), we examined whether firing frequencies of individual neurons remained stable across different SWS sessions. For these comparisons, electrophysiological parameters were recorded in the home cage (sleep before), in the running-wheel apparatus (familiar), and again in the home cage (sleep after; $n = 6$ rats). Stability of the recordings was determined by continuously monitoring the amplitude of the units on each of the four recording sites of a tetrode.

The discharge frequencies of individual cells in sleep before and sleep after sessions were robustly correlated (Fig. 3*A*; $r = 0.90$; $P < 0.0001$; $n = 62$ cells). The high degree of firing rate correlation across behavioral states was true for both wheel cells ($r = 0.86$, $P < 0.0005$; $n = 12$ cells) and "non-wheel" cells ($r = 0.92$, $P < 0.0001$; $n = 50$ cells). In addition to the similar firing rates in successive sleep episodes, Fig. 3*B* shows that significant correlations were also found between firing rates in sleep before vs. wheel-running session comparison ($r = 0.64$, $P < 0.0001$), as well as in sleep after vs. wheel-running comparison ($r = 0.49$, $P < 0.0001$). In a single animal, seven continuous wake–sleep sessions were recorded. In the 10 h of recording, the firing rates of the units during subsequent sleep episodes remained virtually identical. Thus, these findings demonstrated that the minute-scale relative firing rates of pyramidal cells remained correlated across various behavioral conditions despite the large subsecond variations in discharge frequency of individual cells.

The next set of experiments addressed whether the stability of firing rates in successive sleep episodes can be perturbed by behavior. The rats were placed in a large rectangular plywood box during the day for 4–7 days. Similar to the wheel-running experiment, comparison of firing rates in two successive sleep sessions, separated by spontaneous exploration in the already familiar environment, yielded a significant correlation ($r = 0.95$; $P < 0.001$; $n = 16$ cells). To activate novel sets of pyramidal cells relative to the previous awake session, the animals then were made to explore a novel environment (20, 21). Comparison of "sleep before novelty" and "sleep after novelty" episodes revealed that the discharge rates of individual pyramidal cells were not significantly correlated (Fig. 3*C*; $r = 0.28$; $P > 0.09$; $n = 37$ cells in 5 rats). Nevertheless, firing rates of pyramidal cells during exploration in the novelty session still correlated with firing rates of both sleep before ($r = 0.47$; $P < 0.05$) and sleep after ($r = 0.69$; $P < 0.01$) episodes. This finding indicates that only a portion of the recorded neurons was affected by the novel experience. Because the number of recorded neurons in the novel environment was less than in the familiar environment ($n = 37$ vs. 62), it may be argued that the different correlations simply emerged because not enough observation points were available in the novel environment. To address this issue, we examined 100 random subsets of 37 neurons recorded in the familiar environment. All of the 100 correlation coefficients were larger ($rs = 0.84–0.95$) than the observed r value in the novel

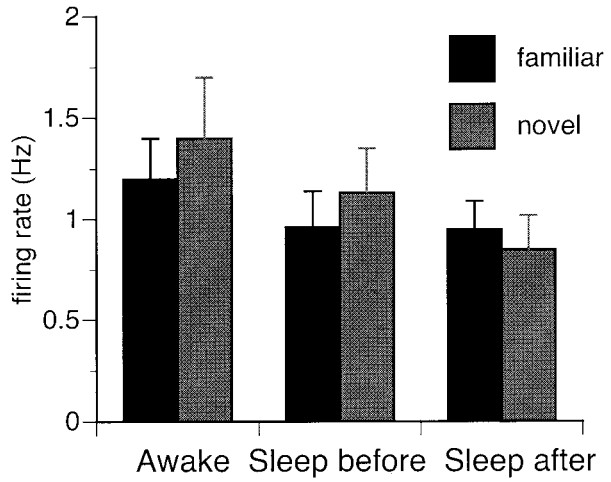

Fig. 4. Mean population firing rates (±SE) in awake and sleep states in the running-wheel task (familiar) and novel environment. None of the comparisons are significantly different.

environment, indicating that the role of chance, because of the smaller sample, was negligible. In addition, we calculated the variance of firing-rate differences between sleep before and sleep after sessions for both sets of experiments. The variance of firing-rate differences was significantly larger in the "novelty" experiment as compared with the familiar testing environment ($F = 8.91$; $P < 0.001$), even when four "outlying" points in Fig. 3*B* were excluded from the analysis ($F = 2.90$; $P < 0.001$).

As shown in Fig. 4, the overall firing rates of pyramidal cells in the waking rat were similar in the novel and familiar environments (1.44 ± 0.26 Hz, $n = 37$ cells and 1.2 ± 0.2 Hz, $n = 62$ cells, respectively; $P > 0.4$). Furthermore, firing rates of pyramidal cells during sleep before and sleep after sessions were also similar, independent whether the awake time was spent in the familiar task (sleep before familiar: 1 ± 0.12 Hz, $n = 62$ cells; sleep after familiar: 0.96 ± 0.1 Hz, $P > 0.05$) or in the novel environment (Fig. 4; sleep before novel: 1.13 ± 0.18 Hz, $n = 37$ cells; sleep after novel: 0.83 ± 0.14 Hz, $P > 0.05$). The incidence of sharp wave-associated "ripple" episodes (18) during SWS was not affected by the familiar (sleep before: 0.62 ± 0.09 Hz; sleep after: 0.65 ± 0.15 Hz; $P > 0.05$) or novel (sleep before: 0.65 ± 0.16 Hz; sleep after: 0.61 ± 0.18 Hz; $P > 0.05$) experience.

In addition to firing rates, spike-train cross-correlations were also computed for all pairs of simultaneously recorded pyramidal cells. A short (100-msec) time window was used to assess coactivation, because this epoch approximates the duration of theta cycles and sharp waves (5, 12–14). The magnitude of coactivation remained similar in subsequent sleep episodes separated by awake activity in a familiar environment as indicated by the linear regression of pairwise correlations (Fig. 5*A*; $r = 0.66$; $P < 0.0001$; $n = 427$ pairs). In agreement with previous studies, we estimated that the cutoff value of $r = 0.01$ for awake pairwise correlations reasonably reflected the difference between pairs of cells that had or had no overlapping place fields (12–14). The correlation values during sleep are shown separately for the low ($n = 296$ pairs) and highly correlated ($n = 131$ pairs) cell pairs in Fig. 5*B*. Pairs with high awake correlations also had high correlations in both sleep sessions (Fig. 5*B*). Furthermore, neuron pairs with high awake correlations showed an increase in correlation during the sleep after relative to the sleep before session ($P < 0.05$).

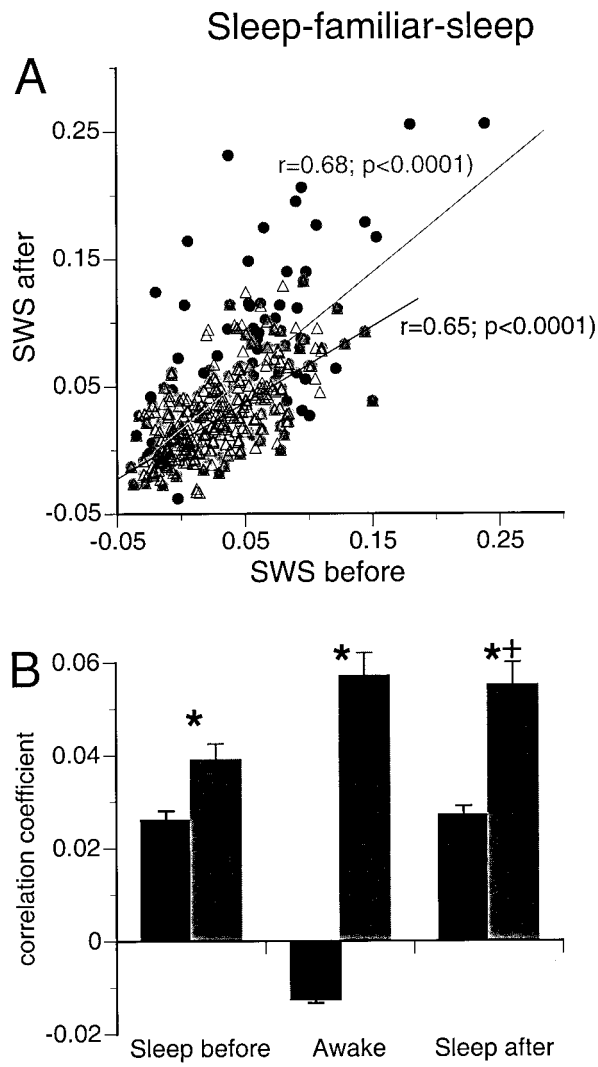

Fig. 5. Comparison between pairwise correlations of pyramidal cells recorded during SWS before and SWS after a wheel-running session. Each data point in *A* corresponds to one cell pair. Pairs with high (>0.05) and low (<0.05) correlations in the awake state are shown by filled red circles and open triangles, respectively. (*B*) Mean cross-correlation (±50 msec) for neuron pairs during sleep before and after wheel running (awake). Data are shown separately for neuron pairs with high (red) and low (black) awake correlation. Neuron pairs with high and low awake correlations were significantly different in both sleep sessions (*, $P < 0.01$). The sleep before vs. sleep after comparison was also significant (+, $P < 0.05$) for cell pairs with high awake correlation.

When the two sleep sessions were separated by novel experience, the correlation between neuron pairs decreased substantially ($r = 0.35$; $n = 75$ pairs). To compensate for the smaller number of neuron pairs in the novel environment, we examined 100 random subsets of 75 pairs recorded in the familiar environment. All of the 100 correlation coefficients were larger (mean $r = 0.45$–0.80) than the observed r value in the novel environment, indicating the decreased correlation in the novel environment was not caused by a smaller sample size.

Discussion

Our observations indicate that in an unchanging environment the discharge rates of individual CA1 pyramidal neurons are correlated across various behaviors, including awake exploration, SWS, and REM sleep. The discharge rate of the CA1

population and coactivity of cell pairs remained highly correlated in consecutive sleep sessions when a stereotypic task was performed during the interim waking period. However, the stability of discharge rates and coactivity of cell pairs across sleep sessions could be perturbed by activating a novel set of neurons in the awake state, without altering the global firing rate of the whole population. The similar incidence of ripple episodes after familiar or novel environments indicated that the overall structure of sleep was not affected by the novel experience.

The fundamental design of our "sleep–familiar–sleep" test was similar to that of Pavlides and Winson (11). Similar to their observations, we found that faster firing cells in the awake state fired faster during sleep. However, in contrast to their findings, we found that the awake firing rates also correlated with the firing rates of the preceding sleep. In their study, the animals were confined to part of the apparatus by wall partitions or restrained there by holding only for 15 min, whereas in our experiment the animals performed the same stereotypic behavior daily. These findings, together with our observations in the novel environment experiment, indicate that repeated and/or extensive exposure to the same environment is required to induce firing-rate changes that last for at least 24 h (24).

Similar to studies by Wilson and McNaughton (13) and Skaggs and McNaughton (14), pyramidal cell pairs with high awake coactivation correlated somewhat better during sleep after than during sleep before, indicating daily changes even in a well trained task (25). In contrast to these studies, however, we found that cell pairs with high and low awake correlations were also significantly different from each other in both sleep episodes. In other words, the awake training effect on both coactivation and firing rates was preserved in both sleep sessions. Our findings therefore indicate a long-term effect of daily training, lasting for at least 24 h. Previous studies suggested that the effect of previous experience fades with a time constant of 15–30 min. (11, 13). In the Wilson and McNaughton study, 2 of the 3 rats were trained in a large open box and their exact routes could change from day to day, whereas in our task the rat's locomotor path was stereotypic. Activation of different sets of cells in successive awake sessions could be a possible explanation for the different firing patterns in the two sleep episodes in the Wilson and McNaughton study. Recent experiments, using more structured behavior, found that coactivation patterns during exploration could sometimes be predicted from patterns during sleep before (12), which is in agreement with the present observations. Altogether, these findings indicate that awake experience can induce long-term changes in both firing rates and neuronal coactivation (12, 26).

The preservation of the firing rates of individual cells in awake–sleep sequences in familiar environments and their alteration in novel situations may be brought about by modification of the intrinsic biophysical properties of neurons or can be explained by circuit properties. If synaptic modification is the primary mechanism responsible for the internal dynamics of the hippocampal network, a candidate pathway is the CA3 associational/commissural input to CA1 pyramidal cells. This pathway can be active during both awake and SWS states (5, 8), contrasting with the entorhinal input that is relatively silent during SWS (27).

Although exposure to novelty altered the firing rates of individual pyramidal cells and their coactivation during subsequent sleep, the grand mean firing rate of the recorded neuronal population was remarkably similar during exploration in novel and familiar environments. Furthermore, the mean population firing rates in different SWS sessions were also indistinguishable, independent of the familiar/novel nature of the preceding awake session. These findings demonstrate that the global firing rate of the CA1 neuronal population remains constant at the minute time scale, despite the very large dynamic range of the firing rate of individual pyramidal cells (13, 28, 29) and transient 2–3-fold increases of population excitability at the subsecond scale (18). We hypothesize that increased firing rates of selected neuronal subsets coincide with a commensurate decrease in the discharge activity of the remaining neurons so that the overall firing rate of the population remains similar. This postulated homeostatic mechanism can maintain constant network excitability after use-dependent changes of synaptic weights (1).

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