Sleep deprivation and hippocampal ripple disruption after one-session learning eliminate memory expression the next day

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Memory reactivation during non–rapid-eye-movement ripples is thought to communicate new information to a systems-wide network and thus can be a key player mediating the positive effect of sleep on memory consolidation. Causal experiments disrupting ripples have only been performed in multiday training paradigms, which decrease but do not eliminate memory performance, and no comparison with sleep deprivation has been made. To enable such investigations, we developed a one-session learning paradigm in a Plusmaze and show that disruption of either sleep with gentle handling or hippocampal ripples with electrical stimulation impaired long-term memory. Furthermore, we detected hippocampal ripples and parietal high-frequency oscillations after different behaviors, and a bimodal frequency distribution in the cortical events was observed. Faster cortical high-frequency oscillations increased after normal learning, a change not seen in the hippocampal ripple-disruption condition, consistent with these having a role in memory consolidation.

sleep | memory | consolidation | ripples | cortical ripples

Sleep is important for memory consolidation (1). Critical network interactions associated with systems consolidation are thought to occur during sleep (2, 3). Specifically, reactivation of previous experiences during hippocampal ripples (HPC-R) during sleep is a long-known phenomenon that has been proposed to enable systems consolidation (4, 5). While early studies provided correlative links between HPC-R, memory reactivations, and memory performance (6, 7), it is only over the last decade that several studies started to explore and reveal a causal relationship. They use closed-loop ripple disruption, through which ripples during either rest/sleep (i.e., targeting memory consolidation) or wakefulness (e.g., targeting memory retrieval, working memory, planning, or consolidation) are detected on-line and disrupted, and test if this can alter subsequent memory performance (8). However, closed-loop approaches have been applied in multiday memory paradigms for only 1 h posttraining and, while memory performance was impaired, it was still above chance in the disruption groups (9, 10). Further, while ripple activity has been proposed to be the main mechanism during sleep enabling consolidation, ripple-disruption effects have not yet been directly compared with sleep-deprivation effects on memory consolidation. To examine whether disruption of ripples or sleep deprivation is needed for consolidation, a one-session learning paradigm that leads to long-term memory expression is needed.

To test this, we developed a one-session learning paradigm in a Plusmaze that results in long-term memory. We compared new goal location learning with different behaviors in the event arena (11, 12): (1) a nonlearning "Baseline" condition; (2) Foraging, a mix of open-field foraging and track running with small chocolate rewards spread along a track; and (3) Novelty, exploration of a new environment with very novel cues/textures.

Results

HPC Disruption and Sleep Deprivation. Initially, we established that our one-session learning paradigm in a Plusmaze led to long-term memory (24 h test) and was dependent on sleep. Plusmaze learning was performed in the event arena (11–13), with curtains included to limit the influence of uncontrolled room cues, but with large cues for spatial orientation placed on the curtain. Further, the walls of the event arena were inverted so that a cross-shaped maze was created covering 1.5×1.5 m with a track width of 15 cm. Each session consisted of a training and 24 h test and had a new goal location. During training, first, the animal could explore the Plusmaze freely for 10 min with chocolate cereal rewards placed at the new goal. Then, the animal was trained for 15 trials from different starting locations with the goal arm baited with more rewards (each trial ended once the animal reached the goal), which usually would take another 10 min. After the animals were trained to find a new goal location in the maze from each of the other three arms of the Plusmaze, they either were allowed to

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sleep or were sleep deprived by gentle handling for 4 h. Each animal ($n = 16$) had a different condition sequence and each day was trained with a new goal location and new extramaze cues (Fig. 1A). The animals performed above chance at the 24 h test (no food present), but performance fell to chance if they were sleep deprived after learning (Fig. 1A, repeated measures ANOVA condition (rmANOVA cond) $P = 0.05$, $F_{1,15} = 4.45$; sleep t test to chance $P < 0.001$, $T_{15} = 4.56$). Next, we examined whether this memory depended on HPC-R activity. To test this, we implanted animals with stimulating electrodes to the ventral hippocampal commissure (anterior-posterior (AP), -1.3; medial-lateral (ML), 1; dorsal-ventral (DV), 3.8) as well as tetrodes targeting the dorsal hippocampus (AP, -3.2; ML, 2). Using similar methods, others (8–10) have shown that disrupting HPC-R activity daily (for 1 h/d) slows down learning in tasks trained over many days. Our one-session Plusmaze task allowed us to target a longer sleep period (4 h) and compare this with our sleep-deprivation group. Implanted animals were trained to a new daily goal location and then had sharp-wave ripple disruption (SWR-D), control disruption (200 ms after SWR, Con-D), and Baseline (no stimulation, No-D). Each animal ($n = 6$) had a different counterbalanced condition sequence with each day a new goal location and new extramaze cues (Fig. 1B). SWR-D mimicked the sleep-deprivation effect, while both No-D and Con-D showed above-chance performance (Fig. 1B, rmANOVA cond $P = 0.025$, $F_{2,10} = 5.42$; t test to chance $P = 0.025$, $P = 0.003$). Therefore, both sleep and neural activity related to HPC-R are necessary for long-term memory performance in this task.

The same sharp-wave ripple-dependent control disruption and sleep deprivation were also performed after a memory-competition paradigm in the watermaze in pilot experiments (14). In the watermaze, dwell times at the correct escape platform location after a memory delay of a 24 h test were unaffected, indicating that memory for the platform location can remain intact across interventions. However, sleep deprivation as well as ripple disruption tended to affect which platform location the animals swam to first. Animals seemed to prefer first going to the trained platform that had not been followed by ripple disruption or sleep deprivation (*SI Appendix*, Fig. S11). This indicates that while, in contrast to the Plusmaze task, the watermaze memory was strong enough to survive ripple disruption and sleep deprivation; the memory representation was nonetheless compromised in comparison with the control conditions and was reflected in a weaker behavior response. This finding is in correspondence to sleep deprivation effects on simple, one-platform learning in the watermaze; as shown previously (15), sleep deprivation after allocentric training leads to poorer behavioral memory expression, although even after sleep deprivation, animals performed above chance (15).

Comparing Different Behaviors. We next investigated neural activity in sleep that was specific to our training in the Plusmaze. For this, we continued with three animals that had good hippocampal signals and, in addition to the hippocampal tetrodes, had a screw electrode (electrocorticogram (ECoG)) touching the posterior parietal cortex (PPC; AP, -4.5; ML, 5) as well as one above the prefrontal cortex (PFC; AP, 3.5; ML, 0.5). We recorded electrophysiological signals for 4 h of sleep in these rats after four different conditions (Baseline, Foraging, Novelty, and Plusmaze, Fig. 2A). Each behavioral condition was performed in the event arena (11, 12), which was adapted to each condition. For Foraging, white curtains surrounded the arena, and a divider was added to create a single 1.5 m track, which was 15 cm wide. Small chocolate cereal pieces were spread along the track to encourage the animal to move along it to search for chocolate rewards. Once the animal had eaten these, the track was refilled so that the animal kept moving back and forth on the track over the 20 min training period. For Novelty, the curtains were removed around the same event arena and the arena was filled with novel objects and textures, such as bubble wrap and newspaper; the animal was allowed to explore freely for 20 min. Of note, especially, the novel floor textures are likely to help create this form of strong novelty in rats, which was the aim. This type of novelty (termed "distinct novelty" (16)) has previously been shown to lead to immediate early gene expression changes in the hippocampus and prelimbic cortex that are independent of sleep (14). This is in contrast to memories that are certainly novel but align with previous experience ("common novelty" (16)), such as new goal locations in the Plusmaze or novel objects in familiar arenas (17). For Baseline recordings, no specific behavior was performed; the animals were transported directly from the home cage to the recording box. After each of these distinct behavioral experiences, the animals were placed in a recording box and given a 4 h sleep period, during which electrophysiological signals were recorded. These signals were used to manually score the level of sleep over the 4 h period (scorer blinded to condition, average $\pm$ SEM – NonREM (non–rapid eye movement) 93.34 min $\pm$ 3.45, Transitional sleep 2.6 min $\pm$ 0.78, REM 7.9 min $\pm$ 1.38; *SI Appendix*, Fig. S1). Only the NonREM sleep periods were used in the subsequent analysis. Each behavior was performed on a different day, the sequence of conditions was different for each animal, and the recording time was kept constant within-animal (rat26 always 10:00–14:30, rat24 and rat27 always 14:30–19:00) to ensure that results were not confounded by time of day or sequence.

Ripples and High-Frequency Oscillations. Initially, we focused on characteristics of NonREM ripples in the hippocampus (100–250 Hz) as well as PPC high-frequency oscillations (HFOs
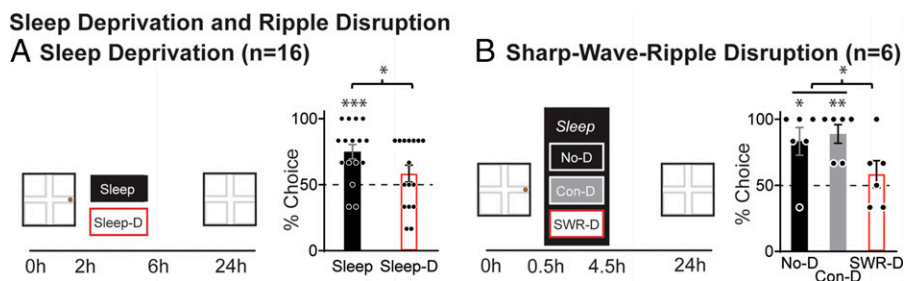

Fig. 1. Sleep deprivation and hippocampal ripple disruption. (A) Animals were trained in the Plusmaze and were either sleep deprived (gentle handling) or allowed to sleep for 4 h and then retested 24 h later (no food present). Only after sleep and not sleep deprivation (Sleep-D), the animals remembered the previous day's goal location. (B) As A but now implanted animals were trained in the Plusmaze and then received sharp-wave ripple disruption (SWR-D), control disruption (200 ms delay, Con-D), or no-disruption (No-D) for 4 h. Only with intact hippocampal ripples, the animals remembered the previous day's goal location. Performance as % choice, with 100% no wrong arm entry and -25% for each arm entry. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
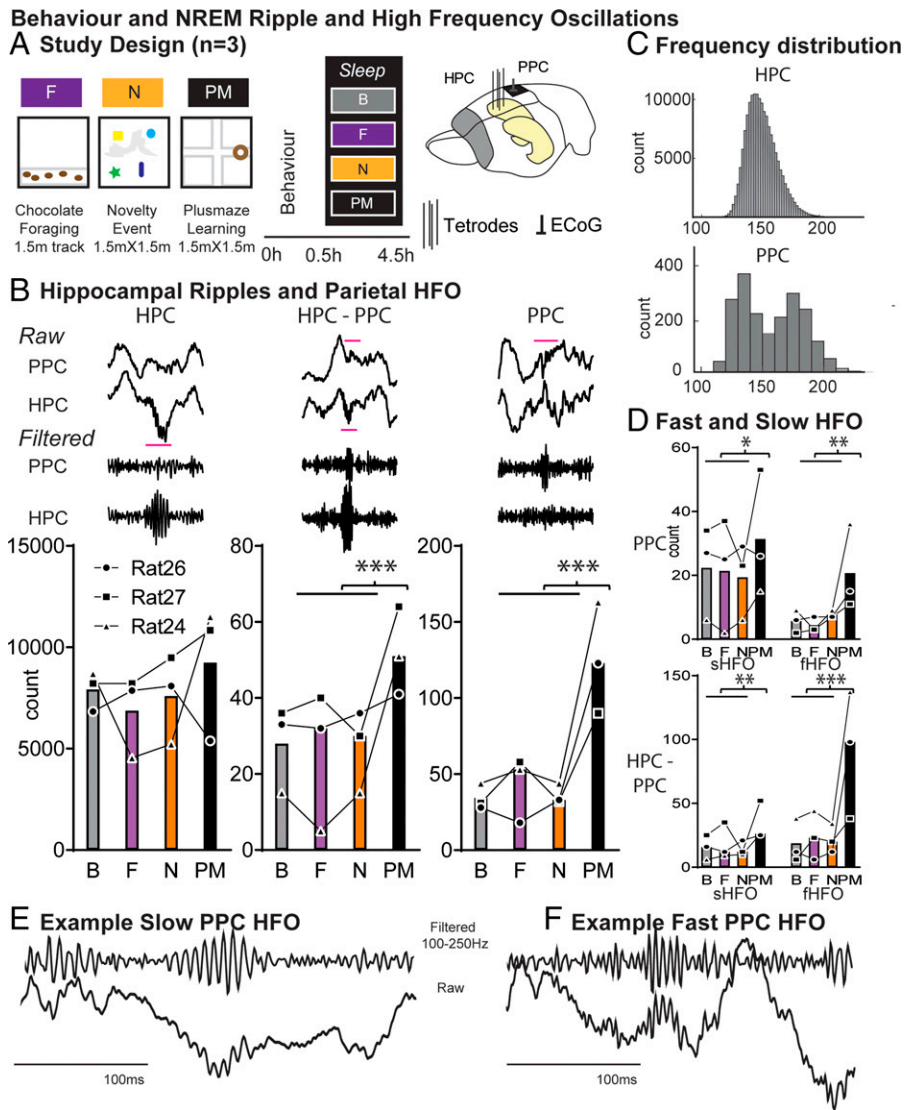
Fig. 2. Behavior and NonREM (NREM) ripples and high-frequency oscillations. (A) Study design. Three animals underwent three different behavioral conditions in the event arena: Foraging on a linear track with chocolate crumbs (F, 1.5 m × 15 cm, 20 min), Novelty experience (N, 1.5 × 1.5 m open-field with novel objects/textures, 20 min), and Plusmaze learning (PM, 1.5 × 1.5 m, 10 min free exploration, then 15 trials to goal with chocolate cereal). We recorded a 4 h sleep period after these behaviors and a nonlearning Baseline (B). (B) We detected ripple events in the hippocampus (yellow, HPC) and high-frequency oscillations in the right posterior parietal cortex (black, PPC) during NonREM sleep and classified events into single HPC, co-occurring HPC-PPC, and single PPC. There were more HPC-PPC and more PPC events after Plusmaze training than other behaviors. (C) Histogram of hippocampal ripples (HPC) and parietal high-frequency oscillations (PPC-HFO). For the latter, the distribution was bimodal, and they were thus divided by ~155 Hz (individual threshold, slow high-frequency oscillations [sHFO], fast high-frequency oscillation [fHFO]). (D) After Plusmaze training, the largest increase was seen in the fast single PPC events. (E) and (F) Example traces of slow and fast PPC-HFO events both filtered for 100–250 Hs and raw local field potential (LFP) trace. Baseline (B), Foraging (F), Novelty (N), and Plusmaze (PM). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

or cortical ripples) and detected both of these as discrete events (event detections across time, *SI Appendix,* Fig. S2). HPC-R were detected and then checked for co-occurring PPC events. We divided them into three different types of events: individual HPC-R, co-occurring hippocampal and cortical events (two events occurring within 50 ms of each other's peak, HPC-PPC) and single HFO in PPC. The occurrence (count and rate) of single HPC events remained broadly the same after all behavior conditions (but see below), but after Plusmaze, more HPC-PPC events and more single PPC-HFOs were detected than in the other conditions (Fig. 2B, rmANOVA cond: HPC $P = 0.66$, $F_{3,6} = 0.55$; HPC-PPC $P = 0.037$, $F_{3,6} = 5.5$; PPC $P = 0.003$, $F_{3,6} = 15.33$). Since reactivation events are mostly observed in the first hour after learning, we also divided the data into 1 h bins. The increase in PPC-HFO was seen over the whole 4 h period (*SI Appendix,* Fig. S3).

HPC-R are known to occur as single events, but also in groupings of doublets and more (called multiplets) (18). To check if it would be more likely to have HPC-PPC events during doublets and multiplets and if, in general, the occurrence of these was influenced by our different behavioral conditions, the HPC events were classified as singlets, doublets, and multiplets (triplets and more). Overall, HPC events were more likely to occur as hippocampal singlets (rmANOVA $P = 0.001$, $F_{2,4} = 84.69$), and there was no difference for the frequency of occurrence of each type (singlets, doublets, multiplets) for HPC events across conditions (*SI Appendix,* Fig. S3C). However, HPC-PPC events were more prominent as singlets in the hippocampus (rmANOVA $P = 0.014$, $F_{2,4} = 15.18$) and also showed a significant interaction between conditions and type of HPC-R (rmANOVA $P = 0.005$, $F_{6,12} = 5.62$). Only HPC-PPC events in which the HPC-R were singlets but not in

doublets or multiplets came with increases after Plusmaze (rmANOVA $P = 0.013$, $F_{3,6} = 8.88$, *SI Appendix,* Fig. S3*B*).

To summarize, only cortical events showed an increase after Plusmaze training and not individual HPC-R or HPC doublets or multiplets. The increase in co-occurring HFOs between the cortex and hippocampus does not survive further rigorous analyses, as will be shown below.

Slow and Fast HFOs. When investigating the PPC-HFOs further, a bimodal frequency distribution was noticeable (Fig. 2*C*), which was not seen for HPC-R. Accordingly, the PPC events were subdivided by their individual theoretical determined split, which was at ~155 Hz for each animal. All types of events showed a striking increase after Plusmaze learning, but the largest effect was seen in the fast (>155 Hz) single PPC events (Fig. 2*D* rmANOVA Full Model [HPC-PPC/PPC events, Slow/Fast, cond]: cond Effect $P = 0.002$, $F_{3,6} = 17.94$; HPC-PPC/PPC X Slow/Fast interaction $P = 0.036$, $F_{1,2} = 28.29$; HPC-PPC/PPC X cond interaction $P = 0.019$, $F_{3,6} = 7.52$; HPC-PPC/PPC X Slow/Fast X cond interaction $P = 0.039$, $F_{3,6} = 5.39$; other $P > 0.19$, $F < 3.6$). The same pattern was seen when using the rate of occurrence for these events (count/time spent in NonREM sleep) instead of the absolute number of events (*SI Appendix,* Fig. S3).

To check if the condition effect of HPC-PPC events and the overall frequency of occurrence of HPC-PPC events was only a random byproduct of the occurrence of both HPC and PPC events, we performed two control analyses. First, we randomly assigned time-stamps within the NonREM periods to PPC events and checked separately, in this simulated data for HPC-PPC events (1,000 iterations), for slow and fast HFOs. This simulation showed that co-occurrence of HPC-R with slow PPC events was above chance (permutation test $P = 0.016$, for each rat individually $P < 0.049$), but this was not the case for the fast PPC events ($P = 0.21$). Thus, only the slow but not fast PPC events were significantly coupled to HPC-R. Second, to check if the increase in HPC-PPC events after Plusmaze was just due to the overall increase in PPC events after Plusmaze or a specific but separate effect, we randomly downsampled PPC events to the number occurring in each of the other conditions and then checked for co-occurrence. Surprisingly, this analysis showed that there was no specific effect of Plusmaze on co-occurrences (both slow and fast PPC events, slow HFOs $P = 0.26$, fast HFOs $P = 0.48$). This showed that the general increase of PPC events occurred only after the Plusmaze condition.

To summarize, there seem to be two distinct types of PPC high-frequency events: slower and faster ones. Especially single, fast PPC-HFOs show an increase after Plusmaze training. Further, only slow and not fast PPC-HFOs were significantly coupled to HPC-R, and the increase of HPC-PPC events after Plusmaze was due to the overall increase of PPC events.

Spectral Profile of Different Events. The implanted animals also had an ECoG placed above the PFC, but due to the anatomical distance between the prelimbic cortex, in which HFOs have been shown to occur (19), and the brain surface, individual HFO events could not be detected. To still be able to investigate any effects in the PFC, we next switched to measuring spectral power across all three brain regions in the same frequency range during the different types of detected events. We analyzed single HPC-R, as well as slow and fast PPC-HFOs. Events classified as co-occurring PPC-HPCs or single PPCs did not show any differences in spectral profile; instead, only differences were seen for slow versus fast PPC-HFOs (see *SI Appendix,* Fig. S5 for five event-type splits). For each type of

event, the same number of events was included across all four behavioral conditions for each animal, with the number determined by the condition with the smallest numbers of events. Oscillatory power in both cortical ECoGs placed above the prefrontal and PPC as well as derived from the hippocampal tetrode targeting the ripple range (100–250 Hz) (19) was extracted for ±100 ms of the event (ripple or HFO) peak (Fig. 3*A*). Contrasting events showed that slow HFOs had less power in this range in the hippocampus but more in the PPC in comparison with single HPC-R. Fast HFOs also had less power in the hippocampus in comparison with ripples, but showed increased power in the PPC and PFC. Finally, contrasting the two cortical events revealed that fast HFOs had less hippocampal power in the ripple range but more in the PFC. We confirmed these effects in each animal individually (*SI Appendix,* Fig. S6).

In addition, statistical analyses were conducted based on the number of animals, not events. For this, the power was extracted for ±50 ms of event peak and normalized for each animal across all conditions and event types within each brain area to allow direct comparison of modulation across events. Overall, the three event types differed in the spectral profiles across brain areas, and there was a significant event-type x brain area, type x condition and three-way interaction (Fig. 3 *B–D*, rmANOVA Full Model [brain area (BA), Type 3 levels, cond]: type $P = 0.003$, $F_{2,4} = 31.93$; BA $P = 0.007$, $F_{2,4} = 21.36$; cond $P = 0.0856$, $F_{3,6} = 3.6$; type X BA interaction $P < 0.001$, $F_{4,8} = 26.26$; type x cond interaction $P = 0.035$, $F_{62,12} = 3.36$; type x BA x cond $P = 0.058$, $F_{12,24} = 2.11$). As with the event-based analysis, individual HPC-R showed large hippocampal but less cortical power. Slow PPC-HFOs showed similar hippocampal power but more PPC cortical power in comparison with HPC-R. Finally, fast PPC-HFOs showed larger PFC and PPC but smaller hippocampal spectral power (linear increase in power from ripple to slow and then fast PPC-HFOs for PPC $P = 0.007$ and PFC $P = 0.005$). The only condition effect was seen for fast PPC oscillations, as there was an increase in power after Plusmaze in both cortical regions during these events (PPC cond $P = 0.011$, $F_{3,6} = 9.26$; PFC cond $P = 0.034$, $F_{3,6} = 5.75$). This condition effect was also seen in the event analysis for each animal (*SI Appendix,* Fig. S7).

In sum, fast PPC-HFOs showed larger PFC and PPC, and smaller hippocampal spectral power and a condition effect, with an additional increase in cortical power after Plusmaze. This pattern was seen in the analysis pooling events from all animals, but also in the event analysis within each animal and when extracting data and analyzing across animals. The effects in hippocampal spectral power across events corresponds well to the co-occurrence analysis, in which only slow but not fast PPC events showed above-chance coupling to HPC-R. Overall, this analysis indicates that fast events correspond to a prefrontal-parietal network and slow events to a hippocampal-parietal network, and only the former and not the latter increase in size specifically with Plusmaze learning.

Granger Analysis of Different Events. Parametric Granger analysis was then conducted on the same event types with a window size of 2.4 s including all causality flows between hippocampus, PFC, and parietal (PPC) cortices (Fig. 3 *E* and *F*; nonparametric Granger analysis as control, see *SI Appendix,* Fig. S8). We divided the analysis into two frequency ranges: 0–20 and 20–300 Hz. Slower oscillations are more specific for sleep and are thought to represent coordination across brain areas, while faster oscillation ranges are thought to represent information exchange. Upon visual inspection, the event types did not show any differences across conditions in the Granger analysis (*SI Appendix,* Fig. S9).
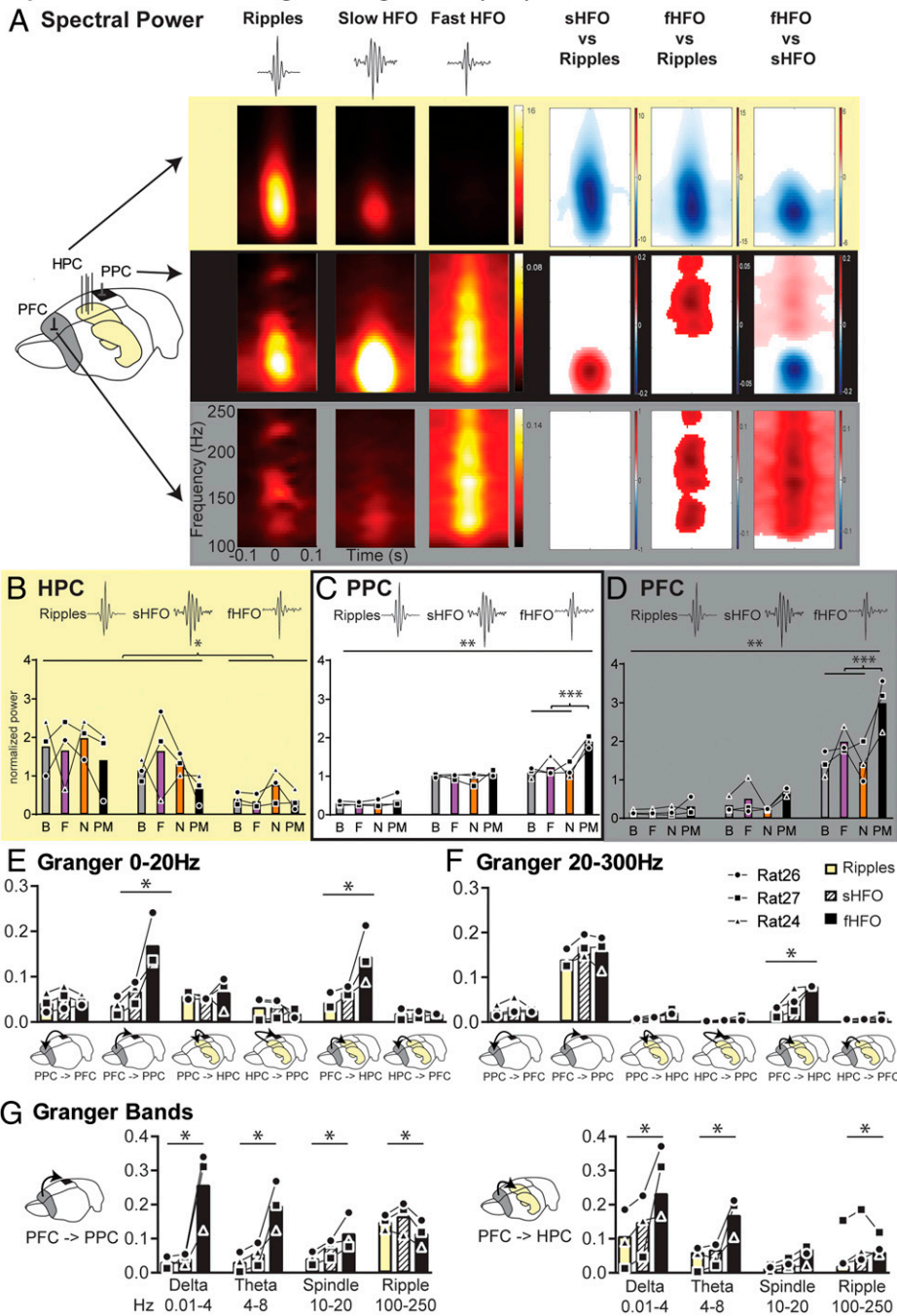
Fig. 3. Spectral power and Granger during events: (A) Spectrogram for all three brain areas (*Top*, hippocampus; *Middle*, parietal cortex; and *Bottom*, prefrontal cortex) for three event types for 100–250 Hz ±100 ms (same color scale all events) and average event trace (above). On the *Right*, statistical contrast of slow HFO vs. ripples, fast HFO vs. ripples, and fast vs. slow HFOs with cluster-based correction for multiple comparison (red, first event higher power; blue, second event higher power). (B–D) For all three brain areas normalized power (for each animal across event type and brain area) for 100–250 Hz ±50 ms around the events in each condition (same number of events across conditions for each type). (B) Hippocampus (HPC), (C) posterior parietal cortex (PPC), and (D) prefrontal cortex (PFC). Overall, the three event types differed in their spectral profiles across brain areas. Individual hippocampal ripples showed large hippocampal power but less cortical; slow PPC-HFO showed less hippocampal power but more cortical power than hippocampal ripples. Finally, fast PPC-HFO showed larger PFC but smaller HPC spectral power. These general effects were the same if separated for those cortical events that were classified as coupled or not coupled to hippocampal ripples (see *SI Appendix*, Fig. S4). As for condition effect, there was an increase in power after Plusmaze training in PPC and PFC for the fast cortical events. (E and F) Granger causality analysis (parametric) is shown for both 0–20 Hz and 20–300 Hz oscillation bands for the different event types (single hippocampal ripples HPC [yellow], slow [black and white shading], and fast [black shading] posterior parietal cortex high-frequency oscillations [PPC-HFO]) with the six possible directionalities. (E) In the slower frequencies, fast PPC-HFO induced an increase in prefrontal cortex to hippocampal and to parietal Granger values (linear increase from ripples, slow and fast HFO). (F) In contrast, in the faster frequency band, overall PFC to PPC was increased for all events and PPC-HFO showed an increase in PFC to HPC values (linear increase from ripples, slow and fast HFO). (G) Granger for selected bands focused on PFC to PPC (*Left*) and PFC to HPC (*Right*). Prefrontal cortex, PFC; hippocampus, HPC; posterior parietal cortex, PPC. *P < 0.05, **P < 0.01, ***P < 0.001.

5 of 10

However, we continued with averages across condition per animal. In the slower frequency ranges (0–20 Hz) PFC→HPC and PFC→PPC showed an increase in Granger values according to event types from HPC ripples to slower and then faster PPC events (rmANOVA Full Model with Frequency (Freq) range [FR], Directionality, Event types: direct $P < 0.001$, $F_{5,10} = 24.85$; types $P = 0.066$, $F_{2,4} = 5.76$; direct X FR interaction $P < 0.001$, $F_{5,10} = 12.93$; types X FR interaction $P = 0.0882$, $F_{2,4} = 43.75$; direct X types interaction $P < 0.001$, $F_{10,20} = 12.79$; direct X types X FR interaction $P < 0.001$, $F_{10,20} = 8.04$; For each oscillatory band separately: 0–20 Hz direct $P = 0.007$, $F_{5,10} = 6.28$; types $P = 0.065$, $F_{2,4} = 4.43$; direct X types interaction $P < 0.001$, $F_{10,20} = 11.111$). In the faster frequency ranges (20–300 Hz), PFC→PAR showed higher Granger values for all types of events. Further, PFC→HPC showed increases across the event types as already seen in the 0–20 Hz frequency range (20–300 Hz direct $P < 0.001$, $F_{5,10} = 54.97$; types $P = 0.097$, $F_{2,4} = 5.83$; direct X types interaction $P < 0.001$, $F_{10,20} = 7.71$). As with the spectral power analysis, it did not make a difference if we divided the HFO events into single or co-occurring (*SI Appendix*, Fig. S8–S10).

Finally, we focused on the two directionalities that showed effects in the slow and fast frequency ranges—PFC to PPC and PFC to HPC—and extracted Granger values for smaller, more specific frequency bands. Specifically, these were delta (0.01–4 Hz), theta (4–8 Hz), beta/spindles (10–20 Hz), and ripples (100–250 Hz). For both directionalities, we found main effects of frequency band and event types as well as the interaction of the two (rmANOVAs PFC→PPC Freq band $P = 0.043$, $F_{3,6} = 5.11$; event type $P = 0.023$, $F_{2,4} = 11.26$; interaction $P < 0.001$, $F_{6,12} = 14.82$; PFC→HPC Freq band $P = 0.045$, $F_{3,6} = 4.98$; event type $P = 0.02$, $F_{2,4} = 12.16$; interaction $P = 0.016$, $F_{6,12} = 4.25$). Following up with individual rmANOVA for each frequency band showed a significant effect of event types for all but the spindle range in PFC→HPC (all $P = 0.01$–0.045, $P = 0.136$ for spindle PFC→HPC, Fig. 3G). Thus, in summary, faster PPC events showed a stronger lead of the PFC over other brain areas, which was independent if they occurred on their own or together with HPC ripples.

Delta and Spindle Analysis. Other oscillations during sleep have been proposed to interact with HPC-R to enable memory consolidation. Specifically, these are slow oscillations and spindles (20). Slow oscillations are thought to synchronize other oscillations and brain areas. When detected as events, these slow oscillations are termed delta waves (20). Spindles are often reported to occur after HPCs (20). HPC-R are also reported to occur in the troughs of the spindle (21). Further, cortical high-frequency events have been reported to be associated with spindles (19). Finally, it has been reported that spindle number and size both increase after learning events in humans (22, 23), from whom we also know that one can divide spindles into frontal and parietal spindles, which each show different characteristics in individual typical rates of occurrence and average frequency (24). Typically, after learning, the faster, parietal spindles show increases in humans.

Our study enabled a comparable investigation in rodents; delta and spindle events were detected as well as coupled delta-spindle events in the PFC and PPC, and showed that while all three showed a trend toward an increase after all behavioral conditions relative to Baseline, this was not statistically significant (Fig. 4 *A–C*, rmANOVA for each event type all $P > 0.14$). Coupling between HPC-R and both types of spindles (Fig. 4D) did not show any changes across conditions, but ripples showed marginally significant higher coupling with PPC than PFC spindles (rmANOVA brain area $P = 0.058$, $F_{1,2} = 15.7$). Coupling of both fast and slow high-frequency PPC events with spindles also showed a marginally significant effect after Plusmaze (rmANOVA slow HFO cond $P = 0.059$, $F_{3,6} = 4.37$; fast HFO cond $P = 0.06$, $F_{3,6} = 4.35$), and there was more coupling between fast events and PPC in comparison with PFC spindles (Fig. 4 *E* and *F*, brain area $P = 0.006$, $F_{1,2} = 169.0$). Since, as with ripple-HFO coupling, the condition effect could just be a result of a general increase in number of HFO events after training, we performed a control analysis comparing co-occurrences with random time-stamps within the NonREM periods for the spindles, as was done for ripple-HFO coupling. Surprisingly, for the high-frequency events, the coupling was never above chance (all $P > 0.15$), while HPCs were coupled to both spindle types (comparison with random shuffle: ripple-PFC spindle $P = 0.0005$, ripple-PPC spindle $P = 0.0003$). The significant coupling between ripples and spindles was also seen for ripples occurring before spindles (comparison with random shuffle: ripple-pre-PFC spindle $P = 0.05$, ripple-pre-PPC spindle $P = 0.025$), but not for HPCs occurring after spindles (comparison with random shuffle: ripple-post-PFC spindle $P = 0.72$, ripple-post-PPC spindle $P = 0.93$).

In summary, we showed that after Plusmaze learning, there was a consistent pattern favoring higher cortical HFOs during spindles, even though the coupling of these events was not above chance. Only HPC-R showed above-chance coupling to parietal and PFC spindles. This coupling was present both for HPC ripples occurring before as well as during spindles.

Percentage of Events. Until now, the absolute number of events was used in our co-occurring analyses. To enhance intuition about how likely certain co-occurring events are, we next calculated percentages of these events in relation to the absolute number of each oscillation (Fig. 4H). Sixteen percent of HPC-R occurred before, 20% during, and 14% after PPC spindles (rmANOVA timing to ripples $P < 0.001$, $F_{2,4} = 323.12$). For PPC spindles, 69% had a HPC ripple occurring before, 79% during, and 62% after the spindle (pre/during/post-rmANOVA $P < 0.001$, $F_{2,4} = 184.56$). Fifty-one percent of slow HFOs were coupled to HPC ripples, but only 24% of the fast HFOs (paired t test slow vs. fast $P = 0.031$, $T_2 = 5.58$); further, 27% of slow HFOs and 10% of fast HFOs occurred during spindles (paired t test slow vs. fast $P = 0.033$, $T_2 = 5.39$). Finally, 0.35% of HPC ripples were coupled to slow HFOs and 0.11% of ripples to fast HFOs, and 1.8% of PPC spindles occurred with a slow HFO and 0.88% occurred with a fast HFO.

In sum, this analysis mirrored the coupling analysis emphasizing that HPC-R are more likely to occur before and during a spindle and that slow cortical HFOs are more likely to occur with a ripple but this is not the case with fast HFOs.

HFO in SWR-D and Con-D. Initially (Fig. 1), we had shown that memory performance in the Plusmaze is affected by HPC-R disruption (SWR-D). To investigate if SWR-D after Plusmaze training also affected the number of HFOs; we detected these events in the SWR-D and Con-D condition in those animals that had PPC screw electrodes (five out of six). We focused on the single events that do not occur together with HPC ripples, since co-occurring events would naturally be affected more by ripple-triggered disruption relative to Con-D. SWR-D led to a decrease of both slow and fast single HFOs in comparison with Con-D (rmANOVA SWR-D/Con-D $F_{1,4} = 7.7$, $P = 0.05$; Slow/Fast $F_{1,4} = 0.7$, $P = 0.45$; interaction $F_{1,4} = 0.45$, $P = 0.54$,

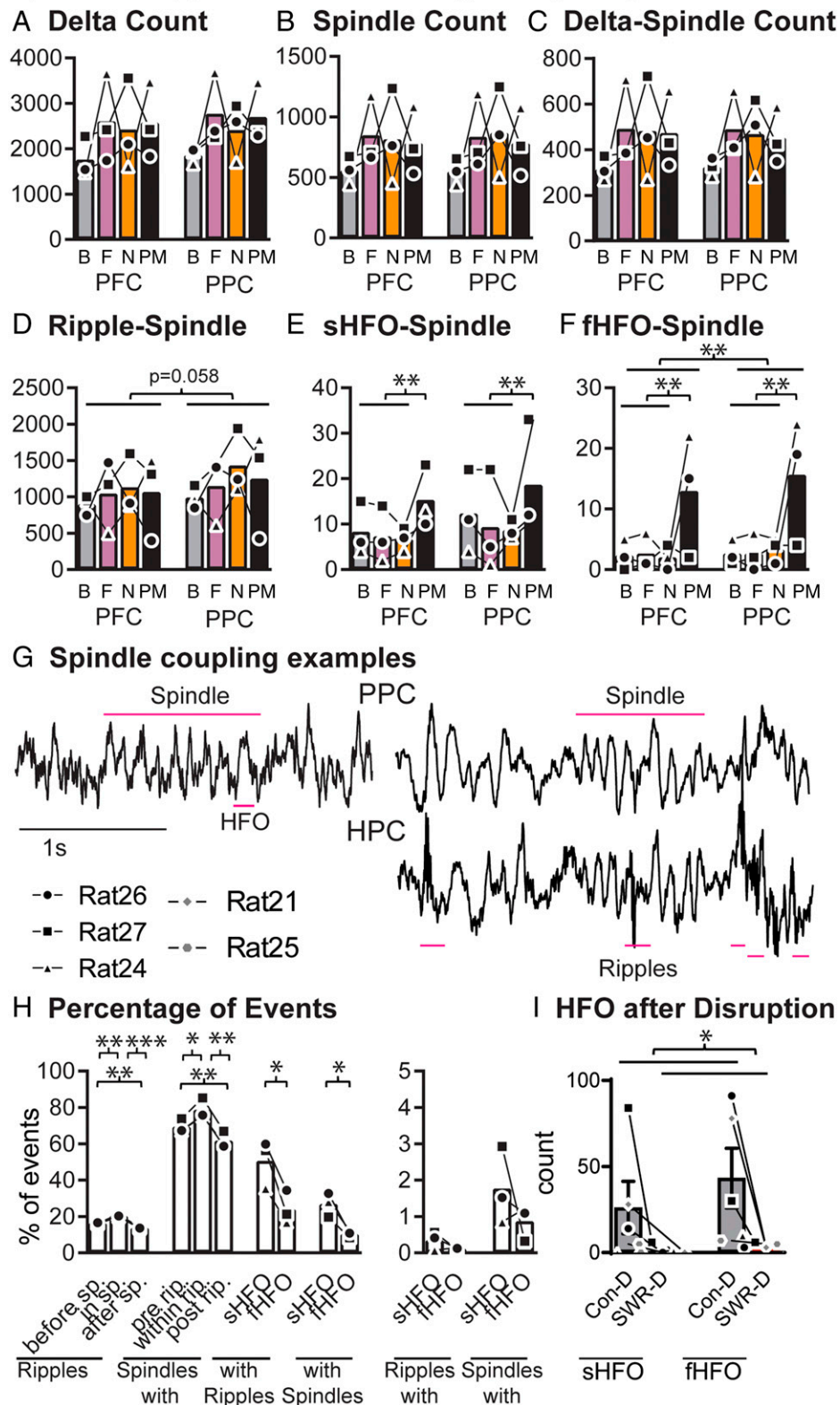# Spindles, Ripples and Cortical High-Frequency Oscillations

Fig. 4. Spindle coupling during events: We detected delta waves (*A*), spindles (*B*), and delta-spindle coupled event (*C*) in the two cortical areas (prefrontal cortex [PFC] and parietal cortex [PPC]). (*D*) Across conditions, there was no change in spindle-ripple coupling, but there was an increase in high-frequency oscillation to spindle coupling after Plusmaze training for both slow (*E*) and fast (*F*) events. (*G*) Example traces for spindle coupling with high-frequency oscillations and hippocampal ripples. (*H*) We calculated the percentage of each co-occurring event; of note is the change in axis for the different event groupings. From *Left* to *Right* are the percentages of ripples that occur before, during, or after a PPC spindle; the percentage of PPC spindles that have a ripple before, during, or after; the percentage of HFOs that occur with a ripple; and the percentage of HFOs that occur during PPC spindles. Next, the figure has the percentage of ripples that occur with a HFO and the percentage of PPC spindles that have a slow or fast HFO. Above the figure are *P* values of contrasts. (*I*) HFOs after disruption conditions. Sharp-wave ripple disruption (SWR-D, *n* = 5 animals from Fig. 1) led to a decrease of both slow and fast HFOs in PPC. Baseline (B), Foraging (F), Novelty (N), Plusmaze (PM), *P < 0.05, **P < 0.01, ***P < 0.001.

Fig. 4*I*). The same effect was seen including both single and co-occurring events (rmANOVA single/co-occurring $F_{1,4} = 9.3$, $P = 0.038$; SWR-D/Con-D $F_{1,4} = 7.8$, $P = 0.05$; single/co-occurring X SWR-D/Con-D $F_{1,4} = 7.3$, $P = 0.054$, other $P > 0.33$). In sum, SWR disruption led to a decrease of slow and fast HFOs that were not co-occurring with HPCs.

Discussion

The main findings of this study were as follows: (1) the development of a one-session learning task that leads to long-term memory; (2) that both extended (4 h) sleep deprivation and HPC disruption led to memory falling to chance at test; (3) among the electrophysiological recording observations, it was observed that training on a Plusmaze—encoding a new goal location across multiple trials—induced changes across the hippocampal-prefrontal-parietal network during ripples and HFOs in NonREM sleep, which was not seen after other behaviors such as experiencing novelty or foraging for chocolate; and (4) successful Plusmaze learning was associated with an increase in HFOs in the cortex (also known as cortical ripples). Two different types of cortical HFOs were identified: low and high frequency, categorized as below or above 155 Hz. Only the faster HFOs showed a training-specific increase, occurring more often and becoming larger after Plusmaze training, as measured quantitatively using spectral power. These points are considered in turn.

First, it is important to clarify precisely what is meant by a "one-session" learning, as behavioral training actually takes place repeatedly over many sessions. The value of the event-arena protocol (25, 26), here modified into a Plusmaze, is that the animals first learn the spatial context and are then given a new problem each day. Thus, by the time the animals reach the point where the experimental manipulations are conducted, there is no further spatial context learning to be accomplished—that is, in the past. Rather, the animals are faced with the task of remembering where to go each day—a form of spatial "recency." They have only each single session to do this, and the levels of performance they reach (Fig. 1) constitute their performance on that day. As a counterbalanced sequence of conditions is deployed within subject, there are several sessions of "one-session" learning to collate, which is potentially confusing. However, critically, the impact of, for example, sleep deprivation for 4 h after training is not on their knowledge of the spatial context; it is a test of what the animals have encoded that day. Such a protocol and its results highlight that it is critical to consider which behaviors are used to measure "learning" and postlearning sleep processes. Especially in rodent research, this term is loosely used to describe any of the behaviors harnessed in these experiments. In electrophysiological experiments, simple tasks that can be repeated daily and result in many perfect performance trials are often preferred for practical reasons. However, our novel task allows investigation of whether neural signatures of consolidation during sleep can be seen in tasks that correspond to significant learning within a day, i.e., the extraction of salient, novel information across multiple trials during a short period of time that can be retrieved 24 h later.

Second, the value of this novel task is vindicated by the second observation of Fig. 1, namely, that 4 h sleep deprivation (1A) or HPC disruption (1B) has an impact on memory retention. Not only was it observed that the experimental conditions were consistently and significantly below the performance of relevant controls, but also that performance fell to chance. These findings might be usefully compared with studies such as Girardeau et al. (10) and Ego-Stengel and Wilson (9), in which

ripple disruption was performed daily for 1 h in multiday training paradigms. In these studies, ripple disruption led to sloweddown learning, but performance remained above chance.

Third, the fast HFOs were associated with higher prefrontal cortical power but lower hippocampal power. In contrast, slower HFOs showed more hippocampal and less PFC power, and only for these slower events was the coupling to the HPC-R above chance. Spindle-HFO coupling was not above chance (both for PPC and PFC spindles); only spindle-ripple coupling was. In the Granger analysis, the fast, cortical high-frequency events also showed increased lead of the PFC over both the parietal cortex and HPC. While there was no training-specific effect for the number or size of HPC-R, they were still necessary for memory performance the next day. Finally, HPC disruption also led to a decrease of parietal HFOs.

The seminal paper by Khodagholy et al. (19) was the first to describe cortical high-frequency events (cortical ripples). They observed these events in default-mode network regions (prefrontal and retrosplenial cortex), as well as the PPC, and they tended to occur together with HPC-R. Later, these oscillations were also reported in human subjects (27–31). It was also shown that these co-occurring events became more common after learning (19). We replicated this observation in our Plusmaze paradigm, but now add that there seem to be two different types of cortical events—slower as well as the faster ones. These two different types were already visible in the coherence figures for retrosplenial to parietal cortex in Khodagholy et al. (19) but not explicitly described in their article.

The main effect of training to a new goal location was seen in cortical HFOs that occurred independently of HPC-R. However, as noted above, we nonetheless observed the necessity of the HPC-R for memory performance during the next day's memory test in our disruption experiment. Interestingly, this disruption also led to a decrease in HFOs, even though they were not directly targeted. The conceptual point is that new information is thought to be transmitted to the cortex during HPC-R that then has to be processed in the cortex to create a long-lasting memory trace. Perhaps it is this processing that is occurring in the cortical events. However, while these cortical events would then show stronger learning-related responses, the HPC-R with their information content would still be necessary. This may also explain why disrupting ripples caused less cortical events. It has been proposed that the hippocampus records everything we experience throughout the day, albeit retaining only a subset via the process of cellular consolidation (32). During the night, when we sleep, our brains sort through all these memories by reactivating them during HPC-R but only postprocess and retain those memories that are recognized to be salient (2). This theory fit to our results: HPC-R remained the same after all experiences as one would expect if all that we do during the day is recorded, with reactivation largely restricted to sleep. However, only after Plusmaze learning—a salient experience—did a significant amount of postprocessing of this new information occur during cortical high-frequency events. Further, if ripples are disrupted, no postprocessing will occur; therefore, HPC-R disruption would lead to fewer cortical HFOs. Of note, our pilot experiments in the watermaze indicate that ripple-related activity, as well as sleep, is not necessary for consolidating memories that are very strong.

Our fourth main finding emerged from our investigation of the association of these events with sleep spindles. Spindles are often reported to occur after HPCs (20) as well as to have ripples occurring in their troughs (21). Further, cortical high-frequency events have been associated with spindles (19), and

spindles increase in number and size after learning events, at least in humans (22, 23). From humans subjects, we also know that spindles can be divided into frontal and parietal spindles, which each show different characteristics in their individual rates of occurrence and intrinsic frequency (24). After learning, the faster, parietal spindles are typically shown to increase. In contrast, most rodent studies only record from one site and have tended to focus on frontal recording sites. Here, we show that there were more ripple-PPC spindle events than ripple-PFC spindle events despite HPC-R being significantly coupled to both types of spindles. Further, cortical HFOs occurred more often together with spindles after Plusmaze (both for PPC and PFC spindles). Interestingly, this coupling was not above chance but only a byproduct of the increased number of events after Plusmaze. This incidental increase was also seen in the ripple and HFO coupling but that does not preclude these couplings serving a purpose during memory consolidation, only that there seems to be no additional regulation increasing coupling after training. It does highlight that one should be careful when discussing coupling between events that occur very often. We confirmed significant ripple-spindle coupling, which has often been reported. Interestingly, coupling was significant for both HPCs occurring before as well as during spindles. Many rodent researchers focus on the ripples before the spindle (20, 33), while others, especially those working with human intracranial data, focus on ripples occurring during spindles (34). Here, the analyses provided evidence for both associations, HPC ripples tending to occur before as well as during spindles. Examples of these trains of events were already depicted in Maingret et al., a study in which an artificial enhancement of the triple-oscillation coupling was created with stimulations triggered on ripple events (20). Thus, while that study focused on the spindles occurring after the ripples, additional ripples were observed occurring during the spindle. It would be tempting to speculate that the sequence of "ripple-before" spindle and "ripple-within" spindle events represent the dialogue between the hippocampus and cortex, with the hippocampus initiating and "preparing" the cortex with the first HPC-R to receive another input during a spindle (i.e., the next ripple).

A potential alternative account for the results is that only training in the Plusmaze involved the PPC. The importance of the PPC during consolidation in our Plusmaze task is most likely due to its spatial nature. The PPC serves as a cortical integration site for hippocampally generated allocentric spatial information and egocentric spatial orientation to permit goal-directed navigation (19, 35–37). Further, memory reactivation during sleep has been observed in the parietal cortex as in the PFC (33, 38), and the importance of PPC-PFC pathway for memory updating was recently highlighted (39). Therefore, the other behaviors may also elicit sleep-related consolidation effects, but these may not involve the PPC due to absence of goal-directed behavior and because the Plusmaze is the only task of the three that utilized a compartment structure.

Of note, while the analysis is based on few animals, we took special care to ensure that effects were seen when events were pooled across animals but also when analyzing events within each animal (each case *n* based on events) and extracting data to run statistics across animals (*n* based on animal). However, this still means that these results should be viewed as exploratory and preliminary; it will be important that they are reexamined by other laboratories in the future.

In sum, we show that encoding and then consolidating the most recent goal location in a familiar maze across multiple trials induces changes across the hippocampal-prefrontal-parietal network during hippocampal NonREM ripples and cortical HFOs. Further, HPC-R activity and sleep after learning in the Plusmaze is necessary for long-term memory performance in this task, as well as for the occurrence of cortical HFOs. These results are also the first direct experimental support for the hypothesis that different types of novelty affect sleep-related consolidation differently (2, 3, 16). This fits into a large body of evidence that factors surrounding learning, such as memory strength, degree of emotion, and future salience, can change how sleep affects consolidation (40–45).

Methods

Animals. Lister-hooded rats of 2 mo of age (Charles River) were group-housed in a 12 h:12 h light:dark condition with water and food provided ad libitum (*n* = 16 unimplanted for behavioral experiments, *n* = 6 implanted for electrophysiology experiments). For the six animals, under isoflurane anesthesia, a 0.5 mm AP × 0.5 mm ML craniotomy above the right hemisphere was performed (AP, −3.2 mm; ML, 2 mm from bregma) for later placement of the tetrode drive (seven tetrodes, individually movable) targeting CA1. One small screw (M1 × 4) was driven into the bone above the cerebellum as a ground electrode for recordings, and another four additional screws were fixed to the skull to stabilize the structure. Two more screws (M1 × 4) were soldered to wires for ECoGs and implanted above right parietal cortex (AP, −4.5; ML, 5; PPC) and the right PFC (AP, 3.5; ML, 0.5; ECoG, PFC). All experiments were performed in accordance with the UK Animals (Scientific Procedures) Act 1986, conducted under a Project License (PPL 60/4566) held by R.G.M.M.

Training.
Plusmaze. Plusmaze learning was performed in the event arena (11–13); curtains were included, and large cues were placed on the curtain. Further, the walls of the event arena were inverted so that a cross-shaped maze was created, covering 1.5 × 1.5 m with a track width of 15 cm. Each session had a new goal arm and new cues on the curtain walls surrounding the maze. The first trial had 1.5 Weetos (chocolate cereal) at the end of the goal arm, and animals were allowed to explore freely for 10 min; this was followed by 15 trials with 0.5 Weetos at the goal location with different starting locations. Training lasted around 20 min. After the training, animals were placed in the recording box (implanted animals) or sleep box/home cage for sleep deprivation (unimplanted animals) for 4 h. In implanted animals, the undisrupted (Baseline/No-D), SWR-D, and Con-D conditions were run with a different sequence across animals, followed by the nonlearning Baseline, Foraging, and Novelty conditions (see below). Sessions were either in the morning or afternoon, but time of day was kept constant for each animal. In unimplanted animals, sleep and sleep deprivation were counterbalanced over animals and sessions (two rounds of each per animal).
Novelty. Animals were placed in a 1.5 × 1.5 m event arena filled with novel objects, textures, and smells, and could explore freely for 20 min; they were then placed in the recording box for 4 h.
Foraging. Animals ran along a 1.5 m track with chocolate crumbles for 20 min and were then placed in the recording box for 4 h. Each animal had a different sequence of the different conditions in the Plusmaze (SWR-D, Con-D, No-D), as well as Foraging, Baseline (home cage), and Novelty. The same was done for sleep and sleep deprivation in the unimplanted animals. If a condition was performed twice (e.g., No-D or Sleep/Sleep deprivation), the average of both performances was used for analysis.

Event Detection. Only NonREM periods were extracted from the original recordings of all brain areas. In order to identify the ripples, the hippocampal recordings were bandpass filtered on the ripple spectrum (100–300 Hz), with a third-order zero-phased Butterworth filter. The resulting signals were used to find the ripples' start, end, and peak times by thresholding voltage peaks, which lasted a minimum duration of 30 ms. The thresholds were determined following a visual inspection of the detections examining the rate of missed detections and false positives, and for each animal, the same threshold was used across conditions. Two detected ripple peaks closer than 50 ms were considered a single ripple. The same procedure was done with the parietal recording to detect HFOs, and a maximum duration criterion of 100 ms was included to control for microarousals. HFOs were classified as slow or fast based on their mean

frequency, which was computed with the *meanfreq* Matlab function (46). The cut-off frequency used to classify the events was obtained by first fitting all events' mean frequencies into a Gaussian mixture model with two components and a shared covariance using the *fitgmdist* function from Matlab. In addition, the mixture model was used to cluster the mean frequencies into two groups. The maximum mean frequency value found in the low frequencies cluster was identified as the cutoff frequency. This cutoff frequency was first computed per condition to later find a single mean value per rat, which was used to split the events among all conditions. A comparison among rats resulted in a mean value close to 155 Hz.

Spindle and delta events were detected in PPC and PFC single channels by using the *FindSpindles* and *FindDeltaWaves* functions from the Freely Moving Animal (FMA) Toolbox (https://fmatoolbox.sourceforge.net/) (47). The NonREM cortical signals were bandpass filtered between 9 and 20 Hz for spindles and between 1 and 6 Hz for delta waves. Events were considered a spindle if they crossed a z-scored peak amplitude threshold of 4 and had a duration between

0.5 and 2 s. Spindles that were closer than 500 ms were merged together. Events were considered delta waves if they had a wave duration between 150 and 450 ms, and their trough and peak z-scored amplitudes were within the ranges of −1.5–0 and 1.5–3 SDs. All data analysis was performed with custom scripts (48) and standard scripts from the community (e.g., Fieldtrip (49), FMA Toolbox); for the other analyses and more details, please see *SI Appendix, SI Methods*.

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