Differential locus coeruleus–hippocampus interactions during offline states

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Abstract Patterns of locus coeruleus (LC) activity and norepinephrine (NE) release during non-rapid-eye-movement (NREM) sleep suggest a critical role for the LC–NE system in offline modulation of forebrain circuits. NE transmission promotes synaptic plasticity and is required for memory consolidation, but the field has only begun to uncover how LC activity contributes to coordinated forebrain network dynamics. Hippocampal ripples, a hallmark of memory replay, are temporally coupled with thalamocortical oscillations; however, the circuit mechanisms underlying systems-level consolidation across larger brain networks remain incompletely understood. Here, using multi-site electrophysiology, we examined LC firing in relation to hippocampal ripples in freely behaving rats. LC activity and ripple occurrence were state-dependent and inversely related: heightened arousal was associated with increased LC firing and reduced ripple rates. At finer timescales, LC spiking decreased ∼1–2 seconds before ripple onset, with the strongest modulation during awake ripples but minimal change during ripple–spindle coupling. These findings reveal state-dependent dynamics of LC-hippocampal interactions, positioning the LC as a key component of a cortical–subcortical network supporting systems-level memory consolidation.

Introduction

Norepinephrine (NE) modulation of the forebrain circuits supporting cognition has long been considered to play a role during vigilant states (***Sara, 2009***; ***Sara and Bouret, 2012***), whereas its impact during low arousal (or 'offline') states, including sleep, has received less attention. The pioneering discovery of greatly reduced firing of the locus coeruleus (LC) neurons during sleep (***Aston-Jones and Bloom, 1981***), for decades, directed research focus toward the role of LC, as a part of the ascending arousal system, for 'online' information processing. At the same time, pharmacological studies in both animals (***Sara et al., 1999***; ***Roullet and Sara, 1998***; ***Clayton and Williams, 2000***; ***Galeotti et al., 2004***; ***Gazarini et al., 2013***) and humans (***Groch et al., 2011***; ***Gais et al., 2011***; ***Kuffel et al., 2014***; ***Cahill et al., 1994***) have demonstrated the importance of post-learning NE transmission for memory consolidation. The results of pharmacology studies were consistent with a well-established facilitatory role of NE for synaptic plasticity, which also takes place offline (***Straube and Frey, 2003***; ***Gelinas and Nguyen, 2005***; ***Harley, 2007***; ***Hansen and Manahan-Vaughan, 2015***; ***Hagena et al., 2016***; ***Palacios-Filardo and Mellor, 2019***).

During offline states such as awake immobility and non-rapid eye movement (NREM) sleep, hippocampal activity is marked by transient episodes of synchronized firing, detected in CA1 local field potentials (LFPs) as high-frequency ∼150Hz oscillations known as ripples ***Buzsaki*** (***1996***). Hippocampal ripples, a hallmark of memory replay, are temporally coupled with thalamocortical

sleep spindles (10–16 Hz) and cortical slow (~1Hz) oscillations, which together represent key components of the mechanism underlying systems-level memory consolidation (***Klinzing et al., 2019***). In recent years, it became evident that ripples reflect not only a coordinated local activity within the hippocampus but also indicate the emergence of large-scale functional networks (***Logothetis et al., 2012***; ***Nitzan et al., 2022***). The ripple-associated cross-regional communication may occur through a coordinated up/down-regulation of neural activity across cortical and subcortical structures, including neuromodulatory centers (***Skelin et al., 2018***; ***Maingret et al., 2016***; ***Brodt et al., 2023***). Several studies have demonstrated temporally coordinated cross-regional neuronal activity around ripples, involving the amygdala (***Girardeau et al., 2017***), the ventral tegmental area (***Gomperts et al., 2015***), the median raphe (***Wang et al., 2015***), and the thalamus (***Logothetis, 2015***; ***Yang et al., 2019***; ***Varela et al., 2001***).

While some indirect evidence suggests a link (***Logothetis et al., 2012***), the relationship between LC neuron spiking and hippocampal ripples has not been directly characterized. For example, a study in the murine slice showed that increasing NE concentration increased ripple incidence and their amplitudes (***Ul Haq et al., 2012***). Consistently, in behaving rats, we showed that pharmacological suppression of NE transmission decreased the occurrence of ripples and impaired spatial memory consolidation (***Duran et al., 2023***). Finally, experimentally induced LC activation affected the temporal pattern of ripple occurrence (***Novitskaya et al., 2016***; ***Swift et al., 2018***). Earlier studies have shown close temporal relations between LC and sleep spindles (***Aston-Jones and Bloom, 1981***; ***Swift et al., 2018***; ***Osorio-Forero et al., 2021***; ***Kjaerby et al., 2022***). In our previous work, we have shown that firing of a subpopulation of LC neurons was temporally coordinated with slow oscillations (***Eschenko et al., 2012***; ***Totah et al., 2018***), which in turn orchestrate spindle and ripple activity (***Molle et al., 2006***).

In the present study, we characterized the ripple-associated LC firing patterns in freely behaving rats. We report that LC activity was anticorrelated with the ripple rate at both large and fine temporal scales. Our results also provide evidence for a state-dependent engagement of the LC in offline memory processing and hippocampal-cortical communication.

Results

We analyzed a total of 20 recording sessions (n = 7 rats, 2 to 8 sessions per rat with an average duration of 6458.48 ± 190.43 sec), including two datasets (n = 1 rat) that contributed to our previous publication (***Eschenko et al., 2012***). All datasets contained simultaneously recorded extracellular spikes of putative LC-NE neurons, local field potentials (LFPs) from the CA1 subfield of the dorsal hippocampus (HPC), and frontal EEG (Figure 1). The recordings were performed in freely behaving adult male rats placed in a small chamber (30 x 30 x 40 cm) in dim light during the dark phase of the animal's circadian rhythm. Electrode positioning was fine-tuned using movable microdrives to ensure optimal detection of hippocampal ripples and LC spikes. The recordings from putative LC-NE neurons were verified using multiple electrophysiological criteria (see Methods for details) and confirmed by histological examination (Figure 1B).

LC-NE neuron spiking is suppressed around hippocampal ripples

We first characterized the temporal relationships between the LC neuron spiking and ripple occurrence. Ripples were detected from a power envelope of a band-passed (140-250 Hz), smoothed (at 25Hz), and z-score normalized CA1 LFPs (Figure 1C). The average ripple rate (18.2 ± 1.5 ripples/min) was with a ripple amplitude of 10.3 ± 0.3 standard deviation (SD). There was a robust CA1 LFP power increase in the ripple band (140-250 Hz) around peaks of detected ripples (Figure 2A) and a transient power increase in the EEG delta (1-4Hz) and spindle (12-16Hz) bands (Figure 2B) immediately after the ripple onset, most likely reflecting the well-known temporal coupling of ripples with slow waves and sleep spindles (***Molle et al., 2006***).

The LC multiunit activity (MUA) was extracted by thresholding a high-pass filtered (300 Hz–8 kHz) extracellular signal recorded from the LC (Figure 1C). For each recording session, we computed

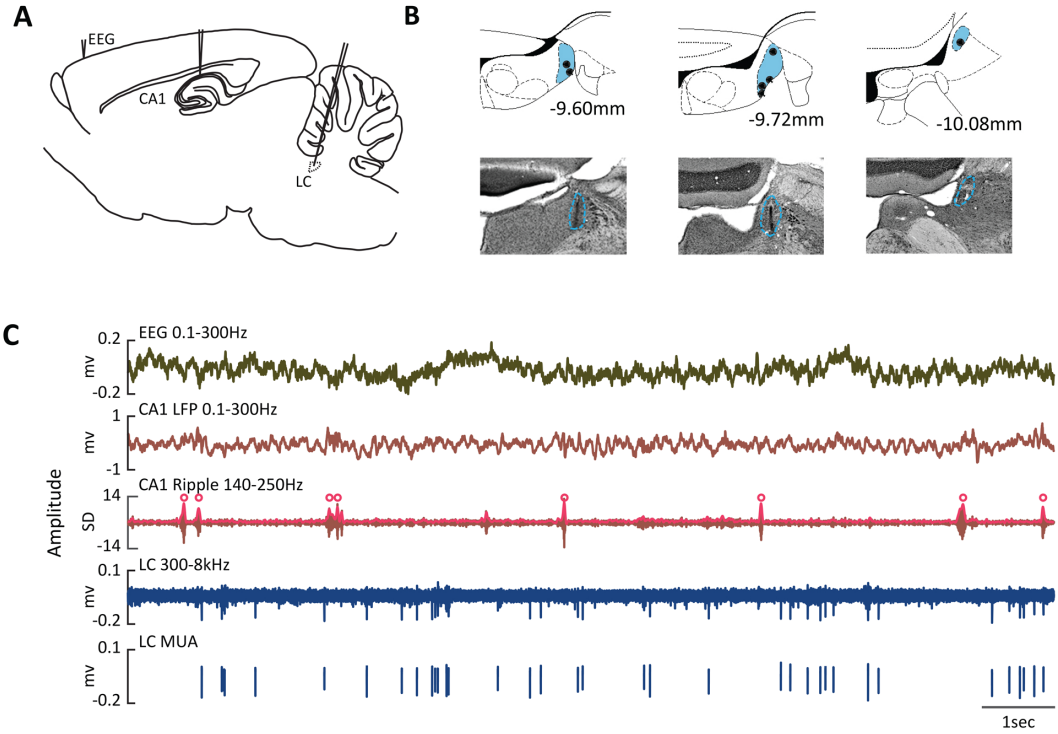

Figure 1. Multi-site extracellular recordings in freely behaving rats. (A) Schematic of chronically implanted electrodes for recording the frontal EEG, local field potentials (LFPs) in the dorsal hippocampus (CA1), and neuron spiking in the locus coeruleus (LC). **(B)** Histological verification and reconstruction of electrode placements (black dots) within the LC (blue area). Numbers indicate anterior–posterior coordinates relative to bregma (***Paxinos and Watson, 2005***). **(C)** Representative traces of simultaneously recorded EEG, hippocampal LFPs, and LC neuron spikes. Red dots indicate hippocampal ripples.

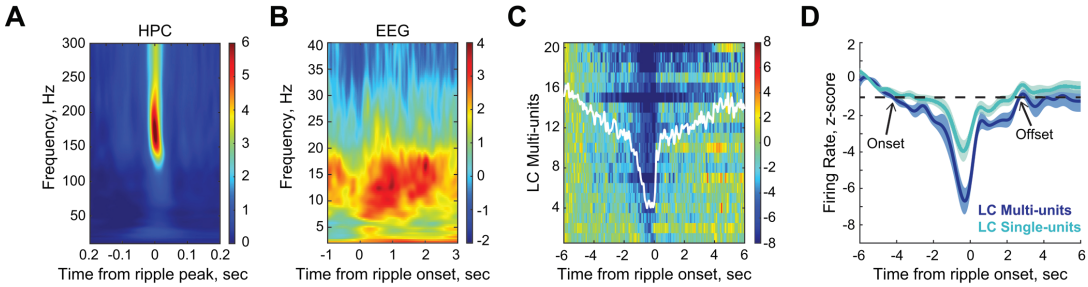

Figure 2. LC-NE neuron spiking is suppressed around hippocampal ripples. (A, B) Representative peri-ripple spectrograms of hippocampal CA1 local field potentials (LFPs) **(A)** and frontal EEG **(B)**. **(C)** Normalized peri-ripple LC multi-unit activity (MUA). Each row shows LC-MUA from an individual dataset; the overlaid trace represents the average across sessions. **(D)** Comparison of peri-ripple LC-MUA and single-unit activity (SUA). Normalized firing rates were averaged and smoothed with a 1 Hz low-pass filter. The dashed line marks the 1 SD threshold used to define the onset and offset of ripple-associated LC activity modulation.

the LC-MUA firing rate in a [-6, 6] sec window centered on ripple onsets and then averaged across ripples. This analysis revealed a prolonged and consistent suppression of LC activity both before and after ripple onset, with peak suppression < -2 SD in all sessions.

In 6 out of a total of 20 datasets with reliable LC-MUA, we could isolate 15 spike trains from LC single units (LC-SUA, n = 4 rats). A significant peri-ripple decrease in LC-SUA (maximum suppression amplitude < -2 SD) was observed in 13 of 15 cases (n = 4 rats). To quantify the peri-ripple LC activity change, we calculated the modulation onset, duration, and magnitude (Figure 2D). The modulation magnitude (through on the peri-event histogram) was greater for LC-MUA (-6.83 ± 0.84 SD) compared to LC-SUA (-4.01 ± 0.65 SD). Despite the difference in magnitude (Kolmogorov–Smirnov test, p = 0.019), the temporal profile of both LC-MUA and LC-SUA around ripples was remarkably similar (Figure 2D). Specifically, the onset of spiking suppression (MUA: -4.08 ± 0.71 sec vs. SUA: -2.90 ± 0.50 sec, p = 0.138), duration (MUA: 8.28 ± 1.37 sec vs. SUA: 5.16 ± 0.92 sec, p = 0.069), and peak time (MUA: -0.29 ± 0.04 sec vs. SUA: -0.35 ± 0.04 sec, p = 0.561) did not differ significantly (Figure 2D). Together, these findings indicated that the majority of LC-NE neurons showed a stereotypic activity pattern around hippocampal ripples. Therefore, we used the LC-MUA datasets for subsequent analyses.

LC firing and ripple occurrence are state-dependent and inversely related

The LC activity suppression was observed as early as ~4-6 s before the ripple onset. The LC activity fluctuation with the brain state could have accounted for this relatively slow temporal dynamics. Indeed, EEG transients coincided with the occurrence of hippocampal ripples (Figure 2B). We thus examined the temporal relationships between the ripple and LC activity with cortical state. To this end, we computed the ripple and LC-MUA rates within 4-s windows and quantified the corresponding cortical state using a synchronization index (SI), calculated as a power ratio (1–4 Hz/30–90 Hz) of the frontal EEG. Across sessions, LC-MUA was consistently negatively correlated with ripple rate (r = –0.38 to –0.11, p < 0.01, n = 20; Figure 3A). SI values were negatively correlated with LC-MUA (r = –0.56 to –0.21, p < 0.01; Figure 3A) and positively correlated with ripple rate (r = 0.10 to 0.50, p < 0.01; Figure 3A). Together, these results demonstrate that LC neuronal activity, cortical state, and ripple occurrence are strongly interrelated, suggesting that the slow (multi-second) dynamics of peri-ripple LC modulation may, in part, reflect underlying brain-state fluctuations.

To minimize the influence of cortical state, we generated surrogate time series for each session by shuffling ripple onset times (see Methods). As expected, robust power increases in the ripple band (140–250 Hz) were observed around detected ripples but not around shuffled events (Figure 3B). Comparisons of SI values before and after ripples and surrogate events confirmed that surrogate events preserved the cortical states in which ripples occurred (Figure 3C). Subtracting LC-MUA aligned to shuffled events from peri-ripple LC-MUA revealed a consistent suppression of

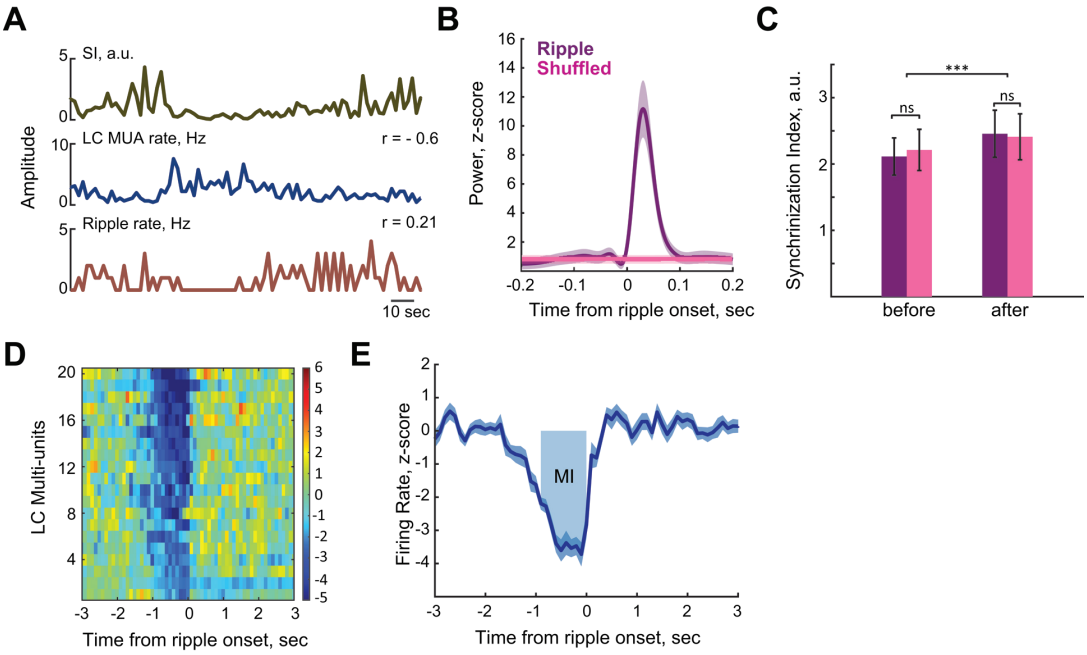

Figure 3. The relationship between LC and ripple activity at different temporal scales. (A) Cortical state–dependent anticorrelation between LC spiking and ripple occurrence. Cortical state was quantified by the Synchronization Index (SI), calculated as the ratio of delta (1–4 Hz) to gamma (30–90 Hz) EEG power. **(B)** Average ripple-band (140–250 Hz) power in CA1 LFPs aligned to ripple onsets (purple) and shuffled control events (pink). **(C)** SI values before and after ripple (purple) and shuffled events (pink), showing no bias in cortical state. **(D)** Normalized peri-ripple LC-MUA for individual sessions. **(E)** Session-averaged peri-ripple LC-MUA. Shaded area denotes the [-1, 0] sec window used for modulation index (MI) calculation.

LC activity at a finer (1-2 seconds) temporal scale, although the temporal profile and magnitude of modulation varied across sessions (Figure 3D).

To quantify the degree of peri-ripple LC activity modulation, we extracted the onset time, the duration, and the modulation index (MI) as the area under the curve in the peri-event time histogram within 1 second preceding the ripple onset (see Methods for details; Figure 3E). On average, LC activity significantly decreased 1.41 ± 0.06 sec (range: 1.02 – 1.88 sec) before the ripple onset and returned to the baseline after 1.70 ± 0.08 sec (range: 1.10 – 2.58 sec). Notably, maximal LC activity suppression occurred approximately 200 ms before the ripple onset (0.24 ± 0.04 sec; range: 0.03 – 0.73 sec). For all 20 datasets, the MI exceeded a 95% confidence interval (CI) of the MIs calculated around the shuffled time series, confirming a substantial decrease in LC activity around ripples.

Differential LC modulation across ripple subsets

The overall transient suppression of LC activity around hippocampal ripples, reported above, does not preclude differential LC modulation depending on ripple subtype. We therefore examined potential heterogeneity in peri-ripple LC modulation. To this end, we randomly selected 30% of ripples from each dataset, calculated the modulation index (subMI) for this subset, and repeated the procedure to generate 5000 ripple subsets (537.6 ± 53.0 ripples per subset). SubMI values showed substantial variability across subsets (range: –45.70 to 1.38 a.u.; Figure 4A). On average, more than half of the subsets (65.99 ± 7.08%) exhibited significant peri-ripple LC modulation (subMI >95% CI), whereas change of LC activity in the remaining subsets did not exceed 95% CI. Importantly, ripple intrinsic properties did not account for this variability: no significant differences were found in peak amplitude (Wilcoxon signed-rank test, $Z = 0.63$, $p = 0.53$), duration ($Z = -0.52$, $p = 0.60$), or inter-ripple frequency ($Z = 1.47$, $p = 0.14$) between ripples in the 10th and 90th percentiles of the subMI distribution.

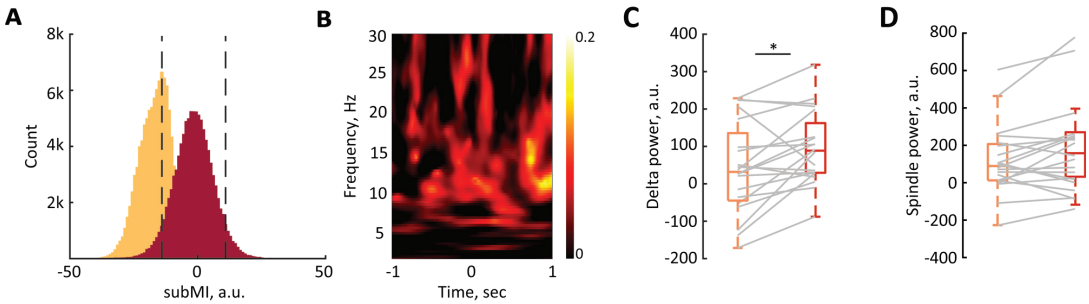

Figure 4. Differential LC modulation across ripple subsets.(A) Distribution of Modulation Index (MI) values for different subsets of ripples (subMI). SubMIs were computed from the peri-event histograms of LC-MUA aligned to the ripple peak (yellow) or shuffled time series (red) for each of 5000 subsets of ripples. Vertical dashed lines indicate the 95% confidence interval (CI) boundaries for the shuffled time series. **(B)** The EEG spectral power difference between EEG spectrograms corresponding to ripples (n = 35.5 ± 3.70) in the 10th and 90th percentiles of the subMI distribution. **(C, D)** The EEG delta **(C)** and spindle **(D)** power preceding the ripple onset for two ripple subtypes with differential degrees of LC modulation (10th and 90th percentiles of the subMI distribution). Note a higher EEG delta power preceding ripples that were not associated with LC activity modulation.

Instead, differences in the ongoing cortical state appeared to underlie the variability in LC modulation. Ripple subsets not associated with LC suppression were preceded by significantly higher EEG delta (1-4Hz) power (Wilcoxon signed-rank test, Z = –2.576, p = 0.01; Figures 4B–C) and showed a trend toward increased spindle-band (10-16Hz) power (Z = –1.829, p = 0.0674; Figures 4B–D).

Peri-ripple LC modulation depends on the cortical-hippocampal interaction

Building on our findings, we predicted that the LC-ripple interactions might vary with arousal. Using a standard sleep scoring procedure (***Novitskaya et al., 2016***; ***Yang et al., 2019***), we classified rat behavior as awake (37.4% ± 2.9% of total recording time), NREM sleep (53.1% ± 3.2%), or REM sleep (1.2% ± 0.9%). Since ripples were extremely rare or essentially absent during REM sleep, we limited further analysis to ripples occurring during awake (awRipple) or NREM sleep (NREM-Ripple). For each data set and each behavioral state, we extracted the percent of ripple subsets with significant LC modulation (subMI >95% CI). We then correlated the subMIs with the total time spent in each behavioral state. The time spent awake, but not in NREM sleep, was significantly correlated with the proportion of ripples associated with LC suppression (r = 0.48, p = 0.03), indicating a more consistent peri-ripple LC modulation during wakefulness. We also examined whether differential peri-ripple LC profiles are related to ripple-spindle temporal coupling, which is known to occur during NREM sleep (***Molle et al., 2006***). We detected sleep spindles (504.5 ± 57.5 per session) occurring at a rate of 8.4 ± 0.8 spindles per minute and split NREM-Ripples into spindle-coupled (spRipple) and isolated (isoRipple). Next, we compared the modulation of the LC around three subtypes of ripples: awRipple (30.1% ± 3.6% of all detected ripples), spRipple (17.2% ± 1.9%), and isoRipple (48.6% ± 3.4%). The ripple subtypes differed in the inter-ripple frequency (Friedman test, $\chi 2$ = 35.62, p < 0.0001), with awRipples being the fastest and spRipples the slowest (Figure 5A). There was no difference in the ripple peak amplitude (Friedman test, $\chi 2$ = 3.7, p = 0.16; Figure 5B). Comparison of the peri-ripple LC MUA rates across three ripple subtypes revealed a significant difference in the proportion of cases showing LC modulation (MI > 95%CI). Specifically, a significant decrease in the LC MUA was detected around awRipples in all 20 sessions (Figure 5C, left), whereas around isoRipples and spRipples, a significant change in LC-MUA was present in 13 (65%) and 4 (20%) sessions, respectively (Figure 5C). This observation was further supported by higher MI values for awRipples, intermediate MIs for isoRipples, and lowest MIs for spRipples (Figure 5D).

Due to the overall very weak or absent LC modulation around spRipples, we compared the LC MUA dynamics around awRipples and isoRipples and only in the sessions showing MI > 95% CI (Figure 5E). This analysis revealed that the onset of the LC spiking suppression occurred significantly

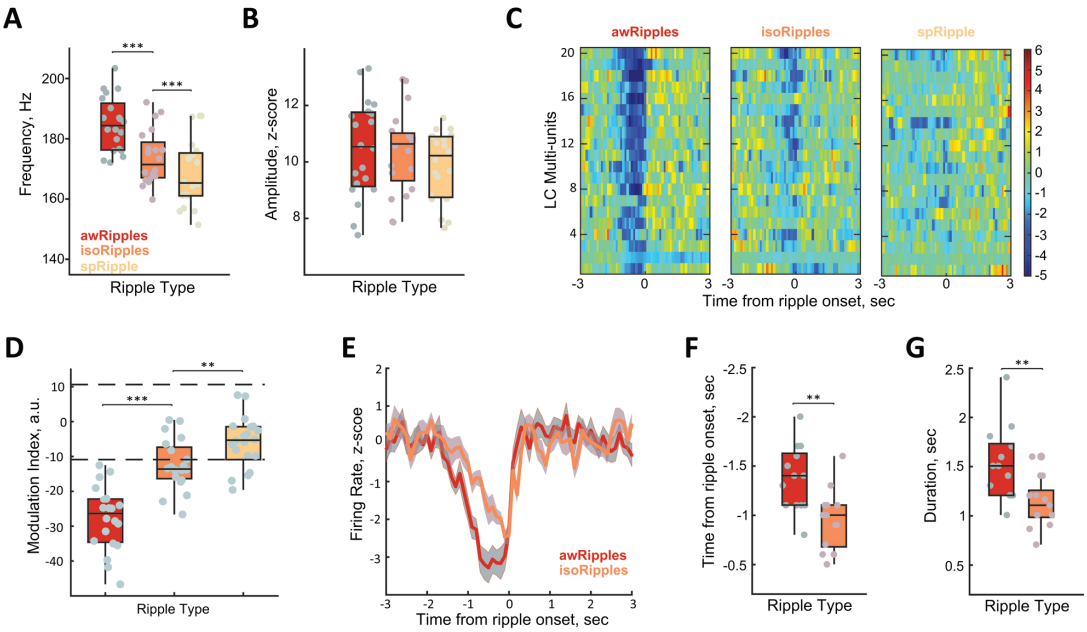

Figure 5. State-dependent modulation of LC activity across ripple subtypes. (A, B) Inter-ripple frequency **(A)** and peak amplitude **(B)** for different ripple types. **(C, D)** Differential LC activity modulation across ripple types. Session-averaged LC multi-unit activity (MUA) aligned to the ripple onset **(C)** and MI **(D)** is shown for different ripple types. The LC MUA rate is color-coded and plotted for individual sessions. Note the strongest LC activity suppression around ripples occurring in wakefulness and the weakest around ripples coupled with sleep spindles. **(E-G)** The patterns of LC activity around different ripple types. The temporal dynamics **(E)**, the onset **(F)**, and the duration **(G)** of ripple-associated LC MUA modulation are shown for ripples occurring during awake and NREM sleep. The data from sessions with significant LC MUA rate decreases are shown. Note an earlier onset and longer duration of LC activity modulation around awake ripples. Due to an overall weak or absent LC activity modulation, data from spindle-coupled ripples are not shown.

earlier preceding awRipples (Wilcoxon signed-rank test, Z = -2.83, p = 0.005; Figure 5F) and the LC suppression was more sustained (Z = -2.80, p = 0.005; Figure 5G).

Thus, the peri-ripple LC modulation depended on the cortical-hippocampal functional connectivity, with LC activity being preserved during the periods of hippocampal-cortical communication, as indicated by the ripple-spindle coupling.

LC activity modulation around sleep spindles

Consistent with previous studies (***Aston-Jones and Bloom, 1981***; ***Swift et al., 2018***), we observed LC activity modulation around sleep spindles. As expected, both spindle and LC activity were cortical state-dependent (Figure 6A). The correlation analysis confirmed that a higher spindle rate occurred during the EEG epochs with higher SI (r = 0.28 to 0.70, p < 0.0001 for all sessions), whereas LC-MUA and SI were anticorrelated (r = -0.56 to -0.21, p < 0.01 for all sessions). LC-MUA around sleep spindles exhibited bidirectional modulation, characterized by a gradual decrease before spindle onset, followed by a rapid overshoot (Figure 6B). Similar to peri-ripple LC suppression, this relatively slow (multi-second) temporal profile may reflect a network shift in thalamo-cortical functional connectivity during sleep spindles. To isolate the LC activity pattern that is not state-dependent, we subtracted LC-MUA aligned to shuffled time series from LC-MUA aligned to spindle onsets . This procedure refined the time window of a transient LC-MUA change (Figure 6B). Specifically, LC-MUA exhibited a sharp decrease 2.5 ± 0.09 s before spindle onset, followed by a rapid return to baseline and a brief overshoot roughly corresponding to the duration of a sleep spindle (1.1 to 2.8 s). Overall, a significant LC modulation (MI > 95% CI) around sleep spindles was present in 17 out of 20 sessions (Figure 6C).

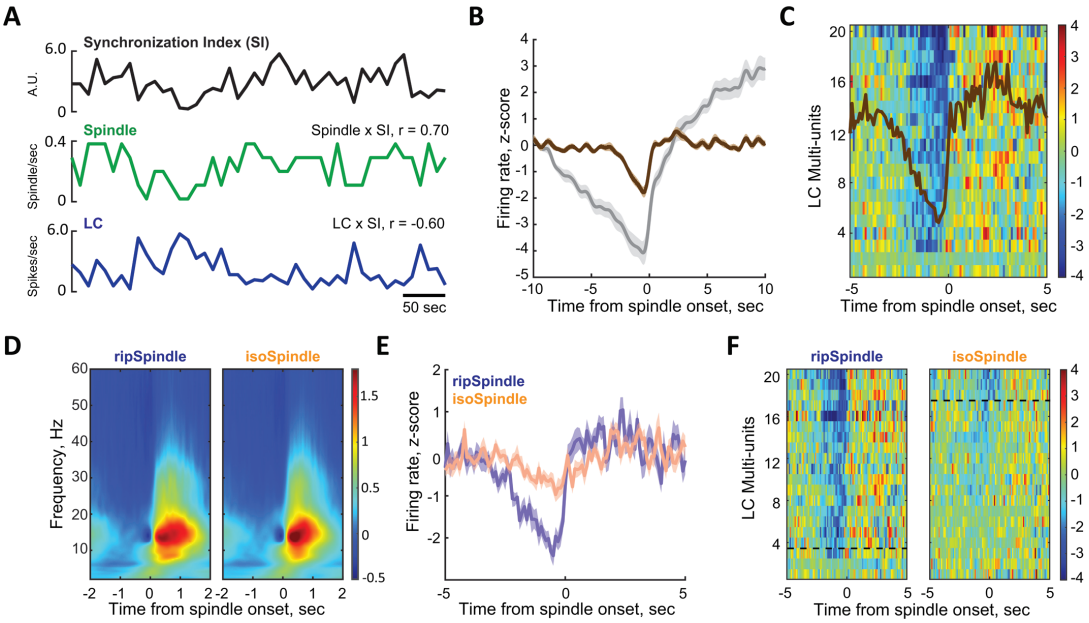

Figure 6. LC modulation around sleep spindles. (A) Cortical-state dependent spindle occurrence and LC activity. **(B)** Spindle-associated LC activity modulation at multiple temporal scales. LC-MUA rate aligned to spindle onset without (gray) and with (brown) permutation of spindle onset times. Normalized firing rates were averaged and smoothed with a 1-Hz low-pass filter. **(C)** Spindle-specific and cortical state-independent dynamics of LC-MUA around sleep spindles. Color-coded normalized LC-MUA rate aligned to spindle onset is shown for each dataset, with the overlay representing the grand average across all sessions (n = 20). **(D)** EEG spectrogram around ripple-coupled (left) and isolated (right) spindles. **(E, F)** Grand-average **(E)** and session-averaged **(F)** LC activity profiles around ripple-coupled and isolated spindles.

Finally, we explored if the temporal profile of spindle-associated LC-MUA differed around ripple-coupled (ripSpindle, 41.3 ± 3.1% of all detected spindles) and ripple-uncoupled (isoSpindle, 58.7 ± 3.1%) spindles. The two subtypes of sleep spindles did not differ in frequency (ripSpindle: 15.37 ± 0.11 Hz, isoSpindle: 15.33 ± 0.09 Hz; Wilcoxon signed-rank test, Z = –0.22, p = 0.82) or maximum power (ripSpindle: 1.98 ± 0.14 a.u., isoSpindle: 2.08 ± 0.15 a.u.; Z = 1.27, p = 0.20). Notably, isoSpindles were significantly shorter compared to ripSpindles (1.32 ± 0.05 sec and 1.51 ± 0.06 sec, respectively; Z = –3.92, p = 0.000089; Figure 6D). Importantly, neither the LC-MUA rate nor SIs differed during a 2-sec time window preceding either group of spindles (Kolmogorov-Smirnov test, p > 0.05 for both variables and all sessions). Across sessions, MI values exceeded 95% CI in 17/20 datasets for isoSpindles and only 3/20 for ripSpindles. Thus, LC modulation was more consistent and pronounced around isoSpindles compared to ripSpindles (Figures 6E and 6F). Together, this result provided further evidence that LC activity is preserved during hippocampal–cortical communication, as reflected by ripple–spindle coupling.

Discussion

Using multi-site electrophysiology in freely behaving adult male rats, we characterized the dynamics of LC neuronal activity and hippocampal ripples across two temporal scales. Both LC firing and ripple occurrence were strongly state-dependent, yet inversely related: periods of heightened arousal were marked by increased LC activity and reduced ripple rates. At a finer temporal resolution, LC spiking consistently decreased approximately 1–2 seconds before ripple onset. The magnitude of peri-ripple LC modulation varied across ripple subsets but was not correlated with ripple intrinsic properties. Notably, the strongest LC modulation occurred around ripples in the awake state, whereas LC activity remained largely unchanged around ripples coupled with sleep spindles during NREM sleep. Together, these findings provide novel insight into the state-dependent

dynamics of cross-regional interactions and highlight the LC as a key component of a large-scale cortical–subcortical network supporting offline information processing.

LC-NE dynamics during NREM sleep and its functional implications

LC activity has long been established to fluctuate with arousal level; it is higher during vigilant states and lower during sleep (***Aston-Jones and Bloom, 1981***). This pioneering work has promoted extensive research that has established the critical engagement of the LC-NE system in many cognitive functions dependent on real-time processing of incoming information (***Berridge and Waterhouse, 2003***; ***Sara and Bouret, 2012***; ***Sara, 2009***). However, only recently has the field begun to uncover the temporal dynamics of LC-NE activity and its functional significance during states of low vigilance, such as NREM sleep. Using opto- and chemogenetic tools, it has been confirmed that LC activation induces awakening, whereas LC inhibition promotes sleep (***Carter et al., 2010***; ***Vazey and Aston-Jones, 2014***). Consistent with earlier studies, we observed cortical state-dependent fluctuation of LC neuronal activity in naturally behaving rats. By quantifying cortical state dynamics during NREM sleep at a 4-s resolution, we found an inverse correlation between the LC firing rate and the degree of cortical arousal as indicated by SI. Furthermore, LC activity during NREM sleep was inversely correlated with the incidence of hippocampal ripples and sleep spindles; the latter result is in agreement with inverse relationships between NE release and the power of spindle oscillations (***Osorio-Forero et al., 2021***). Collectively, these observations suggest the existence of a large-scale coordinated network regulating the NREM sleep microstructure and possibly mediating offline information processing.

In our earlier study, by recording LC spiking activity in naturally behaving rats, we observed a delayed time window of enhanced LC neuron firing, specifically during NREM sleep episodes after learning (***Eschenko and Sara, 2008***). Recent studies in mice uncovered infra-slow (~0.02 Hz) fluctuations of cortical and thalamic NE release during NREM sleep and related the LC activity dynamics to the regulation of sleep microstructure and state transitions (***Osorio-Forero et al., 2021***; ***Kjaerby et al., 2022***). Furthermore, optogenetic LC stimulation at 2Hz during NREM sleep after exposure to a spatial memory task, whilst not affecting ripple occurrence, decreased the stability of replay of hippocampal place cells and caused a memory deficit (***Swift et al., 2018***). This finding aligns with our previous results demonstrating that phasic LC activation time-locked to ripples during post-learning sleep disrupts spatial memory consolidation (***Novitskaya et al., 2016***).

While the mechanisms and functional significance of LC activity patterns during NREM sleep remain to be fully understood (***Foustoukos and Lüthi, 2025***; ***Sara, 2017***; ***Poe, 2017***), these observations align with pharmacological evidence showing that experimental manipulation of NE transmission following learning can alter memory strength (***Przybyslawski et al., 1999***; ***Sara et al., 1999***; ***Roullet and Sara, 1998***; ***Miranda et al., 2009***; ***Gibbs et al., 2010***; ***Gazarini et al., 2013***; ***Gais et al., 2011***). Our recent work suggested a potential network mechanism by which the LC–NE system contributes to sleep-dependent memory consolidation (***Duran et al., 2023***). Specifically, we demonstrated that both $\alpha 2$- and β-adrenoceptors are involved in the generation of hippocampal ripples. Moreover, pharmacological manipulation of noradrenergic transmission after learning altered all major NREM sleep oscillations and their coupling, potentially leading to less efficient spatial memory consolidation (***Duran et al., 2023***). The present findings extend this work by providing new insights into how LC neuronal activity contributes to the expression of normal sleep microarchitecture.

Coerulear-hippocampal interactions for memory consolidation

Hippocampal ripples are broadly recognized as a central mechanism of memory consolidation (***Klinzing et al., 2019***; ***Skelin et al., 2018***). Emerging work has begun to reveal the circuit mechanisms by which hippocampal ripples engage a larger brain network that includes the prefrontal cortex, thalamus, amygdala, and ventral tegmental area (VTA) for offline information processing (***Girardeau et al., 2017***; ***Latchoumane et al., 2017***; ***Gomperts et al., 2015***; ***Wang and Ikemoto, 2016***;

Yang et al., 2019). Our findings expand this memory-supporting circuit to the LC-NE system. By characterizing LC and hippocampal activity at a fine temporal scale, we revealed differential patterns of coerulear-hippocampal interactions. First, we observed consistent transient suppression of LC activity occurring 1-2 seconds before the ripple onset. This cessation of LC neuron spiking and the corresponding depletion of NE might have enabled a network to shift to a transient state of enhanced synchronization, allowing ripple generation. This view is indirectly supported by an increase of the EEG delta power during time windows of peri-ripple LC activity suppression.

Second, we showed that the degree of LC modulation varied across different subsets of ripples. The strongest and most consistent peri-ripple LC inhibition was observed during the awake state. Interestingly, ripples occurring during wakefulness have been associated with stronger and more structured neuron ensemble reactivation, which was correlated with recent experience (***Tang et al., 2017***). Therefore, a transient silence of LC might be beneficial for the ripple-associated reactivation of recent memory traces. Similarly, coordinated activity of reward-related VTA neurons was greater around ripples that were associated with reactivation of neuronal ensembles that relayed recent learning experience (***Gomperts et al., 2015***). Conversely, LC activation induces arousal, shifts the network to a state incompatible with ripple generation, and thereby might cause interference for the consolidation of recently acquired information (***Novitskaya et al., 2016***; ***Swift et al., 2018***).

During NREM sleep, despite substantially reduced LC activity, we observed a fine-tuned LC activity dynamics around ripples. Specifically, LC neuron discharge was only mildly reduced around isolated ripples, and it was largely preserved during ripples co-occurring with sleep spindles. Differential firing patterns for spindle-coupled and -uncoupled ripples have been reported for cortical and thalamic neurons (***Peyrache et al., 2011***; ***Varela et al., 2001***; ***Yang et al., 2019***). During NREM sleep, hippocampal ripples occur in coordination with cortical slow oscillations and sleep spindles (***Maingret et al., 2016***). The precise temporal correlation between the oscillatory patterns expressed during NREM sleep has been causally linked to memory consolidation by mediating the transfer of newly encoded information from the hippocampus to the cortex for long-term storage (***Latchoumane et al., 2017***; ***Buzsaki, 1996***; ***Molle et al., 2006***; ***Maingret et al., 2016***; ***Klinzing et al., 2019***).

At first glance, the suppression of LC activity around ripples that we observed in the present study may seem inconsistent with the established role of NE in facilitating ripple-mediated synaptic plasticity (***Norimoto et al., 2018***; ***Sadowski et al., 2016***). Remarkably, LC activity was indeed preserved around some subsets of ripples, and we showed that these were time windows marking hippocampal-cortical communication mediating offline memory consolidation.

Differential modulation of LC activity that was observed in the present study supports the idea that reduced NE release in the hippocampus might bias the content of memory trace during the subsequent ripples and weaken the reactivation of irrelevant experiences. In general, our results highlight the importance of preserved NE transmission at times of cross-regional information transfer. An overall higher LC firing rate during states of elevated arousal may require a larger dynamic range of LC activity modulation (***Kjaerby et al., 2022***). Therefore, in the awake state, a more pronounced suppression of LC activity may be required for the network shift permitting ripple generation.

In summary, our results demonstrate a state-dependent noradrenergic influence on the thalamocortical–hippocampal circuit and position the LC as part of an extended brain network whose coordinated activity supports system-level memory consolidation. Our results suggest that during wakefulness, transient suppression of noradrenergic transmission facilitates the generation of hippocampal ripples and sleep spindles by enhancing network synchrony. We propose that reduced peri-ripple LC activity during the awake state may preferentially promote the replay of recent memory traces by limiting interference from remote memories, which are more likely to be reactivated in more alert states. In contrast, during NREM sleep, preserved LC activity during ripples coinciding with sleep spindles suggests a role for NE in facilitating cross-regional communication underlying memory-related information transfer. These results provide new insight into how the

LC–NE system shapes memory processing across brain states and open the way for future causal investigations using modern circuit-level tools.

Methods and Materials

Animals

Seven adult male Sprague-Dawley rats were used. Data from one rat has been collected for a previous study ***Eschenko et al.*** (***2012***) and reanalyzed. An additional six rats (Charles River Laboratory, Germany) were kept on a 12-hour light-dark cycle (8:00 am lights on) and single-housed after surgery. Recordings were performed during the dark cycle. Similar surgery and recording procedures were used as reported in detail elsewhere (***Yang et al., 2019***; ***Eschenko et al., 2012***). The study was performed in accordance with the German Animal Welfare Act (TierSchG) and Animal Welfare Laboratory Animal Ordinance (TierSchVersV). This is in full compliance with the guidelines of the EU Directive on the protection of animals used for scientific purposes (2010/63/EU). The study was reviewed by the ethics commission (§15 TierSchG) and approved by the state authority (Regierungspräsidium, Tübingen, Baden-Württemberg, Germany).

Surgery and electrode placement

Procedures for stereotaxic surgery under isoflurane anesthesia have been described in detail elsewhere (***Yang et al., 2019***). Briefly, anesthesia was initiated with 4% and maintained with 1.5-2.0% isoflurane. Body temperature, heart rate, and blood oxygenation were monitored throughout the entire anesthesia period. The depth of anesthesia was controlled by a lack of pain and sensory response (hind paw pinch). A fully anesthetized rat was fixed in a stereotaxic frame with the head angle at zero degrees. The skull was exposed and a local anesthetic (Lidocard 2%, B. Braun, Melsungen, Germany) was applied to the skin edges. Craniotomies were performed on the right hemisphere above the target regions. Additional burr holes were made for EEG, grown, and anchor screws (stainless steel, 0.86-1.19 mm diameter, Fine Science Tools, Heidelberg, Germany). Dura mater was removed when necessary. For extracellular recording, single platinum-iridium electrodes (FHC, Bowdoin, ME) were placed in the anterior cingulate cortex (ACC, AP/ML: 2.8 mm/0.8mm from Bregma and DV: 1.8 mm from the dura surface). For the recording of the hippocampal ripples, the electrode was mounted on a self-made movable microdrive and inserted above the CA1 subfield of the dorsal hippocampus (dHPC, -3mm/2mm/ 2mm). For LC recording, single platinum-iridium electrodes (FHC, Bowdoin, ME, n = 1), microwires brush electrode (MicroProbes, MD, n = 2), and a silicon probe (Cambridge Neurotech, Cambridge, UK, n = 2) are mounted on a microdrive (Cambridge Neurotech, Cambridge, UK) were implanted above LC (4.2 mm/1.2 mm from Lamda; DV: 5.5-6.2 mm) at a 15-degree angle. We also implanted one rat with a polymer electrode array (LLNL, Livermore, CA). The accuracy of LC targeting was verified by online monitoring of neural activity. The LC neurons were identified by broad spike widths (0.6 msec), regular low firing rate (1 –2 spikes/s), and biphasic (excitation followed by inhibition) response to paw pinch. For EEG recording, a screw was placed above the frontal cortex. The ground screw was placed above the cerebellum. Screws were fixed in the skull and additionally secured with tissue adhesive. The entire implant was secured on the skull with dental cement (RelyX™ Unicem 2 Automix, 3M, MN). A copper mesh was mounted around the implant for shielding and protection of exposed connection wires. During the post-surgery recovery period, analgesic (2.5 mg/kg, s.c.; Rimadyl, Zoetis) and antibiotic (5.0 mg/kg, s.c.; Baytril®) were given for 3 and 5 days, respectively. Electrode placements were histologically verified.

Electrophysiological recording and data analysis

Rats were first habituated to the sleeping box (30 x 30 x 40 cm) and cable plugging procedure. The electrodes were either connected to the Neuralynx Digital Lynx or FreeLynx wireless acquisition system via two 32-channel head stages (Neuralynx, Bozeman, MT). The electrode placement in the

LC was optimized by lowering the electrodes with a maximal 0.05 mm step and monitoring spiking activity on the high-passed (300 Hz – 8kHz) extracellular signal. The depth of dHPC electrodes was adjusted by gradually lowering the electrode (maximum 0.05 mm per day) until reliable ripple activity was observed. Once the electrode position was optimized, the broadband (0.1Hz - 8kHz) extracellular signals were acquired and digitized at 32kHz and referenced to the ground screw. The animals' movement was monitored by an EMG electrode attached to the neck muscle. All recordings were performed between 10 a.m. and 7 p.m.

Classification of behavioral states

We classified the rat's spontaneous behavior into awake and NREM sleep using frontal EEG or cortical LFPs by applying a standard sleep scoring algorithm described in detail elsewhere (***Novitskaya et al., 2016***). Briefly, animal movement speed was extracted from the video recording synchronized with a neural signal. The theta/delta (θ/δ) ratio was calculated from the artifact-free EEG in 2.5-sec epochs. The epochs of the awake state were identified by the presence of active locomotion and above θ/δ threshold; the epochs of NREM sleep were identified by the absence of motor activity and below θ/δ threshold. The minimal duration of the same behavioral state was set to 20 sec; data segments with less steady behavioral states were excluded from further analysis.

Event detection

For detection of the hippocampal ripples, a broadband (0.1Hz - 8kHz) extracellular signal recorded from the dHPC (pyramidal layer, CA1 subfield) was band-pass (120 – 250 Hz) filtered, rectified, and low-pass filtered (25Hz). The resulting signal was z-score normalized and ripple oscillations were detected by signal thresholding at 5 standard deviations (SDs). Ascending and descending crossings at 1 SD defined the ripple on- and off-set, respectively. Clustered and isolated ripples were classified based on the inter-ripple interval (IRI) as described in detail elsewhere {Selinger, 2007 #6031}. Briefly, IRIs were extracted and log(IRI) distribution was analyzed. Bimodal log(IRI) distribution indicated ripple occurrence with shorter and longer IRI. A crossing point of two distributions was used for classifying the ripple type. Ripples with short IRI (< 0.33 sec) were classified as 'clustered' and treated as a single ripple event; the onset time was defined by the first ripple in a cluster. Ripples with IRI > 0.33 sec were classified as 'isolated'.

For the detection of sleep spindles, the EEG signal was band-pass (12 - 16 Hz) filtered, downsampled (200 Hz) and the root mean square (0.2 s smoothing) was calculated. The spindle detection threshold was defined at 3 SD of the signal amplitude during NREM sleep episodes. Ascending and descending signal crossings at 1SD defined spindle on- and off-set, respectively. The minimal sleep spindle duration was set to 0.5 sec.

Analysis of peri-event neural activity

For analysis of peri-ripple modulation of LC activity, we used a method described in detail elsewhere (REF). First, the spike times of LC multiunit activity (MUA) were extracted by high-pass (600Hz) filtering of the broadband extracellular signal recorded from LC and thresholding at -0.05 mV. The LC MUA was triggered on ripple/spindle onset and the averaged peri-event spike histogram (PETH) was generated either ± 6 sec or ± 3 sec around all detected ripples and ± 5 sec around sleep spindles (5-ms bins, Gaussian smoothed with a 10 ms-window). To compensate for possible state-dependent fluctuations of LC MUA, a 'surrogate' event sequence was generated by distributing randomly the same number of time points within a 4-second time window around each event; the jittering procedure was repeated 100 times. The averaged PETH was generated around jittered events. Time series of LC MUA around the jittered events were subtracted from the corresponding values around real events and the resulting ('corrected') PETHs were z-score normalized. To further smooth the PETH, we extracted the area above/below the curve of each PETH every 100ms and z-scored the modulation response. To quantify peri-event dynamics of LC MUA, a modulation index (MI) was calculated by modulation response within 1 sec before the event onsets. To determine

the significance of modulation, we calculated the modulation responses around 'shuffled' ripple times generated by permutation of the IRIs and calculated the MIs for each of the 5000 shuffled PETHs; a 95% confidence interval (CI) served as the significance threshold. To quantify the LC MUA modulation around subsets of ripples, subsampled MI (s-MI) was computed for a subset of ripples (20% of all detected ripples in each session), and the same procedure was repeated 5000 times. The s-MI distribution was analyzed.

Spectral analysis

For LFP analysis, we applied the Morlet-wavelet time-frequency analysis to estimate spectral power around ripple onsets. To compare delta and spindle band activity preceding ripples associated with either strong or weak LC activity modulation, we first averaged the spectral power within the delta (1–4 Hz) and spindle (12–16 Hz) frequency bands over a 2-second window prior to ripple onset. We then quantified the power by calculating the area under the curve for each frequency band.

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