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A hypothalamo-septo-hippocampal circuit for REM sleep-dependent consolidation of social memory

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eLife Assessment

This study systematically characterizes the activity patterns of a lateral supramammillary nucleus (SuM)-medial septum (MS)-hippocampus circuit across sleep-wake cycles and its role in memory consolidation. This work is **fundamental** because it identifies a previously unrecognized brain hub that helps coordinate how different types of memory are supported during a specific sleep state, advancing our understanding of how sleep contributes to memory organization. The work is well-designed, and the data are **solid**, supporting clear and significant conclusions; however, some mechanistic details and causal relationships would benefit from further clarification or additional experiments. The paper provides new insights into how distinct memory modalities could be processed by parallel, sleep-active subcortical-hippocampal circuits, which would be of general interest to a broad neuroscience audience.

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Abstract

REM sleep constitutes a critical window for memory consolidation, yet the brain circuits orchestrating this process remain incompletely defined. Here, we identify a lateral supramammillary nucleus (SuM)-medial septum (MS) projection as a REM sleep-specialized pathway essential for hippocampal memory consolidation. Fiber photometry and optrode recordings revealed that lateral SuM-MS projecting neurons were selectively active during REM sleep. REM-specific optogenetic silencing of this projection impaired consolidation of both social and contextual fear memories. Crucially, silencing of its downstream target, the MS-CA2 pathway, during REM sleep selectively disrupted social memory while sparing contextual fear memory. This functional dissection establishes a hypothalamo-septo-hippocampal circuit (lateral SuM-MS-CA2) dedicated to social memory processing, in parallel to the recently-described direct SuM-CA2 pathway. These results also position the SuM as a REM sleep-hub that routes information via parallel septal pathways to consolidate distinct memory modalities.

Introduction

Sleep is a critical period for memory consolidation, during which newly encoded memories undergo a series of active processes to be strengthened and integrated into long-term memory networks (Brodt et al., 2023 [↗](#); Diekelmann and Born, 2010 [↗](#); Rasch and Born, 2013 [↗](#)). This process does not occur uniformly but is accomplished through the synergistic efforts of both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Falup-Pecurariu et al., 2021 [↗](#); Rial et al., 2023 [↗](#)). NREM and REM sleep together form a complementary memory processing system essential for transforming transient experiences into lasting, accessible memory (Ackermann and Rasch, 2014 [↗](#); Kaida et al., 2023 [↗](#)).

The prevailing concept in the field is that memory consolidation during NREM sleep is critically supported by the reactivation of hippocampal neurons through sharp-wave ripples (SWRs) and neocortical slow-waves (Poe et al., 2010 [↗](#)). These coupled oscillatory events are thought to facilitate the redistribution of newly encoded information from the hippocampus to neocortical networks for long-term storage, a process essential for system-level memory consolidation (Born et al., 2006 [↗](#); Buzsáki, 2015 [↗](#); Duan et al., 2025 [↗](#); Robinson et al., 2025 [↗](#)).

Notably, such SWR-mediated reactivation originates primarily in the CA3 region and has been consistently shown to be necessary for the consolidation of spatial memory (Ego-Stengel and Wilson, 2010 [↗](#); Sasaki et al., 2018 [↗](#)). Experimental suppression of SWRs or selective disruption of CA3 neuronal activity during sleep impairs the stabilization of spatial representations, underscoring the functional importance of this mechanism (Ego-Stengel and Wilson, 2010 [↗](#); Fernandez-Ruiz et al., 2019 [↗](#); Girardeau et al., 2009 [↗](#); Roux et al., 2017 [↗](#)). In a similar vein, recent work by Oliva et al. has extended this framework by demonstrating that the reactivation of CA2 pyramidal neurons during SWRs is essential for social memory consolidation (Karaba et al., 2024 [↗](#); Oliva et al., 2016 [↗](#); Oliva et al., 2020 [↗](#)). These findings not only implicate a previously underappreciated hippocampal subregion in sleep-dependent memory processes but also suggest that distinct cell populations within the hippocampus may support the consolidation of different memory types through a shared SWR-mediated mechanism (Xie et al., 2023 [↗](#)).

The REM sleep stage, defined by high-frequency brain activity and vivid dreaming, is considered critical for memory consolidation (Peever and Fuller, 2017 [↗](#)). It has been established that the suppression of medial septal (MS) GABAergic neurons during REM sleep leads to a marked decrease in CA1 theta power, resulting in deficits in spatial and contextual memory (Boyce et al., 2016 [↗](#)). Complementing this, the work by Kumar et al. revealed a reactivation of adult-born neurons in the dentate gyrus (DG) during REM sleep following contextual fear learning, and this reactivation is essential for memory consolidation (Kumar et al., 2020 [↗](#)). Our previous research demonstrated that the hypothalamic supramammillary nucleus (SuM) to hippocampal DG and CA2 pathways are selectively active during REM sleep. We established a causal link through optogenetic interventions, showing that REM-selective silencing of SuM-DG projections impairs spatial and contextual fear memory, whereas similar silencing of SuM-CA2 projections specifically disrupts social memory consolidation (Qin et al., 2022 [↗](#)). Furthermore, Liu et al. elucidated how oxytocin modulates the inhibitory balance in the prefrontal cortex to promote social memory consolidation during REM sleep (Liu et al., 2025 [↗](#)). Despite these advances, a key question remains: whether additional neural pathways are involved in REM sleep-related social memory consolidation.

SuM and MS are interconnected subcortical hubs that collectively influence a range of behavioral states and cognitive functions. The SuM regulates processes such as episodic memory (Luo et al., 2025 [↗](#); Qin et al., 2022 [↗](#)), social and contextual novelty detection (Chen et al., 2020 [↗](#)), and wakefulness (Pedersen et al., 2017 [↗](#)), whereas the MS, composed of cholinergic, GABAergic, and glutamatergic neurons (Hajszan et al., 2004 [↗](#); Kiss et al., 1990 [↗](#)), is critical for hippocampal theta generation (Buzsáki, 2002 [↗](#); Király et al., 2023 [↗](#)), memory and the modulation of arousal (An et al., 2021 [↗](#); Osborne, 1994 [↗](#)). Building upon this anatomical and functional background, we previously investigated the SuM-MS pathway and found that its activation potently promotes wakefulness (Liang et al., 2023 [↗](#)). Furthermore, we identified two functionally distinct

subpopulations within this pathway: wake-active and REM-active neurons. Although the wake-active neurons have been causally linked to arousal control, the functional role of the concomitant REM-active neurons remains unknown.

In this study, we employed a comprehensive approach combining optical Ca^{2+} imaging, optrode recordings, and optogenetics to investigate the role of REM sleep in consolidating social memory via a specific hypothalamic-septal-CA2 circuit in mice. We identified a distinct neuronal ensemble within the lateral SuM that projects to the MS and is selectively active during REM sleep. Crucially, REM-selective optogenetic silencing of these SuM-MS projecting neurons impaired both contextual and social memory consolidation. Furthermore, optogenetic inhibition of the downstream MS-CA2 projection during REM sleep selectively disrupted social memory, while sparing contextual fear memory. Together, our findings provide evidence that a population of SuM neurons supports social memory consolidation through its REM sleep-locked activity and targeted influence on the septo-hippocampal route.

Results

Lateral SuM-MS projecting neurons are strongly active during REM sleep

SuM neurons have been reported to project to both MS region and hippocampus (Vertes, 1992 [↗](#)). We labeled the MS-projecting and hippocampus-projecting SuM neurons by injecting a retrograde AAV vector expressing enhanced green fluorescent protein (EGFP) into MS, and a retrograde AAV vector expressing red fluorescent protein mCherry into hippocampal DG respectively (Figure 1a [↗](#)). We verified the expression area of EGFP in MS and mCherry in hippocampus by post-hoc histology (Figures 1b [↗](#) and 1c [↗](#)). And the EGFP-and mCherry-labeled cell bodies were observed in SuM in serial sections (Figure 1d [↗](#)). The mCherry-labeled neurons were mainly located in the lateral SuM, while the EGFP-labeled ones were distributed in both medial and lateral SuM (Figure 1d [↗](#)). The co-labelling rate of EGFP and mCherry neurons was relatively low, which was less than 5% (Figure 1e [↗](#)). These results suggest that lateral SuM neurons provide projection to both MS and hippocampus.

A previous study has demonstrated that Ca^{2+} activity in the axonal terminals of SuM-MS projection was activated during both wakefulness and REM sleep (Liang et al., 2023 [↗](#)). However, while these recordings encompassed the entire population of SuM-MS projection (Liang et al., 2023 [↗](#)), the activity patterns of those originating specifically from the lateral SuM during the sleep-wake cycle remain uncharacterized. To address this, we employed a circuit-specific fiber photometry system combined with electroencephalogram (EEG) and electromyogram (EMG) recordings to monitor Ca^{2+} dynamics of lateral SuM-MS projecting neurons in freely moving mice. We injected retroAAV-GCaMP6m into MS to selectively express the calcium indicator GCaMP6m in SuM-MS projecting neurons (Figure 2a [↗](#)). Three weeks post-injection, an optical fiber was implanted above the lateral SuM for Ca^{2+} recording, while EEG and EMG electrodes were affixed to the cortical surface and neck muscles, respectively, to monitor behavioral states (Figure 2a [↗](#)). Viral expression and fiber location were confirmed histologically after recordings (Figure 2b [↗](#)). Notably, lateral SuM-MS projecting neurons exhibited higher Ca^{2+} activity during REM sleep compared to NREM sleep and quiet wakefulness (QW, representative trace in Figure 2c [↗](#); summary in Figure 2d [↗](#)). Furthermore, activity robustly increased during transitions from NREM to REM sleep (Figure 2g [↗](#)) but declined sharply upon transitions from REM sleep to QW (Figure 2h [↗](#)).

To further characterize the firing patterns of lateral SuM-MS projecting neurons at the single-cell level, we performed optrode recordings across sleep-wake cycles. Specifically, we expressed channelrhodopsin-2 (ChR2) selectively in these neurons by injecting a retrograde Cre-dependent AAV (retroAAV-Cre) into MS and a Cre-dependent AAV encoding DIO-ChR2-mCherry into SuM (Figure 3a [↗](#)). An optrode was then implanted in lateral SuM to identify and record from SuM-MS projecting neurons (Figure 2a [↗](#); optrode placement shown in Figure 2b [↗](#)). To identify MS-projecting units, we applied blue light pulses (450 nm, 2 Hz, 10 ms duration, 10 mW). Neurons were classified as MS-projecting if they exhibited short-latency, low-jitter spiking with a high

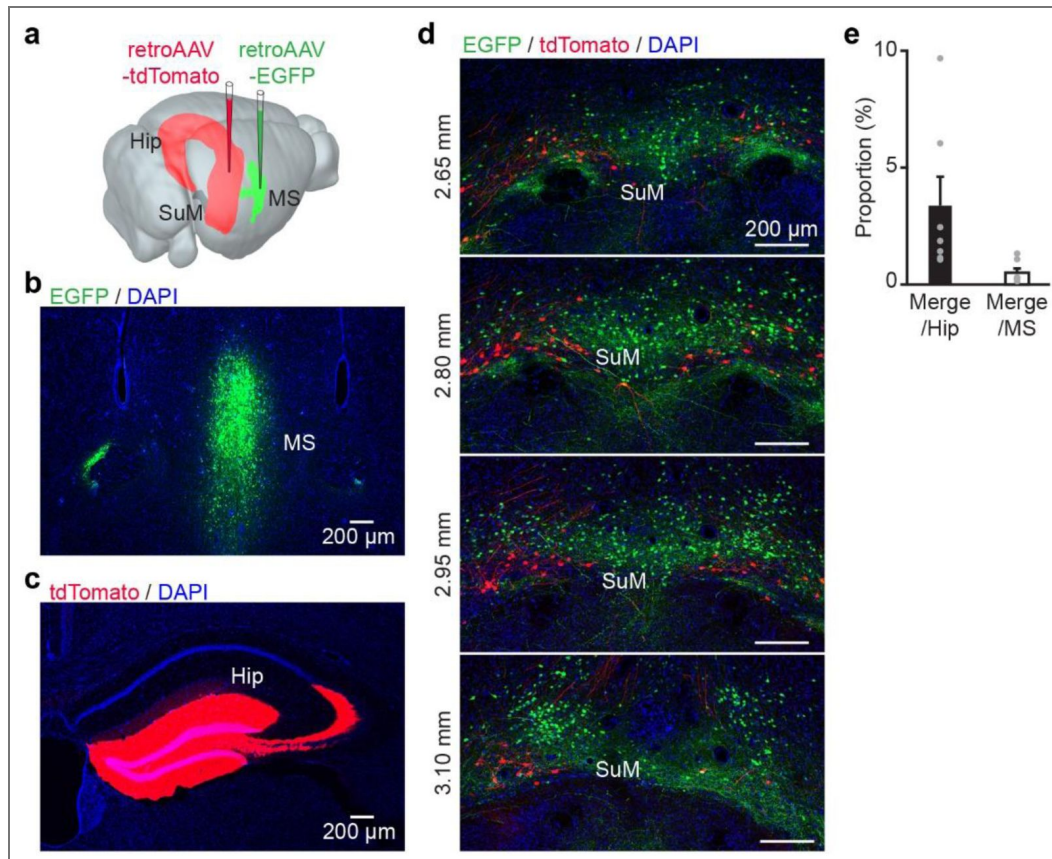


Figure 1. Retrograde labeling of MS-projecting SuM neurons.

a, Diagram of retroAAV-EGFP injection into MS and retroAAV-tdTomato injection into hippocampus. **b,c**, Post-hoc histological images showing the expression of EGFP at the injection site of MS (**b**), and the expression of tdTomato at the injection site of hippocampus (**c**). **d**, Representative serial sections showing the eGFP- and tdTomato-labeled cell bodies in SuM. **e**, Summary of co-labelling proportion of SuM-Hip and SuM-MS projecting neurons, $n = 6$ mice. SuM, supramammillary nucleus; MS, medial septum; Hip, hippocampus.

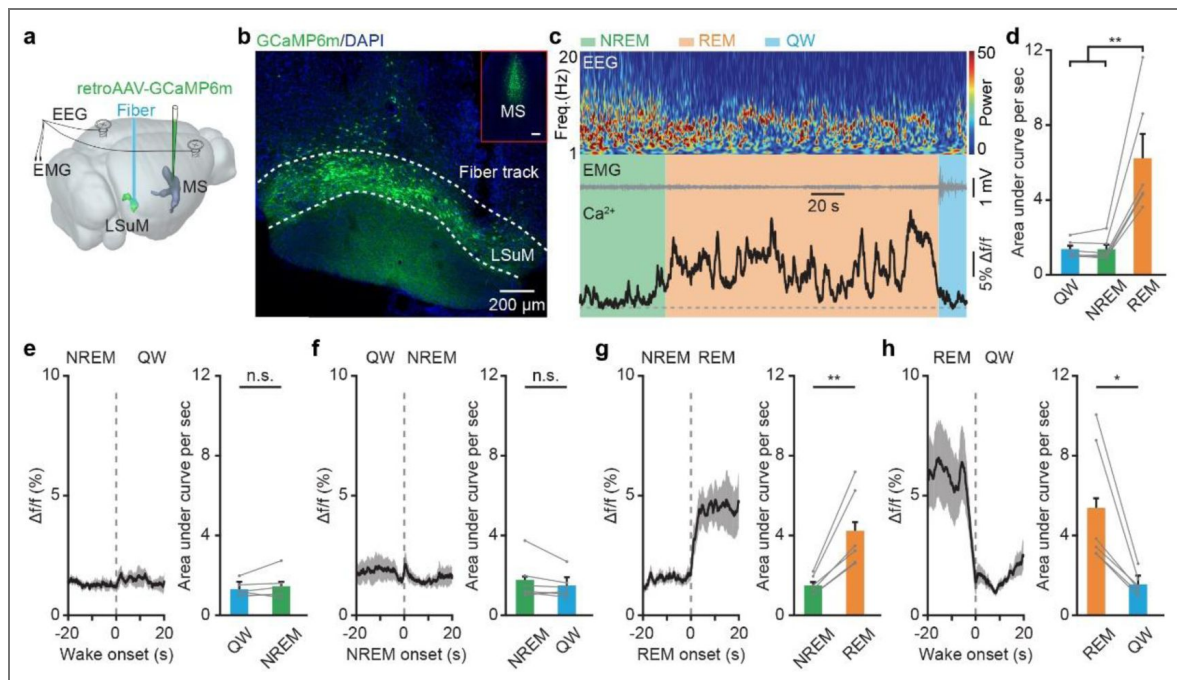


Figure 2. Ca^{2+} recording of lateral SuM-MS projecting neurons across sleep-wakefulness cycle.

a, Experimental design for virus injection in MS and fiber implantation in lateral SuM. **b**, Post-hoc histological image showing the expression of GCaMP6m at injection site in MS (insert) and in SuM cell bodies, and optical fiber location in lateral SuM. **c**, Ca^{2+} activities in lateral SuM-MS projecting neurons across sleep-wakefulness cycles. Color map indicates power spectrum (μV^2) of EEG, Freq., frequency. **d**, Summary of the area under the curve per second during wake, NREM sleep, and REM sleep. $n = 6$ mice, RMs 1-way ANOVA with LSD post-hoc comparison. **e-h**, Ca^{2+} activities during brain state transitions: wake-to-NREM (e), NREM-to-wake (f), NREM-to-REM (g), and REM-to-wake (h). $n = 6$ mice, paired t test. n.s. $P > 0.05$, * $P < 0.05$, ** $P < 0.01$. Data are reported as mean $\pm$ SEM.

success rate and a spike waveform highly correlated with spontaneous spike (mean latency: 3.61 ± 0.27 ms; jitter: 0.73 ± 0.13 ms; success rate: $90\% \pm 2\%$; correlation coefficient: 0.91 ± 0.02 ; $n = 29$ neurons; Figures 2e–2g).

We found that the majority of lateral SuM-MS projecting neurons (26 of 29 units from 15 mice) exhibited a significant increase in firing rates upon transition from NREM to REM sleep, followed by a marked decrease when transitioning from REM sleep to QW (example in Figure 3h; summary in Figure 3i; REM: 11.6 ± 2.0 Hz, NREM: 4.2 ± 0.9 Hz, QW: 4.9 ± 1.0 Hz; Friedman test with Bonferroni correction, $p < 0.001$). Analysis of firing patterns across tagged and untagged neurons recorded with the same tetrodes revealed that approximately 90% of tagged neurons were REM-active, with the remaining 10% active primarily during NREM sleep. In contrast, among untagged neurons ($n = 130$), about 41% showed high activity during REM sleep, while the rest were predominantly active during NREM sleep (31%) or QW (28%; Figures 3j and 3k). Collectively, these results indicate that lateral SuM-MS projecting neurons are highly active during REM sleep, but not during QW.

Silencing of Lateral SuM-MS projecting neurons during REM sleep impairs both social and contextual memory

Previous studies have revealed that strong activation of SuM-CA2 projection during REM sleep promotes social memory consolidation (Qin et al., 2022). It remains unknown whether the similarly strong activation of lateral SuM-MS projection contributes to hippocampal memory consolidation during REM sleep. To address this, we tested hippocampus-dependent memory after REM sleep-specific silencing of the lateral SuM-MS projection using projection-targeted optogenetics. Specifically, the inhibitory opsin *Guillardia theta* anion-conducting channelrhodopsin 1 (GtACR1, Govorunova et al., 2015) was expressed in lateral SuM-MS projecting neurons via retrograde AAV-Cre injected into the MS and Cre-dependent AAV-DIO-GtACR1-mCherry delivered into the lateral SuM (Figures 4a and 4b). We first investigated whether silencing these neurons affects hippocampal CA1 activity during REM sleep by recording local field potentials (LFP). Photoinhibition did not alter LFP power in the dorsal CA1 across the 0–30 Hz frequency range, which includes delta, theta, alpha, and beta rhythms (Figures 4c, d). This contrasts with earlier reports in which silencing other neuronal populations, MS GABAergic neurons (Boyce et al., 2016) or SuM-DG projecting neurons (Qin et al., 2022), significantly reduced theta rhythm in the dorsal CA1.

We next examined the effect of REM sleep-selective silencing of lateral SuM-MS projection on social memory consolidation using the three-chamber social memory test (Hitti and Siegelbaum, 2014). During the training phase, subject mice were allowed to freely explore two chambers for 20 min: one containing an unfamiliar stimulus mouse and the other empty (Figure 4e). All groups showed a significant preference for the chamber with the stimulus mouse during training (Figure 4f top; 201.1 ± 20.9 s vs. 76.7 ± 7.8 s; $P = 0.00003$, Wilcoxon signed-rank test, $n = 23$ mice). A social preference index was calculated based on cumulative exploration time in the two chambers. No significant difference in this index was observed among the GtACR1, mCherry control, and GtACR1 control groups during training (Figures 4g; $P = 0.71$, 1-way ANOVA test). During the first 8 hours post-training (the memory consolidation phase), optogenetic silencing was delivered via implanted optical fibers to lateral SuM-MS projecting neurons. In both the GtACR1 group and the mCherry control group, blue light illumination began approximately 6 seconds after REM sleep detection and continued until the end of each REM episode. In the GtACR1 control group (which also expressed GtACR1 in lateral SuM-MS neurons), light was delivered during NREM sleep or QW for durations matched to the total REM-light time in the experimental group.

On day 2 of testing, mice freely explored a chamber containing a familiar mouse and another chamber with a novel mouse (Figure 4e). As conspecifics typically prefer novel social interactions, control groups were expected to show a novelty preference. The GtACR1 group, however, exhibited no significant preference between the novel and familiar mice (Figure 4f bottom left; 150.1 ± 19.5 s vs. 193.4 ± 24.5 s; $P = 0.2$, Wilcoxon signed-rank test, $n = 8$ mice). In contrast, both the GtACR1 control group (Figure 4f bottom right; 178.8 ± 51.3 s vs. 85.4 ± 24.3 s; P

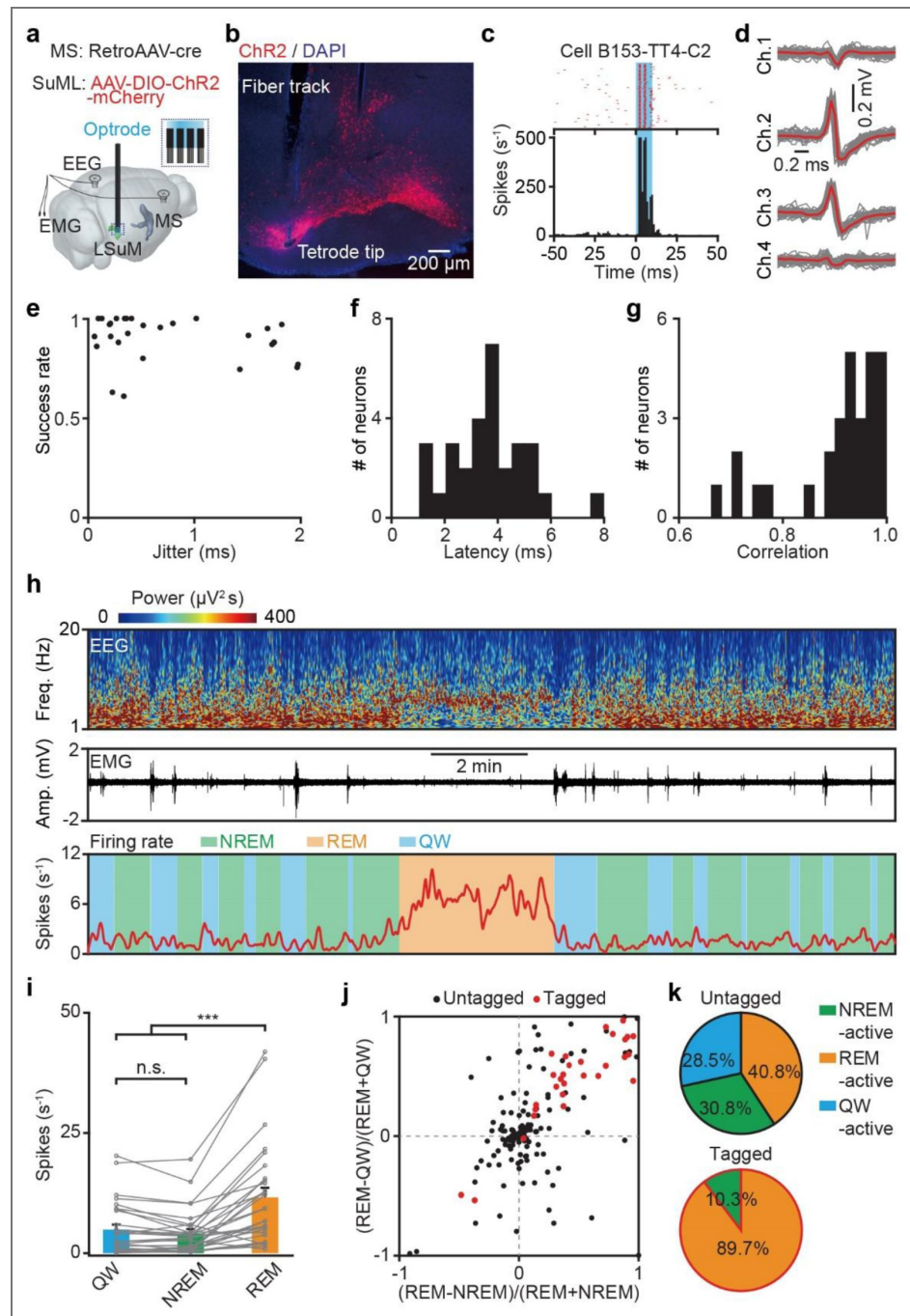
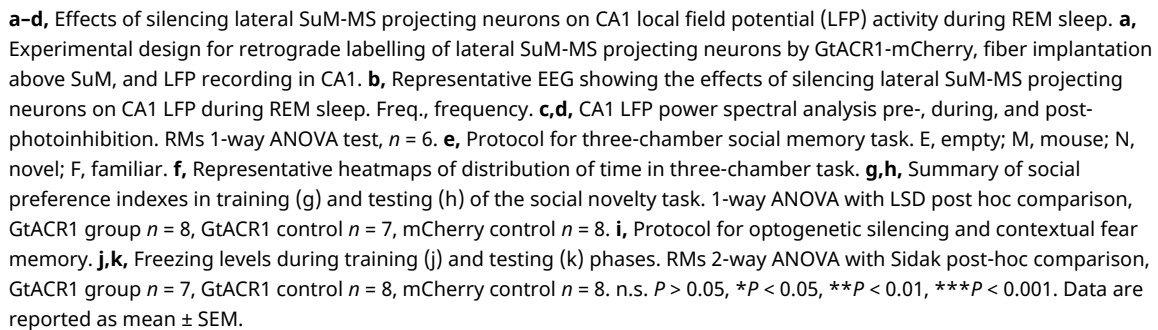


Figure 3. activity patterns of single lateral SuM-MS projecting neurons across sleep-wakefulness cycle.

a, Experimental design for virus injection and optrode implantation in the lateral SuM-MS projection. **b**, Representative image showing virus expression and locations of fiber and tetrode tips in lateral SuM. **c**, Histogram of stimulus time for spikes in a representative lateral SuM-MS projecting neuron (Cell#B153-TT4-C2). **d**, Waveforms of spontaneous (grey) and light-induced (red) spikes from the unit in (c). **e**, Success rate versus temporal jitter of the first light-induced spikes for all recorded lateral SuM-MS projecting neurons, $n = 29$ neurons from 15 mice. **f, g**, Distributions of latencies of the first light-induced spikes (f), and correlation coefficients between light-induced spikes and spontaneous spikes (g) for all recorded lateral SuM-MS projecting neurons, $n = 29$ neurons from 15 mice. **h**, Firing rate of the neuron in (c) across sleep-wakefulness cycles. Freq., frequency. QW, quiet wakefulness. **i**, Firing rates of 29 tagged lateral SuM-MS projecting neurons during three different states. Friedman test with Bonferroni post-hoc comparison. **j**, Firing rate modulation of lateral SuM-MS projecting neurons (red, $n = 29$ neurons from 15 mice) and non-MS-projecting lateral SuM neurons (black, $n = 130$ neurons from 15 mice). **k**, Distribution of REM-active, NREM-active and QW-active neurons of MS-projecting and non-MS-projecting lateral SuM neurons. n.s. $P > 0.05$, *** $P < 0.001$. Data are reported as mean $\pm$ SEM.



= 0.02, $n = 7$ mice) and the mCherry control group (265.5 ± 31.3 s vs. 124.1 ± 10.6 s; $P = 0.01$, $n = 8$ mice) retained a clear preference for the novel mouse. Consistent with these findings, the social preference index was significantly lower in the GtACR1 group compared to both control groups (Figure 4h; GtACR1 vs. GtACR1 control, $P = 0.0008$; vs. mCherry control, $P = 0.0006$; 1-way ANOVA with Bonferroni post hoc comparison).

We further employed contextual fear conditioning to investigate how silencing lateral SuM-MS projecting neurons during REM sleep affects contextual memory consolidation. First, mice were trained via contextual fear learning on day 1 (Figures 4i). During training, mice showed a significant high freezing level after three paired training (Figure 4j; trained 0.55 ± 0.02 vs. baseline 0.24 ± 0.02 ; $P < 0.001$, paired t -test, $n = 23$ mice), with no significant difference in freezing level among the GtACR1, mCherry control and GtACR1 control groups (Figure 4j; $P = 0.4$, 1-way ANOVA). Within the first 8 hours after training, optogenetic inhibition was delivered to lateral SuM-MS projecting neurons selectively during REM sleep (GtACR1 and mCherry control groups) or during NREM/QW (GtACR1 control group). At 24 hours post-training, mice were re-exposed to the conditioned context for 10 min. The GtACR1 group exhibited significantly lower freezing levels compared to both the mCherry control group and the GtACR1 control group (Figure 4k; RMs 2-way ANOVA with Sidak post hoc comparison, $P = 0.003$). Together, these results demonstrate that the lateral SuM-MS projection plays a critical role in consolidating both contextual and social memory during REM sleep.

Silencing of MS-CA2 projecting neurons during REM sleep impairs social but not contextual memory

Previous studies have established the involvement of MS GABAergic neurons in REM sleep-dependent contextual memory consolidation (Boyce et al., 2016). In addition, inhibition of the projection from MS to CA2 has been shown to disrupt social memory encoding (Wu et al., 2021). However, whether the MS-CA2 projection contributes to social memory consolidation remains unclear. To investigate this, we specifically labeled MS-CA2 projecting neurons with GtACR1 by injecting retroAAV-Cre into CA2 and AAV-DIO-GtACR1-mCherry into MS (Figure 5a). We first performed the three-chamber social test to assess the effect of REM-selective silencing of MS-CA2 projection on social memory. Overall, mice spent significantly more time interacting with the social stimulus chamber than the empty chamber (Figure 5b top for example and Figure 5c for summary) in the training phase in all groups. We then applied optogenetic silencing specifically during REM sleep in the 8-hour period following training. When retested 24 hours later with a familiar versus a novel mouse, the GtACR1 group exhibited a significantly reduced social preference index compared to both control groups (Figure 5d; GtACR1: 0.02 ± 0.02 , GtACR1 control: 0.26 ± 0.04 , mCherry control: 0.28 ± 0.04 ; 1-way ANOVA with LSD post hoc comparison, GtACR1 vs. GtACR1 control: $P = 5E-5$, GtACR1 vs. mCherry control: $P = 7E-6$).

We next examined the effect of silencing MS-CA2 projections during REM sleep on contextual fear memory. Mice underwent contextual fear conditioning (Figure 5e), after which MS-CA2 neuronal activity was optogenetically silenced during REM sleep as previously described. During memory retrieval on day 2, no significant differences in freezing level were observed among the three groups (Figure 5f, RMs 2-way ANOVA, $P = 0.5$). Together, these results demonstrate that the MS-CA2 projection, as a downstream pathway of the SuM-MS circuit, is essential for REM sleep-dependent consolidation of social memory but not contextual memory, thereby completing the picture of a dedicated hypothalamo-septal-hippocampal circuit for sleep-dependent social memory processing.

Discussion

Previous work has highlighted the role of SuM-DG and SuM-CA2 projections in REM sleep-dependent memory consolidation (Qin et al., 2022). In contrast, the functional role of SuM-MS pathway is less clear. While it has been implicated in promoting wakefulness (Duan et al., 2025; Li et al., 2025; Li et al., 2025; Liang et al., 2023), the contribution of its REM-active neuronal

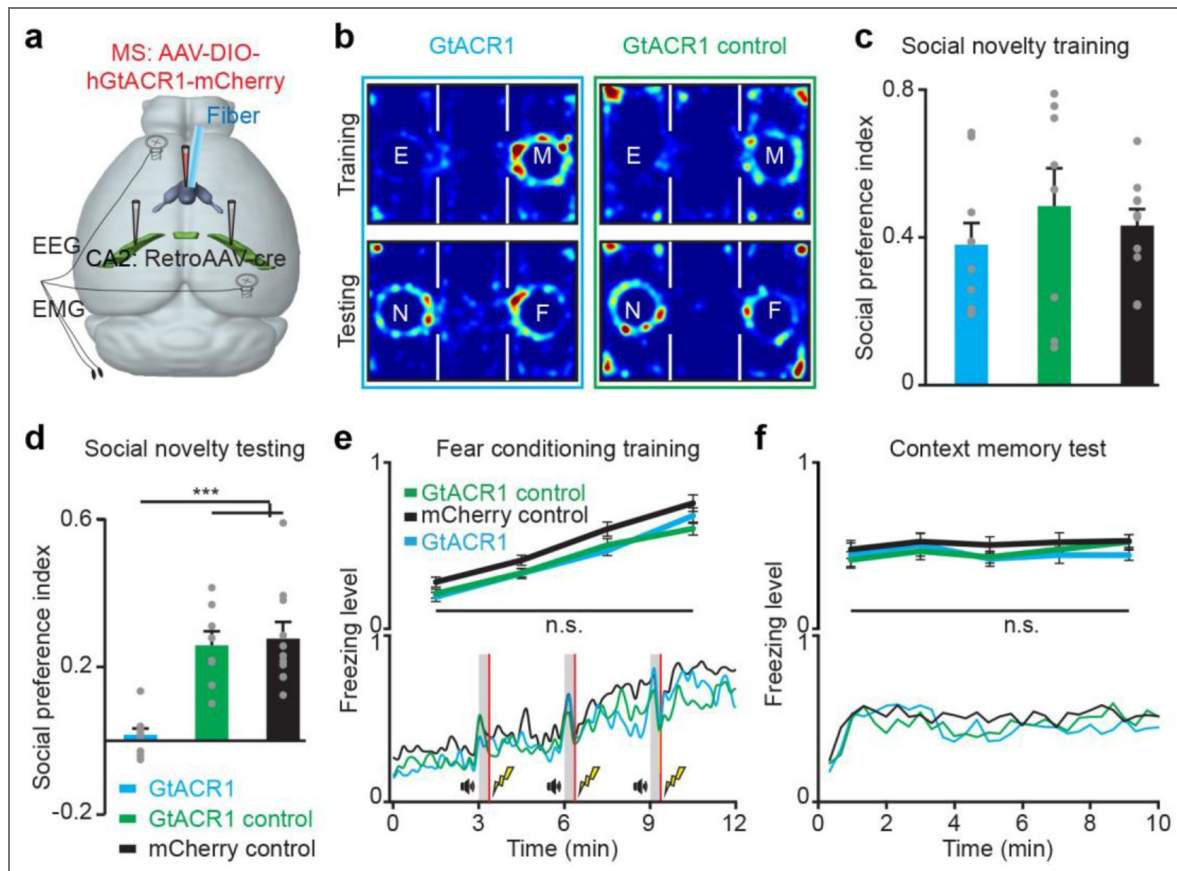


Figure 5. Optogenetic silencing of MS-CA2 projecting neurons during REM sleep impairs social but not contextual fear memory.

a, Experimental design for retrograde labelling of MS-CA2 projecting neurons by GtACR1-mCherry, and fiber implantation above MS. **b**, Representative heatmaps of distribution of time in three-chamber task. **c,d**, Summary of social preference indexes in training (**c**) and testing (**d**) of the social novelty task. 1-way ANOVA with Bonferroni post hoc comparison; GtACR1 group $n = 10$, GtACR1 control $n = 8$, mCherry control $n = 11$. **e,f**, Freezing levels during training (**e**) and testing (**f**) phases. RMS 2-way ANOVA test; GtACR1 group $n = 8$, GtACR1 control group $n = 10$, mCherry control $n = 11$. n.s. $P > 0.05$, *** $P < 0.001$. Data are reported as mean $\pm$ SEM.

subpopulation remains undefined. Here, by combining recording and manipulation of the lateral SuM-MS subpopulation, we show that it is specifically activated during REM sleep and, together with the downstream MS-CA2 projection, serves as a critical circuit for social memory consolidation. These findings suggest that the SuM may orchestrate distinct aspects of sleep-related cognition through functionally specialized subcircuits.

Our results further delineate a functional dissociation within the supramammillary-septo-hippocampal system. While the MS-DG projection is known to consolidate contextual fear memory by gating dentate gyrus granule cell activity (Boyce et al., 2016; Delorme et al., 2021), and the MS-CA2 projection is essential for social memory encoding (Wu et al., 2021), whether the latter also contributes to social memory consolidation remained unclear. Here, by REM sleep-selective inhibition of the MS-CA2 pathway, we demonstrate its necessary role in consolidating social memory during REM sleep. Collectively, these findings suggest that newly encoded social information in CA2 and contextual information in DG may be reactivated and consolidated both through parallel circuits: the direct supramammillary-hippocampal route (Qin et al., 2022) and the indirect supramammillary-septo-hippocampal pathway (Kiss et al., 2000).

Notably, we found that the SuM-MS pathway did not modulate hippocampal theta rhythms in dorsal CA1, in contrast to the established roles of the SuM-DG projection (Qin et al., 2022) and MS GABAergic neurons in theta generation (Boyce et al., 2016). Anatomically, SuM neurons primarily synapse onto glutamatergic neurons within the MS (Duan et al., 2025; Kesner et al., 2021; Liang et al., 2023). Functionally, MS glutamatergic neurons provide broad excitatory drive: they innervate both cholinergic and GABAergic neurons within the septum (Manseau et al., 2005; Robinson et al., 2016) and project to hippocampal pyramidal cells and interneurons (Huh et al., 2010; Sun et al., 2014). The theta entrainment observed upon direct optogenetic activation of MS glutamatergic neurons (Fuhrmann et al., 2015; Robinson et al., 2016) may be indirectly mediated by their strong excitatory drive onto local GABAergic neurons (Manseau et al., 2008; Robinson et al., 2016), which are known pacemakers for this rhythm (Borhegyi et al., 2004; Buzsáki, 2002). Future studies employing direct silencing of MS glutamatergic neurons could further clarify their necessity in hippocampal theta generation. Collectively, these observations suggest that the SuM-MS circuit may support memory consolidation through mechanisms largely independent of global theta synchrony—possibly by modulating synaptic plasticity within specific hippocampal subfields during REM sleep (Aime et al., 2022; Malenka and Bear, 2004).

Methodologically, the pathway-specific tools employed here were crucial for delineating functional heterogeneity within the SuM-MS pathway. From an anatomical perspective, the SuM can be subdivided into medial and lateral subregions, which differ in their cellular composition and in their efferent-afferent circuit organization (Pan and McNaughton, 2004; Vertes, 1992). Our findings reveal a notable regional specialization: lateral SuM-MS projectors are predominantly REM-active (~90%) and lack detectable wake-active populations, in contrast to the mixed wake/REM profile previously described for medial projectors (~43% REM-active, ~57% wake-active, Liang et al., 2023). This suggests that REM-active neurons, particularly in the lateral SuM, are key drivers of the observed REM-related memory effects, although contributions from medial SuM REM-active or wake-active subgroups cannot be excluded. Consequently, future work should refine methods to selectively manipulate REM-active SuM-MS neurons and systematically compare the roles of medial versus lateral SuM subregions in diverse behaviors, including arousal, locomotion, and memory.

In summary, we reveal a supramammillary-septo-hippocampal circuit that is selectively active during REM sleep and necessary for social memory consolidation. Building on prior work, our findings support a model in which the SuM functions as a REM-hub, directing information via specialized downstream pathways to consolidate distinct memory types. This provides a novel framework for understanding how subcortical-hippocampal interactions during REM sleep govern memory consolidation.

Methods

Animals

Adult male C57BL/6CJ mice (3–5 months old) were used in this study. Mice were group-housed (4–5 per cage) unless implanted with optical fibers or tetrodes, in which case they were singly housed. All animals were maintained on a 12 h light/dark cycle (lights on at 7:00) with ad libitum access to food and water. All experimental procedures were approved by the Third Military Medical University Animal Care and Use Committee and conducted in accordance with their guidelines and protocols.

AAVs

The following adeno-associated virus (AAV) constructs were used: AAV2/8-EF1 α -EGFP (titer: 1.49×10^{13} vp/mL), AAV2/2Retro-Syn-GCaMP6m (titer: 1.92×10^{13} vp/mL), AAV2/2Retro Plus-Syn-Cre (titer: 1.92×10^{13} vp/mL), AAV2/9-EF1 α -DIO-hChR2-mCherry (titer: 3.67×10^{13} vp/mL), AAV2/9-Syn-DIO-hGtACR1-mCherry (titer: 1.43×10^{13} vp/mL), AAV2/9-Syn-DIO-mCherry (titer: 1.23×10^{13} vp/mL). All AAVs were purchased from Taitool Bioscience Co., Ltd. (Shanghai, China).

Surgical Procedures

For all surgeries, mice (2–3 months old) were anesthetized with isoflurane (3% induction, 1–2% maintenance in oxygen) and secured in a stereotaxic frame. Body temperature was maintained at 37.5–38°C using a heating pad. Following surgery, mice were returned to warmed cages for full recovery and received daily intraperitoneal injections of dexamethasone sodium phosphate (1 mg/mL; 0.1 mL per 10 g body weight) and ceftriaxone sodium (50 mg/mL; 0.1 mL per 10 g body weight) for three consecutive days to mitigate post-operative inflammation.

For stereotactic injection, viral vectors were pressure-injected using a glass micropipette (tip diameter: 10–20 μ m) into target brain regions at the following coordinates (relative to bregma, mm): SuM, AP: –2.8, ML: $\pm$ 0.5, DV: –5.0 (from dura); MS, AP: 1.0, ML: 0.5, 5° angle toward the midline, DV: 3.8; CA2, AP: –1.8, ML: $\pm$ 2.45, DV: –1.55; DG, AP: –1.8, ML: $\pm$ 1.1, DV: –1.85. Injections were unilateral for tracing/recording experiments and bilateral for behavioral experiments. Viruses were allowed a minimum expression period of 4 weeks prior to subsequent experiments.

For optical fiber implantation, mice expressing GCaMP6m in SuM-MS projection were used. A 200- μ m diameter, 0.53 NA optical fiber (Doric Lenses, MFP_200/230/900-0.53) was glued into a metal cannula (ID 0.51 mm, OD 0.82 mm) with a flat-polished end. The prepared fiber probe was lowered through a cranial window above the lateral SuM (AP: –2.8 mm, ML: 0.5 mm) to the depth of 5.0 mm. The cannula was secured to the skull using blue light-curing dental cement (Tetric EvoFlow). Additional dental cement and cyanoacrylate glue provided reinforcement. The outer surface was coated with black acrylic paint to prevent light leakage. For EEG and EMG electrode implantation, three EEG screws were placed over the skull: two above the frontal cortex (AP: +1.5 mm, ML: $\pm$ 1.5 mm) and one above the parietal cortex (AP: –3.0 mm, ML: +3.0 mm). Two EMG wires were inserted into the nuchal muscles. All electrodes were secured using blue light-curing dental cement, followed by reinforcement with additional dental cement and cyanoacrylate glue.

For optrode implantation, mice expressing ChR2 in SuM-MS projection were used. A custom optrode (Yang et al., 2023 [DOI](#)) was mounted on a microdrive, consisting of four linearly arranged 25- μ m tungsten wire tetrodes spaced at 200- μ m intervals, with tips extending approximately 500 μ m beyond a 200- μ m diameter, 0.37 NA optical fiber. The optrode was initially positioned above the lateral SuM (AP: –2.8 mm, ML: 0.5 mm, DV: –4.7 mm). EEG/EMG electrodes were implanted as described previously. Following one week of recovery, the optrode was gradually advanced to the target depth (–5.0 mm). Finally, an electrolytic lesion (100 μ A, 10 s) was applied to mark the recording site for subsequent histological verification.

For fiber ferrule implantation, mice expressing GtACR1-mCherry or mCherry bilaterally in SuM-MS or MS-CA2 projection were used. Fiber ferrules (200 μ m diameter, 0.37 NA) were implanted above SuM (AP: –2.8 mm, ML: $\pm$ 2.0 mm, DV: –4.6 mm, angled 20° towards midline) or MS (AP: 1.0

mm, ML: 0.5 mm, 5° angle toward the midline, DV: 3.8 mm).

Fiber Photometry Recording

Mice implanted with optical fibers above lateral SuM with SuM-MS projecting neurons expressing GCaMP6m were used. Ca²⁺ signals, EEG/EMG signals, and behavioral videos were recorded simultaneously across sleep-wake cycles. Signals were acquired at 2000 Hz for Ca²⁺, 200 Hz for EEG/EMG, and 25 Hz for video. All data streams were synchronized offline using event markers.

Behavioral Tasks

Mice were handled for 5 min/day for continuous 3 days prior to behavioral habituation. All tasks were conducted between 7:00 - 8:00 am. Optogenetic silencing (473 nm, ~3 mW per ferrule tip, controlled via LabVIEW) was applied bilaterally to SuM-MS projecting neurons during identified REM sleep episodes in GtACR1-expressing or mCherry control group for social and contextual fear memory tasks. In an additional GtACR1 control group, light was delivered during NREM or wakefulness for equivalent cumulative durations.

Three-chamber Social Test

The three-chamber social test was employed to assess social memory, as previously described (Qin et al., 2022 [DOI](#)). The apparatus consisted of a rectangular box (75 cm × 50 cm × 40 cm) divided into three equally sized chambers (each 25 cm × 50 cm) by transparent acrylic partitions. Two transparent cylinders (diameter: 12 cm) with wall air holes were used to contain stimulus mice. On day 1, the subject mouse was habituated to the apparatus during a 10-min session with both cylinders empty. On day 2 (training), the mouse explored for 20 min with one cylinder containing a novel stimulus mouse and the other remaining empty. EEG/EMG recording began immediately after training and continued for the subsequent 8 h. NREM and REM sleep episodes were manually identified based on the scoring criteria detailed later for silencing interventions. In the GtACR1 silencing group and the mCherry control group, blue light was delivered continuously to the SuM starting ~6 s after REM sleep detection and persisting until the end of each REM episode. In the GtACR1 control group, blue light was administered during NREM sleep or quiet wakefulness for a cumulative duration matched to the total REM-light time in the experimental group. On day 3 (test), the subject mouse was reintroduced to the apparatus for a 20-min session, during which one cylinder contained the now-familiar mouse and the other contained a novel mouse. Time spent investigating each cylinder was recorded and the social preference index was calculated as:

$$\text{Social preference index} = (\text{Time}_{\text{Novel}} - \text{Time}_{\text{Familiar}}) / (\text{Time}_{\text{Novel}} + \text{Time}_{\text{Familiar}}).$$

Contextual Fear Conditioning

The task was conducted to test contextual memory as previously described (Boyce et al., 2016 [DOI](#)). On the first day (training), after a 260-s baseline period, each subject mouse received three pairings of a conditioned auditory stimulus (CS: 8964 Hz pure tone, 20 s, 70 dB SPL) followed by an unconditioned stimulus (US: 2 s, 0.6 mA footshock), with 180 s intervals between pairings. EEG/EMG were recorded for 8 h immediately after training, and optogenetic silencing was applied as described earlier. Fear memory was tested 24 h after training. Contextual memory was assessed by re-exposing the mouse to the training context for 10 min. Freezing level was quantified based on the absence of body movement.

Sleep Analysis

EEG and EMG signals were first filtered (0.5–30 Hz and 10–70 Hz, respectively). Sleep-wake states were then determined based on visual inspection of the following features: wakefulness exhibited low-amplitude, high-frequency EEG with elevated EMG; NREM sleep showed high-amplitude delta (0.5–4 Hz) EEG and low EMG tone; REM sleep was marked by theta-dominated EEG (4–10 Hz) with absent tonic EMG activity.

Histology

Mice were transcardially perfused with 4% paraformaldehyde (PFA) in PBS. Brains were post-fixed (4% PFA, 24h), cryoprotected (15% sucrose, 24h), and sectioned coronally (50 μ m). Sections were stained with DAPI and imaged (confocal: Zeiss LSM 700; widefield: Olympus BX51).

Quantification and Statistical Analysis

For fiber recording data, Signals were low-pass filtered using a Savitzky–Golay filter (50-point window, 3rd-order polynomial). $\Delta F/F$ was computed as $(F - F_{\text{baseline}}) / F_{\text{baseline}}$, where F_{baseline} represents the mean fluorescence over the period that without Ca^{2+} transients. The area under the curve (AUC) of $\Delta F/F$ traces was quantified for each defined sleep-wake state.

For single-unit data, extracellular electrophysiological signals were preprocessed (Qin et al., 2018) and spike-sorted with the MClust toolbox (Schmitzer-Torbert and Redish, 2004) based on waveform features. Firing rates were calculated using 2-s sliding windows (100-ms step). Units were classified according to their firing patterns.

For spectral analysis, CA1 LFP and EEG power spectra were obtained via fast Fourier transformation by custom MATLAB code (frequency resolution 0.15 Hz, Qin et al., 2022). Mean power density in the delta (1–4 Hz), theta (6–12 Hz), alpha (12–15 Hz), and beta (15–30 Hz) bands (Billwiller et al., 2020; Boyce et al., 2016) was compared across 4-s windows before, during, and after optogenetic silencing.

For statistics, all analyses were performed in MATLAB and SPSS 22.0. Normality and homogeneity of variance were tested before selecting appropriate tests. If assumptions were met, parametric tests were applied (paired/unpaired t-tests, 1-way ANOVA with LSD post-hoc, or RMs 2-way ANOVA with Sidak post-hoc). Otherwise, non-parametric alternatives were used (Wilcoxon signed-rank test, Wilcoxon rank-sum test, or Friedman test with Bonferroni post-hoc comparison). Data are reported as mean $\pm$ SEM.

Data availability

Figure 1–source data 1, Figure 2–source data 1, Figure 3–source data 1, Figure 4–source data 1 and Figure 5–source data 1 contain the numerical data used to generate the figures.

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Additional information

Author contributions

Conceptualization, H.Q., X.C. and J.H.; Investigation, T.J., W.J., and M.L.; Formal analysis, T.J., X.L., K.Z., S.L., and C.Z.; Visualization, T.J., C.H., H.J., Y.W. and H.Q.; Writing–original draft, H.Q.; Writing–review and editing, H.Q., J.H. and X.C.; Supervision, H.Q., J.H. and X.C.

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Additional files

[Figure 1–source data 1](#) 

[Figure 2–source data 1](#) 

[Figure 3–source data 1](#) 

[Figure 4–source data 1](#) 

[Figure 5–source data 1](#) 

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Peer reviews

Reviewer #1 (Public review):

In this manuscript, the authors aim to define how rapid eye movement sleep supports memory consolidation by identifying the brain circuits that are selectively engaged during this sleep state. They focus on a pathway linking a hypothalamic region involved in sleep regulation to the medial septum and onward to a hippocampal subregion that is critical for social memory. By combining recordings of neural activity with sleep-state-specific circuit manipulations, the study seeks to explain how information is routed during sleep to support distinct types of memory.

A major strength of the work is the use of state-of-the-art circuit-based approaches to link sleep dynamics to defined long-range connections and behavioral outcomes. The authors show that neurons in the lateral supramammillary region projecting to the medial septum are selectively active during rapid eye movement sleep, and that silencing this pathway during this sleep state disrupts consolidation of both social and contextual fear memories. Further dissection of downstream circuitry reveals that inhibition of the medial septum-to-hippocampal CA2 pathway during rapid eye movement sleep selectively impairs social memory. These results provide support for functional specialization within parallel pathways and suggest that this circuit acts as a hub for routing memory-related information during sleep.

While the evidence supporting a role for this circuit in sleep-dependent memory consolidation is compelling, several important mechanistic details remain unresolved. The chemical signaling used by the neurons connecting the hypothalamus to the medial septum is not clearly defined, leaving open whether these cells release excitatory signals, inhibitory signals, or a combination of both. In addition, the medial septum contains multiple neuronal populations with distinct downstream targets, and the specific cell types receiving input from this pathway are not clearly identified. Similarly, the nature of the signals delivered from the medial septum to the hippocampus remains unclear, making it difficult to link circuit anatomy to the observed behavioral specificity. Finally, because different circuit segments are manipulated independently, the causal relationship between upstream and downstream pathways remains suggestive rather than definitive and should be discussed explicitly as a limitation or addressed experimentally.

Overall, the authors largely achieve their aims by identifying a rapid eye movement sleep-specialized circuit that contributes to memory consolidation in a modality-specific manner. The findings are likely to have a meaningful impact on the field by advancing understanding of how sleep organizes memory through parallel neural pathways and by providing a useful framework for future studies of sleep-dependent brain state regulation. With additional clarification of circuit mechanisms or a clearer discussion of current limitations, the study would offer even greater value to the neuroscience community.

<https://doi.org/10.7554/eLife.110519.1.sa1>

Reviewer #2 (Public review):

Summary:

This study systematically characterizes the activity patterns of a lateral supramammillary nucleus (SuM)-medial septum (MS)-hippocampus circuit across sleep-wake cycles and its role in memory consolidation. The authors demonstrate that the lateral SuM-MS projection is specifically active during REM sleep, and that REM-selective inhibition of this circuit, and of its downstream MS-CA2 pathway, impairs the consolidation of social memory. The work is

well-designed, and the data are robust in supporting clear and significant conclusions. It provides important new insights into how distinct memory modalities could be processed by parallel, sleep-active subcortical-hippocampal circuits. The manuscript is of high quality overall, with some points to address as detailed below.

Strengths:

(1) Novel finding:

The identification of a REM-specialized subpopulation within the lateral SuM-MS pathway and its specific role in social memory consolidation via the lateral SuM-MS-CA2 projection is a significant advance. It effectively complements the previously described direct SuM-CA2 pathway and supports a model of the SuM as a "REM-hub" routing information through dedicated downstream targets.

(2) Technical rigor:

The combination of retrograde tracing, in vivo calcium imaging, single-unit identification via optrode recording, and temporally precise (REM-sleep-specific) optogenetic manipulation provides strong correlative and causal evidence.

(3) Appropriate controls:

Behavioral experiments include crucial controls for optogenetic inhibition (GtACR1 group, NREM/Wake inhibition control, mCherry control), effectively ruling out nonspecific effects of light or timing.

Weaknesses:

(1) Figure titles/descriptions:

For clarity, the authors should consider specifying the recording method in the figure titles or legends. For instance, Figure 2: "Bulk Ca²⁺ activity (fiber photometry) of lateral SuM-MS projecting neurons..." and Figure 3: "Single-unit activity patterns (optrode recordings) of lateral SuM-MS projecting neurons..."

(2) Statistical details:

The use of "LSD post-hoc comparison" following ANOVA is noted. LSD is sensitive but can increase Type I error risk with multiple comparisons. Please justify its use or consider employing a more conservative post-hoc test (e.g., Tukey's or Bonferroni) for key comparisons like the social preference index in Figure 4h to bolster robustness.

(3) Data presentation:

When reporting statistical results in figure legends (e.g., Figures 2d, 3i-k), please provide the specific test statistic values (e.g., F , χ^2) and exact P values where possible, rather than only significance asterisks.

(4) Deepening mechanistic insight:

The study excellently demonstrates "what" the circuit does. The discussion could be strengthened by further exploring "how" it might work. The finding that SuM-MS inhibition does not affect CA1 theta power is interesting and distinguishes it from other MS/hippocampal pathways. The suggestion of a theta-independent mechanism is plausible. Could the authors hypothesize more specifically? For example, might this circuit modulate reactivation events in the local CA2 network, neurochemical milieu (e.g., acetylcholine), or synapse-specific plasticity during REM sleep to facilitate social memory consolidation?

(5) Implications of regional heterogeneity:

The functional divergence between lateral (90% REM-active) and medial SuM-MS neurons is intriguing. A brief discussion on the potential anatomical basis (differential inputs/outputs) and functional significance (e.g., integration of specific affective or arousal signals) of this subdivision would be valuable.

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