Neural reactivations during sleep determine network credit assignment

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A fundamental goal of motor learning is to establish the neural patterns that produce a desired behavioral outcome. It remains unclear how and when the nervous system solves this ‘credit assignment’ problem. Using neuroprosthetic learning, in which we could control the causal relationship between neurons and behavior, we found that sleep-dependent processing was required for credit assignment and the establishment of task-related functional connectivity reflecting the causal neuron–behavior relationship. Notably, we observed a strong link between the microstructure of sleep reactivations and credit assignment, with downscaling of non-causal activity. Decoupling of spiking to slow oscillations using optogenetic methods eliminated rescaling. Thus, our results suggest that coordinated firing during sleep is essential for establishing sparse activation patterns that reflect the causal neuron-behavior relationship.

Hallmarks of learning a new skill include a substantial reduction of movement variability and a concomitant reduction in both the extent and variability of neural firing1–7. This process is associated with increasingly sparse task-related neural activation patterns8–11. A theoretical framework for the underlying computation is frequently labeled the ‘credit assignment’ problem, that is, determination of how a single neuron in a highly interconnected biological network causes a behavior9,10. Past work has suggested that a key goal of credit assignment is to select neural activity that truly reflects the causal neuron-behavior relationship8,11. However, it remains unknown how a complex and interconnected biological neural network can solve this computation.

We hypothesized that sleep-dependent reactivations might be important for network credit assignment. A large body of work indicates that sleep is important in memory consolidation12–14. More specifically, reactivation of neural activity during sleep has been implicated in memory consolidation12,14–17. However, there has been a great deal of debate regarding the specific computational role of such reactivations12–14. Two commonly cited possibilities are that sleep-dependent reactivations lead to a general strengthening of functional connectivity or a process of renormalization with both strengthening and weakening of functional connectivity12,14,18. In the case of renormalization, a theoretical prediction is that, after a period of sleep, there may be rescaling of task-related activity (for example, neural activations not causally linked to performance are selectively downscaled)18. Notably, such a process of rescaling of task activations could be used for network credit assignment.

Here we used a neuroprosthetic-learning task, in which the ‘decoder’ and the causality of the neuron–behavior relationship are set by the experimenter8,11,19–24, to evaluate whether NREM sleep has a role in credit assignment. Unlike natural motor behaviors, neuroprosthetic control offers a unique method for studying plasticity; a small set of neurons is chosen to causally control actuator movements (that is, ‘direct’ neurons)8,19. In contrast, ‘indirect’ neurons show task-related activity even though they do not cause actuator movements8,11,25. Notably, although past work has shown that learning proficient control through putative error-correction processes leads to increased activity of direct neurons and diminished activity of indirect neurons8,11,20,25,26, it remains unclear how and when this fundamental credit-assignment process is solved. We found that neural spiking triggered by slow oscillations during sleep is essential for credit assignment.

RESULTS
Rescaling of task activity
In five rats implanted with microwire arrays in primary motor cortex (M1), we monitored sets of direct (TRD) and indirect (TRI) neurons during the initial learning (hereafter referred to as BMI1), during a period of sleep and during subsequent task performance following awakening (hereafter referred to as BMI2). A linear decoder with random-correlated weights converted the firing rates of two randomly chosen TRD neurons into the angular velocity of the actuator. The decoder weights were held constant during the session to exclusively rely on neural learning. Notably, there has been a study demonstrating that decoder adaptation can still induce long-term plasticity27. However, this study was done in non-human primate models performing more complex tasks. In our experiments, rats were trained to control the angular velocity of a feeding tube via modulation of neural activity. At the start of each trial, the angular position of the tube was set to $0^\circ$ ($P_1$; Fig. 1a,b). If the angular position of the tube was held for $>300$ ms at position $P_2$ (90°), a defined amount of water was delivered (that is, a successful trial); a trial was stopped if this was not achieved within

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was found between BMI1Late to BMI2Early (waveforms and inter-spike interval histograms of the neurons analyzed (shown below are the PETHs from BMI1Late and BMI2Early trials for the representative spike rasters from multiple trials. Red dot indicates task completion time for each trial. (Figure 1c) Comparison of trial times. A significant reduction in completion time between BMI1 and BMI2 (mean in solid line ± s.e.m. in box, one-way ANOVA, $F_{3,242} = 34.28, P < 10^{-17}$; significant post hoc t tests, *$P < 0.05$).

Changes in functional coupling during sleep

We next compared the changes in functional connectivity in the recorded M1 neural ensembles during NREM sleep epochs before and after training. We specifically calculated the magnitude of spike–spike coherence (SSC) for TRD – TRD and TRD – TRI pairs both during the sleep that followed training (Sleeppost) and the sleep that preceded training (Sleeppre). The SSC is a pairwise measure of how phase-locked two neurons are across of frequencies\(^{28}\). For TRD – TRD pairs, the TRD neuron with stronger task-related modulation was chosen for the TRD neuron with stronger task-related modulation from Sleeppre to Sleeppost reactivations for TR D and TRI neurons (mean in solid line ± s.e.m. in box, one-way ANOVA, $F_{3,242} = 34.28, P < 10^{-17}$; significant post hoc t tests, *$P < 0.05$).

Changes in functional connectivity of direct neuronal pairs and reactivation microstructure. (a) Example plot of SSC as a function of frequency during sleep before (Sleeppre) and after (Sleeppost for TRD – TRD red for TRD – TRI pairs) skill acquisition. The lighter band is the jackknife error. The box highlights the 0.3–4-Hz band. (b) Relationship between SSC change before and after learning, and change in task-related modulation after sleep, $\Delta$MD of BMI1Late to BMI2Early). Spearman correlation, $r(123) = 0.51, P < 10^{-4}$; $r(113) = 0.35$ (Figure 2a). In addition, we found that the time spent in sleep predicted the extent of TRI downscaling (Spearman correlation, $r = −0.71, P < 0.05$).

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BMI training (that is, BMI fixed ing (that is, microstructure) of sleep reactivations 23,30,31 could also changes were a strong predictor for rescaling (Pearson correlation, used principal components analysis to create a template to reflect the 'reactivation events' that reflect the firing patterns that emerge with learning23,30,31. Notably, we previously found that such reactivation events more closely resembled task-activity during BMI 1 or during BMI neurons during the high-percentile reactivation events (Online Methods). We found that, at the population level, modulation of TRD neurons was significantly greater around the reactivation events than for TRI, thereby resembling the task activations evident during BMI2, or evolve over time during sleep. Detailed analysis of the identified reactivation events revealed that there was no evolution of patterns in sleep (data not shown).

We next examined whether the microstructure of reactivation events more closely resembled task-activity during BMI1 or during BMI2. We therefore examined the specific modulation of TRD and TRI neurons during the high-percentile reactivation events (Online Methods). We found that, at the population level, modulation of TRD neurons was significantly greater around the reactivation events than for TRI, thereby resembling the task activations evident during BMI2. In other words, the identified reactivation events did not resemble BMI1, where there was similar modulation of TRD and TRI. Modulation of TRD neurons was also greater than in Sleeppre whereas they remained unchanged for the TRI population from Sleeppre to Sleeppost (one-way ANOVA, F3,242 = 34.28, P < 10−17; Fig. 2c–e). Such
increased modulation was not apparent in randomly selected parts of Sleeppost (unpaired t test, $t_{121} = -0.69, P = 0.49$; Supplementary Fig. 1). Taken together, these results suggest that, after learning, firing patterns generated by sleep reactivations resemble, on average, the rescaled pattern. Notably, at the level of single neurons, the depth of modulation during reactivations (Fig. 2c–e) predicted how a neuron changed its task-related firing rate during BMI2 (that is, significant relationship between lack of firing during reactivations and downscaling of task activity, linear regression, $R^2 = 0.17, P < 10^{-5}$; Supplementary Fig. 2). Thus, we found that direct task-related units fired more coherently during sleep, as indicated by the elevated SSC, as well as more robustly around reactivations, and their relative modulation depth were significantly greater than for indirect units during task performance in BMI2.

**The role of reward**

What determines the microstructure of reactivations? We first compared the differences between TRD and TRI firing during BMI1; it was difficult to distinguish the two populations on the basis of the evolution of firing patterns locked to trial onset (Fig. 3). However, given that recent studies have suggested that neural activity linked to reward can be preferentially reactivated$^{32–34}$, we also compared activity patterns locked to reward delivery. Notably, we found that it was substantially easier to distinguish the two populations in this ‘frame of reference’; TRD neurons showed a more robust and consistent modulation around reward (Fig. 3a). We quantified this by comparing the activity of pairs of neurons around task start and before reward. The peak modulation depth ratio for TRD neurons around task start versus task end was significantly different ($16.20 \pm 0.96$ versus $26.25 \pm 1.24$, respectively, paired t test, $t_{12} = -6.81, P < 10^{-5}$). On the other hand, the modulation depth of TRI neurons did not significantly vary between the two frames of reference ($13.84 \pm 0.45$ versus $12.86 \pm 0.26$, respectively, paired t test, $t_{119} = 1.95, P = 0.053$).

In general, we also noted that there was an apparent reduction in the variability of firing patterns for TRD neurons as opposed to TRI neurons associated with task completion. We quantified changes using the Fano factor (FF) method$^{35,36}$, which is a statistical measure of the trial-to-trial variability of neural firing. We found that TRD neurons had the lowest FF at task end, which coincided with reward (Fig. 3c). These values were lesser than for task start of successful trials, and even lower than for task start of unsuccessful trials. Notably, when we matched for firing rates between the two frames using a subset of the neurons, we still observed the same decline in FF for the TRD neurons in the task completion frame (TRD neurons’ FF: $0.37 \pm 0.007$ and $0.68 \pm 0.016$ for the task end and task start frames, respectively; TRI neurons’ FF: $0.71 \pm 0.002$ and $0.62 \pm 0.002$ for task end and task start, respectively; one-way ANOVA, $F_{5,350} = 41.20, P < 10^{-32}$). This suggests that the consistency of neural firing relative to reward may be an important determinant of rescaling.

To specifically dissociate task completion from reward, we performed ‘variable reward’ experiments (BMI$_{variable-reward}$) in which we uncoupled task completion from reward (Fig. 3b). This is contrasted from experiments that we outlined above in which the reward was delivered at a fixed interval after task completion (BMI$_{fixed-reward}$). More specifically, the water was delivered after a variable delay of 1–3 s after trial completion. Although the animals could learn the task ($30.62 \pm 6.47\%$ improvement from BMI$_{Early}$ to BMI$_{Late}$; paired t test, $t_5 = 4.46, P < 0.05$), we did not observe significant performance improvement.
gains from BMI\textsubscript{Late} to BMI\textsubscript{Early} as typically seen in BMI\textsubscript{fixed-reward} trials (Fig. 1c). Notably, we also did not observe the rescaling effect; the change in modulation depth from BMI\textsubscript{Late} to BMI\textsubscript{Early} was 14.03 ± 7.89 and 3.35 ± 2.31% for TR\textsubscript{D} and TR\textsubscript{I} populations, respectively (paired \(t\) test, \(t_5 = -1.95, P = 0.10\) for TR\textsubscript{D}; \(t_4 = -1.46, P = 0.15\) for TR\textsubscript{I}).

We then used these experiments to assess whether our observed changes were truly related to reward or simply task completion. For BMI\textsubscript{variable-reward} experiments, we no longer observed the reduction in FF for TR\textsubscript{D} neurons at task completion (one-way ANOVA, \(F_{3,166} = 83.86, P < 10^{-32}\), post hoc \(t\) test, \(P < 0.05\); Fig. 3c). Moreover, they were indistinguishable from indirect neurons. Together, these data suggest that the lack of a temporally precise link between task completion and reward alters the differential modulation of the two populations previously seen. We then examined how the firing patterns of individual neurons changed for each of these two frames. We calculated the pairwise correlation between the sets of neurons during either trial start or trial end. Consistent with our hypothesis, the correlated firing between pairs of TR\textsubscript{D} – TR\textsubscript{D} and TR\textsubscript{D} – TR\textsubscript{I} neurons was significantly different for the reward-based frame for the BMI fixed-reward relative to the BMI variable-reward condition (pairwise correlation; one-way ANOVA, \(F_{2,304} = 8.36, P < 10^{-3};\) post hoc \(t\) test, \(P < 0.05\); Fig. 4a).

What is the effect of reward on reactivations? We found that neural co-firing in the reward frame could strongly predict the microstructure of reactivations for the BMI fixed-reward experiments (Supplementary Fig. 3a) and proportion compared with total time spent in sleep (Supplementary Fig. 3b). All rats tolerated this manipulation without affecting total duration of sleep when compared with the OPTO\textsubscript{OFF} group (Supplementary Fig. 4). Furthermore, there were no quantitative changes in sleep power across the three conditions (Fig. 5f).

We observed significant worsening of performance only in the OPTO\textsubscript{UP} experiments (Fig. 6a,b). Figure 6a shows two examples of learning following pre- and post-sleep from two sessions in the same animal. Typically, we observed a worsening of performance relative to the end of the previous session in OPTO\textsubscript{UP} experiments, but the performance level was still better than that observed in the earliest trials. This was not the case with respective OPTO\textsubscript{DOWN} and OPTO\textsubscript{OFF} experiments. Taken together, these experiments suggest that decoupling of spiking during the UP states of slow oscillations is sufficient to prevent offline gains. This also strongly suggests that such a process is activity dependent and appears to at least require the local firing of action potentials during sleep. In addition, we also found that the performance worsening in BMI\textsubscript{2} in the OPTO\textsubscript{UP} experiments was associated with increased firing variability of TR\textsubscript{D} neurons in both task-start and task-end frames of reference and was comparable to that of TR\textsubscript{I} neurons (TR\textsubscript{D} neuron FF: 1.04 ± 0.04 and 1.11 ± 0.08 at task end and task start, respectively; TR\textsubscript{I} neuron FF: 1.07 ± 0.017 and 1.09 ± 0.02 at task end and task start, respectively; one-way ANOVA, \(F_{3,220} = 0.44, P = 0.72; P > 0.05\) for all post hoc multiple comparisons). This was not the case after robust learning sessions in which TR\textsubscript{D} neurons were associated with a significant reduction in FF at task end (Fig. 3c).

**Optogenetic inhibition and rescaling** We next examined the extent of rescaling for the three experimental groups. Sessions with OPTO\textsubscript{UP} stimulation did not demonstrate rescaling of task activity in BMI\textsubscript{2}, whereas the OPTO\textsubscript{DOWN} and OPTO\textsubscript{OFF} conditions resulted in the expected rescaling of TR\textsubscript{I} neurons as previously observed (Fig. 7a). Furthermore, we evaluated neural dynamics
using spike-field coherence (SFC, see Online Methods regarding equalizing the number of spikes); SFC was significantly reduced for TR1 neurons from Sleep<sub>pre</sub> to Sleep<sub>post</sub> in the OPTO<sub>UP</sub> group (Fig. 7b,c). Finally, we also assessed whether the extent of the average SFC change (∆SFC<sub>mag</sub> from Sleep<sub>pre</sub> to Sleep<sub>post</sub>) of TR<sub>D</sub> neurons could predict the extent of the rescaling of TR<sub>D</sub> neurons from BMI<sub>1</sub> to BMI<sub>2</sub> (MD<sub>D</sub>). Notably, we found a significant relationship between changes in the SSC and the rescaling phenomenon ($R^2 = 0.66, P < 10^{-6}$; Fig. 7d). Together, these results suggest that our measured changes in sleep functional connectivity after learning may be required for the performance gains, the reduced variability of direct neurons and the rescaling of task-related activity.

**DISCUSSION**

In summary, we found evidence for rescaling of task-related neural activity after a period of NREM sleep. We specifically found selective downscaling of TR<sub>D</sub> neural populations (that is, non-causal) in comparison with TR<sub>D</sub> neurons (that is, causal) during task performance after NREM sleep. Our results further reveal how individual TR<sub>D</sub> and TR<sub>I</sub> neurons might be chosen for downscaling; we found that patterns of activity during sleep were predictable of task-related rescaling. During task practice, activity patterns that were most consistently related to rewarded outcomes matches the microstructure of reactivations. A more gross measure of neural firing linked to slow-oscillatory activity (that is, SSC in 0.3–4-Hz band) could also predict rescaling. Finally, we found that closed-loop optogenetic suppression of neural spiking during UP states prevented both performance gains and rescaling. Together, our results suggest that NREM sleep has an essential role in determining task-related functional connectivity that reflects the causal neuron behavior relationship. A net result of this process is to assign network credit assignment and to create sparser patterns of task-related activity.

**Rescaling and sleep-dependent memory processing**

Two commonly cited possibilities for the role of sleep in memory consolidation are a general strengthening of synaptic connectivity and a process of renormalization with net weakening of synaptic connectivity<sup>12,14,18</sup>. In the former, sleep is noted to have an active role in strengthening memories through enhanced local and distant connectivity, thereby resulting in systems consolidation. In contrast, in the latter, renormalization of synaptic strengths is believed to restore synaptic homeostasis and thereby benefit memory functions. It is worth noting that both processes could occur, but may operate over distinct timescales during long periods of sleep<sup>14</sup>. For example, recent evidence suggests that sleep is important for both pruning and growth of new spines<sup>40–42</sup>. Functionally, this could account for both the increases and decreases in neural firing after sleep<sup>29</sup>. Notably, a theoretical prediction is that synaptic renormalization may lead to rescaling of activity<sup>18</sup> to the best of our knowledge there is no direct evidence of this. For natural learning, assessment of task-dependent renormalization is likely to be difficult given that the necessity of neural activity to behavior is largely still unknown.

Neuroprosthetic learning allows us to readily distinguish neural activity that is causal for actuator movements (that is, TR<sub>D</sub>) versus activity that is non-causal. Using this task, we found evidence of rescaling of task activity; specifically, that the task-related modulation of causal neurons were slightly, but significantly, enhanced, whereas non-causal neurons showed selective downscaling of task-related modulation. Although our specific experiments do not allow us to make conclusions regarding changes in synaptic strength, they do reveal that sleep-dependent processing can rescale task-dependent activations. At the very least, our results suggest that sleep-dependent processing does not exclusively strengthen functional connectivity, as assessed by task-related neural firing. Moreover, given that we also found a small, but significant, improvement in task performance as well as increased modulation of direct task-neurons, we cannot not exclude the possibility that a strengthening process may also simultaneously occur. Our experiments using optogenetic suppression of
spiking during the UP states suggests that our observed rescaling is driven by an activity-dependent process. Thus, our results also suggest that reactivations during sleep may be involved in a process of rescaling of task activity; this notion is also broadly consistent with predictions that renormalization may rely on the synchronous activity evident during slow oscillations.

Neuroplastic memory consolidation and slow oscillations

Our closed-loop optogenetic manipulation was triggered by phases of slow oscillations during sleep. We found that, although suppressing neural spiking during UP state Figure 5b,d perturbed sleep-dependent effects, similar perturbations in the DOWN state did not have detectable effects. This suggests that the spontaneous reactivation of both task- and non-task-related neurons during UP states is required for sleep-dependent gains. Notably, our intervention did not appear to grossly affect sleep duration or the power spectrum of sleep. However, it is still possible that other known processes that are linked to slow oscillations might be involved. For example, it is known that spindles are associated with activity during UP states. Although we did not detect gross changes in power, it is still possible that disruption of spiking during slow oscillations could affect spindles. Moreover, there is also a known link between cortical slow oscillations and hippocampal ripples. Future studies can elucidate how other processes might contribute to consolidation after learning.

Our results further suggest that both performance gains and rescaling are regulated by spiking activity linked to slow oscillations. More specifically, NREM sleep appears to have a threefold effect on neural activity and performance. First, there was a significant effect of enhanced performance. Second, there was a slight, but significant, increase in the modulation depth of TRD units. Finally, there was downscaling of TRD activity. The latter two appear to be related to a rescaling effect in which the two populations are differentially modified. Our OPTOUP intervention affected both performance gains and the rescaling effect. Although it might seem that the modulation depth of TRD units was still increased, we observed a significant increase in task-related variability for TRD. Such enhanced variability may reflect poor consolidation of task-activity patterns and underlie the degradation of performance after the OPTOUP intervention. It can be likened to ‘erosion’ of memory, where rats forgot the neural activity pattern in BMI and had to relearn the task again. Together, this suggests that rescaling of the two neural populations may occur simultaneously during UP states.

The SSC analysis shown in Figure 2 suggests that the precise relationship between rescaling and SSC may be complex. There are at least three reasons why we measured a general increase in SSC in the setting of a largely selective enhancement of direct neurons. First, it is possible that there is an elevated threshold for plasticity. In other words, the intercept of our linear regression line suggests that the zero crossing (that is, the threshold for enhancement) is for values greater than a zero change in SSC. Second, it is possible that the general increase in SSC represents active processing of both populations during slow oscillations. In this view, the system might actively sample both weak and strong functional connectivity to ultimately determine credit assignment. Such active sampling would appear to result in a general increase in SSC. It is also worth noting that for hippocampal replay, there may be dissociation between the external experience and internal processing. Thus, third, it is also possible that the elevated SSC represents a schema for internal representation that is not strictly related to the actual awake experience.

Our results might also suggest that both performance gains and rescaling are optimized by the same mechanisms. However, it is still possible that there is differential regulation of these two aspects of task performance. In both rodent and non-human primate models of neuroprosthetic learning, there is a dissociation between performance gains and rescaling. For example, at the end of a typical practice session there were performance gains in the absence of rescaling (that is, firing of non-causal activity). Similarly, past work in non-human primates has indicated that rescaling can take days to occur, even in the presence of performance gains; the task used was substantially more complex than the one we used for rodents. This suggests that performance gains do not absolutely require rescaling. In our experiments, however, we found that sleep-dependent performance gains and rescaling were evident after a period of sleep. Moreover, disruption of spiking linked to slow oscillations resulted in both degradation of performance and rescaling. This suggests that sleep-dependent processing co-regulates both processes. However, given that sleep is a collection of heterogeneous and non-stationary phenomena, it is still quite possible that these two aspects can be dissociated. For example, our optogenetic intervention did not specifically examine the role of spindle activity that is coincident with slow oscillations (as opposed to all spiking linked to it). Future work can help to determine whether performance gains and rescaling are always co-regulated during sleep.

Role of reactivation in credit assignment

Our analysis specifically found that the timing of task activity relative to reward may determine credit assignment. Especially during ‘early learning’, co-firing of direct and indirect neurons occurred over multiple seconds. It is likely that the animals were exploring patterns of neural activity that could successfully complete the task. Notably, traditional task-related peri-event time histograms (PETHs) for neuroprosthetic performance are calculated on the basis of trial start; this is also typical for natural learning. However, based on the extensive history on the role of reward in learning, we also examined PETHs that were associated with task end and reward delivery. Notably, the frame relative to reward was most predictive of rescaling and sleep-related reactivations. We also found that when we perturbed the link between reward and task completion (the variable reward experiments), we no longer observed these phenomena. Together, these results are consistent with the growing notion that the patterns and extent of reward shapes learning and offline processing.
METHODS

Methods, including statements of data availability and any associated accession codes and references, are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

T.G. and K.G. conceived of the experiments. I.G. and T.G. performed surgical procedures and collected data. D.S.R. and T.G. analyzed the data. T.G. and K.G. wrote the manuscript. L.G. and D.S.R. edited the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

Animals/surgery. Experiments were approved by the Institutional Animal Care and Use Committee at the San Francisco VA Medical Center. We used a total of ten adult Long-Evans male rats (n = 5 were used for optogenetic experiments). No statistical methods were used to pre-determine sample sizes, but our sample sizes are similar to those reported in previous publications. Animals were kept under controlled temperature and a 12-h light-dark cycle with lights on at 06:00 a.m. Probes were implanted during a recovery surgery performed under isoflurane (1–3%) anesthesia. Atropine sulfate was also administered before anesthesia (0.02 mg/kg of body weight) The post-operative recovery regimen included administration of buprenorphine at 0.02 mg/kg and meloxicam at 0.2 mg/kg. Dexamethasone at 0.5 mg/kg and Trimethoprim sulfadiazine at 15 mg/kg were also administered post-operatively for 5 d. We used 32-channel microwire arrays; arrays were lowered down to 1,400–1,800 μm in the primary motor cortex (MI) in the upper limb area (1–3 mm anterior to bregma and 2–4 mm lateral from midline). The reference wire was wrapped around a screw inserted in the midline over the cerebellum. Final localization of depth was based on quality of recordings across the array at the time of implantation. All animals were allowed to recover for 1-week before start of experiments. Data collection and analysis were not performed blind to the conditions of the experiments.

Viral injections. We used a red-shifted halorhodopsin, Jaws (AAV8-hSyt-Jaws-KGC-GFP-ER2, UNC Visual Core) for neural silencing in 5 rats for optogenetic experiments. Viral injections were done at least 2.5 weeks before chronic microelectrode array implant surgeries. Rats were anesthetized, as stated above, and body temperature was maintained at 37 °C with a heating pad. Burr hole craniotomies were performed over injection sites, and the virus was injected using a Hamilton Syringe with 34G needle. 500-nl injections (100 nl per min) were made into deep cortical layers (1.4 mm from surface of brain) at two sites in M1 (coordinates relative to bregma: posterior, 0.5 mm and lateral, 3.5 mm; and anterior, 1.5 mm and lateral, 3.5 mm). After the injections, the skin was sutured and the animals were allowed to recover with same regimen as stated above. Viral expression was confirmed with fluorescence imaging. Optogenetic inhibition significantly reduced firing in M1 neurons, with a reduction in 50–70% of recorded cells.

Electrophysiology. We recorded extracellular neural activity using tungsten microwire electrode arrays (MEAs, Tucker-Davis Technologies (TDT)). We recorded spike and LFP activity using a 128-channel TDT-RZ2 system (TDT). Spike data was sampled at 24,414 Hz and LFP data at 1,018 Hz. ZIF-clip-based analog headstages with a unity gain and high impedance (~1 G) was used. Optogenetic experiments, including controls, were done with digital headstages primarily because of the ability to pass the optical fiber through the commutator. Only clearly identifiable units with good waveforms and high signal-to-noise ratio were used. The remaining neural data was recorded for offline analysis. Behavior related timestamps (that is, trial onset, trial completion) were sent to the R22 analog input channel using a digital board and synchronized to neural data. We initially used an online sorting program (SpikePac, TDT) for neuroprosthetic control. We then conducted offline sorting.

Behavior. After recovery, animals were typically handled for several days before the start of experimental sessions. Animals accustomed to a custom plexiglass behavioral box (Fig. 1a) during this period. The box was equipped with a door at one end. Initially, water delivery from the actuator was not introduced and they were just acclimatized to the box. Toward the end of the acclimation period, the rats typically fell asleep while in the box. Animals were then water scheduled such that water (from the feeding tube illustrated in Fig. 1a) was available in a randomized fashion while in the behavioral box. We monitored body weights on a daily basis to ensure that the weight did not drop below 95% of the initial weight. Behavioral sessions were conducted in the morning, with second sessions conducted in the afternoon. We recorded neural data from the rats for 2 h before start of BMI training (that comprised Sleeppost). The rats were then allowed to perform the task over a ~2-h session (BMI1). Recorded neural data was entered in real-time from the TDT workstation to custom routines in Matlab. These then served as control signals for the angular velocity of the feeding tube. The rats typically performed ~180–200 trials per session. These sessions typically lasted from 90–120 min based on the rate of trial completion. Following this, we recorded neural data from animals for a 2-h period (including Sleeppost). The animals then continued with another 90–120-min training session (BMI2). Sorted units at the beginning of the recording were checked for maintenance throughout the second training session.

Neural control of the feeding tube. During the BMI training sessions, we typically randomly selected two well–isolated units as ‘direct’ and allowed their neural activity to control the angular velocity of the feeding tube. In two of the ten sessions (that is, from the 5 non-viral injected rats), there was only one neuron selected as the direct unit. The remaining neurons in all the experiments (that is, indirect) were recorded but not causally linked to actuator movements. We did not find any systematic differences in waveform shape (that is, narrow versus broad) or baseline firing rate for these two populations. These units maintained their stability throughout the recording as evidenced by stability of waveform shape and interspike–interval histograms. We binned the spiking activity into 100-ms bins. We then established a mean firing rate for each neuron over a 3–5 min baseline period. During this period the animals were typically transitioning between walking, exploring and periods of rest.

The mean firing rate was then subtracted from its current firing rate at all times. The specific transform that we used was

\[ \theta_t = C \times (G_1 \times \eta(t) + G_2 \times \tau_2(t)) \]

where \( \theta_t \) was the angular velocity of the feeding tube, \( \eta(t) \) and \( \tau_2(t) \) were firing rates of the direct units. \( G_1 \) and \( G_2 \) were randomized coefficients that ranged from +1 to –1 and were held constant after initialization. C was a fixed constant that scaled the firing rates to arrive at a value for angular velocity. The animals were then allowed to control the feeding tube via modulation of neural activity. The tube started at the same position at the start of each trial (P1 in Fig. 1a). The calculated angular velocity was added to the previous angular position at each time step (100 ms). During each trial, the angular position could range from –45 to +180 degrees. If the tube stayed in the ‘target zone’ (P2) then remained in the same area for a period of 300 ms, a water reward was delivered. In the BMIvariable-reward experiments (n = 4 sessions in two rats), the rats correctly positioned the tube, but reward delivery (that is, the water from the tube) was randomly delayed by a period ranging from 1–3 s. In contrast, the BMIfixed-reward (that is, typical BMI session), the reward was delivered with a fixed delay of ~200 ms relative to task completion. In the beginning of a session, most rats were unsuccessful at bringing the feeding tube to position P2. Most rats steadily improved control and reduced the time to completion of the task during the first session. We obtained multiple learning sessions from each animal. These sessions were typically several days to 1 week apart to ensure that new units were recorded. Consistent with past studies, we also found that incorporation of new units into the control scheme required new learning.

Closed-loop sleep experiments using optogenetics. Three types of experiments were conducted using the five Jaws-injected animals, namely OPTOUP (n = 11), OPTODOWN (n = 8) and OPTOFF (n = 8). These experiments were largely randomly interspersed among the animals. However, while the OPTODOWN experiments were only conducted in three animals, these animals also contributed to the OPTOUP and OPTOFF experiments. In general, we identified the phases of the LFP associated with ‘UP’ and ‘DOWN’ states based on the relationship of the neural spiking to the LFP. For example, as shown in Figure 5, the negativity in our LFP signals was associated with neural spiking and thus consistent with an UP state, which are natural states of increased activity during slow oscillations. The closed-loop interventions were conducted by triggering the LED light based on real-time detection of cortical states. We used a custom script in the RPvdsExPigram (TDT) to identify slow oscillations in real-time during sleep blocks. In the OPTOUPExperiments, we conducted two types of triggering (n = 3 power based; n = 8 filtering based). In both cases, the LED light was delivered during cortical ‘UP’ states by placing a manual threshold on filtered LFP trace; the manual threshold was selected visually to coincide with the respective phase on the slow oscillations as noted below. For the ‘power-based’ triggering, we used the following approach. The algorithm/workstation calculated the LFP power in the 0.1–4 Hz range and compared it to the threshold. Once the threshold was exceeded for >100 ms, LED illumination (625-nm fiber-coupled LED
(ThorLabs), with 200/400-µm diameter optic fibers (Doric Lenses) was triggered for 100 ms. For the 'filtering based' approach, we used a real-time implementation of a Butterworth filter to filter the raw LFP in a 0.1–4-Hz band (Fig. 5d). The UP state was determined by setting a 'negative' threshold on the LFP (that is, as displayed in the convention in Fig. 5d). The LED was again triggered when it was respectively above/below this threshold. Notably, this type of stimulation was exclusive to the UP state. Because we did not observe any differences we combined both sets as the OPTOUP condition.

During OPTODOWN sessions, we directly placed a 'positive' threshold on the filtered LFP; thus the stimulation was triggered during threshold crossings of 'DOWN' (that is, DOWN states with natural periods of quiescence during slow oscillations). These stimulations were also typically brief (that is, 100 ms). A typical example is shown in Figure 5. Supplementary Figure 3 shows that total incidents of 100-ms stimulations were similar in both OPTOUP and OPTODOWN experiments, and the light was on for a similar proportion of time. Finally, a group of control experiments called OPTOOFF (that is, where no stimulation was triggered) was also conducted in the Jaws-injected rats. Durations of total pre and post sleep were similar in all 3 session types (Supplementary Fig. 4). We also calculated LFP power and SFC changes for individual neurons in all three groups.

### Sessions and changes in performance. Analysis was performed in Matlab (Mathworks) with custom-written routines. A total of ten BMIfixed-reward training sessions recorded from five rats were used for our initial analysis. All of these sessions demonstrated 'robust learning' (that is, >3 s.d. drop in time to completion in the last 1/3 of trials or 'late' trials in comparison to the first 1/3 of trials or 'early' trials). These sessions were followed by a second training session (that is, BMI2). In Figure 1c, we compared changes in task performance across sessions. Specifically, we compared the performance change between BMI1Late and BMI2Early and BMI2Late by calculating the mean and standard error of the time to completion during the last third trials in BMI1 and the first and last third trials BMI2 (Fig. 1c). We used a paired t test to assess statistical significance.

### Task-related activity. The distinction between TRD and TR neurons was based on whether units were used for the direct neural control of the feeding tube. The change in modulation depth (MDₐ) was calculated by comparing the peak activity around the task (in the 5-s window after the task start/4 s before task-end/reward) over baseline firing activity (averaged activity of 4 s before task start) on the peri-event time histograms (PETH, bin length 50 ms). In other words, the MDₐ is a measure of the modulation of firing rate relative to the pre-task start baseline rate. Modulation of baseline firing activity after the ‘Go cue’ (task start) or before receipt of ‘reward’ (task end) was calculated and this was compared for TR₂ and TR neurons from BMI₁ to BMI₂ (MDₐ change from BMI₁ to BMI₂). This was calculated across the last third of trials from BMI₁ and first and last third of trials from BMI₂ (BMI1Early and BMI2Late respectively). In a BMI session with approximately 200 trials, these values were averaged across ~65 trials. To ensure that any online training effects were not contributing to the observed reduction in MDₐ of TR units, in a subset of these sessions we also averaged MDₐ for just 30 trials before and after; no significant differences were evident.

For Figures 1 and 3, PETH were smoothed using a Bayesian adaptive-regression spline algorithm, implemented within MATLAB using toolboxes downloaded at (http://www.cnbc.cmu.edu/~rkelly/code.html) [31, 47]. The algorithm automatically optimized for the number and location of ‘knots’ (that is, regions in which a new local regression model improves the overall fit of the curve) was determined automatically using a Markov chain Monte Carlo implemented to optimize the Bayes Information Criteria and thereby, offered a better visualization of dynamic changes in the rate of change of spike trains. These curves were not used for other sets of analysis.

### Identification of NREM oscillations. Identification of pre- and post-NREM epochs was performed by combined visual assessment of presence of low-frequency, high-amplitude slow-wave oscillations as well as a 3 s.d. threshold of the filtered data (0.3–4 Hz). If there was a sustained reduction >1.5 s in the amplitude of the slow-wave activity below threshold during a continuous epoch we excluded these segments [23, 31].

### Coherence measure. We used the Chronux toolbox to calculate the SSC (http://chronux.org/) [48]. Its magnitude is a function of frequency and takes values between 0 and 1. For its calculation, the pre- and post-sleep were segmented into 20-s segments and then the coherency measured was averaged across segments. For the multitaper analysis, we used a time-bandwidth (TW) product of 10 with 19 tapers. To compare coherences across groups, a z score was calculated using the programs available in the Chronux Toolkit. Coherence between activity in two regions, Cₓᵧ, was calculated and defined as

\[ Cₓᵧ = \frac{|Rₓᵧ|}{\sqrt{Rₓₓ Rᵧᵧ}} \]

where Rₓᵧ, Rₓₓ, and Rᵧᵧ are the power spectra and Rₓᵧ is the cross-spectrum. More specifically, it is a pairwise measure of synchronized co-firing of neurons in a frequency dependent manner. For example, during NREM sleep, it can quantify synchronous co-firing relative to low-frequency oscillations in the 0.3–4 Hz range. Our previous work has also shown that SSC values are related to the spike cross-correlogram measured during UP states [23].

Spectral analysis were calculated in segmented NREM epochs and averaged across these epochs across animals. Mean coherence was calculated between 0.3–4 Hz. Significance testing on coherence estimates was performed on mean estimates between TRD – TRD, and TRD – TR pairs using unpaired t tests. The task-related direct unit with the greatest depth modulation was used to calculate SSC for every other unit. Similarly, for SFC analysis in optogenetic experiments, mean power changes in the 0.3–4 Hz band were compared for OPTOUP, OPTODOWN, and OPTOOFF experiments. We also equaled the number of spikes in pre- and post-sleep [23, 28] to account for the changes in firing rates; this was especially pertinent for the optogenetic intervention studies.

### Ensemble activation analyses. To characterize ensemble reactivations following sleep, we performed an analysis that compared neural activity patterns during Sleep₁ and Sleep₂ with a template that was created during task execution in BMI₁ [23, 30, 31]. We first computed a pairwise unit activity correlation matrix during BMI₁ by concatenating binned spike trains (τbin = 50 ms) for each neuron across trials (0.5 s before the onset of trial up to 5 s after the onset of BMI task for each trial). This concatenated spike train was z-transformed, and then organized into a 2-D matrix organized by neurons (x) and time (B for number of time bins). From this spike count matrix, we calculated the correlation matrix (Cₓt), and then calculated the eigenvector for the largest eigenvalue from this correlation matrix to study. This eigenvector was used as the ensemble template of activity, which was then projected back on to the neural activity trains from the same population of neurons during Sleep₁ and Sleep₂. This projection was a linear combination of Z-scored binned neural activity from the two blocks above weighted by the PC ensemble (that is, the eigenvector) calculated from the BMI₁ matrix. This linear combination has been described as the ‘activation strength’ of that particular ensemble. In this analysis we focused on the first eigenvector, as the first PC explained most task-related variance (see Supplementary Fig. 5 for two examples).

### Reactivation triggered peri-event time histogram (microstructure of reactivation). We also constructed time histograms of single unit activity around reactivation events. We binned spike counts from 250 ms before and after ensemble reactivation events using a 5-ms bin size and calculated the mean/standard error of the binned neural firing. The reactivation events that were chosen for PETHs were those with a reactivation strength that was significantly greater than for the pre-sleep block. Usually top 10–20 percentile reactivation strengths from the post-sleep fulfilled this criterion. Once the PETHs were constructed, the modulation depth across reactivations (MDᵣ) was calculated by comparing the peak of firing during reactivation to the mean baseline firing (that is, at the tails). t test was performed to compare MDᵣ between TR and TR units, and also their levels in pre-sleep. We also checked for MDᵣ of TR and TR units at random low-percentile reactivation events and their MDᵣ was indistinguishable (Supplementary Fig. 1).

### Analyses of neural firing variability and neuronal pair correlations. The modulation characteristics of each neuron in the BMI task in the two frames of reference (namely, ‘task-start’ and ‘task-end’) were examined using the following: Fano factor, which is a statistical measure of the dynamics of the firing rate of
a cell\textsuperscript{33,36}; and cross-correlation calculated between the rates of cell pairs. Fano factor, \(F\) is defined as
\[
F = \frac{\sigma^2}{\mu}
\]
where \(\sigma^2\) is the variance and \(\mu\) is the mean of a spike count process (here in a 50-ms time window). \(\mu\) was the average firing rate and was calculated as follows:
\[
\mu = \frac{1}{B} \sum_{n=1}^{B} C(n)
\]
where \(C(n)\) is the spike counts in 50-ms time window and \(B\) is the total window sample number. Since, fano factor can be influenced by firing rate, we also compared fano factor in task start and task end frames of reference where the firing rates were similar and we still found similar trends. Cross-correlation, on the other hand, measured the similarity of two firing rate series (50-ms bins) as a function of the displacement of one relative to the other. This pairwise correlation of the neural activity was calculated for TRD – TRD and TRD – TRI neuronal pairs using Matlab’s \texttt{xcorr} function (Fig. 4). Time series of concatenated binned spike counts were created either around task start (first 1 s) or around task end (from trial end to 1 s prior). Statistical comparisons were performed using a repeated-measures ANOVA, followed by post hoc t tests to identify specific time points that were significantly different.

\textbf{Statistics.} There were a total of 10 robust BMI learning sessions that we used (BMI\textsubscript{fixed-reward}) for analyzing the trends from BMI\textsubscript{1} to BMI\textsubscript{2}. There were a total of 18 TRD and 105 TR units in these experiments. There were also 4 BMI\textsubscript{variable-reward} sessions where we had 6 TRD and 41 TR units. Optogenetics experiments (in Jaws-injected rats) had 11 sessions with OPTO\textsubscript{UP} stimulation (with 17 TRD and 95 TR units), 8 sessions with OPTO\textsubscript{DOWN} stimulation (with 14 TRD and 94 TR units), and 8 sessions with OPTO\textsubscript{OFF} stimulation (with 13 TRD and 62 TR units). We also recorded sleep before (Sleep\textsubscript{pre}) and after (Sleep\textsubscript{post}) after BMI\textsubscript{1}. In all these experiments, we performed paired t-test to compare performance changes from BMI\textsubscript{1} to BMI\textsubscript{2}: MD\textsubscript{reactivation} change and firing rate changes for TRD and TR units from Sleep\textsubscript{pre} to Sleep\textsubscript{post}; SSC\textsubscript{mag} changes for TRD – TRD and TRD – TRI neuronal pairs from Sleep\textsubscript{pre} to Sleep\textsubscript{post} (Figs. 1c and 6b). Data distribution was tested for normality and non-parametric test was substituted if needed (Wilcoxon signed rank test). Unpaired t tests were also used for comparisons such as MD\textsubscript{reactivation} in TRD versus TR units pools; MD\textsubscript{3} change for TRD versus TR units from BMI\textsubscript{1} and BMI\textsubscript{2}; and features of stimulation in OPTO\textsubscript{UP} and OPTO\textsubscript{DOWN} experiments (Figs. 1e and 7a; Supplementary Figs. 1 and 3). We also performed one-way ANOVA with multiple comparisons (test of homogeneity of variances was done) wherever significance assessment was required (Figs. 2c, 3c, 4a, 5c,f and 7c, and Supplementary Fig. 4). We also used linear regression or correlation to evaluate trends between MD\textsubscript{reactivation} versus MD\textsubscript{3} change from BMI\textsubscript{1} and BMI\textsubscript{2}, or correlated firing around task start or task end; pairwise firing correlation of TRD – TRD and TRD – TRI neuronal pairs versus MD\textsubscript{reactivation}; between sleep and MD\textsubscript{3} change from BMI\textsubscript{1} and BMI\textsubscript{2} for different units; and SSC\textsubscript{mag} changes for TRD – TRD and TRD – TRI neuronal pairs versus MD\textsubscript{3} change for TRD or TR units from BMI\textsubscript{1} to BMI\textsubscript{2}; and SFC changes in optogenetics experiments, versus MD\textsubscript{3} change (Figs. 2b, 4b,c and 7d, and Supplementary Fig. 2).

A \textit{Supplementary Methods Checklist} is available.

\textbf{Data availability statement.}\ The data that support the findings from this study are available from the corresponding author upon request.

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Corrigendum: Neural reactivations during sleep determine network credit assignment

Tanuj Gulati, Ling Guo, Dhakshin S Ramanathan, Anitha Bodepudi & Karunesh Ganguly
Nat. Neurosci.; doi:10.1038/nn.4601; corrected online 18 July 2017

In the version of this article initially published online, the abstract read "casual neuron–behavior relationship" instead of "causal neuron–behavior relationship." The error has been corrected in the print, PDF and HTML versions of this article.
Erratum: Neural reactivations during sleep determine network credit assignment

Tanuj Gulati, Ling Guo, Dhakshin S Ramanathan, Anitha Bodepudi & Karunesh Ganguly
Nat. Neurosci.; doi:10.1038/nn.4601; corrected online 31 July 2017

In the version of this article initially published online, the x-axis label for the righthand column in each graph in Figure 6b read BMI1Early; it should have read BMI2Early. The error has been corrected in the print, PDF and HTML versions of this article.
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Note: Mean and standard deviation are not appropriate on small samples, and plotting independent data points is usually more informative. When technical replicates are reported, error and significance measures reflect the experimental variability and not the variability of the biological process; it is misleading not to state this clearly.

| TEST USED | n | DESCRIPTIVE STATS (AVERAGE, VARIANCE) | P VALUE | DEGREES OF FREEDOM & F/T/Z/R/ETC VALUE |
|-----------|---|--------------------------------------|--------|--------------------------------------|
| 1a        |   | error bars are mean +/- SEM          | p = 0.044 | F(3, 36) = 2.97                      |
|           |   |                                      | Fig. legend | Fig. legend |
| 1b        |   | error bars are mean +/- SEM          | p = 0.0006 | t(28) = 2.808                        |
|           |   |                                      | Results, Para6 | Results, Para6 |
| 1c        |   | error bars are mean +/- SEM          | 3.2320e-05 | t(9)=7.62                            |
|           |   |                                      | Results, Para2 | Results, Para2 |
| FIGURE NUMBER | WHICH TEST? | SECTION & PARAGRAPH # | Exact Value | Defined? | Reported? | SECTION & PARAGRAPH # | Exact Value | P VALUE | Degrees of Freedom | ETC Value |
|---------------|-------------|------------------------|-------------|----------|-----------|------------------------|-------------|---------|-------------------|-----------|
| 1e            | unpaired t-test | Results, Para2 | TRd=18, TRi=105 | Modulation depth change from BMI1 to BMI2 early trials | Results, Para2 | box plot with mean +/- SEM | Fig 1 legend | 4.4679e-10 | t(121)=6.7891 | Results, Para2 |
| 1e            | unpaired t-test | Results, Para2 | TRd=18, TRi=105 | Modulation depth change from BMI1 to BMI2 late trials | Results, Para2 | box plot with mean +/- SEM | Fig 1 legend | 4.6799e-09 | t(121)=6.3138 | Results, Para2 |
| 1e            | unpaired t-test | Results, Para2 | TRd=18, TRi=105 | Modulation depth change from BMI1 to all BMI2 trials | Results, Para2 | box plot with mean +/- SEM | Fig 1 legend | 1.8915e-10 | t(121)=6.9596 | Results, Para2 |
| NA            | unpaired t-test | Results, Para3 | TRd-TRd=8, TRd-TRi=105 | SSC change for TRd-TRd and TRd-TRi pairs | Results, Para3 | box plot with mean +/- SEM | Result s, Para3 | 1.4856e-08 | t(121)=6.074 | Results, Para3 |
| 2b            | pearson correlation | Results, Para3 | 228 | SSC vs modulation depth changes for TRd and TRi units from BMI1 to BMI2 | Results, Para3 | correlation | Fig 2, legend | P<0.05 | r(123)=0.51 | Results, Para3 |
| 2e            | one-way ANOVA | Results, Para6 | TRd=18, TRi=105 | Modulation during reactivation for TRd and TRi units from BMI1 to BMI2 | Results, Para6 | box plot with mean +/- SEM | Fig 2 legend | 1.6837e-18 | F(3,242)=34.28 | Results, Para6 |
| Supp Fig 1    | unpaired t-test | Results, Para6 | TRd=18, TRi=105 | Modulation during reactivation vs downsampling from BMI1 to BMI2 | Results, Para6 | box plot with mean +/- SEM | Supp Fig1 legend | 0.4926 | t(121)=0.6883 | Supp Fig1 |
| Supp Fig 2    | Regression | Results, Para6 | TRd=18, TRi=105 | MD reactivation of TRd and TRi cells versus their task modulation change from BMI1 to BMI2 | Results, Para6 | scatter plot | Supp Fig2 legend | 10e-5 | R^2=0.17 | Supp Fig2 |
| 3c            | one-way ANOVA | Results, Para8 | TRd=18, TRi=105 in 3 conditions | Fano factor of TRd and TRi cells around task start and task end for successful and unsuccessful trials (in BMI1 fixed reward) | Results, Para8 | box plot with mean +/- SEM | Fig 3c legend | 2.6661e-33 | F(5,350)=41.2044 | Fig 3c legend |
| 3c            | one-way ANOVA | Results, Para10 | TRd=18, TRi=105 in fixed reward and TRd=6, TRi=41 in variable reward’s task end | Fano factor of TRd and TRi cells around task end BMI fixed reward and BMI variable reward experiments | Results, Para10 | box plot with mean +/- SEM | Fig 3c legend | 4.4874e-33 | F(3,166)=83.8646 | Fig 3c legend |
| # | Paragraph | Method | Results | Correlation | P-value | Fig | ANOVA F-value |
|---|-----------|--------|---------|-------------|----------|-----|---------------|
| 4a | Results, Para10 | one-way ANOVA | TRd-TRd pairs= 8; TRd-TRi pairs=10 in BMI fixed reward; TRd-TRd pairs= 2; TRd-TRi pairs=41 in BMI fixed reward; | Correlated firing around task start and end for TRd-TRd and TRd-TRi neurons in BMI fixed reward and BMI variable reward experiments (in task start and task end frames of reference) | box plot with mean +/- SEM | 2.4089e-09 | F(7,304)=8.3592 |
| 4b | Results, Para11 | Regression | TRd-TRd pairs= 8; TRd-TRi pairs=10 5 with their respective MD reactivations in sleep | Correlated firing during reward (for BMI fixed reward experiments) vs MD reactivation in Sleep | r squared | P < 10e–21 | Fig 4b |
| 4c | Results, Para11 | Regression | TRd-TRd pairs= 2; TRd-TRi pairs=41 with their respective MD reactivations in sleep | Correlated firing during reward (for BMI variable reward experiments) vs MD reactivation in Sleep | r squared | P>0.05 | R^2= 0.07 |
| 5c | Results, Para12 | one-way ANOVA | OPTO_U P TRd= 17, OPTO_D OWN TRd= 14 OPTO_O FF TRd= 13 | Modulation depth of TRd cells in OPTO_UP, OPTO_DOWN and OPTO_OFF experiments from pre sleep to post sleep | box plot with mean +/- SEM | 3.755e-28 | F(2,41)=425.745 |
| 5f | Results, Para12 | one-way ANOVA | OPTO_U P=11 sessions; OPTO_D OWN=8 sessions; OPTO_O FF= 8 sessions | PSD changes in OPTO_UP, OPTO_DOWN and OPTO_OFF experiments from pre sleep to post sleep | box plot with mean +/- SEM | 0.8749 | F(2,27)=0.1344 |
| NA | Results, Para2 | Spearman Correlation | Time spent in sleep vs extent of TRi rescaling | correlation | Result s, Para2 | 0.0101 | Results, Para2 |
| NA | Results, Para2 | Wilcoxon signed rank test | TRd modulation in BMI1 vs BMI2 | mean +/- SEM | Result s, Para2 | 0.0352 | Results, Para2 |
| NA | Results, Para2 | paired t-test | TRI modulation in BMI1 vs BMI2 | mean +/- SEM | Result s, Para2 | 3.43e-27 | Result s, Para2 |
| NA | Results, Para2 | paired t-test | Pre and Post Sleep durations | mean +/- SEM (for Sleep post) | Result s, Para2 | 0.9560 | Result s, Para2 |
| NA | Results, Para3 | paired t-test | Sleep epochs firing rates (Watson style), TRd | mean +/- SEM | Result s, Para3 | 0.1184 | Result s, Para3 |
| NA | Results, Para3 | paired t-test | | | | 3.43e-27 | Result s, Para2 |

*Fig 4a legend: 2.4089e-09
Fig 4b legend: P < 10e–21
Fig 4c legend: R^2= 0.07
Fig 5c legend: 3.755e-28
Fig 5c legend: F(2,27)=0.1344
Fig 5c legend: 0.8749
Fig 5f legend: F(2,41)=425.745
Fig 5f legend: F(2,27)=0.1344

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| Para | Test Type | Description | Results | Significance | Notes |
|------|----------|-------------|---------|--------------|-------|
| 3    | paired t-test | 105 pairs of sleep epochs firing rates (Watson style), TRi | | 0.9605 | Results, Para3 |
| 8    | paired t-test | 4 BMI variable reward sessions | | 0.0105 | Results, Para9 |
| 9    | paired t-test | 4 BMI variable reward experiments | | 0.1086 | Results, Para9 |
| 9    | paired t-test | 100 ms stimulation pulse incidence during OPTO_UP and OPTO_DOWN experiments | | 0.0538 | Results, Para9 |
| 4    | Spearman correlation | Correlated firing during task start (for BMI fixed reward experiments) vs MD reactivation in sleep | | 0.1503 | Results, Para9 |
| 12   | unpaired t-test | 100 ms stimulation duration proportion to total NREM sleep during OPTO_UP and OPTO_DOWN experiments | | 0.3338 | Results, Para12 |
| 12   | unpaired t-test | 100 ms stimulation duration proportion to total NREM sleep during OPTO_UP and OPTO_DOWN experiments | | 0.0538 | Results, Para12 |
| 12   | one-way ANOVA | 112 sessions, OPTO_D OWN=8 sessions | | 0.4740 | Results, Para12 |
| 13   | paired t-test | Performance changes in OPTO_UP experiments from BMI1 late to BMI2 early (both tail) | | 3.8955e-04 | Results, Para13 |
| # | Page | Method          | Results, Para | Description                                                                 | Fig/Para legend | t(7) | t(110) | R^2 | r-squared |
|---|------|-----------------|---------------|-----------------------------------------------------------------------------|-----------------|------|--------|-----|----------|
| 6b | 3     | paired t-test   | Results, Para 13 | Performance changes in OPTO\_DOWN experiments from BMI1 late to BMI2 early | Fig 6b legend   |      |        |     |          |
| 6b | 3     | paired t-test   | Results, Para 13 | Performance changes in OPTO\_OFF experiments from BMI1 late to BMI2 early | Fig 6b legend   |      |        |     |          |
| NA | 5     | one-way ANOVA   | Results, Para 13 | Fano factor of TRd and TRi neurons in OPTO\_UP experiments in BMI2 in task start and task-end frames of references | Results, Para 13 |      | 0.7229 |     |          |
| 7a | 6     | unpaired t-test | Results, Para 14 | MD change of TRd and TRi neurons in OPTO\_DOWN experiments from BMI1 to BMI2 | Fig 7a legend   | 0.64059 |        |     |          |
| 7a | 6     | unpaired t-test | Results, Para 14 | MD change of TRd and TRi neurons in OPTO\_OFF experiments from BMI1 to BMI2 | Fig 7a legend   | 5.0074e-07 |        |     |          |
| NA | 5     | paired t-test   | Results, Para 5 | MD change of TRd neurons from BMI1 to BMI2 in OPTO\_UP experiments          | Discussio, Para 5 | 0.02024 |        |     |          |
| NA | 5     | paired t-test   | Results, Para 5 | MD change of TRd neurons from BMI1 to BMI2 in OPTO\_UP experiments          | Discussio, Para 5 | 6.691e-10 |        |     |          |
| NA | 5     | paired t-test   | Results, Para 5 | SFC change of TRd neurons from pre sleep and post sleep in OPTO\_UP, OPTO\_DOWN, and OPTO\_OFF experiments | Results, Para 14 | 4.79701e-11 |        |     |          |
| NA | 5     | paired t-test   | Results, Para 7 | TRd modulation around task start vs task end                                | Results, Para 7 | 3.0599e-06 |        |     |          |
| NA | 5     | paired t-test   | Results, Para 7 | TRi modulation around task start vs task end                                | Results, Para 7 | 10e-6 |        |     |          |
| 7c | 6     | one-way ANOVA   | Results, Para 14 | Averaged TRd SFC change from Sleep pre to Sleep post versus averaged TRI rescaling from BMI1 to BMI2 in OPTO\_UP, OPTO\_DOWN, and OPTO\_OFF experiments | Results, Para 14 |      | 44.831 |     |          |
| 7d | 6     | regression      | Results, Para 14 | r-squared                                                                    | Fig 7d legend   |      | 0.66   |     |          |
| NA | 7     | paired t-test   | Results, Para 7 | TRd modulation around task start vs task end                                | Results, Para 7 |      | -6.8061 |     |          |
### Representative figures

1. Are any representative images shown (including Western blots and immunohistochemistry/staining) in the paper?
   If so, what figure(s)?

   Yes, following figures show representative performance improvements after sleep, Modulation depth changes after sleep (for direct, TR_d and indirect, TR_i neurons), spike spike coherence changes in sleep sessions before and after BMI training, modulation around reactivation in pre and post sleep, modulation around task start and task end, fano factor in same frames for BMI fixed and variable reward optogenetic inhibition around slow-wave activity in UP, DOWN and OFF experiments, and behavioral learning curves in them, SFC changes in them, 100 ms stimulation pulses incidence and proportion in them, durations of sleep in different kinds of experiments: Fig. 1c,e; Fig 2a,c-e; Fig. 3a,c; Fig. 4a; Fig 5c,f; Fig 6b; Fig 7a,d; Supp Fig 1, Supp Fig 3a,b; Supp Fig 4.

   Yes: Fig. 1: Results para 1 and 2 ; and methods para 1,3,4 8
   Fig. 2: Results para 3 and 6 ; and methods para 1,3,4 8
   Fig. 3: Results para 8 and 10 ; and methods para 1,3,4 8
   Fig. 4: Results para 10 and 11 ; and methods para 1,3,4 8
   Fig. 5: Results para 12 ; and methods para 1,7
   Fig. 6: Results para 13 ; and methods para 1,7
   Fig. 7: Results para 14 ; and methods para 1,7
   Supp Fig 1: Results para 6; and methods para 1,3,4 8
   Supp Fig 3: Results para 12 ; and methods para 1,7
   Supp Fig 4: Results para 12 ; and methods para 1,7

### Statistics and general methods

1. Is there a justification of the sample size?
   If so, how was it justified?
   Where (section, paragraph #)?

   Even if no sample size calculation was performed, authors should report why the sample size is adequate to measure their effect size.

   Our sample size is similar to what is usually used to establish task-related consolidation during sleep, or task-related neural modulation in other studies (for example, n ranging from 5 to 12 in our references). This is stated in online methods, paragraph 1. Number of neurons analyzed in each group are summarized in online methods, paragraph 18.

2. Are statistical tests justified as appropriate for every figure?
   Where (section, paragraph #)?

   a. If there is a section summarizing the statistical methods in the methods, is the statistical test for each experiment clearly defined?

   Yes, in the result sections and methods section appropriate tests are listed. Online methods section, paragraph 18 summarizes these.

   b. Do the data meet the assumptions of the specific statistical test you chose (e.g. normality for a parametric test)?

   Yes, online methods section, paragraph 18 summarizes these.

   b. Do the data meet the assumptions of the specific statistical test you chose (e.g. normality for a parametric test)?

   Yes, we substituted for non-parametric test wherever sample distribution failed the test of normality and this was detailed in methods (paragraph on statistical tests), paragraph 18.
c. Is there any estimate of variance within each group of data?
   Is the variance similar between groups that are being statistically compared?
   Where is this described (section, paragraph #)?

   For one-way ANOVA, test for homogeneity of variances was done. It's described in methods, paragraph 18.

3. To promote transparency, Nature Neuroscience has stopped allowing bar graphs to report statistics in the papers it publishes. If you have bar graphs in your paper, please make sure to switch them to dot-plots (with central and dispersion statistics displayed) or to box-and-whisker plots to show data distributions.
   Yes, dot plots with dispersion statistics are included.

4. Are criteria for excluding data points reported?
   Was this criterion established prior to data collection?
   Where is this described (section, paragraph #)?

   Not applicable. Except Units with high SNR were used for subsequent analysis (see Methods paragraph 3).

5. Define the method of randomization used to assign subjects (or samples) to the experimental groups and to collect and process data.
   If no randomization was used, state so.
   Where does this appear (section, paragraph #)?

   For the optogenetic experiments, sometimes the non-stimulation experiments were done before stimulation or sometimes after optogenetic stimulation experiments. Hence this control was randomized, otherwise there was no blinding, as stated in online methods, paragraph 1.

6. Is a statement of the extent to which investigator knew the group allocation during the experiment and in assessing outcome included?
   If no blinding was done, state so.
   Where (section, paragraph #)?

   No blinding was done, as stated in online methods, paragraph 1.

7. For experiments in live vertebrates, is a statement of compliance with ethical guidelines/regulations included?
   Where (section, paragraph #)?

   Yes, Methods: paragraph 01

8. Is the species of the animals used reported?
   Where (section, paragraph #)?

   Yes, Methods: paragraph 01

9. Is the strain of the animals (including background strains of KO/transgenic animals used) reported?
   Where (section, paragraph #)?

   Yes, Methods: paragraph 01

10. Is the sex of the animals/subjects used reported?
    Where (section, paragraph #)?

    Yes, Methods: paragraph 01
11. Is the age of the animals/subjects reported?
   Where (section, paragraph #)?
   It’s not reported. But all animals were adult male rats. They were procured at body weight ~250 gm (approximately 8 weeks age). Experiments were initiated within 5 days of delivery.

12. For animals housed in a vivarium, is the light/dark cycle reported?
   Where (section, paragraph #)?
   Yes, Methods paragraph 01

13. For animals housed in a vivarium, is the housing group (i.e. number of animals per cage) reported?
   Where (section, paragraph #)?
   Not reported but prior to surgery there were 2 rats/cage. After surgery we put 1 rat/cage due to water feeding restriction schedule.

14. For behavioral experiments, is the time of day reported (e.g. light or dark cycle)?
   Where (section, paragraph #)?
   Yes, Methods paragraph 01

15. Is the previous history of the animals/subjects (e.g. prior drug administration, surgery, behavioral testing) reported?
   Where (section, paragraph #)?
   Yes, Methods paragraph 01 and 02

   a. If multiple behavioral tests were conducted in the same group of animals, is this reported?
      Where (section, paragraph #)?
      Yes, Methods paragraph Animals and Behavior

16. If any animals/subjects were excluded from analysis, is this reported?
   Where (section, paragraph #)?
   Not applicable

   a. How were the criteria for exclusion defined?
      Where is this described (section, paragraph #)?
      NA

   b. Specify reasons for any discrepancy between the number of animals at the beginning and end of the study.
      Where is this described (section, paragraph #)?
      NA

Reagents

1. Have antibodies been validated for use in the system under study (assay and species)?
   NA

   a. Is antibody catalog number given?
      Where does this appear (section, paragraph #)?
      NA
b. Where were the validation data reported (citation, supplementary information, Antibodypedia)?
   Where does this appear (section, paragraph #)?
   NA

2. Cell line identity
   a. Are any cell lines used in this paper listed in the database of commonly misidentified cell lines maintained by ICLAC and NCBI Biosample?
   Where (section, paragraph #)?
   NA

   b. If yes, include in the Methods section a scientific justification of their use--indicate here in which section and paragraph the justification can be found.
   NA

   c. For each cell line, include in the Methods section a statement that specifies:
      - the source of the cell lines
      - have the cell lines been authenticated? If so, by which method?
      - have the cell lines been tested for mycoplasma contamination?
   Where (section, paragraph #)?
   NA
Data availability

Provide a Data availability statement in the Methods section under "Data availability", which should include, where applicable:

- Accession codes for deposited data
- Other unique identifiers (such as DOIs and hyperlinks for any other datasets)
- At a minimum, a statement confirming that all relevant data are available from the authors
- Formal citations of datasets that are assigned DOIs
- A statement regarding data available in the manuscript as source data
- A statement regarding data available with restrictions

See our data availability and data citations policy page for more information.

Data deposition in a public repository is mandatory for:

- Protein, DNA and RNA sequences
- Macromolecular structures
- Crystallographic data for small molecules
- Microarray data

Deposition is strongly recommended for many other datasets for which structured public repositories exist; more details on our data policy are available here. We encourage the provision of other source data in supplementary information or in unstructured repositories such as Figshare and Dryad.

We encourage publication of Data Descriptors (see Scientific Data) to maximize data reuse.

Where is the Data Availability statement provided (section, paragraph #)?

Computer code/software

Any custom algorithm/software that is central to the methods must be supplied by the authors in a usable and readable form for readers at the time of publication. However, referees may ask for this information at any time during the review process.

1. Identify all custom software or scripts that were required to conduct the study and where in the procedures each was used.

   We have used open-source (for example Chronux, ensemble reactivation analysis), as well as in built and custom script in Matlab (for example statistical tests, finding sleep epochs, performance gains, modulation depth, etc.)

2. If computer code was used to generate results that are central to the paper's conclusions, include a statement in the Methods section under "Code availability" to indicate whether and how the code can be accessed. Include version information as necessary and any restrictions on availability.

   A statement of code availability is included in Methods (Data and code availability sub-section) and specific code is available. We also make clear where publicly available code (for example Chronux toolkit) used in this study can be found.

Human subjects
1. Which IRB approved the protocol?
   Where is this stated (section, paragraph #)?
   
   NA for all topics in this section

2. Is demographic information on all subjects provided?
   Where (section, paragraph #)?

3. Is the number of human subjects, their age and sex clearly defined?
   Where (section, paragraph #)?

4. Are the inclusion and exclusion criteria (if any) clearly specified?
   Where (section, paragraph #)?

5. How well were the groups matched?
   Where is this information described (section, paragraph #)?

6. Is a statement included confirming that informed consent was obtained from all subjects?
   Where (section, paragraph #)?

7. For publication of patient photos, is a statement included confirming that consent to publish was obtained?
   Where (section, paragraph #)?

fMRI studies

For papers reporting functional imaging (fMRI) results please ensure that these minimal reporting guidelines are met and that all this information is clearly provided in the methods:

1. Were any subjects scanned but then rejected for the analysis after the data was collected?
   Where (section, paragraph #)?
   
   NA for all topics in this section

   a. If yes, is the number rejected and reasons for rejection described?
      Where (section, paragraph #)?

2. Is the number of blocks, trials or experimental units per session and/or subjects specified?
   Where (section, paragraph #)?

3. Is the length of each trial and interval between trials specified?

4. Is a blocked, event-related, or mixed design being used? If applicable, please specify the block length or how the event-related or mixed design was optimized.

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5. Is the task design clearly described?
   Where (section, paragraph #)?

6. How was behavioral performance measured?

7. Is an ANOVA or factorial design being used?

8. For data acquisition, is a whole brain scan used?
   If not, state area of acquisition.
   a. How was this region determined?

9. Is the field strength (in Tesla) of the MRI system stated?
   a. Is the pulse sequence type (gradient/spin echo, EPI/spiral) stated?
   b. Are the field-of-view, matrix size, slice thickness, and TE/TR/flip angle clearly stated?

10. Are the software and specific parameters (model/functions, smoothing kernel size if applicable, etc.) used for data processing and pre-processing clearly stated?

11. Is the coordinate space for the anatomical/functional imaging data clearly defined as subject/native space or standardized stereotaxic space, e.g., original Talairach, MNI305, ICBM152, etc? Where (section, paragraph #)?

12. If there was data normalization/standardization to a specific space template, are the type of transformation (linear vs. nonlinear) used and image types being transformed clearly described? Where (section, paragraph #)?

13. How were anatomical locations determined, e.g., via an automated labeling algorithm (AAL), standardized coordinate database (Talairach daemon), probabilistic atlases, etc.?

14. Were any additional regressors (behavioral covariates, motion etc) used?

15. Is the contrast construction clearly defined?

16. Is a mixed/random effects or fixed inference used?
   a. If fixed effects inference used, is this justified?

17. Were repeated measures used (multiple measurements per subject)?
a. If so, are the method to account for within subject correlation and the assumptions made about variance clearly stated?

18. If the threshold used for inference and visualization in figures varies, is this clearly stated?

19. Are statistical inferences corrected for multiple comparisons?
   a. If not, is this labeled as uncorrected?

20. Are the results based on an ROI (region of interest) analysis?
   a. If so, is the rationale clearly described?
   b. How were the ROI’s defined (functional vs anatomical localization)?

21. Is there correction for multiple comparisons within each voxel?

22. For cluster-wise significance, is the cluster-defining threshold and the corrected significance level defined?

Additional comments

Additional Comments