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# Sleep and quiet wakefulness signify an idling brain hub for creative insights

Mostafa R. Fayed<sup>1,2,3</sup>, Khaled Ghandour<sup>1,2,4</sup>, Kaoru Inokuchi<sup>1,2\*</sup>

<sup>1</sup>Research Centre for Idling Brain Science, University of Toyama, Toyama 930-0194, Japan

<sup>2</sup>Department of Biochemistry, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama 930-0194, Japan

<sup>3</sup>Department of Pharmacology and Toxicology, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh 33516, Egypt

<sup>4</sup>Department of Biochemistry, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt

MRF, <https://orcid.org/0000-0002-2142-8204>; KG, <https://orcid.org/0000-0002-7354-7918>; KI, <https://orcid.org/0000-0002-5393-3133>

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## Main Text

### Summary

Long-term potentiation of synaptic strength is a fundamental aspect of learning and memory. Memories are believed to be stored within specific populations of neurons known as engram cells, which are subsequently reactivated during sleep, facilitating the consolidation of stored information. However, sleep and offline reactivations are associated not only with past experiences but also with anticipation of future events. During periods of offline reactivation, which occur during sleep and quiet wakefulness, the brain exhibits a capability to form novel connections. This process links various past experiences, often leading to the emergence of qualitatively new information that was not initially available. Brain activity during sleep and quiet wakefulness is referred to as the "idling brain". Idling brain activity is believed to play a pivotal role in abstracting essential information, comprehending underlying rules, generating creative ideas, and fostering insightful thoughts. In this review, we will explore the current state of research and future directions in understanding how sleep and idling brain activity are interconnected with various cognitive functions, especially creative insights. These insights have profound implications for our daily lives, impacting our ability to process information, make decisions, and navigate complex situations effectively.

## 1 Introduction

The ultimate goal of neuroscience research is understanding how cellular activity along with electrical and molecular counterparts are translated to physiological and pathological functionality. Around half a century ago, Bliss and Lømo reported a phenomenon characterized by long-lasting enhancement of synaptic strength [1], which was later widely accepted and is now known as long-term potentiation. Several foundations paved the way for this discovery, starting with the classic concept proposed by the neuropsychologist Donald O. Hebb in 1949: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" [2]. Simply put, synapses can be strengthened upon repeated firing of post-synaptic neurons directed by pre-synaptic neurons, and this wiring leads to the formation of cellular assemblies.

Our understanding of the concept of long-term potentiation revived the term “Engram” proposed by Richard Semon back in the early 20<sup>th</sup> century [3], which represents the physical and/or chemical changes corresponding to a specific memory or learning and its associations [4]. Engrams should possess the following properties: their activity should be correlated with encoding and retrieval, and they should have the ability to be manipulated and artificially implanted, even in the silent form [4, 5]. Engrams are first formed upon encountering a new experience (encoding). Subsequently, they are reactivated during post-learning sleep, facilitating consolidation. Later, upon retrieval or recall, engram cells are reactivated and can potentially alter the behaviour of subjects [6, 7]. Memory engram populations comprising neurons that are active during experience have been identified in various brain regions, including the prefrontal cortex, retrosplenial cortex, amygdala, and hippocampal formation [8, 9]. Immense research on memory unravelled the concept of memory consolidation, which leads to memory stabilization, and post-learning sleep and quiet wakefulness states proved to be crucial for this process. This led to our appreciation of these states, for which we hypothesized that they may collectively represent an idling brain state for even more sophisticated operations than just memory. During idling states, cells in some brain regions, including the prefrontal cortex, are in an active state comparable to online wakefulness. This suggests that these periods play a role in actively processing information. The significance of idling states [10], i.e., sleep or quiet immobile awake periods, for long-term memory consolidation was highlighted long ago by Buzsáki [11] in his proposed two-stage model in which idling states represent a second stage following theta-coupled exploratory behaviours.

Over the past decade, memory and learning have been extensively studied. However, precisely how cells representing these memories behave during offline periods and later time points remains to be investigated. Additionally, the potential connection between memory reactivations and higher order brain functions requires further study. This review aims to explore recent viewpoints on the significance of offline memory reactivations during sleep and their potential correlations with various features, such as creativity, problem-solving, gist abstraction, rule comprehension, and insights. Furthermore, we will highlight potential future research directions and questions that could unravel these mysteries.

## 2 Idling as a substrate for creative cognitive supremacy

### 2.1 Idling and memory consolidation

The role of idling states for memory consolidation is well established. Significant studies have emerged reporting a prominent role of post-experience sleep in consolidating experiences, represented by reactivations of experience-related cells (called replay) during nonrapid eye movement (NREM) and rapid eye movement (REM) sleep stages [12-17]. Sleep and restful wakefulness improved auditory tone sequence learning [18]. Selective inhibition of medial septum g-aminobutyric acid-releasing neurons projecting to the dorsal hippocampus for REM stage specifically impaired the contextual engram representation [19]. Disruption of sharp wave ripples predominant in the NREM stage is known for displaying replay of place cell firing that impairs spatial memory. This probably occurs through prevention of both the spontaneous down-regulation of net synaptic weights and the reactivation of hippocampal cell assembly patterns that would have been related to future novel reinstatement [6, 20-23]. Slow wave sleep was also shown to regulate perceptual memories in a hierarchical manner through axons projecting from the secondary motor cortex (M2) to sensory regions [24].

On cellular and ensemble levels, miniature microscopes have been used to track the activity of engram and non-engram cells on the population level across longitudinal memory-processing stages (learning, sleep, retrieval) [25]. Engram cells were shown to exhibit a characteristic pattern of coordinated activity. A single engram population comprises several sub-ensembles that work in an orchestrated manner. Around half of engram sub-ensembles were reactivated later in subsequent sleep to contribute to the consolidation process of an event [26] (Figure 1). Sleep reactivation was also found to be critical for short-term memories [27]. First, short-term memory exists as a silent engram, inaccessible naturally, but after facilitated consolidation by retraining, it transforms into an active state. In brief, using a simple behavioural paradigm, such as the novel object location task, Wally et al. [27] demonstrated that short-term memory can be retrieved optogenetically at

time points when natural cues cannot induce retrieval. However, retraining after several days can induce natural recall through a facilitated consolidation approach. Optogenetic inhibition of the offline CA1 brain region (specifically during NREM periods) impaired facilitated retrieval consolidation and hence the recall of the short-term memory trace. Consolidation, memory preservation, and ensured effective retrieval upon recall are all vital roles played by sleep. Furthermore, sleep is not only related to activities regarding past behaviour. There is growing evidence indicating that sleep could affect our future decisions and their quality by boosting insights and creativity.

## 2.2 Idling ignites cognitive functions

The classic psychologists David Hartley and Sigmund Freud suggested a powerful capacity for dreams in drawing associations between awake experiences and both conscious and subconscious manifestations [28, 29]. Creativity by itself is useful for finding innovative solutions to confronting problems and tasks. Countless works of paintings, literature, and music were construed within the dreams of their originators [30-32]. Additionally, insights and creative ideas of some renowned breakthroughs, e.g., the neurohumoral transmission of impulses across synapses or the periodic table of chemical elements, emerged to their discoverers during sleep [32, 33]. The discovery of REM sleep in 1953 opened the door for immense research on the functional segregation of idling states and online capabilities [34].

REM sleep has been suggested to relate consciousness-related cognitive attributes [35]. The amount of REM sleep was found to be correlated with task performance in a category learning task [36]. To assess the involvement of REM sleep in problem-solving and creativity, human participants were required to form creative associations within a remote associates test, which they retook several hours later. Only participants who were subjected to REM sleep, but not NREM or quiet rest, showed around 40% improvement for the task, regardless of the total sleep time [37]. Another study used an anagram word puzzle to investigate creative reasoning-dependant problem solving and revealed that REM awakening resulted in 32% better performance than NREM awakening and was comparable to waking performance during the day [38]. Therefore, collective evidence suggests that being unconscious while sleeping does not necessarily mean that we are lacking attention or cognitive capabilities.

## 2.3 Creativity strikes during idling moments

Gaining sudden insight regarding the solution of a persisting problem, the so-called Aha! moment or Archimedes' Eureka! moment, may be subjectively distinct from the non-insightful and analytical trial-and-error approach for problem solving [39, 40]. Not all problems can be attempted through both approaches, neither do all individuals possess the ability to solve problems through the Aha! approach [39]. The concepts of individual differences and intra-group variations are evident in subjects suffering from sleep loss and performing various neurobehavioural tests [41]. Insightful subjects even exhibit discrete resting-state electroencephalograms compared with non-insightful subjects [42]. In line with this, creative thinkers tend to use diffused rather than focused attention strategies; this pattern is much more powerful in drawing associations among hindered hints or clues [43]. Participants who received sufficient nocturnal sleep after training gained better insights about hidden rules than participants who were forced to stay awake [33]. A recent thalamocortical network model-based report suggested that awake learning was replayed in slow waves of NREM, leading to drawing indirect associations within a transitive inference task, and a correlation was present between the amount of slow waves and the improvement in forming the associations [44]. Additionally, a recent study on both humans and rodents revealed that awake hippocampal coactivations, specifically during sharp wave ripples, represent a mnemonic shortcut for nesting inference relationships [45]. Based on this, insightful and creative thinkers seem to benefit from their idling states in drawing associations from the subconscious.

To confront this hypothesis, we designed a deductive reasoning-based inference task with hierarchy between five contexts ( $A > B > C > D > E$ ) within an arena. Mice were taught superiorities in duplicates only ( $A$  vs  $B$ ,  $B$  vs  $C$ ,  $C$  vs  $D$ , and  $D$  vs  $E$ ) [46]. They never got to experience the inference pair ( $B$  vs  $D$ ) together and thus had to

infer the superiority through forming the full hierarchy themselves. We found that sleep-deprived mice lost the ability to infer the superiority between the inference pair, in contrast to the mice that slept normally (Figure 2a). Additionally, artificially inhibiting neuronal activity in the anterior cingulate cortex (ACC) using optogenetics during either NREM or REM sleep, but not during wakefulness, abolished the ability to infer the right choice during the inference pair test. Next, the input from the medial entorhinal cortex (MEC) to the ACC specifically during REM was proven to be necessary for correct inference. Tracking the activity of cells in the ACC using the miniaturized endoscope in freely moving mice performing the reasoning-based inference task revealed that inference-related patterns (B vs D) evolved gradually, reaching their peak activation during REM just after the end of training. Conversely, training-related patterns (A vs B, B vs C, C vs D, and D vs E) were strongly coactivated during NREM. Collectively, the findings highlight the power of the idling brain and that NREM sleep is necessary for reorganizing existing knowledge and inferring the full hierarchy. REM sleep, however, favours insight abstraction about indirect relationships. These findings are in agreement with the complementary roles of NREM and REM for gist extraction and constructing novel associations, respectively, as proposed by Lewis et al. [47].

## 2.4 Memory assimilation necessitates periods of idling

Since birth, we are trained to assimilate knowledge, and through this early psychological functioning, we learn a basic template and then try to crudely assimilate learning [29]. The opportunistic assimilation theory states that intense incubation can result in collecting hints that can later be creatively associated for gaining insights [43]. Breger [29] suggested that due to the flexibility of dreams and their range of availability for psychological elements, they might serve as a hub for creatively assimilating aroused structures within the memory system. If multiple memories are adequately similar, a need arises to merge them, and sleep might enable this reorganization to take place [48]. Mechanistically, integrating new learning into already formed knowledge, a process known as schema assimilation, might rely less on the hippocampus than on the frontal cortical regions, such as the prelimbic cortex or ACC [49, 50]. Additionally, the amount of sleep spindles is correlated with schema-like task performance, where new learning is integrated into pre-existing knowledge [51].

In context, the inferred sequential sorting of novel experiences can be traced within sharp wave ripple-based subsequent resting replay events according to the previously learned sequence sorting rule [52]. For this, we examined the brain's spatiotemporal mechanism for emergence of assimilation and proposed that offline idling brain activity might control this process. Rodents are known to comprehend geometrical differences and similarities in their environment [53]. We used this fact to show that mice can form assimilations between two contexts that share geometrical analogy and separated by 1 day of sleep, rather than two contexts that are geometrically distinct and separated by 1 day of sleep [54] (Figure 2b). For this assimilation to occur, idling activity in the medial prefrontal cortex, and specifically the ACC but not the prelimbic cortex, is required. Labelling engram cell populations for the original context and then selectively disrupting them during the subsequent assimilation sleep period disrupted the assimilation machinery but not the original memory. Visualizing neural calcium activities using a miniature endoscope revealed that co-reactivations of cells representing the two events being assimilated together during idling were higher than the non-assimilated events. It seems that drawing associations between commonalities takes place during idling states, during which the ACC is involved in extracting these implicit relationships.

## 3. Conclusions and perspectives

Memory-bearing cells are often referred to as "Engram cells". Reactivation of engram cells in subsequent sleep and offline periods is crucial for the survival of memories and their recall when the appropriate cues are presented. Evidence suggests that sufficient sleep is indispensable for cognitive functions, to the point that we can implement novel knowledge during sleep. Additionally, the quiet wakefulness, NREM, and REM periods seem to play distinct and crucial roles. For instance, the N1 stage of NREM is the creative sweet spot, quiet

wakefulness periods are optimal for inferring associations, and the roles of NREM and REM are complementary for creative insights and nesting assimilations.

It seems that recent advancements in technology have allowed researchers to make large strides in understanding the roles of idling states. Still, open questions remain to be elucidated. There is an increasing demand for investigating the role of sleep in higher cognitive functions, such as problem-solving, planning, artistry, insight, complex decisions, and creativity (Figure 3). We should also bridge the gap between rodent, non-human primate, and human idling research because each has its own sleeping pattern and staging criteria. Furthermore, our knowledge regarding brain machinery on the molecular, cellular, and assembly levels is still incomplete, and the exact functional segregation between discrete idling states is yet to be fully explored. All of these research gaps warrant future studies with innovative experimental designs.

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## References

- [1] Bliss, T. V. P. & Lømo, T. 1973 Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology* **232**, 331-356. (DOI:<https://doi.org/10.1113/jphysiol.1973.sp010273>).
- [2] Hebb, D. O. 1949 *The organization of behavior : a neuropsychological theory* / D.O. Hebb. New York, Wiley.
- [3] Semon, R. W. 1904 *Die Mneme als erhaltendes Prinzip im Wechsel des organischen Geschehens*. Leipzig, Wilhelm Engelmann.
- [4] Josselyn, S. A. & Tonegawa, S. 2020 Memory engrams: Recalling the past and imagining the future. *Science* **367**, eaaw4325. (DOI:[doi:10.1126/science.aaw4325](https://doi.org/10.1126/science.aaw4325)).
- [5] Nambu, M. F., Lin, Y.-J., Reuschenbach, J. & Tanaka, K. Z. 2022 What does engram encode?: Heterogeneous memory engrams for different aspects of experience. *Current Opinion in Neurobiology* **75**, 102568. (DOI:<https://doi.org/10.1016/j.conb.2022.102568>).
- [6] Girardeau, G., Benchenane, K., Wiener, S. I., Buzsáki, G. & Zugaro, M. B. 2009 Selective suppression of hippocampal ripples impairs spatial memory. *Nature Neuroscience* **12**, 1222-1223. (DOI:[10.1038/nn.2384](https://doi.org/10.1038/nn.2384)).
- [7] Joo, H. R. & Frank, L. M. 2018 The hippocampal sharp wave-ripple in memory retrieval for immediate use and consolidation. *Nature Reviews Neuroscience* **19**, 744-757. (DOI:[10.1038/s41583-018-0077-1](https://doi.org/10.1038/s41583-018-0077-1)).
- [8] Tonegawa, S., Liu, X., Ramirez, S. & Redondo, R. 2015 Memory Engram Cells Have Come of Age. *Neuron* **87**, 918-931. (DOI:<https://doi.org/10.1016/j.neuron.2015.08.002>).
- [9] Asai, H., Ohkawa, N., Saitoh, Y., Ghandour, K., Murayama, E., Nishizono, H., Matsuo, M., Hirayama, T., Kaneko, R., Muramatsu, S.-i., et al. 2020 Pcdh  $\beta$  deficiency affects hippocampal CA1 ensemble activity and contextual fear discrimination. *Molecular Brain* **13**, 7. (DOI:[10.1186/s13041-020-0547-z](https://doi.org/10.1186/s13041-020-0547-z)).

- [10] Buzsáki, G. & Fernández-Ruiz, A. 2019 Utility of the Idling Brain: Abstraction of New Knowledge. *Cell* **178**, 513-515. (DOI:<https://doi.org/10.1016/j.cell.2019.07.004>).
- [11] Buzsáki, G. 1989 Two-stage model of memory trace formation: A role for “noisy” brain states. *Neuroscience* **31**, 551-570. (DOI:[https://doi.org/10.1016/0306-4522\(89\)90423-5](https://doi.org/10.1016/0306-4522(89)90423-5)).
- [12] Pavlides, C. & Winson, J. 1989 Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *The Journal of Neuroscience* **9**, 2907-2918. (DOI:10.1523/jneurosci.09-08-02907.1989).
- [13] Wilson, M. A. & McNaughton, B. L. 1994 Reactivation of Hippocampal Ensemble Memories During Sleep. *Science* **265**, 676-679. (DOI:doi:10.1126/science.8036517).
- [14] Skaggs, W. E. & McNaughton, B. L. 1996 Replay of Neuronal Firing Sequences in Rat Hippocampus During Sleep Following Spatial Experience. *Science* **271**, 1870-1873. (DOI:doi:10.1126/science.271.5257.1870).
- [15] Lee, A. K. & Wilson, M. A. 2002 Memory of Sequential Experience in the Hippocampus during Slow Wave Sleep. *Neuron* **36**, 1183-1194. (DOI:[https://doi.org/10.1016/S0896-6273\(02\)01096-6](https://doi.org/10.1016/S0896-6273(02)01096-6)).
- [16] Louie, K. & Wilson, M. A. 2001 Temporally Structured Replay of Awake Hippocampal Ensemble Activity during Rapid Eye Movement Sleep. *Neuron* **29**, 145-156. (DOI:[https://doi.org/10.1016/S0896-6273\(01\)00186-6](https://doi.org/10.1016/S0896-6273(01)00186-6)).
- [17] Euston, D. R., Tatsuno, M. & McNaughton, B. L. 2007 Fast-Forward Playback of Recent Memory Sequences in Prefrontal Cortex During Sleep. *Science* **318**, 1147-1150. (DOI:doi:10.1126/science.1148979).
- [18] Gottselig, J. M., Hofer-Tinguely, G., Borbély, A. A., Regel, S. J., Landolt, H. P., Rétey, J. V. & Achermann, P. 2004 Sleep and rest facilitate auditory learning. *Neuroscience* **127**, 557-561. (DOI:<https://doi.org/10.1016/j.neuroscience.2004.05.053>).
- [19] Boyce, R., Glasgow, S. D., Williams, S. & Adamantidis, A. 2016 Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* **352**, 812-816. (DOI:doi:10.1126/science.aad5252).
- [20] Diba, K. & Buzsáki, G. 2007 Forward and reverse hippocampal place-cell sequences during ripples. *Nature Neuroscience* **10**, 1241-1242. (DOI:10.1038/nn1961).
- [21] Jiang, X., Gonzalez-Martinez, J. & Halgren, E. 2019 Coordination of Human Hippocampal Sharpwave Ripples during NREM Sleep with Cortical Theta Bursts, Spindles, Downstates, and Upstates. *The Journal of Neuroscience* **39**, 8744-8761. (DOI:10.1523/jneurosci.2857-18.2019).
- [22] Norimoto, H., Makino, K., Gao, M., Shikano, Y., Okamoto, K., Ishikawa, T., Sasaki, T., Hioki, H., Fujisawa, S. & Ikegaya, Y. 2018 Hippocampal ripples down-regulate synapses. *Science* **359**, 1524-1527. (DOI:doi:10.1126/science.aaa0702).
- [23] van de Ven, G. M., Trouche, S., McNamara, C. G., Allen, K. & Dupret, D. 2016 Hippocampal Offline Reactivation Consolidates Recently Formed Cell Assembly Patterns during Sharp Wave-Ripples. *Neuron* **92**, 968-974. (DOI:<https://doi.org/10.1016/j.neuron.2016.10.020>).
- [24] Miyamoto, D., Hirai, D., Fung, C. C. A., Inutsuka, A., Odagawa, M., Suzuki, T., Boehringer, R., Adaikkan, C., Matsubara, C., Matsuki, N., et al. 2016 Top-down cortical input during NREM sleep consolidates perceptual memory. *Science* **352**, 1315-1318. (DOI:doi:10.1126/science.aaf0902).
- [25] Ohkawa, N. & Ghandour, K. 2022 Miniature Microscopy of Hippocampal CA1 to Identify Engram Cells and Record Calcium Transients for Analyses of Ensemble Activities. In *Behavioral Neurogenetics* (ed. D. Yamamoto), pp. 157-174. New York, NY, Springer US.
- [26] Ghandour, K., Ohkawa, N., Fung, C. C. A., Asai, H., Saitoh, Y., Takekawa, T., Okubo-Suzuki, R., Soya, S., Nishizono, H., Matsuo, M., et al. 2019 Orchestrated ensemble activities constitute a hippocampal memory engram. *Nat Commun* **10**, 2637. (DOI:10.1038/s41467-019-10683-2).
- [27] Wally, M. E., Nomoto, M., Abdou, K., Murayama, E. & Inokuchi, K. 2022 A short-term memory trace persists for days in the mouse hippocampus. *Communications Biology* **5**, 1168. (DOI:10.1038/s42003-022-04167-1).
- [28] Stickgold, R., Hobson, J. A., Fosse, R. & Fosse, M. 2001 Sleep, Learning, and Dreams: Off-line Memory Reprocessing. *Science* **294**, 1052-1057. (DOI:doi:10.1126/science.1063530).
- [29] Breger, L. 1967 Function of dreams. *Journal of Abnormal Psychology* **72**, 1-28. (DOI:10.1037/h0025040).

- [30] Ritter, S. M. & Mostert, N. 2017 Enhancement of Creative Thinking Skills Using a Cognitive-Based Creativity Training. *Journal of Cognitive Enhancement* **1**, 243-253. (DOI:10.1007/s41465-016-0002-3).
- [31] Barrett, D. 2017 Dreams and creative problem-solving. *Annals of the New York Academy of Sciences* **1406**, 64-67. (DOI:<https://doi.org/10.1111/nyas.13412>).
- [32] Schredl, M. & Erlacher, D. 2007 Self-Reported Effects of Dreams on Waking-Life Creativity: An Empirical Study. *The Journal of Psychology* **141**, 35-46. (DOI:10.3200/JRLP.141.1.35-46).
- [33] Wagner, U., Gais, S., Haider, H., Verleger, R. & Born, J. 2004 Sleep inspires insight. *Nature* **427**, 352-355. (DOI:10.1038/nature02223).
- [34] Aserinsky, E. & Kleitman, N. 1953 Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, During Sleep. *Science* **118**, 273-274. (DOI:doi:10.1126/science.118.3062.273).
- [35] Senzai, Y. & Scanziani, M. 2022 A cognitive process occurring during sleep is revealed by rapid eye movements. *Science* **377**, 999-1004. (DOI:doi:10.1126/science.abp8852).
- [36] Djonlagic, I., Rosenfeld, A., Shohamy, D., Myers, C., Gluck, M. & Stickgold, R. 2009 Sleep enhances category learning. *Learning & Memory* **16**, 751-755. (DOI:10.1101/lm.1634509).
- [37] Cai, D. J., Mednick, S. A., Harrison, E. M., Kanady, J. C. & Mednick, S. C. 2009 REM, not incubation, improves creativity by priming associative networks. *Proceedings of the National Academy of Sciences* **106**, 10130-10134. (DOI:doi:10.1073/pnas.0900271106).
- [38] Walker, M. P., Liston, C., Hobson, J. A. & Stickgold, R. 2002 Cognitive flexibility across the sleep-wake cycle: REM-sleep enhancement of anagram problem solving. *Cognitive Brain Research* **14**, 317-324. (DOI:[https://doi.org/10.1016/S0926-6410\(02\)00134-9](https://doi.org/10.1016/S0926-6410(02)00134-9)).
- [39] Bowden, E. M., Jung-Beeman, M., Fleck, J. & Kounios, J. 2005 New approaches to demystifying insight. *Trends in Cognitive Sciences* **9**, 322-328. (DOI:<https://doi.org/10.1016/j.tics.2005.05.012>).
- [40] Jung-Beeman, M., Bowden, E. M., Haberman, J., Frymiare, J. L., Arambel-Liu, S., Greenblatt, R., Reber, P. J. & Kounios, J. 2004 Neural Activity When People Solve Verbal Problems with Insight. *PLOS Biology* **2**, e97. (DOI:10.1371/journal.pbio.0020097).
- [41] Van Dongen, P. A., Baynard, M. D., Maislin, G. & Dinges, D. F. 2004 Systematic Interindividual Differences in Neurobehavioral Impairment from Sleep Loss: Evidence of Trait-Like Differential Vulnerability. *Sleep* **27**, 423-433. (DOI:10.1093/sleep/27.3.423).
- [42] Kounios, J., Fleck, J. I., Green, D. L., Payne, L., Stevenson, J. L., Bowden, E. M. & Jung-Beeman, M. 2008 The origins of insight in resting-state brain activity. *Neuropsychologia* **46**, 281-291. (DOI:<https://doi.org/10.1016/j.neuropsychologia.2007.07.013>).
- [43] Ansburg, P. I. & Hill, K. 2003 Creative and analytic thinkers differ in their use of attentional resources. *Personality and Individual Differences* **34**, 1141-1152. (DOI:[https://doi.org/10.1016/S0191-8869\(02\)00104-6](https://doi.org/10.1016/S0191-8869(02)00104-6)).
- [44] Tadros, T. & Bazhenov, M. 2022 Role of Sleep in Formation of Relational Associative Memory. *The Journal of Neuroscience* **42**, 5330-5345. (DOI:10.1523/jneurosci.2044-21.2022).
- [45] Barron, H. C., Reeve, H. M., Koolschijn, R. S., Perestenko, P. V., Shpektor, A., Nili, H., Rothaermel, R., Campo-Urriza, N., O'Reilly, J. X., Bannerman, D. M., et al. 2020 Neuronal Computation Underlying Inferential Reasoning in Humans and Mice. *Cell* **183**, 228-243.e221. (DOI:<https://doi.org/10.1016/j.cell.2020.08.035>).
- [46] Abdou, K., Aly, M. H., Ibrahim, A. Z., Choko, K., Nomoto, M., Okubo-Suzuki, R., Muramatsu, S.-i. & Inokuchi, K. 2023 Prefrontal coding of learned and inferred knowledge during REM & NREM sleep. *bioRxiv*, 2021.2004.2008.439095. (DOI:10.1101/2021.04.08.439095).
- [47] Lewis, P. A., Knoblich, G. & Poe, G. 2018 How Memory Replay in Sleep Boosts Creative Problem-Solving. *Trends in Cognitive Sciences* **22**, 491-503. (DOI:<https://doi.org/10.1016/j.tics.2018.03.009>).
- [48] Heald, J. B., Lengyel, M. & Wolpert, D. M. 2023 Contextual inference in learning and memory. *Trends in Cognitive Sciences* **27**, 43-64. (DOI:<https://doi.org/10.1016/j.tics.2022.10.004>).
- [49] Tse, D., Takeuchi, T., Takeyama, M., Kajii, Y., Okuno, H., Tohyama, C., Bito, H. & Morris, R. G. M. 2011 Schema-Dependent Gene Activation and Memory Encoding in Neocortex. *Science* **333**, 891-895. (DOI:doi:10.1126/science.1205274).

- [50] Wang, S.-H., Tse, D. & Morris, R. G. M. 2012 Anterior cingulate cortex in schema assimilation and expression. *Learning & Memory* **19**, 315-318. (DOI:10.1101/lm.026336.112).
- [51] Jakke, T., Jessica, D. P., Robert, S., Erin, J. W. & Gaskell, M. G. 2010 Sleep Spindle Activity is Associated with the Integration of New Memories and Existing Knowledge. *The Journal of Neuroscience* **30**, 14356. (DOI:10.1523/JNEUROSCI.3028-10.2010).
- [52] Liu, Y., Dolan, R. J., Kurth-Nelson, Z. & Behrens, T. E. J. 2019 Human Replay Spontaneously Reorganizes Experience. *Cell* **178**, 640-652.e614. (DOI:<https://doi.org/10.1016/j.cell.2019.06.012>).
- [53] Wills, T. J., Lever, C., Cacucci, F., Burgess, N. & O'Keefe, J. 2005 Attractor Dynamics in the Hippocampal Representation of the Local Environment. *Science* **308**, 873-876. (DOI:doi:10.1126/science.1108905).
- [54] Aly, M. H., Abdou, K., Okubo-Suzuki, R., Nomoto, M. & Inokuchi, K. 2022 Selective engram coreactivation in idling brain inspires implicit learning. *Proceedings of the National Academy of Sciences* **119**, e2201578119. (DOI:doi:10.1073/pnas.2201578119).



## Figure captions

Figure 1. Activation of engram cell ensembles (filled circles with solid line) during learning, replay, and retrieval

(a) Engram cells activated as several sub-ensembles during novel contextual learning.

(b) Reactivation of sub-ensembles during subsequent sleep.

(c) Reactivated sub-ensembles during sleep are mostly active during the retrieval session.

Figure 2. Sleep is crucial for higher order brain functions such as inference and assimilation

(a) Mice are trained on a series of contexts having a hierarchical order ( $A > B$ ,  $B > C$ ,  $C > D$ , and  $D > E$ ) and asked to choose between two contexts (B and D) that were never presented together. Sleep is essential to gain inference and choose the right answer.

(b) Sleep is necessary to transfer fear memory to a geometrically relevant (triangle, top) but not irrelevant context (circle, bottom) and to form the assimilation.

Figure 3. Idling moments are closely related to higher order brain functions such as gaining insights, problem-solving, planning, future direction, assimilation, and inference.

## Figures

Figure 1

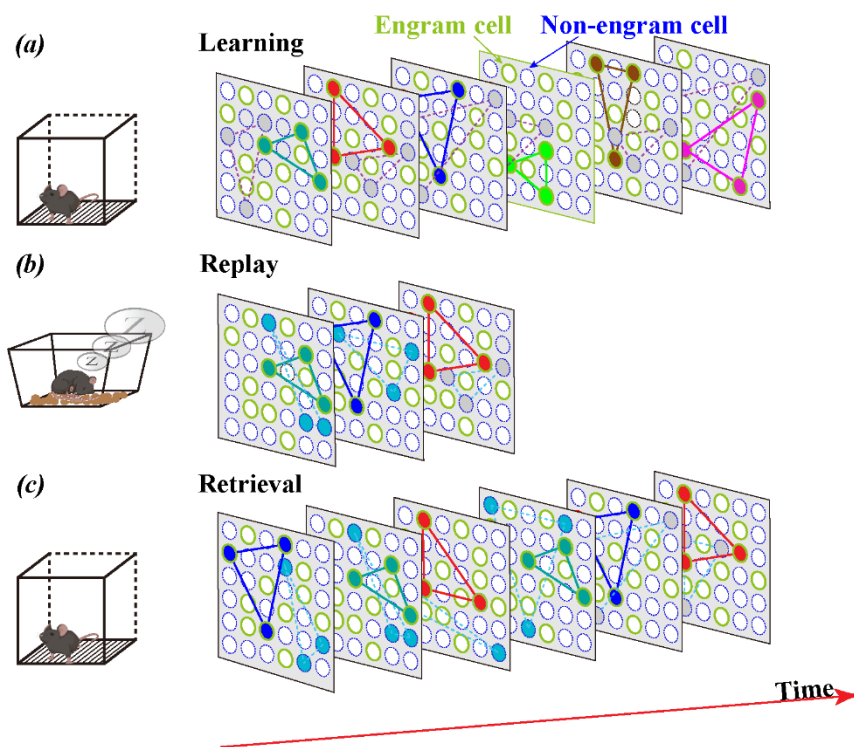


Figure 2

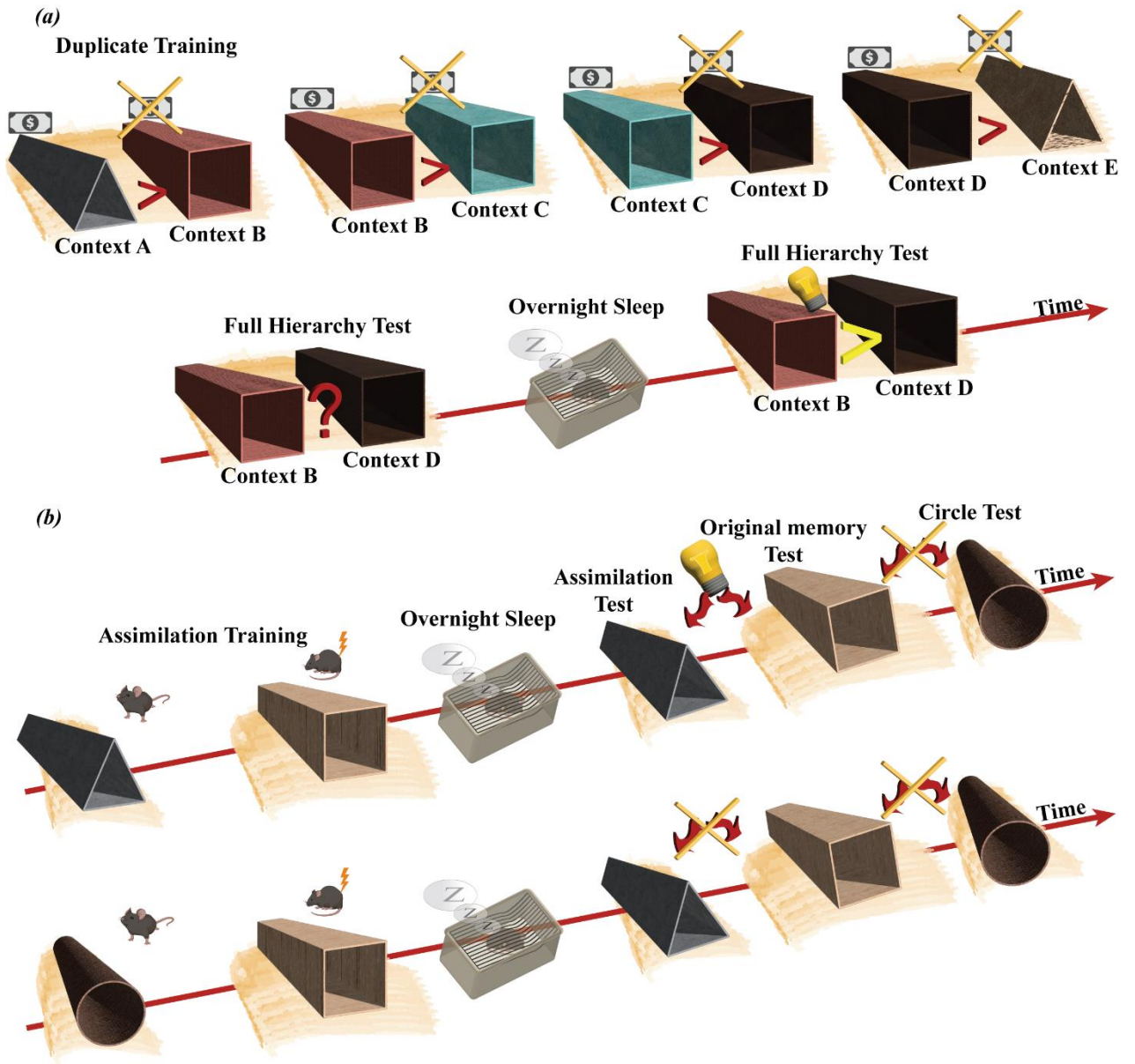
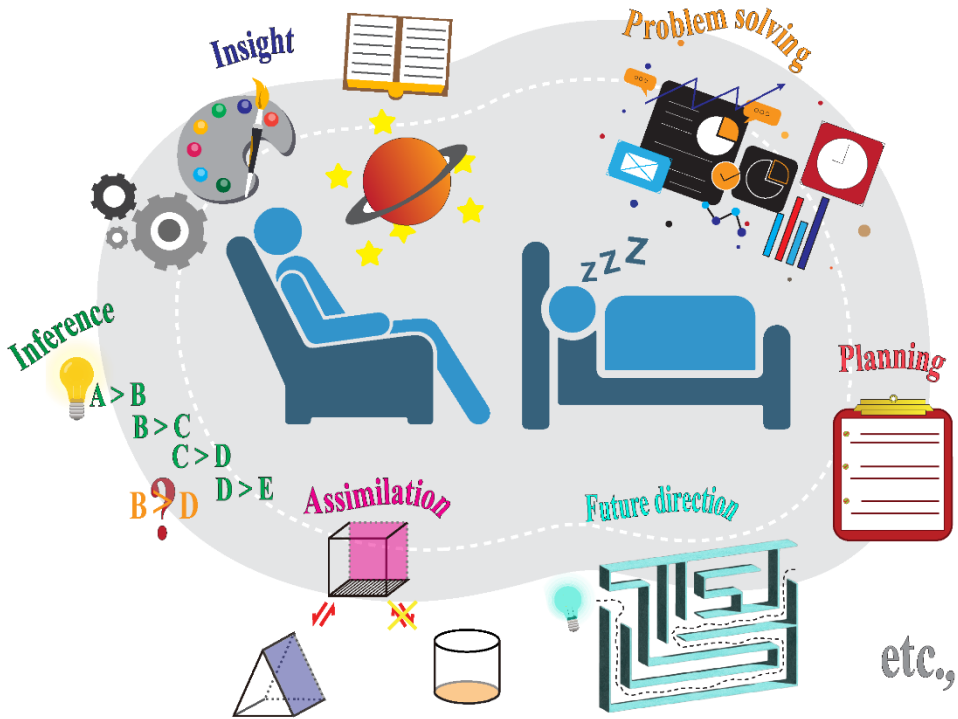


Figure 2

Figure 3



# Additional Information

## **Authors' Contributions**

M.R.F., K.G., and K.I. contributed equally to the conception and writing of the manuscript.

## **Competing Interests**

*We have no competing interests.*