The electrophysiological analysis suggests that there is a relationship between PUFAs and the endocannabinoid system, and biochemical interrogation supports a more direct effect. Specifically, CB_1R coupling was diminished in the n-3–deficient mice. Although the eCBs anandamide and 2-arachidonoylglycerol were present at normal levels in the brain extracts from n-3–deficient mice, increased sensitivity to CB_1R antagonists is consistent with a higher synaptic endocannabinoid concentration, which cannot be readily measured. The authors speculated that an increase would have then led to a subsequent desensitization of the CB_1R pathway, as is observed in the animals.

Lafourcade *et al.*[3] also carried out behavioral studies of the n-3–deficient mice. They found baseline decreases in forced swim test performance in the n-3–deficient mice, which returned to normal after tricyclic antidepressant treatment. In addition, the mice were tested for social and exploratory behaviors that are known to be sensitive to changes in cannabinoid pathway stimulation or blockade. The n-3–deficient mice did not engage new mice socially and they avoided exploration of open fields. Lafourcade *et al.*[3] directly tested the effect of cannabinoid agonists in open-field behavior and found that n-3–deficient mice lacked the anxiogenic response seen in mice fed an n-3–rich diet. However, the limited response to the agonist could be due to a floor effect resulting from the baseline changes seen in the mice. Moreover, the anxiolytic effect of CB_1R stimulation is an example of the complex relationship between eCBs and mood, which in turn complicates the interpretation of the behavioral role of PUFAs.

The health consequences of modern diets are substantial and the mechanisms of these effects are the subjects of much debate. Among the many changes, the ratio of n-6 to n-3 PUFAs remains an important candidate for deleterious effects. By connecting these dietary effects to CNS eCB systems, Lafourcade *et al.*[3] help to make cellular sense of some clinical and epidemiological reports. Although the effects are open to some interpretation, there are clearly behavioral consequences of altered PUFA ratios. These results also help focus future efforts in both human and animal studies of PUFA modifications on eCB systems and behavior.

In the end, how important are PUFA ratios to mood and depression? The mixed results in the literature are unsurprising, as diet is a factor that interacts with other environmental (for example, stress) and biological (for example, genetic) factors to influence the incidence of depression in the population. One attractive element of dietary influence is that it is relatively easy to change this factor, as compared with changing genes or reducing life stress. At the same time, this simplicity has motivated a large industry of supposed treatments for depression, obesity and many other complex disorders. Lafourcade *et al.*[3], in contrast, contribute new and important neurobiology to this discussion and challenge us to think anew about dietary influences on mood. In particular, interactions between diet and stress response deserve more directed neurobiological analysis. For example, biochemical responses to stress may influence the efficiency of biochemical reactions needed for the production of functional long-chain PUFAs from short-chain dietary sources. It is worth noting relationships between fatty acids and inflammation[9], which has in turn been linked to depression and other neurological disorders.

Nutritional influence on depression serves as an example of important behavioral consequences of diet. The widespread synaptic effects of eCBs[8] suggest that the current work has implications that extend beyond mood-related behaviors. Although the authors argue for anatomical specificity of effects by demonstrating no change in the motor cortex, broad effects on behavior might be expected even if the PUFA-eCB interactions are restricted to the prefrontal cortex and nucleus accumbens. Modulation of eCB function in these brain regions would be expected to affect a range of behaviors related to food intake, obesity and drug addiction[10,11]. Food intake would be of particular interest, considering the recent rejection of rimonabant for the treatment of obesity. This CB_1R inverse agonist showed promising effects on body weight, but also increased rates of suicide and depression in patients[12,13]. Lafourcade *et al.*'s study[3] will focus future efforts on evaluating the role of eCBs and related neural plasticity in PUFA-regulated behavior.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Logan, A.C. *Lipids Health Dis.* **3**, 25 (2004).
2. Stahl, L.A., Begg, D.P., Weisinger, R.S. & Sinclair, A.J. *Curr. Opin. Investig. Drugs* **9**, 57–64 (2008).
3. Lafourcade, M. *et al. Nat. Neurosci.* **14**, 345–350 (2011).
4. Simopoulos, A.P. *Biomed. Pharmacother.* **56**, 365–379 (2002).
5. Marszalek, J.R. & Lodish, H.F. *Annu. Rev. Cell Dev. Biol.* **21**, 633–657 (2005).
6. Innis, S.M. *J. Nutr.* **137**, 855–859 (2007).
7. Banni, S. & Di Marzo, V. *Mol. Nutr. Food Res.* **54**, 82–92 (2010).
8. Kano, M., Ohno-Shosaku, T., Hashimotodani, Y., Uchigashima, M. & Watanabe, M. *Physiol. Rev.* **89**, 309–380 (2009).
9. Orr, S.K. & Bazinet, R.P. *Curr. Opin. Investig. Drugs* **9**, 735–743 (2008).
10. Kauer, J.A. & Malenka, R.C. *Nat. Rev. Neurosci.* **8**, 844–858 (2007).
11. Matias, I. & Di Marzo, V. *Trends Endocrinol. Metab.* **18**, 27–37 (2007).
12. Christensen, R., Kristensen, P.K., Bartels, E.M., Bliddal, H. & Astrup, A. *Lancet* **370**, 1706–1713 (2007).
13. Di Marzo, V. & Szallasi, A. *Br. J. Pharmacol.* **154**, 915–917 (2008).

Sleep on it!: stabilizing and transforming memories during sleep

Jessica D Payne

A new study finds that memory reactivation during slow-wave sleep following learning can stabilize memories. Reactivation during wakefulness has the opposite effect, rendering memories labile and susceptible to modest modification.

In the 2004 movie *Eternal Sunshine of the Spotless Mind*, protagonist Joel Barish undergoes a procedure that erases all memories of his painful relationship with his free-spirited ex-girlfriend, Clementine. This process occurs at a fictitious company called Lacuna, Inc., whose name is a clever reference to 'lacunar amnesia': memory loss for a specific event. Interestingly, the procedure for the memory erasure occurs while he sleeps.

As far-fetched as this fictional story might seem, past studies have demonstrated that seemingly permanent memories can be returned to a labile state following reactivation, at which point they can be disrupted unless they are reconsolidated[1]. This notion is in stark contrast with a long-held view arguing that memories are malleable for a limited time after they are

Jessica D. Payne is in the Department of Psychology, University of Notre Dame, Notre Dame, Indiana, USA.
e-mail: jpayne7@nd.edu

acquired, but become consolidated, or fixed permanently, in the brain as time passes[2]. In contrast to the memory erasure that occurs in the aforementioned movie, Diekelmann *et al.*[3] find that memory reactivation during post-learning slow-wave sleep (SWS) can stabilize memories, making them more robust in subsequent recall.

Diekelmann and colleagues[3] extend previous findings by examining whether reactivating memories during SWS produces similar labilization as that seen during waking reactivation. This is a timely question because many studies have shown that neural activity seen during wakeful learning can be reactivated during sleep[4]. Such nocturnal replay of neural activity is thought to aid memory consolidation, with reactivation during SWS being particularly beneficial for hippocampus-dependent memories[4].

Diekelmann *et al.*[3] trained human participants in the evening on a hippocampus-dependent card-location task similar to the memory game Concentration. The training occurred in either the presence or absence of an odor that would later serve as a memory cue. The subjects then either stayed awake or went to sleep for 40 min, during which time they were exposed to the odor. For those who learned the task in the presence of the odor and thus associated it with the card-location task, this re-exposure to the odor presumably acted as a reminder for the task and triggered reactivation of the memory trace. Immediately after the 40-min delay spanning wakefulness or sleep, subjects learned a different set of card-location pairings that was meant to interfere with the original memory.

If reactivation renders the memory malleable, then the new pairings should be incorporated into the original memory, thus interfering with performance at a later memory test. As expected, Diekelmann *et al.*[3] found that presenting the odor during wakefulness rendered memories susceptible to interference. Surprisingly, reactivation during SWS did not labilize, but rather stabilized, memories for the original card-pair locations, resulting in less susceptibility to the influence of new information. Moreover, functional magnetic resonance imaging of the subjects showed that reactivating memories during SWS activated the hippocampus and posterior cortical regions, whereas reactivation during wakefulness primarily activated the prefrontal cortex. Thus, the same reactivation cue (the odor) had different effects on memory processing depending on whether the brain was in a state of wakefulness or sleep. It will be fascinating to determine whether this SWS-based stabilization can be detected across the longer (for example, 24-hour) delay intervals that are more typical of the delays used in animal reconsolidation studies[1].

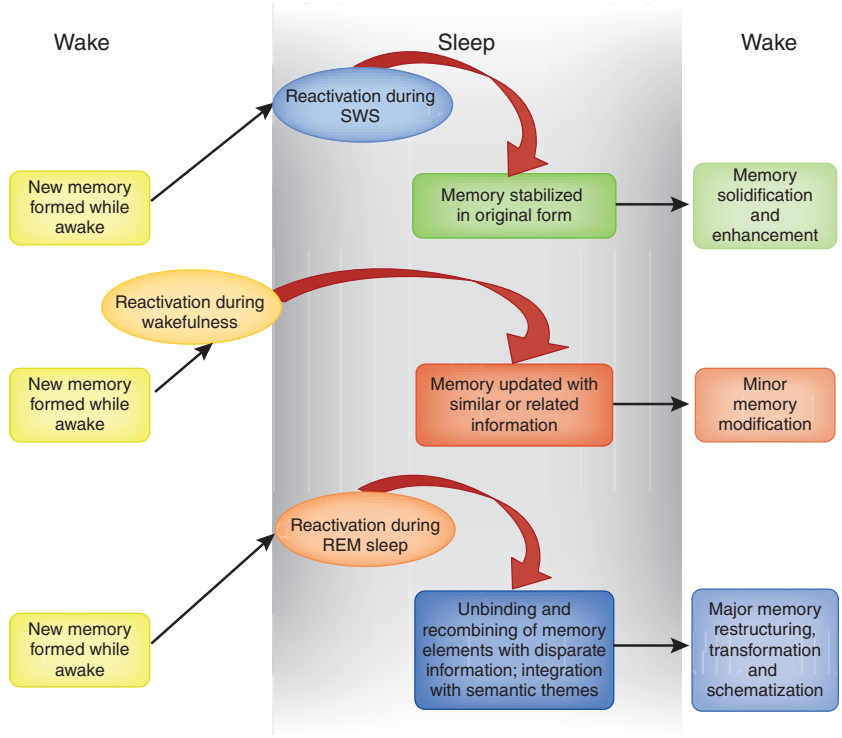

Figure 1 Potential influence of memory reactivation during wakefulness and different stages of sleep. Top: reactivation during SWS causes enhancement and stabilization of memory in its original form, leading to memories that are true representations of originally encoded experience. Reactivating memories during SWS by re-presenting a memory cue (such as an odor) present at initial learning leads to memory stabilization[3]. Middle: reactivation during wakefulness causes memory modification and updating, allowing new but related information to be incorporated into the original memory trace[5,6]. Bottom: reactivation during REM sleep causes substantial memory restructuring and recombination of memory fragments that become isolated in the REM-sleep brain state. Such recombination may lead to insights, creative solutions to problems and memory schematization.

Assuming that the cue triggers roughly similar neural patterns and cognitive processes during wake and sleep (admittedly a big assumption), these findings suggest that reactivating memories during different states of brain activity may serve different purposes. Reactivation during SWS apparently serves to solidify memories, whereas reactivation during wakefulness serves to update memories with related information[5]. This isn't to say that memory is rendered completely malleable when recalled during wakefulness, or even that it should be. Indeed, recent studies place important boundary conditions on how much and under which circumstances memories can be modified during wakefulness[1,5]. Moreover, evidence in humans is limited to very modest forms of updating, often in the form of incorporating semantically similar information into a pre-existing memory[6].

The finding that SWS stabilizes reactivated memories fits well with evidence that SWS can improve performance on hippocampus-dependent tasks the next day[4]. It makes sense that memories would be solidified rather than modified during SWS given that there is minimal mental content in SWS (relative to the elaborate dreams of rapid eye movement (REM) sleep or the intense mental activity of wakefulness) that might overwrite the new information. However, memory retrieval, and thus reactivation, during wakefulness is a different matter. Waking memory retrieval is not only more likely to be a fully conscious process associated with rich mental content, but it is also often triggered when we encounter information that is similar or related to the original memory, allowing updating of the original memory content as needed[5]. For example, say you reactivate your schema for the concept 'reproach' because you learn that a new word, 'upbraid', is similar in meaning. This would allow the updating of the concept with this new word. Or perhaps your partner finally proves to you that his or her version of your first date together is correct. Presumably, one of you won't be sleeping through the conversation. If you were wrong, the memory trace needs to be updated and corrected, if only to avoid another argument with your spouse about getting it wrong again later.

Unlike the traditional view of consolidation, which implies that memories become fixed in their original form, reconsolidation

theory can account for such memory updating during wakefulness[1,5,6]. But can it also account for more drastic forms of memory restructuring? In many cases, our long-term memories are not faithful reproductions but are instead reconstructions or even distortions of experience[7]. Thus, a memory may not be so much a fixed entity as a dynamic process that changes with the passage of time. Although this might seem strikingly maladaptive, such plasticity in memory might allow us to flexibly recombine stored information so that we can develop insight into hidden rules[8], integrate information and draw inferences[9], generalize and selectively remember some aspects of experience while forgetting others[10]. Notably, all of these effects require time and sleep to emerge. But given that SWS appears to stabilize memories, when do these changes occur?

The current findings raise the question of what effect(s) memory reactivation during other stages of sleep, particularly REM sleep, might have. Unlike SWS, REM sleep is a highly active brain state that might allow for memory transformations in which knowledge is restructured in useful, adaptive and sometimes highly creative ways. REM sleep and a process known as unbinding were recently suggested as being critical factors for inducing qualitative transformation of memory[10,11]. If literal remembrance of an experience requires binding its various features to maintain an intact representation in memory[7], then unbinding those features may be critical for memory restructuring (**Fig. 1**). REM sleep may be responsible for these changes, with studies directly demonstrating a role for REM sleep in creative problem solving[12] and the priming of distant semantic associates[13]. If unbinding during REM sleep is involved in major memory modification, how might it work?

When memories are reactivated during REM sleep, transient destabilization might loosen synaptic connections binding components of experience in the hippocampus (or in hippocampal-neocortical ensembles) while activating more distant (weakly associated) cortico-cortical connections. As hippocampal connections are loosened, transfer to neocortical storage sites would support fundamental changes to the memory, including schematization, incorporation of less obvious or less familiar associations, and broadening of semantic networks. REM sleep might provide the ideal neurochemical milieu for such restructuring: acetylcholine levels are high, hippocampal output is blocked (perhaps allowing unchecked communication within cortico-cortical links in the absence of hippocampal indexing), cortisol is elevated[11] and the immediate-early gene *Egr1*, also known as *Zif268* and apparently important for reconsolidation[14], is expressed[15]. It remains to be tested whether similar molecular mechanisms are involved in the memory stabilization during SWS seen by Diekelmann *et al.*[3].

Diekelmann *et al.*[3] wisely focused on SWS, demonstrating that reactivation during this state is involved in memory stabilization. Future experiments will have to address REM sleep's role in reactivation and labilization of memories, as well as how such labilization might help build schemas and detect hidden connections. The different stages of sleep and wakefulness might provide different opportunities to reactivate memories, and reactivation during these different neurochemical states could have vastly different effects on memory. The Diekelmann *et al.* study[3] represents an exciting first step in understanding how and when memories form, persist and change, and raises fascinating theoretical questions about the adaptive nature of a memory system that may be less about retrieving the past and more about using it to behave adaptively in an ever-changing present and an unknown future.

The adaptive nature of memory begs the question of whether intentionally erasing painful experiences from mind, as Joel did at Lacuna, Inc., is a smart thing to do. Rather than losing our negative memories, which could be downright dangerous and doom us to repeat our mistakes, might it not be better to harness the power of reconsolidation to learn from our mistakes instead? Diekelmann *et al.*[3], in this fascinating study of sleep and hippocampus-dependent memory reconsolidation, show us that SWS is not the time for this. Future studies should determine whether REM sleep might be.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

1. Nader, K. & Einarsson, E.O. *Ann. NY Acad. Sci.* **1191**, 27–41 (2010).
2. McGaugh, J.L. *Science* **287**, 248–251 (2000).
3. Diekelmann, S., Buchel, C., Born, J., & Rasch, B. *Nature Neurosci.* **14**, 381–386 (2011).
4. Peigneux, P. *et al. Neuron* **44**, 535–545 (2004).
5. Lee, J.L.C. *Trends Neurosci.* **32**, 413–420 (2009).
6. Hupbach, A., Gomez, R., Hardt, O. & Nadel, L. *Learn. Mem.* **14**, 47–53 (2007).
7. Schacter, D.L. *Am. Psychol.* **54**, 182–203 (1999).
8. Wagner, U., Gais, S. Haider, H., Veleger, R. & Born, J. *Nature* **427**, 352–355 (2004).
9. Ellenbogen, J.M., Hu, P.T., Payne, J.D., Titone, D. & Walker, M.P. *Proc. Natl. Acad. Sci. USA* **104**, 7723–7728 (2007).
10. Payne, J.D. & Kensinger, E.A. *Curr. Dir. Psychol. Sci.* **19**, 290–295 (2010).
11. Payne, J.D. *Int. Rev. Neurobiol.* **92**, 101–134 (2010).
12. Cai, D.J., Mednick, S.A., Harrison, E.M., Kanady, J.C. & Mednick, S.C. *Proc. Natl. Acad. Sci. USA* **106**, 10130–10134 (2009).
13. Stickgold, R. *et al. J. Cogn. Neurosci.* **11**, 182–193 (1999).
14. Bozon, B., Davis, S. & Laroche, S. *Neuron* **40**, 695–701 (2003).
15. Ribeiro, S. *et al. J. Neurosci.* **22**, 10914–10923 (2002).

Presynaptic NMDA receptors also make the switch

Andrés Buonanno

A study shows that NR3A–containing presynaptic NMDA receptors regulate glutamate release, and that a switch in subunit composition underlies the developmental loss of spike timing–dependent LTD at cortical synapses.

In spike timing–dependent plasticity (STDP), the precise temporal association of pre- and postsynaptic spiking events bidirectionally regulates synaptic strength. STDP is important for the maturation of neuronal circuits and could be altered in disease states. Owing to their specialized gating properties, both pre- and postsynaptic NMDA receptors (NMDARs) function as excellent coincidence detectors, and NMDARs are known to modulate spike timing–dependent long-term potentiation and depression (tLTD) at many cortical synapses[1].

In the primary visual cortex, there is a developmental switch at visual cortical synapses that reduces spontaneous glutamate release and the ability to induce tLTD[2], for which the molecular basis has been unknown. Using an impressive combination of genetic, pharmacological and histological approaches, Philpot and colleagues[3] now report how the regulated expression of the NR3A subunit can account for a developmental switch of presynaptic NMDAR

Andrés Buonanno is in the Program of Developmental Neurobiology, Section on Molecular Neurobiology, Eunice Shriver Kennedy National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA.
e-mail: buonanno@mail.nih.gov