To sleep: perchance to learn

Robert Stickgold

Not only can the sleeping brain perceive sensory information, it can learn from this information, leading to changed behaviors the next day: it can come to associate a sound with a pleasant or unpleasant odor and react, both while still asleep and after waking, with a deeper or shallower breath. But classic 'sleep learning' remains just a dream.

When we were both in high school, Nate Bossen tested his theory of 'learning by osmosis', using his Latin textbook as a pillow the night before an exam. He flunked his test and we both considered the issue closed. We were unaware of Simons and Emmons' more rigorous experiments reported in 1956 (ref. 1). They asked 21 subjects 96 factual questions and subsequently played recordings giving the answers at 5-min intervals across a night of sleep. The results were clear. The subjects recalled not a single new fact that they had been exposed to during electroencephalograpy-verified sleep. And thus the issue sat for over half a century. Now, in this issue of *Nature Neuroscience*, Arzi *et al.*[2] refute this longstanding belief, showing that humans can indeed learn while they're asleep and can act on this knowledge both while still asleep and after awakening the next morning.

In retrospect, this perhaps should not be so surprising. The past 20 years have provided evidence that such an ability might exist. In 1990, Smith and Weeden[3] showed that replaying auditory stimuli previously presented during training on a complex cognitive task during rapid eye movement (REM) sleep leads to enhanced task performance a week later, and, in 1995, Hennevin *et al.*[4], using direct brain stimulation in sleeping rats, demonstrated that the brain can both encode and consolidate memories during REM sleep. Over the past decade, evidence of the wide range of memory processing that occurs during sleep has continued to grow[5]. Not only does sleep consolidate and enhance memories[6], it can selectively retain emotional elements from complex scenes[7], integrate new memories into existing memory networks[8], extract the gist from a complex set of stimuli[9] and even foster insight[10]. In addition, both sounds[11] and odors[12] presented during task training can boost sleep-dependent performance enhancement if re-presented during sleep. Still, in none of these studies did externally presented stimuli actually lead to learning new things during sleep.

The success of Arzi *et al.*'s study lies in its elegant design[2]. First, the task did not require the subject to learn new facts, just an association between a tone and an aversive odor. Although learning simple facts might seem simple, it requires complex brain systems that are involved in the phonologic, semantic and syntactic interpretation of speech, all of which would need to be functioning effectively during sleep if sleep learning of such facts were to occur. Only after such interpretation succeeded could the brain potentially go on to store this new information as a memory.

But in Arzi *et al.*'s study, the sleeping brain only needed to be able to distinguish between three tones, spread across an octave and a half, and to distinguish aversive odors (for example, rotten fish) from pleasant ones (for example, shampoo). Both of these discriminations during sleep had already been demonstrated by others[11,12], so the only question remaining was whether the brain could learn, during sleep, to associate the one with the other.

The second trick of the design was the use of an implicit measure of learning, the

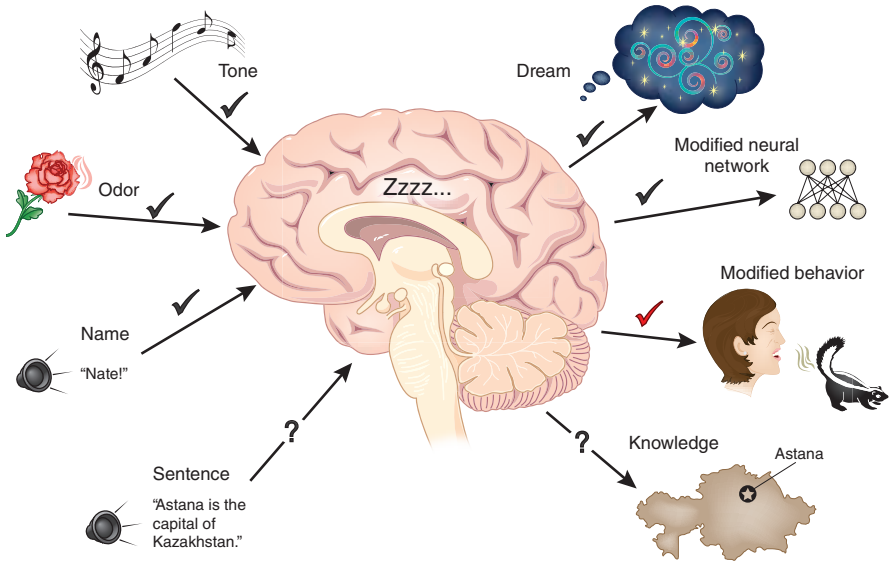

Figure 1 Sleep learning. The sleeping brain is able to discriminate tones and odors and to respond preferentially to one's name. More complex processing of auditory input has not been demonstrated. The dreaming brain can, however, produce complex language output. And it has now been found to be able to learn in response to sensory inputs, modifying subsequent sleep and waking behavior (red checkmark)[2]. Nonetheless, evidence of true sleep learning—acquiring new declarative knowledge while sleeping—remains elusive.

Robert Stickgold is in the Department of Psychiatry, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts, USA.
e-mail: rstickgold@hms.harvard.edu

sniff response[13]. When subjects inhale a pleasant odor, the inhalation volume is greater than when they inhale an unpleasant odor[14], and, although an earlier study by the same group failed to find a difference between pleasant and unpleasant odors during sleep[13], Arzi *et al.*[2] found significantly larger inhalation volumes after pleasant odors than after unpleasant ones, during both REM and non-REM sleep. So the sleeping brain could distinguish the odors and the stage was set for the actual test. Pleasant and unpleasant odors were presented to sleeping subjects, paired with different tones. When the tones were presented the next morning without their accompanying odors, the pleasant odor tone produced a 13% larger inhalation volume than the unpleasant odor tone[2].

Notably, this learned response could already be seen during the night. After the sleeping subjects had been trained with the tone-odor pairs, subsequent presentations of the tones alone, still during sleep, produced 9% larger inhalation volumes after the pleasant odor tone, with similar effects seen in both REM and non-REM sleep. Curiously, when the differential response the next morning was broken down by when the subjects experienced the tone-odor pairs, only the non-REM presentations led to a significant differential response the next morning. Why this would be, as learning clearly occurred during both sleep phases, remains unknown, despite valiant efforts by the authors to provide a convincing rationale for the state difference.

So what can I tell my old friend Nate? Well, sleeping on your Latin textbook will probably never work. But some forms of information, presented to you while you sleep, can make it into your brain, and you can learn from these stimuli (**Fig. 1**). Might playing a tape recording of his Latin have worked better? Probably not. We are able to process new information while awake without consciously perceiving it, but such processing appears to be limited and 'intellectually much simpler'[15] than would be needed for Latin. Although the cleverness of Arzi *et al.*'s[2] design allowed them to extend these findings of unconscious learning to sleep learning, it offers no particular hope for more complex forms of sleep learning. Still, the past decade's studies of sleep-dependent memory processing have demonstrated that the sleeping brain can perform sophisticated memory processing[5], suggesting that the problem is more with getting the information into the brain than getting the brain to learn it. Indeed, the dreaming brain is clearly able to construct phonologically, syntactically and semantically accurate statements, so maybe there's still hope. Nate, *dormio ergo cogito*!

COMPETING FINANCIAL INTERESTS
The author declares competing financial interests: details are available at http://www.nature.com/doifinder/10.1038.nn3223.

1. Simon, C.W. & Emmons, W.H. *Science* **124**, 1066–1069 (1956).
2. Arzi, A. *et al. Nat. Neurosci.* **15**, 1460–1465 (2012).
3. Smith, C. & Weeden, K. *Psychiatr. J. Univ. Ott.* **15**, 85–90 (1990).
4. Hennevin, E., Hars, B., Maho, C. & Bloch, V. *Behav. Brain Res.* **69**, 125–135 (1995).
5. Walker, M.P. & Stickgold, R. *Nat. Rev. Neurosci.* **11**, 218–219 (2010).
6. Karni, A., Tanne, D., Rubenstein, B.S., Askenasy, J.J. & Sagi, D. *Science* **265**, 679–682 (1994).
7. Payne, J.D., Stickgold, R., Swanberg, K. & Kensinger, E.A. *Psychol. Sci.* **19**, 781–788 (2008).
8. Dumay, N. & Gaskell, M.G. *Psychol. Sci.* **18**, 35–39 (2007).
9. Payne, J.D. *et al. Neurobiol. Learn. Mem.* **92**, 327–334 (2009).
10. Wagner, U., Gais, S., Haider, H., Verleger, R. & Born, J. *Nature* **427**, 352–355 (2004).
11. Rudoy, J.D., Voss, J.L., Westerberg, C.E. & Paller, K.A. *Science* **326**, 1079 (2009).
12. Rasch, B., Buchel, C., Gais, S. & Born, J. *Science* **315**, 1426–1429 (2007).
13. Arzi, A. *et al. Chem. Senses* **35**, 31–40 (2010).
14. Bensafi, M. *et al. Nat. Neurosci.* **6**, 1142–1144 (2003).
15. Greenwald, A.G. *Am. Psychol.* **47**, 766–779 (1992).

Arc illuminates Alzheimer's pathophysiology

Mario M Dorostkar & Jochen Herms

Pathological alterations in Alzheimer's disease disrupt neuronal network function. An *in vivo* imaging study using a fluorescent reporter of neuronal activity finds dysfunction specifically in those neurons near amyloid plaques.

Forgetfulness, emotional disturbances and loss of body functions make patients suffering from Alzheimer's disease often appear to be as helpless as infants. At late stages of the disease, many neurons have been lost as a result of accumulation of extracellular β-amyloid plaques and intracellular deposits of hyperphosphorylated tau protein. Yet the disease usually has its onset many years earlier, with mild cognitive impairment and much less pronounced pathological alterations in the brains of affected individuals. Early stages of the disease, before neurodegeneration, also manifest neuronal dysfunction at the synaptic level[1]. Not much is known, however, about the precise relationship between amyloid plaque formation and neuronal dysfunction, particularly relating to the spatial and temporal time course of neuronal dysfunction near amyloid plaques. A study by Rudinskiy *et al.*[2] in this issue of *Nature Neuroscience* shows a functional disruption in the neuronal network associated with visual activity in an animal model of Alzheimer's disease, and this aberrant activity is especially strong near amyloid plaques.

Although the precise mechanisms by which amyloid plaques cause neuronal dysfunction are unclear, there is accumulating evidence that amyloid plaques constitute the initial insult, with tau hyperphosphorylation being a necessary downstream effect[3]. To study plaque-associated pathology, Rudinskiy *et al.*[2] chose a mouse model that expresses two mutations in proteins critical for amyloid production, which are found in patients with familial Alzheimer's disease. These mice develop numerous amyloid plaques as they age and show deficiencies in cognitive tasks[4]. As a reporter of neuronal activity, the authors used a transgenic mouse, the *Arc::dVenus* mouse[5], that expresses the fluorescent protein dVenus under the *Arc* (also known as *Arg3.1*) promoter. *Arc* is an immediate-early gene whose expression is tightly regulated by neuronal activity[6] and has been shown to be important for memory formation[7]. Thus, when neuronal activity increases, more fluorescent protein will accumulate inside a neuron, and it can be visualized in living animals under a multiphoton microscope. As this particular fluorescent protein is also rapidly degraded, fluorescence can be observed only for a limited period of time. The *Arc::dVenus* model therefore provides readout of neuronal activity over a time window of several hours. This is in contrast with widely used calcium sensors, which provide readout of a neuron's current activity. The advantage of the *Arc::dVenus* model is that it provides a measure of activity over a relatively large amount of time without the need to restrain or anesthetize the experimental animals during the presentation of

Mario M. Dorostkar and Jochen Herms are in the Department of Translational Brain Research, DZNE (German Center for Neurodegenerative Diseases), Munich, Germany, and Mario M. Dorostkar is at the Center for Neuropathology, Ludwig Maximilian University, Munich, Germany.
e-mail: jochen.herms@med.uni-muenchen.de