

NEUROSCIENCE

A memory boost while you sleep

Robert Stickgold

It is generally agreed that sleep aids memory consolidation, but the reasons for this are a mystery. Part of the answer may lie in the patterns of synchronous brain activity unique to the state of slumber.

Only ten years ago, discussions about the purpose of sleep offered great hypotheses, but these were based on flimsy evidence. So scant were the data that some researchers argued that sleep might have no use at all. This led Alan Rechtschaffen, a pioneer in the area, to comment wryly that “if sleep doesn’t serve an absolutely vital function, it is the biggest mistake evolution ever made.” Since then, researchers have produced a wealth of evidence for at least one function of slumber — the consolidation of memories. A wide range of converging data show that memories are replayed¹, modified², stabilized³ and even enhanced⁴ as we snooze, but an understanding of how this occurs remains elusive. The proposed mechanisms rely on two effects that are observed in the brain only during sleep: alterations in the levels of chemical neuromodulators⁵ and distinctive oscillations of electrical activity⁶. In this issue (page 610)⁶, Marshall *et al.* provide evidence for the second mechanism*. They show that the direct induction of ‘cortical slow oscillations’ during sleep can improve the recall of word-pairs memorized the previous night.

Human sleep is divided into rapid-eye-movement sleep (REM) and non-REM sleep (NREM), with NREM sleep further divided into stages 1 to 4. These sleep phases are distinguished, in part, by well-defined patterns of oscillatory electrical activity in the brain, as measured by electroencephalography. Theta waves oscillate at 4–8 Hz, and are characteristic of REM sleep; NREM stage 1 is a transitional phase between full wakefulness and sleep, and is characterized by mixed-frequency waves; sleep spindles (12–14 Hz) typify NREM stage 2; and delta waves (1–4 Hz) distinguish NREM stages 3 and 4, which are known collectively as slow-wave sleep. Sleep spindles and delta waves rise and fall in concert with a yet slower (<1 Hz) oscillatory pattern known as cortical slow oscillations — it is these patterns that Marshall *et al.*⁶ have studied.

The authors asked 13 volunteers to learn 46 word-pairs in a training session before they went to sleep. Electrodes were then placed on the scalps of the sleeping subjects, and fluctuating electrical potentials were applied to induce cortical slow oscillations. Remarkably, the morning after this treatment, the subjects demonstrated enhanced recall of the word-pairs compared with their performance the morning after receiving a sham stimulation. This

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effect was not seen for all forms of memory. For example, no improvement was observed for a motor-skill procedural memory task — learning to trace around a shape by looking at its image in a mirror. Furthermore, the memory boost occurred only if the electrical stimulation matched the oscillation frequency of cortical slow waves (0.75 Hz) and not when the stimulation was at the theta frequency (5 Hz) of REM sleep. The time chosen for the stimulation was also crucial — the authors observed no effect on recall if stimulation was during the last 45 minutes of the night instead of the first 45 minutes.

The actual increase in words recalled was small; averaged over the whole group, the subjects remembered only 1.8 more words after stimulation than they did after the sham treatment. But the improvement in subjects’ recall compared with their performance during the training session was statistically significant — on average, after stimulation, 4.8 more words were remembered by the group in the morning than had been recalled the previous night, compared with just 2.1 more words in the control experiments. These increases probably do not reflect a genuine overnight improvement, because they were based on comparisons with performance during the training session (when the words would have been imperfectly memorized), not after it (when peak performance would be expected). Nevertheless, sleep-dependent consolidation, enhanced by direct electrical stimulation, does seem to stabilize memories. But why does this happen?

The authors began electrical stimulation of the subjects’ brains 4 minutes after the volunteers had entered stage 2 of NREM sleep — that is, 5 to 10 minutes before they would normally be expected to progress into slow-wave sleep; the stimulation was applied in five 5-minute periods, separated by stimulation-free pauses lasting 1 minute each. Marshall and colleagues’ analysis of the stimulation-free interludes revealed greater electrical activity in the subjects’ brains at slow-oscillation frequencies (up by 60%) and at sleep-spindle frequencies (up by 51%), as well as a 37% increase in the amount of time spent in slow-wave sleep, compared with sham stimulation in the same subjects. Arguably, any of these effects could underlie the observed enhancement of memory consolidation. Indeed, sleep spindles⁷ and the duration of slow-wave sleep⁸ have previously been implicated in memory consolidation. But

Marshall *et al.*⁶ argue that the spindles are the key players. Spindles produce large influxes of calcium ions into cortical neurons, where they can trigger molecular cascades known to strengthen the connections between neurons — which presumably leads to memory consolidation⁹.

Might the effects⁶ of electrical stimulation be caused by alterations in the levels of neuromodulatory chemicals? The authors argue that they are not. They measured blood levels of some of these compounds — cortisol, growth hormone and noradrenaline — and reported no changes from normal as a result of the stimulation. Other neuromodulators were not studied, most notably acetylcholine, which is known to be involved in memory formation. This crucial point requires further exploration, as earlier reports from the same group indicate that low levels of acetylcholine⁵ and cortisol¹⁰ are required for sleep-dependent consolidation of memories.

Such uncertainty indicates a need for continued research into sleep-dependent memory consolidation. But rapid resolution will not come soon, as several complicating issues remain unresolved. First, many different memory systems exist — those involved in memorizing word-pairs may be different from those required for learning to ride a bicycle, or those concerned with recalling the details of an emotional event. Memory consolidation in different systems clearly correlates with different stages of sleep, and possibly even with different components of those stages. Second, consolidation seems to be a series of events, but we do not know which of these are sleep-dependent (within any given memory system). Finally, our understanding of the cellular and molecular mechanisms underlying waking memory consolidation is still highly primitive. It is time for sleep researchers to tackle these basic issues. ■

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DEVICE PHYSICS

A terahertz modulator

Daniel Mittleman

Tiny metal resonators can be used to create a material with tunable responses to an applied voltage. Combined with a semiconductor substrate, they can be used to control technologically promising terahertz radiation.

Electromagnetic radiation with frequencies lying between the microwave region and the infrared — so-called terahertz radiation — holds great promise for imaging and sensing applications. It is non-ionizing, and therefore causes less damage to biological tissue than conventional, higher-energy X-rays. It penetrates plastics and clothing, but not metal, and so is ideal for security screening and non-contact testing or inspection. But to realize the full potential of terahertz radiation, more sophisticated techniques for its generation, manipulation and detection are required. In this issue, Chen *et al.* (page 597)¹ fill an important gap in our capabilities. They report the development of an efficient, electrically driven modulator for terahertz signals that functions at room temperature.

This work builds on exciting developments in the field of metamaterials. These are materials engineered to have electromagnetic responses that are impossible in naturally occurring materials, such as a negative refractive index. The refractive index of a material, n , is a measure of the speed of light in the material, and is given by $n = (\mu\epsilon)^{1/2}$, where μ is the material's 'permeability' to magnetic fields, and ϵ its 'permittivity' to electric fields. All naturally occurring materials have positive μ ; transparent materials have positive ϵ , too. In these normal materials, therefore, the refractive index is a real and positive number.

In 1968, the Soviet physicist Victor Veselago showed² that a hypothetical material with negative ϵ and μ would also have a real refractive index, meaning that light waves could propagate through the material, but would behave as though its refractive index were negative. This material would have unusual and potentially valuable properties. A flat slab of negative-index material, for example, would focus light in much the same way as a curved slab of ordinary material (a lens), but with a smaller focal spot.

Although negative-index materials do not violate any laws of physics, the absence of a medium with negative μ confined the idea to the realm of speculation. But in the late 1990s, John Pendry found that, by assembling a collection

of appropriately designed metallic structures, a material can be fabricated that has both negative ϵ and negative μ for incident electromagnetic radiation of a particular frequency^{3,4}. Furthermore, if the metal structures are each much smaller than the wavelength of the incident radiation, the radiation interacts with them not individually, but collectively, according to their average properties. These are the engineered materials now known as metamaterials.

Engineering a material with negative ϵ was easy: this equates to opacity, a property of all metals for incident radiation below a certain frequency. It was necessary to show only that a discrete set of thin metallic structures could mimic this property of the bulk metal⁵. The more difficult task was achieving a negative μ . It turned out that this could be done using a pair of concentric metallic rings with gaps that prevent current from circulating. Because these rings are both capacitors (they store electric charge) and inductors (they induce magnetic fields that self-sustain any current flowing through them), the presence of gaps leads to a resonant response, with charge accumulating alternately on one side of the gap and then the other, sloshing back and forth through the rings rather as a mass vibrates back and forth on a spring. At frequencies near the characteristic frequency of this resonant electron flow, ϵ and μ can vary dramatically as a function of frequency. Indeed, either one can become negative if the resonance is strong enough⁴.

The development of the split-ring-resonator concept was significant not only because it permits a negative refractive index, but more generally because it represents a new technique for 'designing' the optical response of a medium. The first experimental demonstration of a negative index⁵, along with nearly all research into metamaterials until now, was performed in the microwave regime. This region encompasses gigahertz frequencies below the terahertz regime, with wavelengths of several millimetres or longer. It was almost immediately recognized, however, that the approach could be extended into the shorter-wavelength, terahertz regime simply by shrinking

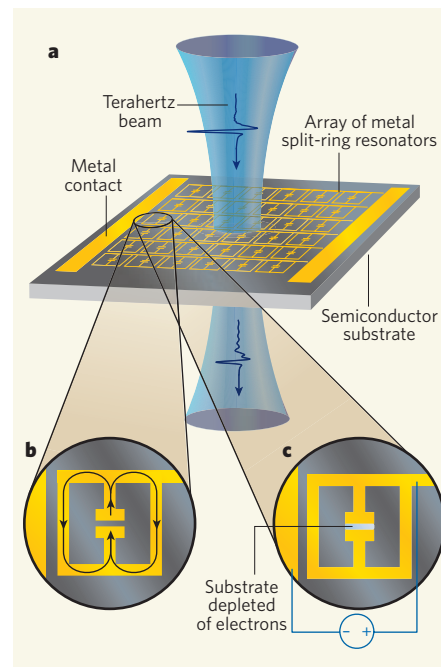


Figure 1 Chen and colleagues' resonant metamaterial modulator¹. **a**, The tunable resonant response of an array of metallic split-ring resonators on a thin semiconductor substrate can be exploited as a modulator, letting more or less of an incident radiation beam through. **b**, When no external voltage is applied, the doped semiconducting substrate conducts. Current circulates around the two lobes of the resonator in response to the applied terahertz field. **c**, When an external voltage is applied, the semiconductor ceases to conduct. Current can no longer flow through the ring gap; this gap instead behaves as a capacitor, storing up charge. The capacitance gives rise to a resonant behaviour at a frequency in the terahertz range, in which the electrons slosh back and forth between the upper and lower gap electrodes. The incident terahertz radiation drives this resonance efficiently, leading to the transfer of more energy from the beam to the electrons of the substrate. Thus, less radiation is transmitted through the device.

the size of the individual metallic components so that they remained smaller than the incident radiation's wavelength. At 1 THz, this is 300 μm , so the fabrication of a negative-index medium requires the technically challenging construction of three-dimensional objects with micrometre-scale features. Two-dimensional patterns on that scale, on the other hand, can be easily generated using conventional photolithography, and these patterns can be designed to exhibit a strong resonance in either ϵ or μ at any frequency of interest.

Chen *et al.*¹ use the split-ring-resonator concept as the basis for a metamaterial that provides a resonant response in ϵ — although not a negative refractive index — in the terahertz range. Furthermore, they have shown that this resonance can be externally controlled, and therefore can be exploited as a modulator for controlling the transmission of terahertz electromagnetic radiation.