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NEUROSCIENCE

Off to night school

One of sleep's most important functions is processing memory. Researchers are now starting to figure out how the brain helps us learn when we're asleep.

BY KERRI SMITH

Neuroscientist Jan Born is quietly jealous of his eight-month-old daughter. "She sleeps when she wants," he says. Then again, he says, sleep is a crucial time for learning, and she probably has more to learn about the world than the average adult. "I think about whether she needs this sleep because her hippocampus is full," he says.

The hippocampus is a node in the brain's memory network, the place memories are first encoded for transferral later to longer-term storage. Sleep is one way its contents are downloaded to other regions of the brain where it is thought they are interpreted and stored. "We know that during sleep the brain processes a wide range of memory types," says Robert Stickgold, a neuroscientist at Beth Israel Deaconess Medical Centre in Boston, Massachusetts.

Researchers know that a bit of shut-eye helps you recall all manner of things, from newly acquired motor skills, such as how to play the piano, to what you wore to the theatre last night.

But sleep is not a passive storage process, like saving a video file to a hard drive. Sleep also reconfigures memory. It helps us edit the files — adding or removing content or emotional tone, for example — and re-save them. "This isn't just memory representation getting stronger," says Born, who studies sleep and memory at the University of Tübingen in Germany. "Memories are reactivated and reprocessed."

And just what is it about the sleeping brain that makes it a memory machine? "We don't know how it does any of this," says Stickgold, "because no one knows how a memory is formed." But that is not going to stop scientists from trying to find out. Working in humans and animal models, researchers are documenting how the sleeping brain behaves, and trying to link that activity to the vast and complex constellation of information it stores.

MEMORY MAKER

A night's sleep has five distinct phases, which the brain cycles through roughly every 90 minutes. In rapid eye movement (REM) sleep, the brain's electrical activity looks much as it does when someone is awake. Researchers assumed that REM was when dreams took place — and that in dreams, perhaps, memories are consolidated, the brain replaying the day's experiences and storing them as enduring recollections.

In support of this idea, in the mid-1990s, researchers at the Weizmann Institute of Science in Rehovot, Israel, showed that sleep helped to improve learning. People performing a task that involved searching a screen for symbols were better at it after they had slept, and that boost particularly correlated with REM sleep[1]. The finding triggered an interest in searching sleep for the root of memory.

But it is clear now that memory processing — and even dreaming — are not the exclusive preserve of REM sleep. The REM phase may help us deal with the emotional processing that memories often need (see 'The dark night', page S14). But much of the legwork of memory is done during other phases of sleep — helping the brain shuffle memories around, reactivating them in the hippocampus, editing them in areas such as the prefrontal cortex, and returning them to areas of the cortex nearer the hippocampus for longer-term storage and retrieval (see 'The anatomy of sleep', page S2). "All parts of sleep contribute in some way," says Matthew Wilson, a neuroscientist at the Massachusetts Institute of Technology (MIT) in Cambridge.

Since the late 1990s, many researchers have been concentrating on the role of slow-wave sleep in memory. Slow-wave sleep is a phase of deep sleep in which the cortex produces very low-frequency electrical oscillations of around 1 Hz that spread through the brain.

The shift in focus to slow-wave sleep is not necessarily because it is more interesting than REM, but it is easier to study. Brain activity is at a more consistent level, and the patterns of activity found in slow-wave sleep can be more readily tied to recent experience. In rats, for example, the same patterns of activity can be seen while the animals explore a maze and when they later sleep. "Non-REM sleep has been more accessible physiologically," Wilson says. "That's where the data are."

There is now plenty of evidence that slow-wave sleep helps consolidate memories. Born's experiments show that brain regions coordinate their slow-wave activity during sleep in people who have been asked to learn lists of word associations[2]. Synchronizing the activity of groups of neurons is thought to be one way in which the brain gets different areas to cooperate to encode new information.

By contrast, disordered sleep may lead to disordered memory. Stickgold's team has shown that people with schizophrenia have fewer sleep 'spindles' — half-second bursts of activity in stage 2 non-REM sleep, the stage before slow-wave sleep. Perhaps as a result, these patients recall learned movements less easily the following day than non-schizophrenic sleepers[3].

CHASING THE TRACE

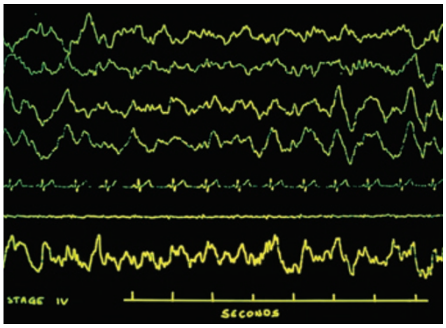
Nobody really knows how these oscillations in brain activity during sleep act at the cellular level to strengthen memory traces. But then, memory in general remains frustratingly mysterious. "If we could pinpoint the location of a single memory," says Stickgold, "we could figure out how sleep changes it."

Work in animals is helping to solve the puzzle. Scientists can insert electrodes that record directly from neurons in a brain region such as the hippocampus, bringing them one step closer to the action than monitoring brain oscillations, which are produced by lots of neurons firing at once. "Animal work gives you access to the basic mechanisms and the degree of control required to test hypotheses," says Wilson, who studies rats.

The evidence so far indicates that, in animals, slow oscillations happen when cells in the hippocampus are busy replaying recollections from the day. For example, in the rat brain, researchers recorded patterns of activity that looked like memories being played back, at the same time as they saw slow oscillations, suggesting that they are functionally linked. Assuming that, at the basic neuronal level, human memory is not radically different to that of lab animals, a similar process could occur during human slow-wave sleep.

At MIT, Wilson and his colleague Daniel Bendor have taken the study of memory one step further. They showed it was possible to influence memory replay in sleeping rats, using cues to prompt and consolidate specific memories[4]. "That's always been the holy grail, to demonstrate the link between memories and specific behaviours," says Wilson. They trained rats to run to the left or right of a track, depending on which of two tones was played. Then, while the rats were asleep, they recorded electrical activity directly from neurons in the hippocampus. By playing a tone associated with the left or right turn, they could influence the replay of the rats' spatial memory of the maze — in essence, manipulating the rats' 'dream' of turning left or right.

Wilson, Bendor and others now want to go beyond the hippocampus, looking at how memories are stored elsewhere. "The story that everyone tells is that sleep is important for transferring memories to the rest of the brain," says Loren Frank, who studies memory at the University of California, San Francisco. "But the problem is there's basically no direct evidence for this idea." There are indirect hints from functional magnetic resonance imaging (fMRI) studies that memories are transferred via an inner brain region called the striatum to the cortex for long-term storage, but the pathway still needs to be confirmed.



Brain and muscle activity traces in slow-wave sleep.

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SLEEP TIGHT

How much time your brain spends in slow-wave mode could influence the value of a night's sleep. Children spend more time in slow-wave sleep than adults, and Born wanted to see if this made a difference to how they recalled a task.

In a study published earlier this year, Born and colleagues asked children and adults to press a sequence of buttons depending on which one was lit at the time. Then they let them sleep. In the morning, both groups were asked to recall the series from memory, without performing the task. Children were better at converting their practice of the task, which gave them implicit knowledge about the sequence, as shown by the decreasing time it took them to press the buttons, to explicit knowledge about it — a memory of the task sequence they could reproduce on demand[5]. This greater explicit knowledge was linked to children's greater slow-wave activity, suggesting that adults who spend longer in slow-wave sleep could reap the benefits too.

Work from neuroscientist Matthew Walker's lab at the University of California, Berkeley, focuses on what happens to memory in our twilight years. "We know as we get older our ability for learning and memory gets worse," Walker says. His team wanted to know whether the decline had anything to do with sleep (see 'Amyloid awakenings', page S19). A study using recordings of electrical brain activity during sleep, and fMRI after sleep to investigate patterns of brain activity during recall of a task, suggested that we are no longer as efficient at laying down new memories as we age. A reduction in the amount of deep, slow-wave sleep seems to be crucial[6]. "Older people can't generate the depth of sleep — so they can't hit the 'save' button so easily."

Older brains may be losing their plasticity — the ability to adapt and change dependent on experience, which underlies learning. Neuroscientist Marcos Frank at the University of Pennsylvania in Philadelphia has shown how sleep and plasticity interact in cats. He covered one of the cats' eyes during a critical period of development when they were a month old, and looked at the difference in the visual cortex in animals that were sleep deprived or allowed to sleep normally. In the cats allowed to sleep, the visual cortex responded more to input from the remaining open eye. But in the sleep-deprived cats, this consolidation process was blocked[7].

A DAY TO REMEMBER

Sleep is not the only time that memories are processed. Loren Frank and his colleague Mattias Karlsson showed that rats reactivate memories and consolidate them even while they are awake and quietly resting[8]. They are now studying what differences there might be between reactivations in a waking versus a sleeping state.

Wilson agrees that sleep, rest and anything in between might have different roles in memory processing. "The question is not 'is it processed or not', but how is it processed differently in these different states?" And he has even more ambitious goals for sleep researchers. "In studying sleep," he says, "we should be able to come to a new understanding of what memory is."

If we understand it better, perhaps we can use that knowledge to make our memories sharper. Born's lab has already used low-level electrical stimulation to boost people's memory. Just last month they showed that synchronized sounds can enhance slow waves during sleep and increase memory for word pairs[9]. In the meantime, there is no denying the importance of a good night's sleep. And, for Born's eight-month-old daughter, the importance of spending most of your infancy with your eyes shut. ■

Kerri Smith *is senior audio editor for* Nature.

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