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REMembering what you learned:

Specific brain activity during REM sleep affects memory consolidation

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Which memories are retained, where, and in what form depends on a long afterlife of the acquired information in the brain. Initial steps of consolidation may be completed within a few hours during wakefulness, but other forms of postacquisition processing take longer, extending into sleep (1, 2). The relationship between brain activity during sleep and memory consolidation remains controversial and poorly understood. On page 812 of this issue, Boyce *et al.* (3) demonstrate that a distinct form of hippocampal neural activity, called theta oscillation, is critical for memory formation during the rapid eye movement (REM) phase of sleep.

The two-stage process of memory acquisition and “offline” processing is observed in rodents that experience alternating episodes of exploration and quiet waking, and is also linked to distinct patterns of synchronized hippocampal activity (1, 4). Exploration is characterized by regular theta (6 to 10 Hz) and nested gamma (30 to 90 Hz) oscillatory activity in hippocampal neural networks that are open to new information via cortical input. By contrast, synchronized neuronal activity in quiet waking appears as irregular sharp waves and ripple oscillations, during which processed hippocampal content is transferred to distributed cortical circuits to support memory consolidation. The waking theta-gamma versus sharp wave–ripple dichotomy extends to sleep as the dominant pattern of synchronization in the alternating periods of REM sleep and slow-wave (non-REM) sleep. Extensive evidence supports the role of hippocampal sharp wave–ripple events and related cortical oscillations (“spindles”) in non-REM sleep in memory consolidation (1, 4), but the relationship between theta rhythm during sleep and wakefulness appears more difficult to conceptualize. The subregional theta-gamma pattern in REM sleep, compared with waking exploration, suggests enhanced offline processing in the dentate gyrus and CA3 regions of the hippocampus, and short bursts of their synchronization with the output stages in the CA1 region promote communication with neocortical targets (5). These short bursts of super-synchronized activity co-occur with pontine waves, previously implicated in memory consolidation (6).

Boyce *et al.* used two hippocampus-dependent learning paradigms to test the role of REM sleep theta activity in memory consolidation. The novel object place recognition test is widely used to study rodent models of memory, and is translatable, i.e., similar aspects of recognition memory can be assessed in the human Brief Visuospatial Memory Test (7). The task is based on a rodent’s natural drive to explore novelty; when a mouse returns to a familiar environment, it pays more attention to novel or misplaced objects compared with prior visits. Boyce *et al.* used selective optogenetic silencing of γ -aminobutyric acid–

releasing neurons in the medial septum (MS-GABA) to reduce hippocampal theta power (mice were engineered to express a light-driven ion pump in MS-GABA neurons; pump activation drives hyperpolarization, which inhibits neuron firing). Boyce *et al.* found that suppressing MS-GABA neuron activity in all REM sleep episodes during the critical 4-hour window after learning erased subsequent novel object place recognition (see the figure). Mice receiving light delivery to MS-GABA neurons outside of REM sleep showed normal performance, as did mice in control groups in which either expression of the pump in these neurons or the light stimulus was left out of the treatment.

Another test paradigm was based on fear conditioning to assess the role of REM sleep theta activity in processing the contextual component of emotionally loaded memories (8). Mice received mild electrical shocks paired with auditory cue stimuli in a distinct context of the testing chamber, and their task was to remember the circumstances of the negative experience a day later. When returning to the same chamber (hippocampus-dependent context-recall) or when hearing the auditory signal in a new environment (cue-recall, independent of hippocampal processing) on the following day, normal mice and mice in control groups showed robust freezing response without electric shocks. However, if MS-GABA neurons were silenced during REM sleep after learning, mice only reacted to the auditory cue but showed less freezing in the context chamber, indicating impaired hippocampal memory consolidation.

The two most influential current theories—memory consolidation (1, 2) and homeostatic synaptic depotentiation in sleep (9)—are non-committal and unenthusiastic with respect to the role of REM sleep in brain function, although REM sleep was historically believed to contribute to memory consolidation, and the first theoretical proposal of depotentiating certain “parasitic associations” was first attributed to REM sleep (10). But REM sleep eventually lost to non-REM sleep on both accounts: homeostatic synaptic depotentiation was associated with non-REM sleep delta rhythm, and consolidation was associated with non-REM sharp wave–ripple oscillations and spindles. However, REM sleep appears to be regaining acceptance in the recent sequential hypotheses, which emphasize linked REM–non-REM–REM sleep mechanisms. REM sleep’s role in synaptic consolidation was demonstrated by linking REM sleep to pre-REM spindles (11), and its role in homeostatic regulation by linking to post-REM delta rhythm and spindles (12). Theta oscillations may have importance for memory consolidation by affecting both mechanisms.

The details of how theta oscillations and MS-GABA neurons are involved in synaptic consolidation and homeostatic regulation were not the focus of Boyce *et al.* Their approach, however, is a radical departure from prior system-level correlational and sleep deprivation studies, offering new opportunities to explore, without disrupting sleep behavior, the role of REM sleep theta activity. Detailed knowledge of wake theta activity—including rhythmic coupling between hippocampus and other structures (prefrontal cortex and amygdala) that are involved in different aspects of memory processing, bidirectional communication between the MS-GABA theta generator and intrinsic intrahippocampal theta synchronization (13, 14), and phase segregation for diverse types of neurons enabling spatial and possibly “mental” travel (15)—provides a template for future progress. It should be noted, however, that REM sleep is a complex state, and, thus, establishing a causal link between learning and

MS-GABA activity does not exclude the roles of REM sleep in other memory- and non-memory-related functions.

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Figure 1. Offline processing

Reducing hippocampal theta oscillations during REM sleep affects what mice remember from learning sessions in the prior waking period.