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Flipping the switch: mechanisms that regulate memory consolidation

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Memories can follow different processing routes. For example, some memories are enhanced during wakefulness while the enhancement of others is delayed until sleep. Converging evidence suggests that inhibitory mechanisms can 'switch off' a processing route, thereby preventing the consolidation of select memories during wakefulness. This switch arises due to an actively imposed 'bottleneck' generated by the brain. Transcranial magnetic stimulation (TMS) can interfere with this bottleneck, allowing multiple memories to be consolidated simultaneously during wakefulness. This bottleneck restricts memory processing, perhaps allowing for the selection of only rewarded, or relevant memories. Overall, this bottleneck makes it necessary to select memories for consolidation, and the state of a switch ('on' or 'off') determines whether or not a memory is subsequently consolidated. Understanding how memory consolidation is regulated may provide novel therapeutic strategies.

Switching memory consolidation off and on

Neuroscience research has provided scientists with an increasingly sophisticated appreciation of how memories are processed. Perhaps the best example of this is our rich understanding of how memories continue to be processed and consolidated after their acquisition [1,2]. Memories are enhanced, made resistant to interference, and integrated with other memories following the reactivation of neural circuits 'off-line' following learning [3–5]. These different expressions of consolidation ensure the long-term retention of a memory, and therefore are vital in determining the fate of that memory. Despite the clear importance of consolidation, we understand very little about how this memory processing is regulated and controlled.

Memories follow different processing routes during consolidation, and these different routes lead to different fates. For example, some memories are enhanced during wakefulness: participants show a 20–30% off-line improvement in performance between testing and subsequent retesting 12 h later. By contrast, other memories have their enhancement prevented or at least delayed until an interval of sleep [3,6]. Motor skill memories that are rewarded are significantly enhanced during consolidation; whereas, other memories that go unrewarded are substantially less enhanced [7]. These and other examples of memories undergoing consolidation at different times and to varying extents are well established; however, how these different fates are achieved remains poorly understood [8]. In this opinion article, we discuss the mechanisms responsible for controlling memory consolidation during wakefulness. Converging evidence suggests that inhibitory mechanisms 'switch off' a processing route, preventing the processing of select memories during wakefulness while allowing the processing of others. Selecting one memory over another occurs because the brain creates a 'bottleneck', allowing only one memory to be consolidated. The bottleneck appears to be actively generated because when the function of the brain is disrupted; for example with TMS, multiple memories can be consolidated simultaneously [9]. Subsequent work may show that these same mechanisms are responsible not only for the control of memory enhancement, but also for other forms of consolidation, including memory stabilization, and for controlling consolidation during other brain states, such as sleep.

Sleep may control when consolidation occurs

Some memories are enhanced during wakefulness, while others have their enhancement delayed until sleep. Perhaps the simplest explanation for these different fates is that sleep provides a unique environment for memory processing, and so it is only during sleep that specific memories can be consolidated [5,10,11]. For example, sleep spindles are high frequency waveforms that have been implicated in plastic processes and are correlated with memory changes over sleep [12–19]. Sleep is also a state in which new memories are generally not being formed, which may allow the neural circuits normally dedicated to supporting memory acquisition to instead support memory consolidation [20]. Sleep, and specifically, slow-wave sleep is also thought to cause a general decrease in synaptic efficacy, which improves the signal-to-noise ratio for memories acquired the previous day, and so may lead to performance improvements that are correlated with slow-wave activity [21–23]. While some studies have found evidence of improved performance at both motor and declarative learning tasks after sleep [24–27], others have found little evidence of such improvements, and still others have suggested that sleep's contribution to memory processing may be limited to the stabilization of memories [28,29].

Our focus here is not on discussing the potential sleep-dependent mechanisms for consolidation, which have already been widely described (for recent reviews; [2,5,11]).

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Instead, our focus is upon the complementary, but largely overlooked question of how memory consolidation is controlled. Sleep may regulate when memory consolidation occurs via unique neurophysiological features, such as sleep spindles that may be critical for consolidation. These features may ensure that consolidation only occurs during sleep. However, converging evidence is starting to suggest that control processes during wakefulness may actively prevent or at least delay memory consolidation until sleep. Mechanisms that prevent consolidation may ensure that only specific memories receive the benefits of consolidation, while delaying consolidation may ensure that a memory is consolidated during a brain state, such as sleep, which is particularly suited to changing or extracting features from the memory that enhance its adaptive value [30].

Inhibitory control of memory consolidation during wakefulness

Cognitive insights

Many behaviors are supported by a combination of motor skill and declarative knowledge. For example, both types of knowledge are involved in knowing and skillfully tapping out your personal ID number to get cash from an ATM machine [1]. When a motor skill and declarative knowledge are acquired simultaneously – as occurs during explicit learning – subsequent enhancement of the motor skill memory only occurs during sleep, not during wakefulness (Figure 1A; [1,31,32]). For example, motor tasks such as phoneme learning or video games, which may involve a declarative component, are only consolidated during a night of sleep [32,33]. By contrast, when a motor skill is acquired with little or no declarative knowledge – as occurs during implicit learning – the enhancement of the motor memory does not wait until sleep and instead occurs during wakefulness [6,31]. Together these findings suggest that declarative knowledge may prevent the enhancement of motor skill memories during wakefulness.

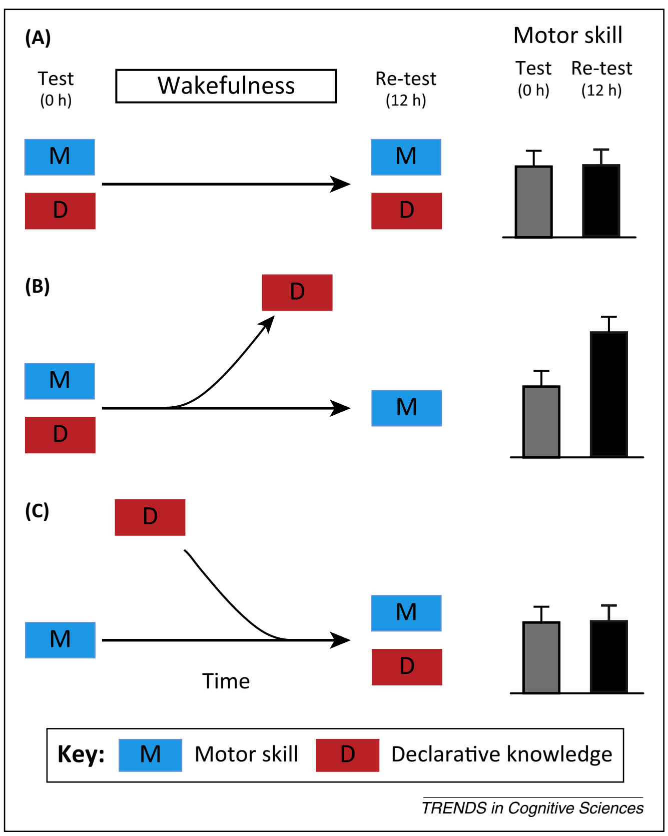

Figure 1. Declarative knowledge acts as a brake on motor memory consolidation. **(A)** Our behaviors are frequently supported by a blend of declarative (D; red rectangles) and motor skill (M; blue rectangles) memories, and under these circumstances there are no off-line improvements during wakefulness [24,25,31]. **(B)** However, when the declarative memory is disrupted – for example, by learning an interfering word list after an explicit motor task – there is a substantial off-line enhancement during wakefulness in motor performance [34]. **(C)** Conversely, acquiring declarative knowledge for example, by learning a list of words after an implicit motor task – can prevent the development of off-line improvements [36].

Two important predictions flow from this hypothesis. Firstly, removing or disrupting a declarative memory that had previously been acquired along with a motor skill (the so-called explicit task) should induce off-line motor memory processing, leading to enhanced performance. Consistent with this prediction, when declarative knowledge for a previously acquired motor skill is experimentally disrupted by subsequently learning another task or by applying TMS, it induces the development of off-line improvements during wakefulness (Figure 1B; [34,35]). Secondly, when a motor skill is acquired without any declarative knowledge (the so-called implicit task), the subsequent off-line motor memory processing should be blocked by declarative learning [36]. Consistent with this prediction, when declarative knowledge is learnt following the implicit motor learning task, there is a decrease in motor skill performance. This decrement in performance is positively correlated with the extent of prior declarative learning (Figure 1B; [36]). Furthermore, the effects of declarative knowledge are not limited to affecting memory enhancement during consolidation. Declarative knowledge can also prevent other expressions of consolidation during wakefulness, such as the stabilization of a motor memory [37]. Thus, declarative knowledge can prevent motor memory consolidation during wakefulness, suggesting perhaps that an inhibitory mechanism controls when consolidation occurs.

Physiological insights

The cognitive insights into the mechanisms controlling memory consolidation are starting to be translated into a physiological understanding. Cortical excitability can provide a measure of functional changes within motor circuits, and has recently been used to identify the changes that occur after learning motor tasks that either do or do not show subsequent consolidation [38–40]. Typically, excitability is measured as the magnitude of the motor evoked potential (MEP) elicited by applying a single pulse of TMS over the primary motor cortex (M1 [41]; for a review, see [42]). In a recent study, participants learnt a motor sequence with or without declarative knowledge for that sequence (i.e., implicit versus explicit learning). Cortical excitability was then measured by applying single pulses of TMS over the left M1 and recording the subsequent MEPs from the right hand at time points extending up to 2 h after learning. Participants then returned in the evening to be retested on the motor sequence task.

When participants had simply learnt a motor sequence with little or no declarative knowledge for the sequence (so-called implicit learning) there was no change in cortical