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New Insights in Human Memory Interference and Consolidation

Minireview

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Learning new facts and skills in succession can be frustrating because no sooner has new knowledge been acquired than its retention is being jeopardized by learning another set of skills or facts. Interference between memories has recently provided important new insights into the neural and psychological systems responsible for memory processing. For example, interference not only occurs between the same types of memories, but can also occur between different types of memories, which has important implications for our understanding of memory organization. Converging evidence has begun to reveal that the brain produces interference independently from other aspects of memory processing, which suggests that interference may have an important but previously overlooked function. A memory's initial susceptibility to interference and subsequent resistance to interference after its acquisition has revealed that memories continue to be processed 'off-line' during consolidation. Recent work has demonstrated that off-line processing is not limited to just the stabilization of a memory, which was once the defining characteristic of consolidation; instead, off-line processing can have a rich diversity of effects, from enhancing performance to making hidden rules explicit. Off-line processing also occurs after memory retrieval when memories are destabilized and then subsequently restabalized during reconsolidation. Studies are beginning to reveal the function of reconsolidation, its mechanistic relationship to consolidation and its potential as a therapeutic target for the modification of memories.

Introduction

Memory interference is a beguilingly simple observation. For example, when you learn one word-list and then another in quick succession, the latter interferes with the original word-list, impairing its retention [1]. Learning another memory is not unique in its capacity to cause interference; for example, disrupting neural activity by applying transcranial magnetic stimulation (TMS), or blocking protein synthesis by applying a protein synthesis inhibitor immediately after learning can also impair memory retention (Figure 1) [2–5]; for discussion about TMS see [6]. Yet, despite its apparent simplicity memory interference has had, and continues to have, a remarkable impact upon our understanding of the human brain. Many studies have focused upon the possible cellular, synaptic and network basis for memory interference (for review see [7,8]). By contrast, an account of memory interference and its implications from a systems neuroscience and psychological perspective has not been discussed as much. Yet recent studies have had a profound impact upon our understanding of memory organization, have given new insights into the systems responsible for memory interference, and have revealed that stabilizing a memory, which makes it resistant to interference, is just one of a diverse array of 'off-line' processes that continue to change, and so consolidate memories long after their initial acquisition.

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Memory Organization

Memories for facts and events (so-called declarative memories) are thought to be processed and retained within a set of neural circuits that are independent from the set of circuits responsible for processing and retaining skills (so-called procedural memories) [9]. Recent studies showing interference between declarative and motor skill memories have challenged the concept of independent memory systems.

The concept of independent memory systems arose in part because diseases such as Alzheimer's disease affect patients' ability to learn and recall facts and events, whereas their ability to learn new skills is relatively preserved [10]. Conversely in other diseases, such as Huntington's disease, patients' ability to learn and recall facts and events is relatively preserved, but their ability to learn new skills is impaired (Figure 2) [11]. Converging with these neuropsychological studies have been functional imaging studies, which have shown that anatomically distinct neural circuits are involved in the processing of declarative and procedural memories [12]. Over the last ten years, however, the situation has become more complex. For example, functional imaging work has shown that activation within the mediotemporal lobe (MTL), a brain area associated with the processing of declarative memories, can be correlated with activation within the striatum, which is associated with the processing of procedural memories. Thus rather than being independent, there may be a functional connection between different memory processes (Figure 2) [13].

A functional connection between memory systems makes it at least conceivable that declarative and procedural memories can interact, and interference between these memories, which has been seen in a number of recent studies, demonstrates that these memories not only can, but do interact [14–16]. For example, learning a word-list and then a motor skill impairs subsequent word-recall by 10%, and similarly, learning a motor skill and then a word-list impairs the subsequent performance of the motor skill by 25% [15]. Thus, memory interference has helped to reshape our understanding of how memories are organized within the human brain by demonstrating that the processing of declarative and procedural memories is not always confined to entirely independent systems.

Interference Mechanisms

Interference between memories may be due to an overlap between otherwise independent systems (Figure 2) [17]. Any overlap need not be complete because declarative memories may only interfere with a specific component of a procedural memory [16]. The concept of an overlapping architecture explaining the interference between different memories is appealing because human functional imaging studies have demonstrated that brain areas such as the

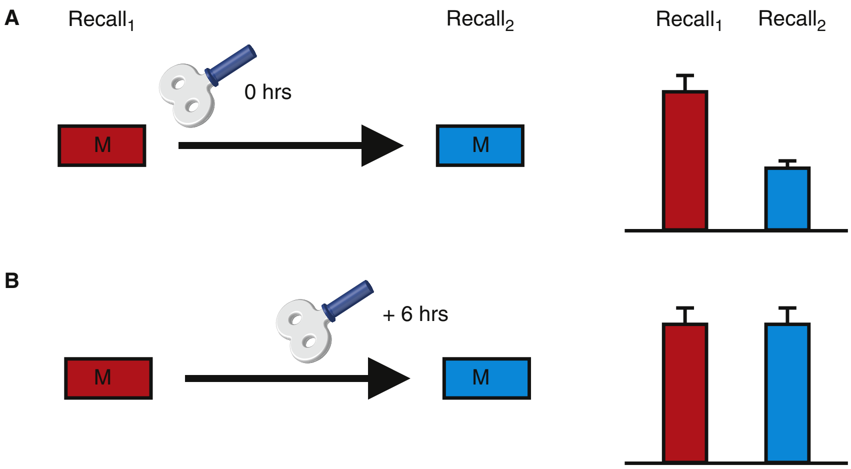

Figure 1. Memory interference.

(A) Immediately following its acquisition or retrieval a memory (M) is susceptible to interference, and so a disruptive technique such as applying TMS (coil) over a particular brain area can impair recall. (B) By contrast, after acquisition a memory is consolidated, and similarly following its retrieval a memory is reconsolidated, making the memory resistant to interference. So, applying TMS several hours (for example, +6 hours) after acquisition or retrieval has little or no effect upon recall because by this time the memory has been stabilized and is no longer susceptible to interference.

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MTL are activated during both declarative and procedural learning, and so there is experimental evidence for an overlap between declarative and procedural processing [18,19]. Thus, interference could arise from a competition between declarative and procedural processing for a shared overlapping resource. However, several recent studies have started to challenge the classical idea that memory interference arises from a competition between memories.

Converging animal and human work has begun to suggest that memory interference arises from brain areas generating a coupling or bridge between otherwise independent declarative and procedural processing, and this coupling causes the interference between the memories (Figure 2). For example, damage to the brain, and specifically to the frontal cortex, in mice can prevent interference between memories [20]. Furthermore, when a memory is reactivated by an odor during wakefulness and becomes susceptible to interference there is increased activity within the dorsolateral prefrontal cortex (DLPFC). By contrast, when a memory is reactivated during sleep and does not become susceptible to interference there is no increased activity within the DLPFC (Figure 3) ([21]; see also [15,17]). Together, these results suggest that memory interference may be dependent upon the DLPFC.

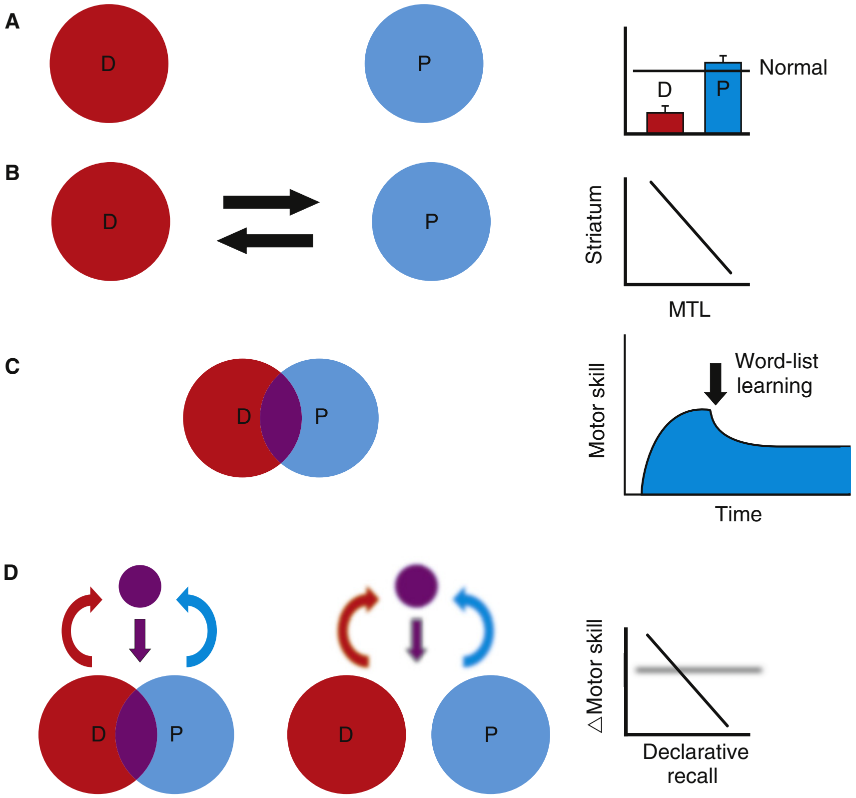

Figure 2. Examples of memory organization in the human brain.

(A) There may be independent procedural (P; for example, a learning motor skill) and declarative (D; for example, learning a word-list) memory systems within the human brain. For example, impairment in declarative learning can occur without any impairment in procedural learning [9]. (B) Alternatively, there may be an interaction between different types of memories. Functional imaging work has shown that there is a correlation between activity within the procedural (the striatum) and declarative memory systems (the MTL) [13]. So, there is a functional coupling between memory systems with activity within one memory system affecting the other, and this coupling could support interactions between different memories. (C) There may only be a partial overlap between declarative and procedural processing, which would explain word-list learning impairing only a component, but not all of a motor skill [16]. (D) Brain areas can control the interference between memories. When the brain state is altered artificially (blur) — for example, by applying TMS — there is no longer interference of a motor skill by a word-list memory (blurred line) [22]. The organization of human memories may also shift naturally depending upon brain state; for example, interference occurs between memories during wakefulness but not during sleep [15,17,21].

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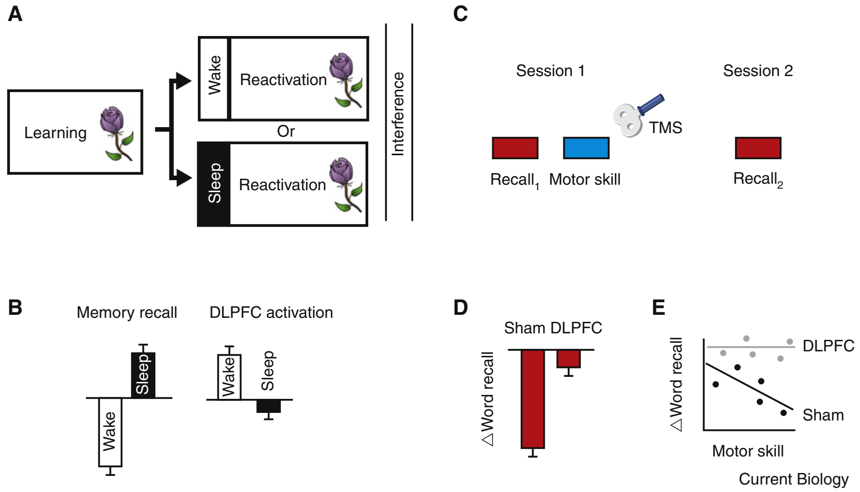

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Figure 3. Memory interference and the prefrontal cortex.

(A) Participants learnt a spatial location task while being exposed to a rose petal odor. The odor was subsequently used to reactivate the spatial memory when participants were either awake or asleep. Immediately after reactivation participants performed an interference task. (B) There was a decrease in memory recall and activation of the DLPFC in the wake group, whereas there was an increase in recall and little activation of the DLPFC in the sleep group. Thus, for a memory to be susceptible to interference — as shown by a decrease in memory recall — the DLPFC has to be activated. (C) In another set of experiments, participants learnt a word-list (red box; Recall$_1$) and a motor skill (blue box) in quick succession, sham TMS or real TMS was applied to the DLPFC, and participants recall for the word-list was retested (Recall$_2$). (D) Interference from the motor skill task caused a substantial decrease in word-recall (Recall$_2$ – Recall$_1$) in the sham group. In contrast, this expected decrease in word-recall did not occur following DLPFC stimulation. (E) The correlation between memory interference (Δ Word recall) and initial motor skill, which was present following sham stimulation, was abolished by applying real stimulation to the DLPFC. Thus, disrupting the function of DLPFC by applying stimulation prevented interference between the tasks.

Disrupting the function of the right DLPFC with TMS can prevent interference between different memory tasks [22]. When a word-list and a motor skill are learnt in quick succession there is normally a decrease in the subsequent word-recall, which is correlated to the amount of motor skill acquired earlier [15]. By contrast, when TMS is applied to the right DLPFC immediately after learning the two tasks there is no longer a decrease in word-recall, and the correlation between the two tasks is no longer present (Figure 3) [22].

A similar pattern of results occurs when the order of the tasks is reversed, except this time the interference is prevented by applying TMS to M1 [22]. Across the experiments, stimulation prevented interference without affecting either of the individual memories; for example, stimulation did not disrupt the interfering memory, nor did it enhance the other memory and so mitigate against the effects of the interfering memory. Thus, interference is occurring independently from the processing of the individual memories, and so is not simply a by-product of a competition between different memory processes. Instead, brain areas such as the right DLPFC and M1 are actively producing interference between memories.

Broadly, brain areas may be critical for memory interference either by acting to control the communication between memories that are inherently susceptible to interference, or alternatively, by selecting when and which memories should become unstable and so susceptible to interference. The prefrontal cortex can control the processing within the visual association cortex and it has been shown to control the processing of individual memories, and so the contribution of the DLPFC to memory interference may emerge from its more general role in executive control (for example, [23,24]). M1 may have a similar, but as yet, unappreciated role in executive control, allowing it to control the communication between different types of memory, which would explain its contribution to memory interference. Alternatively, the brain may select which memory becomes susceptible to interference. For example, when two memories are learnt in quick succession, it is usually the first that is susceptible to interference; however, when a reward is given for recalling the first memory, then the interference shifts to affect and so impair the recall of the second memory [25] (see [26] for other affects of reward upon the long-term retention of a motor skill).

The DLPFC or M1 may be responsible for selecting the memory that becomes susceptible to interference through reward mechanisms or because of their role in memory retrieval. When an old memory is retrieved as a result of the acquisition of a new related memory it becomes unstable, and so both the old and the new memories are unstable (see 'Memory stability' below) [8]. Retrieving the old memory may trigger a set of processes that not only makes the old memory unstable but also ensures that the new memory is unstable, perhaps because it is only in this unstable state that both the old and new memories can be reorganized and integrated together. So, preventing retrieval of the old memory, for example by applying TMS to the right DLPFC or M1, would also prevent the new memory from becoming unstable and so prevent it from being susceptible to interference [22]. So, applying TMS to the right M1 would prevent a motor skill memory from being susceptible to interference from either another memory or from applying TMS to the left M1 (see 'Memory stability') [3,4,27].

Overall, the right DLPFC or right MI may make a critical contribution to memory interference by exerting executive control over memory processes, perhaps by coupling together memories that are already susceptible to interference; alternatively, they may select those memories that are susceptible to interference, for instance through reward or retrieval mechanisms, or through some combination of these.

Changing Patterns of Memory Interference

Functional changes in neural circuits can modify memory interference without affecting the rest of memory processing, and so memory interference may be an optional addition to processing occurring on some occasions but not on others. For example, substantial interference occurs between memories over wakefulness, whereas minimal interference occurs between memories over sleep [15,17,21]. As the human brain shifts into sleep there are changes in functional connectivity amongst brain areas, which may minimize the interference between memories [17]. Thus, brain state can change the organization of memories from being interactive to being independent. Yet, brain state may not be unique in promoting changes in the organization of human memories. Memory processes may operate independently during learning, and so declarative and procedural knowledge associated with a task are acquired independently [28], whereas, after learning, memory processes may interact allowing, for example, a declarative memory to interfere with a procedural memory [15,16].

Development may also affect memory interference. The interference between memories can depend upon the prefrontal cortex, which changes substantially during development, and so in turn the organization of human memories may alter during development. Declarative and procedural knowledge may be independent in childhood, when the prefrontal cortex is immature, but may become interactive in young adults when the prefrontal cortex reaches maturity [22,29]. A changing memory organization due to structural and functional changes in the prefrontal cortex as humans age may also reconcile studies showing memory interactions in young adults with other studies showing independent memories in older adults, when the function of the prefrontal cortex has perhaps declined (for example [16], compared to [10]). There are presumably limits to the flexibility of the organization of human memories; for example, for the DLPFC to control memory interactions it may be necessary for both memory processes to be dependent upon the MTL with which the DLPFC is intimately interconnected.

Manipulating Interference to Improve Performance

Manipulating those mechanisms responsible for memory interference, as has been done with TMS, or could be done using specific drugs or behavioral tasks, provides a means to prevent interference between memories, which could enhance the long-term retention of memories and so may have some clinical benefit. For example, those seeking to re-learn old skills lost following a stroke may benefit from reduced interference from other forms of learning, which would enhance motor skill retention and so improve recovery. Similarly, education strategies could exploit the different maturity of children's cortical areas to reduce memory interference by manipulating the order in which facts and skills are learnt. For example, education strategies could bypass interference mechanisms that are mature in children (the M1-dependent mechanism), and activate only immature and possibly less effective interference mechanisms (the DLPFC-dependent mechanism).

Simply switching the order of the tasks would not change the information acquired during learning, but it may substantially reduce the interference between the memories, and so enhance the long-term retention of facts and skills. Thus, different strategies could be used to reduce or prevent the interference between memories, which would improve the long-term retention of knowledge, and so enhance education and rehabilitation. Yet impairing interference may not only improve the long-term retention of knowledge, it may also come with a cost, because memory interference may have a function.

Functional Contributions of Memory Interference

The brain produces interference between memories, but when disrupting neural circuits with TMS prevents this interference there is no impairment to other aspects of memory processing [22]. Generating memory interference for no apparent benefit, but with the substantial cost of impaired long-term memory retention, seems paradoxical. One way to resolve this paradox is to imagine that memory interference has some, as yet poorly understood and appreciated, function.

For example, interference may allow the interaction between memories and so support their integration. Interference between memories can also control the consolidation of memories; for example, interference from a declarative memory can prevent the consolidation of motor skill memories over wakefulness [14–16]. Thus, memory interference may allow the combining of memories or serve to control memory processes.

Memory Stability

A memory is susceptible to interference immediately after its acquisition, but a series of molecular and cellular events, along with changes in functional connectivity, combine to make a memory resistant to interference several hours after its acquisition [7,30]. The biological mechanisms responsible for making a memory resistant to interference can be affected by even subtle changes to the type of learning. For example, a motor skill memory learnt in a single block can be disrupted by applying TMS to M1 or the supplementary motor area (SMA) immediately after practice; but when the type of practice is changed (from a single block to multiple interleaved blocks) applying TMS to either M1 or SMA is no longer effective, and instead the motor skill memory is disrupted by applying TMS to the DLPFC [31,32]. A change in the type or length of practice can lead to a change in the circuits responsible for learning, and perhaps in turn to a change in the circuits that are critical for the stabilization of a memory [17,33]. Together, these observations reveal that a memory is initially unstable after acquisition, and that it continues to be processed 'off-line' so the memory becomes stabilized and resistant to interference [30,34].

The realization that memories can be processed off-line has sparked a stream of studies, which have shown that not only can a memory be stabilized off-line during consolidation it can also be enhanced, integrated with other memories, reorganized and transformed [30,34–37]. For example, a motor skill can be enhanced by 20–30% over a night of sleep. Similar behavioral changes can also occur during learning, and so the processes engaged off-line to consolidate a memory may not be qualitatively different from those engaged during learning. Learning and consolidation are both dependent upon similar brain areas; for example, motor skill learning and consolidation are both dependent upon M1 [3,4,38] and they have molecular mechanisms in common, for example, involvement of brain-derived neurotrophic factor (BDNF) [39,40]. Thus, learning and consolidation have important behavioral, neural and molecular features in common. Yet unlike learning, some expressions of consolidation are dependent upon a specific brain state, and so only occur over sleep or only over wakefulness, and so at the very least there is a difference in how learning and consolidation are triggered [30,34,41].

From neural circuits to molecular processes the mechanisms responsible for consolidation are increasingly being understood. Yet the function of these changes has yet to be articulated beyond simply re-describing the behavioral expression of consolidation, which should not be confused with its function any more than the function of a boot should be confused with the impression that it leaves on a muddy field. Overall, memory interference experiments have deepened our understanding of memory processing by establishing that memories continue to be processed off-line after their acquisition, and the challenge for future work is to deepen our understanding of these processes, their relationship with learning, and to begin to understand the function of consolidation.

Memories can also become unstable and so susceptible to interference during their retrieval [5,42] (for recent review see [8]). For example, applying TMS to M1 immediately after performance of a well-learnt sequence of finger movements disrupts the motor sequence memory and so impairs subsequent motor performance [43]. So, just as happens at acquisition, a memory can become susceptible to interference at retrieval. Another similarity is that at acquisition and retrieval, a memory is only susceptible to interference for a limited time; for example, six hours after retrieval a fear memory has become resistant to interference [5]. Yet memories can remain resistant to interference even at their retrieval, and may only become susceptible to interference when the retrieved memory is to be modified by freshly acquired information.

The requirement for new learning may mean that a memory only becomes vulnerable to interference when freshly acquired information has to be integrated into the existing memory, and for that integration to occur the memory may have to become unstable [44,45]. For example, an existing memory becomes unstable when its strength is modified [45]. As a new memory is being learnt, existing related memories are being made susceptible to interference; they are then stabilized through reconsolidation and, simultaneously, the new memory is itself being stabilized through consolidation. Consolidation and reconsolidation may operate simultaneously as two distinct independent off-line processes, and they have distinct underlying molecular mechanisms [40]. Alternatively, consolidation and reconsolidation may be coordinated together within the same process operating to reorganize existing memories by incorporating new memories [8].

Therapeutic Implications

Not all memories are useful or adaptive. For example, soldiers may remember horrible scenes from their last deployment, we may remember waiting for a feared diagnosis or the sadness of watching a loved one die, and these memories can become pathological. Unresolved grief can turn into depression and the recollection of combat can become post-traumatic stress disorder (PTSD). Similarly, maladaptive memories support addiction to drugs such as alcohol, tobacco or cocaine. The instability of memories after their retrieval may provide a window of opportunity to interfere and so disrupt maladaptive memories, which holds the promise of curing patients from a wide range of devastating conditions. For example, administering the β-blocker propranolol during memory retrieval disrupted the retention of the fear memory in humans [46]. Specifically, the β-blocker disrupted the physiological fear response (the startle) while leaving participants' knowledge of what had been learnt intact (recollection of the learning). Similar findings of disrupting the retention of a physiological response to a learnt fearful stimulus by administering propranolol at, or around, the time of memory retrieval have been made in animals [47,48]. Administering propranolol during memory retrieval can also disrupt the retention of drug seeking behavior [49]. Thus, the instability of maladaptive memories at retrieval provides a window of opportunity to interfere with those memories, impairing their long-term retention, and so potentially curing individuals from conditions such as PTSD or drug addiction.

Interfering with maladaptive memories to cause their impairment or erasure may be fraught with difficulties. Manipulating any memory means that what is subsequently recalled is, in some sense, an invention, yet this may be helpful and improve the quality of individuals' lives provided that any treatment strategy is able to identify and specifically manipulate only those memories that are responsible for maladaptive behaviors.

Interfering with one memory could perturb other memories because each memory is embedded within an associative network of other memories. For example, we define our moments of fear and sadness with respect to our moments of joy and happiness, and so an important question is whether ablating a memory for a fearful incident even though it has become maladaptive could have damaging consequences for those memories that bring us much joy and comfort. Being able to recall frightening incidents does not by itself lead to diseases such as PTSD, and so to conceptualize these conditions as maladies stemming from there being too much memory may not be appropriate. Rather than attempting to eradicate a memory, it may be more efficacious to place them within a new context or perspective; after all, it is not the incidents that we recall, which defines us, but instead the narrative that we put those incidents into [50].

Concluding Remarks

Memory interference has not only allowed the identification of a novel strategy for modifying maladaptive memories, it has also shown that the organization of memories in the human brain shifts depending, for example, upon brain state (sleep *versus* wakefulness), so that at some times, declarative and motor skill memories are processed independently, whereas at other times, those memories interact and interfere with one another. Interference occurs independently of other aspects of memory processing, so that disrupting brain areas with TMS can specifically prevent interference while leaving the rest of memory processing intact. Having neuronal resources dedicated to generating memory interference, which impairs the long-term retention of facts and skills, seems paradoxical. One way to resolve the paradox is to imagine that there is a trade-off between the impaired retention caused by interference and some, as yet not fully appreciated, function. Memory interference has changed our understanding of how knowledge is organized in the human brain, and recent work has changed our understanding of how the brain enables memory interference.

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