CHAPTER

21 Memory Consolidation

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Abstract

Memory consolidation is a multifaceted concept. At a minimum, it refers to both cellular consolidation and systems consolidation. Cellular consolidation takes place in the hours after learning, stabilizing the memory trace—a process that may involve structural changes in hippocampal neurons. Systems consolidation refers to a more protracted process by which memories become independent of the hippocampus as they are established in cortical neurons—a process that may involve neural replay. Both forms of consolidation may preferentially unfold whenever the hippocampus is not encoding new information, although some theories hold that consolidation occurs exclusively during sleep. In recent years, the notion of reconsolidation has been added to the mix. According to this idea, previously consolidated memories, when later retrieved, undergo consolidation all over again. With new findings coming to light seemingly every day, the concept of consolidation will likely evolve in interesting and unpredictable ways in the years to come.

Key Words: cellular consolidation, systems consolidation, reconsolidation, sleep and consolidation

The idea that memories require time to consolidate has a long history, but the understanding of what consolidation means has evolved over time. In 1900, the German experimental psychologists Georg Müller and Alfons Pilzecker published a monograph in which a new theory of memory and forgetting was proposed, one that included—for the first time—a role for consolidation. Their basic method involved asking subjects to study a list of paired-associate nonsense syllables and then testing their memory using cued recall after a delay of several minutes. Typically, some of the list items were forgotten, and to investigate why that occurred, Müller and Pilzecker (1900) presented subjects with a second, interfering list of items to study before memory for the target list was tested. They found that this interpolated list reduced memory for the target list compared with a control group that was not exposed to any intervening activity. Critically, the position of the interfering list within the retention interval mattered such that interference occurring soon after learning had a more disruptive effect than interference occurring later in the retention interval. This led them to propose that memories require time to consolidate and that retroactive interference is a force that compromises the integrity of recently formed (and not-yet-consolidated) memories. In this chapter, we review the major theories of consolidation—beginning with the still-relevant account proposed by Müller and Pilzecker (1900)—and we consider a variety of recent developments in what has become a rapidly evolving field.

The Early View: Consolidation and Resistance to Interference

According to Müller and Pilzecker's (1900) view, consolidation consists of "trace hardening" (cf. Wickelgren, 1974) in the sense that some

physiological process perseverates and eventually renders the memory trace less vulnerable to interference caused by new learning. The kind of interference that a consolidated trace theoretically resists differs from the kind of interference that most experimental psychologists have in mind when they study forgetting. In the field of experimental psychology, new learning has long been thought to generate interference by creating competing associations linked to a retrieval cue, not by affecting the integrity of a fragile memory trace (e.g., Keppel, 1968; Underwood, 1957; Watkins & Watkins, 1975). Traditionally, this kind of interference has been investigated using an A-B, A-C paired-associates paradigm in which the same cue words (the A items) are paired with different to-be-remembered target words across two lists (the B and C items, respectively). In a standard retroactive interference paradigm, for example, the memory test consists of presenting the A items and asking participants to recall the B items. Having learned the A-C associations after learning the A-B associations, the ability of participants to recall the B items is typically impaired, and this impairment is usually assumed to reflect retrieval competition from the C items. The powerful effect of this kind of "cue overload" interference on retention has been well established by decades of psychological research, but it is almost certainly not the only kind of interference that causes forgetting.

The kind of interference envisioned by Müller and Pilzecker (1900) does not involve overloading a retrieval cue but instead involves directly compromising the integrity of a partially consolidated memory trace. In what even today seems like a radical notion to many experimental psychologists, Müller and Pilzecker (1900) assumed that the interference was nonspecific in the sense that the interfering material did not have to be similar to the originally memorized material for interference to occur. Instead, mental exertion of any kind was thought to be the interfering force (Lechner et al., 1999). "Mental exertion" is fairly vague concept, and Wixted (2004a) suggested that the kind of intervening mental exertion that Müller and Pilzecker (1900) probably had in mind consists specifically of new learning. The basic idea is that new learning, per se, serves as an interfering force that degrades recently formed and still fragile memory traces.

Loosely speaking, it can be said that Müller and Pilzecker (1900) believed that the memory trace becomes *strengthened* by the process of consolidation. However, there is more than one way that a trace can become stronger, so it is important to keep in mind which meaning of a "stronger memory trace" applies in any discussion of consolidation. One way that a trace might become stronger is that it comes to more accurately reflect past experience than it did when it was first formed, much like a snapshot taken from a Polaroid camera comes into sharper focus over time. A trace that consolidated in this manner would yield an ever-clearer memory of the encoding event in response to the same retrieval cue. Another way that a trace might become stronger is that it becomes ever more likely to spring to mind in response to a retrieval cue (even more likely than it was when the memory was first formed). A memory trace that consolidated in either of these two ways would support a higher level of performance than it did at the end of training, as if additional learning occurred despite the absence of additional training.

Still another way that a trace can become stronger is that it becomes hardened against the destructive forces of interference. A trace that hardens over time (i.e., a trace that consolidates in that sense) may simultaneously become degraded over time due to the interfering force of new learning or to some other force of decay. As an analogy, a clay replica of the Statue of Liberty will be at its finest when it has just been completed and the clay is still wet, but it will also be at its most vulnerable. With the passage of time, however, the statue dries and becomes more resistant to damage even though it may now be a less accurate replica than it once was (because of the damage that occurred before the clay dried). Müller and Pilzecker's (1900) original view of consolidation, which was later elaborated by Wickelgren (1974), was analogous to this. That is, the consolidation process was not thought to render the trace more representative of past experience or to render it more likely to come to mind than it was at the time of formation; instead, consolidation was assumed to render the trace (or its association with a retrieval cue) more resistant to interference even while the integrity of the trace was gradually being compromised by interference.

These considerations suggest a relationship between Müller and Pilzecker's (1900) view of consolidation and the time course of forgetting. More specifically, the fact that a memory trace hardens in such a way as to become increasingly resistant to interference even as the trace fades may help to explain the general shape of the forgetting function (Wixted, 2004b). Since the seminal work of Ebbinghaus (1885), a consistent body of evidence has indicated that the proportional rate of

forgetting is rapid at first and then slows to a point at which almost no further forgetting occurs. This general property is captured by the power law of forgetting (Anderson & Schooler, 1991; Wixted & Carpenter, 2007; Wixted & Ebbesen, 1991), and it is enshrined in Jost's law of forgetting, which states that if two memory traces have equal strength but different ages, the older trace will decay at a slower rate than the younger one from that moment on (Jost, 1897). One possibility is that the continuous reduction in the rate of forgetting as a trace ages is a reflection of the increased resistance to interference as the trace undergoes a slow process of consolidation (Wickelgren, 1974; Wixted, 2004b).

Modern Views of Consolidation

The view of consolidation advanced by the pioneering experimental psychologists Müller and Pilzecker was not embraced by the field of experimental psychology in the latter half of the twentieth century. Ironically, during that same period of time, the notion that memories consolidate became the "standard story" in the field of neuroscience. The impetus for this way of thinking among neuroscientists can be traced in large part to the realization that the structures of medial temporal lobe (MTL) play a critical role in the formation of new memories. The importance of these structures became clear when patient H.M. received a bilateral medial temporal lobe resection in an effort to control his epileptic seizures (Scoville & Milner, 1957). Although successful in that regard, H.M. was also unexpectedly left with a profound case of anterograde amnesia (i.e., the inability to form new memories from that point on) despite retaining normal perceptual and intellectual functioning, including normal working memory capacity. Another outcome—one that is relevant to the issue of consolidation—was that H.M. also exhibited temporally graded retrograde amnesia (Scoville & Milner, 1957; Squire, 2009). That is, memories that were formed before surgery were also impaired, and the degree of impairment was greater for memories that had been formed just before surgery than for memories that had been formed well before. Although memories of up to 3 years before his surgery were seemingly impaired, H.M.'s older memories appeared to be largely intact (Scoville & Milner, 1957). This result suggests that the brain systems involved in the maintenance of memory change over time.

Systems Consolidation

The temporal gradient of retrograde amnesia that is associated with injury and disease was noted long ago by Ribot (1881/1882), but he had no way of knowing what brain structures were centrally involved in this phenomenon. The experience of H.M. made it clear that the relevant structures reside in the MTL, and the phenomenon of temporally graded retrograde amnesia suggests an extended but time-limited role for the MTL in the encoding and retrieval of new memories. That is, the MTL is needed to encode new memories, and it is needed for a time after they are encoded, but it is not needed indefinitely. The decreasing dependence of memories on the MTL is known as *systems consolidation* (Frankland & Bontempi, 2005; McGaugh, 2000). As a result of this process, which may last as long as several years in humans, memories are eventually reorganized and established in the neocortex in such a way that they become independent of the MTL (Squire et al., 2001). Note that this is a different view of consolidation than the resistance-to-interference view proposed by Müller and Pilzecker (1900).

The temporal gradient of retrograde amnesia exhibited by patient H.M. (documented during early years after surgery) prompted more controlled investigations using both humans and nonhumans. These studies have shown that the temporal gradient is real and that it is evident even when bilateral lesions are limited to the hippocampus (a central structure of the MTL). For example, in a particularly well-controlled study, Anagnostaras et al. (1999) investigated the effect of hippocampal lesions in rats using a context fear-conditioning paradigm. In this task, a tone conditional stimulus (CS) is paired with a shock unconditional stimulus (US) several times in a novel context. Such training results in a fear of both the tone and the training context (measured behaviorally as the proportion of time spent freezing), and memory for the context-shock association in particular is known to depend on the hippocampus. Anagnostaras et al. (1999) trained a group of rats in two different contexts, and this training was later followed by surgical lesions of the hippocampus. Each rat received training in Context A 50 days before surgery and training in Context B 1 day before surgery. Thus, at the time lesions were induced, memory for learning in Context A was relatively old, whereas memory for learning in Context B was still new. A later test of retention showed that remote (i.e., 50-day-old) memory for contextual fear was similar to that of controls, whereas recent (i.e., 1-day-old) memory for contextual fear was greatly impaired. Thus, in rats, hippocampus-dependent memories appear to

become independent of the hippocampus in a matter of weeks.

Controlled studies in humans sometimes suggest that the time course of systems consolidation often plays out over a much longer period of time period, a finding that is consistent with the time window of retrograde amnesia observed for H.M. However, the time course is rather variable, and the basis for the variability is not known. Both semantic and episodic memory have been assessed in studies investigating the temporal gradient of retrograde amnesia. Semantic memory refers to memory for factual knowledge (e.g., what is the capital of Texas?), whereas episodic memory refers to memory for specific events (e.g., memory for a recently presented list of words or memory for an autobiographical event, such as a trip to the Bahamas).

TEMPORAL GRADIENT OF SEMANTIC MEMORY

Semantic knowledge is generally acquired gradually across multiple episodes of learning and is forgotten slowly, so it seems reasonable to suppose that the systems consolidation of such knowledge would be extended in time. In one recent study of this issue, Manns et al. (2003) measured factual knowledge in six amnesic patients with damage limited to the hippocampal region. Participants were asked questions about news events that had occurred from 1950 to early 2002 (e.g., Which tire manufacturer recalled thousands of tires? [Firestone] What software company was accused of running a monopoly? [Microsoft]). The data for a particular patient (and for several controls matched to that patient) were analyzed according to the year in which the patient became amnesic. As might be expected, memory for factual knowledge was reduced for the period of time following the onset of memory impairment. Thus, for example, if a patient became amnesic in 1985, then memory for news events that occurred after 1985 was impaired (i.e., anterograde amnesia was observed). In addition, and more to the point, factual knowledge for news events that occurred during the several years immediately *before* the onset of memory impairment (e.g., 1980 to 1985) was also impaired, particularly when memory was measured by free recall rather than by recognition. However, memory for events that occurred 11 to 30 years before the onset of memory impairment (e.g., 1955 to 1974) was intact. These older memories, it seems, had become fully consolidated in the neocortex and were no longer dependent on the structures of the MTL.

The findings from lesion studies have sometimes been corroborated by neuroimaging studies performed on unimpaired subjects, though the relevant literature is somewhat mixed in this regard. Although some studies found more activity in the MTL during the recollection of recent semantic memories compared with remote semantic memories (Douville et al., 2005; Haist et al., 2001; Smith & Squire, 2009), other studies found no difference (e.g., Bernard et al., 2004; Maguire et al., 2001; Maguire & Frith, 2003). For example, using functional magnetic resonance imaging (fMRI), Bernard et al. (2004) identified brain regions associated with recognizing famous faces from two different periods: people who became famous in the 1960s to 1970s and people who became famous in the 1990s. They found that the hippocampus was similarly active during the recognition of faces from both periods (i.e., no temporal gradient was observed). It is not clear why studies vary in this regard, but one possibility is that the detection of a temporal gradient is more likely when multiple time points are assessed, especially during the several years immediately preceding memory impairment, than when only two time points are assessed (as in Bernard et al., 2004).

In an imaging study that was patterned after the lesion study reported by Manns et al. (2003), Smith and Squire (2009) measured brain activity while subjects recalled news events from multiple time points over the past 30 years. In agreement with the lesion study, they found that regions in the MTL exhibited a decrease in brain activity as a function of the age of the memory over a 12-year period (whereas activity was constant for memories from 13 to 30 years ago). In addition, they found that regions in the frontal lobe, temporal lobe, and parietal lobe exhibited an increase in activity as a function of the age of the trace. Thus, it seems that the (systems) consolidation of semantic memories is a slow process that may require years to complete.

TEMPORAL GRADIENT OF AUTOBIOGRAPHICAL (EPISODIC) MEMORY

Although lesion studies and neuroimaging studies point to a temporal gradient for semantic memory lasting years, there is some debate about whether episodic memory—in particular autobiographical memory—exhibits any temporal gradient at all. For example, some recent studies performed on H.M. that were conducted not long before he passed away in 2008 showed that his memory for remote personal experiences, unlike his memory for remote factual knowledge, was not preserved (Steinvorth, Levine, & Corkin, 2005). In addition,

a number of case studies of memory-impaired patients have reported impairments of childhood memories (Cipolotti et al., 2001; Eslinger, 1998; Hirano & Noguchi, 1998; Kitchener et al., 1998; Maguire et al., 2006; Rosenbaum et al., 2004).

These findings appear to suggest that the MTL plays a role in recalling personal episodes even if they happened long ago, and the apparent implication is that autobiographical memories do not undergo systems consolidation. However, by the time H.M.'s remote autobiographical memory impairment was documented, he was an elderly patient, and his brain was exhibiting signs of cortical thinning, abnormal white matter, and subcortical infarcts (Squire, 2009). Thus, these late-life brain abnormalities could account for the loss of remote memories. In addition, in most of the case studies that have documented remote autobiographical memory impairment, damage was not restricted to the MTL. To compare the remote memory effects of limited MTL damage and damage that also involved areas of the neocortex, Bayley et al. (2005) measured the ability of eight amnesic patients to recollect detailed autobiographical memories from their early life. Five of the patients had damage limited to the MTL, whereas three had damage to the neocortex in addition to MTL damage. They found that the remote autobiographical memories of the five MTL patients were quantitatively and qualitatively similar to the recollections of the control group, whereas the autobiographical memories of the three patients with additional neocortical damage were severely impaired. This result suggests that semantic memory and episodic memory both eventually become independent of the MTL through a process of systems consolidation, but the temporal gradient of retroactive amnesia associated with that process can be obscured if damage extends to the neocortex. MacKinnon and Squire (1989) also found that the temporal gradient of autobiographical memories for five MTL patients was similar in duration to the multiyear gradient associated with semantic memory.

TEMPORAL GRADIENTS INVOLVING A SHORTER TIME SCALE

Recent neuroimaging studies have documented a temporal gradient of activity for memory of simple laboratory stimuli on a time scale that is vastly shorter than the multiyear process of consolidation suggested by lesion studies of semantic memory and autobiographical memory. For example, using fMRI, Yamashita et al. (2009) measured activity in the hippocampus and temporal neocortex associated with memory for two sets of paired-associate figures that subjects had previously memorized. One set was studied 8 weeks before the memory test (old memories), and the other was studied immediately before the memory test (new memories). Overall accuracy at the time of test was equated for the two conditions by providing extra study time for the items that were studied 8 weeks before. Thus, any differences in activity associated with old and new memories could not be attributed to differences in memory strength. The results showed that a region in right hippocampus was associated with greater activity during retrieval of new memories than old memories, whereas in left temporal neocortex, the opposite activation pattern (i.e., old > new) was observed. These results are consistent with a decreasing role of the hippocampus and increasing role of the neocortex as memories age over a period as short as 50 days (cf. Takashima et al., 2006), a time scale of consolidation that is similar to that observed in experimental animals (e.g., Anagnostaras et al., 1999).

An even shorter time scale for systems consolidation was evident in a recent fMRI study reported by Takashima et al. (2009). Subjects in that study memorized two sets of face–location stimuli, one studied 24 hours before the memory test (old memories) and the other studied 15 minutes before the memory test (new memories). To control for differences in memory strength, they compared activity for high-confidence hits associated with the old and new memories and found that hippocampal activity decreased and neocortical activity increased over the course of 24 hours. In addition, the connectivity between the hippocampus and the neocortical regions decreased, whereas cortico-cortical connectivity increased (all over the course of only 24 hours). Results like these suggest that the process of systems consolidation can occur very quickly.

What determines whether the temporal gradient is short or long? The answer is not known, but Frankland and Bontempi (2006) suggested that the critical variable may be the richness of the memorized material. To-be-remembered stimuli presented in a laboratory are largely unrelated to a subject's personal history and thus might be integrated with prior knowledge represented in the cortex in a rather sparse (yet rapid) manner. Autobiographical memories, by contrast, are generally related to a large preexisting knowledge base. The integration of such memories into an intricate knowledge base may require more extended dialogue between

the hippocampus and neocortex (McClelland, McNaughton, & O'Reilly, 1995). Alternatively, Tse et al. (2007) suggested that when memories can be incorporated into an associative "schema" of preexisting knowledge (i.e., when newly learned information is compatible with previously learned information), the process of systems consolidation is completed very rapidly (within 48 hours for rats). However, it is not clear whether this idea can account for the rapid systems consolidation that is apparent for memories of arbitrary laboratory-based stimuli in humans (e.g., Takashima et al., 2009). The as-yet-unresolved question of why memories vary in how quickly they undergo systems consolidation seems likely to remain a focus of research in this area for some time to come.

DECREASING HIPPOCAMPAL ACTIVITY VERSUS INCREASING NEOCORTICAL ACTIVITY

The findings discussed above support the view that memories undergo a process of systems consolidation in which the structures of the MTL play a decreasing role with the passage of time. An interesting feature of several of the neuroimaging studies discussed above is that not only does MTL activity often decrease with time, but also neocortical activity *increases* over time (Smith & Squire, 2009; Takashima et al., 2009; Yamashita et al., 2009). What might that increased activity signify?

The memory of a past experience that is elicited by a retrieval cue presumably consists of the reactivation of distributed neocortical areas that were active at the time the trace was initially encoded (Damasio, 1989; Hoffman & McNaughton, 2002; Johnson, McDuff, Rugg, & Norman, 2009; McClelland, McNaughton, & O'Reilly, 1995; Squire & Alvarez, 1995). The primary sensory areas of the brain (e.g., the brain areas activated by the sights, sounds, and smells associated with a visit to the county fair) converge on association areas of the brain, which, in turn, are heavily interconnected with the MTL. Conceivably, memories are stored in widely distributed neocortical areas from the outset, but the hippocampus and other structures of the MTL are required to bind them together until cortico-cortical associations develop, eventually rendering the memory trace independent of the MTL (Wixted & Squire, 2011). In studies using fMRI, the increasing role of the direct cortico-cortical connections may be reflected in increased neocortical activity as time passes since the memory trace was formed (Takashima et al., 2009).

In agreement with this possibility, a series of trace eyeblink conditioning studies conducted by Takehara-Nishiuchi and colleagues has shown that an area of the medial prefrontal cortex (mPFC) in rats becomes increasingly necessary for the retrieval of memories as they become decreasingly dependent on the hippocampus over the course of several weeks. This was shown both by lesion studies and by direct neural recordings of task-related activity in the mPFC (Takehara, Kawahara, & Kirino, 2003; Takehara-Nishiuchi & McNaughton, 2008). In one particularly relevant experiment, Takehara-Nishiuchi and McNaughton (2008) showed that task-related activity of mPFC neurons in rats increased over the course of several weeks even in the absence of further training. In a conceptually related study, Frankland et al. (2004) trained mice in a fear-conditioning procedure and tested memory either 1 day (recent) or 36 days (remote) after training. They found that activity in multiple association cortical regions (measured by the expression of activity-regulated genes) was greater for remote than for recent memories. In addition, they found that the increased cortical activity for remote memories was not evident in mice with a gene mutation that selectively impairs remote memory. Results like these would seem to provide direct evidence of the kind of cortical reorganization that has long been thought to underlie systems consolidation.

Cellular Consolidation

Systems consolidation is not what Müller and Pilzecker (1900) had in mind when they first introduced the concept of consolidation. Their view was that a memory trace becomes increasingly resistant to interference caused by new learning as the trace consolidates, not that the trace becomes reorganized in the neocortex (and, therefore, less dependent on the MTL) over time.

Whereas a role for systems consolidation came into sharper focus in the years following the recognition of H.M.'s memory impairment, evidence for a second kind of consolidation began to emerge in the early 1970s. This kind of consolidation—called *cellular consolidation*—occurs at the level of neurons (not brain systems) and takes place over the hours (and, perhaps, days) after a memory is formed in the hippocampus (McGaugh, 2000). Cellular consolidation seems more directly relevant to the trace-hardening physiological processes that Müller and Pilzecker (1900) had in mind, and it had its origins in the discovery of a phenomenon known as *long-term potentiation* (LTP; Bliss & Lomo, 1973).

LTP is a relatively long-lasting enhancement of synaptic efficacy that is induced by a brief burst of high-frequency electrical stimulation (a tetanus) delivered to presynaptic neurons (Bliss & Collingridge, 1993). Before the tetanus, a single (weak) test pulse of electrical stimulation applied to the presynaptic neuron elicits a certain baseline response in the postsynaptic neuron, but after the tetanus, that same test pulse elicits a greater response. The enhanced reactivity typically lasts hours or days (and sometimes weeks), so it presumably does not represent the way in which memories are permanently coded. Still, LTP is readily induced in hippocampal neurons, and it is, by far, the leading approach to modeling the neural basis of initial memory formation (Bliss, Collingridge, & Morris, 2003; Martin, Grimwood, & Morris, 2000). In this model, tetanic stimulation is analogous to the effect of a behavioral experience, and the enhanced efficacy of the synapse is analogous to the memory of that experience.

Although LTP looks like neural memory for an experience (albeit an artificial experience consisting of a train of electrical impulses), what reason is there to believe that a similar process plays a role in real memories? The induction of LTP in hippocampal neurons involves the opening of calcium channels in postsynaptic *N*-methyl-D-aspartate (NMDA) receptors (Bliss & Collingridge, 1993). When those receptors are blocked by an NMDA antagonist, high-frequency stimulation fails to induce LTP. Perhaps not coincidentally, NMDA antagonists have often been shown to impair the learning of hippocampus-dependent tasks in animals (e.g., Morris et al., 1986; Morris, 1989), as if an LTP-like process in the hippocampus plays an important role in the formation of new episodic memories. One study suggests that the encoding of actual memories (not just an artificial train of electrical pulses) also gives rise to LTP in the hippocampus. Whitlock et al. (2006) trained rats on an inhibitory avoidance task (a task known to be dependent on the hippocampus), and they were able to find neurons in the hippocampus that exhibited sustained LTP after training (not after an artificial tetanus). In addition, tetanic stimulation applied to these neurons after training now had a lesser effect (as if those neurons were already close to ceiling levels of LTP) than tetanic stimulation applied to the neurons of animals who had not received training. These findings suggest that LTP may be more than just a model for memory formation; it may, in fact, be part of the mechanism that underlies the initial encoding of memory.

What does LTP have to do with the story of consolidation? The induction of LTP unleashes a molecular cascade in postsynaptic neurons that continues for hours and results in structural changes to those neurons. The postsynaptic changes are protein-synthesis dependent and involve morphological changes in dendritic spines (Yuste & Bonhoeffer, 2001) and the insertion of additional AMPA receptors into dendritic membranes (Lu et al., 2001). These changes are generally thought to stabilize LTP because LTP degrades rapidly if they do not occur (or are prevented from occurring by the use of a protein synthesis inhibitor).

LTP exhibits all of the characteristics of consolidation envisioned by Müller and Pilzecker (1900). In their own work, Müller and Pilzecker (1900) used an original learning phase (L1), followed by an interfering learning phase (L2), followed by a memory test for the original list (T1). Holding the retention interval between L1 and T1 constant, they essentially showed that L1-L2-----T1 yields greater interference than L1---L2---T (where the dashes represent units of time). In experimental animals, memories formed in the hippocampus and LTP induced in the hippocampus both exhibit a similar temporal gradient with respect to retroactive interference (Izquierdo et al., 1999; Xu et al., 1998). Whether L1 and L2 both involve hippocampus-dependent learning tasks (e.g., L1 = one-trial inhibitory avoidance learning, L2 = exploration of a novel environment), as reported by Izquierdo et al. (1999), or one involves the induction of LTP (L1) while the other involves exposure to a learning task (L2), as reported by Xu et al. (1998), the same pattern emerges. Specifically, L2 interferes with L1 when the time between them is relatively short (e.g., 1 hour), but not when the time between them is relatively long (e.g., 6 or more hours). Moreover, if an NMDA antagonist is infused into the hippocampus before L2 (thereby blocking the induction of interfering LTP that might be associated with the learning of a potentially interfering task), no interference effect is observed even when the L1-L2 temporal interval is short.

The point is that hippocampus-dependent memories and hippocampal LTP both appear to be vulnerable to interference early on and then become more resistant to interference with the passage of time. Moreover, the interfering force is the formation of new memories (or, analogously, the induction of LTP). Newly induced LTP, like a newly encoded memory, begins life in a fragile state. Over time, as the process of cellular consolidation

unfolds, recently formed LTP and recently encoded memories become more stable, which is to say that they become more resistant to interference caused by the induction of new LTP or by the encoding of new memories.

The use of an NMDA antagonist in rats is not the only way to induce a temporary period of anterograde amnesia (thereby protecting recently induced LTP or recently formed memories). In sufficient quantities, alcohol and benzodiazepines have been shown to do the same in humans. Moreover, like NMDA antagonists, these drugs not only induce anterograde amnesia but also inhibit the induction of LTP in the hippocampus (Del Cerro et al., 1992; Evans & Viola-McCabe, 1996; Givens & McMahon, 1995; Roberto et al., 2002, Sinclair & Lo, 1986). Interestingly, they also result in a phenomenon known as *retrograde facilitation*. That is, numerous studies have reported that even though alcohol induces amnesia for information studied under the influence of the drug, it actually results in improved memory for material studied just before consumption (e.g., Bruce & Pihl, 1997; Lamberty, Beckwith, & Petros, 1990; Mann, Cho-Young, & Vogel-Sprott, 1984; Parker et al., 1980, 1981). Similar findings have been frequently reported for benzodiazepines such as diazepam and triazolam (Coenen & Van Luijtelaar, 1997; Fillmore et al., 2001; Ghoneim, Hinrichs, & Mewaldt, 1984; Hinrichs, Ghoneim, & Mewaldt, 1984; Weingartner et al., 1995). Predrug memories, it seems, are protected from interference that would have been created during the postdrug amnesic state.

It is important to emphasize that postlearning amnesia-inducing agents (such as NMDA antagonists used in rats or alcohol and benzodiazepines used in humans) do not enhance predrug memories in an absolute sense. That is, in response to these drugs, the memories do not more accurately represent past experience and are not more likely to be retrieved than they were at the end of learning. Instead, memories formed before drug intake are forgotten to a lesser degree than memories formed before placebo. By limiting the formation of new memories, alcohol and benzodiazepines (like NMDA antagonists) may protect memories that were formed just before drug intake. While protected from the trace-degrading force of new memory formation, these memories may be allowed to consolidate (via cellular consolidation) in a way that hardens them against the interference they will later encounter when new memories are once again formed. If so, then less forgetting should be observed than would otherwise be the case.

All of these findings are easily understood in terms of cellular consolidation (not systems consolidation), but a recent explosion of research on the role of sleep and consolidation has begun to suggest that the distinction between cellular consolidation and systems consolidation may not be as sharp as previously thought.

Sleep and Consolidation

In recent years, the idea that sleep plays a special role in the consolidation of both declarative and nondeclarative memory has received a great deal of attention. Declarative memory consists of the conscious remembrance of either factual information (i.e., semantic memory) or past experience (i.e., episodic memory), and it is the kind of memory that we have discussed thus far in connection with systems consolidation and cellular consolidation. Nondeclarative memory, on the other hand, refers to the acquisition and retention of nonconscious skills and abilities, with the prototypical example being the ability to ride a bike. With practice, one's riding ability improves, but the memory of how to balance on two wheels is not realized by consciously remembering anything about the past (as in the case of declarative memory). Instead, that memory is realized by climbing on the bike and discovering that you can ride it without falling off. Whereas declarative memory depends on the structures of the MTL, nondeclarative memories do not (Squire, 1992; Squire & Zola, 1996). As a result, amnesic patients with MTL damage have an impairment of declarative memory (both anterograde amnesia and temporally graded retrograde amnesia), but they are generally unimpaired at learning and retaining procedural skills (Squire, 1992). An amnesic could, for example, learn to ride a bike as easily as you could, but, unlike you, the amnesic would have no conscious declarative memory of the practice sessions. Recent research suggests that sleep plays a role in the consolidation of both declarative and nondeclarative memories.

Because sleep is not an undifferentiated state, one focus of this line of research has been to identify the specific stage of sleep that is important for consolidation. Sleep is divided into five stages that occur in a regular sequence within 90-minute cycles throughout the night. Stages 1 through 4 refer to ever-deeper levels of sleep, with stages 3 and 4 often being referred to as slow-wave sleep. Rapid eye movement (REM) sleep is a lighter stage of sleep

associated with vivid dreams. Although every stage of sleep occurs during each 90-minute sleep cycle, the early sleep cycles of the night are dominated by slow-wave sleep, and the later sleep cycles are dominated by REM sleep. For declarative memory, the beneficial effects of sleep have been almost exclusively associated with slow-wave sleep, and this is true of its possible role in systems consolidation and cellular consolidation. For nondeclarative memories, the beneficial effects of sleep are more often associated with REM sleep.

Sleep-Related Consolidation of Declarative Memory

Much evidence dating back at least to Jenkins and Dallenbach (1924) has shown that less forgetting occurs if one sleeps during the retention interval than if one remains awake. A reduction in interference is generally thought to play some role in this sleep-related benefit, but there appears to be much more to the story than that. In particular, consolidation is an important part of the story, and the different stages of sleep play very different roles.

Ekstrand and colleagues (Ekstrand, 1972; Yaroush, Sullivan, & Ekstrand, 1971) were the first to address the question of whether the different stages of sleep differentially benefit what we now call declarative memory. These researchers took advantage of the fact that most REM sleep occurs in the second half of the night, whereas most non-REM sleep occurs in the first half. Some subjects in this experiment learned a list, went to sleep immediately, and were awakened 4 hours later for a test of recall. These subjects experienced mostly slow-wave sleep during the 4-hour retention interval. Others slept for 4 hours, were awakened to learn a list, slept for another 4 hours, and then took a recall test. These subjects experienced mostly REM sleep during the 4-hour retention interval. The control (i.e., awake) subjects learned a list during the day and were tested for recall 4 hours later. The subjects all learned the initial list to a similar degree, but the results showed that 4 hours of mostly non-REM sleep resulted in less forgetting relative to the other two conditions, which did not differ from each other (i.e., REM sleep did not facilitate memory). Barrett and Ekstrand (1972) reported similar results in a study that controlled for time-of-day and circadian rhythm confounds, and the effect was later replicated in studies by Plihal and Born (1997, 1999). Slow-wave sleep may play a role in both cellular consolidation and systems consolidation.

SLOW-WAVE SLEEP AND CELLULAR CONSOLIDATION

Why is slow-wave sleep more protective of recently formed memories than REM sleep? One possibility is that slow-wave sleep is more conducive to cellular consolidation than REM sleep. In experiments performed on sleeping rats, Jones Leonard et al. (1987) showed that LTP can be induced in the hippocampus during REM sleep but not during slow-wave sleep. Whereas slow-wave sleep inhibits the induction of LTP, it does not disrupt the maintenance of previously induced LTP (Bramham & Srebo 1989). In that sense, slow-wave sleep is like the NMDA antagonists discussed earlier (i.e., they block the induction of new LTP but not the maintenance of previously induced LTP). By contrast, with regard to synaptic plasticity in the hippocampus, REM sleep is similar to the awake state (i.e., LTP can be induced during REM).

Even during a night of sleep, interference may occur, especially during REM sleep, when considerable mental activity (mainly vivid dreaming) takes place and memories can be encoded in the hippocampus. But memories are probably never formed during slow-wave sleep. This is true despite the fact that a considerable degree of mental activity (consisting of static visual images, thinking, reflecting, etc.) occurs during slow-wave sleep. Indeed, perhaps half as much mental activity occurs during non-REM sleep as during REM sleep (Nielsen, 2000). However, mental activity and the formation of memories are not one and the same. The mental activity that occurs during slow-wave sleep is not remembered, perhaps because it occurs during a time when hippocampal plasticity is minimized. Because no new memories are formed in the hippocampus during this time, cellular consolidation can presumably proceed in the absence of interference. During REM sleep, however, electroencephalogram (EEG) recordings suggest that the hippocampus is in an awake-like state, and LTP can be induced (and memories can be formed), so interference is more likely to occur.

If slow-wave sleep protects recently formed memories from interference while allowing cellular consolidation to move forward, then a temporal gradient of interference should be observed. That is, sleep soon after learning should confer more protection than sleep that is delayed. This can be tested by holding the retention interval between learning (L1) and test (T1) constant (e.g., at 24 hours), with the location of sleep (S) within that retention interval varied. Using the notation introduced earlier, the

prediction would be that L1-S-----T1 will confer greater protection than L1---S---T1. If a temporal gradient is observed (i.e., if memory performance at T1 is greater in the first condition than the second), it would suggest that sleep does more than simply subtract out a period of retroactive interference that would otherwise occur. Instead, it would suggest that sleep (presumably slow-wave sleep) also allows the process of cellular consolidation to proceed in the absence of interference.

Once again, Ekstrand (1972) performed the pioneering experiment on this issue. In that experiment, memory was tested for paired-associate words following a 24-hour retention interval in which subjects slept either during the 8 hours that followed list presentation or during the 8 hours that preceded the recall test. In the immediate sleep condition (in which L1 occurred at night, just before sleep), he found that 81 percent of the items were recalled 24 hours later; in the delayed sleep condition (in which L1 occurred in the morning), only 66 percent were recalled. In other words, a clear temporal gradient associated with the subtraction of retroactive interference was observed, one that is the mirror image of the temporal gradient associated with the addition of retroactive interference reported by Müller and Pilzecker (1900). More recent sleep studies have reinforced the idea that the temporal gradient of retrograde facilitation is a real phenomenon, and they have addressed various confounds that could have accounted for the results that Ekstrand (1972) obtained (Gais, Lucas, & Born, 2006; Talamini et al., 2008). The temporal gradient associated with sleep, like the LTP and animal learning research described earlier, is consistent with the notion that when memory formation is temporarily halted, recently formed and still-fragile memories are protected from interference. As a result, they are given a chance to become hardened against the forces of retroactive interference that they will later encounter (perhaps through a process of cellular consolidation).

SLOW-WAVE SLEEP AND SYSTEMS CONSOLIDATION

Recent sleep studies have also shed light on the mechanism that may account for systems consolidation, which presumably involves some relatively long-lasting form of communication between the hippocampus and the neocortex (Marr, 1971). The mechanism of communication is not known, but a leading candidate is *neural replay*, and most of the work on this topic comes from sleep studies. The phenomenon of neural replay was initially observed in hippocampal cells of sleeping rats after they had run along a familiar track, and its discovery was tied to the earlier discovery of *place cells* in the hippocampus.

Long ago, it was discovered that the firing of particular hippocampal cells in awake rats is coupled to specific points in the rat's environment (O'Keefe & Dostrovsky, 1971). These cells are known as "place cells" because they fire only when the rat traverses a particular place in the environment. Usually, hippocampal place cells fire in relation to the rat's position on a running track. That is, as the rat traverses point A along the track, place cell 1 will reliably fire. As it traverses point B, place cell 2 will fire (and so on). An intriguing finding that may be relevant to the mechanism that underlies systems consolidation is that cells that fire in sequence in the hippocampus during a behavioral task tend to become sequentially coactive again during sleep (Wilson & McNaughton, 1994). This is the phenomenon of neural replay.

Neural reply has most often been observed in rats during slow-wave sleep. It has also occasionally been observed during REM sleep, but, in that case, it occurs at a rate that is similar to the neuron firing that occurred during learning (Louie & Wilson, 2001) and thus may simply reflect dreaming. The neural replay that occurs during slow-wave sleep occurs at a rate five to ten times faster than it did during the waking state (e.g., Ji & Wilson, 2007) and may therefore reflect a biological consolidation process separate from mental activity like dreaming. It is as if the hippocampus is replaying the earlier behavioral experience, perhaps as a way to reorganize the representation of that experience in the neocortex.

The fact that replay of sequential place cell activity in the hippocampus occurs during slow-wave sleep does not, by itself, suggest anything about communication between the hippocampus and the neocortex (the kind of communication that is presumably required for systems consolidation to take place). However, Ji and Wilson (2007) reported that hippocampal replay during slow-wave sleep in rats was coordinated with firing patterns in the visual cortex, which is consistent with the idea that this process underlies the reorganization of memories in the neocortex. In addition, Lansink et al. (2009) performed multineuron recordings from the hippocampus and ventral striatum during waking and sleeping states. While the rats were awake, the hippocampal cells fired when the rat traversed a

particular point in the environment (i.e., they were place cells), whereas the striatal cells generally fired in response to rewards. During slow-wave sleep (but not during REM sleep), they found that the hippocampal and striatal cells reactivated together. The coordinated firing was particularly evident for pairs in which the hippocampal place cell fired *before* the striatal reward-related neuron. Thus, the hippocampus leads reactivation in a projection area, and this mechanism may underlie the systems consolidation of place–reward associations.

One concern about studies of neural replay is that the animals are generally overtrained, so little or no learning actually occurs. Thus, it is not clear whether learning-related neural replay takes place. However, Peyrache et al. (2009) recorded neurons in prefrontal cortex during the course of learning. Rats were trained on a Y-maze task in which they learned to select the rewarded arm using one rule (e.g., choose the left arm) that changed to a different rule as soon as a criterion level of performance was achieved (e.g., choose the right arm). They identified sets of neuronal assemblies with reliable coactivations in prefrontal cortex, and some of these coactivations became stronger when the rat started the first run of correct trials associated with the acquisition of the new rule. Following these sessions, replay during slow-wave sleep mainly involved the learning-related coactivations. Thus, learning-related replay—the mechanism that may underlie systems consolidation—can be identified and appears to get underway very soon after learning.

Other evidence suggests that something akin to neural replay occurs in humans as well. An intriguing study by Rasch et al. (2007) showed that cuing recently formed odor-associated memories by odor re-exposure during slow-wave sleep—but not during REM sleep—prompted hippocampal activation (as measured by fMRI) and resulted in less forgetting after sleep compared with a control group. This result is consistent with the notion that systems consolidation results from the reactivation of newly encoded hippocampal representations during slow-wave sleep. In a conceptually related study, Peigneux et al. (2004) measured regional cerebral blood flow and showed that hippocampal areas that were activated during route learning in a virtual town (a hippocampus-dependent, spatial learning task) were activated again during subsequent slow-wave sleep. Moreover, the degree of activation during slow-wave sleep correlated with performance on the task the next day.

In both these studies, the hippocampal reactivation (perhaps reflective of hippocampo-neocortical dialogue) occurred within hours of the learning episode, a time course of consolidation ordinarily associated with cellular consolidation. The timing observed in these studies is not unlike that observed in a neuroimaging study discussed earlier in which hippocampal activity decreased, and neocortical activity increased, over a period as short as 24 hours (Takashima et al., 2009). Moreover, the timing fits with studies in rats showing that learning-related neural replay is evident in the first slow-wave sleep episode that follows learning (Peyrache et al., 2009).

In a sleep-deprivation study that also points to an almost immediate role for systems-level consolidation processes, Sterpenich et al. (2009), using human subjects, investigated memory for emotional and neutral pictures 6 months after encoding. Half the subjects were deprived of sleep on the first postencoding night, and half were allowed to sleep (and then all subjects slept normally each night thereafter). Six months later, subjects completed a recognition test in the scanner in which each test item was given a judgment of "remember" (previously seen and subjectively recollected), "know" (previously seen but not subjectively recollected), or "new" (not previously seen). A contrast between activity associated with remembered items and known items yielded a smaller difference in the sleep-deprived subjects across a variety of brain areas (ventral mPFC, precuneus, amygdala, and occipital cortex), even though the items had been memorized 6 months earlier, and these results were interpreted to mean that sleep during the first postencoding night influences the long-term systems-level consolidation of emotional memory.

The unmistakable implication from all of these studies is that the process thought to underlie systems consolidation—namely, neural replay (or neural reactivation)—begins to unfold in a measurable way along a time course ordinarily associated with cellular consolidation. That is, in the hours after a trace is formed, hippocampal LTP stabilizes, and neural replay in the hippocampus gets underway. These findings would seem to raise the possibility that the molecular cascade that underlies cellular consolidation also plays a role in initiating neural replay (Mednick, Cai, Shuman, Anagnostaras, & Wixted, 2011). If interference occurs while the trace is still fragile, then LTP will not stabilize, and presumably, neural replay will not be initiated. In that case, the memory will be lost. But if hippocampal

LTP is allowed to stabilize (e.g., if potentially interfering memories are blocked, or if a period of slow-wave sleep ensues after learning), then (1) the LTP will stabilize and become more resistant to interference and (2) neural replay in the hippocampus will commence and the memory will start to become reorganized in the neocortex. Thus, on this view, cellular consolidation is an early component of systems consolidation.

With these considerations in mind, it is interesting to consider why Rasch et al. (2007) and Peigneux et al. (2004) both observed performance benefits associated with reactivation during slow-wave sleep. Results like these suggest that reactivation not only serves to reorganize the memory trace in the neocortex but also strengthens the memory trace in some way. But in what way is the trace strengthened? Did the reactivation process that occurred during slow-wave sleep act as a kind of rehearsal, strengthening the memory in much the same way that ordinary conscious rehearsal strengthens a memory (increasing the probability that the memory will later be retrieved)? Or did the reactivation instead serve to render the memory trace less dependent on the hippocampus and, in so doing, protect the trace from interference caused by the encoding of new memories in the hippocampus (e.g., Litman & Davachi, 2008)? Either way, less forgetting would be (and was) observed following a period of reactivation compared with a control condition.

The available evidence showing that increased reactivation during slow-wave sleep results in decreased forgetting after a night of sleep does not shed any direct light on why reactivation causes the information to be better retained. Evidence uniquely favoring a rehearsal-like strengthening mechanism (as opposed to protection from interference) would come from a study showing that reactivation during sleep can be associated with an actual enhancement of performance beyond the level that was observed at the end of training. Very few declarative memory studies exhibit that pattern, but one such study was reported by Cai, Shuman, Gorman, Sage, and Anagnostaras (2009). Using a Pavlovian fear-conditioning task, they found that hippocampus-dependent contextual memory in mice was enhanced (in an absolute sense) following a period of sleep whether the sleep phase occurred immediately after training or 12 hours later. More specifically, following sleep, the percentage of time spent freezing (the main dependent measure of memory) increased beyond that observed at the end of training. This is a rare pattern in studies of declarative memory, but it is the kind of finding that raises the possibility that sleep-related consolidation can sometimes increase the probability that a memory will be retrieved (i.e., it can strengthen memories in that sense).

ROLE OF BRAIN RHYTHMS IN THE ENCODING AND CONSOLIDATION STATES OF THE HIPPOCAMPUS

Most of the work on hippocampal replay of past experience has looked for the phenomenon during sleep, as if it might be a sleep-specific phenomenon. However, the key condition for consolidation to occur may not be sleep, per se. Instead, the key condition may arise whenever the hippocampus is not in an encoding state, with slow-wave sleep being an example of such a condition. Indeed, Karlsson and Frank (2009) found frequent awake replay of sequences of hippocampal place cells in the rat. The rats were exposed to two environments (i.e., two different running tracks) each day, and each environment was associated with a different sequence of place cell activity. The interesting finding was that during pauses in awake activity in environment 2, replay of sequential place cell activity associated with environment 1 was observed (replay of the local environment was also observed). The finding that the hippocampus exhibits replay of the remote environment while the rat is awake suggests that the hippocampus may take advantage of any down time (including, but not limited to, sleep) to consolidate memory. That is to say, the processes that underlie systems consolidation may unfold whenever the hippocampus is not encoding new memories (e.g., Buzsáki, 1989).

In a two-stage model advanced by Buzsáki (1989), the hippocampus is assumed to alternate between what might be referred to as an "encoding state" and a "consolidating state." In the encoding state, the hippocampus receives (and encodes) information from the sensory and association areas of the neocortex. In the consolidating state, the hippocampus sends encoded information back to the neocortex. Hasselmo (1999) argued that changes in the level of acetylcholine (Ach) mediate the directional flow of information to and from the hippocampus. High levels of Ach, which occur during both active-awake and REM sleep, are associated with the encoding state, whereas low levels of Ach, which occur during both quiet awake (i.e., when the animal is passive) and slow-wave sleep, are associated with the consolidating state. Thus, according to this view, the consolidating state is not specific to sleep, but it does occur during sleep. Critically,

the encoding and consolidating states are also associated with characteristic rhythmic activity, and a basic assumption of this account is that communication between the hippocampus and neocortex is mediated by coordinated oscillatory rhythms across different structures of the brain (Sirota, Csicsvari, Buhl, & Buzsáki, 2003).

In the encoding state, the cortex is characterized by beta oscillations (i.e., 12 to 20 Hz), whereas the hippocampus is characterized by theta oscillations (i.e., 4 to 8 Hz). Hippocampal theta oscillations are thought to synchronize neural firing along an input pathway into the hippocampus. For example, in the presence of theta (but not in its absence), the hippocampus receives rhythmic input from neurons in the input layers of the adjacent entorhinal cortex (Chrobak & Buzsáki, 1996). In addition, Siapas, Lubenov, and Wilson (2005) showed that neural activity in the prefrontal cortex of rats was "phase-locked" to theta oscillations in the hippocampus in freely behaving (i.e., active-awake) rats. Findings like these are consistent with the idea that theta rhythms coordinate the flow of information into the hippocampus, and still other findings suggest that theta rhythms may facilitate the encoding of information flowing into the hippocampus. During the high-Ach encoding state—which is a time when hippocampal synaptic plasticity is high (Rasmusson, 2000)—electrical stimuli delivered at intervals equal to theta frequency are more likely to induce LTP than stimulation delivered at other frequencies (Larson & Lynch, 1986). Thus, theta appears to play a role both in organizing the flow of information into the hippocampus and in facilitating the encoding of that information.

Lower levels of Ach prevail during quite-awake and slow-wave sleep, and this is thought to shift the hippocampus into the consolidating state (see Rasch, Born, & Gais, 2006). In this state, activity along input pathways (ordinarily facilitated by theta rhythms) is suppressed, and hippocampal plasticity is low (i.e., hippocampal LTP is not readily induced). As such, and as indicated earlier, recently induced LTP is protected from interference and is given a chance to stabilize as the process of cellular consolidation unfolds. In addition, under these conditions, the cortex is characterized by low-frequency spindle oscillations (i.e., 7 to 14 Hz) and delta oscillations (i.e., 4 Hz or less), whereas the hippocampus is associated with a more broad-spectrum pattern punctuated by brief, high-frequency sharp waves (i.e., 30 Hz or more) and very-high-frequency "ripples" (about 200 Hz). These sharp wave oscillations occur within the hippocampal-entorhinal *output* network, and synchronized neural discharges tend to occur along this pathway during sharp-wave/ripple events (Buzsáki, 1986; Chrobak & Buzsáki, 1996). Thus, once again, rhythmic activity seems to coordinate communication between adjacent brain structures, and such communication has been found to occur between more distant brain structures as well. For example, ripples observed during hippocampal sharp waves have been correlated with the occurrence of spindles in prefrontal cortex (Siapas & Wilson, 1998). Moreover, the neural replay discussed earlier preferentially takes place during the high-frequency bursts of spindle waves (Wilson & McNaughton, 1994). All of this suggests that rhythmically based feedback activity from the hippocampus may serve to "train" the neocortex and thus facilitate the process of systems consolidation. When it occurs in the hours after learning, this kind of systems-level communication presumably involves hippocampal neurons that have encoded information and that are successfully undergoing the process of cellular consolidation. If so, then, again, cellular consolidation could be regarded as an early component of the systems consolidation process.

Sleep-Related Consolidation of Nondeclarative Memory

A novel line of research concerned with the role of sleep in consolidation was initiated by a study suggesting that sleep also plays a role in the consolidation of *nondeclarative* memories. Karni et al. (1994) presented subjects with computer-generated stimulus displays that sometimes contained a small target consisting of three adjacent diagonal bars (arranged either vertically or horizontally) embedded within a background of many horizontal bars. The displays were presented very briefly (10 ms) and then occluded by a visual mask, and the subject's job on a given trial was to indicate whether the target items were arranged vertically or horizontally in the just-presented display. Performance on this task improves with practice in that subjects can correctly identify the target with shorter and shorter delays between the stimulus and the mask.

The detection of element orientation differences in these visual displays is a preattentive process that occurs rapidly and automatically (i.e., no deliberate search is required). In addition, the learning that takes place with practice presumably reflects plasticity in the early processing areas of the visual cortex, which would account for why the learning is extremely specific to the trained stimuli (e.g., if the

targets always appear in one quadrant of the screen during training, no transfer of learning is apparent when the targets are presented in a different quadrant). Thus, the visual segregation task is not a hippocampus-dependent task involving conscious memory (i.e., it is not a declarative memory task); instead, it is a nondeclarative memory task.

A remarkable finding reported by Karni et al. (1994; Karni & Sagi, 1993) was that, following a night of normal sleep, performance improved on this task to levels that were higher than the level that had been achieved at the end of training—as if further learning took place offline during sleep. This is unlike what is typically observed on declarative memory tasks, which only rarely show an actual performance enhancement. Various control conditions showed that the enhanced learning effect was not simply due to a reduction in general fatigue. Instead, some kind of performance-enhancing consolidation apparently occurred while the subjects slept.

Karni et al. (1994) found that depriving subjects of slow-wave sleep after learning did not prevent the improvement of postsleep performance from occurring, but depriving them of REM sleep did. Thus, REM sleep seems critical for the sleep-related enhancement of procedural learning to occur, and similar results have been reported in a number of other studies (Atienza et al., 2004; Gais et al., 2000; Mednick et al., 2002, 2003; Stickgold, James, & Hobson, 2000; Walker et al., 2005). These findings have been taken to mean that nondeclarative memories require a period of consolidation and that REM sleep in particular is critical for such consolidation to occur. Although most work has pointed to REM, some work has suggested a role for slow-wave sleep as well. For example, using the same texture-discrimination task, Stickgold et al. (2000) found that the sleep-dependent gains were correlated with the amount of slow-wave sleep early in the night and with the amount of REM sleep late in the night (cf. Gais et al., 2000).

In the case of nondeclarative memories, the evidence for consolidation does not consist of decreasing dependence on one brain system (as in systems consolidation) or of increasing resistance to interference (as in cellular consolidation). Instead, the evidence consists of an *enhancement of learning* beyond the level that was achieved at the end of training. At the time Karni et al. (1994) published their findings, this was an altogether new phenomenon, and it was followed by similar demonstrations of sleep-related enhancement using other procedural memory tasks, such as the sequential finger-tapping task (Walker et al., 2002, 2003a, 2003b). In this task, subjects learn a sequence of finger presses, and performance improves with training (i.e., the sequence is completed with increasing speed) and improves still further following a night of sleep, with the degree of improvement often correlating with time spent in stage 2 sleep. Fischer, Hallschmid, Elsner, and Born (2002) reported similar results, except that performance gains correlated with amount of REM sleep. However, one aspect of this motor-sequence-learning phenomenon—namely, the fact that performance improves beyond what was observed at the end of training—has been called into question. Rickard et al. (2008) recently presented evidence suggesting that the apparent absolute enhancement of performance on this task following sleep may have resulted from a combination of averaging artifacts, time-of-day confounds (cf. Keisler, Ashe, & Willingham, 2007; Song et al., 2007), and the buildup of fatigue (creating the impression of less presleep learning than actually occurred). This result does not necessarily question the special role of sleep in the consolidation of motor-sequence learning, but it does call into question the absolute increase in performance that has been observed following a period of sleep.

Somewhat more puzzling for the idea that REM plays a special role in the consolidation of nondeclarative memory is that Rasch, Pommer, Diekelmann, and Born (2008) found that the use of antidepressant drugs, which virtually eliminate REM sleep, did not eliminate the apparent sleep-related enhancement of performance on two nondeclarative memory tasks (mirror tracing and motor sequence learning). This result would appear to suggest that REM sleep, per se, is not critical for the consolidation of learning on either task. Instead, conditions that happen to prevail during REM sleep (rather than REM sleep per se) may be critical. Consistent with this possibility, Rasch, Gais, and Born (2009) showed that cholinergic receptor blockade during REM significantly impaired motor skill consolidation. This finding suggests that the consolidation of motor skill depends on the high cholinergic activity that typically occurs during REM (and that presumably occurs even when REM is eliminated by antidepressant drugs).

What consolidation mechanism is responsible for sleep-related enhancement of performance on perceptual learning tasks? Hippocampal replay discussed earlier seems like an unlikely candidate because this is not a hippocampus-dependent

task. However, some form of neural reactivation in the cortex may be involved, as suggested by one study using positron emission tomography (PET). Specifically, Maquet et al. (2000) showed that patterns of widely distributed brain activity evident during the learning of an implicit serial reaction time task were again evident during REM sleep. Such offline rehearsal may reflect a neural replay mechanism that underlies the consolidation of procedural learning, but the evidence on this point is currently quite limited.

ROLE OF SLEEP IN CREATIVE PROBLEM-SOLVING

In addition to facilitating the consolidation of rote perceptual and (perhaps) motor learning, REM might also be an optimal state for reorganizing semantic knowledge (via spreading activation) in neocortical networks. This could occur because hippocampal input to the neocortex is suppressed during REM, thus allowing for cortical-cortical communication without interference from the hippocampus. Consolidation of this kind could facilitate insight and creative problem solving (Wagner et al., 2004). In this regard, a recent study by Cai, Mednick, Harrison, Kanady, and Mednick (2009) found that REM sleep, compared with quiet rest and non-REM sleep, enhanced the integration of previously primed items with new unrelated items to create new and useful associations. They used the Remote Associations Test, in which subjects are asked to find a fourth word that could serve as an associative link between three presented words (such as COOKIES, SIXTEEN, HEART). The answer to this item is SWEET (cookies are sweet, sweet sixteen, sweetheart). It is generally thought that insight is required to hit upon solutions to problems such as these because the correct answer is usually not the strongest associate of any of the individual items. After priming the answers earlier in the day using an unrelated analogies task, subjects took an afternoon nap. Cai et al. (2009) found that quiet rest and non-REM sleep did not facilitate performance on this task, but REM sleep did. Importantly, the ability to successfully create new associations was not attributable to conscious memory for the previously primed items because there were no differences in recall or recognition for the primed items between the quiet rest, non-REM sleep, and REM sleep groups. This finding reinforces the notion that REM sleep is important for nondeclarative memory, possibly by providing a brain state in which the association of the neocortex can reorganize without being disrupted by input from the MTL.

Reconsolidation

In recent years, a great deal of attention has focused on the possibility that it is not just new memories that are labile for a period of time; instead, any recently reactivated memory—even one that consolidated long ago—may become labile again as a result of having been reactivated. That is, according to this idea, an old declarative memory retrieved to conscious awareness again becomes vulnerable to disruption and modification and must undergo the process of cellular consolidation (and, perhaps, systems consolidation) all over again.

The idea that recently retrieved memories once again become labile was proposed long ago (Misanin, Miller, & Lewis, 1968), but the recent resurrection of interest in the subject was sparked by Nader, Schafe, and Le Doux (2000). Rats in this study were exposed to a fear-conditioning procedure in which a tone was paired with shock in one chamber (context A). The next day, the rats were placed in another chamber (context B) and presented with the tone to reactivate memory of the tone–shock pairing. For half the rats, a protein synthesis inhibitor (anisomycin) was then infused into the amygdala (a structure that is adjacent to the hippocampus and that is involved in the consolidation of emotional memory). If the tone-induced reactivation of the fear memory required the memory to again undergo the process of consolidation in order to become stabilized, then anisomycin should prevent that from happening, and the memory should be lost. This, in fact, was what Nader et al. (2000) reported. Whereas control rats exhibited considerable freezing when the tone was presented again 1 day later (indicating long-term memory for the original tone–shock pairing), the anisomycin-treated rats did not (as if they had forgotten the tone–shock pairing).

In the absence of a protein synthesis inhibitor, a reactivated memory should consolidate over the course of the next several hours. In accordance with this prediction, Nader et al. (2000) also reported that when the administration of anisomycin was delayed for 6 hours after the memory was reactivated (thereby giving the memory a chance to reconsolidate before protein synthesis was inhibited), little effect on long-term learning was observed. More specifically, in a test 24 hours after reactivation, the treated rats and the control rats exhibited a comparable level of freezing in response to the tone (indicating memory for the tone–shock pairing).

All these results parallel the effects of anisomycin on tone–shock memory when it is infused after a conditioning trial (Schafe & LeDoux, 2000). What was remarkable about the Nader et al. (2000) results was that similar consolidation effects were also observed well after conditioning and in response to the reactivation of memory caused by the presentation of the tone. Similar findings have now been reported for other tasks and other species (see Nader & Hardt, 2009, for a review).

The notion that a consolidated memory becomes fragile again merely because it is reactivated might seem implausible because personal experience does not suggest that we place our memories at risk by retrieving them. In fact, the well-known *testing effect*—the finding that successful retrieval enhances memory more than additional study—seems to suggest that the opposite may be true (e.g., Roediger & Karpicke, 2006). However, a fragile trace is also a malleable trace, and it has been suggested that the updating of memory—not its erasure—may be a benefit of what otherwise seems like a problematic state of affairs. As noted by Dudai (2004), the susceptibility to corruption of a retrieved memory "might be the price paid for modifiability" (p. 75). If the reactivated trace is susceptible only to agents such as anisomycin, which is not a drug that is encountered on a regular basis, then the price for modifiability might be low indeed. On the other hand, if the trace is vulnerable to corruption by new learning, as a newly learned memory trace appears to be, then the price could be considerably higher. In an intriguing new study, Monfils, Cowansage, Klann, and LeDoux (2009) showed that contextual fear memories in rats can be more readily eliminated by extinction trials if the fear memory is first reactivated by a reminder trial. For the first time, this raises the possibility that reactivated memories are vulnerable to disruption and modification by new learning (not just by protein synthesis inhibitors).

Much remains unknown about reconsolidation, and there is some debate as to whether the disruption of a recently retrieved trace is a permanent or a transient phenomenon. For example, Stafford and Lattal (2009) recently compared the effects of anisomycin administered shortly after fear conditioning (which would disrupt the consolidation of a new memory) or shortly after a reminder trial (which would disrupt the consolidation of a newly retrieved memory). With both groups equated on important variables such as prior learning experience, they found that the anisomycin-induced deficit on a test of long-term memory was larger and more persistent in the consolidation group compared with the reconsolidation group. Still, this study adds to a large and growing literature showing that reactivated memories are in some way vulnerable in a way that was not fully appreciated until Nader et al. (2000) drove the point home with their compelling study.

Conclusion

The idea that memories require time to consolidate was proposed more than a century ago, but empirical inquiry into the mechanisms of consolidation is now more intense than ever. With that inquiry has come the realization that the issue is complex, so much so that, used in isolation, the word "consolidation" no longer has a clear meaning. One can speak of consolidation in terms of memory becoming less dependent on the hippocampus (systems consolidation) or in terms of a trace becoming stabilized (cellular consolidation). Alternatively, one can speak of consolidation in terms of enhanced performance (over and above the level of performance achieved at the end of training), in terms of increased resistance to interference (i.e., less forgetting), or in terms of a presumed mechanism, such as neural replay or neural reactivation. A clear implication is that any use of the word *consolidation* should be accompanied by a statement of what it means. Similarly, any suggestion that consolidation "strengthens" the memory trace should be accompanied by a clear statement of the way (or ways) in which the trace is thought be stronger than it was before. A more precise use of the terminology commonly used in this domain of investigation will help to make sense of the rapidly burgeoning literature on the always fascinating topic of memory consolidation.

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