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New Circuits for Old Memories: The Role of the Neocortex in Consolidation

Review

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Studies of learning and memory have provided a great deal of evidence implicating hippocampal mechanisms in the initial storage of facts and events. However, until recently, there were few hints as to how and where this information was permanently stored. A recent series of rodent molecular and cellular cognition studies provide compelling evidence for the involvment of specific neocortical regions in the storage of information initially processed in the hippocampus. Areas of the prefrontal cortex, including the anterior cingulate and prelimbic cortices, and the temporal cortex show robust increases in activity specifically following remote memory retrieval. Importantly, damage to or inactivation of these areas produces selective remote memory deficits. Additionally, transgenic studies provide glimpses into the molecular and cellular mechanisms underlying cortical memory consolidation. The studies reviewed here represent the first exciting steps toward the understanding of the molecular, cellular, and systems mechanisms of how the brain stores our oldest and perhaps most defining memories.

Introduction

Consolidation is the process that stabilizes memory. The term was first used in studies of memory interference where it was observed that newly formed memories changed from a vulnerable to an invulnerable state minutes after learning (Müller and Pilzecker, 1900). A similar phenomenon was also observed, on a much longer time scale, in patients suffering from amnesia. Memories formed in the months and years nearest the onset of amnesia were more disrupted than those formed in the remote past (Ribot, 1882; Burnham, 1903). These observations suggested that new memories are initially vulnerable but are gradually strengthened over time. Today, explanations of memory consolidation include molecular, cellular, and systems processes that work in concert to mature and stabilize information in the brain (McGaugh, 2000; Debiec et al., 2002; Dudai, 2004; Dash et al., 2004).

In humans, research on consolidation has focused on declarative memories and their temporary dependence on structures in the medial temporal lobe (MTL). These memories initially require the MTL and are thought to eventually be stored in neocortical circuits without a significant MTL contribution (McClelland et al., 1995; Squire et al., 2004; but see Nadel and Moscovitch, 1997). Studies of hippocampus-dependent memory in animals have largely confirmed this idea (Zola-Morgan and Squire, 1990; Kim and Fanselow, 1992; Kim et al., 1995; Anagnostaras et al., 1999; Frankland et al., 2001; Clark et al., 2002; but see R.E. Clark et al., 2003, Soc. Neurosci., abstract; Sutherland et al., 2001). However, these studies have revealed remarkably little about the sites and mechanisms of remote memory storage. Similarly, the introduction of transgenic techniques fueled an expansion of molecular and cellular studies of memory consolidation in hippocampal networks (Chen and Tonegawa, 1997; Mayford and Kandel, 1999; Sweatt, 2001; Matynia et al., 2002) but uncovered little about the mechanisms responsible for remote memory storage.

Fortunately, current molecular and cellular investigations of memory are beginning to uncover fundamental information about the storage and recall of remote memory. A series of recent experiments demonstrate that specific regions of the neocortex and plastic mechanisms in these areas are critical for cortical memory consolidation (Bontempi et al., 1999; Frankland et al., 2001; Takehara et al., 2003; Cui et al., 2004; Frankland et al., 2004; Hayashi et al., 2004; Maviel et al., 2004). This review highlights these studies and their implications for future research. We begin by discussing the current model of systems consolidation and the molecular and cellular mechanisms underlying this fascinating process.

Hippocampal-Neocortical Interactions during Consolidation

Hints of the involvement of multiple brain systems in consolidation came initially from studies of amnesic patients. These patients could not recall recent events, but memories from their past remained intact (Ribot, 1882; Burnham, 1903). Subsequent studies confirmed that disease, head trauma, and ischemic injury often produced a loss of recent but not remotely acquired information (Barbizet et al., 1970; Korsakoff, 1887; Rose and Symonds, 1960). Squire et al. (1975) demonstrated this experimentally by showing that ECS treatment in depressed patients produced a selective loss of recent declarative memories. These findings established that old memories were more resistant to disruption than new ones and suggested that they may depend on distinct brain systems.

Determination of the specific systems involved in memory consolidation began with the finding that damage to the MTL produced severe amnesia. Patients with MTL damage have great difficulty forming new long-term memories (Scoville and Milner, 1957; Penfield and Milner, 1958; Corkin, 1984). Additionally, while remote memories usually remain intact, recently acquired declarative memories do not. These findings suggested that the MTL was essential for the initial acquisition and retrieval of new declarative memories but that eventually this structure was no longer involved (Squire, 1992).

A second observation is that when brain pathology includes damage to the neocortex remote memory is

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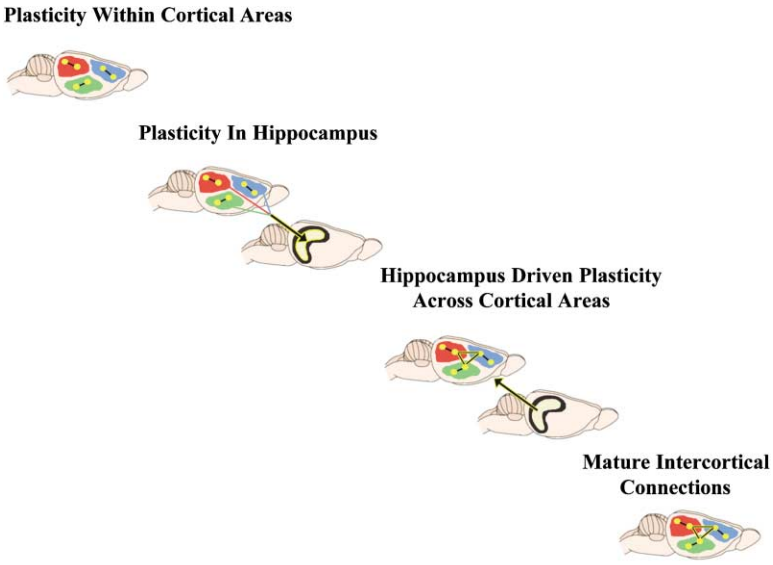

Figure 1. Cortical Consolidation

Information is processed and encoded in various neocortical regions and then rapidly linked in the hippocampus. During periods of inactivity and sleep, the hippocampus activates areas of the neocortex involved in the initial learning event. Simultaneous activation of these disparate neocortical areas allows connections to gradually form between them. Once these neocortical connections are sufficiently strong, the memory is consolidated and becomes independent of the hippocampus.

often impaired (Graham and Hodges, 1997; Squire et al., 2001; Bayley et al., 2003). This suggests that neocortical areas serve as remote memory storage sites and that, although new memories are initially dependent on the MTL, they gradually become independent of this area as they are consolidated in neocortical circuits (Alvarez and Squire, 1994; Squire and Alvarez, 1995). But why does the brain need two complementary memory systems?

McClelland et al. (1995) extended earlier ideas by Marr (1970, 1971) and argued that *gradual* interleaving of memories into the neocortex is essential for the discovery of generalities and the eventual formation of knowledge structures. Using connectionist models, they showed that the rapid incorporation of new information into an existing knowledge system would cause catastrophic interference. Essentially, new information would dominate and erase previously acquired information. The authors suggested that this is why cortical consolidation is a slow, extended process, and why the hippocampus is needed as a temporary link between distributed cortical memories. New memories need to be incorporated into existing knowledge structures in the cortex through a gradual, interleaving process to avoid losing old information. In contrast, the hippocampus is designed to do exactly the opposite: encode new information rapidly. This information could be lost via spontaneous decay and/or interference caused by new learning (McClelland et al., 1995; Shimizu et al., 2000). Alternatively, a recent study suggests that the generation of new neurons in the dentate gyrus may contribute to the periodic clearance of hippocampal memories (Feng et al., 2001).

Besides its role in temporarily linking distributed cortical memories, the hippocampus is also thought to have a critical role in reactivating them. Reactivation by the hippocampus serves to gradually strengthen the weak connections between neocortical sites. Eventually, the complete representation of the original event can be activated in cortex in the absence of the hippocampus. Based on ideas by Marr (1970, 1971), Buzsaki (1989) proposed a two-stage model of consolidation where specific patterns of activity in the hippocampus trigger a shift between a recording and playback mode. Recording occurs as the animal explores its environment. During these active periods, hippocampal theta waves (5–10 Hz) are generated which facilitate information storage (Greenstein et al., 1988). Presumably, this would be the stage in which synaptic changes in the hippocampus, specifically in the highly interconnected CA3 region, link distributed cortical memories. Playback occurs during subsequent periods of inactivity and sleep, when unique bursts of activity, called sharp-waves (SPWs), are generated in CA3 (Buzsaki, 1989; Hasselmo, 1999). SPWs could provide the activation required to drive intercortical plasticity and therefore promote cortical consolidation. Recent experiments suggest that periodic activation of NMDAR receptors contributes to this process via a mechanism called synaptic reentry reinforcement (Shimizu et al., 2000; Cui et al., 2004; Wittenberg and Tsien, 2002).

In conclusion, contemporary ideas about memory consolidation in cortical networks could be summarized as follows (Figure 1): information from various neocortical regions is rapidly and temporarily linked through the hippocampus via well-established plasticity mechanisms (Chen and Tonegawa, 1997; Mayford and Kandel, 1999; Matynia et al., 2002). Besides linking this information, the hippocampus also activates the neocortex during periods of inactivity and sleep via SPWs, where connections between disparate cortical regions gradually develop. Once these neocortical connections are sufficiently strong, the memory is consolidated and becomes independent of the hippocampus. The highly interconnected nature of the CA3 region may facilitate the integration of distributed memory fragments stored in the cortex, giving recent memories their high content and episodic-like character. In contrast, the sparser intercortical connections may degrade some of the less well-represented content of the original memory, making remote memories more general and semantic-like in nature. It is possible that areas like the prefrontal cortex (PFC) play a special role in organizing the recall and

retrieval of distributed cortical memories, once the hippocampus is no longer involved in this process.

Consolidation and the Neocortex

As discussed, most lesion studies suggest that hippocampus damage affects recent memories more severely than remote ones. This is consistent with the idea that the hippocampus plays a time-limited role in the storage and/or retrieval of memory. However, these studies did not demonstrate that, as memories age and the hippocampus becomes disengaged, specific neocortical regions come online and mediate access to remote memories. Only recently was compelling evidence for this assumption uncovered (Bontempi et al., 1999; Takehara et al., 2003; Frankland et al., 2004).

Bontempi et al. (1999) trained animals on a hippocampus-dependent spatial learning task and then monitored brain activity [using (^{14}C) 2-deoxyglucose uptake] following retrieval of either recent or remote memories. Retrieval of recent spatial memories produced more robust hippocampus activation than remote memories, a result consistent with the model that proposes progressive disengagement of the hippocampus during memory consolidation. In contrast, several neocortical areas studied, including the PFC, showed the opposite pattern of activation, with more activation during remote memory tests. These results are compelling evidence in favor of the participation of cortical networks in remote memory storage. They revealed, for the first time, that specific neocortical areas do in fact become more engaged as memories become remote.

Bontempi et al. (1999) were also the first to point to specific regions of the neocortex that become activated during memory consolidation. The data revealed that as memories change from recent to remote the PFC (anterior cingulate), frontal, and temporal cortex all became more engaged. This allowed researchers to examine remote memory processes by targeting specific areas of the neocortex. Studies employing this strategy found that regions of the PFC are critical for the consolidation of hippocampus-dependent memories (Takehara et al., 2003; Frankland et al., 2004; Maviel et al., 2004). For example, Takehara et al. (2003) showed that hippocampal lesions in rats cause a large deficit in trace conditioning when made early but not late after training. In contrast, lesions of the medial PFC (including the prelimbic and anterior cingulate cortex) produced the reverse gradient; they had no effect early after training but were devastating when made at later time points. These results parallel Bontempi's activation data (1999) and provide strong evidence that activation of PFC regions is critical for access to remote memories.

Frankland et al. (2004) found increases in neocortical immediate early gene (IEG) expression following the retrieval of remote context fear memories in mice. IEGs can be used as markers of neuronal activation, and some of these genes, such as Zif268, are also required for long-term potentiation and memory (Vann et al., 2000; Hall et al., 2001; Jones et al., 2001; Fleischmann et al., 2003; Davis et al., 2003). Frankland and colleagues found that retrieval of recent memories produced robust IEG expression in the hippocampus, but not in specific cortical areas such as the PFC and temporal cortex.

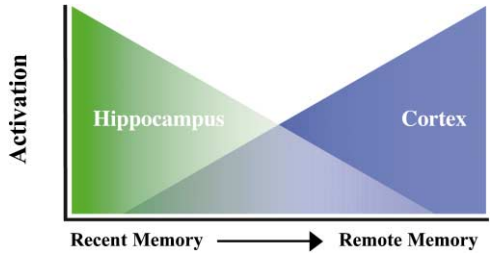

Figure 2. Activation of the Hippocampus and Neocortex by Recent and Remote Memories

Recent and remote memories differentially activate the hippocampus and neocortex. As memories age, the hippocampus becomes disengaged. This is evidenced by decreases in activity following remote memory retrieval and the inability of lesions to affect performance. In contrast, neocortical areas become more engaged as memories age. This is evidenced by increases in activity following retrieval and the emergence of lesion effects on performance.

However, retrieval of remote context memories produced the opposite effect: reduced IEG expression in the hippocampus and increased expression in neocortical areas. The functional importance of this activation was demonstrated by blocking activity in the anterior cingulate cortex (ACC) during memory tests. It was found that inactivation of this PFC structure impaired retrieval of remote but not recent context fear memories. This suggests that while the hippocampus is engaged, context fear memories do not require the PFC, but with the progressive disengagement of the hippocampus, the PFC becomes essential for the consolidation, storage, or retrieval of these memories.

In a similar fashion, a recent paper by Maviel et al. (2004) found increased IEG expression in neocortical regions following the retrieval of remote but not recent spatial memories in mice. Targeted inactivation of the ACC or prelimbic cortex impaired the retrieval of remote but not recent spatial memory. Consistent with similar findings by Frankland et al. (2004), this study also revealed evidence that suggests synaptic structural changes take place in the neocortex during remote memory consolidation. Animals tested 30 days after training showed increases in the expression of the growth-associated protein GAP43 compared to a 1 day retention group. This suggests that synaptic changes in cortical regions may underlie the formation or stabilization of remote memories in the cortex. A related finding is that mice with a dominant-negative transgenic PAK, a regulator of actin remodeling, also exhibit remote memory impairments (Hayashi et al., 2004). The dominant-negative PAK transgene produced changes in plasticity and spine morphology in the cortex but not the hippocampus. These changes did not affect the acquisition or retention of recent spatial memories, as mice exhibited normal performance 1 day after learning. However, the changes in synaptic morphology did affect the long-term stability of spatial memories. In contrast, contextual memories were already affected 1 day after training, suggesting that the deficits caused by the PAK transgene are not restricted to remote memory.

Taken together, these papers suggest that specific areas of the neocortex are more activated by remote then by recent memory retrieval (Figure 2). Damage or

inactivation of some of these activated regions selectively impairs the retrieval of remote memories. These studies also suggest that synaptic remodeling is an important part of cortical memory consolidation, suggesting a dynamic reorganization of neocortical circuitry mediating access to remote memories. Initial cortical memories are not simply stabilized by the hippocampus over time. Instead, the observed synaptic changes and increases in activity indicate that new connections are formed in the cortex, perhaps as part of an elaborative encoding process that incorporates new memories with existing ones (McClelland et al., 1995). It is important to note that although remote memory activates the cortex more robustly than recent memory, the results do indicate that the cortex is activated during recent memory. It is possible that initial cortical representations are diffuse, making increases in activity more difficult to detect until substantial consolidated transcortical networks have been established. In contrast, a large number of hippocampal neurons (as many as 40%) are engaged by new learning experiences (Guzowski et al., 1999; Moyer et al., 1996), making activation much easier to observe in this structure.

If plastic changes are occurring in specific neocortical areas during consolidation, one may ask what are the cellular and molecular mechanisms mediating these changes? A similar question was asked about hippocampal learning, and we now have a plethora of information on this topic (Silva, 2003). In similar fashion, the studies discussed in this section have set the stage for a comprehensive analysis of neocortical plasticity mechanisms mediating remote memory consolidation. In fact, studies have already begun to elucidate some of these mechanisms.

Molecular Mechanisms of Cortical Consolidation

In contrast to the well-described hippocampal system, there is a paucity of information about the mechanisms of information storage in cortex. Previous work has shown that α-CaMKII is essential for LTP and hippocampus-dependent learning (Silva et al., 1992a, 1992b; Giese et al., 1998; Elgersma et al., 2002; Lisman et al., 2002). Recently, this kinase was also identified as playing a critical role in cortical memory consolidation (Frankland et al., 2001). Spatial and contextual memory studies showed that an α-CaMKII heterozygous null mutation disrupted remote memory more severely than recent memory. Remarkably, electrophysiological analysis of these mice found normal hippocampal but impaired neocortical LTP (likely the result of robust α-CaMKII expression in the hippocampus relative to the cortex). The authors speculated that the loss of cortical LTP prevented memory consolidation in the cortex and produced the unusual amnesic phenotype seen in these mice. The implication is that α-CaMKII is a critical factor for the cortical plasticity underlying consolidation.

In a subsequent paper, Frankland et al. (2004) showed that the increases in neocortical activation, as measured by IEG induction, observed during remote memory retrieval were completely absent in the α-CaMKII mutants. Early hippocampal activation was normal in the mutants, while the delayed neocortical activation observed in controls never emerged. This suggests that memory consolidation and the development of remote memory networks in the neocortex depend critically on α-CaMKII. Consistent with this idea, Wang et al. (2003) recently found that sustained increases or decreases in CaMKII activity during the first week after training impaired memory tested at 1 month.

Studies of NMDAR function have mainly focused on the role of these receptors during training, where their activation is needed for triggering synaptic changes required for memory (Tsien et al., 1996; Nakazawa et al., 2004). Recent evidence suggests that, similar to α-CaMKII, NMDARs may also have a role in cortical memory. Cui et al. (2004) showed that that NMDARs are still needed (presumably in the cortex) many months after training. The authors used inducible and reversible knockouts of the NMDAR to demonstrate that transient deletion of NMDARs in the forebrain 6–7 months after training interfered with cortical LTP and remote contextual memory tested 9 months after training. Although the authors did not provide direct evidence that the loss of cortical NMDARs produced this surprising memory deficit, it is reasonable to propose that NMDARs in the cortex had a critical role in this phenotype since the contextual conditioning tests the authors used to assess remote memory are cortical dependent (Frankland et al., 2004). Based on these results, the authors propose that periodic activation of NMDARs is required for the maintenance of synaptic changes underlying cortical memory traces, an idea that they had previously explored computationally (Wittenberg et al., 2002). Interestingly, it is still unknown whether NMDARs are required for the initial storage of remote memory in cortical networks.

The results presented above demonstrate that memory researchers are beginning to delineate the molecular and cellular mechanisms involved in cortical consolidation. These findings suggest that at least some of the molecules involved in hippocampal plasticity (e.g., PKA, PKC, MAPK, CREB) may also be required for remote memory storage in cortical networks. However, it is possible that distinct cortical molecular and cellular mechanisms will also be found. Enhancing or inhibiting these mechanisms in the neocortex may augment or reduce the strength and/or speed of memory consolidation. With ever more sophisticated methods to manipulate the function of molecules in defined brain regions, it is now possible to investigate in more depth the mechanisms that trigger and stabilize memory representations in the cortex (Mayford et al., 1997; Mansuy et al., 1998; Shimizu et al., 2000; Ohno et al., 2001; Wang et al., 2003). Recent studies have only started to explore the range of possible molecular, cellular, and systems mechanisms involved in cortical memory consolidation. The last section of this review discusses possible directions of this area of memory research and highlights a few topics that will be critical to our understanding of cortical memory consolidation.

Future Studies

The Role of Specific Neocortical Areas in Consolidation

Current studies demonstrate that several neocortical regions become activated as memories age. Surprisingly, several regions of the PFC are reliably activated

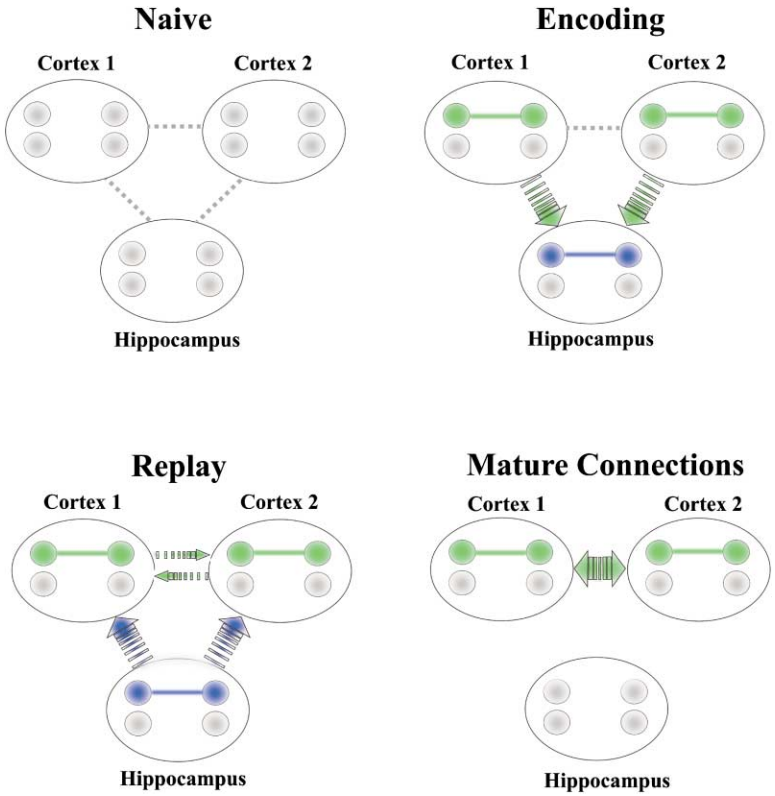

Figure 3. Excitability as a Mechanism of Cortical Consolidation

Under initial conditions both intra- and intercortical connections are weak. During acquisition, synaptic plasticity forms networks in different areas (green and blue links). Additionally, changes in intrinsic excitability tag recently coactivated neurons in both the hippocampus (blue cells) and cortex (green cells). Repeated hippocampal activity (SPWs) enables strengthening of intercortical connections among tagged cortical cells. Over time, the intercortical connections mature sufficiently and enable hippocampus-independent recall.

during remote but not recent memory tests (Bontempi et al., 1999; Frankland et al., 2004; Maviel et al., 2004). Previous studies had implicated these areas in executive processes and working memory (Goldman-Rakic, 1987, 1995; Fuster, 2000; Miller and Cohen, 2001). Perhaps the PFC performs similar functions during the consolidation process as during memory acquisition, organizing and orchestrating the formation of remote memories. In addition, the PFC has also been implicated in memory retrieval (Markowitsch, 1995; Nyberg et al., 1996; Tomita et al., 1999; Fuster, 2001; Simons and Spiers, 2003; Xiang and Brown, 2004), with some areas being particularly engaged when it is explicit or effortful (Schacter and Buckner, 1998). Remote memories may be more difficult to retrieve and thus require greater PFC activation. Given its widespread connections, the PFC could orchestrate the activation of multiple neocortical areas, a process that is likely essential for memory retrieval and consolidation. In addition, the PFC may also inhibit the hippocampus during the retrieval of remote memories and prevent it from reencoding redundant information. This would explain why the hippocampus shows reduced activity when remote memories are retrieved and provide a mechanism that allows this structure to distinguish old and new information (Bontempi et al., 1999; Frankland et al., 2004; Maviel et al., 2004). This idea is consistent with models suggesting that the PFC monitors ongoing activity and exhibits top-down control over processing in other areas (Miller and Cohen, 2001; Simons and Spiers, 2003). Determining the role of the PFC and other specific neocortical areas by addressing these issues will be critical to our understanding of the consolidation process.

Distinct Molecular Mechanisms of Cortical Consolidation

Recent findings suggest that the molecular and cellular mechanisms underlying information storage in cortical networks are similar to those observed in the hippocampus. However, differences are also likely given the unique time course and character of cortical memories. Consistent with this idea, a recent study found that adrenergic modulation is required for the retrieval of recent but not remote contextual memories (Murchison et al., 2004). Mice lacking epinephrine and norepinephrine exhibited impaired context fear 1 and 4 days after training. Remarkably, these mice showed normal memory when tested at more remote time points (7, 10, and 13 days), as if the retrieval of cortically consolidated memories did not require adrenergic function. Future studies may find modulatory neurotransmitters that are required specifically for memory retrieval in the neocortex. Similar molecular distinctions may also be found during storage of information in hippocampal and cortical networks.

Mechanisms of Hippocampal-Neocortical Interactions

Hippocampal SPWs may have a role in the activation of cortical networks, thus driving memory consolidation (see above). But how is it that these bursts of activity do not activate the wrong cortical memory fragments during consolidation? Hebbian learning theories propose that changes in synaptic strength among neurons encoding a distributed memory ensure proper coactivation during retrieval. However, since changes in synaptic strength are thought to emerge slowly in cortical networks, additional mechanisms are needed to temporarily mark memory traces and make sure that correct

coactivation occurs during cortical consolidation. One intriguing possibility is that molecular and cellular changes that facilitate intrinsic neuronal firing ("excitability tags") are one of the mechanisms hippocampal/cortical networks use to coordinate proper activation during consolidation. Excitability tags could temporarily mark distributed memory traces and ensure that hippocampal SPWs drive synaptic changes in the correct set of cortical neurons. Once these cortical synaptic changes mature, the excitability increases would dissipate and new excitability tags could then be used to mark other consolidating memories. An illustration of this process is presented in Figure 3.

Disterhoft and colleagues have shown that, after trace eye-blink conditioning, a hippocampal-dependent task, a significant number of CA1 and CA3 hippocampal neurons fire more readily than in naive animals, as if they were marked by "excitability tags"; importantly, this increase in excitability lasts approximately 7 days and then dissipates (Moyer et al., 1996; Thompson et al., 1996). Interestingly, the time course of this increase in hippocampal excitability is similar to the length of time this region is required for trace conditioning (Takehara et al., 2003), suggesting that changes in excitability play a role in consolidation (Daoudal and Debanne, 2003; Zhang and Linden, 2003). There is also evidence that experience induces temporary increases in the intrinsic excitability of certain cortical neurons (Aou et al., 1992; Saar et al., 1998; Egorov et al., 2002). These results show that learning marks hippocampal and neocortical neurons with increases in excitability, a seemingly ideal mechanism to ensure the coactivation of maturing fragmented memory traces. Future studies should address the nature of the molecular and cellular mechanisms that ensure the correct coactivation of emerging memory traces in cortical networks.

Here, we reviewed exciting new findings that have opened the door to molecular, cellular, and systems studies of cortical memory consolidation. These results are an eloquent demonstration of how approaches from the new field of molecular and cellular cognition, together with traditional behavioral neuroscience methods, are shaping the way we think about plasticity and behavior.

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