local synthesis is part of the mechanism through which the modification in synaptic strength is rendered? It would be instructive to compare MAP kinase activation and immediate early gene (IEG) induction in 3′UTR mutant and control animals. If these signal transduction cascades were not activated to the same degree, this would suggest that local synthesis was critical for creating the multiprotein signaling complex that triggers LTP. If MAP kinase was activated and IEGs were induced to a normal degree in 3′UTR mutant animals, this would support the idea that local synthesis was critical for the actual rendering of the synaptic modification.

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Systems-Level Reconsolidation: Reengagement of the Hippocampus with Memory Reactivation

Certain types of memories are dependent on the hippocampus for a short period of time following training, after which they are no longer susceptible to hippocampal manipulations. Having completed this initial consolidation process, a memory may once again engage the hippocampus (undergo reconsolidation) when recalled. Two studies in the current issue of *Neuron* (Debiec et al., 2002, and Milekic and Alberini, 2002) make important advances in our understanding of reconsolidation but reach different conclusions about the modifiability of old memories.

The transition from short-term (STM) to long-term memory (LTM) is marked by a process known as consolidation, in which the initially fragile memory trace is solidified and made more permanent through a variety of neural mechanisms (McGaugh, 2000). It has become commonplace to distinguish between consolidation as observed at a systems and a cellular level of analysis, although it is generally assumed that the two are closely related. Systems consolidation refers to the process by which new declarative memories, which are initially dependent on the hippocampus, eventually lose their sensitivity to hippocampal manipulations, presumably because they are stored in other brain regions such as the cortex (Squire and Alvarez, 1995). Cellular consolidation encompasses processes such as activation of second messenger cascades, induction of gene transcription, and synthesis of proteins, which underlie the biochemical and morphological changes in neurons that mark the transition from short-term to long-term forms of plasticity (Bailey et al., 1996). Disruption of consolidation at either level, as with posttraining hippocampal lesions or infusions of protein synthesis inhibitors, typically has little effect on STM but severely disrupts LTM.

Historically, consolidation has been viewed as a unidirectional process affecting only newly acquired memories. Thus it is assumed that a memory, once consolidated, never returns to the labile state in which it was maintained following encoding but instead achieves a state that renders it relatively impervious to modulation. This aspect of consolidation theory has been applied with considerable success to findings from a great variety of experimental circumstances; however, empirical challenges have also arisen that have cast doubt on the validity of the concept. Among the most striking of these is the apparently renewed susceptibility of consolidated memory traces to disruptive influences for a period of time following their retrieval, as evident in observations of behavioral deficits following memory reactivation and administration of an amnestic treatment. Such findings were first reported in the 1960s (Misanin et al., 1968) and continue to the present day, most notably in the seminal study of Nader, Schafe, and LeDoux (2000), demonstrating that a reactivated fear memory is sensitive to intra-amygdalar, postreactivation infusions of the protein synthesis inhibitor anisomycin. This phenomenon has been taken as suggestive of a reconsolidation process in which an activated, consolidated memory trace returns to a state of lability and must undergo consolidation once more if it is to remain in long-term storage.

The contemporary literature on reconsolidation emphasizes the involvement of cellular processes such as NMDA receptor activation, CREB phosphorylation, and protein synthesis in the maintenance of a reactivated memory trace (Kida et al., 2002; Przybyslawski and Sara, 1997; Taubenfeld et al., 2001). However, the observation that recalled memories seem to be returned to an earlier level of processing begs the question as to whether reconsolidation might also be observable on a systems level of analysis. In other words, is it possible that fully consolidated memories, which have become independent of the hippocampus and presumably are stored within other brain structures, might reengage the hippocampus for further processing and reconsolidation each

time they are reactivated? If so, are older memories more resistant to renewed hippocampal processing than are newer memories? These intriguing issues are addressed in two papers in this issue of *Neuron*, each of which provides evidence that systems reconsolidation does indeed occur.

Debiec, LeDoux, and Nader ([2002], in this issue of *Neuron*) present an extensive analysis of the hippocampus dependence of reactivated Pavlovian contextual fear memories that in many ways mimics the study of Nader et al. (2000) on amygdala-dependent conditioned fear. They begin by presenting evidence that cellular reconsolidation occurs within the hippocampus, using an experimental design involving nonreinforced exposure to a previously shocked context followed by intrahippocampal infusions of anisomycin. Rats that received reactivation and anisomycin were impaired in a subsequent retention test relative to control groups that experienced either reactivation followed by vehicle infusions or anisomycin in the absence of reactivation, an outcome typical of studies purporting to provide evidence for reconsolidation.

Next, the authors evaluate the susceptibility of reactivated memories of varying ages to the impairing effect of hippocampal manipulations. Rats were exposed to a context-footshock pairing and then were reexposed to the context either 15 or 45 days later. Rats receiving intra-hippocampal anisomycin infusions immediately following memory reactivation exhibited significant impairments of contextual fear assessed 24 hr later, regardless of the interval between initial acquisition and context reexposure. Electrolytic lesions of the hippocampus following reactivation produced a similar impairing effect in a separate group of rats for which the acquisition to reactivation interval was 45 days. Thus, even though 45-day-old Pavlovian contextual fear memories are not affected by hippocampal lesions in traditional consolidation studies, whereas 15-day-old memories are (cf. Squire et al, 2001), both are dependent on the functional integrity of the hippocampus for a period of time following their reactivation.

Finally, Debiec et al. turn to the question of the temporal gradient of this renewed hippocampal involvement in the maintenance of contextual fear memory. Rats were exposed to a context-footshock pairing and 45 days later were reexposed to the context. Separate groups of rats then received hippocampal lesions 4, 24, or 48 hr after the reactivation session and were tested for freezing to the context 7 days later. Contrary to a large literature indicating that systems consolidation is a prolonged process lasting on the order of weeks (Squire et al., 2001), rats were impaired when the reactivation to lesion interval was 4 or 24 hr, but not when it was 48 hr, suggesting that systems reconsolidation is relatively brief. A similarly foreshortened gradient was obtained in a separate experiment examining the duration of a third round of hippocampal processing of a memory that had been reactivated twice.

In sum, it appears that systems reconsolidation is evident in the renewed hippocampus dependence of reactivated contextual fear memories and that it applies to memories of any age and persists for a relatively short period of time. Like other detractors to traditional consolidation theory (cf. Lewis, 1979), Debiec et al. interpret their findings to indicate that dormant memories (i.e., those that have not been recalled recently) are stably encoded, but active memories may be altered in the interest of incorporating new information available at the time of recall. Reconsolidation, then, is a process whereby altered memories are stabilized and returned to long-term storage. This constructive view of memory features prominently in cognitive theories of memory and memory distortion (cf. Hyman and Loftus, 1998), and its application to neural, as well as purely behavioral, phenomena is a satisfying extension of these views.

Milekic and Alberini ([2002], this issue of *Neuron*) address the question of the hippocampus dependence of reactivated memories of varying ages using a one-trial inhibitory avoidance paradigm. In their experiment, rats were placed into the lighted compartment of a shuttle box, and their latency to enter the darkened compartment, where a mild footshock was administered, was assessed. Separate groups of rats were then placed back into the lighted compartment 2, 7, 14, or 28 days later, and their latency to enter the darkened compartment (where the footshock was now omitted) was again measured. Immediately following this memory reactivation test, half of the rats of each group were injected subcutaneously with anisomycin and the other half with vehicle. Two days later, the rats were returned once more to the lighted compartment of the shuttle box and their latency to enter the darkened compartment was taken as a measure of memory retention. As expected, no differences were evident among groups in either the training session (in which latencies were uniformly very short) or the reactivation session (in which latencies were considerably longer). There were, however, striking differences in the retention test, where vehicle-treated rats of all groups exhibited long latencies (i.e., good retention) comparable to those seen in the reactivation session, but anisomycin-treated rats were impaired when the acquisition to reactivation interval was relatively brief (2 or 7 days), but not when it was longer (14 or 28 days). Thus, it appeared that older memories were less susceptible to the disruptive effect of anisomycin than were younger memories. Importantly, separate groups of rats that were injected with anisomycin but did not experience the reactivation session at 2 or 7 days postacquisition performed as well in the retention test as did vehicle-treated controls, indicating that the impairment in the experimental groups could not be attributed to an effect of anisomycin on consolidation of the original memory trace or a disruption of performance.

Unlike Debiec, LeDoux, and Nader, who reject traditional consolidation theory and its implied isomorphism between the age and consolidation state of a memory, Milekic and Alberini argue that a relatively modest modification of this view may be sufficient. Among the possibilities they consider is a hybrid of age- and activity-based consolidation theories that emphasizes the incorporation of new information into a previously established memory trace but maintains that the degree to which the initial trace is modified varies with its age. Reactivation occurring before the initial trace is completely consolidated results in reengagement of many of the same synapses representing the original information, with the effect that the initial memory is partially overwritten in

Table 1. Comparison of Recent Reactivation Experiments

Acqusition to Reactivation (Days)	Reactivation to LTM Test (Hours)					
	24	24	24	24	48	48
1	–	Facilitated	No effect	Impaired	–	–
2	–	–	–	–	Impaired	Impaired
3	Impaired	–	–	–	–	–
7	–	–	–	–	–	Impaired
14	–	–	–	–	–	Not impaired
15	Impaired	–	–	–	–	–
24	–	–	–	–	–	–
28	–	–	–	–	–	Not impaired
45	Impaired	–	–	–	–	–
Reference	Debiec et al., 2002	Vianna et al., 2001	Lattal and Abel, 2001	Kida et al., 2002	Taubenfeld et al., 2001	Milekic and Alberini, 2002
Species	Rat	Rat	Mouse	Mouse	Rat	Rat
Task	Pavlovian fear conditioning	Inhibitory avoidance	Pavlovian fear conditioning	Pavlovian fear conditioning	Inhibitory avoidance	Inhibitory avoidance
Measure	Freezing	Latency	Freezing	Freezing	Latency	Latency
Drug	Anisomycin	Anisomycin	Anisomycin	Anisomycin	Anisomycin	Anisomycin
Administration	Intra-hippocampus	Intra-hippocampus	Systemic	Systemic	Intra-hippocampus	Systemic
Time	Postreactivation	Postreactivation	Postreactivation	Prereactivation	Postreactivation	Postreactivation
Dose	125 μg/μl/side	160 μg/μl/side	150 mg/kg	150 mg/kg	150 mg/kg	210 mg/kg

the interest of storing more recently acquired information. By contrast, older memory traces are less readily modifiable because they are represented by a larger number of synapses and/or are localized to "storage" circuits that are physically separate from "encoding" circuits.

Clearly, we are placed in a difficult situation with respect to these two papers, with one reporting no variation in the susceptibility of reactivated memories of different ages to the impairing effect of hippocampal manipulations and the other reporting a temporal gradient whereby memories become increasingly impervious to modification as they grow older. In fact, such inconsistencies seem endemic within the broader reconsolidation literature and underscore the degree to which the reconsolidation phenomenon has defied simple explanation (Cahill et al., 2001; Myers and Davis, 2002; Riccio and Richardson, 1984; Lattal and Abel, 2001). Table 1 compares six studies published within the last 2 years that examine the effect of pre- or postreactivation anisomycin administration upon memory retention in a hippocampus-dependent task. The differences among the outcomes of the studies, particularly those involving relatively short acquisition to reactivation intervals (1–3 days), are striking, and yet there is no single procedural variable (including those that differ between the two studies in this issue) that seems to differentiate studies reporting one effect from those reporting another. Further complicating matters is the observation (not included in Table 1) that experimentally induced amnesia following memory reactivation may under some circumstances be temporary, suggesting a retrieval rather than a storage deficit (Riccio and Richardson, 1984; Lattal and Abel, 2001).

In trying to make sense of these inconsistencies, it may be useful to consider processes other than reconsolidation that may be engaged during a so-called reactivation session. Elsewhere (Myers and Davis, 2002), we have stressed the isomorphism between reactivation and extinction procedures, each of which typically involves nonreinforced presentation of a conditioned stimulus. Theoretical accounts of extinction emphasize the development and strengthening of an inhibitory memory trace that counteracts the excitatory trace established in acquisition. It is conceivable that a manipulation imposed after a reactivation session might partially or selectively affect this inhibitory trace, sometimes leading to an outcome consistent with a reconsolidation deficit (i.e., if the development of inhibition is facilitated) and sometimes producing an apparent improvement in retention (i.e., if the development of inhibition is impaired; cf. Vianna et al., 2001). Moreover, because extinction itself appears to undergo consolidation (Santini et al., 2001), complex time-dependent interactions could occur between consolidation of extinction and reconsolidation of original learning. The nature of such interactions might well depend on a number of variables about which we know very little, such as the rate at which extinction proceeds when initiated at varying intervals after acquisition and the manner in which this might be affected by pharmacological treatments. Thus, it may be useful to explore questions of this nature as a means of shedding light on the more complex issue of reconsolidation.

In any event, it is clear that there is much to be done if the reconsolidation phenomenon is to be completely understood. The two papers published in this issue are an important step in this direction but, at the same time, it is fair to say that they raise as many questions as they resolve. The significance of the issues they address

ensures that they will receive considerable attention in future investigations.

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