

Reconsolidation: A brief history, a retrieval view, and some recent issues

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This review briefly traces some of the history of the phenomenon of what has come to be called “reconsolidation.” The early findings of retrograde amnesia for an old but reactivated memory led to several interesting but largely behaviorally oriented studies. With only a few sporadic exceptions, research in the area languished until about 2000, when several articles caught the attention of the neuroscience community and led to a number of studies examining the phenomenon at several different levels of analysis. We consider several of the current issues generated by those studies, present a retrieval based model that may account for some findings, and indicate some possible new directions on this topic.

A brief history of consolidation and reconsolidation

Early clinical observations indicated that closed head injury or other traumatic insults to the brain led to forgetting of recent memories while sparing earlier ones (Ribot 1882; Russell and Nathan 1946). This time-dependent gradient of retrograde amnesia (RA), in which new but not old memories were susceptible to disruption, was later substantiated by experimental laboratory studies using animals (typically, rats or mice) and with a variety of amnesic treatments including electroconvulsive shock (ECS), carbon dioxide exposure, concussive head injury, and thermoregulatory disruptions (for review, see Spear and Riccio 1994). The possibility that the performance impairments reflected a delay of punishment gradient from the potentially aversive consequences of the amnesia agents rather than a true memory effect was convincingly eliminated with the introduction of the inhibitory avoidance (IA) or passive avoidance paradigm (Madsen and McGaugh 1961).

The publication of *Organization of Behavior* by D.O. Hebb (1949), in which he speculated on the role of reverberating neural circuits in the establishment of learning, suggested a likely mechanism for the temporal gradient of RA: Disruption of reverberating circuits would prevent the synaptic changes necessary for long-term memory, but the impairment would decrease as more of the changes were completed. In his now classic article, McGaugh (1966) reviewed the literature on time-dependent modulation of memory and elaborated the concept of what came to be the standard model of consolidation. (Although Muller and Pilzecker [1900] had originally proposed “consolidation” to account for retroactive interference, that view gained little acceptance in traditional research on human memory.)

The notion that storage of new information required time (a “fixation” period), and that the storage could thus be prevented or terminated by an amnesic event, seemed to explain the RA gradient very nicely. An immediate treatment prevented storage, but with longer delays consolidation increased until at some point no memory loss was obtained. This consolidation model quickly caught on and was widely accepted by many laboratories, including this one (Riccio et al. 1968).

However, several challenges to the consolidation disruption view began to develop in the late 1960s (for review, see Riccio

and Richardson 1984). Among the challenges, the finding that RA could be induced for old, presumably well consolidated, information was particularly intriguing. That it is of interest today is evidenced by the theme of this special issue of *Learning & Memory*. The seminal observation was reported by Misanin et al. (1968), who administered ECS 1 d after rats were trained in a simple Pavlovian fear conditioning task (conditioned suppression, or “CER”). As expected, this interval exceeded the temporal gradient for ECS-induced RA, and controls showed no impairment when tested. In contrast, a group briefly re-exposed to the fear cue (conditional stimulus, or CS) just prior to the ECS displayed very little fear when tested; i.e., substantial RA was induced. Reactivating the old information by a cueing exposure then had made the memory vulnerable to an amnesic agent. They summed up the then current understanding of reconsolidation by stating that “the primary determinant of amnesia for an event is not the ‘recency of memory’ for the event, but the state of the corresponding memory trace at the time of ECS.” Since the traditional view of consolidation involved a time limited process following a learning episode in which neural and synaptic changes were established that provided the substrate for long-term memory, RA for old memory appeared to be an oxymoron. Once consolidated, a memory should not have to undergo the same process all over again.

Lewis and his colleagues (Lewis et al. 1968; Misanin et al. 1968; Lewis 1979) were quick to point out that the well-established, time-dependent gradient of RA actually confounded two variables: time since an episode and the activity level of memory. By introducing a cueing procedure, a situation was produced in which the memory (old and inactive) was now made active again. (It might be noted that the converse manipulation of “deactivating” a newly acquired memory appears not to have been done successfully, although attempts have been made [Richardson et al. 1982b].)

A series of studies from D. Meyer’s laboratory (for review, see Meyer 1972), published shortly after the initial work by the Lewis group, also provided support for the view that old memory could be disrupted by an amnesic treatment. The general approach was to train rats sequentially on three different complex mazes, with two being learned in one motivational state and the other under a different drive condition. For example, the first and third tasks might involve escape from shock, while the second was hunger motivated with food as a reward. When ECS was administered after the final maze, the memory for the much earlier shock

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based task was impaired, while the memory for the more recent second maze (hunger motivation) remained intact. Although Meyer focused on “motivational control” over memory, the concept of drive states reactivating (controlling) an earlier memory to permit induction of RA clearly has much in common with reactivation based on re-exposure to a CS.

Despite some failures to replicate the findings of RA for a reactivated memory that soon appeared, the phenomenon seemed intriguing. As our laboratory had already done some work using deep body cooling (hypothermia) as an amnesic treatment to examine several aspects of RA for newly acquired memory, we decided to pursue the topic. An initial study (Mactutus et al. 1979) confirmed and extended the generality of the Misanin et al. (1968) work by obtaining a similar outcome using a different task (IA) and a different amnesic agent (hypothermia). An unexpected but interesting finding was that after reactivation, the 1-d-old memory was also disrupted by mild hypothermia. Since a moderate reduction in body temperature was known to have no amnesic effect on new learning, the mild cooling had been intended as a control condition.

But the differential susceptibility of new and old memory to RA suggested that a comparison of the characteristics of these amnesias might be fruitful—in what ways were they similar and in what ways different? Accordingly, a rather extensive study was undertaken by Charles Mactutus in my laboratory (Mactutus et al. 1982). To summarize the findings, both new and old memory showed a temporal gradient of RA, suggesting that the processes occurring after acquisition or reactivation subside over time. There was a suggestion in the data that the temporal gradient of susceptibility was steeper in the reactivation condition, and that finding was more firmly established by Judge and Quartermain (1982) using inhibition of protein synthesis. Also, both amnesias could be reversed or alleviated by recooling the rats just prior to testing, an outcome of some theoretical import, to be discussed shortly. (It should be noted that control groups were included to rule out performance artifacts such as motor impairment at testing).

However, several differences became apparent as well. As already indicated, RA for reactivated but not new memory could be induced with a relatively weak treatment (mild hypothermia). Also, for the reactivated memory, the impairment was already present 4 h after the hypothermia administration, whereas the onset of RA was delayed well beyond this time for new memory (see also Hinderliter et al. 1975; Mactutus and Riccio 1978). Furthermore, with repeated daily tests, the RA for reactivated memory substantially diminished, while no attenuation of forgetting was seen with new learning under these conditions. Although repeated testing is a less than ideal design to evaluate “spontaneous recovery” (SR) from amnesia (since the testing procedure itself may act as a reminder), it should be noted that the same testing regimen had no apparent effect on the RA in the new memory condition. Moreover, Judge and Quartermain (1982) also reported evidence of SR from RA induced after a cue exposure. As it happens, several of these comparisons reappear in contemporary research and are the basis of some rather lively discussions (see below).

Would it be possible to reactivate an old memory with procedures not involving a brief exposure to the CS alone, which is a nominal extinction treatment? Although control groups not receiving the amnesic agent displayed little loss of fear produced by the short CS cuing exposures, a variety of reminder studies from other domains suggested that memory could be reactivated with other manipulations as well. Accordingly, we (Richardson et al. 1982a) were able to demonstrate that presenting the training footshock (the unconditional stimulus, or UCS) in an apparatus unrelated to that used in training (noncontingent footshock) was

an effective reactivation condition, as indicated by the presence of RA when rats received hypothermia after the shock. Furthermore, various combinations of CS exposure shortly prior to, or immediately after, the footshock also served to reactivate old memory, as did a direct repairing of the CS and the shock.

A retrieval-oriented concept

In the 1970s, a series of important contributions by Spear (1973, 1978) argued persuasively for the importance of retrieval deficits in many cases of forgetting, and studies by R. Miller (see Miller and Springer 1972) and others (Sara 1973; Sara et al. 1975) showed that ECS-induced RA for new memory could also be viewed as a problem of retrieval rather than a loss of storage. Prominent among the findings was evidence that RA could be reversed or alleviated by reminder treatments, such as exposure to the context or training apparatus or to a noncontingent footshock prior to testing, as well as the demonstration that old memories could become vulnerable to amnesic agents following reactivation.

On the basis of an experiment showing that hypothermia-induced RA could be partially reversed by moderately recooling rats prior to the test, Hinderliter et al. (1975) proposed a modified state-dependent retention (MSDR) model of RA. In the standard state-dependent paradigm, the drug or other manipulation precedes training; i.e., the phenomenon is anterograde in nature. In RA the learning episode itself occurs in a normal state, since the amnesic event follows the learning. Accordingly, the modified version of state-dependency assumed that processing of information continued for a brief period of time after the learning episode. However, rather than the amnesic treatment disrupting storage, the information became associated with (encoded in) the altered internal contextual state produced by the treatment. Thus, encoding was intact and the internal context would become a critical cue for retrieving the memory. The absence of the internal context at testing led to a retrieval impairment because of a mismatch between the encoding and retrieval environments, as Tulving’s encoding specificity principle (Tulving and Thomson 1973) would predict. With longer training to hypothermia delays, less of the encoding would occur in the unusual internal context, and thus the memory was more likely to be retrieved; i.e., a temporal gradient of RA would be obtained. This model allows one to conceptualize the delay gradient in terms of a continuum of retrieval deficits rather than of storage failures.

Importantly, although body temperature was seen as a convenient marker for the internal context, the variety of stress-related effects from the amnesic insult, including hormone shifts and changes in brain activity, were also assumed to constitute the special internal environmental state. To extend this model to RA for old memory required only the small step of assuming that the cue-reactivated information, similar to newly acquired memory, also underwent processing that got linked to this unusual internal context (Mactutus et al. 1980, 1982; Millin et al. 2001; Riccio et al. 2002).

The concept of reactivating an old memory by cuing did not assume that the processes involved were an exact replication of those occurring at training. Or, as Spear (1981) has argued, the processes at retrieval may be similar but not necessarily identical. A similar view has recently been expressed by Dudai (2004) in terms of a literary allusion, the Lady MacBeth argument: “What is done, cannot be undone.” That is, it would be virtually impossible for the brain to exactly “undo” the physiological steps that it took to consolidate a memory. If one considers a memory to consist of a variety of attributes (Spear 1973; Spear and Riccio 1994), then from a stimulus sampling view (see Estes 1950) it seems unlikely that all these attributes get reactivated during

exposure to the CS. Mactutus et al. (1982) suggested that the failure of cueing to reactivate some attributes would prevent those attributes from being re-encoded in the altered state, and that the presence of these attributes could account for the unexpected observation of SR from RA in the old-reactivated memory condition.

In any event, the representation present at the time of the amnesic manipulation would not be expected to be identical to that at training, and “reconsolidation” as a recapitulation of the original event was not an issue. Further, the representation may be modified each time that it is activated. An interesting implication is that administering an amnesic agent after the first reactivation should be qualitatively different from administering it after multiple reactivations. In the latter case, the successive reactivations have allowed the establishment of other retrieval associations or modifications before the amnesic treatment. When the treatment follows the initial reactivation, no such opportunity for transforming the representation has been afforded.

Finally, it has sometimes been argued that if the memory loss produced by various agents can be reversed, then the phenomenon under investigation is not RA. For example, “reconsolidation” is “unlikely to be true amnesia as the supposedly lost memories show spontaneous recovery” (Cahill et al. 2001; see also Power et al. 2006). However, it may be more useful to remain agnostic about that definitional issue with respect to RA for either new or old memory. Just as “forgetting” refers to a decrement in performance but does not assume that the information is permanently lost (most of us have had momentary lapses!), we think it remains an empirical question of whether, and under what conditions, memory might be recovered in RA paradigms.

Amnesia for old memory revisited

Perhaps because the zeitgeist was not right, the issue of amnesia for a reactivated memory remained largely dormant for several decades, with the exception of a few sporadic reports, such as the one by Przybylski and Sara (1997). In that study, rats were overtrained on a maze task that was spatially cued. The investigators found that when they injected very small intraperitoneal (IP) doses of MK-801 (a noncompetitive NMDA antagonist) immediately following a trial, they could produce marked disruption of the animal’s performance in the maze on one or two subsequent daily trials. In addition, if the MK-801 injections were delayed for ≥ 2 h after training, the rats’ performance in the maze was unaffected. When the complexity of the maze task was markedly increased, the MK-801 induced a longer RA gradient. The investigators suggested that the degree of lability of the memory representation following reactivation is a function of the age and complexity of the original memory, as well as the amount of new information that may be integrated into the trace by the circumstances surrounding the reactivation itself.

It was not until 2000, when three independent but conceptually related articles appeared, that renewed interest in amnesia for old memory began to develop. One of these articles was a review that examined the biological mechanisms of memory (Sara 2000). There is some debate about when the term “reconsolidation” was first introduced. It appears in 1997 in the empirical article from Sara’s laboratory mentioned above, but the term seems to have gained special prominence when it appeared in the title of Sara’s later review: “Retrieval and Reconsolidation: Toward a Neurobiology of Remembering” (Sara 2000). Sara used the word as a shorthand descriptor for the modification and reorganization of reactivated memory that can be observed, rather than as a theoretical statement. For many investigators, however, the term “reconsolidation” later acquired some of the same theoretical overtones (baggage?) as did consolidation.

A second article by Land et al. (2000) examined the effects of dorsal hippocampal lesions in old memory. Rats receiving the lesions 1 mo after learning a discriminative avoidance task showed RA, but only if a cue exposure was used to reactivate the memory prior to the brain injury. The third contribution was the careful and analytic study by Nader et al. (2000), showing that injection of anisomycin (ANI), a protein synthesis inhibitor (PSI), into the basolateral nucleus of the amygdala after re-exposure to the training cues produced RA for an earlier fear memory, whether 1 or 14 d old. As with new memory, the amnesia was time dependent, decreasing as the interval between cueing and treatment increased.

A sampling of current issues

Nader et al.’s (2000) important article, which revisited and expanded the concept of reconsolidation and caught the attention of the neuroscience community, has both re-ignited the decades-old debate regarding the consolidation hypothesis and stimulated some very interesting new research regarding reconsolidation. The explosive increase in the number of articles in this area (see Dudai 2006) preclude digesting and presenting all of them, so we have chosen to sample several of the issues.

First, we revisit the question of whether reconsolidation is a recapitulation of original consolidation, requiring common mechanisms (such as new protein synthesis) and systems (such as the amygdala and hippocampus), or is fundamentally different, involving separate mechanisms and systems. Although our focus is primarily behavioral, this question is being examined at cellular, systems, and behavioral levels of analyses, which have yielded interesting albeit sometimes conflicting results (Mactutus et al. 1982; Alberini 2005). A second area of interest is the question of the nature of RA that results from disruption of reconsolidation, i.e., whether it is the result of storage or retrieval deficits. This issue has become entangled with the first, since some scientists support the view that the mechanisms of consolidation and reconsolidation are similar. Therefore, if RA following new learning can be shown to be either a storage or a retrieval failure, then RA following reactivation is also due to that same failure (Nader 2003). Since the first and second issues are not easily separable, they will be discussed together.

Recent work makes it increasingly clear that reconsolidation and consolidation share some similarities, but they also differ in several important ways (cf. Mactutus et al. 1982). Findings supporting the similarity include those demonstrating that PSI (Nader et al. 2000; Anokhin et al. 2002), inhibition of post-translational glycoprotein fucosylation (Anokhin et al. 2002), and hippocampal lesions (Land et al. 2000; Debiec et al. 2002) induce RA for both new and reactivated memories. The target memory in most of these studies has been fear conditioning or its conceptual cousin, IA, but these findings have recently been extended in an interesting way to include memory for incentive value associated with reward (Wang et al. 2005). In that study, rats were trained in a two lever operant task where each lever produced a different outcome (food rewards). One of the foods was then devalued by satiation. Subjects were later tested in extinction to preclude feedback from the food, i.e., to ensure that responding was based on a memory representation. Vehicle-injected controls responded less to the lever that had predicted the devalued incentive. However, this differential responding was not found in rats receiving PSI injections into the amygdala after new learning or after reactivation exposure to the devalued incentive.

On the other hand, these similar outcomes are not universal, and several studies have reported that treatments that disrupted initial consolidation had either no effect or exerted a

more transient effect on reconsolidation (for a review, see Alberini 2005). For example, Taubenfeld et al. (2001) found that consolidation, but not reconsolidation, of an IA task required hippocampal protein synthesis and C/EBP β . An extensive study by Lee et al. (2004), using manipulations to block brain derived neurotrophic factor (BDNF) or the transcription factor *Zif268* in the hippocampus, demonstrated a double dissociation of cellular processes in RA for new and old reactivated memory. More specifically, BDNF was necessary for consolidation of contextual fear memory but not for reconsolidation. Conversely, *Zif268* was required for establishing a reactivated memory but not for original consolidation.

Evidence of reconsolidation as a partial recapitulation of the original consolidation is also seen in a study by von Herten and Giese (2005). The investigators examined two immediate-early genes that are specific to the cue-shock association and that are expressed in the hippocampus. One of these, serum and glucocorticoid kinase 3 (*SKG3*), was expressed during both consolidation and reconsolidation. However, the other, nerve growth factor-inducible gene B (*NGFI-B*), was regulated only during consolidation. In addition, in an extensive review, Alberini (2005) elaborates on a number of differences between newly established and reactivated information, such as the possibility that consolidation and reconsolidation involve different areas of the brain and/or different molecular mechanisms.

Although discrepancies in the characteristics of RA for reactivated old memory may be related to differences in tasks and amnesic agents, a potentially important source of disparities that has not received much attention concerns the effectiveness of the reactivation treatment. A Pavlovian type of exposure to the conditioned stimulus, in which the duration of the cue exposure is controlled by the experimenter, is not only operationally different from an instrumental test trial in IA as a reactivation, but it may well have different consequences in terms of retrieval of the memory. Thus, the degree of reactivation and/or the nature of the memory attributes reactivated by these manipulations are unlikely to be identical, so it would not be surprising to find differences in the RA outcomes as well.

As reported in the early work of Mactutus et al. (1982), the window of vulnerability for disruption of a fear memory by hypothermia was shorter following reactivation than following original learning, a difference that has since been replicated in procedures using PSI as the amnesic agent (Anokhin et al. 2002). Also consistent with the earlier findings of Mactutus et al. (1982), Anokhin et al. (2002) found that a reactivated memory was rendered amnesic by a “weak” treatment that left a newly acquired memory intact. In other words, a reactivated memory was more vulnerable to disruption than new learning. This outcome is in contrast to the recent findings of Lattal and Abel (2004), who reported that a reactivated memory required multiple ANI injections (a stronger treatment) to be rendered amnesic, whereas newly acquired memory was susceptible to a single ANI injection.

Given the consistent finding that reconsolidation involves an abbreviated version of consolidation (Gordon 1977; Mactutus et al. 1982; Nader et al. 2000; Anokhin et al. 2002), Debiec et al. (2002) have suggested that it may require less new protein synthesis than original consolidation. This difference might mean that incomplete PSI would allow reconsolidation to proceed uninterrupted, contributing to Lattal and Abel’s (2004) finding that reconsolidation was impeded only when the procedure involved repeated and prolonged ANI administration. It might also account for instances in which PSI disrupted consolidation but not reconsolidation (for a discussion of this issue, see Debiec et al. 2002). Thus, it is possible that reactivated memories are generally more vulnerable to disruption, particularly when the amnesic treat-

ment involves a more global insult to the central nervous system (CNS), such as hypothermia or ECS (but see Anokhin et al. 2002).

As part of their early comparison of RA for new and reactivated memory, Mactutus et al. (1982) also reported that hypothermia-induced RA for new memory was more enduring (as measured by the lack of SR) than was RA for a reactivated memory, a finding that has since been replicated by a number of other laboratories using various learning paradigms, species, and amnesic agents (Judge and Quartermain 1982; Anokhin et al. 2002; Lattal and Abel 2004). This discrepancy suggests a possible difference between the underlying mechanisms of consolidation (storage failure) and reconsolidation (retrieval failure); however, there are alternative interpretations of recovery following reconsolidation disruption, as well as a number of studies that have failed to find SR (Debiec et al. 2002; Duvarci and Nader 2004) and, conversely, studies that have been able to induce recovery following disruption of initial consolidation (Lewis et al. 1968; Miller and Springer 1972; Hinderliter et al. 1975; Radyushkin and Anokhin 1999).

One criticism of studies reporting SR following reconsolidation disruption is that in most of them (but see Litvin and Anokhin 2000; Anokhin et al. 2002), there was no test of the status of short-term memory (Nader et al. 2000) following amnesic insult. According to Duvarci and Nader (2004), this leaves the door open to the possibility that poor performance following post-reactivation treatments results from transient nonspecific effects of the treatment that disappear with time, rather than a blockade of reconsolidation. Although it is true that most of the studies demonstrating SR did not explicitly test for intact short-term memory, many did include a control group that did not receive the reminder prior to the amnesic treatment, with the ubiquitous finding that in the absence of reactivation, memory for training was intact (for example, see Anokhin et al. 2002; Lattal and Abel 2004). Any nonspecific effect of the amnesic treatment, such as permanent brain damage or motivational changes, would be expected to affect groups that received the amnesic treatment equally; and yet nonreminded groups consistently demonstrate excellent performance at test. Therefore, the argument that SR might reflect recovery from nonspecific treatment effects over time seems strained.

An additional interpretation of recovery following reconsolidation disruption that has been discussed by Lattal and Abel (2004), and that speaks to another area of recent interest in the reconsolidation debate, is the possibility that SR involves the effect of PSI on extinction learning that occurs as a result of reactivation treatments involving nonreinforced exposure to (in their study) the conditioning context. Specifically, these investigators suggest that when animals receive cueing treatments involving nonreinforced exposures to the CS, they may learn that the previously fearful context is no longer associated with shock, promoting extinction of fear conditioning. Furthermore, the investigators speculate that when testing occurs shortly after this context exposure, animals retrieve the extinction memory, expressed as poor memory for the original conditioning. At longer test intervals, retrieval of the original training contingencies is more likely due to SR, resulting in good memory for training. The investigators acknowledge that this possibility depends on the assumption that PSI would somehow facilitate extinction, an idea that is admittedly “counterintuitive” since PSI following extinction should lead to RA for extinction (but see Fischer et al. 2004). Although this explanation is appealing and in line with general theories of SR, it would be limited to situations in which the reactivation treatment is procedurally similar to an extinction trial. It would not be applicable to instances in the literature in which reactivation just prior to PSI was accomplished by exposing the organism to noncontingent footshock (Richardson et

al. 1982a) or to a second training trial (Sangha et al. 2003; Duvarci and Nader 2004; Eisenberg and Dudai 2004). In these cases, some other mechanism must be invoked, making the facilitated extinction theory unparsonomious. Moreover, this theory would have particular difficulty explaining the ability of post-reactivation treatments, such as glucose (Rodriguez et al. 2000), or activation of protein kinase A in the amygdala (Tronson et al. 2006) to enhance memory for training. If the nonreinforced reactivation treatment causes extinction, memory-enhancing drugs should facilitate retrieval of extinction rather than the original memory trace.

Further diminishing the viability of the facilitated extinction hypothesis is a recent report by Duvarci and Nader (2004), who took advantage of the context specificity of extinction by employing a renewal paradigm (see Bouton 2004), in which extinction (or reactivation) and testing occurred in different contexts. These investigators reported that control, but not post-reactivation ANI-treated, rats showed renewal of conditioned fear responding when testing occurred in a context different from extinction. If post-reactivation ANI were decreasing performance by facilitating extinction (caused by the reactivation treatment), testing in a nonextinction context should have improved performance, i.e., produced renewal.

A somewhat different aspect of the extinction issue arises with respect to what memory the amnesic agent is modifying. There is now substantial evidence (for summaries, see Bouton 2002, 2004) that extinction involves a form of new learning. Thus, when re-exposure to the CS is used to reactivate old memory and to initiate the putative reconsolidation process, the question arises as to whether the amnesic treatment is acting on the original memory or on the new learning occurring during extinction (i.e., that the CS no longer predicts the anticipated outcome). In fact, both outcomes are possible. By using fear conditioning in medaka fish, Eisenberg et al. (2003) have shown that RA for reactivated memory will occur if the amnesic treatment is administered after a single retrieval trial (re-exposure to the CS). However, if the same agent is applied after repeated nonreinforced trials, RA is obtained for the extinction exposure; i.e., the original fear response returns. In a conceptually similar experiment that used duration of exposure of a test trial as the extinction manipulation, Power et al. (2006) have recently reported that injection of ANI after a brief exposure disrupted later retention of IA, but impaired memory for extinction if a longer test trial (exposure) was used.

Dudai and his colleagues (Eisenberg et al. 2003; Eisenberg and Dudai 2004) have proposed the notion of a "dominant trace," a dynamic effect referring to the shift in the information that the predictive stimulus retrieves. This solution seems quite compatible with other evidence from learning research that a CS exposure can have multiple effects serving both to remind and to alter a representation. For example, Rohrbaugh and Riccio (1970) and Rohrbaugh et al. (1972) found that a brief exposure to a CS for fear in rats could increase that fear (paradoxical enhancement) but that longer exposures led to a loss of fear, as would be anticipated from an extinction manipulation (see also Eysenck 1968).

A recently completed study by James Briggs (Briggs and Riccio 2006) has further established the characteristics of RA for extinction. One day after IA conditioning, rats received a 12-min CS only exposure, a period far longer than we have used in RA for old memory. Administration of deep hypothermia after the exposure produced amnesia for the extinction (i.e., return of the conditioned fear) and did so in a time-dependent manner, since no RA was seen with an hour delay between exposure and hypothermia. Moreover, the RA was reversible if rats were re-cooled prior to testing, as seen in the return of the extinction effect.

Although this type of recovery has been obtained with RA for new and old memory, it appears to be the first demonstration of the reversal of amnesia for extinction.

An extensive and more molecular study by Suzuki et al. (2004) investigated, among other things, the distinct biochemical signatures associated with extinction and compared them to those signatures left by reconsolidation. In one of their experiments, mice were given IP injections of antagonists for cannabinoid receptors, for voltage gated calcium channels, or for NMDA receptors or given an injection of ANI immediately after contextual fear conditioning or after a 3-min reactivation exposure. In another portion of the study, mice were re-exposed to the same context in which they had been shocked for 30 min to produce extinction, followed by administration of the same four drugs noted above.

In the case of consolidation and reconsolidation, it was noted that only the pharmacological agents blocking protein synthesis or NMDA receptors showed RA, as seen in a reduction of freezing. These observations support the notion that although they are far from identical, consolidation and reconsolidation employ at least some of the same inherent neurological processes. With respect to extinction, however, Suzuki et al. (2004) found that injection of any four of the above-mentioned pharmacological manipulations significantly increased freezing, i.e., induced RA for the extinction exposure. Their findings suggest that extinction produces a signature very distinct from that associated with consolidation and reconsolidation.

Apart from the issue of whether reactivation treatments initiate extinction in some cases (and what effect this may have on the nature of the resultant amnesia), a more general issue, which may elucidate the relative commonness of SR from post-retrieval amnesic treatments, involves possible differences between the specific characteristics of new and reactivated memories. If we assume that reactivation treatments make active (and thus labile) only some components of the original learning episode, then the memory trace(s) representing dormant components ought to remain intact following an amnesic insult, capable of supporting retrieval at a later time (Mactutus et al. 1982; for a neural variant of this idea, see Judge and Quartermain 1982). This interesting possibility, however, does not explain why intact portions of the trace would fail to support retrieval during the initial memory test (for further discussion of this issue, see Litvin and Anokhin 2000). But it seems clear that if new and reactivated representations differ fundamentally (either quantitatively, qualitatively, or both), then direct comparisons of RA resulting from disruption of these processes must be made with caution (Nader 2003).

Given these various findings, should we conclude that consolidation and reconsolidation involve separate processes, or that they involve similar processes that impinge on different components or proportions of the memory trace? Is it possible that consolidation blockade disrupts memory storage while reconsolidation blockade interferes with memory retrieval? Or that they both disrupt storage, but because only reactivated attributes are affected when reconsolidation is disrupted, the memory can still be retrieved over time? Although the later possibility is consistent with the common finding that RA for reactivated memory dissipates while RA for new memory is more enduring, storage disruption is not consistent with reported findings of cued recovery following initial consolidation for new learning (for review, see Millin et al. 2001). The latter type of finding seems to suggest that if consolidation and reconsolidation blockade involve the same mechanism, that mechanism is impaired retrieval. This notion could account for both the finding that memory following consolidation disruption can recover, and that such recovery is less common than following reconsolidation disruption. Accordingly, any treatment that impairs retrieval would have a more

detrimental effect when it impinges on all attributes of the training memory (immediately following acquisition) than when it affects only a proportion of the training attributes (following reactivation).

In their recent article, Lattal and Abel (2004), commenting on their finding that memory for fear learning recovered 21 d following post-reactivation PSI, stated that their results are “consistent with the idea that post-retrieval deficits reflect the animal’s inability to retrieve a stored contextual memory” and that “the challenge for retrieval theories is to determine what mechanism would allow the original memory to be preserved while temporarily preventing the animal from having access to it.” As previously discussed, we have suggested that this temporary inability to access a previously stored memory may result from processes akin to state-dependency (for review, see Riccio et al. 2003). Accordingly, when a memory (either in its entirety or some proportion of its attributes) is encoded under an amnesic state (due to PSI, ECS, hypothermia, or other treatments), it will be less retrievable when testing occurs under a nonamnesic state, as is typically the case. This view is supported by the counterintuitive (from a storage failure perspective of RA) finding that reinduction of the amnesic state prior to testing can alleviate RA (Hinderliter et al. 1975), even when the amnesic insult involves PSI (Bradley and Galal 1988; Nishioka and Millin 2005). If the role of the amnesic insult is to disrupt storage of the engram, it is unclear how a second insult might restore it. Such findings with PSIs strain the view that protein synthesis is a critical link in the molecular chain of events leading to stable long-term memory storage (for an excellent review of other issues problematic for the protein synthesis account of memory storage, see Routtenberg and Rekart 2005; Rudy et al. 2006. For example, Rudy et al. note that although ANI inhibits protein synthesis, it has a complicating side effect: It can trigger neuronal apoptosis, resulting in premature cell death. Thus, inferences about PSI inducing RA may be confounded by neuronal destruction. For their part, Routtenberg and Rekart question whether reconsolidation involves *de novo* protein synthesis at all.)

According to the MS DR view, because amnesia results from a retrieval failure, it is not surprising that it often reverses (i.e., is temporary), either spontaneously or in response to an appropriate reminder. A study by Meehan et al. (1994) suggests that traditional drug state-dependency, similar to amnesia, can be reversed by a potent stress-related reminder. In their study, both hypothermia-induced amnesia and pentobarbital-induced state-dependency were reversed by reminder treatments involving the UCS from training. Their study demonstrated that state-dependency, similar to other sources of retrieval failure, can be alleviated by common cueing procedures. In a relevant study, Quartermain et al. (1988) showed that pre-test administration of the retrieval enhancing drug, amphetamine, alleviated forgetting due to protein synthesis inhibition, cholinergic receptor blockade, inhibition of norepinephrine synthesis, stimulation of serotonin receptors, ECS, a 2.5-mo training-to-test interval, and senescence. Taken together, it would appear that at least some instances of amnesia simply reflect a period of temporary inaccessibility that can be overcome by a number of state and nonstate treatments. However, the fact that some cases of amnesia are reversible does necessarily not rule out that other cases involve failures of consolidation.

The evidence of memory recovery following various cueing treatments bears on an important theoretical dispute. If recovery of memory following consolidation or reconsolidation has been one of the major challenges to a storage disruption view, then the question of whether such recovery might be attributable to new learning, rather than the retrieval of the target memory, has been an important rejoinder (see Gold and King 1974). In that con-

nection, however, the studies that induce recovery based on re-exposure to the amnesic treatment cannot easily be viewed as based on transfer of new learning. Clearly, the procedures involved in recoling rats, e.g., are orthogonal to the procedures used in the fear conditioning or inhibitory learning task. Whatever the merits of the MS DR notion that we have offered, the empirical outcome of reversibility cannot easily be dismissed.

A quite different but particularly innovative approach to the issue of memory retrieval versus transfer of new learning has recently been provided by de Hoz et al. (2004). Rats trained in the Morris water maze were subjected to partial hippocampal damage that severely disrupted their performance in this spatial memory task. The reminder treatments involved providing the animals with the escape platform either in the correct location, or in an incorrect position. The striking outcome was that both conditions produced greatly improved test performance. Since the incorrect information could not be used directly to solve the problem, the findings indicate that the reminder enabled the rats to access a previously stored memory and suggest that the lesion-induced disruption of performance was based on an impairment of memory retrieval.

While a number of studies have demonstrated cued recovery following consolidation (Miller and Springer 1972; DeVietti and Hopfer 1974; Gordon and Mowrer 1980; Radyushkin and Anohkin 1999) or reconsolidation disruption (Land et al. 2000; Anohkin et al. 2002), at least one study we are aware of failed to observe alleviation of post-reactivation, ANI-induced RA when a shock UCS was used as the reminder (Duvarci and Nader 2004). Although this finding may be seen as evidence that the amnesia was the result of a storage failure, this latter study did not include a state-dependency test in which the amnesic agent was readministered prior to test. The importance of such a strategy is seen in a recent study from the second author’s laboratory, which suggests that nonstate cues, while sometimes capable of supporting recovery, may be less effective than reinduction of the state (Nishioka and Millin 2005). In a series of experiments, it was found that morphine-induced, state-dependent memory loss for a passive avoidance task (via morphine given 45 min prior to training) was only partially alleviated by treatments involving contextual, CS, warm-up, or combination reminders, but was completely reversed by administration of morphine 45 min prior to test. This same pattern of results was found when the PSI cycloheximide was used to induce RA immediately following PA training. None of the nonstate reminders were as effective in alleviating RA as readministration of cycloheximide 20 min prior to testing, which completely reversed the amnesia. A control group was included that received cycloheximide both immediately following pseudo-training (in which rats were exposed to the CS and US in a noncontingent manner) and 20 min prior to test. This group’s poor performance compared with that of trained animals receiving the same drug injections suggests that recovery in the cycloheximide reinstatement group was not due to nonspecific effects of multiple cycloheximide injections or drug effects on motor performance during the test. These findings suggest both that state cues may be the strongest test of an amnesic memory’s ability to recover, and that memory loss due to traditional state-dependency and RA may share a common mechanism. Because forgetting in this study was induced following original learning, the superiority of state cues for alleviating RA for reactivated memory remains to be investigated; however, the results of at least one study (Mactutus et al. 1982) suggest that RA for new and reactivated memories is similarly alleviated by pre-test reinduction of the internal amnesic state (in that case, hypothermia).

It should be noted that there have been failures to alleviate amnesia by reinducing the amnesic state prior to testing. For

example, Lee et al. (2004) demonstrated that in rats, intrahippocampal infusion of BDNF anti-sense oligodeoxynucleotides (ODNs) 90 min prior to contextual fear conditioning disrupted conditioned freezing 24 h after training, supporting the view that consolidation requires BDNF in the hippocampus. Importantly, these investigators included a group of rats that received infusion of BDNF anti-sense ODN 90 min before both conditioning and testing and reported that this treatment had no facilitative effect on memory recovery. In another study, Xu and Davis (1992) demonstrated in goldfish that amnesia induced via intracranial MK-801 (a noncompetitive NMDA antagonist) administration 30 min prior to classical fear conditioning was not reversed by re-administering MK-801 prior to testing. Moreover, Schulz et al. (2002) demonstrated a similar failure to alleviate the amnesia produced by pre-training intra-amygdala clonidine (a noradrenergic α_2 -receptor agonist) injections. Again, since these studies induced forgetting following original learning, it remains to be seen if amnesia for a reactivated memory can be reversed by reinducing the state.

A subtle but potentially important methodological issue in studies failing to observe memory recovery concerns the functional “matching” of the states. While a second administration of the agent provides a nominal match, it is not clear to what extent the conditions are the same. For example, is the time course of the effects of the agent at the second administration the same as at the first? Is the magnitude of the internal change equal to that of the initial administration? As with other types of drug studies, a variety of parameter values may need to be sampled before accepting a negative result.

In summary, we agree with Lattal and Abel’s (2004) estimation that their findings, and indeed all findings demonstrating recovery following post-retrieval induced RA, challenge a reconsolidation theory that assumes that post-retrieval amnesic treatments destabilize and destroy the original engram. In fact, we would extend their analysis to RA for newly acquired memory, since many studies have shown cue-potentiated reversal of amnesia in these cases as well. As we have stated before (Millin et al. 2001), we believe that any reconsolidation model that interprets post-retrieval RA as a storage failure suffers from many of the same difficulties as the original consolidation hypothesis, and we have provided a specific mechanism, post-learning or post-reactivation state-dependency, by which amnesic treatments might create a transient memory loss. While the modified state-dependent model will surely prove incorrect or inadequate in many cases, we think it offers a plausible alternative to the widely held presumption that amnesic agents disrupt the storage (or restorage) of a memory representation.

Reconsolidation: Some new directions

Whatever the limits of the model that we have described, we think it may have heuristic value in generating new experiments. For example, if a memory representation, whether new or reactivated, becomes associated with the salient internal context induced by an amnesic treatment, then it might be possible to establish such a retrieval linkage to other types of contextual cues as well. Based on this view, a series of recent studies by Briggs (Briggs et al. 2005, 2006a,b) asked whether external contextual cues presented shortly after training or after a cued reactivation could come to control retrieval of the target memory. The strategy was to take advantage of the context shift effect, in which performance is disrupted when rats are tested in a context (e.g., room) different from where they were trained. When the rats were exposed to the test context either after fear conditioning or after reactivation, the disruptive effect of the context shift was largely eliminated. Importantly, and as is the case with RA, the

effect was time dependent, an outcome that also rules out mere familiarity with the test context as an explanation. This “transfer of control” over retrieval by cues that were not directly present at the time of learning or reactivation provides another example of the way in which processing of information subsequent to an episode can affect memory for that episode.

It is clear that extensive cueing can produce extinction, but what might be the effect of giving several cue exposures, too brief to yield extinction, before administering a single amnesic treatment? If reactivation of an old memory simply results in the retrieved information becoming active (albeit transiently) and held in a buffer-like state, then presumably such multiple reactivations would not alter the vulnerability to amnesia, although they might influence the length of time that memory remains active. Alternatively, if each reactivation results in the establishment of a slightly different representation of the original episode, then these multiple representations may tend to protect the memory. (It should be noted that a single reactivation is qualitatively different from multiple cueing episodes: Since a single reactivation is followed by the amnesic agent, only the situation with repeated reactivations would permit the establishment of additional representations of the engram.) Work by A. Bogart in our laboratory has begun examining the effects of several brief reactivation exposures separated by an hour. At this point the data strongly suggest that old memory becomes more resistant to amnesia when hypothermia is administered after a second reactivation. Whether this finding reflects an increase in retrieval linkages or a smaller proportion of attributes reactivated during a second cue exposure are among the questions yet to be explored. Clearly, the spacing (e.g., hours vs. days) and the number of reactivations (e.g., the relationship may not be a linear function) are likely to be important variables, so additional experiments will be needed to address these issues.

Finally, although extinction has been an important form of treatment in behavior therapy for many years, the topic has received a resurgence of interest with respect to reconsolidation. Extending a suggestion made by Cahill (1997) for new memory following traumatic stress, Przybylski et al. (1999) proposed that β -Blockers following reactivation might be useful in weakening memories associated with traumatic events. More recently, both Dudai (2004) and Riccio et al. (2003) have speculated in more general terms that amnesia for reactivated memory could have implications for dealing with traumatically induced disorders. It is intriguing to note that >30 yr ago D. Meyer (1972) proposed that ECS alleviated depression not by disrupting storage but by “suppression of access” (impaired retrieval) of the engrams of motivational states associated with their illness.

Since the therapist is necessarily confronted with old memory when dealing with disorders such as post-traumatic stress disorder (PTSD), any extinction treatment will involve some form of cued reactivation. If basic research can illuminate the fundamental processes in reconsolidation this pre-clinical information could be useful to the therapist. Based on animal research by McGaugh and his colleagues (see Gold and van Buskirk 1975; McGaugh, 2000; McGaugh and Roozendaal 2002), Pitman (1989) has proposed that not only does the flood of stress related hormones after a trauma enhance the memory but that the various reminders that set off intrusive or flashback memories also trigger the same hormones, creating a kind of positive feedback cycle.

One interesting approach currently being undertaken by Pitman and Delahanty (2005) with PTSD victims is to use pharmacological agents to reduce or block the stress hormones enhancing consolidation after the incident (secondary prevention) or at the time of reactivation of memory (tertiary treatment). Whatever the fate of the concept of reconsolidation, the phe-

nomenon of reconsolidation seems likely to have an enduring effect on many aspects of memory research.

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Reconsolidation: A brief history, a retrieval view, and some recent issues

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