The many faces of amnesia

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Results from studies of retrograde amnesia provide much of the evidence for theories of memory consolidation. Retrograde amnesia gradients are often interpreted as revealing the time needed for the formation of long-term memories. The rapid forgetting observed after many amnesic treatments, including protein synthesis inhibitors, and the parallel decay seen in long-term potentiation experiments are presumed to reveal the duration of short-term memory processing. However, there is clear and consistent evidence that the time courses obtained in these amnesia experiments are highly variable within and across experiments and treatments. The evidence is inconsistent with identification of basic temporal properties of memory consolidation. Alternative views include modulation of memory and emphasize the roles that hormones and neurotransmitters have in regulating memory formation. Of related interest, converging lines of evidence suggest that inhibitors of protein synthesis and of other biochemical processes act on modulators of memory formation rather than on mechanisms of memory formation. Based on these findings, memory consolidation and reconsolidation studies might better be identified as memory modulation and "remodulation" studies. Beyond a missing and perhaps unattainable time constant of memory consolidation, some current views of memory consolidation assume that memories, once formed, are generally unmodifiable. It is this perspective that appears to have led to the recent interest in memory reconsolidation. But the view adopted here is that memories are continually malleable, being updated by new experiences and, at the same time, altering the memories of later experiences. Studies of memory remodulation offer promise of understanding the neurobiological bases by which new memories are altered by prior experiences and by which old memories are altered by new experiences.

Many treatments impair memory when administered soon after an experience. The efficacy of these treatments in impairing later memory decreases as the time between training and treatment increases, forming the basis for the idea that memory processes initiated by an experience continue for some time after training until they become consolidated. The past few years have seen a re-emergence of earlier (cf. Sara 2000) interest in the possibility that retrieval of old memories renders them once again susceptible to amnesic treatments, i.e., returning an old memory to a state in which the memory is again sensitive to amnesic treatments, supporting the idea that old memories can be reconsolidated (for reviews, see Nader et al. 2000; Sara 2000; Nader 2003; Dudai 2004; Dudai and Eisenberg 2004; Alberini 2005; Rudy et al. 2006).

There are important assumptions embedded in these descriptions of consolidation and reconsolidation. First, one must accept a version of consolidation theory that claims that memories are formed over time until they reach an immutable state. Second, one must accept the interpretation of studies of amnesia as indicating that the treatments interfere with key biological processes that are the substrate mechanisms for memory. However, there are many alternatives to both positions that may be useful when interpreting the results of consolidation–reconsolidation experiments.

The goal of the present article is to open dialogues that include broader discussions of the significance of consolidation–reconsolidation experiments. This article has two main components. The first, and longest, section addresses the question: What are the neurobiological bases for amnesias and how do the multiple bases for amnesia inform what we know about memory

processes? In addition to discussing a traditional memory consolidation interpretation of amnesia, three other possibilities will be considered. Also, within this broad topic, the article will consider what the consolidation theory is against which reconsolidation is a reaction. The second main section will offer a perspective on the significance of the phenomenon termed reconsolidation, including evaluating the importance of identifying some common and some distinct features of consolidation and reconsolidation.

Multiple faces of amnesia

Retrograde amnesia is most often used to make inferences about underlying memory processes, with amnesia taken as the basis for time-dependent processes involved in the formation of memory. However, while it is reasonable to make such inferences, there are alternative views of the mechanisms of retrograde amnesia with significant implications for interpreting the basic findings related to memory formation. This section attempts to refocus the use of retrograde amnesia as the bedrock for memory consolidation to other reasonable interpretations, each leading to different considerations of the relationships between amnesia and memory formation.

Memory consolidation

There are several different ways in which the term memory consolidation is used (Dudai 2004). In the past, memory consolidation was based largely on findings that memories are susceptible to impairing treatments administered near the time of training. The temporal characteristics of retrograde amnesia gradients were used to define the time course of memory formation. More recently, memory consolidation has been used to identify times

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when post-learning cellular and molecular events contribute to memory formation. Finally, memory consolidation also refers to the time-limited effects of hippocampal damage on memory formation in experiments showing very long-term (weeks in rodents, years in humans) retrograde amnesias (Kim et al. 1995; Anagnostaras et al. 1999; Mumby et al. 1999; Squire et al. 2001, 2004; Winocur et al. 2001). With very different time courses and with treatments that largely involve removal of different memory systems after experience, this latter usage of the term may well involve mechanisms not shared by the memory consolidation studies concerned with shorter times after an experience. However, as discussed below, these experiments too may fit readily into a continuum of retrograde amnesia gradients.

The perseveration-consolidation hypothesis of Müller and Pilzecker (1900) presaged the retrograde amnesia studies of soldiers who sustained head injuries in World War II (Russell and Nathan 1946) as well as the influential early experimental demonstration of retrograde amnesia in rodents (Duncan 1949). It was in the 1960s and 1970s that studies of retrograde amnesia became a major component of research on the neurobiology of memory (cf. McGaugh 2000). There were several main goals of that era directly pertaining to the neurobiology of memory. One was to identify the number of processes through which memories were formed—e.g., short- and long-term memory. The results of studies addressing these points were decidedly mixed, with single-, dual-, triple-, and multiple memory processes proposed (McGaugh 1966, 2000; Gold and McGaugh 1975; Izquierdo et al. 2002). A second goal was to determine whether the memory processes were organized in a serial or parallel manner. Here too the results were mixed, with evidence obtained across experiments favoring different organizational schemes for multiple memory processes, though parallel models now appear to be well supported (McGaugh 2000; Izquierdo et al. 2002).

A third goal, perhaps the most enduring, was to identify the time constant for memory formation. Through the 1960s and early 1970s, the results were perplexing. Experiments identified retrograde amnesia gradients varying from 500 msec to 48 h, generating confusion as well as consternation over which gradient was the “right” one, i.e., which reflected the time needed for memory formation, and leading to questions about the validity of the approach (see, e.g., Chorover 1976). In contrast to the lingering doubts about the number and organization of memory processes, the results of studies of retrograde amnesia gradients were very clear: *Time courses of retrograde amnesia gradients do not reveal time courses of memory processes*. The variability of the temporal gradients across laboratories suggested this possibility, but demonstrations of systematic variability of temporal gradients within laboratories settled the issue. One set of findings showed that fluorothyl, a convulsant that produces reliable retrograde amnesia in chicks, impaired 48-h memory at relatively low doses only if administered within a few minutes of training but impaired 48-h memory at high doses if administered as late as 24 h after training (Cherkin 1969). Also, the duration of retrograde amnesia gradients after electroconvulsive shock varied with the duration of the shock (Alpern and McGaugh 1968). Similarly, electrical stimulation of neocortex in rats, at intensities that induce behavioral and electrographic seizures, produced retrograde amnesia with gradients lasting from 0.5 sec to 4 h depending on the intensity of the stimulation (Gold et al. 1973, 1974).

These findings of dose and stimulation intensity effects show that the time courses of retrograde amnesia gradients vary as a function of treatment efficacy and do not directly reflect the time course of memory formation. Thus, the temporal windows

of susceptibility depend not only on the task and type of blocker (Dudai 2004), but also depend on the dose or intensity within a given treatment class used to impair memory. This is a very important finding in amnesia studies. If the duration of an amnesia gradient varies within a treatment class, then the results do not reveal the time course of the biological process inferred to be a part of memory formation. The supporting findings span a wide range of treatments, though direct tests with many contemporary treatments have not, to the author's knowledge, yet been tried. Nonetheless, the statement applies conceptually to both old and new treatments, including actions of brain seizures to disrupt reverberating neural activity, actions of drugs that interfere with neurotransmitter functions to disrupt cell-cell communication, actions of kinase inhibitors to disrupt signal transduction mechanisms, and actions of drugs to inhibit protein synthesis. The view that retrograde amnesia gradients fall on a temporal continuum based on severity of the treatment might even include the long amnesia gradients evident after irreversible and generally large lesions of the hippocampus (Kim et al. 1995; Anagnostaras et al. 1999; Mumby et al. 1999; Squire et al. 2001, 2004; Winocur et al. 2001).

Of interest too were the findings that decay of memory after amnesic treatment also varied across training and treatment conditions. Using cycloheximide to induce amnesia in mice, Squire and Barondes (1972) found that the rate of decay in mice trained on a visual discrimination task varied from 1–3 h to 12–24 h after training with different numbers of trials. In other experiments, cycloheximide-induced impairment of memory was not evident at times up to 6 h, but emerged at 24 h (Quartermain and McEwen 1970) and was not evident either immediately or 30 min after training, but emerged at 6 h (Andry and Luttges 1972). Thus, the rates of decay of memory in the presence of protein synthesis inhibition vary considerably, in these examples from 1 to 24 h. Moreover, using intra-amygdala injections of anisomycin, there is an instance of behaviorally assessed early memory that is evident only at a particular time after training, 4 h, but not at earlier or later times (Schafe and LeDoux 2000). Most recent studies assess early memory at only a single time within a rather large range, e.g., 30–240 min after training, and compare that to 24- or 48-h memory. Studies of the effects of protein synthesis inhibitors on long-term potentiation (LTP) provide a good way to track the time course of decay. Because LTP studies can readily include repeated test pulses for hours after LTP induction, studies of the effects of protein synthesis inhibitors on early versus late LTP permit repeated assessments of LTP throughout the time of decay. In these instances, decay rates across experiments are also variable, ranging from ~10 min (Tang et al. 1999) to 30 min (e.g., Abel et al. 1994) to 2–3 h (Pang et al. 2004) or 3–4 h (Huang et al. 1994).

The lessons of the earlier research on memory consolidation revealed clear dangers in using retrograde amnesia gradients and time courses of memory decay into amnesia to define the temporal properties of memory processes, or more directly, contradicted the notion that any one amnesia gradient reflected the time of memory formation. Thus, the multiple time courses of retrograde amnesia gradients and decay of memory are more directly relevant to understanding the bases for the amnesias than to understanding the neurobiological bases of memory formation.

Memory modulation

These findings suggested that specific amnesia time courses may not reflect the time for the formation of memory. Nonetheless, the general phenomenon of retrograde effects on memory remained intact. Whatever the time course, a given treatment had

greatest effects if administered soon after training and diminished effects if administered relatively long after training. The results led to attempts to identify the more general meaning of the findings that post-training treatments could impair—or enhance—memory in a time-dependent manner. The question to be answered was: Why do memories remain susceptible to modification by many treatments for a period of time after training? The question led to investigations of endogenous responses to experience, such as release of epinephrine and corticosterone into the circulation and the release of neurotransmitters and modulators such as norepinephrine and acetylcholine.

One view was that memories retain susceptibility to up- and down-regulation by the arousing features of the experience to be remembered. This alternative to memory consolidation was termed “memory modulation” (Gold and McGaugh 1975), and was the basis for examining the effects of many hormones and neuromodulators on memory, of particular note including circulating epinephrine, glucose, and corticosterone as well as brain norepinephrine and acetylcholine (McGaugh 1983, 2000; Roozendaal et al. 1999; Roozendaal 2000; Gold 2001, 2003, 2005; McGaugh and Roozendaal 2002). According to this view, memory formation is modulated by endogenous responses elicited by a salient experience to promote the memory for that experience. For example, post-training treatment with epinephrine enhances memory for inhibitory avoidance training with low footshock, resulting in memory scores like those seen after training with higher footshock levels. Enhancement of memory with epinephrine occurs optimally at doses that match the endogenous circulating levels of epinephrine attained after training with more intense footshock (Gold and McCarty 1995). Findings like these suggest that memory retains susceptibility to modulation by hormonal and neuromodulator responses to an experience. In addition, epinephrine is most effective at enhancing memory when administered soon after training and, like effects of other memory-enhancing and -impairing treatments, the efficacy decays with time after training. In this context, the time-dependent nature of modulation of memory reflects the biological synchrony that normally accompanies experiences; hormones are released soon after training rather than long after training.

Thus, the findings showed clearly that mimicking endogenous responses to arousing experiences enhanced memory for those experiences. Of particular interest, removal of these responses, pharmacologically, by brain lesion, or by adrenalectomy, had only modest effects on memory, leading to the conclusion that these factors were important in modulating the substrate mechanisms required for the formation of new memories but were not themselves components of those substrate mechanisms. Modulators of memory formation might exert their effects on memory at levels of analysis from molecular to systems to cognitive functions, i.e., by regulating the generation of durable neural changes that are the substrates of memory, by activating specific memory systems, or by initiating cognitive processes like rehearsal, respectively. Of course, these interacting functions are not mutually exclusive. Importantly, the property of memory discussed in this way is one of time-dependent susceptibility to modulation rather than, as in memory consolidation, time for a memory to become fixed.

Modulators of memory can also set conditions that influence amnesia. For example, an α -adrenergic receptor antagonist blocked retrograde amnesia produced by supraseizure electrical stimulation of frontal cortex, subseizure electrical stimulation of the amygdala, inhibition of norepinephrine synthesis by diethyldithiocarbamate, a convulsant dose of pentylenetetrazol, and inhibition of protein synthesis by cycloheximide (Gold and Sternberg 1978). Relatedly, injections of β -adrenergic receptor

antagonists directly into the amygdala block both impairments and enhancements of memory produced by many treatments (McGaugh et al. 1993; McGaugh 2002; McIntyre et al. 2003; Roozendaal et al. 2004).

Conversely, retrograde amnesia gradients can apparently be greatly extended by manipulations of the hormonal milieu at the time of treatment. For example, administration of epinephrine just before supraseizure stimulation of neocortex extends a 1-h retrograde amnesia gradient to as much as 1 wk (Gold and Reigel 1980). When viewed with evidence that epinephrine levels are typically high after inhibitory avoidance training during the shorter temporal gradient (McCarty and Gold 1981), the findings suggest that hormonal status at the time of amnesic treatment is an important variable. Or, perhaps changes in hormonal response to memory tests presented after forgetting has begun underlie observations that cycloheximide can impair memory (Quartermain and Botwinick 1975) and that amphetamine or electrical stimulation of the midbrain reticular formation can enhance retrieval of partially forgotten memories (Sara et al. 1980; Quartermain et al. 1988). These findings raise the possibility that decreases as well as increases in hormonal responses elicited by reinstatement conditions may modulate the ability of treatments to influence memory long after the initial experience.

Although modulation of memory was originally intended to address the issue of endogenous endocrine and brain mechanisms that regulated neural plasticity and memory, treatments with actions intended to act on the substrates of memory may instead act by altering modulators of memory. Note that this view leads to very different interpretations of the mechanisms by which a specific treatment may alter memory. Amnesia produced by protein synthesis inhibitors might fit this category. Amnesias produced by puromycin, cycloheximide, acetoxycycloheximide, and anisomycin can be blocked or rescued by administration near the time of training of many treatments that modulate memory (cf. Martinez Jr. et al. 1981; Davis and Squire 1984; Routtenberg and Rekart 2005). Importantly, treatments that reverse the effects of protein synthesis inhibitors on memory do so without concomitant attenuation of the extent of inhibition of protein synthesis (e.g., Barondes and Cohen 1968; Serota et al. 1972; Hall et al. 1976; Flood et al. 1977; Sershen et al. 1982).

Like general protein synthesis inhibitors, interference with the activation of the transcription factor, CREB, also impairs memory, effects attributed to blockade of selective gene expression and subsequent protein synthesis important for converting short- to long-term memory (Silva et al. 1998; Bozon et al. 2003; Jackson and Ramaswami 2003; Tully et al. 2003; Mizuno and Giese 2005). As seen with inhibitors of protein synthesis, recent findings obtained with interference with CREB functions appear to include effects related to modulators of memory. CREB knockout mice exhibit impairments in memory that can be reversed by administration of epinephrine (Frankland et al. 2004). Direct injections of CREB antisense into the amygdala impair memory but also impair training-related increases in norepinephrine release in the amygdala (Chang et al. 2005). Thus, although less frequently tested, it appears that amnesias in rodents with impaired CREB functions can be rescued by drugs related to modulation of memory and may reflect alterations in mechanisms related to modulation of memory rather than substrate mechanisms of memory.

Thus, there are many examples of pharmacological reversals of amnesias produced by protein synthesis inhibitors, most often seen using treatments that themselves modulate memory. As pointed out elsewhere (Routtenberg and Rekart 2005; Rudy et al. 2006), there is general agreement that protein synthesis inhibi-

tors block protein synthesis and impair memory. An interesting alternative position is that memory formation may be handled by post-translational modifications of pre-existing proteins; protein synthesis is necessary for replenishment of materials lost to the processes of memory formation (Routtenberg and Rekart 2005).

However, the currently dominant view that impaired long-term memory after treatment with protein synthesis inhibitors means that new protein synthesis per se is necessary for memory formation appears to contradict the data. The findings that the effects of the protein synthesis inhibitors can be rescued by a wide range of treatments indicate that protein synthesis is not necessary for memory formation. In their comprehensive review of protein synthesis inhibitors and memory, Davis and Squire (1984) correctly noted that the findings that many modulators of memory can rescue amnesias produced by protein synthesis inhibitors may be accomplished by parallel actions, and do not necessarily reveal a common site of action between the amnesic agent and the memory rescuer. Thus, for example, the findings that protein synthesis inhibitors block memory and interfere with catecholamine functions, and that treatments like amphetamine reverse the memory effects, may reflect amphetamine actions on memory independent of effects of protein synthesis. Perhaps the enhancement results in short-term memory that lasts longer than the inhibition of protein synthesis, enabling later return of protein synthesis to form the memory (Davis and Squire 1984). However, as noted above, most current evidence suggests independence of short- and long-term memory processes (McGaugh 2000; Izquierdo et al. 2002). Or, protein synthesis may reduce but not eliminate memory; most experiments indeed show some residual memory after treatment. The residual memory might then provide a mnemonic substrate that can be enhanced by amphetamine just as a weak memory, e.g., after avoidance training with low footshock, can be enhanced by amphetamine (Davis and Squire 1984). However, even this quite reasonable view means that long-term memory may be independent of protein synthesis not only because the residual memory survives the insult of the inhibitor but also because amphetamine administration can produce a healthy and long-lasting memory in the presence of protein synthesis inhibition.

Consolidation versus modulation

Although the experiments dealing with both consolidation and modulation of memory involve post-training treatments that affect later memory, the results obtained with a given treatment do not distinguish between memory consolidation and memory modulation as a mediating basis for altered memory processing. In terms of experimental design, a treatment is administered near the time of training and the memory for training is modified. Generally, studies with hormones and neuromodulators such as epinephrine, corticosterone, and norepinephrine refer to the effects as modulation of memory, while those involving electroconvulsive shock, protein synthesis inhibition, or signal transduction blockers refer to consolidation of memory. In the absence of far better understanding of underlying mechanisms, this appears to be for now a distinction of style.

Hypermnnesia and amnesia—The inverted U

A major characteristic of modulation of memory is that most pharmacological modulators of memory exhibit a nonlinear dose-response function in which low doses are ineffective, intermediate doses enhance later memory, and high doses impair later memory (cf. Koob 1991; Gold 1995), reflecting results and predictions from Yerkes and Dodson (1908). For example, the

inverted-U relationship is evident in studies of enhancement of memory and neural plasticity by epinephrine (Gold and van Buskirk 1975, 1978a, b), glucose (Gold 1986), ACTH (Gold and van Buskirk 1976) and corticosterone (Diamond et al. 1992; Conrad et al. 1999; Okuda et al. 2004) as well as cortisol and verbal memory (Domes et al. 2005). Given the extensive history of inverted-U functions, it is somewhat surprising to see the dearth of dose-response curves in contemporary studies of the molecular bases of memory consolidation and reconsolidation.

The findings that modulation of memory appears to have inverted-U functions for many treatments suggest that it may be possible to demonstrate functional inverted-U curves by varying the stress-related release of hormones while keeping the dose of the memory modulator constant. Indeed, these findings have been observed regularly. For example, a dose of epinephrine (Gold and van Buskirk 1978a), ACTH (Gold and van Buskirk 1976), or glucose (Gold et al. 1986) that enhances memory for inhibitory avoidance training with mild footshock impairs memory for inhibitory avoidance training with a more intense footshock. Similarly, subseizure electrical stimulation of the amygdala enhances memory for training with weak footshock but impairs memory for training with strong footshock (Gold et al. 1975). These findings extend to treatments typically viewed as only amnesic agents. Under low footshock conditions, post-training injections of an inhibitor of norepinephrine synthesis (diethylthiocarbamate) (Haycock et al. 1976), seizure-producing electrical stimulation of neocortex (Sternberg et al. 1983), and intra-amygdala injections of the NMDA receptor antagonist, AP5 (LaLumiere et al. 2004) facilitate later memory. These findings are readily incorporated into the view that many amnesic treatments induce hypermnnesia.

Within neuroscience, inverted-U functions extend well beyond modulation of memory and include corticosterone modulation of motor functions (Metz et al. 2005) and dopamine modulation of arousal in *Drosophila* (Andreatic et al. 2005). In addition, tonic discharges of neurons in locus coeruleus, the source of cells providing forebrain norepinephrine, result in an inverted-U facilitating response profile of some neurons in the ventroposterior medial thalamus and barrel field somatosensory neocortex (Devilbiss and Waterhouse 2004). Leaving the domain of neuroscience, one finds many other examples of inverted-U functions, including one in which tetrachlorodibenzodioxin (TCDD) exhibits an inverted-U dose-response function in rats, suppressing immune function at low and high doses (Fan et al. 1996; Popp et al. 2006). Of interest, TCDD exposure to cell culture results in expression profiles for some genes up- or down-regulated in a linear manner and other profiles that have an inverted-U dose-response relationship (Ahn et al. 2005), a finding that might offer guidance to gene microarray experiments in learning and memory in which increases and decreases in expression levels may vary in a nonmonotonic manner with a variety of training variables and with neuromodulatory responses to training.

One interpretation of the inverted-U dose-response curves seen in studies of modulation of memory is that there are two components, a low-dose component that enhances memory and might be characterized as moderate arousal, mediated perhaps by catecholamines, and a high-dose component that impairs memory and might be characterized as high stress, mediated perhaps by opiate mechanisms (Introini-Collison and McGaugh 1987). According to this view, the inverted U is formed by the conjunct actions of ascending and descending linear functions.

An alternative view is that the inverted-U function observed for memory scores represents a linear function in terms of the underlying modulation of neural plasticity—a “too much of a

good thing” hypothesis. According to this view, memory for the key event is enhanced but, at high doses, so are memories for a host of extraneous features of the experience. These would include unassessed memories for incidental information that do not effectively guide later expression of learned behaviors and that interfere with the extraction of the relevant information. The increased neural plasticity, and increased memory, becomes detrimental as a consequence of “learned noise,” extraneous information obtained at the time of training. In this way, rats with extreme hypermnnesia would behave in an amnesic manner with standard tests of memory, though there may be other tests of memory—e.g., for otherwise extraneous information—that might reveal the hypermnnesia.

An extension of this idea comes from consideration of multiple memory systems (White and McDonald 2002; Gold 2004; Squire 2004), and particularly from findings demonstrating competition across those systems for control over learning. An important finding is that impaired learning of an attribute associated with one neural system can enhance learning of an attribute associated with another neural system. These results can be interpreted as hypermnnesia for nonpredictive information, in this case across neural systems instead of within a system. For example, like other methods of impairing hippocampal function, inactivation of the hippocampus with injections of lidocaine impairs acquisition of place learning, as generally expected, but also enhances acquisition of response learning sensitive to interference with striatal dysfunctions (Schroeder et al. 2002; Chang and Gold 2003). Of particular relevance here, up-regulation of the dorsolateral striatum with direct glucose injections impairs acquisition of place learning (Pyck et al. 2006), and glucose injections into the hippocampus or dorsolateral striatum modulate learning rates and strategy selection in a dual-solution T-maze (Canal et al. 2005). Thus, down-regulation of learning and memory processing in one domain can enhance learning and memory processing in another. More importantly here, up-regulation of learning and memory processing—hypermnnesia—in one neural system can impair learning and memory processing in another.

Noise without meaning

In contrast to hypermnnesia, another reasonable possibility is that some treatments add meaningless “neural noise” to memories, e.g., in response to injection of a protein synthesis inhibitor. Although such memory impairments are typically interpreted as showing that the absent mechanism, e.g., protein synthesis, is necessary for memory, an alternative possibility is that the insult of protein synthesis inhibition may introduce changes in neural processing activity that have no meaning for the behavioral output in response to the training experience but that are interwoven with the meaningful information that is lost by, or even overwritten within, a larger network change. Therefore, it may be important to view the amnesic effects of some treatments as a matter of inserting something bad into the system rather than of taking away something good. In emphasizing the negative consequences of temporary inhibition of protein synthesis for functions of both cells and neural systems, this view offers an alternative position not only to the role of protein synthesis in memory formation but also to a role of protein synthesis in replenishment of proteins needed to make new memories.

This perspective offers a very different way to view decay of memory after treatment. Rather than revealing the decay of a specific process, i.e., short-term memory, the results may reveal the time needed to insert noise into a network responsible for holding the memory, with gradually accumulating noise leading

to decay of memory during the ensuing hours. Note that here, as in hypermnnesia, the memory trace is not presumed to be blocked, erased, or otherwise eliminated but is instead lost in neural activity and in neural changes that are not useful when it is time to perform the appropriate response.

Memory remodulation

Our state of mind is never precisely the same. Every thought we have of a given fact is, strictly speaking, unique, and only bears a resemblance of kind with our other thoughts of the same fact. When the identical fact recurs, we must think of it in a fresh manner, see it under a somewhat different angle, apprehend in it different relations from those in which it last appeared . . . Experience is remoulding us every moment, and our mental reaction on every given thing is really a resultant of our experience of the whole world up to that date . . . Every sensation corresponds to some cerebral action. For an identical sensation to recur it would have to occur the second time in an unmodified brain . . . a physiological impossibility (James 1890).

Most interpretations of the phenomenon termed memory reconsolidation seem predicated on the view that a memory, once formed, is immutable. From that perspective, it is surprising that a memory can be “reopened” to modification. However, it appears that memories are dynamic, ever changing, and certainly not immutable, removing the major current rationale for studies using memory reconsolidation procedures. As elaborated below, these procedures may instead address the important issue of how a later experience can modify an earlier memory and how an earlier memory can modify what is learned by a later experience, providing a way to examine integration of new and old memories.

Over a century ago, it was clear to William James that the idea that an old memory could be retrieved in its original form at either a cognitive or a brain level was strikingly illogical. In contemporary terms, there is considerable evidence that old memories are changed by new experiences. This is the basis of memory distortion experiments in which, for example, memory of a list of items with a coherent theme will result, at recall, in intrusion of items from the same theme that did not appear on the original list (Roediger III and McDermott 2000; Schacter 2001). Of interest, the false memories are associated with different patterns of activation seen with brain imaging techniques (Schacter and Slotnick 2004). This is apparently not a time-dependent phenomenon, with memories remaining susceptible to change by later information even if offered many years after an earlier experience (Loftus 2005).

All reconsolidation experiments include a repeated experience. However, as William James pointed out, it is impossible to have the same experience twice. Having an experience once changes the cognitive approach to later experiences, even those that an investigator might deem identical. Indeed, when one adds to this James’ view that all memories are idiosyncratic because they are embedded in an individual’s prior experience, we have one of the basic problems of defining the biology of memory: The details of any memory cannot be duplicated within an individual at two different times or across any two individuals. However, this view is not as obstructive to memory research as it seems. While two memories may never be identical in specifics, the processes by which memories are made, maintained, and modulated may well be the same across many experiences and individuals and the neural systems that handle these processes may be comparable for identifiable classes of memory.

Still, it is clear that there are important differences in the neurobiological bases for different types of memory. Different neural systems appear to have special roles in processing different

attributes of memory (e.g., LeDoux 2000; White and McDonald 2002; Poldrack and Packard 2003; Gold 2004; Kesner and Rogers 2004; Korol 2004; Squire 2004; Fanselow and Poulos 2005). For example, lesion by task dissociations of memory systems reveal deficits in place, response, and high affect tasks for the hippocampus, striatum, and amygdala, respectively. As the cellular mechanisms of memory processing are elucidated, it is likely that there will be both similarities and differences by neural system and by task (Mizuno and Giese 2005). Post-training injections of a CaMKII inhibitor, KN-62, into either the hippocampus or amygdala impair later memory for inhibitory avoidance training (Wolfman et al. 1994; Izquierdo et al. 1997), revealing similarities of molecular mechanisms in both brain areas. However, drugs that stimulate protein kinase A enhance memory when infused into the hippocampus but not into the amygdala (Bernabeu et al. 1997), revealing differences across brain areas (see also Barros et al. 1999). Similarly, extinction of learning involves some brain areas (Anglada-Figueroa and Quirk 2005; Izquierdo and Murray 2005; Likhtik et al. 2005) and some molecular (Cammarota et al. 2005a) and neurotransmitter (Berlau and McGaugh 2006) mechanisms common to and some different from those important for original learning. In this light, it seems entirely reasonable that some of the molecular mechanisms involved in processing memory for a second experience are similar to (Bevilaqua et al. 2005; Inda et al. 2005; Nader et al. 2005) or different from (Alberini 2005; Cammarota et al. 2005b; von Herten and Giese 2005) those important for the original learning.

Thus, it may be useful to view studies investigating reconsolidation in the context of findings that different forms of learning share some neurobiological properties at the levels of systems and cellular mechanisms and do not share other properties. The idea that different kinds of memory—e.g., place, response, emotional—involve participation of sometimes different and sometimes overlapping neural systems and involve contributions of sometimes similar and sometimes different cell and molecular biological responses has a wide array of support. If one compares an original experience and a second related experience as resulting in different learning, it is not at all surprising that here too there are differences in the underlying biology. These differences need not reflect boundary conditions of reconsolidation, but might be viewed more simply as task or experiential differences generating overlapping as well as unique neural mechanisms of memory formation.

The key reconsolidation finding, of course, is that memory for the original events at the time of first consolidation is reopened to amnesic or enhancing treatment. However, there seems to be little reason to think of the original memory as the one being reconsolidated. As above, a new experience—the reconsolidation events—will be integrated with prior events for this as for many memories. While this phenomenon can be characterized as a change in old memories, the change is not a particular challenge to typical consolidation theories. Indeed, findings that the integration of old and new memories is susceptible to treatments that modulate memory formation are consistent with those theories (cf. Rodriguez-Ortiz et al. 2005).

Similarly, findings that times of integration of old and new memories are times when modulators of memory can enhance or impair those processes are consistent with theories of modulation of memory. Modulators are most likely to enhance memories for recent events that are otherwise weakly remembered. Also, weak memories may be more susceptible than are strong memories to modulation of cognitive reorganization after new related information is presented (e.g., Quartermain and Botwinick 1975; Sara et al. 1980; Quartermain et al. 1988; Suzuki et al. 2004).

With some evidence showing that the ability of a second

experience to enable modulation of the new memory complex—old plus new memory—decreases with time between experiences (e.g., Litvin and Anokhin 2000; Milekic and Alberini 2002; Suzuki et al. 2004; Alberini 2005), there may be time dependency within the phenomena of memory integration as well. While the importance of the temporal relationship between the experiences is not settled (Nader et al. 2005), and while there may not be time dependency comparable to that of traditional retrograde amnesia studies, the issue is an important one. Just as memory formation is most susceptible to modulatory influences in the time soon after a first or second experience, does the ability to integrate old and new memories decrease with time after the earlier experience?

The neural bases for integrating new and old memories has received little attention, an unfortunate omission because the continuing processing of memories based on new experiences is a very important attribute of memory. In this context, experiments now termed “reconsolidation studies” may have much to offer regarding how new memories interact with old ones. However, in this author’s view, the idea that this non-time-dependent integration of old and new memories in some way contradicts traditional memory consolidation theory is distracting from a key issue: What are the neurobiological mechanisms by which new memories are altered by prior experiences and by which old memories are altered by new experiences? By examining the dynamic nature of memories and the ways in which new experiences build upon old experiences to form coherent cognitions, attention to these processes may begin to address important issues about the richness and the “life histories” of memories.

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Gold

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