systems, but must also account for the observation that acquired information can survive systemic disruption of ongoing neural activity and transmission as little as 0.5 seconds after the induction of the neural representation. So studies of experimental amnesia set constraints for the speed of the synaptic and molecular events that underlie the maintenance of memories. In other words, it is the relative stability of acquired performance, rather than the gradient for experimental amnesia, that is potentially informative about the nature of memory maintenance.

We must recognize that acquired behaviour involves several processes and that only one of these is the establishment of a stable maintenance representation, whatever the speed of that process. Suppose that we were interested in how information is encoded in a computer, and as a probe technique we disconnected the cable to the monitor. When the computer stopped displaying information on the monitor, would it be reasonable to assume that the disconnected wire was essential for storage of information within the computer? Obviously not. So why are researchers so ready to assume, when an animal's behaviour does not reflect training after they have disrupted some neurological process, that they have somehow prevented the animal from creating a neurological representation of the training event?

The real challenge is to determine which manipulations impair or facilitate performance (not to be confused with memory), at what times after training they do so, how these effects on performance depend on stimulus conditions during the manipulation and how permanent these effects are. Armed with this information, we could move ahead with understanding the neurophysiological basis for these effects.

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REPLY — RECONSOLIDATION

# The labile nature of consolidation theory

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'Consolidation' has been used to describe distinct but related processes. In considering the implications of our recent findings on the lability of reactivated fear memories, we view consolidation and reconsolidation in terms of molecular events taking place within neurons as opposed to interactions between brain regions. Our findings open up a new dimension in the study of memory consolidation. We argue that consolidation is not a one-time event, but instead is reiterated with subsequent activation of the memories.

Memories are often defined in terms of time. Shortly after learning, memory is in a labile state (short-term memory, STM) that is sensitive to disruption. Later on, memory enters into a stable form (long-term memory, LTM), insensitive to the same disruptive factors. The process by which labile new memories are stabilized into long-lasting memories is generally referred to as consolidation[1,2].

In spite of being widely accepted in psychology and neuroscience, consolidation theory has been challenged from time to time. One challenge has come from studies showing that memories are not only labile after learning but also after reactivation or retrieval[3,4]. Another challenge has come from ideas such as Moscovitch and Nadel's multiple-trace hypothesis[5,6], which suggests that key aspects of consolidation can also be accounted for by proposing that the brain lays down different traces of an experience at different times. A third challenge, as discussed in the commentary by Nadel and Land[6], has come from research showing that memories presumed to be lost after disrupting their initial consolidation can be recovered by different methods. Experiments of this kind have been taken to suggest that the disruptive manipulations did not interfere with memory consolidation (storage) but, instead, with the ability to retrieve the memory.

In this commentary, we will expand on our view of the implications of our reconsolidation study[3] for understanding consolidation and other aspects of memory formation, and will discuss some of the issues raised by the authors of the other commentaries[6–8].

### Views of consolidation

It is important to differentiate between at least three ways in which the term consolidation has been used. One view emphasizes the transfer of memory representations over time between brain areas, typically from the hippocampus to the neocortex[9–11]. We will refer to this view as "trace-transfer consolidation theory". A second view relates to the manner in which the strength of memory representations in a given brain area are modulated as a result of activity from other areas or hormonal influences[12]. We call this version "modulation-of-consolidation theory". Trace transfer and modulation theories focus largely on interactions across brain regions and therefore are phenomena at the systems level. The third view, by contrast, does not focus directly on the interactions between brain systems but, instead, on the cellular and molecular events within cells in a given region that convert memories from short-term, labile representations into stable representations that persist over time[13–16]. We refer to this as "molecular consolidation theory". This is the view of consolidation addressed by our recent data[3] and it will constitute the foundation of most of our discussion in this article.

The three views of consolidation are not completely independent but instead reflect different points of emphasis. For example, it is well established that protein synthesis within neurons is a key molecular step in consolidation[15–18]. When researchers use the term consolidation to refer to the transfer of memory from the hippocampus to the neocortex[9–11], they do not question that molecular events within hippocampal cells are involved in the consolidation of the representation immediately after learning. Similarly, the modulatory effects of hormones on memory strength may well involve alterations in protein synthesis or molecular processes upstream or downstream from protein synthesis[19].

Much of the research in the field of memory consolidation has focused on hippocampus-dependent learning tasks. In studies of this memory system, the three views of consolidation theory apply. For example, many studies have used the inhibitory avoidance task, in which a rat is placed in a two-compartment chamber and learns to avoid entering one of the compartments after receiving a shock. Damage to the hippocampus disrupts memory for this task[20], and blockade of protein synthesis in this area interferes with memory consolidation of inhibitory avoidance[21]. It is important to note in this context that, whereas activity in specific brain areas may be necessary for the formation of a memory (the hippocampus in this case), other areas may have a modulatory function during consolidation. For example, the amygdala is not necessary for the formation of the long-term memory in the inhibitory avoidance task, but the strength of the memory can be modulated by manipulations of the amygdala immediately after training. This observation indicates that the amygdala does not participate in the learning process itself but, instead, that it modulates memory consolidation after learning has taken place[22–24].

Our recent reconsolidation study[3] involved classical fear conditioning, a task that differs in important ways from inhibitory avoidance[25–27]. For example, inactivation of the amygdala immediately after training disrupts the formation of long-term memory for inhibitory avoidance. However, this manipulation has no effect on long-term memory for classical fear conditioning[25,26]. Furthermore, disruption of protein synthesis in the amygdala prevents long-term memory for fear conditioning, indicating that this brain region is important for the consolidation of this form of memory[27].These observations indicate that the amygdala may be involved in the modulation of memories formed in the hippocampus but that it does not participate in the modulation of memories consolidated by cells within the amygdala itself (but see REF. 28). This is not to suggest that brain monoamines or peripheral hormones have no modulatory role in fear conditioning, but simply that the amygdala is not involved in the modulation of its own memories.

We therefore use the molecular view of consolidation as a reference when considering our reconsolidation findings, highlighting a local as opposed to a systems-orientated view[29].

### Memory reactivation and stability

Two lines of evidence have traditionally supported the distinction between labile STM and stable LTM. First, amnesia for a particular experience can result following certain insults to the brain, such as electroconvulsive shock (ECS), inhibition of protein synthesis, or brain injury, but only if they occur shortly after learning[16,30,31]. Second, if a subject learns one task, and then a second task shortly afterwards, the memory of the first task can be compromised[1]. However, if the second task is learned several hours after the initial learning, then there is no interference. The ability of either insults to the brain or of new learning to disrupt the formation of LTM in a temporally constrained manner are the two main operational methods for differentiating different memory states and are the pillars on which consolidation theory rests.

Over the years, several studies have shown that the same manipulations that cause memory loss after initial learning can also lead to memory loss after reactivation or retrieval. So ECS, disruption of protein synthesis[4,32] (but see REF. 33) and new learning[34] can interfere with reactivated memories as well as with new memories. Furthermore, the same temporal limits apply to both new and reactivated memories: manipulations right after learning or reactivation, but not some time later, interfere with the persistence of the memory.

In our reactivation study[3] we used targeted infusions of anisomycin into the lateral amygdala, the site thought to mediate consolidation of the memory for auditory fear conditioning[35,36]. Our findings are consistent with earlier results on the lability of memory after retrieval. However, as the earlier studies involved gross systemic manipulations of the brain in tasks for which the exact site of learning was unclear, our studies should not be viewed as a direct validation of the past studies.

From the behavioural point of view, one alternative explanation of our results is that during the reactivation trial, animals form new associations (memory traces) with other cues. For example, presentation of a conditioned stimulus (CS) in a new context leads to second-order conditioning — the animal begins to fear the new context because it has become associated with the aversively conditioned CS[37]. Accordingly, the second memory test in our study assessed this new learning, which anisomycin prevented from being consolidated.

The fundamental problem with this interpretation is that it cannot explain why animals do not remember the original conditioning session — why they do not respond robustly to the original CS. In fact, in studies of first-order conditioning with similar conditioning parameters, animals respond strongly to the CS over several days of testing in the absence of drugs or other manipulations. If we reconsider this situation under the light of consolidation theory, which predicts that only new learning is blocked by protein synthesis, then the rats should remember the original association without any loss of fidelity introduced by learning during the reactivation session. In other words, even if all new learning was blocked during reactivation, the rats should show memory of the old learning. The 'new memory trace' interpretation of reconsolidation makes the same predictions as consolidation theory. If the consolidation of the new memory trace formed during the reactivation

session is blocked, then animals should remember their original training experience and perform at a high level. The fact that rats show significant impairment on the second test suggests that reconsolidation cannot be interpreted in terms of a blockade of new learning or of new trace consolidation.

### Migrating versus multiple traces

As noted above, Nadel has proposed the creation of a new trace every time a memory is reactivated. According to this hypothesis, the reason why hippocampal lesions are less effective at disrupting memory long after learning is that there are more copies of the memory stored later than earlier and it is therefore more difficult for a particular insult to eliminate them all.

Nadel and Land[6] have suggested that our reconsolidation findings support the multiple-trace hypothesis, as reconsolidating a memory can be viewed as the formation of a new memory trace. However, we disagree with this view for two reasons. First, we do not think that reconsolidation will contribute to the creation of new memories. A new trace will undergo consolidation. It is the old trace that undergoes reconsolidation. In fact, Nadel[38] himself has suggested that the process by which memories become stablized need not be the creation of multiple memories but, instead, alternative processes such as the creation of "new nodes or retrieval routes added to the initial memory trace every time it is reactivated". If we take this alternative position into account, then reconsolidation could be related to the multiple-trace hypothesis, as reactivation of a memory will transform it into a labile state during which new retrieval routes can be added. However, this does not imply that an altogether new memory trace is formed after retrieval. Second, as we have already noted, our study focused on a kind of memory that is formed and seems to remain in one brain region — the lateral amygdala — and not on a memory stored in different areas at different times.

### Encoding versus retrieval

The question of whether amnesia produced by brain manipulations is due to a deficit in storage or retrieval was intensely debated for decades and eventually led to a stalemate[39,40]. However, this debate focused mostly on systems in which memories are stored in sites different from those where learning originally took place; for example, the hippocampal–cortical memory system. If memories are stored in pathways that transmit CS information, as is thought to occur for implicit memories, then subsequent activation of these pathways will automatically activate the memory[35,36,42,43]. In this case, there is no engram that needs to be searched out and retrieved. As a result, the issue of storage versus retrieval may be meaningful mainly for hippocampus-dependent tasks.

> "When considering our reconsolidation findings, we highlight a local, as opposed to a systems-orientated, view of consolidation"

Nadel and Land[6] , and Miller and Matzel[7], have pointed out that if the initial storage of a memory is prevented, then this memory should never be recovered because it was never formed. They therefore argue that findings on the recovery of memory are best interpreted as supporting a retrieval failure rather than a consolidation failure. However, as amnesic treatments seldom block storage of memories completely[43], partial encoding of the memory may actually occur. On the basis of this idea, consolidation theorists re-explain recovery and savings (the faster re-acquisition of a forgotten memory after retraining) in terms of a storage deficit. In other words, when subjects are retrained after an incomplete blockade of memory, they have some memory of the task and therefore require less training than naive subjects.

If some aspects of the memory can indeed be stored under conditions typically used to block consolidation, it becomes much more difficult to distinguish between failures of retrieval and failures of consolidation. Nevertheless, there are some experiments that are not readily explained by an encoding-deficit interpretation, regardless of whether partial encoding occurred or not. For example, Miller has shown that electroconvulsive shock can induce recovery of amnesia for an aversive task reinforced by immersion in ice water[44].

Previous debates on the topic of encoding versus retrieval have not provided any definitive solution to the problem. An alternative approach may be to find an independent neurobiological marker of memories. It would then be possible to test whether amnesic treatments eliminate this marker or not. If the marker is still there after the disruptive treatment, then the memory is still in the brain and the deficit must be one of retrieval. Conversely, if the marker is absent, then the memory is not in the brain, which would support an interpretation based on storage impairments. In other words, this debate might benefit from a shift from behavioural to biological, especially molecular, mechanisms.

### Molecular mechanisms

As Miller points out[7], there are several possible mechanisms that could mediate reconsolidation. As he suggests, the LTM trace could be actively destroyed and then rewritten. Nevertheless, we favour a different possibility based on the observations that LTM requires protein synthesis in a time-dependent manner both after learning and reactivation.

Animals show normal conditioned fear responses if protein synthesis in the lateral amygdala is blocked 4 hours or more after memory reactivation. This suggests that the long-term structural modifications mediating the LTM are stable for at least 4 hours independent of new protein synthesis. The most parsimonious role for the new proteins therefore seems to be the stabilization of the morphological changes that mediate LTM. In other words, the structural or functional changes that normally establish LTM cannot be maintained when protein synthesis is blocked.

One of the mechanistic implications of these findings is that the structural changes underlying LTM may have unique molecular identifiers. For example, assume that consolidation of a new memory requires the growth of new synapses in the pathway carrying CS information to the lateral amygdala. On reactivation of the memory and subsequent protein synthesis inhibition, the system must be able to distinguish between the synapses that were part of the original CS pathway and the synapses that mediated the memory after the original consolidation. How could this distinction be made?

Current models of how specific connections are marked during synaptic plasticity invoke a molecular tag of a poorly understood nature[45,46]. Strong activation is thought to insert the tag into the active synapse, which then sequesters the molecules required to stabilize the connection between pre- and postsynaptic cells. Therefore, one possibility to account for the identification of synapses formed by the original memory consolidation is to argue that the insertion of a second tag into a consolidated synapse causes it to become destabilized structurally or functionally. This synapse can continue to function normally for a short period of time in the absence of new protein production, but over longer time intervals, it requires new proteins to be stabilized again.

## Conclusions and general implications

The different commentaries that constitute this series make it clear that the traditional view of memory consolidation needs to be reconsidered. Originally, the theory was created to explain why brain insults and new learning interfere with the consolidation of a new memory. Now, it must extend beyond new memories to include reactivated memories. Indeed, one of the main conclusions to be drawn from the reconsolidation studies is that reactivated and new memories exist in similar states. As a consequence, any theory of consolidation that considers the time after training as a critical factor that determines the stability of the memory trace is likely to be incorrect as it cannot fully account for the available data. Similar findings motivated Lewis[47] to suggest the existence of two forms of memory — active (composed of new and reactivated memories) versus inactive (memories that are consolidated and not reactivated) — instead of the dichotomy between STM and LTM. The division between active and inactive memories is not referential to a particular point in time and can account for both consolidation and reconsolidation studies. We believe that Lewis's dichotomy between active and inactive memories provides, at present, a useful heuristic framework for conceptualizing the different states of a memory and for guiding new research.

Clearly, it seems unlikely that all reactivated memories return to a labile state and, therefore, active and inactive memories may be too broad a dichotomy. However, this division explains the available data and can be refined as the theory is tested across diverse learning systems and using different learning parameters. For example, does blockade of local protein synthesis in the hippocampus disrupt the persistence of spatial memory after reactivation? Does overtraining keep memory of fear conditioning from returning to a labile state?

Numerous other implications arise from the finding that reactivated memories return to a labile state. First, it might be possible to treat persons with post-traumatic stress disorder or other related anxiety conditions by reactivating traumatic memories under conditions that would prevent reconsolidation. The ethical implications of these kinds of treatment would obviously need to be considered carefully. Another implication is that the mechanisms mediating reconsolidation provide a way to study how the brain normally updates memory in the light of new experiences. Sara[8], for example, has discussed how memories can be strengthened by reconsolidation. At the other end of the spectrum, reconsolidation may help understand the mechanisms of forgetting, a topic on which few neurobiological insights have been obtained and that may help to explain some of the well-documented inaccuracies of memory[48]. For instance, during periods when memories are labile, they may reconsolidate with erroneous information.

The behavioural study of consolidation has progressed over the years by virtue of its close ties to neuroscientific research. Reconsolidation, viewed in terms of molecular events taking place in plastic components of the neural systems that mediate well-defined behaviours can now start to share this advantage.

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### Nadel Biography

Lynn Nadel received his Ph.D. from McGill University in 1967, and was then a postdoctoral fellow with Jan Bures in Prague (1967–1970). He spent six years in London at the Cerebral Functions Research Group where he co-authored *The Hippocampus as a Cognitive Map* with J. O'Keefe. After brief stays in San Diego, Halifax (Dalhousie) and University of California Irvine, he went to Arizona in 1985, where he has served as Head of Psychology since 1989. His research focuses on the hippocampus, memory and spatial cognition, as well as on various implications of the cognitive map theory for understanding context, stress and trauma, the mental retardation in Down's syndrome, and consciousness. He has been co-Director of the Complex Systems Summer School, held in Santa Fe, New Mexico, since 1990.

Cantey Land received her Ph.D. from Kent State University in 1998 under the supervision of Dr David C. Riccio. She then received further post-doctoral training in developmental psychobiology with Dr. Norman E. Spear at Binghamton University. At present, she is a NIDA research fellow at the University of Kentucky, and her research program is focused on exploring periadolescent memory processes.

### Sara Biography

Susan J. Sara is a Director of Research at the Centre National de la Recherche Scientifique and head of the group 'Neuromodulation and Memory Processes' at the Université Paris 6. Born in New York City, she earned a B.A. in Psychology from Sarah Lawrence College and a Ph.D. from the University of Louvain, Belgium. She then did postdoctoral work at Oxford and New York University Medical School, with David Quartermain.

Her research interests are centred on the neurobiology of memory, using single unit recording, pharmacology and immunohistochemistry combined with behaviour to study the role of neuromodulatory systems in attention memory formation and retrieval. She is Editor-in-Chief of the journal *Neural Plasticity*. She has been a member of the scientific advisory board of the Euresco conferences on Neural Mechanisms of Memory since 1993 and she was Chair of the 1997 Conference in that series. She has been the General Secretary of European Brain and Behaviour Society since 1995.

### Miller Bios

Louis Matzel received his Ph.D. in experimental psychology from the State University of New York at Binghamton under the direction of Ralph Miller. He subsequently trained as a neurophysiologist at the National Institutes of Health (NINDS), and is now an associate professor and Vice Chairman for Graduate Studies at Rutgers University. His current research integrates studies of basic neurophysiology with learning processes in the invertebrate Hermissenda, as well as in rats and mice. At present, the principal focus in his laboratory is on the synaptic and molecular basis for individual differences in learning.

Ralph Miller was trained in particle physics and later behavioural neuroscience at MIT and Rutgers University. His research focuses on elementary learning in animals and humans. The common thread in his research programme is determination of what gets represented in the brain during a training experience and the conditions under which this acquired knowledge is expressed in behaviour. Much of his recent research has been directed towards evidence that: first, organisms respond to 'anticipated' changes in the likelihood of biologically significant events, not their absolute likelihoods; and second, that encoded links ('associations') between the representations of two events always include the temporal and spatial relationships between the events. He is now editor of *Animal Learning & Behavior*.

### LeDoux Bios

Karim Nader received his Ph.D. from the University of Toronto under the supervision of Derek van der Kooy. After completing his Ph.D., which was aimed at elucidating how many motivational systems there are in the brain, he moved to New York University to commence postdoctoral work with Joseph E. LeDoux. In the past few years, he has published work addressing the neural organization of fear systems at systems, neurochemical and molecular levels of analysis. He is now a Research Assistant Professor at the Center for Neural Science, New York University.

Glenn E. Schafe received his Ph.D. from the University of Washington in 1997. He has since been working as a postdoctoral fellow in the laboratory of Professor Joseph LeDoux at New York University, where he is conducting research aimed at defining the cellular and molecular mechanisms underlying memory consolidation of fear conditioning in the amygdala. He is now a Research Assistant Professor at the Center for Neural Science at New York University.

Joseph LeDoux is the Henry and Lucy Moses Professor of Science in the Center for Neural Science at New York University. His work is focused on interaction between emotion and memory. He is author of *The Emotional Brain*, published in 1996, and of *Synaptic Self*, to be published later this year.