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Review

Memory reactivation effects independent of reconsolidation

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Memory reactivation is an important process resulting from reexposure to salient training-related information whereby a memory is brought from an inactive to an active state. Reactivation is the first stage of memory retrieval but can result from the exposure to salient cues without any behavioral output. Such cue-induced reactivation, although frequently used by neuroscientists to study reconsolidation, has seldom been considered as a process in its own right and studied as such. This review presents arguments indicating that memory reactivation has two main consequences: (1) to enhance the accessibility of the target memory and (2) to make the memory malleable. Accordingly, reactivation creates a transient state during which the content of the memory is easily accessible and can be modified and/or updated. As both of these aspects can be observed shortly after memory reactivation, this review emphasizes that reconsolidation is not necessarily required for these processes and calls attention to reactivation as a factor in the dynamics of the memory.

Memory retrieval is a complex (multistage) process through which previously acquired information can be used, leading to a behavioral output. Memory reactivation is the first component of retrieval corresponding to the process through which a memory is triggered from a latent state to a state in which it can be retrieved. Reactivation is generated by cues that are either external or self-generated and occurs in two general conditions. First, reactivation is required for retrieval and for every operation that enlarges or modifies previous knowledge. This includes retraining, when coherent supplementary information is provided, extinction when the previously learned response is no longer reinforced, and more generally, all rule-shiftings, i.e., when the contingency governing the response is changed. As a result, reactivation is largely embedded with retrieval and this probably explains why these two terms are often used interchangeably in the literature.⁵ Second, reactivation may also occur when subjects are simply reexposed to some cues or reminder stimuli specific to a particular episode. In some cases where no behavioral response is observable, memory reactivation can be inferred through an effect detected during a subsequent retention test. Such a cue-induced memory reactivation was introduced in the late 1960's in the context of a challenge to the consolidation hypothesis (Lewis 1969). Reactivation has also been used in studies showing that various agents were able to induce retrograde amnesia for an old established memory, but only if animals were exposed to cues associated with the conditioning episode (Misanin et al. 1968). The outcome of this procedure, in which reactivation is inferred, was descriptively referred to as "cue-dependent amnesia." Much later, this descriptive expression was replaced by a term emphasizing

the process presumably taking place after cue-induced reactivation: "reconsolidation" (Przybylski and Sara 1997; Sara 2000), adopting the idea, first introduced by Spear (1973), that "memory (may) reconsolidate anew" in cases of successive experiences, first introduced by Spear (1973).

The first reconsolidation studies proposed that the reactivation of well-consolidated memory renders the trace labile, requiring reconsolidation that recapitulates somehow the cellular events associated with consolidation (Przybylski and Sara 1997; Nader et al. 2000). Over the last decade, many studies have shown the susceptibility of reactivated memories, and these findings have been reviewed extensively in the recent literature (Sara 2010; Alberini 2011; McKenzie and Eichenbaum 2011). Reconsolidation studies propose that reactivation of consolidated memories should be seen as a manipulation that "destabilizes" the memory and returns it to a fragile, labile state requiring another period of protein-synthesis-dependent stabilization, called reconsolidation, to maintain the memory (Tronson and Taylor 2007; Hardt et al. 2010) and allow its updating (Morris et al. 2006; Lee 2010).

Accordingly, and motivated by the initial studies, cue-induced reactivation has primarily been used as a tool aimed at studying effects and processes taking place after reactivation. However, the literature provides considerable evidence indicating that such reactivation induces a variety of effects, but these effects have come to be largely ignored in recent years. It seems timely to bring together these findings to reconsider memory reactivation in its own right, i.e., not merely as the preliminary stage of retrieval or reconsolidation, but as a distinct stage of memory processing that plays a fundamental role with respect to pre-existing memories. The aim of the present study is to review the literature illustrating the various effects of reactivation and to show that reactivation effects recapitulate most of the effects generally assigned to reconsolidation.

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⁵Memory reactivation is also thought to occur during sleep. Evidence obtained both in humans and animals indicated that learning related activity is re-expressed during post-training sleep, suggesting that reactivation during sleep might be a determinant for the integration of recent experience into established remote memory networks (for reviews, see Diekelmann and Born 2010; Buhry et al. 2011). Here we will focus on memory reactivation during the awake state.

Historical background

The standard consolidation hypothesis, which postulates a time-dependent fixation of the memory trace (Glickman 1961; McGaugh 1966; Squire and Alvarez 1995), has two main predictions: (1) disruption of the consolidation phase by preventing

the normal formation of the memory trace should induce permanent disruptive effects for that memory and (2) experimental amnesia should only be obtained for newly acquired information. Almost as soon as the theory was formulated, both of these aspects were questioned as the result of studies using cue-induced memory reactivation.

First, a number of experiments using various treatments found that exposure to training cues could induce recovery from amnesia (e.g., Miller and Springer 1972; Hinderliter et al. 1975; for review, see Riccio and Richardson 1984). These findings led some to the view that amnesia did not correspond to preventing the fixation of memory storage. Rather, amnesia represented a performance impairment in which memory was inaccessible but could still become available (Spear 1978; Miller et al. 1986; Riccio et al. 2003). The debate over whether retrograde amnesia reflects storage impairments (disruption of consolidation) or retrieval deficits, which has a long history and has been reviewed extensively (e.g., Gold and King 1974; Davis and Squire 1984; Riccio and Richardson 1984), still remains unresolved (see debate in Nader and Wang 2006; Riccio et al. 2006; Sara and Hars 2006). A thoughtful review by Nader and Hardt (2009) updates the arguments and notes the limitations on the various interpretations.

Second, as previously noted, it was also established that well-consolidated memories can become susceptible again to “amnesic” treatments provided that animals are exposed to salient training cues just before the treatment was delivered (e.g., Misanin et al. 1968; Mactutus et al. 1979, 1982). These results led to the conclusion that the memory is more dynamic than initially thought and that reexposing the animal to a part of the experimental situation can reactivate the internal representation of the initial episode (Lewis 1969; Spear 1978). Noting that temporal gradients of retrograde amnesia typically confound the age and the activity of the memory representation, Lewis (1979) proposed a distinction between active and inactive memories that appears to be a more relevant distinction than one based on the age of the memory. Over a period of about 15 years, a flurry of studies provided information about reactivation, its characteristics and consequences. Then, the interest in cue-induced memory reactivation became largely dormant with only a few sporadic reports, mainly because the discovery of long-term potentiation (LTP) reinstated the consolidation hypothesis.

In 1973, Bliss and Lomo provided a model of synaptic plasticity that has been viewed as a potential cellular mechanism of memory storage (Bliss and Lomo 1973), and thus caught the attention of the neuroscience community. From this perspective, if long-term memory is related to an LTP-like phenomenon, then any treatment that interferes with LTP would also interfere with consolidation, and thus produce amnesia. During more than 20 years, there have been remarkable advances in our knowledge concerning the development of molecular and cellular mechanisms associated with different aspects of memory and the different phases of synaptic plasticity (Bloch and Laroche 1984; Martin et al. 2000; Morris et al. 2006). Extensive research using pharmacological, biochemical, and genetic methods has done much to define common cellular and molecular events underlying both LTP and consolidation (Abel and Lattal 2001). As a consequence, early criticisms provided by the use of cue-induced memory reactivation have largely been ignored, and the consolidation hypothesis since that time has recovered its dominant position.

Interest in reactivation was regenerated in 2000 with Nader's Nature study that rediscovered amnesia for well-consolidated memory (Nader et al. 2000), as well as with Land et al. (2000) who reported that hippocampal lesions could produce amnesia for an old but reactivated memory. The research by Nader showed that an established auditory fear-conditioning memory again becomes transiently sensitive to injection of a protein-synthesis in-

hibitor into the basal nucleus of the amygdala. This study replicated previous studies of the 1960s in showing that memory reactivation can return a consolidated memory to a labile state. Sara (2000), in reminding researchers of the original literature, proposed that reactivation renders the memory fragile and that a “reconsolidation” process was required for the restabilization of that memory. Parallel to earlier views of consolidation, the main interest of neuroscientists became focused on understanding the molecular mechanisms of memory reconsolidation, which emphasizes the processes taking place after memory reactivation. The restabilization of a memory, either in its identical form or with additional characteristics, is considered to take place over a relatively long period of time, hours or even days. Reconsolidation is considered to involve changes in a number of molecular substrates, including the degradation of postsynaptic proteins (Lee 2008; Jarome et al. 2011), and especially involving the production of new proteins required to restabilize the memory (Nader et al. 2000; Dudai and Eisenberg 2004; Rudy 2008b; Monfils et al. 2009).

Although reconsolidation studies have made it clear that reactivation places the memory into an active and malleable state, memory reactivation is generally not considered to play another role. In the present review, we provide substantial evidence indicating that memory reactivation is responsible for many important memory phenomena. Moreover, these phenomena can often be detected very rapidly, suggesting that they are direct consequences of reactivation and are likely to be independent of a reconsolidation process.

Roles of memory reactivation

Studies investigating the effects of cue-induced memory reactivation have been able to establish that reactivating a specific memory trace has two main consequences: (1) inducing the malleability of the memory and (2) improving subsequent retention performance (for reviews, see Spear 1978; Spear and Riccio 1994). Both effects lead to reinstating the original memory. Each of these aspects will be reviewed with a particular focus on the rapidity with which many of the effects can be seen. Rapid consequences can be interpreted as resulting directly from reactivation.

Reactivation induces malleability of memory

An important consequence of reactivation, which has been largely emphasized and explored by reconsolidation studies, is the malleability of memory, an effect extensively reported in the numerous reconsolidation reviews (e.g., Nader and Hardt 2009; Sara 2010; Alberini 2011; McKenzie and Eichenbaum 2011). Experiments showing that retrograde amnesia can be obtained on well-consolidated memory have demonstrated that reactivation reintroduces a phase of malleability similar to that obtained after initial training. There is now a general tendency to consider that malleability resulting from reactivation constitutes the basic process required to update the memories (Lee 2010; Alberini 2011). In acquiring new information, we have to reactivate our old knowledge in order to integrate the new elements. While this aspect has long been recognized in cognitive psychology, and very well documented in animals in the past, it has only recently been reintroduced in the current field of behavioral neurosciences. In this section we will see that numerous and different types of information can be added to a memory trace after it has been reactivated

Reactivation allows induction of retrograde amnesia for well-consolidated memory

Numerous studies have established that treatments given shortly after training that can modify the retention performance (i.e.,

amnesic agents) have the same potential when given shortly after memory reactivation. For example, initial studies demonstrating amnesia for old memory emphasized that the memory must be previously reactivated (Misanin et al. 1968; Mactutus et al. 1979, 1980). This cue-dependent amnesia was rediscovered more than 30 years later by Nader et al. (2000) and resulted in an explosion of research aimed at defining molecular mechanisms thought to underlie reconsolidation (for review, see Sara and Hars 2006; Tronson and Taylor 2007; Nader and Hardt 2009).

The development of this research was motivated in part by its potential clinical value: Interfering with the reconsolidation process was seen as an opportunity to decrease the influence of disrupting or intrusive memories that may contribute to the development of psychiatric disorders such as post-traumatic stress disorder or addiction (see Przybylski et al. 1999; Debiec and Ledoux 2004; Gisquet-Verrier 2009). Several pharmacological compounds have been tested in animal models in order to identify those that can be potentially relevant for clinical trials. Particular attention has been given to antagonists of β -adrenergic receptors or glucocorticoid receptors (Debiec et al. 2006; Brunet et al. 2008, 2011; Taubenfeld et al. 2009; Muravieva and Alberini 2010; Alberini 2011). Despite numerous positive studies in animals, results obtained in humans up to now are controversial (Brunet et al. 2008; Pitman 2011), and it seems that disrupting reconsolidation with pharmacological agents fails to erase fear responses from trauma memory in humans (Schiller and Phelps 2011). These studies suggest that treatments delivered shortly after reactivation may affect the retention performance by mechanisms other than by interfering with a reconsolidation process.

In addition to a temporal gradient, another similarity of amnesia for old memory and amnesia for recent memory is that disruption of the retention performance is usually not obtained immediately. Substantial evidence indicates that when a retention test occurs within the first few hours following memory reactivation, the retention performance is not disrupted (e.g., Hinderliter et al. 1975; Mactutus et al. 1982; Nader et al. 2000; Languille et al. 2009). The delayed onset of amnesia has been taken as a demonstration that it takes time for the amnesic event to disrupt the memory trace, a view supporting the hypothesis of a lingering reconsolidation process (Dudai and Eisenberg 2004).

Reactivation allows the facilitation of well-consolidated memory

Effects of hypermnesic treatments mirror those of amnesic treatments: treatments known to improve retention performance when given shortly after training have the same potential when given in association with memory reactivation. For instance, DeVietti et al. (1977) demonstrated that electrical stimulation of the mesencephalic reticular formation, which improves retention performance when delivered within a short time period after acquisition, improved memory for a well-consolidated conditioned fear response when it was applied shortly after memory reactivation. The reactivation treatment consisted of a 15-sec exposure to the conditional stimulus (tone) in the training chamber, followed by a test 24 h later. A similar electrical stimulation delivered 1 h before the retention test has been shown to reduce long-term forgetting of an appetitive task when paired with the exposure to the experimental context, whereas none of these treatments were able to affect the retention performance when delivered alone (Dekeyne et al. 1987). In various training paradigms, strychnine, glucose, amphetamine or ethanol injections, when administered just after reactivation, have been shown to increase retention performance 24 or 48 h later. (Gordon and Spear 1973b; Rodriguez et al. 1999; Blaiss and Janak 2006; Nomura and Matsuki 2008). Similar results have been obtained with more specific treatments, such as activating protein kinase A within the amygdala (Tronson

et al. 2006) or NMDA receptors (Lee et al. 2006). Most of these studies investigated the effects of post-reactivation treatments 24 h or more later. We found two exceptions: in the Dekeyne et al. (1987) study, the facilitative effect was obtained 1 h after the reactivation associated with the facilitative treatment, suggesting that the facilitation does not require reconsolidation process. On the other hand, a study performed on the crab *Chasmagnathus* (Frenkel et al. 2005) showed a positive modulation of post-reactivation water deprivation inducing a rise in brain angiotensin II measured 24 or 72 h after a reexposure to the training context. This effect, however, was not obtained with a shorter delay (4 h). Thus, it seems that complementary studies are required to determine the precise time duration required for the cue-dependent hypermnesia.

Reactivation allows the integration of new information

The idea that a memory trace is updated when new information is acquired has long been accepted in cognitive psychology. In her paper entitled "The malleability of human memory," Elisabeth Loftus (Loftus 1979), on the basis of her work on false memory in humans, convincingly reported that information presented at the time of retrieval may become integrated with the original memory. In a set of experiments studying memory of visual scenes, she showed that information given immediately after the initial episode or when the memory trace is in an active state may alter and transform the initial memory. The altered memory can be seen in subsequent retention tests, which, in some cases, were within 15 min of the manipulation (Stark et al. 2010). These results were the first to demonstrate clearly not only that eyewitness testimony can be unreliable but also that information proposed while the memory trace is in an active state can be integrated to that memory trace to create a "false memory" (for reviews, see Loftus and Davis 2006; Zaragoza et al. 2006).

In 1983, in line with Loftus' work, William Gordon addressed the question of malleability of the memory in animals: If the processes responsible for the formation of the original memory are reinstated during memory reactivation, would new information then be integrated within that memory? To investigate this possibility, Gordon et al. (1981) trained rats in a one-way avoidance task in context A and tested them in a retraining session. Testing took place either in context A or in context B, i.e., in a room differing in terms of illumination, size, odor, and noise levels. These investigators showed that the disruptive effect due to a contextual change was no longer obtained when the reactivation of the original task (exposure to the training compartment) occurred in room B, the context used for the retention test. These experiments suggested that during memory reactivation, the new context was integrated within the initial memory. From these and other experiments, Gordon provided strong arguments supporting the fact that when in an active state, the memory trace is malleable, independent of its age (Gordon 1981, 1983). Importantly, the integration of the new information seems to result from the memory reactivation itself, as it can be evidenced as soon as 5 min after the reactivation (Gordon 1981).

More recently, Briggs and collaborators showed that exposing rats to the altered test context shortly after training or after the reactivation of an old memory prevented the disruptive effect resulting from a contextual change (Briggs et al. 2007; Briggs and Riccio 2008).

As the effect was not obtained with a long delay between acquisition or reactivation and the context exposure, the investigators suggested that the active representation of the context became integrated into the initial memory trace.

Memory reactivation may be used to link new information to a prior memory in order to obtain second-order conditioning.

Tronel et al. (2005) established first-order conditioning by pairing a light with shock during the entry in a dark compartment while rats were in context A. Two days later, while in a new context (B), the experimental rats were exposed to the light for 90 sec in order to reactivate the initial memory. Consistent with higher-order conditioning, when the rats were tested 2 d later, they showed more avoidance of the dark box in context B than a control group receiving similar exposure to context B, but without the cue-induced reactivation. Another set of experiments demonstrated that a memory associated with a neutral context can be transformed into a contextual fear-conditioned memory by administering foot shocks following reactivation of the memory associated with the neutral context (Rudy et al. 2002; Lee 2010).

In these few cases, however, retention was investigated 1 or 2 d later, and it is thus difficult to determine whether the integration of the new information is the result of a rapid reactivation effect not involving reconsolidation.

Reactivation has also been shown to induce integration of new information in human episodic memory (Hupbach et al. 2007). Subjects first learned a list of objects. Two days later, they were either reminded or not of the first session, and immediately afterward learned a second list of objects. Again, 2 d later subjects were asked to recall the first list only. Reminded subjects showed a high number of intrusions from the second list. Subjects who had not been reminded showed almost no intrusions. In addition, when subjects were recalling the second list, there was no intrusion from the first list, even when subjects were reminded. This study demonstrates that reactivation of the first list was responsible for the integration of second list material, while the reverse did not occur. Interestingly, these investigators indicated that integration of list 2 within list 1 was evidenced 48 h later, but not detectable immediately after the acquisition of list 2 (Hupbach et al. 2007). In other situations, however, interference has been found to rapidly affect the performance, as illustrated in a study performed on rats. In that research, a brief cue exposure to interfering information resulted in an impairment in an alternation task when the test followed cueing by only a few seconds (Gordon and Feldman 1978).

In a recent experiment using tone fear conditioning, it was shown that extinction given shortly after reactivation was more robust than in the absence of prior reactivation (Monfils et al. 2009). More precisely, it was shown that reactivating the initial memory either 10 or 60 min, but not 6 h, before starting the extinction rendered the rats less susceptible to spontaneous recovery, renewal, and reinstatement, three procedures known to induce recovery from extinction (Bouton 2004). Although Monfils et al. (2009) interpreted findings to mean that reactivation destabilizes the memory, it is possible to view them as resulting from the integration of the new extinction information with the initial memory. This effect echoes a similar effect shown when extinction occurs immediately after initial conditioning (Myers et al. 2006). Interestingly, Monfils's results in rats have recently been reproduced in human subjects (Schiller et al. 2010). Using a discriminative fear-conditioning task, the investigators gave subjects a brief exposure to a reminder. When further extinction trials began 10 min later, the resulting extinction was much more durable and profound than when the extinction began 6 h later. Thus, although some studies report difficulties in reproducing Monfils's results (Chan et al. 2010; Costanzi et al. 2011), these findings by Monfils and Schiller suggest promising possibilities for therapeutic treatments for fear and anxiety. The research indicates that memory reactivation is necessary, but because of floor effects due to extinction itself, the work is not able to provide information about the length of time required for the integration of the extinction information within the memory trace.

Selectivity of reactivation

There is some evidence indicating that the effects of reactivation are very selective. In interference studies, it has been shown that proactive interference depended on exposure to cues associated with the first task rather than to cues associated with a foot-shock, which was common to both tasks (Gordon et al. 1979). Another study showed that in the case of a second-order fear-conditioning task, reactivation of the first-order task induced malleability of that memory which did not extend to the second-order memory (Debiec et al. 2006). This suggests that memory reactivation produces malleability in the memory restricted to aspects of the memory network that are specifically and directly reactivated.

Conclusion

Since 2000, numerous reconsolidation studies have firmly established that reactivation is able to reintroduce a phase of malleability, similar to the one taking place after training. Cue-induced memory reactivation is a necessary condition to produce malleability. Integration of new information can only result from material introduced during reactivation, or shortly thereafter. In this section we have summarized research showing that reactivation allows the integration of very different types of information: new context, new links, new facts... It seems that a variety of materials provided while the memory is in an active state potentially become integrated to the memory. The integration of some information (new context, false memory) can be detected after only a few minutes, indicating that integration resulted from reactivation *per se*. It must be acknowledged that the effects of treatments known to disrupt or facilitate the memory may be somewhat different, as they may take time before their integration can be measured.

Memory reactivation strengthens retention performance

Studies performed more than 20 years ago suggested that memory reactivation has another function, which is now largely ignored: to improve retention performance, although this aspect has been recently reported again (see Alberini 2011).

Reactivation alleviates or reverses memory impairment induced by experimental amnesia

Memory reactivation has repeatedly been shown to be an efficient way to recover memory from experimental amnesia arising from various sources (see Riccio et al. 2006). In many of those studies, recovery from amnesia was investigated at least 24 h after reactivation. However, several studies indicate that reactivation can be followed by a rapid recovery of memory. This has been well illustrated when reactivation was induced by pharmacological manipulations designed to reinstate the training internal context. In one study Quartermain and Altman (1982) administered the protein synthesis inhibitor, anisomycin, immediately after lick-suppression training in mice to induce amnesia. They found that administering d-amphetamine (0.5–2.0 mg/kg) 30 min prior to testing resulted in substantial recovery of the target memory. The generality of these findings was extended by showing that amphetamine given 30 min before testing substantially alleviated memory deficits resulting from a variety of sources of forgetting including electroconvulsive shock and long-term spontaneous retention loss (Quartermain et al. 1988). Other studies using pharmacological manipulations and other amnesic agents have also found recovery of memory within 20–30 min after the drug administration (Davis et al. 1971; Concannon and Carr 1981).

The rapid recovery of memory after a reactivation manipulation is not limited to drugs. Sara (1973) showed that exposure to the training environment 30 min prior to testing alleviated

retrograde amnesia produced by hypoxia. A similar outcome was observed with electroconvulsive shock-induced retrograde amnesia, and in this experiment the exposure to the test interval was shortened to 5 min. Gordon and Mowrer (1980) found recovery from electroconvulsive shock-induced retrograde amnesia when a brief exposure to the conditioned stimulus alone (i.e., in extinction) was followed by a test 15 min later. Exposure to the unconditional stimulus, a foot shock presented outside of the training situation, can also serve as the reactivation event (Miller and Springer 1972). Substantial recovery of memory was obtained when the rats were tested 8 h after the reactivation treatment. Interestingly, in these circumstances, cue-induced memory reactivation had an enduring effect and lasted for several days.

By way of summary of this section, a number of studies show that exposure to a drug or a reminder cue can produce rapid recovery from amnesia. This rapidly induced return of memory seems likely attributable to reactivation per se. In addition, once obtained, the recovery of amnesia may persist over long intervals, suggesting that reactivation reinstates conditions for effective retrieval (for review, see Spear and Riccio 1994).

Memory reactivation alleviates or reverses performance disruptions resulting from natural causes

As first described by Spear and Parsons (1976), memory reactivation can improve retention affected by spontaneous changes of performance such as long-term forgetting. As is the case with experimental amnesia, pharmacological treatments can compensate for spontaneous performance disruptions. A valuable series of studies from Sara's lab investigating the role of norepinephrine in memory retrieval have shown not only that this catecholamine can alleviate spontaneous long-term forgetting, but that the recovery occurs rapidly after drug administration (Sara and Deweer 1982; Sara and Devauges 1989). For example, in rats trained in an appetitively rewarded maze, amphetamine administered 20 min before testing has been shown to reduce the number of errors obtained after a 3-wk retention interval (Sara and Deweer 1982). Other research investigated the role of the noradrenergic nucleus locus coeruleus in alleviating memory loss after 4- to 5-wk intervals. These experiments demonstrated that electrical stimulation of the area shortly before testing again demonstrated a significant reduction in errors in the maze (Sara and Devauges 1988).

Several experiments have indicated that a short exposure to specific features of the training episode can compensate for the disruption due to long-term forgetting (Spear and Parsons 1976; Spear et al. 1980). The experimental context seems to be a particularly effective reminder to alleviate performance disruption due to long-term forgetting in rats trained in an appetitive or in an aversive discrimination task (Deweer et al. 1980; Gisquet-Verrier et al. 1989). In these studies, the improvement resulting from the pretest exposure to the retrieval cues is evidenced shortly thereafter (from 0 to 10 min) and is not maintained over time (Gisquet-Verrier 2009). It seems, however, that the duration of the facilitative effect can be extended to 1 h by using longer exposure to the cues or successive exposures to different cues (Deweer and Sara 1984). Feldman and Gordon (1979) showed that forgetting of short-term memory can also be alleviated by a reminder cue exposure presented 40 sec before testing in a spatial alternation task.

Memory reactivation has also been shown to alleviate performance disruption resulting from several transient retention deficits that may spontaneously occur in particular circumstances. The "Kamin effect" corresponds to a U-shaped change in performance in which retention is impaired one to several hours following aversive training (Brush 1971; Gisquet-Verrier 1983). Exposure to training cues such as a few foot shocks or the conditioned stimulus delivered in a neutral chamber, just prior to the retention

test, has been shown to improve the transiently disrupted retention performance (Klein and Spear 1970; Gisquet-Verrier et al. 1989). In one study of active avoidance in a Y-maze, the retention test always occurred 1 h after training but the interval between exposure to the discriminative stimulus and the test was systematically varied (Gisquet-Verrier and Alexinsky 1990). The Kamin effect seen in controls at 1 h was eliminated or reduced in groups receiving the reactivation 5 or 10 min before the test, but not in the group reactivated 20 min prior to testing. The Kamin effect can also be alleviated after the administration of ACTH directly into the hypothalamus or by electrical stimulation in the anterior hypothalamus, just prior to the retention test (Klein 1972). Again, these findings point to the rapid and transient nature of reactivation effects.

The warm-up decrement is defined as poor performance during initial trials of a daily session relative to the last trials in the preceding session. This transient disruptive effect can be prevented by a pre-test exposure to some salient cues associated with the training situation (Spear 1973). Typically, all of these effects have been investigated shortly after the reactivation; generally, the treatments ended 5 min before the retention test.

Disruptions associated with particular stages of development can also be overcome by memory reactivation. Thus, distinctive contextual cues introduced at the time of testing have an immediate effect of reducing infantile amnesia in rats (Richardson et al. 1986). Extensive research from the Rovee-Collier lab has shown the effectiveness of reactivation for young infants. In one study, retention of 6-mo-old infants was somewhat improved 1 h after reactivation and substantially increased after 2 or 4 h (Boller et al. 1990; see also Hayne and Herbert 2004). Reactivation has also been shown to reduce the effects of aging on memory performance in humans (Winocur et al. 1987). In the case of natural disruption, it seems that memory reactivation improves the retention performance very rapidly after the exposure to the retrieval cues, but only for a transient period.

Memory reactivation facilitates retention performance

Several lines of evidence indicate that memory reactivation can even improve retention performance that has not been impaired. It has been found that a brief exposure to a conditioned fear cue resulted in an increase in suppression of a drinking response measured 30 min later (Rohrbaugh and Riccio 1970). In a subsequent study (Rohrbaugh et al. 1972), this so-called "paradoxical enhancement" of fear was seen in a test administered only 6 min after a brief conditioned stimulus-alone exposure. Following partial training of a brightness avoidance discrimination, a short exposure to the light discriminative cue, 1 d after training, has been shown to improve the retention performance assessed 5 min later (Gisquet-Verrier and Alexinsky 1990). This paradoxical enhancement of performance obtained for different cues seems to be transient, as it is no longer obtained when the retention test is delayed for 10–20 min (Gisquet-Verrier 2009). This effect, however, seems to be restricted to cases where animals are partially trained (see Gold and King 1974) and when their retention performance is not at its maximum level (Gisquet-Verrier et al. 1989). Taken together, these results suggest that memory reactivation enhances the retention performance provided that the accessibility of the target information is not already at a maximum level. Such improvements of retention performance have been observed very soon after exposure to the retrieval cues, indicating that they result from memory reactivation.

Conclusion

Memory reactivation results in enhanced retention performance observed in various circumstances following disruption either

induced by post-training treatments or resulting from various natural changes in performance that occur over time. Furthermore, improved performance can be seen even in the absence of memory disruption. Reactivation does not seem to strengthen the memory: Its effects are transient and progressively vanish as the time interval between the reactivation and the retention test increases. These findings rather encourage the view that reactivation transiently increases the accessibility of the memory. Most, if not all, of these facilitative effects can be detected shortly after reactivation, indicating that they result from the memory reactivation itself.

A slightly different picture emerges when we consider the effect of memory reactivation after an experimentally induced disruption. Under these conditions, memory reactivation is again able to compensate for the performance disruption but in some cases the effects seem to be more or less permanent, suggesting that the reactivation engages different processes in reinstating accessibility to the memory (see Riccio et al. 2003, 2006).

Reactivation reinstates the initial memory

Lewis (1979) proposed that reactivation is a process through which memories are returned to an active state similar to the one characterizing newly formed memories. Besides the evidence provided above, other relevant findings are provided in the present section.

It is known that interference occurs when two conflicting situations take place, one shortly after the other, while often reduced when the tasks are widely spaced (e.g., 24 h). For instance, there is no interference between a passive avoidance (no-go) task and an active avoidance (go) task when they are acquired separately on two consecutive days. However, when rats received a brief reexposure to the training cues 30 sec before active avoidance training, the level of interference is similar to that of a group where the inter-task interval was short (Gordon and Spear 1973a). These results demonstrate that reactivation rejuvenates the first learning memory such that it interferes with the retention of the second task. More recently, these effects have been reproduced in humans. In one study, subjects were trained at separate times on two different procedural motor-skill tasks (Walker et al. 2003). The results demonstrated that although the accuracy in performance for the first task was not affected by the acquisition of the second task, reactivation of the first task just before the acquisition of the second task affected the retention of the initial task, indicating a retroactive interference effect. In another study, similar interference has been obtained for episodic memory. As already reported, Hupbach et al. (2007, 2008) demonstrated that the retention of a list of objects was altered when the acquisition of a second list presented a day later occurred following the reactivation of the first list, an effect not obtained in the absence of the reactivation. Comparable results were also obtained in subjects trained in an episodic memory task consisting of paired-associated learning (Forcato et al. 2007). Taken together, these experiments show that reactivating the initial memory induced effects similar to shortening the delay between the acquisitions of the two tasks. In other words, reactivation seems to reinstate the initial memory in such a way that it may interfere with a new memory acquired shortly thereafter.

The disruptive effect of contextual change, an effect easily obtained shortly after training, but which progressively vanishes with increases in the duration of the retention interval (Perkins and Weyant 1958; Steinman 1967; Zhou and Riccio 1996), can be reinstated by reactivation. A brief reexposure to the original training context (90–120 sec) has been found to reinstate a context-shift effect when testing occurred 5 min later (Gisquet-Verrier and Alexinsky 1986). Reactivation, however, has only a transient effect

on the capacity to express a contextual-shift effect, as the effect can still be observed 30 min after the cue exposure, but not after 1 or 6 h (Zhou and Riccio 1994).

Anticipating a contemporary issue, Gordon (1977) investigated the similarities and differences between new and reactivated memories as sources of proactive interference. In both cases, the interfering effect diminished as the time interval increased between either original learning or reactivation of original learning and the acquisition of the second task, although the decline in proactive interference was more rapid following reactivation. Cue-induced reactivation seems also to be able to reinstate the initial time-course of a memory. Spear et al. (1980) indicated rather similar time courses of the retention performance obtained 3 min, 1, 3, or 7 d after either fear conditioning or its reactivation, performed 27 d after the initial conditioning (see Alvares et al. 2011). Hence, it seems that reactivation may start a new time-course for retention of information. Accordingly, reactivation may be seen as a way to strengthen memory, but this seems to be achieved through its increased accessibility and consequently its facilitated retrieval. This fits very well with the recent findings in cognitive psychology that retrieval practice in the classroom can boost academic performance (Agarwal and Roediger 2011).

All of these arguments support the contention that reactivation reinstates the memory in its initial state, and thus renders it susceptible to manipulations such as interference, contextual shift, or forgetting, much like a newly formed memory.

Do we need reconsolidation?

Here we have presented studies indicating that reactivation can occur at the time of a behavioral test or following exposure to reminder cues. Common to these two forms of memory reactivation is the malleability of the memory. In both cases, new information can be integrated into preexisting memories. Reactivation occurring during a retention test allows the strengthening of memory by additional trials, extinction, and rule shifting. Cue-induced reactivation allows the integration of new information such as a new context or new links between information, possibly leading to false memory. It is clear from the literature that the capacity to integrate new information is transient and can be detected shortly after reactivation, indicating that transformations of memory representations can be achieved without requiring a reconsolidation process.

Cue-induced memory reactivation includes another characteristic extensively explored long ago, but now largely ignored: its potential to strengthen the retention performance. Cue-induced memory reactivation has been shown to compensate for memory disruption resulting from retrograde amnesia, as well as for various types of performance impairment resulting from natural sources such as the Kamin effect, warm-up decrement, infantile amnesia, forgetting, and aging. Cue-induced reactivation is also able to facilitate retention, even in the absence of any performance disruption. As already emphasized, improvement of performance resulting from reactivation more likely results from an increased accessibility to the memory rather than to an “absolute” strengthening of the memory. The enhancement of retention performance obtained after cue-induced reactivation might be related to the length of time until the retention test. While the effects of reactivation during a retention test have no time to develop, they are delayed in the case of cue-induced memory reactivation (Gisquet-Verrier and Alexinsky 1990; Hupbach et al. 2007). We have noted that after various types of disruption, a few minutes are generally required to increase the memory accessibility. Why might this be the case? Although any explanation to account for this delayed effect is speculative, we note that emotion seems to

be one of the main features through which retrieval cues are able to reinstate the memory in its initial state (Boujabit et al. 2003; Gisquet-Verrier 2009; Béroule and Gisquet-Verrier 2012). As emotion is supported by hormonal process, it might be essential for these processes to take place in order to observe the facilitation of performance (Rigter 1975; Roozendaal 2002; Gisquet-Verrier et al. 2004).

In two different respects, a somewhat different picture emerges for the treatments applied after reactivation known to disrupt or facilitate the memory. First, contrary to the rapid effect of reactivation alone, the effects of amnesic treatments do not take place immediately when associated with cue-induced reactivation but require several hours to be evidenced, replicating what happens when delivered after initial training. Second, while the facilitative effect of reactivation on natural memory impairments are transient, the effect of reactivation after retrograde amnesia persists over time, being more or less permanent. Cue-induced reactivation may thus be viewed as a way to reinstate the accessibility of the memory. Recovery resulting from reactivation after amnesia can be evidenced rapidly thereafter, much as is found for natural memory impairment. Although less well-documented, it seems that a similar process can also be observed for hypermnesic treatments. The delayed onset of amnesia and possibly the hypermnesic effects appear to be the few conditions consistent with the hypothesis of reconsolidation.

As previously mentioned, reactivation is considered to destabilize the memory, which returns to a fragile, labile state, requiring another period of protein-synthesis-dependent stabilization, i.e., reconsolidation. This idea of destabilization receives some support in studies indicating that reactivation is accompanied by synaptic protein degradation, which could be analyzed as the signature of memory destabilization (Lee et al. 2008). Research from Helmstetter's lab also indicates that protein degradation in the amygdala plays an important role in regulating synaptic plasticity following cued reactivation of fear memory (Jarome et al. 2011). Similar destabilization can be evidenced not only after reactivation, but also when supplementary training is provided, suggesting similar processes supporting reconsolidation and memory strengthening (Lee 2008; Rudy 2008a). Curiously, however, synaptic protein degradation has also been reported during memory formation (e.g., Artinian et al. 2008; Jarome et al. 2011). In addition, the synaptic protein degradation taking place very rapidly following reactivation is not accompanied by any performance disruption when examined shortly thereafter, and as previously emphasized, reactivation alone has even frequently been reported to have a facilitative effect on the retention performance (Gold and King 1974; Gisquet-Verrier and Alexinsky 1990; Nader et al. 2000). Importantly, the roles of protein degradation and synthesis seem unrelated to the phenomena we have presented. Although speculative, our view is that the malleability of memory resulting from reactivation can perfectly account for its "fragility."

Conclusion

Reactivation is a general process through which the memory is placed in an active state. Here we have reviewed evidence indicating that reactivation has two main consequences, which are (1) to restore the accessibility of the memory and (2) to induce the malleability of that memory, both of these aspects being essential for updating processes. Furthermore, both of these aspects can be obtained following exposure to reminder cues. In addition, cue-induced reactivation may further facilitate the subsequent retention performance, especially when memory has been impaired by natural causes. All of these outcomes (increased accessibility possibly leading to an improvement of the retention performance

and the capacity to integrate new information) are achieved rapidly and thus are directly the result of memory reactivation per se. From this review, it appears that, contrary to what has frequently been proposed, the integration of new information does not seem to require a restabilization process, suggesting that updating processes do not necessarily involve reconsolidation (Lee 2010; Alberini 2011). The major circumstance during which a time-dependent process is required is the case of amnesic and possibly hypermnesic treatments. The role of reconsolidation may thus be limited to these conditions. However, it should be emphasized that these treatments are always presented while memories are in an active state, i.e., when the memory is malleable. We have seen that any information presented during that time becomes integrated to the memory trace, suggesting that this interpretation may be relevant for amnesic and hypermnesic treatments as well.

In conclusion, we have reviewed evidence that strongly suggests that reactivation is worthy of consideration in its own right as a process fundamental to the plasticity and dynamic quality of memory.

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