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Revisiting systems consolidation and the concept of consolidation

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ABSTRACT

For more than 50 years, knowledge of memory processes has been based on the consolidation hypothesis, which postulates that new memories require time to become stabilized. Two forms of the consolidation model exist. The Cellular Consolidation concept is based upon retrograde amnesia induced by amnesic treatments, the severity of which decreases as the learning to treatment increases over minutes or hours. In contrast, The Systems Consolidation model is based on post-training hippocampal lesions, which produce more severe retrograde amnesia when induced after days than after weeks. Except for the temporal parameters, Cellular and Systems Consolidation show many similarities. Here we propose that Systems consolidation, such as Cellular Consolidation (see Gisquet-Verrier and Riccio, 2018), can be explained in terms of a form of state-dependency. Accordingly, lesions of the hippocampus induce a change in the internal state of the animal, which disrupts retrieval processes. But the effect of contextual change is known to decrease with the length of the retention intervals, consistent with time-dependent retrograde amnesia. We provide evidence supporting this new view.

Foreword

To make progress in science, reconsideration of old schemes is often necessary. This process has frequently occurred since the controversy about the nature of physics between Aristotle and Galileo. The present analysis continues that tradition. For more than 50 years, memory research has been centered around the consolidation hypothesis postulating that memory requires time-consuming storage processes. Beginning as a simple hypothesis, the consolidation view became increasingly accepted over time, incorporating more and more sophisticated and complex processes involving molecular cascades, new proteins, genes, and replays during sleep, among other features. Furthermore, two different time scales of consolidation became recognized. We propose that it is time to reconsider the reality of these hypothetical consolidation processes, which are based on a basic experimental paradigm leading to temporally graded retrograde amnesias. Consolidation was a reasonable way to account for the results obtained, but there are other explanations, which have been largely neglected and which need to be reconsidered because they may open a new area for future research on memory. Accordingly, it seems important and timely to consider these possibilities.

1. General framework

Consolidation is a generic term used to describe time dependent processes aimed at establishing memory in a more permanent form. Two types of consolidation, based on two different time scales, have been considered in the field of memory.

The original memory consolidation model is based upon an idea originally formulated by the German psychologists, Müller and Pilzecker (Müller and Pilzecker, 1900), who found that memory of newly learned information was disrupted by the learning of other information shortly after the original learning. This outcome led them to suggest that processes underlying new memories initially persist in a fragile state and consolidate over time.

Consolidation was first used to describe encoding processes taking place at the time of an event. This concept was taken up and broadly developed in the 1960's using experimental studies conducted on animal models and based on the same experimental paradigm. The general scheme was to deliver a treatment, severe enough to disrupt the normal brain functioning (drug, electroconvulsive shocks, hypercapnia...), after various time intervals following initial training. All these studies led to similar results indicating that the sooner the treatments were delivered after learning, the greater the retention deficit seen in performance (see Fig. 1). These time-dependent retrograde amnesias have been confirmed

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in a number of different species and after a large variety of training experiences and treatments. The dominant explanation proposed that newly acquired information is initially in a labile state where it is susceptible to disruption, but over time is gradually transformed to a more permanent state that is more resistant to amnesic treatments and can persist indefinitely (for review, see [McGaugh, 2000](#)). The consolidation hypothesis refers to this time-dependent process, occurring within the first few hours after learning, to form long-term memories ([McGaugh, 1966](#)). Based on these experimental studies, the duration of the consolidation process has been considered to take place over a period of several minutes to several hours, depending on the parameters of training and of the experimental treatment. This consolidation process, which postulated local plastic changes lasting from minutes to hours and involving new protein synthesis in the recruited neuronal network to re-structure synaptic connections,¹ has been termed Cellular (or Synaptic) Consolidation ([Lee, 2009](#); [Hardt et al., 2010](#); [Dudai et al., 2015](#); for more details [Gisquet-Verrier and Riccio, 2018, 2019b](#))

In 1990, based on a series of experiments initiated by Zola-Morgan and Squire ([Zola-Morgan and Squire, 1990](#)) showing that hippocampal lesions, performed on monkeys after varying time-intervals following training, impaired recent but spared remote memories, another type of consolidation was proposed. Unlike synaptic consolidation, the temporal intervals were in the order of days rather than minutes or hours. These results have been related to repeated clinical evidence indicating that in humans, cerebral trauma induces loss of recent memory but preserves remote memory, as reported early on by Ribot ([Ribot, 1882](#)).

The former results have been extensively replicated with a number of different species and lesion procedures (e.g. [Squire et al., 2001](#); [Squire and Wixted, 2011](#); [Wiltgen and Tanaka, 2013](#)), which reliably showed that the sooner the lesions were delivered after learning, the greater the performance retention deficit (see [Fig. 1](#)). Various types of tasks have been used, such as the contextual fear response, socially transmitted

food preferences and trace eyeblink conditioning ([Kim and Fanselow, 1992](#); [Kim et al., 1995](#); [Anagnostaras et al., 1999](#); [Winocur et al., 2001, 2009](#); [Clark et al., 2002](#); [Debiec et al., 2002](#); [Ross and Eichenbaum, 2006](#); [Wiltgen and Silva, 2007](#); [Quinn et al., 2008](#)). In these experiments hippocampal lesions induce a time-dependent retrograde amnesia extending from a few days ([Winocur, 1990](#)) to several weeks ([Cho et al., 1993](#)), clearly over a much longer time period than seen in Cellular Consolidation. The dominant explanation has been to consider that since the hippocampus is thought to play a time-limited role in memory, a long-term reorganization of the memory was required for its definite stabilization. This gave rise to the idea of a second type of consolidation, known as the standard model of Systems Consolidation, which is considered to extend over a period of time running from days to weeks, and even years ([Frankland and Bontempi, 2005](#); [Winocur et al., 2010](#); [Squire et al., 2015](#)). According to that view, retrieval of long-term memories is initially dependent on the hippocampus, but with time acquires a progressive independence from the hippocampus and its adjacent cortices to the benefit of the neocortical areas, presumed to store long-term memories ([McClelland et al., 1995](#); [Squire and Alvarez, 1995](#); [Squire et al., 2001](#); [Squire, 2004](#); [Wiltgen et al., 2004](#); [Frankland and Bontempi, 2005](#)). It must be emphasized that although both types of consolidations are usually treated in separate studies, and frequently by different authors, they are considered as part of one continuous and dynamic process, leading to a final establishment of memory.

2. The issue

Interestingly, despite their main difference concerning the time scale (minutes to hours versus days to weeks), the two forms of consolidation present a number of similarities:

- Both are based on experimental studies in animals, which have been

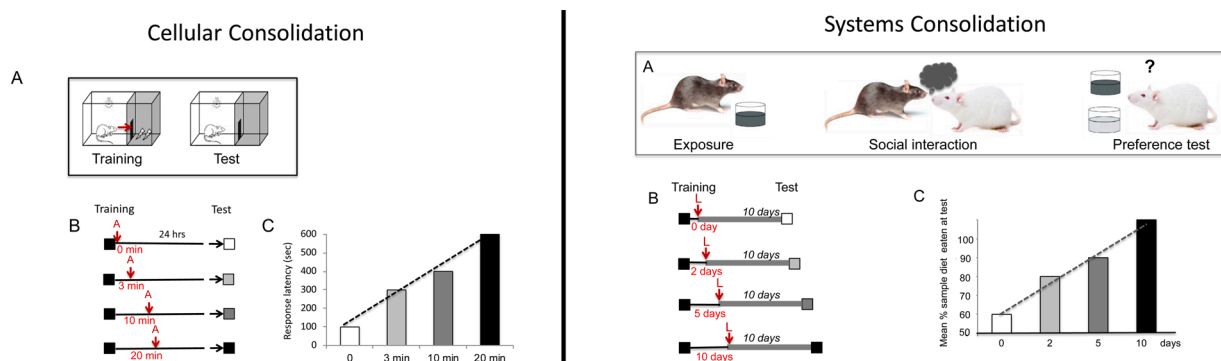


Fig. 1. Left part: Cellular Consolidation: Experimental paradigm using inhibitory avoidance, typically used in Cellular Consolidation studies (inspired by [Madsen and McGaugh \(1961\)](#)): A- Control rats refrain from returning to the shocked area unlike rats with amnesia that re-enter the area. B- Amnesic treatments (A) are delivered after varying time intervals following training and the retention performance is observed after a fixed training to test interval (generally 24 or 48 h). C- Amnesia is strongest when the treatment is delivered immediately after training and progressively decreases, over a period of min to 1 to 2 h, when the delay between training and treatment increases, leading to a time dependent retrograde amnesia.

Right part: Systems Consolidation: Experimental paradigm using socially transmitted food preference, typically used in Systems Consolidation (based on [Winocur, 1990](#)): A- a demonstrator rat samples a particular food before interacting with a naïve rat, which then acquires a preference for the food that persists at a declining rate over several days. B- Hippocampal lesions (L) are performed after varying intervals following training (0–10 days). All groups are tested 15 days after the lesions (ie 17–25 days after training). C- Amnesia is strongest when the lesion is performed shortly after training and progressively decreases, over a period of days to weeks, when the delay between training and lesion increases. As described more completely in the caption for [Fig. 2](#), this time dependent retrograde amnesia is typical in Systems Consolidation studies.

¹ More recently, the fact that time-dependent retrograde amnesia can also be obtained when treatments are delivered in similar conditions after the reactivation of an old memory, has led to the proposal that a similar type of process, termed reconsolidation, will render a memory, previously stored and established, susceptible to disruption again ([Misanin et al., 1968](#); [Mactutus et al., 1979](#); [Nader et al., 2000](#); [Sara, 2000](#); [Riccio et al., 2006](#); [Sara and Hars, 2006](#)).

related to observations in humans. ([Müller and Pilzecker, 1900](#); [Ribot, 1882](#)).

- Both rely principally on a set of experiments using the same experimental procedure: delivering treatments after different time delays following a training episode.

- Both are based on data indicating temporally graded retrograde amnesia, with strong disruptive effects of treatments delivered shortly after training and no effect for those delivered long after.
- Both propose to explain these gradients by the disruption of time dependent processes necessary to gradually transform a memory from an initial state to a more permanent state.
- Both propose to explain the performance disruption as due to a permanent memory loss.

Interestingly, there is another similarity which has not previously been noted: in both cases, animals are in a different internal state during training and testing. In the Cellular Consolidation studies, mismatched states come from the amnesic treatment delivered in temporal proximity to the training episode, but absent at the time of testing. In the case of the Systems Consolidation, animals learn the task with an intact hippocampal formation, but are tested with an altered structure.

We recently showed that temporally graded retrograde amnesia could be reinterpreted as being due to a particular form of state dependency induced by the post training treatments and proposed a challenge to the Cellular Consolidation hypothesis (Gisquet-Verrier and Riccio, 2018, 2019b). In the present paper we investigate the possibility of interpreting the results supporting Systems Consolidation as being due to a type of state dependency resulting from post-training hippocampal lesions, and propose a number of consequences generated by this new view.

3. Systems consolidation and state dependency

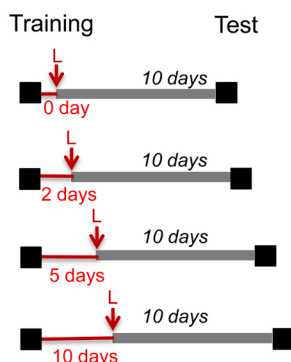
As previously mentioned, all the studies investigating retrograde amnesia after hippocampal lesions typically follow the same experimental procedure (see Fig. 2). Animals are trained in a task and lesioned after various time intervals ranging from a few hours to a few days for the shortest time interval and from several days to weeks for the longest one. Animals are all tested after a fixed time interval following the lesion (generally 7–14 days). The resulting temporally graded amnesias are interpreted as indicating that the hippocampal formation is necessary for successful retrieval only during the first few days (0–2/5 days in Fig. 1), and that memory retrieval becomes progressively independent of the hippocampus integrity for longer periods of time (after 5/10 days, in Fig. 1). In all the studies supporting the Systems Consolidation hypothesis, the training to lesion interval is the only variable considered, but as illustrated in Fig. 2 another parameter also differs among groups: the training to test interval (here ranging from 10 to 20 days), introducing large differences with respect to the age of the memory. In addition, and more importantly, another essential factor, the state of the animal, is not considered in the experimental scheme supporting the Systems Consolidation. Since in these experiments animals

learn with a functional hippocampus but are tested without it (see Fig. 2), the internal state of the animals differs substantially between post-training and testing. The mismatch in state induced by the post training hippocampal lesion can be viewed as a contextual change between training and testing. The effects of contextual change on the retention performance are well documented in the literature (see Riccio et al., 1984; Spear and Riccio, 1994). Numerous evidence indicates that when the retention test occurs relatively shortly after training, the difference between the training and testing is easily perceived and largely disrupt the retention performance, but long after training, the same contextual change has no longer any effect. It is generally considered that the transient performance disruption is due to difficulty to retrieve the initial information since a pretest exposure to a retrieval cue can abolish the disruptive effect (e.g. Zhou and Riccio, 1994). As a consequence, the disruption is maximal for the shortest training-to-test interval (TTI), and progressively decreases over time as the contextual change effect progressively weakens, inducing a temporally graded performance disruption. We propose that hippocampal lesions modify the animal's internal state producing a particular case of contextual change, close to a state dependency. Accordingly, animals learning with an hippocampus are unable to retrieve correctly the information when tested without their hippocampus. However, as for contextual change, the effects of the lesion dramatically affect the performance for events experienced shortly before hippocampal lesions, but not for those occurring long before the lesion, because at that time, the state difference no longer affects the retention performance. The aim of the present paper is thus to consider the possibility that the temporally graded retrograde amnesia resulting from hippocampal lesions could be due to retrieval difficulties originating from the modification of the animal's internal state.

4. State dependent memory

State dependency is an old concept, largely ignored with respect to amnesia for many years but recently resurrected and rejuvenated (Radulovic et al., 2017; Gisquet-Verrier and Riccio, 2018). The effect of changes in internal state on memory was first illustrated in an early study, performed by Girden and Culler (Girden and Culler, 1937), who found that when an isolated muscle was conditioned in dogs under curare the learning appeared to be absent if testing was given in the absence of the drug state. However, the conditioning became evident again if curare was reintroduced at testing. This finding was subsequently referred to as state dependent learning (or more accurately, state dependent memory, reflecting the nature of the test). Given the rather unusual nature of that preparation, the first demonstration of state dependent effects in a paradigm with substantial generality came from a study by Overton (Overton, 1964. See Fig. 3A). Rats were trained

A Systems Consolidation



B State Dependency

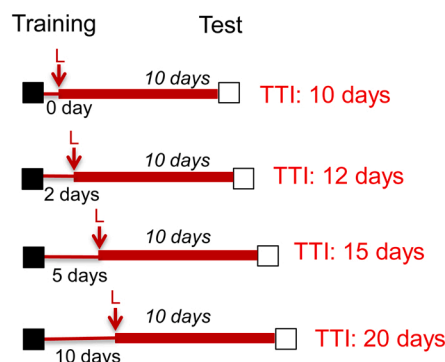


Fig. 2. A- According to the Systems Consolidation hypothesis, the delay between training and lesion (from a few hours to several days) is the only factor to be considered. The state of the animal during training and testing as well as the length after which testing occurred are not considered. B- The State dependency hypothesis draws attention to the state of the animal which differed between training (full square) and testing (empty square) due to the hippocampal lesions, as well as the training-to-test interval (TTI) varying from 10 to 20 days in this example). In that case, the training-to-lesion interval is not a critical factor except that it determines the length of the TTI.

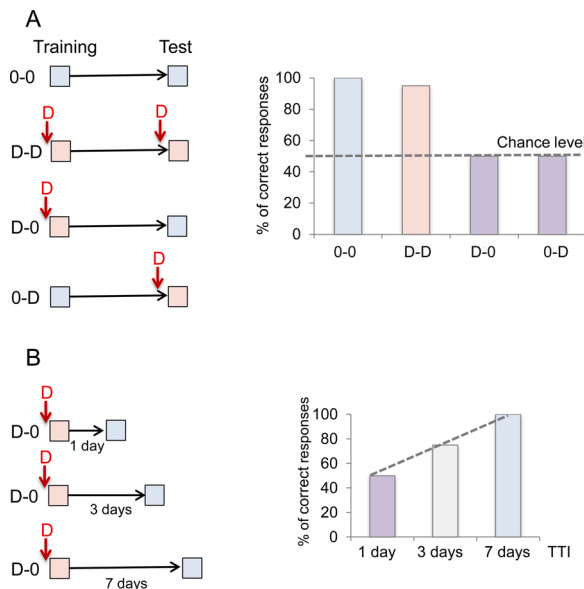


Fig. 3. A- State dependency: Experimental design used by [Overton \(1964\)](#). Rats were trained under drug (D) or no drug (O) to escape from shock in a T maze and were tested either in the same or different state. Rats performed well in the state in which training had been given but performed almost randomly in the other state.

B- Contextual dependency induces strong performance disruptions when occurring after short training-to test intervals (TTI) but weaken when TTIs increase, mimicking temporally graded retrograde amnesia.

to escape mild shock by choosing the correct goal in a T-maze while either lightly drugged, or not, with pentobarbital. Testing the following days was under either the same condition as training or the opposite, creating a classic 2×2 design. Retention was seen only when the rats were tested in the same state, i.e. internal context (drug or no drug) present at training. The performance disruption was obtained when the treatment was delivered either before training or before testing, creating a mismatch between the two conditions. Thus, the performance disruption is not due to the drug per se but to the differences between the states at training and testing. The drug induced state dependency has now been replicated in hundreds of studies using different drugs, tasks, and parameters (for review see [Overton, 1982](#)). Importantly, state dependency is not limited to internal stimuli but is a special case of a more general process involving contextual cues, including external as well as internal cues i.e., the « context shift effect » (for reviews, see [Riccio et al., 1984](#); [Spear and Riccio, 1994](#)), reflecting retrieval difficulties.

As previously noted, an important point is the critical evidence that the disruption of the retention performance due a contextual shift is maximal shortly after initial training but then decreases progressively over periods of days/weeks (See [Fig. 3B](#)). Thus, performance is impaired when testing occurs in a different context shortly after learning (e.g., one day), but shows little or no impairment after a long delay (e.g., one week). Such a phenomenon has since been largely documented in various experimental situations, although the delay after which context change may no longer affect performance varies with numerous parameters such as type of “state”, type of treatments, conditioning, species, strength of training ([Perkins and Weyant, 1958](#); [Hinderliter et al., 1975](#); [Gisquet-Verrier and Alexinsky, 1986](#); [MacArdy and Riccio, 1991](#); [Zhou and Riccio, 1995](#); [Biedenkapp and Rudy, 2007](#); [Wiltgen and Silva, 2007](#); [Ruediger et al., 2011](#)). In all, these studies demonstrate that the learned response itself (what to do) is not forgotten but the place in which to make the response (where to do it) progressively loses its control over the retention performance ([Gisquet-Verrier et al., 1989](#); [Spear and Riccio, 1994](#); [Jasnow et al., 2012](#)). Interestingly, it must be noted that state dependency induced by drugs follows the same time

course, inducing a strong performance disruption of memories which becomes weaker as the retention interval increases ([MacArdy and Riccio, 1991](#)). As emphasized by [Radulovic et al. \(2017\)](#), “state” must be considered as a largely non-specific terminology, involving various components, including such factors as drug treatments, emotion, mood, and background cues. Accordingly, changes due to brain lesions performed between training and testing are also good candidates to induce a context shift effect. In the experiments supporting the Systems Consolidation, animals learn in a normal state and are tested in an altered state. Lesions can thus be considered as an important contextual change. Consistent with that possibility, a strong disruption of performance at a relatively short training to test interval that then decreases as the time until testing increases, i.e. a temporally graded performance disruption, should be expected, a result which has been frequently reported.

5. Findings from the literature

Here, we propose that post training hippocampal lesions induce a contextual change between training and testing, responsible for the resulting temporally graded retrograde amnesia. This view leads to several implications which will be addressed through an examination of the literature.

5.1. Disruptive effects should be obtained after post- but not pretraining lesions

According to our view, for tasks not known to critically depend on the integrity of the hippocampus, disruption obtained with post-training lesions should not happen with pretraining lesions when animals are trained and tested in the same state, i.e. without a fully functional hippocampus. For instance, using a socially transmitted food preference task, [Winocur](#) showed that rats with lesions made to the dorsal hippocampus two weeks before the task acquired the preference normally, and were able to retain the specific information for relatively brief periods of time (up to one day; [Winocur, 1990](#)). In contrast, when administered shortly after learning (0–2 days), hippocampal lesions abolished memory for the food preference. Similarly, with contextual fear conditioning, [Maren](#) and collaborators repeatedly reported that pre-training lesions (1 week) induce less substantial deficits than post-training lesions (1 day; [Maren and Fanselow, 1997](#); [Maren et al., 1998](#)). Similar findings have been reported for contextual fear ([Cho et al., 1998](#); [Frankland et al., 1998](#); [Gerlai, 1998](#)), as well as for a simple discrimination learning task ([Epp et al., 2008](#)). With respect to contextual fear conditioning [Maren and Fanselow \(1997\)](#) showed that, contrary to electrolytic lesions, neurotoxic lesions of the dorsal hippocampus did not affect contextual freezing when delivered before conditioning. However, the same lesions induced a temporally graded retrograde amnesia with a disruption of freezing for lesions delivered after 1 or 28 days, but not after 100 days. Thus, results provided by the literature are clear and reliable: animals without a functional hippocampus are able to learn and to retain some training information, but are clearly disrupted when the lesion is administered after the acquisition of the same tasks

Explanations based on alternate solutions to contextual interpretations have been proposed to explain the discrepancy between pre- and post-training hippocampal lesions ([Maren and Fanselow, 1997](#); [Frankland et al., 1998](#); [Maren et al., 1998](#); [Anagnostaras et al., 2001](#)). For instance, the use of compensatory brain circuits that could circumvent the loss of the brain structure has also been proposed (for discussion, see [Fanselow, 2010](#)). Nevertheless, the fact that more disruption is obtained after post- than pre- training lesions suggests that being trained and tested without a functional hippocampus is less disruptive than being trained with an hippocampus and tested without it, fits nicely with a state dependent interpretation.

5.2. Tasks requiring the integrity of the hippocampus should lead to flat gradients

For tasks requiring an intact dorsal hippocampus to be acquired, such as allocentric spatial tasks, continuous disruption of performance that is invariant over time for spatial navigation tasks should be obtained in animals with post-training hippocampal lesions. Interestingly, permanent performance disruption with no time-dependent decreases of retrograde amnesia following hippocampal damage performed after the acquisition of spatial navigation tasks, has been frequently reported (Bolhuis et al., 1994; Mumby et al., 1999; Riedel et al., 1999; Sutherland et al., 2001; Clark et al., 2005; Martin et al., 2005; Winocur et al., 2005; Broadbent et al., 2006; Kubie et al., 2013). These results, which are not explained by the Systems Consolidation, have been the starting point of alternative positions such as the multiple trace theory (Nadel and Moscovitch, 1997; see below). Interestingly, permanent performance disruption with no temporal gradient for retrograde amnesia has also been reported after lesions concerning another brain structure, the amygdala (Maren et al., 1996). In that case, amnesia was obtained when animals were trained to contextual and tone fear conditioning. This finding emphasizes that when a structure is required to express the retention performance, such as fear with respect to the amygdala or spatial abilities for the hippocampus, the disruption is not due to a form of state dependency and there is no possibility of recovery.

5.3. Temporally graded RA should also be obtained for tasks not known to require the integrity of the hippocampus

The hippocampus is an important structure, which, even when not essential, participates in most cognitive abilities. If temporally graded retrograde amnesia results from a state dependent effect, which disrupts retrieval processes, retrograde amnesia should be obtained with various tasks including those which are not known to be affected by lesions of the hippocampus. This is the case for simple discrimination learning (Sutherland et al., 1989; Whishaw and Tomie, 1991; Alvarado and Rudy, 1995), as well as for visual discrimination tasks (Sara, 1981; Ross et al., 1984; Sutherland et al., 2001; Driscoll et al., 2004; Epp et al., 2008). However, for each of these tasks, temporally graded retrograde amnesias have been reported following post training hippocampal lesions. In the same way, socially acquired food preference has been largely used to demonstrate the effects of post-training lesions to the hippocampal formation (e.g. Winocur, 1990). However, this test can be acquired without a functional hippocampus (Winocur et al., 2001). All these data have been interpreted as indicating that, although acquisition of these tasks does not require the integrity of the hippocampus, this structure may, however, play a determinant role in the retrieval of long term memory. Nevertheless, these data clearly show that temporally graded retrograde amnesias are not restricted to tasks generally affected by hippocampal lesions, often qualified as “contextual memory” (Sekerer et al., 2018a), but can also be obtained after tasks generally analyzed as procedural in nature. This observation, enlarging the effects of post training hippocampal lesions to all types of tasks, is in agreement with our view considering that the performance impairments result from retrieval difficulties due to “state” changes between training and testing.

5.4. Temporally graded RA should not be restricted to lesions of the hippocampus

If temporally graded retrograde amnesia induced by post-training hippocampal lesions results from state dependency, similar findings should be obtained with lesions of other brain areas. Since studies exploring retrograde amnesia due to brain lesions are performed to explore the Systems Consolidation, most of them used partial or complete damage to the hippocampus (Sutherland et al., 2008), or dorsal hippocampal inactivation (Parsons and Otto, 2010). However, similar results have been reported after post-training lesions of related brain

areas, such as the entorhinal cortex (Cho et al., 1993), the perirhinal cortex, or the fornix, when lesioned either separately or conjointly (Wiig et al., 1996). Temporally graded retrograde amnesia has also been reported after damage to the amygdala. Liang et al. (Liang et al., 1982) showed that retention of an inhibitory avoidance response in rats was impaired when the amygdala was electrolytically lesioned 2 but not 10 days after learning. Similar results have also been reported with thalamic lesions. Winocur (1990) reported that rats with dorsomedial thalamic lesions failed to recall an acquired food preference when lesions occurred shortly after training but had no effect when performed more than two days later. These findings have been analyzed as suggesting that these brain structures (the amygdala and the thalamus), like the hippocampus, play a temporally limited role in memory processing and are not a permanent memory storage site. However, they also demonstrate that lesions of brain structures other than those involving the hippocampal formation may lead to temporally graded retrograde amnesia, supporting the possibility that brain lesions induce contextual changes. It is important to emphasize that, just as not all drugs produce state dependent effects, not all lesions lead to a state dependency. The literature reports many cases in which specific brain lesions do not disrupt memory. However, it seems very likely that a brain structure highly involved during training, or playing a determinant part in brain functioning, should be more likely to induce a state dependence, than lesions of less determinant brain structures. This seems particularly true for cortical lesions. This null effect was demonstrated years ago by Lashley (Lashley, 1950) who did not find any evidence that cortical lesions affected performance, regardless of the size or location of the lesion. The fact that memory traces are largely redundant and stored in widespread cortical areas could explain why their lesions could have less impact than lesions in a memory specialized area (Gaffan, 2002).

5.5. Effects of hippocampal lesions should mimic effect of contextual changes

If temporally graded retrograde amnesia resulting from post training hippocampal lesions is due to retrieval difficulties coming from changes between the training and testing conditions, similar gradients should be expected with changes others than those induced by hippocampal lesions, such as changes in external contextual cues. This has been demonstrated by Winocur, Moscovitch and Sekeres (Winocur et al., 2007), who trained normal rats in both a food-preference and contextual fear conditioning task and tested their memories at short or long delays, in either the same training environment or a new environment (see Fig. 4). For both tasks a performance disruption was obtained at short delays, when rats were tested in the new context. By contrast, after long delays (8 days for food preference and 28 days for contextual fear conditioning), normal rats performed well regardless of context. Such temporally graded retrograde amnesias obtained after a contextual change completely reproduced the results obtained in the same tasks after hippocampal lesions (Winocur, 1990). Similar results have been obtained in mice trained for contextual fear memory (Wiltgen and Silva, 2007). In this latter study, a change of contextual environment between training and testing disrupted the retention performance up to 14 days following fear conditioning, but had no effect after 36 days (see also Wang et al., 2009).

These experiments demonstrate that the retention of the precise context in which training took place progressively loses its control over the retention performance. More importantly for our purpose, they further demonstrate that a change of the initial state transiently disrupts the retrieval processes but this effect diminishes over a period of time. Hence, “classic” contextual changes concerning the environmental cues fully mimic the effects of post training hippocampal lesions, strengthening our view suggesting that these lesions could be understood as a form of contextual change.

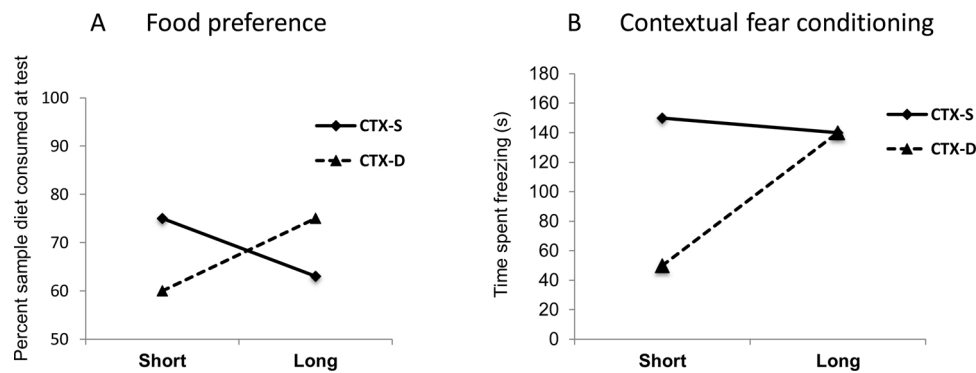


Fig. 4. Contextual change effect (adapted from Winocur et al., 2007). Normal rats were trained in either a food-preference (A) or a contextual fear conditioning (B) task and tested at short or long delays in either the same (S) or a different (D) context. Note that the contextual change effect obtained in normal rats only affects the retention performance shortly after training, perfectly replicating the effects of hippocampal lesions performed shortly or long after training in the same tasks.

5.6. Temporal gradients of retrograde amnesia due to post training hippocampal lesions should be obtained for remote memories when reactivated

Memory reactivation is known to replace the memory in an active state close to the one prevailing at the time of training. There is some evidence indicating that the reactivation of a remote memory can reinstate its susceptibility to a contextual change (Gisquet-Verrier and Alexinsky, 1986; Zhou and Riccio, 1994; Briggs and Riccio, 2008). According to our hypothesis, the reactivation of a remote memory should thus re-introduce its susceptibility to hippocampal lesions. In fact, a few studies have demonstrated that retrograde amnesia can be obtained for remote memories, provided that a reminder was delivered sometime before the lesions. For instance, Land, Bunsey and Riccio (2000- see Fig. 5) showed that rats trained in a Y-maze discrimination avoidance task demonstrated retrograde amnesia when the lesions to the hippocampus were delivered 3 h after training but not when performed 30 days later. However, when lesions performed after 30 days occurred 3 h after exposure to a reminder of the initial task, retrograde amnesia was obtained.

In another experiment, Debiec et al. (2002) showed that intra-hippocampal infusions of the protein synthesis inhibitor anisomycin performed 45 days after contextual fear conditioning caused amnesia only when animals received a reactivation session before the lesions. In the same way, Winocur et al. (2009) using a test of contextual fear conditioning, showed that a re-exposure to the fear-conditioning environment presented 28 days after the lesions was able to reinstate the vulnerability of the memory to the effects of hippocampal lesions. To

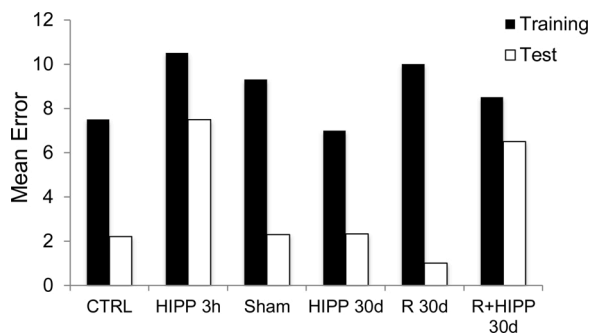


Fig. 5. Hippocampal lesions induce retrograde amnesia for remote memory (adapted from Land et al., 2000). Compared to normal rats (CTRL), rats demonstrated strong retrograde amnesia when lesions to the hippocampus were performed 3 h after training (HIPP 3 h). The same lesions had no effect when performed after 30 days (HIPP 30d versus Sham), except when lesions occurred after the reactivation of the initial training (R + HIPP 30d), while the reactivation in itself (R 30d) had no effect on the test performance.

explain these results it has been proposed that the reminder-induced reactivation process causes the trace to become again hippocampus-dependent and thus susceptible to hippocampal disruption (Hardt et al., 2009; Sara, 2000; Winocur et al., 2009). However, we know that the reactivation rejuvenates the memory, including its contextual component, rendering it susceptible again to a contextual change (Gisquet-Verrier and Alexinsky, 1986; Gisquet-Verrier and Riccio, 2012), and thus likely susceptible again to an internal change such as hippocampal lesions. Similarly, reactivation has been shown to render the memory trace susceptible again to state dependency (Sierra et al., 2013).

These data clearly show that contrary to what is generally emphasized, post training hippocampal lesions can also disrupt remote memories when they are previously reactivated, suggesting that memory representations are multiple and flexible. They further indicate that retrograde amnesia following hippocampal lesions is not determined by the age of the memory (recent vs remote) but by the activity state of memory (active vs non active)².

5.7. Retrograde amnesia due to hippocampal lesions should be weakened by techniques known to reduce state dependency

The literature indicates the performance disruption due to state dependency can be weakened and even abolished in different ways:

- 1 Reinstating the initial state before the retention test abolishes state dependency and post training hippocampal lesions.

One way to demonstrate state-dependency in a case of performance disruption is to reproduce the initial state at the time of testing and obtain recovery of performance (see Gisquet-Verrier and Riccio, 2018). Obviously such a possibility cannot be investigated in the case of brain lesions. However, it can simply be mentioned that techniques tending to reduce the lesions such as grafts of fetal hippocampal cells have been reported to be highly effective in improving recall of simple discrimination tasks learned before lesioning (Cassel et al., 1997; Sinden et al., 1997; Virley et al., 1999). Although not conclusive, this result may, however, be considered as support to the state-dependency view. An indirect evidence for our hypothesis comes from a study showing that increasing the level of neurogenesis after an contextual fear conditioning disrupts subsequent retrieval (Akers et al., 2014). The authors proposed that neurogenesis induces forgetting or memory clearance. However, a state dependency hypothesis can also adequately account for

² This point has also been well-documented for cellular consolidation (Misanin et al., 1968; Lewis, 1969; Alberini and LeDoux, 2013. See Gisquet-Verrier and Riccio, 2018, 2019b).

the performance disruption because of differences in the hippocampus between training and testing (see [Josselyn and Frankland \(2012\)](#) for a similar interpretation concerning infantile amnesia).

2 Reminder cue delivered just before the retention test reduces state dependency and post training hippocampal lesions.

Delivering a pretest exposure to a reminder cue just before the retention test is able to abolish various sources of retrieval difficulties including those resulting from state dependency ([Gisquet-Verrier et al., 2015](#); [Radulovic et al., 2017](#)). In one study, Land and colleagues (2000) trained rats in a brightness discrimination avoidance task in a Y maze and showed that hippocampal lesions delivered within 3 h following training produced strong retrograde amnesia.

However, when these lesioned rats were exposed to noncontingent footshocks delivered in a different room before testing, they performed significantly better than non-reminded rats, and no longer differed from control non lesioned animals (see [Fig. 6](#)). It must be noted that rats trained in a spatial task, requiring the hippocampus to be performed, cannot benefit from reminder exposures ([Martin et al., 2005](#)), demonstrating that reminders are only effective in cases of performance disruption resulting from retrieval difficulties. In a more recent study, recently acquired fear memory in a mouse was disrupted by a contextual change ([Liu et al., 2012](#)). The authors showed that reactivating the hippocampal engram by optogenetic stimulation of hippocampal cells engaged during memory encoding can trigger memory expression. This experiment suggests that the optogenetic stimulation plays the same role as reminders thought to activate a part of the neuronal cell pattern involved during initial training, thus allowing memory retrieval. In the case of contextual change, the external/internal cues are unable to trigger the reactivation of the brain pattern. The optogenetic stimulation by directly activating the brain pattern, bypasses this first step and allows memory retrieval, despite a contextual change.

Interestingly, exposure to salient reminder cues in humans has also been shown to possibly reverse retrograde amnesia (but not anterograde amnesia) due to brain lesions (left internal capsule and thalamus; [Lucchelli et al., 1995](#)).

These studies clearly demonstrate that reminders delivered before

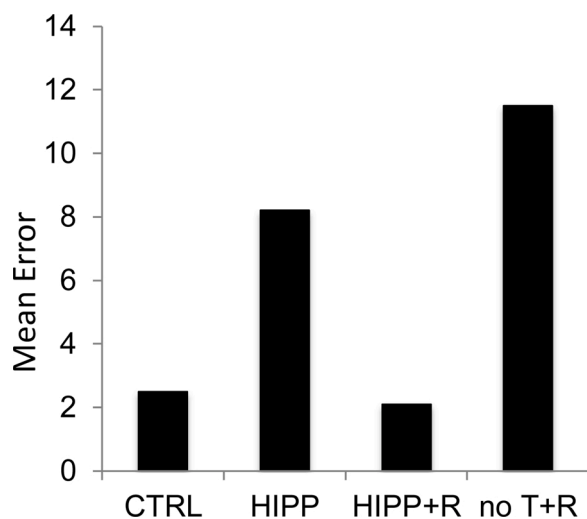


Fig. 6. Reversibility of retrograde amnesia induced by hippocampal lesions (adapted from [Land et al., 2000](#)). Rats trained in a brightness discrimination avoidance task demonstrated retrograde amnesia following lesions to the hippocampus administered shortly after training (HIPP vs CTRL). However, a pretest exposure to non contingent “reminder” footshock (HIPP + R), which in itself did not improve the performance in non trained rats (no T + R), was able to reverse the disruptive effect of the hippocampal lesions, indicating that the performance disruption was due to retrieval difficulties.

testing are able to abolish the performance disruption induced by post training lesions. This result indicates that hippocampal lesions do not destroy the memory but prevent its retrieval, supporting our view that the disruptive effects result from retrieval difficulties.

3 Pre-exposures to the training context can prevent state dependency and post training hippocampal lesions.

The literature provides evidence indicating that state dependency can be avoided by providing pre-exposure to the training context (see [Gisquet-Verrier and Riccio, 2018](#)). For example, pre-exposure to the training apparatus (familiarization) prevented ECS induced retrograde amnesia ([Lewis et al., 1968](#)). Other studies have extended the pre-exposure effect to include the prevention of amnesia by repeated exposures to the amnestic agent ([Hinderliter and Riccio, 1977](#)) and to reduction of drug induced state dependency by prior injections of the drug ([Ahlers et al., 1991](#)). In the same way, context pre-exposure has been shown to be effective to protect rats from the amnesia due to hippocampal lesions in a contextual fear conditioning ([Young et al., 1994](#)).

4 Strong training episodes reduce state dependency and post training hippocampal lesions.

Strong training episodes are known to protect from state dependency as well as from contextual changes (see [Gisquet-Verrier and Riccio, 2018](#)). There is some evidence that similar effects are also observed for post training hippocampal lesions. For example, it is well accepted that contextual fear induces weaker memories than tone-fear conditioning. [Kim and Fanselow \(1992\)](#) showed that post-training hippocampal lesions induces a temporally graded retrograde amnesia for contextual fear memories, while having no effect on tone-fear memories. More generally, strengthening the original learning seems to reduce the effects induced by hippocampal lesions. Most studies involving weak training (5 or fewer context-shock pairings) find a substantial amnesia with flat gradients ([Lehmann et al., 2007](#); [Sutherland et al., 2008](#); [Sparks et al., 2011](#)), whereas the ones delivering strong training (10 or more trials) report a temporal gradient ([Anagnostaras et al., 1999](#); [Kim and Fanselow, 1992](#); [Winocur et al., 2009](#)). In the same way, it has been reported that repeated conditioning sessions make context fear memories more resistant to post training hippocampal damage ([Lehmann et al., 2009, 2013](#); [Lehmann and McNamara, 2011](#)). All these observations suggest that the magnitude of the deficit (i.e., no effect, gradient, flat gradient) is largely determined by the strength of the initial conditioning.

6. Neural bases of systems consolidation

Aside from lesions studies, another approach to systems consolidation was to investigate brain activity during retrieval of recent and remote memories. Initially, studies investigating the neural activity during the retrieval of recent and remote memory, using metabolic activities or early gene expression as well as morphological alterations in rodents, showed increases of hippocampal activity relative to that seen in cortical structures (mainly prefrontal and anterior cingulate cortex) at short delays and the opposite patterns at long delays ([Bontempi et al., 1999](#); [Takehara et al., 2003](#); [Frankland et al., 2004](#); [Maviel et al., 2004](#); [Restivo et al., 2009](#)). Globally, all these studies indicated increases of hippocampal activity associated with the expression of new memories and of cortical activities for remote memories. However, this view is challenged by several types of data coming from more recent studies. Using fast optogenetic methods, Goshen ([Goshen et al., 2011](#)) showed that temporary inhibition of CA1 can reversibly abolish contextual fear memory recall even weeks after training, while the artificial activation of the hippocampal neurons engaged during the initial acquisition produces the expression of the context memory even long after training ([Liu et al., 2012](#); [Ramirez et al., 2013](#)). These findings have been

interpreted as revealing that the hippocampus is always required during retrieval, even for the activation of neocortical memory traces. Such a position has been strengthened by several studies involving neuroimaging techniques. This growing literature indicates that the hippocampus plays an enduring role in mediating episodic memory in humans, even long after training, when the performance is no longer affected by contextual changes (see Yonelinas et al., 2019; Sekeres et al., 2020). In addition, other studies indicate that the neocortex presents structural and functional neuronal alterations very rapidly after contextual fear conditioning (Bero et al., 2014; Vetere et al., 2019) and that post training disruption of cortical activity can prevent recent recall (Tse et al., 2011). In sum, results from activation studies of both humans and rodents suggest that despite the fact that recent memories preferentially activate the hippocampus while remote memories stimulate medial regions of the prefrontal cortex, the hippocampus as well as the neocortex are engaged during initial training and play a role both in recent and in remote memory.

It must be noted that these studies do not demonstrate that an elaborative process takes place after training. They more likely show that a memory is coded through several representations (see Gilboa and Moscovitch, 2021), which can alternately be used to express the memory. They suggest that the hippocampus dependent representation is predominantly required shortly after training when contextual cues and details control the retrieval processes, while cortical dependent representations are involved long after training, when these cues no longer affect retrieval processes, but both brain areas are involved in recent as well as in remote memory.

7. Current systems consolidation views

Taken together, these latter results do not support the original *Standard Consolidation Theory*, which proposed that the retention and retrieval of long term memory initially rely on the hippocampus, but that, with the passage of time, the memory reorganizes. After the reorganization the information becomes independent of the hippocampus and is supported by cortico-cortical connections constituting a final form of memory, which is a replica of the original hippocampal form (Kim and Fanselow, 1992; Squire and Alvarez, 1995; Squire et al., 2015).

Results obtained with the new technologies described above are in agreement with the general position concerning the way contextual information evolves in memories. Recent memory remains detailed, context-specific (in animals), and vivid (in humans) and very susceptible to contextual changes. With the passage of time, however, memories become less precise and the retention performance less and less affected by contextual changes (Riccio et al., 1984; Gisquet-Verrier and Alexinsky, 1986; Bouton et al., 1999; Balogh et al., 2002; Wiltgen and Silva, 2007), including changes induced by drugs (i.e., state dependency; MacArdy and Riccio, 1991). Such a view appears more in agreement with the *Multiple Trace Theory*, which then became the *Transformation hypothesis*, postulating that each time a memory is retrieved, a new trace is registered, thereby strengthening the memory. It is proposed that, on the basis of the multiple representations, a more schematic version of the memory is extracted containing only the gist of the initial memory (termed schematic or semantic memory), which is thought to be represented in the neocortex. According to that view, the hippocampus is always required to provide memory details (typical for episodic memory), but when the hippocampus is not functional, a schematic version of the memory (a form close to semantic memory) is still available. Hence the transformed memory does not replace the initial memory but co-exists and may interact with it (Nadel and Moscovitch, 1997, 2001; Winocur and Moscovitch, 2011; Winocur et al., 2013; Sekeres et al., 2018b, 2018a). Sekeres et al. (2018a, 2020) include in their view the fact that exposure to a reminder can reinstate a vividness of the memory supported by the return of hippocampal activity. This led them to propose a dynamic interplay between hippocampal and prefrontal cortical regions for episodic memory in humans and contextual memory in

animals. Despite the fact that many aspects of their position are close to our view, differences still remain, including among other things analyses of the temporal retrograde amnesia induced by hippocampal lesions, the idea that an elaborative process take place after training, and the restriction of this process to episodic memories (see Section 8).

During the last few years, the relationships between the temporal development of context information memory and remote memory have been emphasized and considered in the framework of Systems Consolidation (Nadel et al., 2007; Sekeres et al., 2018a, b; Winocur et al., 2010). Recently, Yonelinas et al. (2019) proposed the *Contextual Binding Theory*, as an alternative to Systems consolidation. According to that view, the hippocampus binds together item and context information originating from various brain regions, including the neocortex. Only the representation in the hippocampus is able to provide details of the memory but this representation is highly sensitive to interference provided by events occurring immediately before or after the event, which may impede later retrieval. *Contextual Binding* assumes that the hippocampus supports the encoding and retrieval of episodic memory and remains necessary across time, while other structures, especially the neocortex, support different types of memory such as semantic. As previously emphasized, the *Contextual Binding* presents some aspects close to our view (see Gisquet-Verrier and Riccio, 2019a). However, an important difference is that despite the fact that the authors strongly emphasize that recent memories are highly susceptible to contextual changes, they do not consider the possibility that hippocampal lesions may constitute a major contextual change as we have proposed.

8. An alternative view

Systems consolidation hypothesis has been widely adopted by behavioral neuroscientists mainly because temporally graded retrograde amnesia obtained in animals after post training hippocampal lesions were considered to mirror observations from amnesic patients. As a consequence, temporal changes in the effect of hippocampal lesions has extensively been taken as a useful model to understand memory functioning. So, it is important to consider (1) whether the performance disruptions obtained in experimental studies on animals replicate memory disruption evidenced in amnesic patients and (2) whether the temporally graded amnesia induced by delayed hippocampal lesions can be analyzed as resulting from a memory disruption.

The French psychologist Ribot (1882) was one of the first to note that amnesic patients demonstrated memory loss for recent events but well preserved remote memories, which constitutes an historical root of systems consolidation. However, it should be noted that this observation was performed on patients suffering from head trauma, i.e. patients with an intact hippocampus. This historic finding clearly indicates that in humans as well as in animals, temporally graded retrograde amnesia is not specific for hippocampal damage.

At the end of the 50's, initial observations from Milner and her colleagues mentioned that patients with bilateral damage to the hippocampus and medial temporal lobe exhibited a temporally graded retrograde amnesia characterized by a profound loss of memory for events that occurred shortly before surgery but preserved memory for events experienced long before (Scoville and Milner, 1957; Penfield and Milner, 1958). However, more recent observations, using new methods to assess autobiographical memory, revealed that HM exhibited severely impaired memory for details of specific episodes for remote as well as for recent episodes, illustrating a severe and non-graded retrograde amnesia for episodic memory, with relative sparing for semantic memory (Steinvorth et al., 2005). In addition, a careful examination of the literature on humans with medial temporal lobe damage has yielded mixed results, with most of them reporting profound memory loss for both recent and remote episodic memory, with no temporal gradient (for more details see Yonelinas et al., 2019). Hence, the apparently well-documented idea of a severe loss of recent information associated with a preserved remote memory does not seem so well established in

amnesic patients with hippocampal damage.

In addition, it should be emphasized that there are important differences between amnesic humans and animals with post training hippocampal lesions. Amnesia due to damage to the hippocampal formation in human results in a profound and unlimited anterograde amnesia for declarative memory. However, except for navigational tasks, hippocampal lesions in animals often result in weak anterograde amnesia, a result which appears to conflict with data from amnesics. Moreover, memory failures in humans are generally considered to be specific to declarative, as opposed to nondeclarative memory, but this point requires better documentation because it does not seem that it has been experimentally investigated and because it is clear that in animals, post training hippocampal lesions affect all types of tasks.

All these elements suggest that post training hippocampal lesions performed in the framework of systems consolidation do not fully replicate what is observed in amnesic patients for whom hippocampal lesions are frequently associated with larger areas of damage, including parts of the surrounding cortex.

With respect to the analysis of the performance disruption induced by post training hippocampal lesions, we presented evidence that:

- Temporally graded amnesia is not specific for hippocampal lesions, since similar gradients can be obtained with post training brain lesions other than that of the hippocampus, or even a head trauma, suggesting that the disruption results more from the alteration of the subject's initial state rather than the lesion of the hippocampus *per se*.
- Temporally graded amnesia induced by hippocampal lesions is not specific for contextual/episodic tasks, as similar gradients have been obtained for tasks which can be acquired without a functional hippocampus, indicating that the lesions have a general effect on the retention performance of newly acquired information.
- Temporally graded amnesia resulting from post training hippocampal lesions is not an effect restricted to recent memory since similar gradients can be obtained for reactivated remote memory.
- Contextual changes in normal rats induce temporally graded retrograde amnesia, supporting its analogy with hippocampal lesion.
- Post training hippocampal lesions do not induce a permanent amnesia since it has been repeatedly shown that a pretest exposure to a reminder can abolish the induced performance disruption.
- Retrograde amnesia resulting from post training hippocampal lesions can be largely reduced by the same manipulations as those known to alleviate state dependency/contextual change.
- Hippocampal lesions performed before training typically have weaker disruptive effects on memory than post-training hippocampal lesions. This finding indicates that the complete absence of hippocampus during training and testing is less disruptive than its absence during the retention test only, supporting the view that the memory impairment is related to a change between the training and the testing conditions.

All these assertions provide strong support for the view that temporally graded retrograde amnesia resulting from progressively delayed hippocampal lesions is not due to the disruption of an elaborative process aimed at reorganizing memory overtime. We propose instead that temporally graded retrograde amnesia results from retrieval difficulties induced by a profound contextual change due to post training hippocampal lesions.

Accordingly, temporally graded retrograde amnesia is only one illustration of a very general process by which memory progressively becomes less sensitive to changes in the experimental context. This finding is not new and has often been presented and discussed (e.g., Riccio et al., 1984; Jasnow et al., 2012). Although the mechanisms underlying the changes in memory precision over time are a matter of debate and have not yet been fully determined, progress is being made (Jasnow et al., 2017).

Such a view is consistent with the encoding specificity principle of

memory proposed by Tulving and Thomson (1973), which states that memories are maximally recalled when information available at encoding (both internal and external closely match with those available at retrieval).

It is interesting to note that whereas the cellular consolidation is considered to be engaged for several types of memory, the hypothetical process of Systems consolidation is only considered to take place for episodic/contextual memory. In fact, neuroimaging studies clearly showed that the acquisition of experiences leading to motor skills also engage the activation of the hippocampus (Gheysen et al., 2010; Albouy et al., 2013).

As illustrated by the present paper, memories do not seem to reach an immutable form, since as previously noted, the initial susceptibility to contextual change of remote memory can reliably be reinstated by a reminder exposure (Briggs and Riccio, 2008; Gisquet-Verrier and Alexinsky, 1986; Sekeres et al., 2020; Winocur et al., 2009; Zhou and Riccio, 1994). Under these conditions, it has been shown that the reactivated memory is also sensitive to hippocampal lesions, even long after training (Debiec et al., 2002; Land et al., 2000; Winocur et al., 2009). Hence, even when not expressed, the representation of the original context remains and the memory can shift from a context-independent form after a long interval to a context dependent form typical of a short retention interval. This evidence indicates that both forms may co-exist, challenging the sequential view proposed by the original version of the Systems Consolidation hypothesis. The notion of interplay recently adopted by the *Transformation hypothesis* (Sekeres et al., 2018a, 2020) is close to this view of both forms of memory co-existing. Recently, Gilboa and Moscovitch (2021) went further in proposing that new information is coded in multiple forms of representations which continue to coexist over time. Such a concept implies a considerable flexibility of the memory representation, and is not easily made consistent with the idea of a progressive and sequential elaborative process occurring between the hippocampus and the prefrontal cortex and restricted to episodic memory.

In fact, contextual changes concerning details that link the target event to any other aspects surrounding that event, including external and internal cues, disrupt memory retrieval in animals for a wide range of memory tasks, even those which are not known to be disrupted by hippocampal lesions, such as runway alley training, tone fear conditioning (for review see Jasnow et al., 2012). Similarly, in humans, contextual change has repeatedly been described to disrupt the retention of various tasks including learning lists of words and motor tasks (Wapner et al., 1967; Godden and Baddeley, 1975; Smith et al., 1978, 2014; Borovsky and Rovee-Collier, 1990; Smith and Vela, 2001).

As previously noted, contextual changes largely affect relatively new memories but their effects are strongly reduced and even abolished after repeated experiences in the original context and for memories with strong emotional contents. This could explain why contextual changes in general and hippocampal lesions in particular typically affect contextual memory in animals and episodic memory in humans more than extensively trained learning or strong conditioning in animals, as well as automatized procedural memory and semantic memory in humans (Sekeres et al., 2018a, 2018b; Yonelinas et al., 2019). One may thus propose that contextual changes, including those resulting from hippocampal lesions, induce retrieval difficulties for conscious/explicit retrieval but not for implicit retrieval. Interestingly, this hypothesis can account further for the effects reminders may have on retrieval processes impaired by contextual changes, including those induced by post training hippocampal lesions, a finding reported both for humans and animals (Land et al., 2000; Lucchelli et al., 1995). There is some evidence indicating that reminders are effective even in the absence of hippocampal integrity, suggesting that they facilitate retrieval through implicit processes (Winocur and Black, 1978; Gisquet-Verrier and Schenk, 1994; Lucchelli et al., 1995; Gisquet-Verrier, 2009).

9. Concluding remarks

The present paper provides evidence indicating that post training hippocampal lesions may not disrupt a systemic consolidation process for long term memory. We propose instead to consider these lesions as inducing post-training contextual changes responsible for retrieval difficulties. In a previous paper, we showed that poor retention performance due to an amnesic treatment delivered just after a training episode may not disrupt the presumed Cellular Consolidation process. Alternatively, we proposed that immediate post-training treatments are integrated within the training information content, and that the performance disruption results from retrieval difficulties due to their subsequent absence during the retention test i.e., another case of state dependency (our best evidence is that reintroducing the amnesic treatment before the retention test abolishes the performance disruption (see [Gisquet-Verrier and Riccio, 2018, 2019b](#)))

For both types of consolidation, treatments (amnesic agents or hippocampal lesions) delivered after varying intervals following a training episode induce temporally graded retrograde amnesia. These gradients have been interpreted as evidence supporting the hypothesis of elaborative processes taking place after training, allowing either the progressive stabilization of the memory for Cellular Consolidation or the progressive independence of the memory from the hippocampus for Systems Consolidation. We have proposed an alternative interpretation of the results taking into account the general conditions in which memory is encoded and retrieved. In both situations, the post training treatments introduce a contextual change between training and testing that is known to affect the retrieval process. From this perspective, temporally graded retrograde amnesias result from strong retrieval difficulties when the lesion is produced shortly after training. However, the impaired retrieval decreases over time due to the progressive loss of control that the altered context exerts on the retrieval processes.

Cellular and Systems memory consolidations refer to the transformation over time of a new memory trace, first at the cellular level and then at the level of brain circuits. The roots of these memory consolidation interpretations rely on an impressive number of studies adopting a single and unique experimental design: delivering a treatment (drug or lesions) between the training and the testing phase, and studying its effect on the retention performance. This experimental design has led to very consistent data indicating time-dependent retrograde amnesias. These results are replicable and not questioned, but what can be called into question is the way they have been interpreted. In the field of memory research, poor retention performance typically tended to be equated with a permanent loss of memory, without considering alternative possibilities. Analyzing temporal gradients of retrograde amnesia as resulting from the disruption of some elaborative processes required to establish a more permanent representation was clearly an option, but it is not the only one. An alternative position is that amnesia instead reflects retrieval difficulties due to contextual changes induced either by an immediate post-training treatment (Cellular Consolidation) or by the hippocampal lesions (Systems Consolidation). As reviewed in the present paper and in our previous ones, such a simple explanation is able to account for most, if not all, of the results obtained in consolidation studies.

The consolidation hypotheses postulate a long series of various and time consuming elaborative processes that come to protect the memory from disruption after various periods of time. For more than fifty years, the consolidation hypotheses led to the idea that (1) memories are fragile and can easily be disrupted and (2) memories require several hours to be encoded (Cellular Consolidation), and very extensive periods of time (days to weeks and even months and years), to be definitely stabilized (Systems Consolidation). Although these views rely on well substantiated findings, their interpretation can be called into question. We suggest that it will be fruitful to consider the brain as a powerful, plastic, dynamic and sophisticated organ able to create memories immediately fixed on line ([Lewis, 1969](#); [Hebscher et al., 2019](#)), highly

flexible and rapidly updated.

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The authors declare that there are no conflicts of interest with respect to the authorship or the publication of this article.

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