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How does reactivating a memory influence what we remember of it? Studies on reconsolidation of episodic memories
Ana Margarida de Almeida Brandão Capelo
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Universidade do Minho
Escola de Psicologia

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Tese de Doutoramento em Psicologia Básica

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DECLARAÇÃO

Nome: Ana Margarida de Almeida Brandão Capelo

Endereço electrónico: ana.margarida.capelo@gmail.com

Número do Bilhete de Identidade: 13740163

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Não tenhamos pressa, mas não percamos tempo.

José Saramago

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How does reactivating a memory influence what we remember of it? Studies on reconsolidation of episodic memories

Abstract

Far from being considered a true depiction of facts, our memory is deeply characterized by its reconstructive nature. The dynamics of human memory allow us to continuously update our knowledge, and successfully accommodate new and relevant information into old memories. However, it can also give rise to the incorporation of new and false information. But in what circumstances can a memory be modified?

The present dissertation is focused on one hypothesis that has recently emerged: the reconsolidation hypothesis. According to it, the reactivation of an acquired and well-established memory renders memory fragile and susceptible to modifications. Remarkable advances on the understanding of cellular and molecular mechanisms of memory reconsolidation in the animal field have been achieved, but research on humans faces specific challenges.

Seeking to develop a reliable experimental approach for this phenomenon, this dissertation explores one paradigm that has been widely cited as evidence for reconsolidation processes in episodic memory: an object-learning paradigm proposed by Hupbach, Gomez, Hardt, and Nadel (2007). This paradigm involves three sessions: two encoding sessions and one retrieval session, with an in-between period of 48 hours. In the first two sessions participants learn two sets of 20 unrelated objects. However, in Session 2, memory for Session 1 could be reactivated or not. Memory reactivation was achieved by two contextual cues (experimental room and experimenter) and by a reminder question, inquiring about the procedure of Session 1. In Session 3, memory for List 1 is tested. An intriguing intrusion-effect was found: if an existing memory trace is reactivated, the information that is presented immediately after becomes "incorporated" in that memory trace. Up until now, progresses have been made in improving the knowledge that came from this paradigm and that is driving data interpretation. However, the paradigm raises some questions that have been overlooked or dismissed.

In Experiment 1, we provide a replication study of Hupbach's intrusion-effect. Beyond the successfully replication, we extended the evidence in favor of the results' interpretation under the

reconsolidation umbrella. This was accomplished by means of new data analyses methods frequently used in human memory research.

In Experiment 2, we aimed to investigate if the intrusion-effect was restrictedly associated with the reactivated memory (List 1). Our results go in line with previous findings, revealing that no intrusions were observed when List 2 was tested. Considering that intrusions were only observed when the List 1 was tested, source-monitoring difficulties as an explanation for the intrusion effect seem to be ruled out.

Experiments 3 and 4 were dedicated to exploring the role of retrieval context in the paradigm under scrutiny. Experiment 3 revealed that the intrusion-effect is generalized to a new experimental context, excluding alternative explanations for the present phenomenon based on context-dependent memory effects. Additionally, Experiment 4 revealed that even when the intrusion rate probability is increased (i.e., List 1 memory test is performed in List 2 learning context), no intrusions were observed in groups that did not reactivate the original memory. Taken together, these results pointed memory reactivation as a fundamental key for the intrusion-effect and unveiled that potential alternative hypotheses cannot account for the reported intrusion-effect.

In sum, the work accomplished in the framework of this dissertation provides a more comprehensive picture on the role of reactivation in one's ability to retrieve information. This dissertation also emphasizes the importance of a critical and investigative stance over the reported effect and it will hopefully propel new research and experimental approaches in the future.

De que forma é que a reactivação de uma memória influencia aquilo que conseguimos recordar? Estudos sobre a reconsolidação de memórias episódicas

Resumo

Longe de ser considerada uma verdadeira descrição dos factos, a nossa memória é profundamente caracterizada pela sua natureza reconstrutiva. A natureza dinâmica da memória humana permite-nos manter o nosso conhecimento atualizado e acomodar informações novas e relevantes em memórias antigas. Porém, este processo pode dar origem à incorporação de informações falsas. Mas em que circunstâncias é que uma memória pode ser modificada?

A presente dissertação foca-se numa hipótese explicativa que emergiu recentemente: a reconsolidação. De acordo com esta hipótese, a reactivação de uma memória adquirida e bem estabelecida torna a memória frágil e suscetível a modificações. Até à data foram realizados avanços notáveis em estudos com animais, permitindo a compreensão dos mecanismos celulares e moleculares envolvidos na reconsolidação da memória. Contudo, a investigaçao em humanos enfrenta desafios específicos.

Procurando desenvolver uma abordagem experimental rigorosa para este fenómeno, esta dissertação explora um paradigma que tem sido amplamente citado como evidência de processos de reconsolidação na memória episódica: um paradigma de aprendizagem de objetos proposto por Hupbach, Gomez, Hardt e Nadel (2007). Este paradigma envolve três sessões: duas sessões de codificação e uma sessão de recuperação, separadas por 48 horas. Nas duas primeiras sessões, os participantes aprendem dois conjuntos de 20 objetos não relacionados. Contudo, na Sessão 2, a memória para Sessão 1 pode ser reactivada ou não. A reactivação da memória é conseguida através do recurso a duas pistas contextuais (sala experimental e experimentador) e por uma questão “lembrete”, indagando sobre o procedimento utilizado Sessão 1. Na terceira sessão, a memória para a Lista 1 é testada. Um curioso efeito de intrusão foi reportado: se um traço de memória existente é reactivado, a informação que é apresentada imediatamente depois torna-se "incorporada" nesse mesmo traço de memória. Até ao momento, foram realizados progressos no sentido da melhoria do conhecimento proveniente deste paradigma e da evidência que está a direccionar a interpretação dos resultados. No entanto, o paradigma levanta algumas questões que têm sido ignoradas ou desvalorizadas.

Na Experiência 1, apresentamos um estudo de replicação do efeito de intrusão reportado por Hupbach. Além da replicação bem sucedida, ampliamos a evidência a favor da interpretação dos resultados à luz da teoria da reconsolidação. Tal foi realizado com recurso a novos métodos de análises de dados frequentemente utilizados em pesquisas no âmbito da memória humana.

Na Experiência 2, pretendemos investigar se o efeito de intrusão era restrito à memória reactivada (Lista 1). Os nossos resultados vão em linha com investigações anteriores, revelando que não houve intrusões quando a Lista 2 foi testada. Tendo em consideração que só foram observadas intrusões quando a Lista 1 foi testada, dificuldades de monitorização da fonte como uma explicação para o efeito de intrusão parecem poder ser descartadas.

As Experiências 3 e 4 foram dedicadas a explorar o papel do contexto de recuperação no paradigma sob escrutínio. A Experiência 3 revelou que o efeito de intrusão é generalizado para um novo contexto experimental, excluindo explicações alternativas para o fenómeno reportado com base em estudos sobre efeito de memória dependente do contexto. Adicionalmente, a Experiência 4 revelou que, mesmo quando a probabilidade de ocorrência de intrusões é aumentada (i.e., realização do teste de memória da Lista 1 no contexto de aprendizagem da Lista 2), não foram observadas intrusões em grupos que não reactivaram a memória original. Em conjunto, estes resultados apontam a reactivação da memória como um mecanismo fundamental para o efeito de intrusão e revelam que explicações alternativas podem não ser adequadas para explicar este efeito.

Em suma, o trabalho realizado no âmbito desta dissertação fornece uma imagem mais abrangente sobre o papel da reactivação na capacidade de recuperar uma memória. Esta dissertação também enfatiza a importância de uma posição crítica e investigativa sobre o efeito relatado, esperando-se que tal impulsione novas pesquisas e abordagens experimentais no futuro.

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Abreviations

ACSF - Artificial Cerebrospinal Fluid

CS - Conditioned Stimulus

ECS - Electroconvulsive Shock

hr - hour

LTM - Long-Term Memory

M - Mean

min - minute

ms - milliseconds

PSI - Protein-Synthesis Inhibitors

s - second

SD - Standard Deviation

STM - Short-Term Memory

US - Unconditioned Stimulus

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PART I

GENERAL INTRODUCTION

Chapter 1. Introduction

The stream of thought flows on; but most of its segments fall into the bottomless abyss of oblivion. Of some, no memory survives the instant of their passage. Of others, it is confined to a few moments, hours, or days. Others, again, leave vestiges which are indestructible, and by means of which they may be recalled as long as life endures. Can we explain these differences?

(James, 1890, p. 643)

For more than a century, researchers have been dedicated to the understanding of the phenomenon of learning and memory (Ebbinghaus, 1885; James, 1890; Müller & Pilzecker, 1900; Ribot, 1906). Historically, memory traces have been classified according to its time-dependent nature. The early contributions of Ebbinghaus (1885) were later formalized by William James (1980), who had differentiated primary and secondary memory. From that on, it appears that memory has at least two forms: short-term memories (STM) and long-term memories (LTM). In this classification, new memories are assumed to be in a labile and transient state (STM), and to be later fixed (consolidated) into the physical structure of the brain (LTM; Glickman, 1961; Hebb, 1949; McGaugh, 1966). In accordance with this conceptualization, amnesia was proved to be induced when an electroconvulsive shock (ECS) was applied immediately after memory acquisition (STM), but not if given a few hours later (LTM). Also, new learning was demonstrated to interfere with a previous learning in a time-dependent fashion: the longer the interval between the two learnings, the lower the interference of the second list on the first (Müller & Pilzecker, 1900) The time-dependent nature of these effects was the foundation of the consolidation theory, the most

prominent model of memory formation. This theory assumes a one-way road from plasticity (STM) to (relative) permanence and stability (LTM), as a result of a synaptic memory consolidation.

The distinction between STM and LTM has been useful and productive to animal and human cognitive research. Acquisition and memory stabilization have been conceptualized as active processes, involving the synthesis of new RNA and proteins for a successful reconsolidation process. Once completed, memory processes were thought as passive readouts of long-term memory. However, the picture has recently changed. The finding that the retrieval from LTM can induce states of fragility that require a re-stabilization (reconsolidation) process challenged the linear model of memory formation proposed by consolidation theory.

The excitement around the topic has now captured the scientific community. Evidence has been massively collected, revealing that well-consolidated memories can be destabilized and become susceptible to interference of amnesic agents (Besnard, Caboche, & Laroche, 2012; Lee, Nader, & Schiller, 2017; Nader, 2015; Nader, Schafe, & LeDoux, 2000; Schiller & Phelps, 2011; Tronson & Taylor, 2007). While, for neuroscientists, reconsolidation theory describes the molecular mechanisms unfolding after reactivation which change memory on the neuronal level (Dudai, 2004), for cognitive psychologists, it offers a new approach to what has been occupying the field for decades: the study of the malleability of memory (e.g., Bartlett, 1932; Loftus & Hoffman, 1989; Schacter, 1995). In fact, the historical dissociation between cognitive psychologists and brain researchers had hindered an appropriate and beneficial cross-migration of concepts (Dudai, 2009; Roediger & Geraci, 2007; Wixted, 2004). However, the current state of research on both fields seems to be a privileged opportunity to fill this gap. In this vein, Hardt, Einarsson and Nader (2010) have identified cognitive and neuroscience traditions as twins separated at birth, and, critically, reconsolidation theory as an emerged framework allowing them to reunite.

Reconsolidation effect has been extensively replicated in several animal species, experimental paradigms, and memory types. Considering the practical, theoretical, and ethical implications of such effect, researchers have been devoting efforts in translating the animal research on reconsolidation to humans (e.g., Agren, 2014; Schiller & Phelps, 2011). One of the main challenges of this translation process is related to the invasive nature of the techniques that are typically employed in animals in order to interfere with reconsolidation process.

This dissertation focus on reconsolidation theory as a way of approaching a challenging and relevant follow-up question to the present William James's opening citation: How can supposedly enduring and stable memories be actually so malleable and seemingly plastic?

1.1 Thesis outline

In this dissertation, we will examine the existing evidence for episodic memory reconsolidation. In this first chapter, introductory notes concerning the reconceptualization of long-term memories that reconsolidation theory imposes were approached.

Chapter 2 provides a brief historical contextualization of research on consolidation and reconsolidation theory. This chapter is highly focused on exploring the birth of reconsolidation theory in order to provide an enlightening journey of how this research topic emerged and the challenges it had faced.

Chapter 3 is dedicated to presenting recent findings in memory reconsolidation across different research fields. The chapter starts with the examination of empirical research that led to a renewed interest in memory reconsolidation. Then, recent studies are reviewed and the empirical design used to approach this phenomenon is discussed. With this background, we describe the first studies conducted in humans, focusing on how they have been implemented, their limitations and the methodological solutions that have been proposed. In the final section of this chapter, the discussion will be centred in some criticism over translational studies.

Chapter 4 provides a brief review of the studies conducted in reconsolidation of episodic memories and the main challenges that are imposed. A comprehensive review of the pioneer and widely recognized paradigm designed to study this issue (Hupbach, Gomez, Hardt, & Nadel, 2007) is presented. This chapter also outlines a critical perspective over the object-learning paradigm under review. Finally, we present the main goals of the research presented in this dissertation.

Chapter 5 reports two studies: a replication study of the cited paradigm, enhanced by innovating data analyses techniques (Experiment 1) and a study designed to examine if the intrusion effect is restrictedly associated with the reactivated memory (Experiment 2).

Chapter 6 presents two studies that explore the role of retrieval context in the reported reconsolidation effect. The first study (Experiment 3) evaluates whether a reconsolidation effect generalizes to new retrieval contexts, and the second study (Experiment 4) explores how determinant is memory reactivation for the asymmetrical intrusion effect (that is taken as evidence for a reconsolidation effect).

Chapter 7 will be reserved for final conclusions, providing a summary of the findings presented in this dissertation and prospects of future avenues for episodic memory research.

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Chapter 2. From consolidation theory to reconsolidation theory

The facts of both psychology and neurology show a degree of plasticity, of organization, and of adaptation in behavior which is far beyond any present possibility of explanation. For immediate progress it is not very important that we should have a correct theory of brain activity, but it is essential that we shall not be handicapped by a false one.

(Lashley, 1930, p. 24)

2.1 Consolidation theory: Empirical evidence

The origin of the idea of memory consolidation as a post-training time-dependent process of maturation dates back to the writings of Quintilian (first century A.D.), in *Institutio Oratoria* translated by Butler (1921): "(...) the power of recollection (...) undergoes a process of ripening and maturing during the time which intervenes" (p. 237). However, the concept of memory consolidation is credited to George Elias Müller (1850-1934), one of the founders of experimental psychology. Greatly inspired by Gustav Fechner, Wilhelm Wundt, and Herman Ebbinghaus, Müller was committed to finding laws that govern learning and memory. In collaboration with Pilzecker, between 1892 and 1900, Müller developed a scientific approach to the study of the labile state of newly acquired information. Throughout 40 experiments, the authors explored the topic of memory formation and retrieval, with the use of nonsense syllables as stimuli. Although the experiments reported in Müller and Pilzecker's (1900) monograph are widely recognized and cited, an English

translation is not available. Fortunately, Lechner, Squire, and Byrne (1999) provided a close revisit of some of their more important studies.

Müller and Pilzecker's (1900) standard procedure, was as follows: after being trained using pairs of nonsense syllables, memory was tested with a cued-recall task. Specifically, the first syllable of each pair was presented and participants were asked to recall the second syllable. The number of training trails was fixed and memory performance was measured by the percentage of correctly recall syllables and incorrect or recall failures.

Participants' reports during training sessions lifted the veil to the concept of memory consolidation. As they reported that syllable pairs come to their mind repeatedly during training sessions, despite their intentional efforts to suppress this interference. The authors adopted the word *perseveration* (p. 60), used in previous descriptions of psychiatry pathologies, to describe this specific phenomenon. Two types of errors/mistakes that occurred during recall were considered the first evidence for perseveration of recently acquired information: (a) the same answer was given for different cues; (b) immediately after training, the percentage of incorrect answers, which were the correct answers for other cues to that training list, was very high, but showed a rapid decrease. Müller and Pilzecker assigned to perseveration a rule in the strengthening of association between syllable pairs, in a way that the disruption of preservation was thought to interfere with the formation of associative learning:

> One might deem that the perseverative tendencies of syllables of a previously read list might also serve to consolidate the associations between these syllables and that accordingly, weakening of the perseverative tendencies of syllables from a previously read list, due to other intense mental occupations, might have the additional effect of obstructing the associations between these syllables. (Müller & Pilzecker, 1900, p. 68)

Pursuing the idea that perseveration mirrored a physiological process that allowed the consolidation (i.e., strengthening of associations), 10 experiments were conducted. In one of these experiments, perseveration was disrupted by the use of a second learning, in a within-subjects design. Thus, two conditions were contrasted, here named as interference condition and no-interference condition (see Figure 1). In the interference condition, before the learning of the first pair of syllables (List A), participants learned an interfering list (List X). Then, after 6 min, memory for the List A and the List X was examined. The percentage of correctly recalled pairs of List A was collected. Then, in the no-interference condition, a third list (List B) was learned and tested after

an equivalent interval of time (but with no interfering learning). Again, the percentage of correctly recalled items was measured.

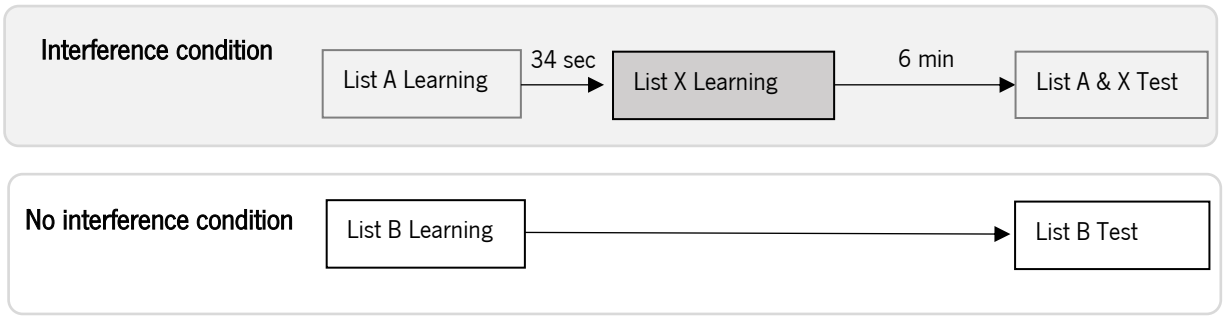


FIGURE 1. Schematic representation of Muller and Pilzecker's (1900) procedure.

Results revealed that the presentation of interfering material impaired memory for an initial learning: memory performance in the interference condition was 23% for items of List A, and memory performance in no-interference condition was 48%. The same pattern of results was found when the interval between List A and List X was 1 minute, and the memory test was 24 hours later. The manipulation of the interval between the initial learning (List A), and the interfering learning (List X) led to an important finding. In a subsequent experiment (Experiment 34), Müller and Pilzecker found that the impact of the interfering learning on the initial learning was time-dependent: the interfering material impaired memory if it was learned after a short interval (17 sec) but not after a longer interval (6 min).

In a subsequent experiment, the authors explored the role of the nature of the interfering material in the impairment effect reported in their previous experiments. As both interfering and target material were nonsense syllable, the authors were interested in testing if the results would be the same when the interfering stimuli and target lists were different in nature. Here, the experimental procedure was the same, however, images were used as the interfering material. So, 6 minutes after List A learning, a list of images was displayed, and participants had to describe the landscapes they represent. Then, memory for List 1 was measured. As a control condition, memory for List B was tested with an equivalent retention interval. The results' pattern was equivalent to their previous findings, memory performance of List A (24%) was lower than List B (56%). This finding led to the conclusion that, when some material (independently of its nature) is presented after an initial learning, memory impairment is expected to occur (Müller & Pilzecker, 1900).

Contemporary with Müller and Pilzecker findings, a French psychiatrist, named Théodule-Armand Ribot, contributed with very influential observations and theoretical elaborations

for the concept of memory consolidation. Based on clinical data of patients with retrograde amnesia (1881, 1882), who reported the loss of memory-access to information that was encoded immediately before an injury, Ribot formulated "la Loi de regression" (commonly know as "Ribot's Law"). This law notes that with the passage of time memories become more resistant to trauma-induced amnesia:

> We thus see that the progressive destruction of memory follows a logical order- a law. It advances progressively from the unstable to the stable. It begins with the most recent recollections, which, lightly impressed upon the nervous elements, rarely repeated and consequently having no permanent associations, represent organization in this feeblest form. It ends with the sensorial, instinctive memory, which, become a permanent and integral part of the organism, represents organisation in its most highly developed stage. (Ribot, 1882, pp. 121-122)

The consolidation theory was rapidly used to approach the temporally graded retrograde amnesia (e.g., Burnham, 1903), strengthening the idea that memories need time to consolidate, and so that recent memories are more likely to be lost than the more remote memories.

Almost 50 years after Müller and Pilzecker monograph, Carl Duncan conducted pioneer systematic laboratory studies on retrograde amnesia (Duncan, 1949). The subjects were rats and an ECS was used as an amnesic treatment. The experimental paradigm with non-human subjects increased the experimental control and allowed the administration of an invasive amnesic treatment (the ECS), which presumably influenced the biological substrates of the consolidation process. Duncan used an active avoidance task: rats were placed into an environment that had both a "dangerous" and a "safe" compartments. After 10 seconds, a foot shock was delivered, causing the rats to move to the safe compartment. One of these learning trials occurred each day for a period of 18 days. Researchers measure the number of "anticipatory runs" (moves towards the safe compartment) in order to examine if the animals learned the compartment-shock contingency. The experimental manipulation was the time delay of ECS administration following learning (20 s, 40 s, 60 s, 4 min, 15 min, 1 hr, 4 hr, and 14 hr). A control group received no ECS. The authors found that the speed of learning varied inversely with the delay between training and amnesic treatment. The number of anticipatory runs gradually improved from the 20 seconds group to the 1 hour group. The performance stabilized in the 1 hr, 4 hr, and 14 hr groups, who performed similarly to the control group (see Figure 2). The authors concluded:

The results were interpreted in terms of a consolidation theory. It was suggested that newly learned material undergoes a period of consolidation or perseveration. Early in this period a cerebral electroshock may practically wipe out the effect of learning. The material rapidly becomes more resistant to such disruption; at the end of an hour no retroactive effect of cerebral electroshock was found. (p. 44)

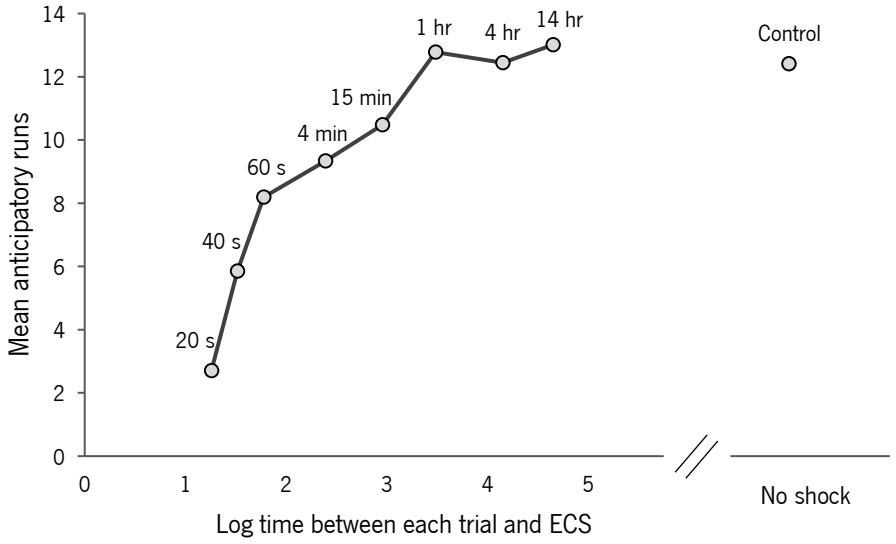


FIGURE 2. Duncan's (1949) findings: higher interference with learning as the trial-shock interval becomes shorter, Mean anticipatory runs across 18 training trials as a function of the delay between trial and ECS. Adapted from Duncan (1949).

Ducan's work motivated many researchers to examine the time course of memory consolidation by the use of ECS-induced retrograde amnesia (e.g., Thompson & Bryant, 1955; for reviews see Glickman, 1961; McGaugh, 2000).

However, several f replication failures of the aforementioned Müller and Pilzecker's findings (e.g., McGeoch, 1933, reviewed and analyzed in Wixted, 2004) led the field of psychology to lose interest in the concept of consolidation. Moreover, experimental psychology has relied on interference theory to explain the impaired retention of the initial material. According to the interference theory, memories acquired close together compete at the time of retrieval. This theory accounts for Müller and Pilzcker results, as well as it provides an explanation for the moderator influence of the similarity between interfering and target information. However, for biological and neuroscience-oriented studies, the concepts of memory consolidation and perseveration remained essential to the study of memory and learning.

Thus, the understanding of the biological substrates underlying memory acquisition had a remarkable growth in the XX century. What started as simply pseudo-neurological speculations, as in DeCamp (1915):

> From the neurological standpoint, in the learning of a series of syllables, we may assume that a certain group of synapses, nerve cells, nerve paths, centres, etc., are involved. Immediately after the learning process, the after-discharge continues for a short time, tending to List associations between just learned syllables. Any mental activity engaged in during this after-discharge, involving or partially involving the same neurological group, tends, more or less, to block the after-discharge, and give rise to retroactive inhibition. (p. 62)

was later supported by dual-trace theory for memory formation proposed by Donald Hebb (1949). In a series of experiments, Hebb had identified structural changes that suggest the role of protein synthesis in memory storage. This theory was a shift in the approach memory consolidation and is considered a hallmark of memory research. Thenceforth, a frequent approach to study the structural changes for the persistence of information in LTM, involve the use of pharmacological protein-synthesis inhibitors (PSIs), such as anisomycin and cycloheximide (for reviews see Barraco & Stettner, 1976; Davis & Squire, 1984).

A great body of research leads to the conclusion that is depicted, for an illustrative case, in Figure 3. In this experiment, Schafe and LeDoux (2000) examined if the administration of a PSI, or an inhibitor of protein kinase A (PKA) activity, interfere with the consolidation of a fear conditioning memory. After an auditory pavlovian fear conditioning training, which consisted in several pairings of tone (Conditioned Stimuli, CS) - footshock (Unconditioned Stimuli, US)], rats received infusions of anisomycin (a PSI) or Rp-cAMPS (an inhibitor of PKA activity) in the lateral nucleus of the amygdala. These two experimental groups were contrasted with an artificial cerebrospinal fluid (ACSF)-injected control group. Fear responses, indexed by the percentage of freezing, were measured when the CS (tone) was presented after training (STM) and 24 hours later (LTM). The results revealed that the administration of such drugs (anisomycin or Rp-cAMPS) impaired the consolidation (fixation) of memories: although groups did not differ in STM test, LTM was impaired. Importantly, the administration of such drugs did not damage fear conditioning systems, as both groups were able to reacquire fear when they were reconditioned one week later. Thus, these results revealed the role of the lateral amygdala in the acquisition of a fear conditioned

memory, as well demonstrate that memory consolidation is a PKA and protein-synthesis dependent process.

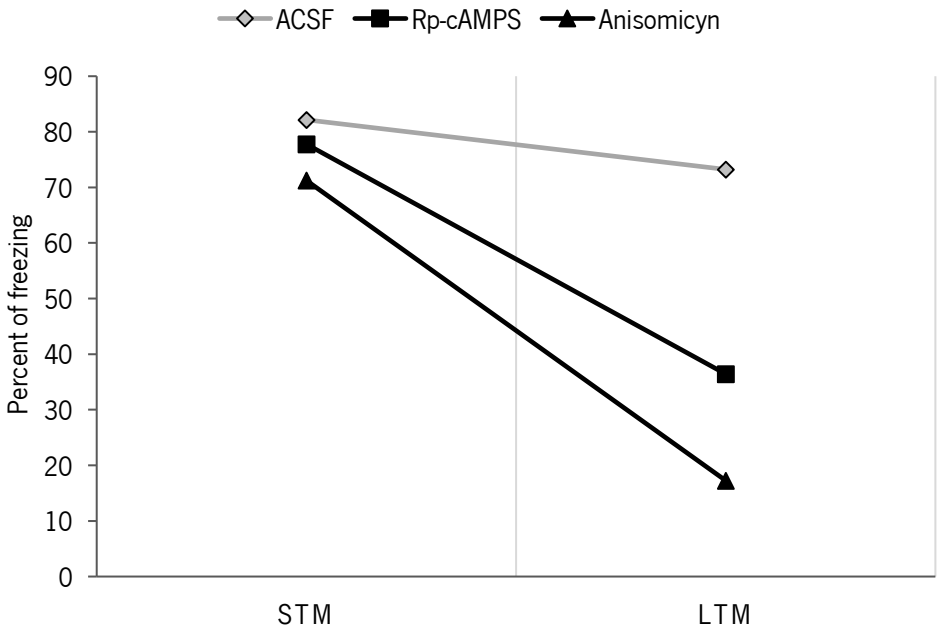


FIGURE 3. Findings of Schafe and LeDoux (2000). A demonstration of consolidation blockage: applying anisomycin or Rp-cAMPS after fear conditioning has no impact in STM but impaired LTM. Adapted from Schafe and LeDoux (2000).

Schafe and LeDoux (2000) have also found that the administration of anisomycin or Rp-cAMPS 6 hours after training had no effect on fear retention.

The above-mentioned results summarize the two important aspects of consolidation theory, namely: (a) immediately after acquisition memory is highly vulnerable to interference, (b) the process of memory consolidation is time-dependent. Regarding the former, there are several studies that manipulate the delay between acquisition and post-acquisition interventions, showing a time-dependent effectiveness of the interventions. For instance, memory performance can be impaired by amnesic treatment (ECS: Duncan, 1949; protein synthesis inhibitors: Flexner, Flexner, & Stellar, 1965; new learning: Gordon & Spear, 1973) or enhanced by certain compounds (strychnine: McGaugh & Krivanek, 1970), when they are administered immediately after learning. Critically, the influence of such manipulations was only observed when they were applied soon after learning and not after a delay. This empirical evidence gave rise to the conceptualization of memories according to two states: a labile and a stable state. The labile state represented an initial phase of the memory trace, which is highly vulnerable to amnesic treatments. In turn, the stable

state corresponded to an immune state, insensible to the amnesic treatments (Dudai, 1996, 2004; McGaugh, 1966). The amnesic agents are only effective if given within a relatively restricted time window near the time of training, when the memory trace is still in an active state, and the memory system is enrolled in the fixation of that memory (Bourtchouladze et al., 1998; Davis & Squire, 1984; Schafe, Nadel, Sullivan, Harris, & LeDoux, 1999). Additionally, the consequences of post-acquisition interventions are expressed in a long-term test (when the process of consolidation is finished), and not immediately (Dudai, 1996; Glickman, 1961; McGaugh, 1966).

Today, the textbook account for cellular consolidation states that in the course of encoding (training), or immediately after it, molecular cascades elicit changes in neurons' properties, allowing the memory trace to persist in the long term. In other words, consolidation refers to a process that leads to the permanent storage of newly acquired information (Glikmann, 1961). Additionally, cumulative evidence has been found regarding the need for a continuous maintenance of memories in LTM, expressed in terms of constant phosphorylation by the protein kinase Mζ (Pastalkova et al., 2006; Sacktor, 2008). It is worth noticing that the term "consolidation" is currently used in neuroscience field to designate two distinctive processes (Dudai, 1996, 2004; Dudai & Morris, 2000): (a) system consolidation, which expresses the overtime reorganization of brain circuits and the transition of its dependence on parts of the circuits that have sub-served memory acquisition (for instance, hippocampal-depended memory becomes hippocampal-independent over time; Kim & Fanselow, 1992; Scoville & Milner, 1957; Squire & Alvarez, 1995); (b) synaptic consolidation , which refers to the changes in synaptic efficacy that occurs within the first minutes to hours after encoding (Dudai, 2004; Kandel, 2001; Martin, Grimwood, & Morris, 2000). Although at a different level of analysis, both fields support the idea of a time-dependent process of stabilization of memories.

In sum, a rich biologically-oriented research conducted across species, paradigms, and post-acquisition interventions (ECS, PSIs; also hypothermia, hypoxia, convulsant drugs, and brain lesions; for a review see McGaugh & Dawson, 1971) robustly supports the idea of a consolidation process. The effectiveness of post-acquisition interventions progressively decreases over time: initially, memories are highly susceptible to its effect, to the point that they eventually become immune (once consolidation process is complete). This process reflects the fixation of memories in a long-term memory format (McGaugh, 1966, 2000).

The next section of this chapter is dedicated to examining some findings that questioned the consolidation theory predictions and to presenting the empirical backbone for reconsolidation theory.

2.2 Challenges to consolidation theory: The birth of reconsolidation theory

As stated in the previous section, consolidation theory claims the existence of a time-dependent process, responsible for the structural fixation of memory traces in a long-term storage. Memory plasticity is conceptualized in a one-way road: from a labile STM state to a fixed LTM state. Thus, the consolidation theory made (at least) two important empirical predictions: manipulations that interfere with the normal fixation of memories should result in permanent disruptive effects (Prediction A); only newly acquired information is vulnerable to amnesic agents, thus if no intervention is applied during the normal course of memory formation, memory traces become immune to alterations (Prediction B).

However, these predictions were early questioned. Almost contemporary to consolidation theory formulation, the conceptualization of amnesia as a failure to consolidate newly acquired information (McGaugh, 1966) was challenged (Prediction A). Great contributions were made by Spear (1973), and by Miller and Springer (1974) who argued that a lack of recovery does not prove that recovery is impossible. The authors claimed for the importance of retrieval deficits explanations in forgetting and amnesia. The debate was empirically supported by experiments which found that the exposure to specific reminders could induce recovery from amnesia (e.g., Hinderliter, Webster, & Riccio, 1975; Miller & Springer, 1972; for a review see Riccio, Richardson, & Ebner, 1984), an effect that became known as *reminder effect or reminder-induced recovery*. A pioneering study developed by Koppenaal, Jagoda, and Cruce (1967) revealed that the presentation of a reminder (brief presentation of US- footshock) before the test session, led to the recovery of an ECS-induced amnesia. This finding was later replicated (e.g., Geller & Jarvik, 1968; Lewis, Misanin, and Miller 1968; for a review see Miller & Springer, 1973). The reminder-induced recovery was also observed for cases in which ECS (Geller & Jarvik, 1968; Koppenaal et al., 1967; Miller & Springer, 1972) or PSIs (e.g., Quartermain, McEwen, & Azmitia, 1970; Radyushkin & Anokhin, 1999; Squire &

Barondes, 1972) were used as the amnesic treatment. Also, different reminders (rather than the unconditioned stimuli; US) proved to be effective. Some behavioural reminders, as the re-exposure of the training context (e.g., Sara, 1973), the single presentation of CS (extinction trials) prior to the test (Gordon & Mowrer, 1980), or even repeated tests (Sara, 1973; Schneider, Tyler, & Jinich, 1974; Zinkin & Miller, 1967) also proved to be effective. Also, the presentation of the amnesic treatment itself resulted in the amnesia recovery (Hinderliter et al., 1975; Thompson & Neely, 1970). For instance, hypothermia-induced amnesic rats, recovered their memory if they were re-exposed to the amnesic agent (cooled 2 hours prior to the test; Hinderliter et al., 1975).

In fact, along with reminder-induced recovery studies, there was further evidence against the predictions derived from consolidation theory, with the demonstrations of recovery from experimentally-induced amnesia due to the passage of time (for reviews see Lewis & Maker, 1965; Miller & Matzel, 2006; Miller & Springer, 1973; Riccio & Richardson, 1984; Spear, 1973). Similar to *spontaneous recovery*, observed in extinction and counter-conditioning (Bouton, 2002) the effects of experimentally-induced amnesia could dissipate over time. For instance, studies in non-human animals found that an ECS applied immediately after training, led to a memory impairment (tested 24 hours later the intervention). However, when tested 48 hours or 72 hours later, a substantial recovery was observed (Zinkin & Miller, 1967). Also, Young and Galluscio (1971), applied ECS immediately after training and tested the memory 24 hours or 10 days after the treatment. In the former, rats showed amnesia (a reduced suppression of the lever press response). However, in the later, an apparent spontaneous recovery was observed: the group did not differ from another that did not receive any treatment after training. Squire (1975) found that memory loss was temporary in a human paradigm. Here, depressive patients received ECS to alleviate the unwanted symptoms and were invited to enumerate TV shows of the last decades. The authors found an amnesia for the last three years. However, in follow-up sessions (1-2 weeks later), memory was recovered. So, a number of studies have shown spontaneous recovery of memory in animals previously classified as amnesic (Cooper & Koppenaal, 1964; Kohlenberg & Trabasso, 1968; for a review see Davis & Squire, 1984). However, other researchers failed to replicate these findings (Herz & Peeke, 1968; Luttges & McGaugh, 1967).

Overall, this set of studies that called the attention that experimentally-induced amnesia cannot be conceived as a failure of memory fixation, as proposed by consolidation theory (Prediction A). Therefore, the nature of amnesia was reconsidered due to the gathered evidence showing that memory retrieval depends on memory state at the time of retrieval, and thus a

memory can return to expression if the appropriate conditions are re-created at retrieval (Spear, 1973). In the same vein, amnesia could be understood as a consequence of inaccessibility to stored information and not a storage impairment.

> As an analogy, consider the acquisition of a new book by a library. Placing the book on a shelf may be viewed as equivalent to consolidation and making the appropriate entry in the card catalog could be considered a retrieval function, one that must be performed soon after acquisition. Without the appropriate entry in the card catalog, the book may be physically present in the library but not available on request. (Miller & Springer, 1973, p. 71)

In this analogy, it is clear the concern with the interpretation of amnesia as a storage-based impairment. The claim of "gone, but not forgotten" (Riccio & Richardson, 1984), which is closely related to Tulving's distinction of a memory that can be available but inaccessible (e.g., Tulving & Arbuckle, 1966; Tulving & Psotka, 1971), seemed appropriate to conceptualize experimentally-induced amnesia. However, this approach was not consensual at the time (Cherkin, 1972; Gold & King, 1974; Squire, 2006), and even after decades of debate, no resolution to this issue was found (Miller & Matzel, 2006; Nader & Hardt, 2009; Nader & Wang, 2006; Riccio, Millin, & Bogart, 2006; Sara & Hars, 2006).

Critically, Misanin, Miller, and Lewis (1968) published a seminal paper identifying the conditions under which ECS produces amnesia for well-consolidated memories (calling into question Prediction B). The procedure was as follows: at a first stage, animals learned to drink from a drinking tube and, once the behaviour was well established, a cue was presented (CS) followed by a foot shock (US). In the following trials, the presentation of CS led to the cessation of the response. Then, five groups of rats were compared. In group 1, ECS was administered immediately after training. In group 2, a CS was briefly presented 24 hr after training (memory was reactivated) and an ECS was administered immediately after. In group 3, memory was reactivated but no intervention was applied (no ECS). In group 4, an ECS was administered without memory reactivation. Finally, group 5 served as a control group, with no intervention. In a third session (24 hr later), all groups had to perform a test session in which CS was presented. Results are displayed in Figure 4.

The comparison between groups 1 and 4 replicated the typical finding of retrograde amnesia: the administration of an ECS immediately after acquisition led to amnesia (indexed by a

higher rate of licking) and ECS delivered after a 24 hr delay did not. However, the presentation of a reminder (CS) 24 hr after training, immediately followed by an ECS (group 2) resulted in a profound amnesia. The amnesia observed in group 1 (in which consolidation was disrupted), was comparable to the amnesia observed in group 2 (the group that reactivated the memory and suffer an intervention). Importantly, the effect could not be attributed to extinction promoted by the presentation of CS because the group that reactivated the memory without any subsequent intervention (group 3) showed only a small decline in performance. In sum, the reactivation or the administration of an ECS, *per se*, did not interfere with memory (equivalent performance in group 3, group 4 and group 5). These findings led the authors to conclude that "apparently, the primary determinant of amnesia for an event is not the 'recency of memory' for the event, but the state of the corresponding memory trace at the time of ECS" (p. 555).

Misanin and colleagues (1968) proposed the concept of memory state, which was later formalized by Lewis (1979). They suggested that the intervention could produce memory impairment by "interfering with a trace in transit from stored to active memory" (p. 555), which implies a process for which consolidation theory does not account for. A process from stabilization to destabilization (which it is eventually followed by another stabilization process).

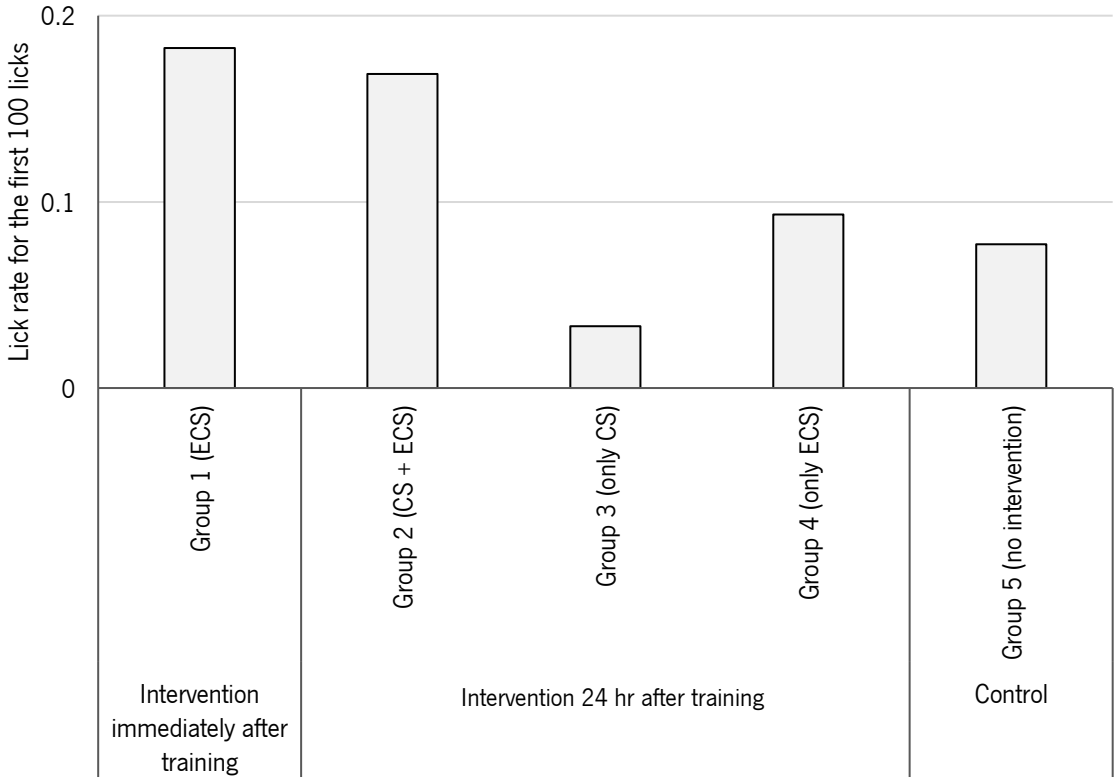


FIGURE 4. Mean lick rate [(1/sec) x 100] for the 100 licks before CS onset. Amnesia is indexed by a higher lick rate. Adapted from Misanin, Miller, and Lewis (1968).

The finding that ECS acted as a blocker of an active memory rather than a blocker of a newly acquired memory, started the investigation of amnesia for well-consolidated memories, commonly referred as *cue-dependent amnesia* (Lewis, 1976). Subsequent studies found evidence for cue-dependent amnesia in different paradigms (appetitive conditioning : Lewis, Bregman, & Mahan, 1972; Lewis & Bregman, 1973; fear conditioning: Devietti & Holliday, 1972; active/passive avoidance conditioning: Gerson & Hendersen, 1978; Mactutus, Ferek, & Riccio, 1980), intervention types (ECS: Devietti & Holliday, 1972; Gerson & Hendersen, 1978; Lewis et al., 1972; Schneider & Sherman, 1968; pharmacological agents: Davis & Klinger, 1969; Judge & Quartermain, 1982; hyperthermia and hypothermia: Mactutus et al., 1980), and different memory reactivation procedures (memory cues: Lewis et al., 1972; specific conditioning cues but not others: Devietti & Holliday, 1972; Gerson & Hendersen, 1978; exposure to the training apparatus: Judge & Quartermain, 1982; US: Mactutus et al., 1980; Schneider & Sherman, 1968).

Importantly, as the post-acquisition amnesic effects of memory consolidation, cue-dependent amnesia also appeared to be temporally graded (in other words, the susceptibility for memory to disruption decreases over time following reactivation; e.g., Judge & Quartermain, 1982; Mactutus, Ferek, George, & Riccio, 1982; Richardson, Riccio, & Mowrey, 1982).

To sum up, in the late 60's, researchers questioned an important postulate of the consolidation theory: the idea that consolidation process leads to the permanent storage of a memory (for a review see Riccio et al., 1984). The studies reviewed in this section revealed evidence for spontaneous recovery and for reminder-induced recovery, suggesting that experimentally-induced amnesia does not correspond to the prevention of storage (disruption of memory consolidation). On the contrary, it is suggested that amnesia corresponds to an impairment of performance due to a problem of accessibility to the information and that a memory could be inaccessible in a given moment and later become accessible (Miller & Matzel, 2006; Riccio, Millin, & Gisquet-Verrier, 2003). Also, studies on cue-dependent amnesia revealed that a well-consolidated memory can become susceptible again to "amnesic" treatments after its reactivation (e.g., Mactutus et al., 1982; Mactutus, Riccio, & Ferek, 1979; Misanin et al., 1968). Together, these findings opened a new perspective on the nature of long-term memory: unveiling its dynamic, rather than static, nature. Memory plasticity was just paused when the memory was not being used. Therefore, new theories of memory were proposed (Lewis, 1979; Miller & Springer, 1973; Spear & Mueller, 1984).

Lewis (1979) proposed a memory model assuming memory to oscillate between two states: an active and an inactive state. The inactive state comprised the memories that were not being used and remained immune to modifications. The reactivation of a memory, turned an inactive memory into an active one. The active state was also used to describe the state of a new memory. When in an active state, memories are susceptible to modifications. This model proposes that the distinction between active and inactive memory does not imply different stored locations and adopted a more functional conceptualization of memory states.

This perspective outlines that the temporal gradient of retrograde amnesia was misattributed to the age (new memories as susceptible to modifications, while old memories as resistant to such modifications), when it should be attributed to the memory state. Memory modifications appear to be with mechanisms beyond the initial stage into a permanent storage. Figure 5 contrasts the perspective over memory stability and memory retrieval claimed by consolidation theory and reconsolidation theory.

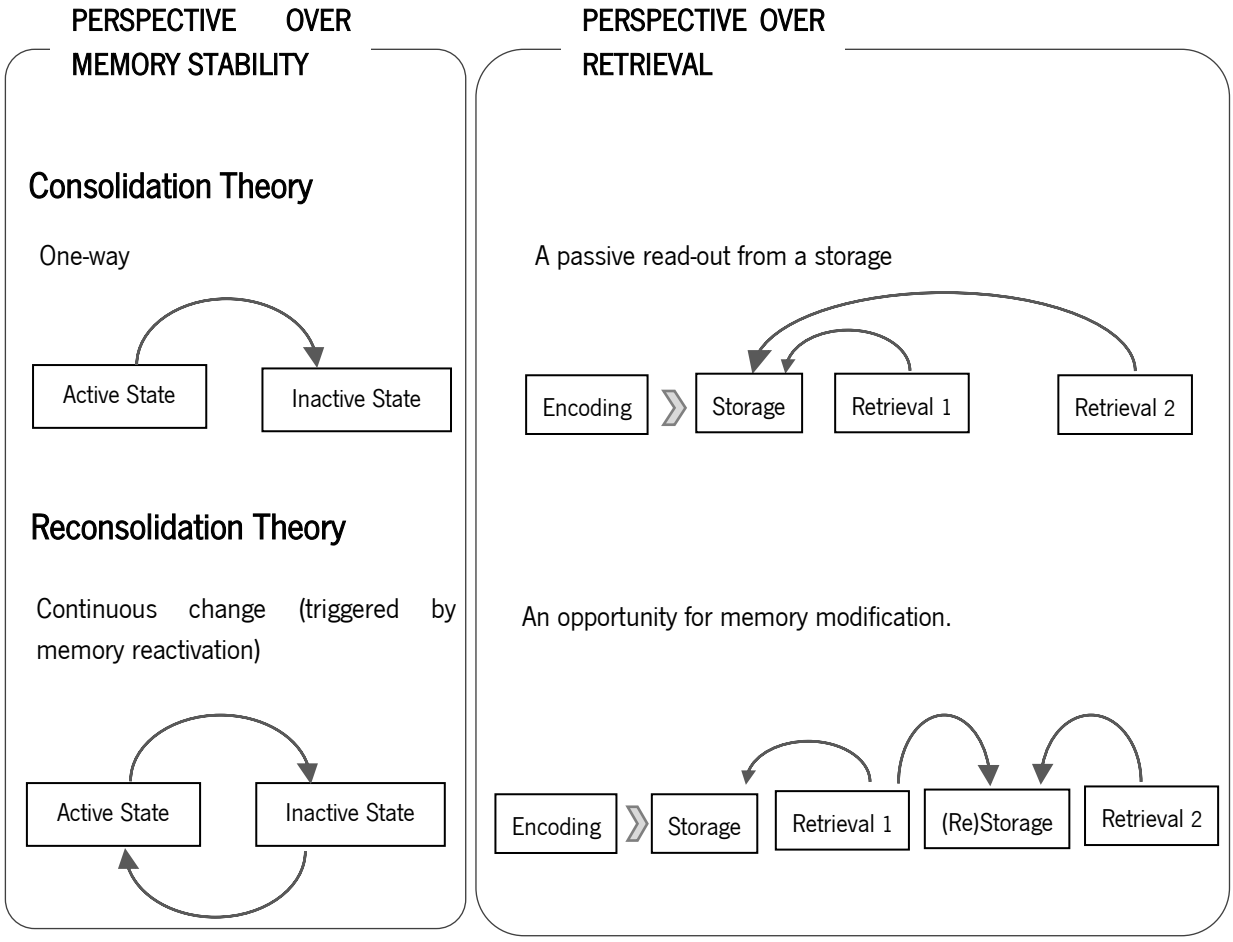


FIGURE 5. Summary of consolidation and reconsolidation theory.

Although backed by well-replicated findings, Lewis's theory was considerably unrecognized. Thus, together with the concept of memory malleability, introduced in cognitive psychology at least since Bartlett (1932), the evidence for plasticity of consolidated memories was pushed aside by consolidation theory. The reasons for that remain unclear (Dudai, 2004), however we speculate some of the reasons behind it:

- Early replication difficulties: The evidence for spontaneous recovery and reminder-induced recovery was overshadowed by a less documented reports of cases in which spontaneous recovery was not observed. Also, some researchers did not find cue-dependent amnesia effects (Banker et al., 1969; Dawson & McGaugh, 1969; Gold & King, 1972; Jamieson & Albert, 1970; Squire et al., 1976);
- Alternative interpretations: Some authors argued that demonstrations of recovery from amnesia did not rule out the consolidation hypothesis. The argument was based on the idea that the amnesic agent did not have to act in an all-or-none fashion, and that the reminder treatment may be a learning opportunity, leading to a residual memory to rise above the threshold of behavioural expression (Cherkin, 1972; Gold & King, 1974). Although the argument seems plausible to situations in which the US is used as a reminder, it is weakened when also CS is used as a reminder. These cases represent an extinction trial, so it is expected to see an impairment in performance and not a recovery. Additionally, the administration of psychostimulant (e.g., strychnine: Gordon & Spear, 1973; Sara & Remacle, 1977; amphetamine: Quartermain, Judge, & Jung, 1988) before the memory test, lead to a decrease in experimentally induced amnesia, a finding that is not associated to the CS-US contingency;
- Advances in neuroscience: This period was also marked by relevant findings in the understanding of the cellular mechanisms underlying memory storage. For instance, in 1973, Bliss and Lomo proposed a model of synaptic plasticity that caught the attention of neuroscience.

Thus, an influent research field was devoted to the understanding of memory consolidation along with many researchers that were searching for what has been considered the "holy grail" of memory research: the engram (Axmacher, 2016; Lashley, 1950), the unique trace of an experience in the brain. Regarding the studies conducted in cognitive psychology that favour the reconstructive nature of memory, proponents of the consolidation hypothesis established a distinction between the postulated immutability of consolidated memories and the dynamic nature of behaviour

(McGaugh, 1966). Consolidation theory continued to shape much of memory research across different research fields until the early scepticism returned to the spotlight at the beginning of XXI century. The next chapter is precisely dedicated to the revival interest on reconsolidation theory.

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Chapter 3. The revival of reconsolidation theory

It is somewhat ironic that this once minority opinion has become the new de facto standard within the past 12 years, (...).

(Nader, 2013, p. 1)

3.1 Introduction

The term *reconsolidation* was introduced by Spear (1973, p. 188) in a seminal review paper regarding the evidence against consolidation theory's predictions, emphasizing its failure to account for cue-dependent amnesia and recovery effects. However, the concept of reconsolidation was mentioned almost in a passing, briefly mentioning that memory (may) "reconsolidate anew" in cases of successive learning trials or related experiences. For the reasons explored in the previous chapter, there was a period of stagnation of research on this topic. Thus, the concept of reconsolidation was only clearly specified in a later work of Sara and colleagues (Przybyslawski & Sara, 1997; Sara, 2000), in which reconsolidation appears as a process that a reactivated memory has to undergo. In this paper, reconsolidation is described as a recapitulation of a process that new memories are submitted, as follows: "memory is reconsolidated, so to speak, each time it is retrieved, and these reconsolidation processes are dependent on the NMDA receptor for at least 2 h after the reactivation" (Przybyslawski & Sara, 1997,p. 245).

In 2000, three major articles emerged, renewing the interest in the investigation of the fate of long-term or consolidated memories.

A first contribution was made by Sara (2000) in a paper entitled *Retrieval and reconsolidation: toward a neurobiology of remembering*. This paper provided a rich revision of the biological mechanisms underlying memory. Reconsolidation was defined as a process that allows the re-organization of reactivated memories, and reactivation was described as a trigger for cellular processes that also occur after memory acquisition (Przybyslawski, Roullet, & Sara, 1999; Przybyslawski & Sara, 1997; Roullet & Sara, 1998).

A second contribution was made by Land, Bunsey, and Riccio (2000), with two experiments that examined the consolidation theory's interpretation of hippocampal lesion-induced retrograde amnesia. The results were incompatible with consolidation theory: rats that were reminded of an old memory prior to the amnesic treatment (hippocampal lesion), showed amnesia (Experiment 1); however, a reactivation treatment reversed retrograde amnesia: when amnesic rats were presented to a part of the training treatment (reactivation) a memory recovery was observed (Experiment 2).

A third and well-recognized investigation was conducted by Nader, Schaffe, and LeDoux (2000). This paper is the one that has been acknowledged to bring a renewed interest on the topic of cue-dependent amnesia, and reconsolidation theory. For that reason, we will provide a detailed description of it. See Figure 6 for a full description of Nader and colleagues' experiments and findings.

Inspired by cue-dependent amnesia studies, Nader and collaborators (2000) aimed to examine if the reactivation of a memory could induce a new labile state. The procedure was as follows: twenty-four hours after the auditory fear conditioning training [several pairings of tone(CS)-footshock(US)] memory was reactivated by the presentation of the CS (tone). Immediately after reactivation, rats were injected with a high or low dose of anisomycin (a PSI) or with a vehicle (ACSF) in the lateral and basal nuclei of the amygdala (a brain region known to be involved in fear learning). Memory was tested in two moments: (a) Test 1: immediately after intervention; (b) Test 2: 24 hours after the intervention. In each test, the CS was presented to the animals, and a freezing response was used as an index of fear learning. Results from Test 1 revealed that the fear response to the CS was comparable across groups, so STM was intact. Importantly, the administration of anisomycin led to a dose-dependent decrease in freezing: although the group that had a low dose of anisomycin did not differ from the control group (ACS), the high dose group revealed a significantly lower fear response. In sum, evidence was gathered for the existence of consolidation-like process triggered by memory reactivation. Considering the results, the authors

drop the "low dose" group, and the following experiments contrasted the "high-dose" with the control group (ACSF group). In a second experiment, it was examined if Experiment 1's results could be due to non-specific effects, such as damage of amygdala by the administration of the drug. The procedure was similar to Experiment 1 however, memory was not reactivated before administration of the drug. Results revealed a normal conditioned fear response both in Test 1 and Test 2. Thus, the treatment with anisomycin *per se* could not account for the lower fear response of anisomycin-group in Test 2: the administration of the drug in the absence of memory reactivation left memory intact. In a third experiment, the authors took a step further in the understanding of reconsolidation as a recapitulation of consolidation. Previous studies on consolidation (Duncan, 1949; McGaugh, 1966), had defined a discrete time-window during which post-acquisition treatment could efficiently disrupt memory consolidation. Nader and collaborators (2000) asked if the same principle could be applied for reconsolidation. Here, the administration of anisomycin was delayed 6 hoours after memory reactivation. The results revealed no differences between anisomycin and control group, leading to the conclusion that (like consolidation) the post-reactivation re-stabilization process is probably time-dependent. A subsequent experiment tested if reconsolidation process had a temporal gradient: if older memories would be more resistant to becoming fragile after its reactivation. In this experiment a similar procedure was used, however the time between conditioning and testing was delayed 14 days. Although Test 1 performances were similar in both groups, there was not the case for Test 2: rats that had infusions of anisomycin showed a significantly lower fear response. Hence, even well-consolidated memories were subject to modifications when reactivated. The last experiment, intended to examine the performance of the rats shortly after the intervention. This study was inspired by other studies on consolidation, which showed that when an amnesic treatment was applied after training, memory was intact shortly after the intervention, but impaired later on. The purpose was to see if there was evidence to claim for a manipulation that acted on the molecular mechanisms that are involved in memory consolidation, rather than a non-specific effect. It was hypothesized that the administration of the amnesic treatment after memory reactivation, should result in a normal fear response after 4 hours (Post-Reactivation Short-Term Memory – PR-STM), but diminished after 24 hours (Post-Reactivation Long-Term Test- PR-LTM). Results revealed that freezing response of anisomycin and control group was comparable in PR-STM. However, in PR-LTM, anisomycin group revealed a significant decrease in fear response. This result suggested that amygdala is functional in a period

close to the intervention (rats exhibited the fear response in PR-STM), and that the drug acted on the molecular mechanisms of memory (re)storage.

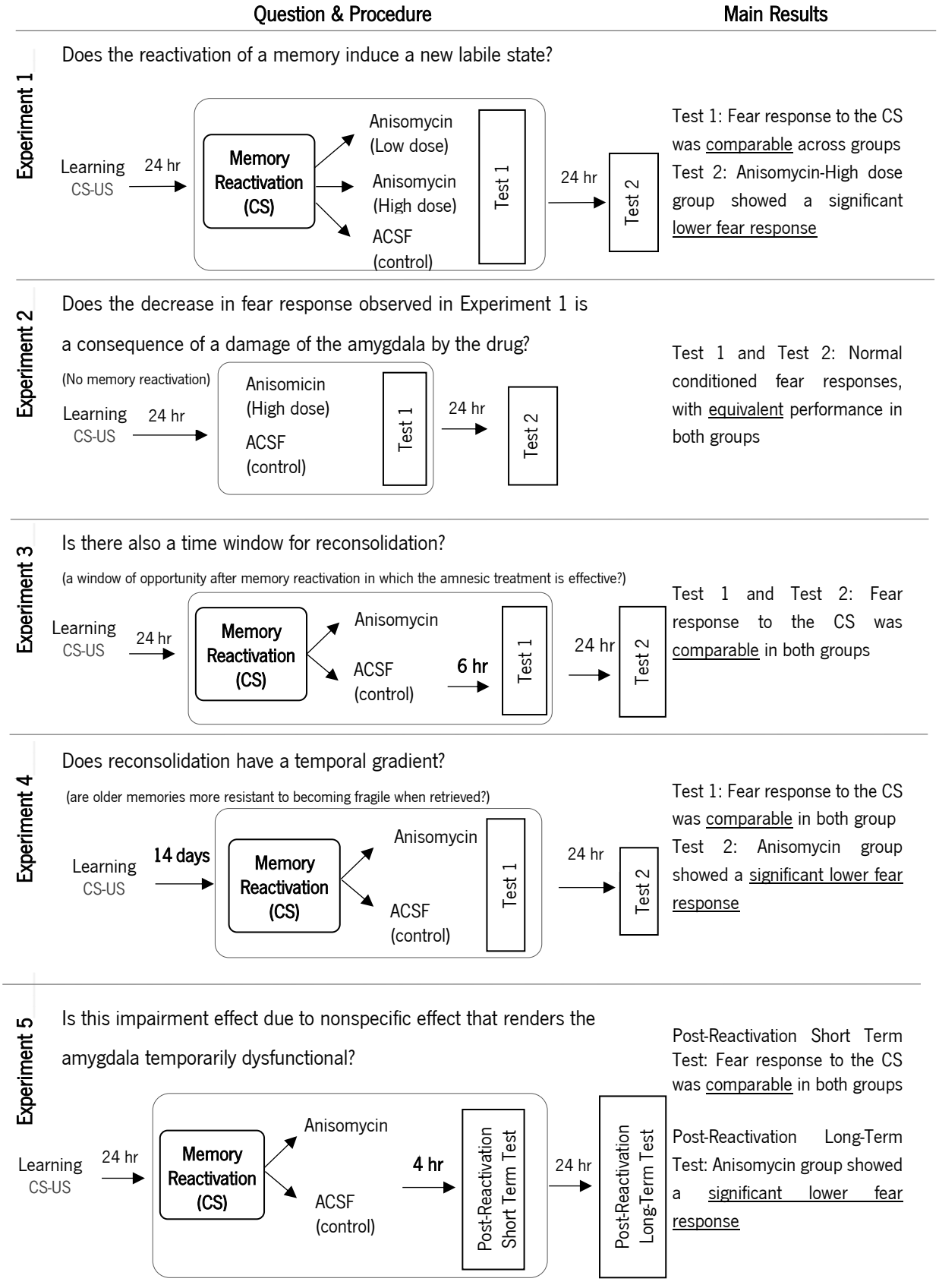


FIGURE 6. Full description of Nader and collaborators (2000) experiments.

This paper promoted a remarkable rediscovered of the amnesia for well-consolidated memories, and several conclusions can be drawn from it. Some of those conclusions, include aspects that are nowadays considered hallmarks of reconsolidation theory:

1. A consolidated memory is insensitive to an amnesic treatment, unless it is reactivated. The reactivation of a consolidated memory renders a memory trace susceptible to amnesia;
2. The observation of an intact STM and impaired LTM implies that a consolidation-like process is triggered by memory reactivation;
3. Reconsolidation is a time-dependent process: the amnesic treatment only produces the amnesic effect when is given soon after memory reactivation, and it is absent when longer delays are implied (e.g., 6 hr delay).

Underlying these findings is the idea that memory reactivation returns the memory trace to a labile state, which will be followed by a *de-novo* process of stabilization (Nader & Hardt, 2009; Tronson & Taylor, 2007).

Consolidation and reconsolidation theory both bear on the evidence of a momentary period of vulnerability or instability, but the theories diverge on the definition of its onset. According to consolidation theory, a window of vulnerability is initiated immediately after memory acquisition. According to reconsolidation theory, this window is initiated when a memory is in an active state. In turn, the active state refers to the state that characterizes newly acquired memories and reactivated memories. As so, reconsolidation maintains the explanatory coverage of consolidation theory, and accommodates demonstrations of cue-dependent amnesia which, in turn, appeared as evidentiary lines that undermined consolidation theory's validity. As in the case of consolidation, only during the re-stabilization phase, memory can be impaired by amnesic agents (Misanin, Miller, & Lewis, 1968) or by new learning (Gordon, 1977a) or it can be enhanced (Gordon, 1977b; Rodriguez, Rodriguez, Phillips, & Martinez, 1993). Critically, after memory reconsolidation these treatments are ineffective.

Although Nader and collaborators cautiously referred in their paper that "It is possible that not all memories require reconsolidation" (Nader et al., 2000, p. 725), following studies suggested that this is not the case. The phenomenon was taken seriously by the research community, and a considerable amount of studies have flourished, providing evidence for a post-reactivation memory modification across different species. The phenomenon was broadened to invertebrates and vertebrates, aversive and reward conditioning and simple to more complex learning. The large number of studies published in this area (Alberini, 2007; Besnard, Caboche, & Laroche, 2012;

Dudai, 2006) preclude presenting all of them, so we have selected some examples with different species and protocols in Appendix 1.

Over the last years, and up to the present time of writing, research on reconsolidation process has been growing at different levels of analysis, in order to get a better understanding of the transient malleability of post-reactivated memories. For instance, researchers were able to find cellular correlates of the behaviourally shown reconsolidation impairment, which had led to the proposal of a cellular model of reconsolidation (e.g., Fonseca, Nägerl, & Bonhoeffer, 2006). Additionally, studies have been demonstrating that the disruption of reconsolidation reverse, in a time-dependent fashion, the cellular and molecular signatures of well-consolidated memories (e.g., Doyère, Dębiec, Monfils, Schafe, & LeDoux, 2007; Rose & Rankin, 2006). Thus, now reconsolidation is firmly established as a time-dependent re-stabilization process that is triggered by the reactivation of a consolidated memory (for general reviews see Alberini, 2011; Besnard et al., 2012; Dudai, 2004, 2012; Nader, 2015; Nader & Hardt, 2009; Tronson & Taylor, 2007).

This massive research interest has resulted in the definition of an appropriate procedure to study memory reconsolidation, which has been applied across different research fields. Thus, reconsolidation processes are typically studied with a three-day experimental design (Figure 7). Typically, an interval of at least 24 hr is applied between each experimental day[1]. On the first day, learning takes place. On the second experimental day memory is reactivated and an intervention is applied. This intervention is used to interfere with the reconsolidation process (e.g., pharmacological agent that inhibit the synthesis of proteins), so it is commonly applied within the timeframe of the "reconsolidation window". The experimental group (referred as reactivation group in Figure 7), the one that has memory reactivation and intervention, is contrasted with two control groups. The most conventional control group is the one that does not reactivate the original memory but suffers the intervention (control group$_{Reactivation}$). The comparison with the reactivation group with this control group would test if the effectiveness of the intervention depends on the previous

[1] The time interval of, at least, 24 hr is used as a "rule of thumb", to ensure that consolidation-like processes had time to be completed or, in other words, that consolidation window has closed (Dudai, 2004). This methodological approach has been used since the beginning of the reconsolidation studies (Misanin et al., 1968), raised from the need to ensure that the processes underlying memory consolidation were complete, and perhaps because of the lack of precise methods to study the consolidation windows at that time. However, the use of shorter time interval could also be valid, on the basis of an operational demonstration that the consolidation window has closed (e.g., 6 hr see Tronson & Taylor, 2007). Nevertheless, considering the role of particular stages of sleep for consolidation and reconsolidation (e.g., Stickgold & Walker, 2005), the interval of 24 hr is commonly applied.

reactivation. The other control group (control group$_{Intervention}$) does not receive the intervention or receives it after a delay. In the third experimental day, a test for the original memory is conducted. Modifications in trace-dependent performance in the experimental group are taken as evidence for reconsolidation.

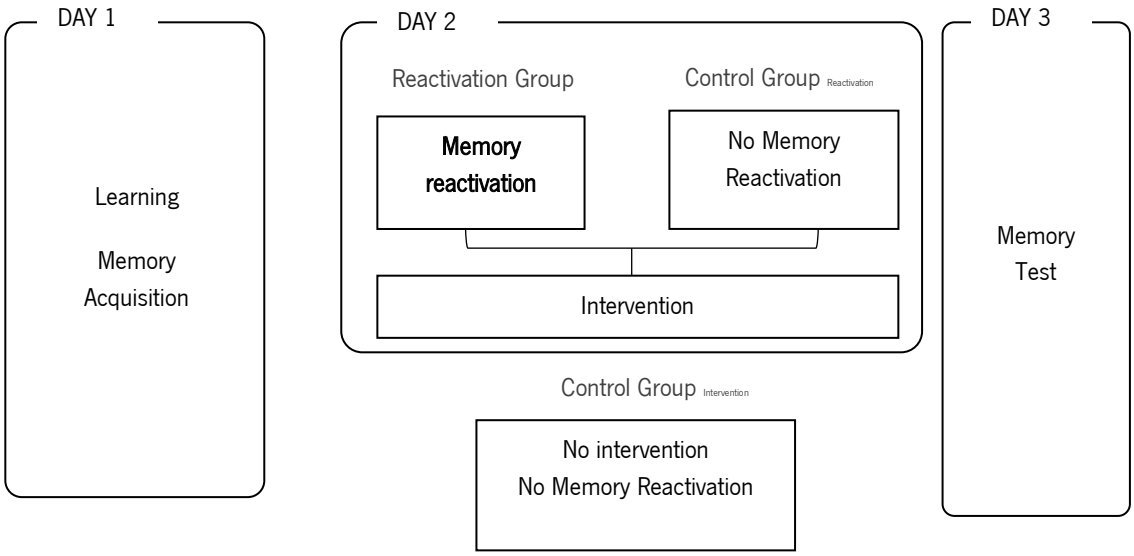


FIGURE 7. Typical three-day experimental design for the study of reconsolidation.

3.2 Translational research

The investigation of reconsolidation hypothesis in humans attracted researchers' attention from early on. The first translational study applied a cue-dependent amnesia paradigm to the clinical scope, more specifically, on patients suffering from obsessive-compulsive disorder (OCD) and hallucinations (e.g., Rubin, 1976). Rubin hypothesized that the reactivation of the maladaptive memory (e.g., fear of contamination) could open an opportunity to disrupt it. The reactivation of the memory was achieved by prompting the patients to think on the subject matter of their psychopathology. After memory reactivation, an ECS was administered (as in an animal protocol). The results revealed that patients' OCD symptoms were altered. Squire, Slater, and Chace (1976) tried to extend the consequences of memory reactivation on patients suffering from depression. However, contrarily to previous findings in animals, the authors failed to find evidence for memory disruption when an ECS is delivered after the reactivation of a declarative memory. Squire and

colleagues argued that the reason for such discrepancy rely on the memory systems involved, namely episodic versus emotional associative memories (in animal studies): declarative memories' research cannot be confounded by arousal and motivational state. Also, the authors claimed that human subject is not under the same arousal or motivation as animals (which used foot shocks or hunger to motivate learning), arguing that previous studies are only measuring interactive effects of ECS and arousal on performance, but not a memory phenomenon. So, they concluded that cue-dependent amnesia is not a general characteristic of memory, and it may only occur under limited experimental conditions. Despite this initial scepticism and criticism, the interest on reconsolidation of human memory have gained considerable traction throughout the last decades.

In fact, the growth in the research of human reconsolidation process has accompanied the growth in the animal field, although at a considerably smaller rate. The main difficulty faced by the translational studies concerned a methodological issue: the invasive interventions that are typically used to block re-storage processes in animals. For instance, ECT is deemed too risky for general experimental use and protein synthesis inhibitors are also unsuitable for humans. So, researchers have been devoting efforts in translating the animal research on reconsolidation to humans (Schiller & Phelps, 2011) using alternative methodological approaches. Today, reconsolidation research has been relying in less toxic pharmacological agents that are safe for humans (Brunet et al., 2008; Kindt, Soeter, & Vervliet, 2009), as the beta-blocker propranolol, or in situations where electroconvulsive shock treatment is being used as a treatment for patients with depression (Kroes et al., 2014).

Several studies have been exploring the clinical relevance of fear memory reconsolidation. For instance, in patients with post-traumatic stress disorder (PTSD; Brunet et al., 2008). In this study, in order to reactivate a traumatic memory, participants were invited to describe the traumatic event that they experienced. All participants descriptions were recorded and, immediately afterwards, they received either propranolol or a placebo. One week later, physiologic responses (e.g., heart rate, skin conductance response) were measured during the exposure to a recording of their previous personal descriptions of the traumatic event. Participants who received propranolol physiologic responses typical of trauma victims without PTSD, whereas patients who received placebo after reactivation showed physiologic responses typical of trauma victims with PTSD. These results suggested that a treatment (propranolol) after the reactivation of maladaptive memories, can alleviate the physiological symptoms associated with that "pathological" memory traces. Critically in this experiment, a non-specific and more general effect of propranolol could not be

ruled out (a crucial control group, in which it was administered propranolol without memory reactivation, was absent). Nonetheless, the findings were very attractive and motivated the conduction of new experimental studies. For instance, in a fear-conditioning paradigm, researchers were able to demonstrate that propranolol reduced the fear response and thus prevented the return of fear (Kindt et al., 2009). This study used a pavlovian fear conditioning training, in which fear-relevant images were paired (or not) with unpleasant electric shock. Learning was measured by conscious expectancy of shock and startle responding. As expected, on the first day participants developed a startle response to the stimulus that was paired with shock (the CS+) relative to the unpaired stimulus (CS-), known as differential fear-potentiated startle (FPS). In a second session (one day later) participants received propranolol before memory reactivation (a single unreinforced presentation of the CS+). As control groups, some participants received placebo after memory reactivation, and some received propranolol without memory reactivation. In a third session (one day later), all participants performed extinction trials (CS+ and CS- for several unreinforced trials). Although the declarative memory for the conditioning procedure remained intact, participants of both control groups (memory reactivation+placebo; propranolol without memory reactivation) displayed differential FPS. Critically, the differential FPS was eliminated in participants that received propranolol after memory reactivation. This same lab has been developing particularly interesting studies revealing the role of noradrenaline in the aetiology and maintenance of anxiety disorders (Soeter & Kindt, 2011, 2012). Considering its high relevant clinical implications, the studies on maladaptive memories have increased significantly, providing new insights for a better understanding of the processes involved, and for psychotherapeutic interventions (for reviews see Beckers & Kindt, 2017; Dunbar & Taylor, 2017; Elsey & Kindt, 2017; Lane, Ryan, Nadel, & Greenberg, 2015; Schwabe, Nader, & Pruessner, 2014).

However, the use of pharmacological agents in humans have been criticized by ones who argue that it is difficult to isolate the impact of drug administration on the on-going and preceding memory processes. For instance, Schiller and Phelps (2011) claimed that drugs should be administered after the memory reactivation, so as not to influence the preceding memory retrieval process. Still, because the drug typically takes around 90 min to reach peak plasma concentration in the blood, several researchers have been administering it prior to memory reactivation (e.g., Brunet et al., 2011; Kindt et al., 2009). Considering the limitations of these studies and the ethical considerations that they raise, most studies use non-pharmacological and more ecological interventions to interfere with the processes of reconsolidation. So, the vast majority of human

research has employed new learning as a post-reactivation intervention (Agren, 2014; Schiller & Phelps, 2011; Schwabe et al., 2014).

The study of reconsolidation phenomena has shown a noticeable growth in recent years, and a considerable number of researchers have been testing reconsolidation assumptions in humans (see Figure 8). The study of reconsolidation phenomenon has broadened into different memory subtypes as fear memories (e.g., Monfils, Cowansage, Klann, & Ledoux, 2009; Oyarzún et al., 2012; Schiller et al., 2010), appetitive memories (e.g., Xue et al., 2013) procedural memories (e.g., Walker, Brakefield, & Hobson, 2003) and declarative memories (e.g., Finn & Roediger , 2013; Forcato et al., 2007; Hupbach, Gomez, Hardt, & Nadel, 2007; Schwabe & Wolf, 2009).

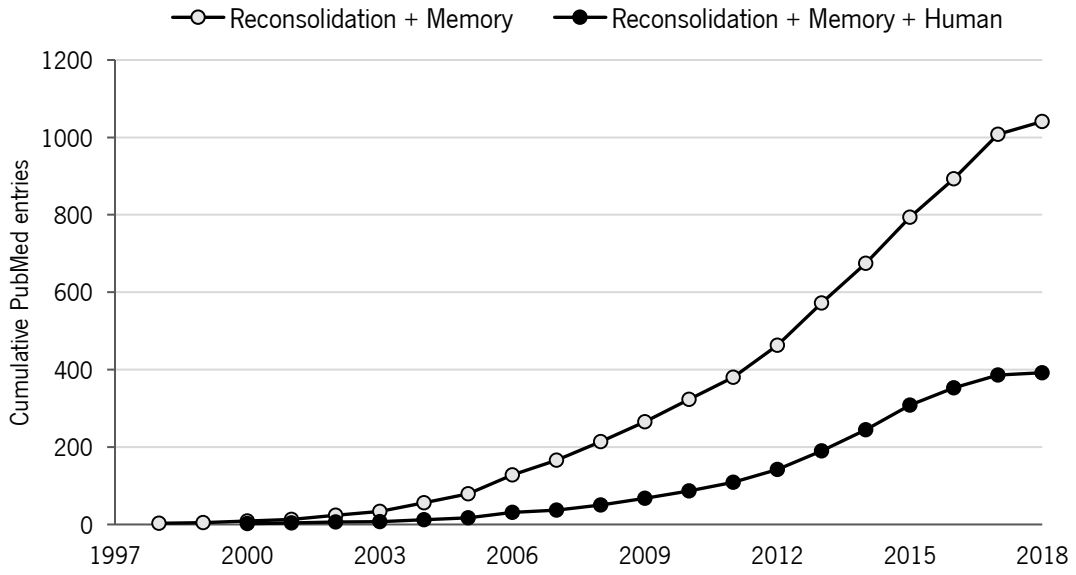


FIGURE 8. Research trends for memory reconsolidation: Cumulative Pubmed entries for the search terms ["memory" AND "reconsolidation"] and ["memory" AND "reconsolidation" AND "human"] (search conducted 12/03/2018).

However, digging in the human reconsolidation investigations, a considerable heterogeneity is found in various methodological parameters. This heterogeneity may afford greater external validity, although it could be compromising reliability and internal validity, questioning if there is convincing evidence for reconsolidation in humans. In the next section we will address in detail the challenges that human research has been facing.

3.3 Barriers faced by reconsolidation theory

Along with this rapid growth of reconsolidation studies in humans, there is a stance of scepticism for a number of reasons. Firstly, it is questionable whether behavioural interference (typically used in humans) and drug administration (typically used in animals) act on the molecular substrates of memory reconsolidation in a comparable fashion. Although the post-reactivation interventions applied in animals are known to directly act on the molecular substrates of reconsolidation (inhibiting the synthesis of proteins that are necessary for memory restore), those effects can only be indirectly inferred from behavioural data. And this is how studies in human memory reconsolidation face a restless question that has been haunting memory research for decades: Is the retrieval failure a synonym for the loss of a memory trace? Particularly with a behavioural intervention, there is an (almost) inevitable and tempting mistake of interpreting retrieval errors in a memory test as a direct indicator of the content of a memory trace. So, we are lead to disregard that a retrieval deficit can be influenced by several variables other than an impaired storage (e.g., Bouton & Moody, 2004; Cahill, McGaugh, & Weinberger, 2001) Moreover, it is not necessarily the case that behavioural plasticity relies directly on physiological plasticity (e.g., Bjork, 1978; Dudai, 2009; Kraemer & Golding, 1997). In other words, modifications in a learned behavioural response do not require a modification in the memory trace. However, this is particularly challenging for the evaluation reconsolidation theory. According to reconsolidation theory, memory changes are due to a re-stabilization process of the original memory. Thus, reconsolidation theory claims that the original memory trace is replaced by an updated one. This perspective resembles the idea of memory overwriting and the "destructive updating" in misinformation paradigm (Loftus, 1979). However, cognitive psychology has been providing evidence that experimentally-induced trace modifications can be achieved via retrieval-based mechanisms. These have a limited temporal influence and do not necessarily imply an impairment of the memory trace. This interpretation follows McCloskey and Zaragoza's "no impairment" claim over misinformation effect (McCloskey & Zaragoza, 1985), and leans on decades of research on cognitive psychology (i.e., retroactive interference: Spear & Riccio, 1994; extinction: Bouton, 2004; Pavlov, 1927; cue-dependent forgetting: Tulving, 1974; or state-dependent retrieval: Eich, 1980). Thus, it is not clear if the memory modifications commonly reported in reconsolidation studies are due to a storage deficit or a retrieval deficit.

Secondly, a considerable number of studies have been offering ad hoc theoretical adaptations, or *boundary conditions*. The identification of boundary conditions, or stated restrictions for the observation of a phenomenon, plays an important role for theoretical progress, however, as Hardwicke (2016) outlined, that is only the case when exploratory hypothesis-generating and confirmatory hypothesis-testing phases of scientific inquiry are clearly differentiated (Jonas & Cesario, 2016; Kerr, 1998; Wagenmakers, Wetzels, Borsboom, van der Maas, & Kievit, 2012). The fact that some of the boundary conditions, such as memory age or training strength, have been generating conflicting evidence creates a very tortuous theoretical landscape (Eisenberg & Dudai, 2004; Eisenberg, Kobilo, Berman, & Dudai, 2003; Suzuki et al., 2004; for opposite examples see Brunet et al., 2008; Diergaarde, Schoffelmeer, & De Vries, 2006; Wang, de Oliveira Alvares, & Nader, 2009). The methodological plurality that we previously mentioned (see section 3.1) limits the comparison between studies, and reinforces the ambiguity for answering the question: Is this conflicting evidence a reflex of theoretically-irrelevant methodological differences, or theoretically-relevant boundary conditions (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013; Haaker, Golkar, Hermans, & Lonsdorf, 2014)?

Finally, other researchers have faced serious difficulties in replicating the phenomenon itself (e.g., Dawson & McGaugh, 1969; Hardwicke, Taqi, & Shanks, 2016; van Schie, van Veen, Hendriks, van den Hout, & Engelhard, 2017).

The reviewed arguments advise for a cautious analysis of the existing evidence for the reconsolidation effects. Nevertheless, the study of memory reconsolidation, as an approach to the understanding of memory malleability, has undeniable theoretical, clinical, and ethical implications, and there is a considerably high number of studies that provide evidence for the phenomenon (Agren, 2014; Lee, Nader, & Schiller, 2017; Nader, 2015; Nader & Hardt, 2009; Schiller & Phelps, 2011; Tronson & Taylor, 2007). However, there is a need to carry out studies that systematically explore this phenomenon. In the next chapter we will briefly review the advances made in reconsolidation of episodic memories and we will present a critical discussion of one of the most acknowledge paradigms: an object-learning paradigm developed by Hupbach and colleagues in 2007. At the end of the next chapter, we will describe in detail the aims of the present studies.

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Chapter 4. Episodic memory reconsolidation

Memory, as everyone knows, is an imperfect archive of our experience.

(Brainerd & Reyna, 2005, p. 4)

4.1 Introduction

Recently, the enthusiasm for the understanding of reconsolidation phenomena has flourished, and a great body of research has been developed. Underlying these studies is the idea that the reactivation of an existing memory trace restores the malleability that was paused after memory consolidation. And, in the course of that process, memory is vulnerable to modifications. Thus, modifications in trace-dependent performances of a previously reactivated memory are taken as evidence for memory reconsolidation and have been helping the understanding of long-term memory's fate (Agren, 2014; Besnard, Caboche, & Laroche, 2012; Gisquet-Verrier & Riccio, 2012; Hardt, Einarsson, & Nader, 2010; Lee, Nader, & Schiller, 2017; Nader & Hardt, 2009; Schiller & Phelps, 2011; Scully, Napper, & Hupbach, 2017).

However, the experimental outcomes taken as evidence for reconsolidation differ considerably. In fact, there is evidence supporting: (a) memory overwriting/ impairment (Chan & LaPaglia, 2013; Schiller et al., 2010; Schwabe & Wolf, 2009; Walker, Brakefield, & Hobson, 2003; Wirkner, Löw, Hamm, & Weymar, 2015); (b) memory updating (Forcato et al., 2007; Hupbach, Gomez, Hardt, & Nadel, 2007; James et al., 2015; St Jacques, Olm, & Schacter, 2013; Wichert,

Wolf, & Schwabe, 2013); and (c) memory strengthening (Finn & Roediger 2013; Forcato et al. 2011; Wichert et al. 2013; Potts & Shanks 2012; Marin, Pilgrim, & Lupien 2010). This heterogeneity is not problematic *per se*, however, the bridge between data interpretation and the experimental approach used (e.g., post-reactivation treatment; reactivation procedure) may not be clearly built. Additionally, there is a lack of consensus in defining reactivation and the precise construction of the reminder has been subject of discussion (Forcato, Argibay, Pedreira, & Maldonado, 2009). In fact, "reactivation" has been used to refer to different types of manipulations such as : (a) retrieving a memory (e.g., Chan & LaPaglia 2013; Marin et al. 2010; Schwabe & Wolf 2009; Walker et al. 2003; Potts & Shanks 2012; Wichert et al. 2013) or (b) the presentation of subtle reminders or partial retrieval cues (Bos, Schuijer, Lodestijn, Beckers, & Kindt, 2014; Diekelmann, Biggel, Rasch, & Born, 2012; Forcato et al., 2007; Hupbach et al., 2007; James et al., 2015; Wirkner et al., 2015; Yacoby, Dudai, Mendelsohn, & Drexler, 2015).

As so, although efforts are being made to test the reconsolidation theory's hypothesis, the consequences of reactivation and post-reactivation manipulations have not been systematically documented yet. While the literature seeks for clarification, a reliable protocol for testing reconsolidation assumptions is urgently needed. As Nadel, Hupbach, Hardt, and Gomez (2008) clearly stated, "If we are to fully understand the neural underpinnings of episodic memory, and we start with the assumption that such memory is open to reconsolidation, it is critical to develop methods for parametrically studying reactivation-induced memory updating in humans" (p. 46).

In this dissertation we will focus on a paradigm developed by Hupbach and collaborators. This paradigm offers a wide range of opportunities to test reconsolidation theory's assumptions, and has been widely recognized and acknowledged (Agren, 2014; Besnard et al., 2012; Gisquet-Verrier & Riccio, 2012; Hardt et al., 2010; Lane, Ryan, Nadel, & Greenberg, 2015; Lee, 2009; Lee et al., 2017; McKenzie & Eichenbaum, 2011; Nadel, Hupbach, Gomez, & Newman-Smith, 2012; Sandrini, Cohen, & Censor, 2015; Schiller & Phelps, 2011; Schwabe, Nader, & Pruessner, 2014; Scully et al., 2017). The authors have been providing interesting and new insights on episodic memory reconsolidation, however, we consider that the paradigm raises questions that should not be overlooked. In the next sections of this chapter, we will review Hupbach's work, present a critical perspective on their work, and establish our main goals and objectives.

4.2 Hupbach's paradigm

In 2007, a pioneering paradigm was developed to study reconsolidation of episodic memories. To that date, in contrast with the animal field, the scant evidence available in humans came from studies in implicit memory. For instance, Walker and collaborators (2003), showed reconsolidation of procedural memories. Twenty-four hours after the learning of a simple finger-tapping sequence, participants learned a new sequence. Critically, memory for the first sequence could be reactivated before the new learning (brief rehearsal of the first sequence) or not. On a final session, memory for the first sequence was tested. Participants that reactivated the first sequence before learning the second sequence, showed memory impairments, both on speed and accuracy. Also, Galluccio (2005) and Galluccio and Rovee-Collier (2005) provided evidence in children for reconsolidation effects. Children were trained to interact with a toy by kicking their foot to active a mobile. Memory was reactivated by a reminder of this event: the mobile was presented, however, no interaction with it was possible. After this reminder, a group of infants learned to interact with a new mobile. This same group revealed modifications of the original memory: they no longer recognized it and only reacted to the second mobile. So, although some evidence for reconsolidation was available, all the reported studies were developed in memories that did not require conscious recollection, which lead Hupbach and collaborators to inquire if the same type of phenomenon could be observed on explicit memories. By reviewing some studies in cognitive psychology on episodic memory malleability, such as the classical studies of Barttlet (1932) and studies on misinformation effect (Loftus, 1979; Loftus & Palmer, 1974), the authors hypothesized that the modification of consolidated memory may imply its reactivation. An idea that was thoroughly explored two years later in an acknowledge paper by Hardt, Einarsson, and Nader (2010).

Hupbach and colleagues (2007) followed the canonical structure of previous reconsolidation studies: three sessions, each one separated by 48 hours (see Figure 9). The first two sessions were encoding sessions, and the third was a retrieval session. Critically, in Session 2 memory for the original memory (Session 1) could be reactivated or not. The authors proposed a way of reactivation of an episodic memory, which they have named as "subtle reminder". This reactivation procedure was as follows: "We asked participants to describe the learning procedure

without asking them to explicitly recall the learned items in order to test whether an incidental reminder can reactivate memory" (Hupbach et al 2007, p. 48).

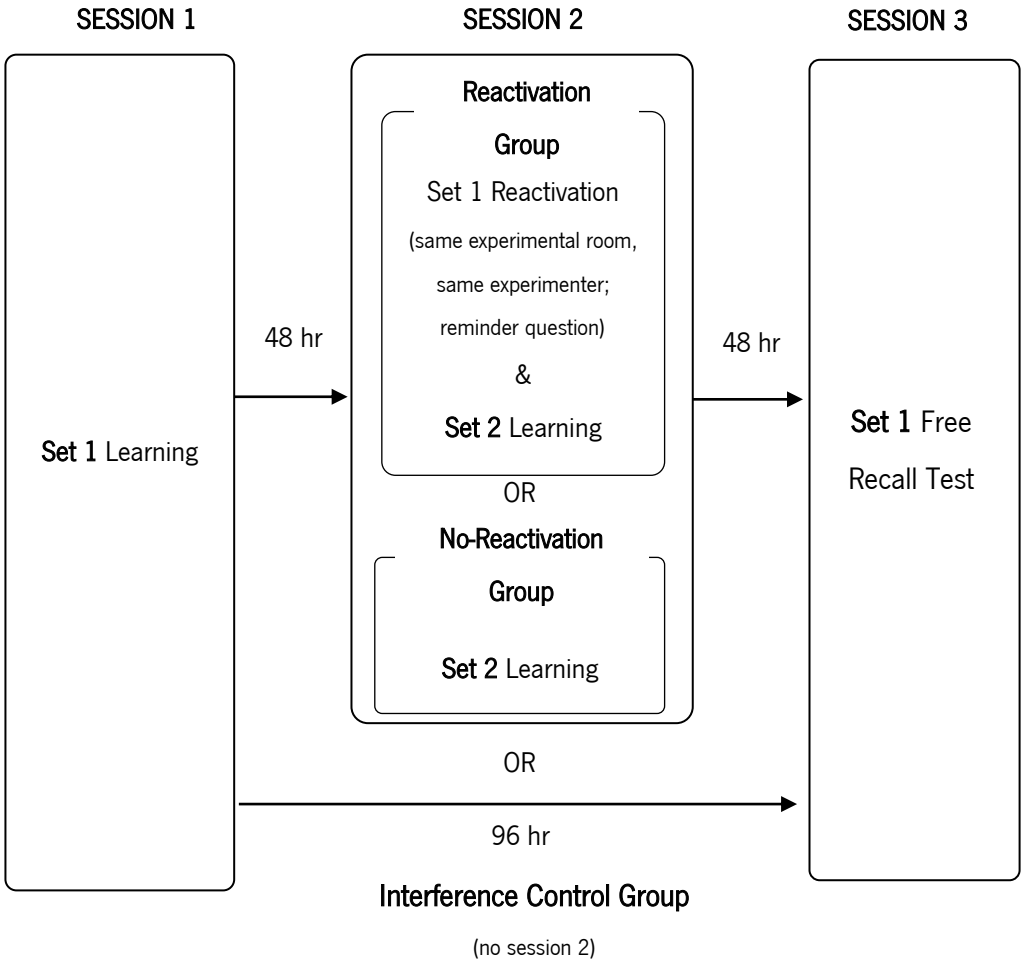


FIGURE 9. Schematic representation the standard procedure used by Hupbach and colleagues (Experiment 1, 2007).

More specifically, in the first session, a list of 20 unrelated objects (List 1) was learned. The learning procedure was as follows: participants had to name each object that was withdrawn from a bag, placed on a table, and then removed to a blue basket. A learning criterion established that participants accurately memorized the list of objects (learning procedure was repeated until at least 17 objects were recalled, or for a maximum of four trials). On a second session, a new list of objects (List 2) was learned. Also, a crucial manipulation was made: memory for the List 1 was reactivated or not. In the reminder group (n = 12), participants reactivated List 1 memory in a subtle fashion, which involved the re-exposure to the blue basket used in Session 1, in order to ask participants for a description of List 1 procedure, and the performance of Session 2 in the same

experimental room and the same experimenter of Session 1. In contrast, participants in the no-reminder group (n = 12) performed Session 2 in a different experimental room, with a new experimenter, and no mention was made to Session 1. The learning procedure was the same for all participants: objects were displayed on a table and participants had to name each one out loud; after the last object was named, a study period of 30 seconds began. The same learning criterion was applied in this second session. A control group (n = 12) that did not perform Session 2 was added (interference control group). In the final session, List 1 memory was tested in a free-recall test, with no limit of time. After the first recall attempt, all participants performed three more recall attempts.

The data analysis of the results involved two main aspects: a baseline comparison of groups and a comparison of the performance in List 1 test (in terms of correct recall or memory errors- intrusions). The baseline comparison between groups was used to discard potential effects of different levels of encoding on retrieval. The comparison of groups' performance on Session 3 allowed to examine the fate of a consolidated memory (List 1 memory) that was a reactivated memory before a new learning (List 2). The main results are presented in Figure 10.

The analysis of correct recall (List 1) was conducted with a mixed ANOVA, with group as a between-subjects variable and trial as a within-group variable. The analysis revealed that correct recall increased across recall trials and no significant differences were observed between groups. These results suggested that learning of a new list did not impact the memory for the original learning in any of the groups. Importantly, reminder group performed similarly to the other groups, so the post-reactivation new learning has not disrupted reconsolidation of the memory trace representing List 1. However, the level of intrusions (List 2 items that were incorrectly recalled in List 1 memory test), was significantly larger in the reminder group. Notably, the number of intrusions did not increase with recall trials. In sum, learning a new list interfered with the recall of an original learning, if, and only if, memory for original learning was reactivated in Session 2.

The absence of a statistical difference in correct recall, together with a significant difference in intrusion rate, led Hupbach and collaborators to claim for a constructive updating of List 1 memory trace due to a reconsolidation process:

> (...) the reminder did reactivate memory of the original list, returning it to a state in which new information could be incorporated: When asked to recall List 1 on Day 3, participants in the reminder group incorrectly intermixed a high number of objects from List 2 in their recall of List 1. (Hupbach, et al., 2007, p. 49)

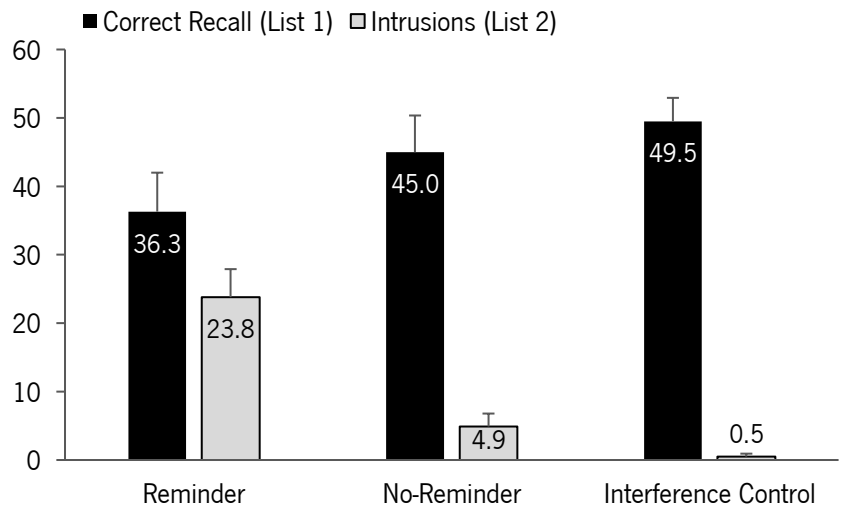


FIGURE 10. Hupbach and colleagues results of List 1 free recall test. Mean percentage of objects correctly and falsely recalled on Session 3 (Experiment 1) in the reminder, the no-reminder, and the interference control group during Experiment 1. Error bars represent standard errors of means. Adapted from Hupbach and colleagues (2007).

In Experiment 2, the authors tested a hallmark of reconsolidation theory: the time-dependent nature of the phenomenon. It was examined if the reactivation had an immediate effect on memory (i.e., observed in a STM test), or if the memory modification is elicited over time, (i.e., only observed in LTM test- Session 3). To tackle this question, the authors compared the results of the original paradigm (that applies a LTM test: memory for List 1 object is tested in Session 3), with the results from a STM test, in which participants of both no-reminder and reminder groups were invited to recall List 1 objects immediately after they had learned List 2. They also added a control group that did not learn List 2 objects (interference control group). According to reconsolidation theory, reactivated memories need to undergo a time-dependent process to persist over time, so no immediate differences in memory performance should be expected between the reminder and no-reminder group. Results were in line with reconsolidation predictions: reactivation had no effect on memory for List 1 in a STM test. More specifically, when tested on memory for List 1 immediately after List 2 acquisition, reminder group and no-reminder group did not differ in terms of correct recall (List 1 items), nor in intrusions rate (List 2 items). In interference control group, the correct recall was significantly higher than in reminder or no-reminder group. Together with the results of Experiment 1, it was concluded that the effect of the reactivation occurs over time.

In the last experiment, the authors questioned if the reported effect could be a consequence of source-monitoring problems in reminder group. Previous source-monitoring studies (Johnson, Hashtroudi, & Lindsay, 1993), suggested that the more features memories share, the more likely source errors are to be observed. So, the rationale behind this experiment came from the fact that in the reminder group, List 1 and List 2 are learned in the same context (spatial context was one of the three components of the reactivation procedure). So, the intrusion effect observed when List 1 was tested could be reflecting source-monitoring difficulties rather than a reconsolidation phenomenon. If this was the case, participants in the reminder group should be as likely intermix List 1 items in List 2 recall, as they intermix List 2 items in List 1 recall (Experiment 1). This hypothesis was tested in Experiment 3, in which participants were asked to recall List 2 (instead of List 1) in Session 3. Reminder and no-reminder groups performed similarly in terms of correct recall (List 2) and revealed very few intrusions (List 1). When tested for List 1 memory (Experiment 1), reminder participants showed significantly more intrusions than when tested for List 2 memory (Experiment 3).

In this first paper the authors collected evidence that supported the interpretation of the results under reconsolidation umbrella: (a) episodic memory traces (List 1) can be modified by information (List 2) that is presented after its reactivation (Experiment 1); (b) the impact of the post-reactivation information on the existing memory trace acts in a time dependent fashion (Experiment 2); (c) the intrusion pattern reported cannot be assign to source-memory difficulties, since only List 2 items intruded List 1 memory and not vice-versa (Experiment 3).

Hupbach and colleagues criticized the assumption in memory research for the existence of a fixed trace or an "engram", emphasizing the need for some theoretical adjustments to account for their findings. In that sense, the authors revisited the *multiple trace theory* (MTT, Moscovitch et al., 2005; Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997): "which takes as given that reactivating a previously 'store' memory leads to the creation of a new version of that memory" (Hupbach, et al., 2007, p. 51).

In sum, the authors claimed that the reactivation of List 1 memory trace rendered memory labile and susceptible to information that was presented afterwards. The labile state was followed by a process of reconsolidation, leading to the creation of a "new version" of List 1 memory trace, also called "updated-version" (e.g., Alberini & Ledoux, 2013). This new version of the memory trace includes information from the original event and the post-reactivation information (List 2). This theoretical interpretation was carried out in the following studies that applied this paradigm.

For instance, in 2008, Hupbach, Hardt, Gomez, and Nadel exhaustively explore the components that triggered memory reactivation in their first study. In that sense, the authors isolated the three components (spatial context, experimenter, reminder question) that could be working for that purpose and examined if one of the components by itself could efficiently reactivate List 1 memory. Thus, in Experiment 1 there were 3 experimental groups which differed in the procedure used in Session 2 for List 1 reactivation. List 1 was reactivated by: (a) spatial context (same spatial context in Session 1 and 2; context group); or (b) experimenter (same experimenter in Session 1 and 2; experimenter group); or (c) reminder question (Session 2 began with a question about the procedure for List 1 learning; question group). As in the standard paradigm, the performance in List 1 free recall test was compared between groups. Results are displayed in Figure 11.A.

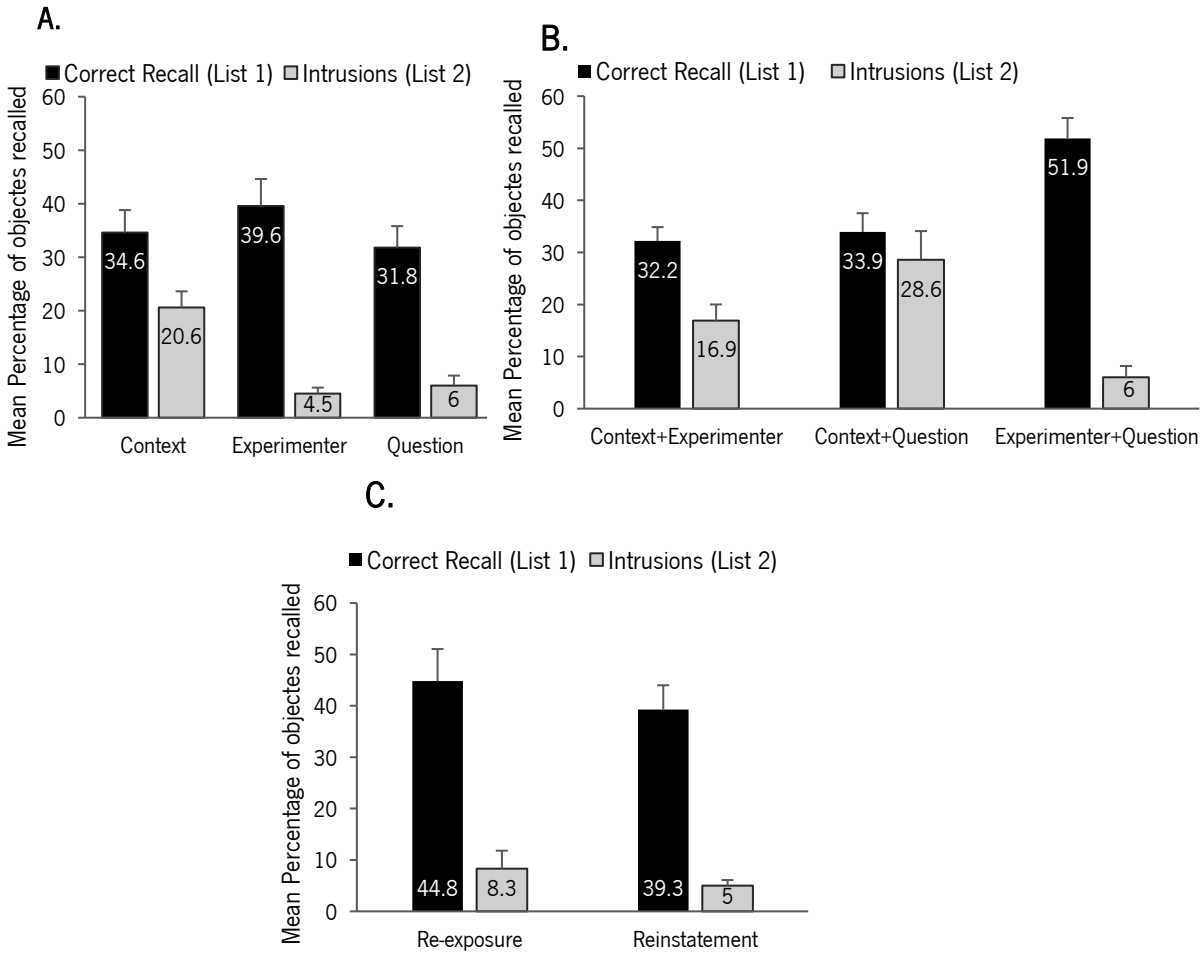


FIGURE 11. Mean number of objects correctly recalled from List 1 and falsely recalled from List 2 in Session 3 as a function of the different reminder components used in Session 2. Panel A displays the results from Experiment 1, Panel B the results from Experiment 2, and Panel C the results of Experiment 3. Error bars represent standard errors of means. Figures adapted from Hupbach et al. (2008).

Context group showed a significantly higher intrusion rate (List 2) than experimenter and question group. Experimenter and question groups showed very few intrusions, and their performance was equivalent to the no-reminder group of the standard procedure. The authors concluded that the spatial context was a sufficient reminder to initiate reconsolidation process. A second experiment provided support for the role of context as a reminder, showing that even when reminder question is used together with the experimenter, the memory-updating effect[2] is not observed (see Figure 11.B). Additionally, both the re-exposure (for a brief period of time to Session 1 experimental room before List 2 learning), and the context reinstatement (achieved by inviting participants to draw a map for the Session 1's room), led to a low level of intrusions (see Figure 11.C).

A final experiment approached the role of retrieval context. As the standard reminder group (see Figure 9) retrieved List 1 objects in a spatial context that both original training of List 1 and subsequent training of List 2 occurred (whereas no-reminder group performed the encoding sessions in different spatial contexts), the authors examined if the congruency of the encoding and retrieval context was playing a role in the updating-effect. In this experiment, the standard reminder and no reminder group were invited to recall List 1 items in a new experimental room. The results revealed that the mean number of intrusion followed a binomial distribution. Regardless of the fact that a considerable number of participants did not demonstrate an "updated memory" (no intrusions), the authors did not deeply examine this result, and claim that: "As hypothesized above, subjects who show no intrusions might rely on other retrieval cues that are more distinctive for the individual Lists of objects." (p. 578). The observation of an updating-effect was taken as "necessarily result" (p. 578) when retrieval is performed in the same spatial context of encoding, however, if the spatial context varied the effect may not be observed. What dictates the occurrence of intrusions, in such cases, is the retrieval cues that participants used to help them recalling the objects. Discussing these results, the authors lift the veil for their next steps:

> We suspect that familiarity of the spatial context may constitute one such boundary. Familiar contexts are associated with a variety of different experiences; thus, a familiar spatial context may not be particularly useful in distinguishing events. In this case other

[2] According to Hupbach and colleagues, memory-updating effect is indexed by a higher intrusion rate in reminder groups. So, "memory-updating effect" and "intrusion effect" are frequently used as synonyms.

> situational elements, such as the experimenter, may be used to discriminate discrete episodes from one another. (Hupbach, et al., 2008, p. 578)

In fact, this was proved to be the case. In 2011, Hupbach, Gomez, and Nadel run a set of experiments that showed that the updating-effect is also observed in 5-years old children (Experiment 1). Also, as in adults, the memory updating-effect was proved to be an unidirectional effect (no intrusions when List 2 is tested in Session 3; Experiment 2B), and a time-dependent effect (no intrusions when List 1 is tested immediately after List 2 learning, Experiment 2B). These results are particularly interesting regarding the well-documented source memory problems observed in children (Foley, 2013). Additionally, this paper provided an important contribution as it showed the role of the familiarity of the spatial contexts (Experiment 2A). In highly familiar spatial context (their houses) the authors contrasted 2 groups of children, which differed in the List 1 reactivation procedure. List 1 memory was reactivated by: (a) spatial context, the experimenter and the reminder question (three-component reminder group) or (b) only the spatial context (Session 2 was conducted with a different experimenter and no question was made regarding Session 1, context reminder group). The results revealed that the three-component reminder group showed significantly more intrusions than the context reminder group. This pattern was not found in previous studies on the dynamic role of context in memory updating-effect which demonstrated that context was a sufficient and necessary reminder component for the effect to be observed (Hupbach, et al., 2008). Importantly, in Hupbach and collaborators (2008) the spatial context was unfamiliar to the participants, and in Hupbach et al, 2011, the context was highly familiar. The author hypothesized that in these cases other cues (such as, experimenter, procedural details,..) take an important role in this mnemonic effect (for comparable results in rats see Hall, Symonds, & Rodriguez, 2009; but for a review see Fanselow, 2007). The authors concluded: “Thus, memory updating following reactivation is a relatively ubiquitous phenomenon, but reactivation is triggered by different cues depending on the test situation” (Hupbach et al., 2011,p. 795).

One of the most valuable evidence for the interpretation of the intrusion partner as a demonstration of reconsolidation phenomenon came from the studies that showed no modification of the memory trace of the interfering material (no intrusions when List 2 is tested). This absence of intrusions suggests an unidirectional mnemonic effect, discarding source-monitoring failure at retrieval. This idea is well-supported in Hupbach, Gomez, and Nadel (2009). Here, the procedure was the same as the standard paradigm (Figure 9) in the first two sessions (reminder and no reminder group), however, in the third session participants had to perform a source recognition

task instead of a free recall test. In addition to the traditional old/new recognition test, in case of an "old" answer participants had to assign the object to List 1 or List 2, and rate how confident they were about their answer. Two outcomes were hypothesized: (a) participants of reminder group could reveal an overall misattribution of source (misattributing either List 1 items and List 2 items) – and in that case, results would suggest a lack of source monitoring at retrieval and reconsolidation hypothesis will be weakened; (b) reminder group could reveal a selectively biased misattribution of source towards List 1. More specifically, participants from the reminder group could misattribute the source of List 2 items (i.e., mistakenly allocating an object that is originally from List 2 to List 1) but do not commit a misattribution of source for items that were originally from List 1. If it is the case, results might suggest that the reactivation of List 1 before List 2 acquisition, made List 1 memory malleable and susceptible to the interference of List 2 items, but not vice-versa. Results were consistent with predictions of reconsolidation theory. Also, the analysis of confidence rates revealed that participants were as confident in the incorrect answers as they were in the correct answers.

Across the reviewed studies, Hupbach used a "subtle reminder", and not an "active" reminder, such as retrieval (test). However, more recently, Hupbach (2015) examined the impact of retrieval practice as a reminder. Retrieval practice or testing is one of the most studied phenomena of memory. Robustly, research demonstrates that it facilitates subsequent performance (in comparison to study conditions; e.g., Roediger & Butler, 2011). However, studies have yield mixed results regarding the role of testing in retroactive interference (RI). Some suggests that retrieval practice diminishes retroactive interference (Halamish & Bjork, 2011; Potts & Shanks, 2012), and others suggest that it can exacerbate the potential negative effects of post-retrieval information (e.g., Chan, Thomas, & Bulevich, 2009; LaPaglia & Chan, 2013; Walker et al., 2003). Hupbach (2015) used her standard reconsolidation paradigm to examine the consequences of "active reminder" in intrusions and RI. So, two variables were manipulated: the reminder (no reminder, reminder and testing group) and the type of task in Session 2 (Sudoku or List 2 learning). The groups' performance in Session 3 (List 1 free recall test) were then compared. The results revealed that learning new material impacts memory (RI): overall participants that encoded List 2 in Session 2 recalled significantly less List 1 items than participants that performed a Sudoku instead. Also, the correct recall was significantly higher in testing groups than in reminder groups or no-reminder groups. When test+sudoku group and test+List 2 where contrasted, groups did not differ in the List 1 test performed in Session 2, but test+sudoku recalled significantly more items

in the List 1 test performed in Session 3. This result suggested that testing did not protect memory for RI. Importantly, regarding intrusions (List 2 items), results revealed that reminder group showed significantly more intrusions than no-reminder and testing groups[3]. Hupbach argued that, although the act of retrieval (free recall test) is a way to reactivate a memory, it goes beyond that, promoting a strengthened memory (Roediger III & Karpicke, 2006) with an increased within-list organization (Congleton & Rajaram, 2012; Szpunar, McDermott, & Roediger III, 2009). These processes that underlie memory retrieval prevented the updating of List 1 memory with List 2 items, which is observed when a subtle reminder is used.

The reviewed studies were especially compelling and provided empirical evidence on a topic with high practical and theoretical implications: memory plasticity. The contribution of these studies is inevitable and has inspired many researchers. Hupbach extended this paradigm to other domains as, for example, forgetting and stress. Based on studies developed with the direct-forgetting paradigm (e.g., Woodward & Bjork, 1971; for a review see Bjork, Bjork, & Anderson, 1998), Hupbach (2013) showed that the instructions to forget List 1 prior to List 2 learning could reverse the effects found in groups that reactivate memory. Later, studies on the effect of stress revealed that stress induction after new learning decreases significantly the intrusions in the reminder group (Experiment 2, Dongaonkar, Hupbach, Gomez, & Nadel, 2013; see also Hupbach & Dorskind, 2014).

In sum, Hupbach developed a reconsolidation paradigm to examine if episodic memory traces undergo updating mechanisms after memory reactivation. With the use of a subtle reactivation procedure, Hupbach and colleagues found that: (a) items presented after reactivation intruded the original memory (intrusion effect); (b) the intrusion effect is not compatible to a source monitoring explanation; (c) the intrusion effect is a consequence of a time-dependent process; and (d) the consequences of a subtle reminder differ from an active retrieval of memory (testing).

Previous studies in animals or other studies in humans (Nader, Schafe, & LeDoux, 2000), mainly reported a destructive updating: impairment in the original memory (Chan & LaPaglia, 2013; Schiller et al., 2010; Walker et al., 2003). However, Hupbach found that correct recall seems to be unaffected (see also St Jacques et al., 2013). Nevertheless, an intriguing intrusion effect was

[3] In order to test if intrusions would emerge if Sessions 1 and 2 took place in the same experimental room (a manipulation used for List 1 memory reactivation), the authors added a group (n = 11) that tested List 1 memory in Session 2, before List 2 learning, in the same experimental room of Session 1. As previously found, the results revealed that testing reduces intrusions (even when contextual cues were presented).

found: if an existing memory trace is reactivated, the information that is presented immediately before becoming "incorporated" in that memory trace.

In 2011, Hupbach wrote a commentary about the absence of an impairment in the correct recall in her paradigm. She argued that her studies differ from other published studies not only with respect to the relative localization vs. distribution of brain systems involved (following an explanation proposed by Schiler et al., 2010) but also regarding how interfering material (material presented after reactivation) relates or competes with the content of the original memory. Hupbach argued that the most evidentiary lines for reconsolidation effect came from fear conditioning studies, in which the information that the animals received after reactivation (CS presentation followed by no shock) directly competes with the previously learned contingency (CS-shock). Also, in procedural memory (Walker et al., 2003), the "new information" was a new finger-tapping sequence that required the movement of the same fingers. In both cases, reconsolidation effect was found through a decreased ability to retrieve the original information. Also, in both cases, the interfering material competed with the content of the original memory. As in her paradigm, List 2 is conceptually unrelated to List 1. Thus, Hupbach argued that the new information did not compete with the old one, so new information can be accommodated in the old one: "Rather, items of both sets can 'coexist' and elements of the new memory can get incorporated into the old reactivated memory" (Hupbach, 2011, p. 1).

A new level was added for the understanding of episodic memory plasticity. Memory modification was seen as a reactivation-dependent effect, and the nature of the memory modification (destructive or constructive updating) seemed to be related to the competition between new and old information. Although the rationale for this prediction was reasonably well explained, it was never tested, and the appealing definition of this effect as constructive updating effect has prevailed.

Despite the unquestionable relevance of Hupbach's findings, we will examine some limitations that were unexplored until the date, which could call into question the interpretation that has been provided to the intrusion effect. However, it is worth noting that reconsolidation falls in a complex theoretical landscape, and, as previous researchers have been arguing, behavioural paradigms struggle to disentangle the reported effects from other effects studied in cognitive established for years. In that sense, some of the limitations that we will present could be generalized to other paradigms designed to study memory reconsolidation.

4.3 A critical analysis of Hupbach's paradigm

Hupbach's pioneer paradigm opened an avenue of opportunities for the discussion of the reactivated memories' fate, and for the understanding of memory modification. Although the reviewed studies provide compelling evidence, and although the paradigm meets several key criteria for the study of reconsolidation theory, alternative perspectives that favour retrieval-based mechanisms should also be considered.

Sederberg, Gershman, Polyn, and Norman (2011), proposed that the asymmetric intrusion effect reported by Hupbach and colleagues could be explained without resorting to a reconsolidation process. Temporal Context Model (TCM) was used as an alternative explanation. According to TCM, temporal context is modelled as a recency-weighted average of past encoded items. It assumes that when an item is encoded it is *bound* to the temporal context in which it is experienced. The act of retrieval involves cueing with a temporal context (e.g., "Recall List 2 from Wednesday"). Thus, a successful retrieval implies the retrieval of the temporal context, which can, in turn, facilitate the retrieval of information associated with that same temporal context. Following TCM, Hupbach's results can be accounted as follows: in Session 1, participants learn List 1 objects, and they also learn that those objects are bind with features of the external environment (e.g., learning procedure, experimenter, experimental room) and the current temporal context (from herein "Temporal Context A"). In Session 2, for participants from reminder group, features of Temporal Context A are again present (same experimenter, in the same room), triggering its reinstatement. The interfering list (List 2) will be linked with these (reinstated) List 1 context features, as well as contextual features uniquely associated with List 2 (Temporal Context B). Thus, for participants in the reminder group Temporal Context A will be linked to List 1 and 2, and critically, whereas Temporal Context B is linked only with List 2. Consequently, cueing List 1 triggers recall of both List 1 objects and List 2 objects, whereas cueing List 2 triggers only recall of List 2 objects. For participants in the no-reminder group, List 1 is only associated with Temporal Context A and List 2 is only associated with Temporal Context B, so intrusions are substantially lower. With the use of computational simulations, Sederberg and colleagues supported the fit of TMC for Hupbach's findings. However, the model has limitations and could not account for other findings that came from Hupbach's paradigm (as, for example, TCM does not explain the critical role of spatial reminders, Hupbach 2008). Additionally, TCM offered behavioural predictions to this

object-learning that were not meet in subsequent studies published by Hupbach's team (Hupbach ,et al., 2011).

To the best of our knowledge, only very recently a different research team tried to replicate Hupbach's findings (Klingmüller, Caplan, & Sommer, 2017), and the fit of Hupbach's paradigm to study reconsolidation was called into question (these findings should be cautiously analysed, and will be discussed them later, see Chapter 7).

In this section, we will present a critical approach to Hupbach's paradigm, in the format of brief considerations.

Consideration 1: Incomplete description of the methodology

Throughout Hupbach's papers, materials (objects) were never described: a list of the objects was provided however with no information about the size, colours or other physical characteristics. Although the set of objects were the same for the experimental groups, the absence of a full description of the objects hinders researchers' attempts to replicate and extend the previous findings and, above all, it hinders the understanding of the mechanism underlying intrusions. For instance, it could be the case that the intruded objects were very similar across participants. If it was the case, it will be suspicious that only specific objects intruded the original memory, thus alternative approach to the occurrence of intrusions will be strengthened (e.g., interference).

Along with this, the procedure was also poorly described. For example, in the learning procedure of List 1, it is unclear if the objects are out of sight of participants (i.e., which type of bag is used to hold the objects before presentation; how big is the basket when the objects are placed during recall). A similar problem is found in List 2 learning procedure: objects are aligned on the table, and after encoding phase, the experimenter hides the objects. However, it is unclear how objects are hidden.

Additionally, clear instructions are never provided. It is unknown if participants were aware of the design of the experiment, and in which tasks they will be involved and, for example, how it is explained the need for four recall attempts in the last session.

All these methodological aspects are crucial for the conduction of a replication study, and all that information should be rigorously described in order to avoid a reproducibility problem.

Consideration 2: Nature of the stimuli (objects)

Hupbach's reasoning for the observation of a constructive updating in reminder group (no impairment in the correct recall) is based on the idea that objects are totally unrelated, with a low competition level between them. As stated in Consideration 1, no detailed information of the objects was ever provided (just a list of the objects), which makes difficult the evaluation of this hypothesis. However, there is an intriguing fact regarding the results from a condition that did not perform Session 2 (nor had ever contacted with List 2; interference control group, Experiment 1, Hupbach et al. 2007): this group recalled on average 0.1 items that belong to List 2. This fact made us sceptical about how unrelated the objects were, and consequently questioned the results' interpretation.

Consideration 3: Small sample size

All the reviewed studies had considerable small sample sizes (ranging from 12-15 participants per condition). A small sample size is problematic because the outcomes are more susceptible to the influence of random variations that undermine the reliability of the findings. Thus, a small sample size produces less reliable estimates of the effect size (Button et al., 2013; Ioannidis, 2005), decreases the chance of detecting true effects when they exist, and increases the likelihood of false discoveries. So, the smaller the sample size of studies that were conducted on a topic, the less likely the research findings are to be true.

Consideration 4: Lack of experimental control

From Hupbach's pioneer study until now, a considerable number of studies were published. However, it is important to notice that these studies were all conducted in a face-to-face situation, from which the role of the experimenter is hardly rolled out. To the best of our knowledge, the randomization of stimuli presentation was determined by the experimenter at the time of data collection, so it is not a truly random process. Also, the set of objects was always the same across studies and the learning procedures were the same (see Hupbach et al., 2008, for an exception: List 1 was learned with the procedure that is commonly used for List 2 learning, and vice-versa).

Consideration 5: Absence of an impairment in the correct recall

Contrarily to what is commonly reported in previous studies both in the animal and human field, Hupbach did not find a destructive updating. According to Hupbach (2011), the absence of correct recall impairment could be related to the low degree of competition between old and new information.

Also, as mentioned above (Considerations 1-3), it could be that Hupbach's findings were not sufficiently powered to detect a true impairment effect. In fact, in several studies, no-reminder groups recalled a higher number of correct items, although they do not differ statistically from reminder groups.

Consideration 6: Evidence for a time dependent-effect

By definition, reconsolidation is thought to involve a time-dependent process. Thus, the consequences of experimentally-induced amnesia tend to emerge on a delayed test (LTM), and they are not apparent in an immediate (or short-delayed) test. In studies using protein-synthesis inhibitors, the rationale behind this pattern of result rely on the action of the drug: it should have no influence on the electrophysiological activity associated with the STM trace but it would disrupt protein-synthesis necessary for the formation of the LTM trace. Curiously the same pattern (intact STM and impaired LTM) is observed when ECSs are used as a post-reactivation treatment (e.g., Geller & Jarvik, 1968; McGaugh & Landfield, 1970). The observation of no amnesia on a STM test, and amnesia on a delayed test (LTM) represents a hallmark of reconsolidation theory, proving that a reconsolidation process has been disrupted (e.g., Nader et al., 2000). However, it is unclear if this pattern generalises to studies using behavioural interventions.

Hupbach and colleagues (2007, Experiment 2) conducted an experiment to test if the reactivation had an immediate effect on memory or, as stated by the reconsolidation theory, if memory modifications emerged over time. To tackle this question, the authors compared the results of the original paradigm (that applies a LTM test: memory for List t 1 object is tested in Session 3), with the results from a STM test, in which participants were invited to recall List 1 objects immediately after List 2 learning. The results of STM test showed no intrusions, and the authors claimed that this result reflected the time-dependent nature of the reconsolidation process. Although the authors briefly mentioned that in this manipulation, participants could be actively suppressing List 2 items during the recall of List 1 items, this argument was raised to explain why interference control group (the one that did not learn List 2), performed significantly better than no-reminder and reminder groups, and it was not extended to an interesting debate on the reliability of this manipulation to test reconsolidation hypothesis. In fact, two aspects led us to question the interpretation of the absence of intrusions in STM test as evidence for a time-dependent reconsolidation process. Firstly, time-dependent effects reported in previous non-human studies are commonly evaluated in a within-subject design, in which memory is tested in a short-term and in a long-term. The predictions of a within-subjects design on behavioural interference paradigms,

such as Hupbach's paradigm, are less clear. Considering the role of test on list separation and list discriminability (e.g., Congleton & Rajaram, 2012; Szpunar et al., 2009), this manipulation could lead to a reduction of intrusion in a long-term test. Secondly, the absence of intrusion in STM could be easily explained by other mechanisms such as *recall-to-reject* (Clark & Gronlund, 1996; Hintzman, Caulton, & Levitin, 1998). The term recall-to-reject is used for those decisions in which the retrieval of specific information is thought to disqualify an item from having occurred in a particular context. In Hupbach's study (2007, Experiment 2), participants could have used a "rejection diagnostic" strategy in order to avoid intrusions, in a way that when List 2 objects come to participants' mind, they could identify that information as an information that was presented minutes before (and not in Session 1). In other words, the mnemonic representations of List 2 objects are so vivid, that the participant can easily disqualify it in the List 1 recall test.

Also, regarding correct recall this experiment revealed that retrieving previously learned information (List 1) immediately after the acquisition of new information (List 2) is a very hard task: both groups recalled very few items, and recall rates were very similar between reminder and no-reminder groups. However, differences at the level of correct recall are expressed (though not significantly) in the LTM test which leads us to believe that in the same way that the differences in intrusions recall emerged over time, so does a potential impairment in the correct recall. The authors did not address this question: they claimed that the low correct recall observed in STM test was a consequence of interference or fatigue.

Consideration 7: Evidence for an updated memory trace

Hupbach's results interpretation is based on the idea the once reactivated, memories are subjected to a process of re-stabilization, and until that process is completed, memory trace remains in a labile state. This process of reconsolidation generates a "new version" of List 1 memory trace, commonly called the "updated version". However, there is no clear evidence to assert that. Despite the fact that the challenge of proving that a memory trace does not exist or was eliminated, is, as Sara and Hars (2006) said, an "impossible challenge" (p. 518), it seems premature to take the evidence collected by Hupbach's and discuss it at that level. However, the examination of recovery effects could contribute to that discussion.

Consideration 8: Evidence for an unidirectional intrusion effect

Hupbach and colleagues took the absence of intrusions in List 2 memory test as evidence for a unidirectional intrusion effect. The finding that intrusions are restrictedly observed when the

original memory is tested seems, at first sight, very appealing for the interpretation of the results' pattern under reconsolidation account: the post-reactivation treatment (List 2 learning) had interfered with the reconsolidation of the reactivated memory (List 1). However, Hupbach's interpretation ignores a crucial question: the relative strengths of the original (List 1 items), and newly learned material (List 2 items) after different time intervals. For instance, in Hupbach's original experiment, participants were asked to recall objects that they had learned 96 hours before. However, in the experiment in which List 2 was tested in Session 3, the target memory was only 48 hours old. Considering the impact of retention interval in humans' ability to recall information, the absence of intrusions in List 2 test could merely reflect an easier access to List 2 memory, and the intrusions observed in List 1 test could be reflecting a decay of List 1 trace.

Consideration 9: Circular reasoning

Hupbach and colleagues (2008) conducted a very interesting study in which they systematically explored the component for triggering memory reactivation. The main finding was that spatial context plays a critical role in memory reactivation: spatial context is a necessary and sufficient component to trigger memory reactivation. As the efficiency of the reactivation was accessed by the observation of an intrusion effect, we argue that we could be following a circular reasoning: memory reactivation is efficient if an intrusion effect is observed, and an intrusion effect is observed when a memory is reactivated. In other words, we believe that other potential explanations could be prematurely dismissed.

Consideration 10: The role of spatial context

As previously cited, when discussing the results, Hupbach and colleagues (2011) said: "(...) reactivation is triggered by different cues depending on the test situation" (p. 795). This quote is unsettling, because it emphasized the role of "test situation" in a process that should only be associated with memory reactivation. One can understand the observation of reconsolidation process as comprising three stages: (a) First stage: encoding; (b) Second stage: memory reactivation (and intervention), (c) Third stage: retrieval. What triggered memory reactivation (Stage 2), cannot be determined by something that happened in testing (Stage 3). Although it is debatable if Hupbach and colleagues were referring to the experimental situation of Session 2 (please recall that this quote came from a study in which the role of spatial context familiarity of all sessions) or if they were referring to the test situation (Session 3) *per se*. Nonetheless, the expression "test situation" is not a clear terminology. In this regard, Hupbach et al. (2008) revealed

that the likelihood of observing intrusion-effect seems to decrease if retrieval session is performed in a novel spatial context. This finding was overlooked and its potential implications for data interpretation were poorly discussed.

The presented considerations will steer the reader in the main goals of this dissertation (see the next section).

4.4 Aims of the research of the current dissertation

The considerations pointed in the previous section were viewed constructively and some of them motivated the studies presented in this dissertation. We recognize a lot of potential in the paradigm under scrutiny, however it is important to face that this paradigm has been widely cited and acknowledged even though some questions can be raised about the validity of the paradigm to test the reconsolidation assumptions.

Four main questions guided the studies presented in this dissertation:

1. Is this intrusion-effect replicable?
2. How can we disentangle the intrusion-effect from an interference effect?
3. Is this intrusion-effect unidirectional?
4. What is the role of retrieval context in the results' pattern?

Our first goal raised from some methodological limitations that could be pointed to Hupbach's paradigm (see Considerations 1-5 in this Chapter). We were primordially interested in the replication of the intrusion-effect (Experiment 1) and in gaining a better understanding of the phenomenon. The use of Bayesian data analysis methods along with the traditional null hypothesis significance testing, allowed us to draw more appropriate conclusions from the collected data. In order to test the evidence for reconsolidation of episodic memory without falling in the same reasoning of Hupbach's (see Consideration 9), and rather relying on knowledge that has been gathered in decades of investigation of cognitive psychology, innovative data analyses were conducted. These allowed us to accomplish our second goal. For instance, output position analyses were used to examine a crucial hallmark of reconsolidation theory (see Consideration 7). Also, with an additional source recognition test we explore potential recovery effects (see Consideration 7).

In Experiment 2, we aimed to extend previous findings that suggested an unidirectional intrusion effect (see Consideration 8).

Experiment 3 and 4 were conducted in order to reach our fourth goal. In Study 3 we tested if reconsolidation effect generalizes to new retrieval contexts (see Consideration 9 and 10). Finally, in Study 4 we examined how determinant is memory reactivation for the asymmetrical intrusion effect (that is taken as evidence for a reconsolidation effect).

4.5 References

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PART II

EMPIRICAL STUDIES

The work presented in Chapter 5 and Chapter 6 were submitted for publication to international peer-reviewed journals:

Capelo, A. M., Albuquerque, P. B., & Cadavid, S. (2017). *Reconsolidation hypotheses of episodic memories withstand critical tests of its theoretical assumptions.* Manuscript submitted for publication.

Capelo, A. M., Albuquerque, P. B., & Cadavid, S. (2018). *Exploring the role of context on the existing evidence for reconsolidation of episodic memory*. Manuscript submitted for publication.

Additionally, the present studies were publicly presented at scientific meetings:

Capelo, A. M., Albuquerque, P. B., & Cadavid, S. (2016, May). How reactivating a memory influences what we remember of it. Poster presented at 2nd International Meeting of the Psychonomic Society, Granada, Spain.

Capelo, A. M., Albuquerque, P. B., & Cadavid, S. (2016, April). Exploring the role of context on memory reconsolidation. Poster presented at 11st Meeting of Portuguese Association of Experimental Psychology, Lisbon, Portugal.

Capelo, A. M., Albuquerque, P. B., & Cadavid, S. (2016, July). Exploring the role of context on the existing evidence for reconsolidation of episodic memory. Poster presented at 6th International Conference on Memory, Budapest, Hungary.

Since this dissertation is organized in the format of scientific papers submitted for publication, some adjustments were made in order to ensure that the dissertation follows a coherent sequence. For instance, the indexation of the figures, tables, footnotes, and designation of the experiments (Experiment 1, 2, 3, and 4) were cumulative. The supplementary materials to the papers were presented as appendix in this dissertation.

Chapter 5. Reconsolidation hypothesis of episodic memories withstand critical tests of its theoretical assumptions

5.1 Abstract

In recent years, the long-standing consolidation theory has been challenged and reconsolidation theory has started to play a key role on understanding long-term memories and their plasticity. Research has shown that, after reactivation, a consolidated memory re-enters a state of vulnerability, leading to a reconsolidation process. This finding has high practical and theoretical implications. Although reconsolidation has been mostly studied in animals, researchers are devoting efforts into the translation of animal-research procedures to the human field. Hupbach, Gomez, Hardt, and Nadel (2007) developed an object-learning paradigm that has been widely recognized as evidence for episodic human memory reconsolidation. This paper provides a successful replication of the original finding: reactivation promotes the incorporation of new information into an existing memory. Plus, the strength of the reconsolidation phenomenon was assessed with innovative data analyses based on output position and data from a source recognition test (Exp. 1). Employing a variant of the original paradigm, this research also provides evidence for a critical assumption of the reconsolidation hypothesis: only the original memory is altered (Exp. 2). Our findings indicate that reactivation plays a critical role on the modification of episodic memories and supports the reliability of Hupbach's paradigm to test reconsolidation assumptions.

Keywords: episodic memory; memory modification; reactivation; reconsolidation.

5.2 Introduction

More than a century of research has been devoted to a better understanding of human memory processes. Scientists have been puzzled by how the human memory maintains a balance between memory states of persistence and malleability. Early theories advocated for the immutability of memories due to time-dependent processes (e.g., Dudai, 2004). Now, we are moving to new theories that support the concept of memory malleability (Hardt, Einarsson, & Nader, 2010).

It has long been accepted that initially labile memory traces are converted into relatively stable ones (i.e., memory consolidation process). This process involves molecular and cellular mechanisms that require time to be completed. After this time, memory traces were thought to be resistant to interference. Evidence for this idea has come mostly from research with amnesic treatments (e.g., electroconvulsive shock, protein-synthesis inhibitors). Only when applied immediately after training, amnesic treatments disrupt memory consolidation and cause memory impairment (Duncan, 1949; McGaugh, 1966). This finding has been sustaining one of the most prominent theories of memory, which assigns to consolidated long-term memories a state of steadiness and stability. Therefore, phases of memory vulnerability were restrictedly associated with the period that shortly follows encoding (McGaugh, 2000). Memory failures were mainly understood as momentary problems of accessibility or source confusions, rather than modifications or loss of stored information.

Consolidation theory's assumptions were early called into question (e.g., Cooper & Koppenaal, 1964; Koppenaal, Jagoda, & Cruce, 1967; Misanin, Miller, & Lewis, 1968), but evidence against it was largely ignored. A renewed interest in the topic emerged in 2000 with the Nader, Schaffe, and LeDoux's paper (Nader, Schafe, & LeDoux, 2000). This paper demonstrated that, upon reactivation, well-consolidated fear conditioning memories become transiently vulnerable to an amnesic treatment (injection of protein-synthesis inhibitor into the basal nucleus of the amygdala). It was shown that, alike newly acquired information, reactivated memories are also in an active state (i.e., highly vulnerable; Lewis, 1976) and require a new protein synthesis to persist over time. Therefore, reconsolidation is understood as the process responsible for the re-stabilization of reactivated memories (Agren, 2014; Alberini & Ledoux, 2013; Nader & Hardt,

2009; Schwabe, Nader, & Pruessner, 2014). Hence, reconsolidation theory advocates that memory is not permanently stored as it was proposed by consolidation theory.

The growing body of research seems to confirm the robustness of memory reconsolidation across numerous animal species, paradigms, and post-reactivation manipulations (Besnard, Caboche, & Laroche, 2012; Nader & Hardt, 2009; Schwabe et al., 2014; Tronson & Taylor, 2007). Due to the unsuitability of the manipulations used in animals for humans, most human research resorts to behavioural interference paradigms. In these paradigms, new learning is used as post-reactivation intervention (Chan & LaPaglia, 2013; Forcato, Argibay, Pedreira, & Maldonado, 2009; Hupbach, Gomez, Hardt, & Nadel, 2007; Wichert, Wolf, & Schwabe, 2013; for reviews see Lee, Nader, & Schiller, 2017; Schiller & Phelps, 2011; Scully, Napper, & Hupbach, 2016). This methodological constraint has raised a stance of scepticism from early on. Interventions applied in animals are known to directly act on the molecular substrates of reconsolidation (inhibiting the synthesis of proteins that are necessary for memory re-storage). However, it is questionable whether behavioural interference and drug administration act on the molecular substrates of reconsolidation in a comparable fashion (Soeter & Kindt, 2011). Thus, as proposed by several authors (e.g., Miller & Matzel, 2006; Nader & Wang, 2006), the interpretation of human reconsolidation effect seems to meet the historical and restless debate: Is the experimentally-induced amnesia a consequence of storage deficit (disruption of consolidation) or retrieval deficit? On the one hand, according to reconsolidation theory, memory changes are due to a re-stabilization process of the original memory. Thus, reconsolidation theory claims that the original memory trace is updated. This perspective goes along with the idea of memory overwriting and the "destructive updating" in misinformation paradigm (Loftus, 1979). On the other hand, experimentally-induced trace modifications have also been achieved via retrieval-based mechanisms. These exert a limited temporal influence, and do not necessarily imply an impairment of the memory trace. This interpretation follows McCloskey and Zaragoza's "no impairment" claim over misinformation effect (McCloskey & Zaragoza, 1985), and leans on decades of research on cognitive psychology (i.e., retroactive interference: Spear & Riccio, 1994; extinction: Bouton, 2004; Pavlov, 1927; "cue-dependent forgetting": Tulving, 1974; or "state-dependent retrieval": Eich, 1980). Thus, it is not clear if the memory modifications commonly reported in reconsolidation studies are due to a storage deficit or a retrieval deficit.

Disentangling this theoretical debate through a diagnostic test seems to be an arduous question to tackle. Therefore, retrieval deficits explanations are scarce and systematically

overlooked in reconsolidation literature (Hardwicke, Taqi, & Shanks, 2016; Millin et al., 2001; Riccio, Millin, & Bogart, 2006). Settling the debate is not easy mainly because of two reasons. First, the experimental outcomes taken as evidence for reconsolidation differ considerably. In fact, there is evidence supporting: (1) memory overwriting/rewriting (Chan & LaPaglia, 2013; Schiller et al., 2010; Walker, Brakefield, & Hobson, 2003); (2) memory updating (Forcato et al., 2007; Hupbach et al., 2007; St Jacques, Olm, & Schacter, 2013), and (3) memory strengthening (Finn & Roediger, 2011; Forcato, Rodríguez, & Pedreira, 2011; Sara, 2000). Second, there is a lack of consensus in defining "reactivation". Reactivation has being used to refer to different types of manipulations such as actually retrieving a memory (e.g., Chan & LaPaglia, 2013; Marin, Pilgrim, & Lupien, 2010; Schwabe & Wolf, 2009; Walker et al., 2003) or providing subtle reminders or partial retrieval cues (Diekelmann, 2012; Forcato et al., 2007, 2009; Hupbach et al., 2007; Yacoby, Dudai, Mendelsohn, & Drexler, 2015). Although efforts are being made to test the reconsolidation hypothesis, the consequences of reactivation and post-reactivation manipulations have not been systematically studied yet. While the literature seeks for clarification, a reliable protocol for testing reconsolidation assumptions is urgently needed.

In this paper, we will explore the evidence coming from one of the most cited paradigms used to study the reconsolidation of human episodic memories (Hupbach et al., 2007). The authors developed an object-learning paradigm composed of three sessions: two for encoding and one for retrieval. In the first session, participants are invited to memorise a set of 20 unrelated everyday objects (List 1). In the second session, all participants learned a new set of 20 objects (List 2). Critically, in this session, memory for List 1 is reactivated or not. In the third session, memory for List 1 is tested. Hupbach's results revealed that reactivation of List 1 memory had a clear impact on recall. When tested for List 1, participants in reactivation group intruded significantly more items from List 2 than the participants from no-reactivation group. Curiously, the increase of intrusions did not affect the recall of List 1. Together, these results suggested an update effect of List 1 memory trace. According to the authors, reactivating an existing episodic memory (List 1 memory) made it vulnerable to modifications. This vulnerability allowed the incorporation of information that was presented immediately afterwards (List 2). This finding was very compelling and motivated further studies that contributed to interpret the results under the reconsolidation umbrella. Namely, Hupbach's team revealed that List 1 memory was intact when tested immediately after List 2 learning. This outcome suggests that List 1 memory modification is only expressed after a certain time interval in which, supposedly, reconsolidation takes place (Hupbach et al., 2007, Exp. 2).

Also, the so-called updating effect was strictly associated with a modification of the reactivated memory (Hupbach et al., 2007, Exp. 3): when tested on memory for List 2, participants showed very few intrusions (List 1 items). Importantly, this paradigm conforms to the canonical 3-day experimental design, an important criteria for the appropriate study of the reconsolidation phenomenon (Nader & Hardt, 2009). Additionally, it offers a wide range of opportunities for further manipulations to test the reconsolidation theory's assumptions.

Until now, relevant progresses have been made on identifying what triggers memory reactivation (Hupbach, Hardt, Gomez, & Nadel, 2008). The mnemonic consequences of specific manipulations on the reactivation procedure has been explored as well (Hupbach, 2015). Nonetheless, to the best of our knowledge, only very recently a different research team replicated Hupbach's studies, and their results called into question the original ones (Klingmüller, Caplan, & Sommer, 2017). At this point, three methodological aspects of Hupbach's paradigm should be cautiously analysed. First, as far as we know, all the studies published by Hupbach's team used the same list of objects, and their physical characteristics are not described. Second, instructions provided to participants are not fully stated. Third, sample sizes are considerably small (12 up to 15 participants per group), which can be undermining the internal and external validity of the phenomenon (Button et al., 2013). To overcome these limitations, this paper provides detailed information about the stimuli and procedure used to replicate Hupbach and collaborators' studies. Along with renewed statistical analyses, larger samples, and procedural innovations, we present a critical results' discussion. We analyse to what extent our findings answer to the reconsolidation theory assumptions.

With this paper, we intend to clarify whether Hupbach's findings can be interpreted in the light of the reconsolidation theory. In Experiment 1, we provide a full replication of Hupbach's paradigm. By introducing a source recognition test, we address the unsolved debate on memory modifications (i.e., memory impairment vs. retrieval deficits). In Experiment 2, we tackle a critical assumption of reconsolidation theory: the post-reactivation manipulation affects only the original memory (List 1), but not the memory for the interfering material (List 2). Overall, we provide accumulating evidence for Hupbach's findings, and compelling evidence towards the interpretation of the results under reconsolidation account.

5.3 Experiment 1

Experiment 1 is a replication study of Hupbach's paradigm (Hupbach, et al. 2007). Here, new insights on reconsolidation of episodic memories are fostered by: (1) innovative analyses inspired by long-standing false memory research (i.e., analyses of the relationship between intrusions and correct recall and the output position of intrusions), and (2) the implementation of a new task at the end of the standard procedure.

The reconsolidation effect reported by Hupbach and colleagues (2007) is based on two fundamental analyses: a baseline and a post-reactivation analysis. The baseline analysis ensures that the groups' performance is equivalent at encoding. The post-reactivation analysis compares the groups' performance on a List 1 memory test. We propose that results can be further analysed. To the best of our knowledge, there is no data available regarding the potential moderation effect of correct recall in intrusion rates (i.e., trade-off between correct and intrusion rate, for example, if a better memory for List 1 items prevents intrusions; or if intrusions are a consequence of the adoption of a lenient recall criterion). Also, there is no information regarding the distribution of intrusions across the free recall protocol or, in other words, the output position of intrusions. According to reconsolidation theory, in reactivation group, List 2 items have become part of the List 1 memory trace. Hence, an updated version of List 1 memory trace is created and stored. Therefore, we should expect similar distributions for List 1 items and List 2 items across the recall protocol. If the intrusions (List 2 items) are confined to the last positions, one could argue that the intrusion rate could be explained by different mechanisms from reconsolidation. A possible explanation could be response inhibition (i.e., searching through memory decreases the effectiveness of the ensuing memory searches; e.g., Anderson, Bjork, & Bjork, 1994; Bjork, 1989). Also, results could be interpreted simply by a relaxation of the accuracy criterion (i.e., accuracy criterion for producing a response is relaxed as the participant progresses in the recall test; e.g., Schwartz, Fisher, & Hebert, 1998). Thus, we believe that output position analysis is relevant in the framework of reconsolidation.

Furthermore, the present study implements an additional task at the end of Hupbach's protocol. Here, after the List 1 free recall test, participants perform a source recognition task. They have to identify if an item belongs to List 1, List 2, or if it is a new object. This additional task helps: (a) to examine the source identification of items previously recalled as belonging to List 1; (b) to

explore the source memory of items that participants were not able to recall. Ultimately, this task contributes to the memory impairment vs. retrieval deficits debate. According to the reconsolidation theory, intrusions are due to irreversible modifications of the target memory trace (List 1 memory trace). Therefore, the restore of the original memory (recovery effect) would be inconsistent with that specific prediction. In the present study, a recovery effect will be indexed by modifications in the source identification of an intrusion. If participants allocate an intruded List 2 item to its correct source (i.e., List 2), an important prediction of reconsolidation would not be met. In that case, the retrieval deficit approach would be strengthened. Non-recalled items are also analysed to explore if the bias demonstrated by participants from reactivation group (of assigning List 2 items to List 1) continues to occur.

5.3.1 Methods

5.3.1.1 Participants

Sixty undergraduate students (five males and 55 females) participated in the study in exchange for partial course credits. Participants signed an informed consent and were on average 21.5 years old (*SD* = 3.3). The local Ethical Committee approved this study.

5.3.1.2 Design

The experiment used a between-subjects design in which the only independent variable manipulated was the procedure implemented on Session 2. In Session 2, specific manipulations were conducted in order to reactivate memory for Session 1 (reactivation group), or not (no-reactivation group). Reactivation of Session 1 was attained using the three reactivation components typically employed in Hupbach's paradigm: (a) spatial context - Session 2 was performed in same experimental room of Session 1; (b) experimenter - in Session 2 participants met the same experimenter of Session 1; (c) reminder question - participants were asked about the procedure on Session 1.

5.3.1.3 Materials

As in previous studies (Hupbach, 2015; Hupbach et al., 2007; Hupbach, Gomez, & Nadel, 2009; Hupbach et al., 2008) two lists of 20 unrelated objects were used (e.g., balloon, sponge, comb, etc.). All verbatim instructions and materials are available in supplementary material (see Appendix 2).

The recognition task conducted in Session 3 included: 20 words designating objects from List 1, 20 words designating List 2 objects, and 40 new words that were used as distractors (see Appendix 2). The selected distractors fulfilled two criteria: all corresponded to objects with a suitable size for the procedure and all objects were as much unrelated to the target objects as possible.

5.3.1.4 Procedure

Participants were randomly assigned to one of the experimental conditions: reactivation or no-reactivation. The procedure consisted in three sessions, each one separated by approximately 48 hours. The first two sessions were encoding sessions, and the last one was a recall session. Participants were unaware of this design. They were informed that their memory would be tested on each session for a different set of objects. Data was individually collected.

In Session 1, participants had to memorise a set of 20 unrelated objects (List 1). The procedure was the same for all participants: each object was withdrawn from a bag and placed on a table. Participants were instructed to name the object and to pay close attention to it because their memory was going to be tested. Once participants named the object, the experimenter placed the object in a blue basket. Once all objects were presented, the blue basket containing the objects was hidden and participants were asked to recall as many objects as possible, in any order. The learning criterion was established at 85% correct recall (17 out of 20 objects). The session ended as soon as the learning criterion was reached, or after a maximum of four learning trials.

In Session 2, a critical manipulation was employed: memory for Session 1 was reactivated or not (reactivation or no-reactivation group, respectively). Participants in the reactivation group returned to the same experimental room and met the same experimenter. Additionally, the blue basket used in Session 1 was presented to them, and it was asked whether they remembered what they had done in the previous session. In a follow-up question, participants were asked to describe the procedure of Session 1. Care was taken to avoid any mention of the objects. If participants spontaneously started to recall the items, the experimenter was instructed to stop them immediately (however, no such cases were observed). After the reminder question, participants had to learn a new set of objects (List 2). The no-reactivation group performed the session with a different experimenter, in a different experimental room, and no mention to Session 1 was made. The learning procedure was the same for all participants. All the objects were displayed on the table and participants were instructed to name each one out loud. Once the last object was named,

participants had 30 seconds to study the items. Afterwards, the objects were covered with a wood-made structure and participants had to freely recall the objects. The learning criterion used in Session 1 was also applied in this session.

In Session 3 all participants returned to the same experimental room of Session 1 and were invited to recall List 1 items. As in the original paradigm, all participants performed four free recall tests, each one separated by approximately one minute. During this period, in order to avoid rehearsal, participants were engaged in an unrelated conversation with the experimenter (e.g., collect demographic information, talk about other academic issues, etc.).

The procedure described above represents a reliable and direct replication of Hupbach's paradigm (Hupbach, 2015; Hupbach et al., 2007; Hupbach, Gomez, & Nadel, 2011; Hupbach et al., 2008). However, in this specific experiment, after the four recall tests of List 1, all participants performed a source recognition task in a soundproof cabin. Five practice trials established that participants understood the task. In this self-paced task, 80 concrete nouns were randomly presented, one at a time, on the centre of the computer screen. Participants had to decide if the word referred to an object belonging to List 1, List 2, or if it was a new object. After each response, a white screen was displayed for 1500 ms.

5.3.2 Results

All the analyses were performed with JASP (JASP Team, 2016, Version 0.8.1.1). For effects involving repeated measures, degrees of freedom were corrected for sphericity violations using the Greenhouse-Geisser estimator. For post hoc single comparisons Bonferroni-corrected *p*-values are reported. Mean Squared Error (*MSE*) values are reported, and eta squared (η^2) and Cohen's d (*d*) were used as measures of effect size.

5.3.2.1 List 1 and List 2 acquisition

The number of trials that participants took to reach the learning criterion was measured. If participants recalled less than 17 objects in the 4th trial a score of five trials was attributed. Participants took on average 2.5 trials (*SD* = 0.79) to reach the learning criterion in Session 1, and 1.95 trials (*SD* = 0.72) in Session 2. There were no significant differences between the groups regarding the number of trials to reach the learning criterion in Session 1, ($M_{reactivation}$ = 2.50 , *SD* = 0.78 ; $M_{no\text{-}reactivation}$ = 2.50, *SD* = 0.90), $t(58) = 0.00$, $p = 1.0$, $d = 0.00$, 95% CI [-0.44, 0.44], nor in Session 2, ($M_{reactivation}$ = 1.93 , *SD* = 0.64; $M_{no\text{-}reactivation}$= 1.97, *SD* = 0.81), $t(58) = 0.18$, $p = .86$,

d = 0.05, 95% CI [-0.34, 0.41].

Analysis of the number of recalled objects on the last recall trial revealed that the groups were also matched on List 1 learning, $t(58) = 0.11$, $p = .91$, $d = 0.03$, 95% CI [-0.58, 0.64], ($M_{reactivation} = 17.97$, $SD = 1.33$; $M_{no\text{-}reactivation} = 18.00$; $SD = 1.02$), and in List 2 learning, $t(58) = -1.41$, $p = .17$, $d = -0.36$, 95% CI [-0.73, 0.13], ($M_{reactivation} = 18.17$; $SD = 0.83$; $M_{no\text{-}reactivation} = 17.87$, $SD = 0.82$).

5.3.2.2 Free recall task (Session 3)

5.3.2.2.1 *Overall recall performance.* The mean number of items recalled from List 1 (correct recall, averaged over all the four recall trials) and the mean number of items intruded from List 2 (intrusions, averaged over all four recall trials) are shown in Figure 12.

To establish whether the reactivation of List 1 memory influenced the performance on List 1 test, we used a 2 x 2 mixed ANOVA with Group (reactivation, no-reactivation) as the between-subjects variable and List recall (List 1; List 2) as the within-subjects variable. The ANOVA revealed a significant main effect of list recall, $F(1, 58) = 291.48$, $MSE = 8.33$, $p < .001$, $\eta^2 = .80$, showing that participants accurately recalled more items from List 1 ($M = 10.75$) than from List 2 ($M = 1.75$). Groups did not differ in the total number of recalled items, $F(1, 58) = 0.16$, $MSE = 6.54$, $p = .69$, $\eta^2 = .003$. The ANOVA revealed a significant interaction effect List recall x Group, $F(1, 58) = 15.95$, $MSE = 8.33$, $p < .001$, $\eta^2 = .04$. Specifically, participants from reactivation group recalled significantly less items from List 1, $t(58) = 2.20$, $p = .03$, $d = 0.57$, 95% CI [0.175, 3.658], and significantly more intrusions, $t(58) = 4.73$, $p < .001$, $d = -1.22$, 95% CI [-3.262, 1.322], than participants from no-reactivation group.

No correlation was found between intrusions and correct recall, neither in reactivation group ($r = -.14$, $p = .45$), nor in no-reactivation group ($r = -.21$, $p = .26$).

Considering the limitations of the traditional null-hypothesis (Dienes, 2011), we conducted Bayesian analyses to examine the evidence in favour of null hypothesis (H0) relative to the reconsolidation hypothesis (H1). We calculated Bayes factors using an "objective" JZS prior (Cauchy prior, width 1.0, Rouder, Speckman, Sun, Morey, & Iverson, 2009). With correct recall as dependent variable, the Bayesian t-test provided anecdotal evidence for the H1, $BF_{01} = 0.605$, that is, no-reactivation group differed from reactivation group in the mean number of correctly recalled items. A Bayesian *t-test* with intrusions as dependent variable, $BF_{01} = 0.0007$, provided decisive evidence for the H1 (H1 = There are significant differences in intrusions between reactivation and

no-reactivation groups). More precisely, it means that the data is 1428.6 times more likely to have occurred under the H1 than under the H0 (H0 = Equivalent intrusions recall between reactivation and no-reactivation group).

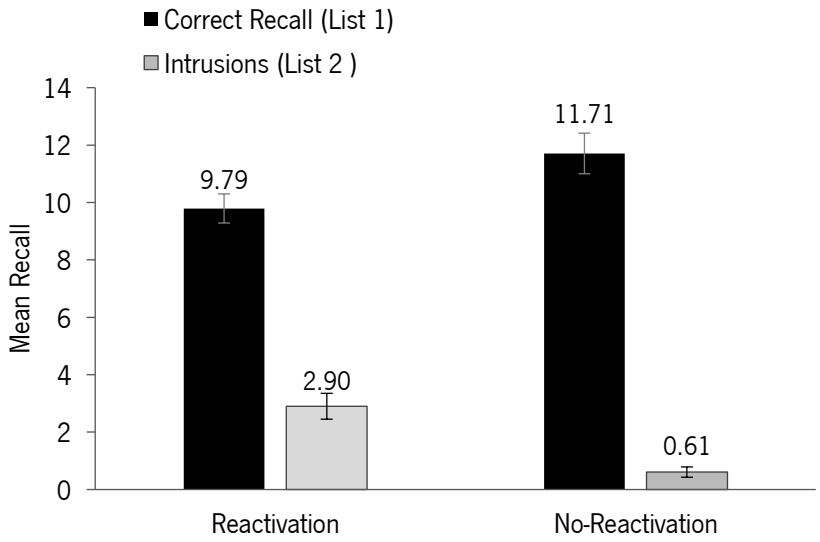


FIGURE 12. Mean number of correctly recalled objects (List 1 items) and intrusions (List 2 items) in Session 3 (List 1 free recall test) separated by group. Error bars represent standard errors of means.

5.3.2.2.2 *Performance across trials.* In order to explore the performance across the four recall attempts (see Appendix 3 for the descriptive statists), correct recall and intrusions were analysed separately with a 2 x 4 mixed ANOVA with Group (reactivation, no-reactivation) as the between-subjects variable and Trial (1–4) as the within-subjects variable. A main effect of trial was found for correct recall, $F(2.17, 126.08) = 23.78$, $MSE = 0.007$, $p < .001$, $\eta^2 = .29$, but not for intrusions, $F(1.60, 92.74) = .19$, $MSE = 0.006$, $p = .78$, $\eta^2 = .003$. Together, these analyses suggest that as the number of recall trials increases, the number of correct recall also increases, but this is not the case for intrusions. A main effect of group was found in both analyses (Correct recall, $F(1, 58) = 4.86$, $p = .03$, $MSE = 0.11$, $\eta^2 = .08$; Intrusions, $F(1, 58) = 22.37$, $MSE = 0.04$, $p < .001$, $\eta^2 = .28$). The reactivation group recalled less correct items (List 1) and showed significantly more intrusions (List 2) than the no-reactivation group. This result suggests a detrimental effect of reactivation. No interaction effects were statistically significant (all $F's \leq 1$, all $p's > .35$). The previous analysis revealed that the trial has a differential impact on intrusion and correct recall, which goes in line with Hupbach's results.

The implementation of four free recall attempts in the original paradigm was never made clear by the authors. According to Hardwicke (2016), the mean recall across trials may not provide

a sensitive estimate of the participants' knowledge, and can lead to its underestimation (diluting higher performance trials with lower performance trials). We then analysed the non-overlapping items recalled across the four trials, in order to have access to the maximum number of correct recalls (List 1) and intrusions (List 2). Again, the analysis revealed that participants in the reactivation group showed significant more intrusions than the no-reactivation group, $t(58) = -5.53$, $p < .001$, $d = -1.43$, 95% CI [-4.59, -2.15], and similar correct recall, $t(58) = 1.97$, $p = .053$, $d = 0.51$, 95% CI [-0.025, 3.92].

5.3.2.2.3 *Output position*. This analysis aimed to explore the output position of intrusions (List 2 items). If the intrusions were restricted to the last positions, the intrusion rate could be explained by different mechanisms from reconsolidation (e.g., response inhibition: Anderson, Bjork, & Bjork, 1994; Bjork, 1989; relaxation of the accuracy criterion: Schwartz, Fisher, & Hebert, 1998).
Figure 13 shows the serial position of correct recall and intrusions in the first trial. Observation of intrusions' distribution suggests that intrusions are evenly distributed across recall protocol.

To proceed with this analysis, the recall protocol of participants who showed intrusions was divided into quartiles. To assign the intrusions to each quartile, we:

(1) Calculated the total number of retrieved items for each participant (sum of correct items and intrusions);
(2) Identified the output position of each intrusion among the total output (e.g., a participant recalled 10 objects, and the 6th object was an intrusion);
(3) Divided the position of the intrusion by the total output (e.g., following the same example: 6/10). If the quotient was between 0 and .249 we assigned it to the first quartile, between .250 and .499 to the second quartile, between .500 and .749 to the third quartile, and between .750 and 1.0 to the fourth quartile (e.g., in the previous example, 6/10 =0.6, so the intrusion would be assigned to the 3rd quartile);
(4) Computed the frequency of intrusions found in each quartile for each participant.

A one-way repeated measures ANOVA revealed that the number of intrusions in each quartile did not differ significantly, ($M_{1st\ Quartile} = 0.76$; $M_{2nd\ Quartile} = 1.10$; $M_{3rd\ Quartile} = 1.43$; $M_{4th\ Quartile} = 1.24$), $F(3, 60) = 1.55$, $MSE = 1.07$, $p = .21$, $\eta^2 = .07$.

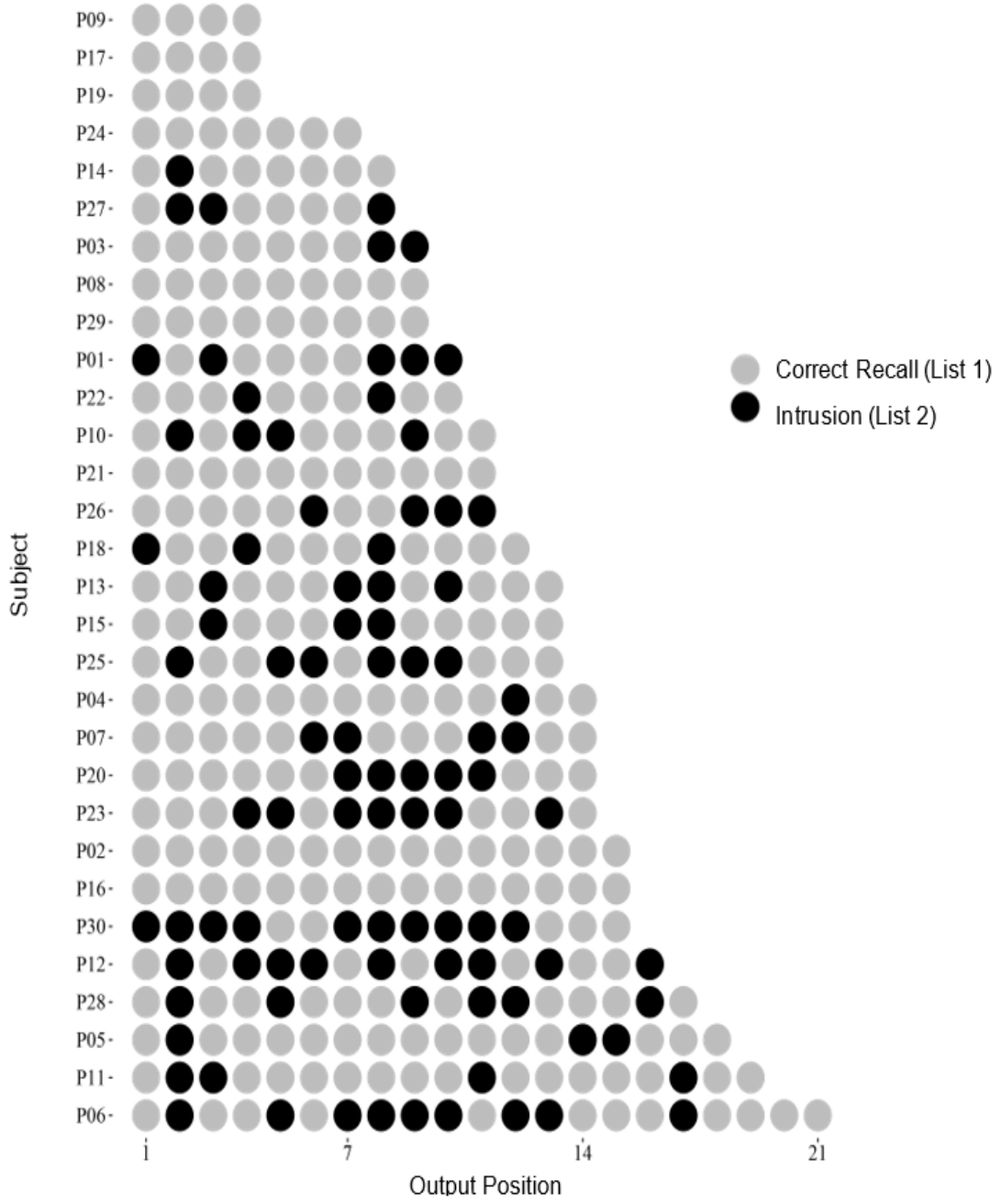


FIGURE 13. Distribution of correct recall (grey) and intrusions (black) across the recall protocol (of first recall attempt).

5.3.2.3 Source recognition test (Session 3)

5.3.2.3.1 Analysis of the source identification of previously recalled items. In this experiment, source recognition test was always performed after List 1 free recall test. From now on, the expression "congruent with recall" will be used to refer to the cases in which participants assigned a previously recalled item to List 1 in the source recognition test, independently of whether that

object actually belonged to List 1 or List 2. In contrast, "incongruent with recall" will be used for the cases in which participants attributed a previously recalled item to List 2, regardless of whether that object actually belonged to List 1 or List 2. The analyses included the items recalled in the last trial of List 1 free-recall test.

We expected to observe congruency between the responses given in the source recognition task and in the recall test (i.e., previously recalled items should be assigned to List 1 in the source recognition). As previously mentioned, deviations from this prediction may challenge data interpretation in light of the reconsolidation theory.

The results of the source memory for the items that participants recalled are depicted in Figure 14.

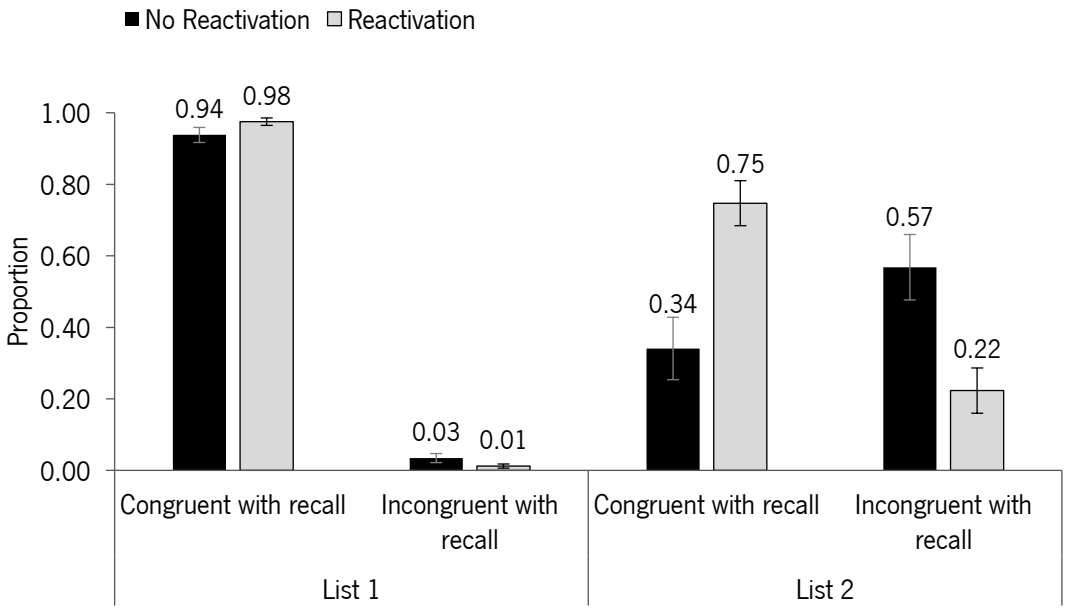


FIGURE 14. Mean proportion of objects from both List 1 and List 2 that were retrieved in List 1 free recall test (Session 3), according to source attribution (congruent and incongruent with recall) and group (Reactivation and No-Reactivation). Error bars represent standard error of the means.

As expected, regarding source attribution of List 1 items, participants from both groups attributed most of the previously retrieved items to List 1 (94% in the no-reactivation and 98% in the reactivation group, $t(58) = 1.58$, $p = .12$, $d = -0.41$, 95% CI [-0.08, 0.01]. Intrusions (List 2 items that were intruded in List 1 test) were also analysed. If an intrusion was attributed to List 2 in the source recognition test, we would be facing a correction of response. Results revealed that, in the no-reactivation group, only 34% of the intrusions were congruent with recall (attributed to List 1), whereas 57% of the intrusions were incongruent with the recall (those intrusions were now

correctly assigned to List 2). Interestingly, an opposite pattern was found in the reactivation group, where 75% of the intrusions were congruent with recall (attributed to List 1), and only 22% were incongruent with recall (intrusions correctly assigned to List 2). Participants in the no-reactivation group were able to correct their answers significantly more often than those in the reactivation group, $t(34) = 2.39$, $p = .022$, $d = 0.87$, 95% CI [0.05, 0.64].

5.3.2.3.2. Analysis of the source identification of non-recalled items. Source identification of non-recalled items was also analysed. We aimed to study the memory for information that was inaccessible for recall (e.g., Tulving & Pearlstone, 1966; Tulving & Psotka, 1971).

Most non-recalled items were correctly attributed to the List they belonged to. Regarding incorrect source attribution, the reactivation group made more errors for items that originally belonged to List 1 than the no-reactivation group, $t(58) = 2.47$, $p = .016$, $d = -0.16$, 95% CI [-0.16, -0.02], ($M_{reactivation} = 1.73$, $SD = 1.62$; $M_{no\text{-}reactivation} = 0.73$, $SD = 0.91$).

5.3.3 Discussion

In this experiment, we replicated and extended the results reported by Hupbach and collaborators (Hupbach, 2015; Hupbach et al., 2007, 2009, 2008). The impact of a new learning (List 2) on the initial learning (List 1) critically depended on the presence of List 1 reactivation in Session 2. Participants who reactivated List 1 memory before List 2 learning recalled significantly more intrusions (List 2 items) when asked about List 1 memory.

We found that reactivation of List 1 memory seems to cause an impairment on correct recall. However, this finding was never reported in previous studies, so it should be cautiously analysed. This difference could be related to the low statistical power of Hupbach's findings, obtained with 12 participants per condition. In fact, the effect size of the difference between reactivation and no-reactivation groups was higher in our study ($d = 0.57$) than in Hupbach's ($d = 0.45$)[4]. Moreover, according to Hupbach (2011), the absence of correct recall impairment

[4] The effect size was not reported in Hupbach's paper. Using G*power (Faul, Erdfelder, Buchner, & Lang, 2009), and the descriptive statistics, we were able to compute Cohen's d effect size. The standard deviations of the mean correct recall and intrusion rate were not reported, and the raw data was not available. To compute standard deviations, we extracted the standard errors from the figure where mean intrusion and correct recall appeared as a function of condition (Figure 12, Hupbach et al., 2007). In this way, we obtained the descriptive statistics for correct recall (reminder: $M = 7.26$; $SD = 3.95$, no-reminder: $M = 9$; $SD = 3.71$) and for intrusions rate (reminder: $M = 4.76$, $SD = 2.84$, no-reminder: $M = 0.98$, $SD = 1.31$).

could be related to the low degree of competition between old and new information. We conjecture that our objects may share more similar properties (e.g., size, colour, etc.), which may have led to a higher competition across lists. However, this variable was not manipulated in this study, making its analysis unfeasible.

Overall, our findings broadly mimic Hupbachs' results. To compare the experimental conditions of our replication study with Hupbach's study, and considering that the samples have unequal variances and unequal sample sizes, Welch t-tests were conducted[5]. In terms of correct recall (List 1 items), our reactivation group did not differ statistically from Hupbach's reactivation group, $t(15) = 2.03$, $p = .06$, 95% CI [-0.13, 5.19]. However, correct recall was significantly higher in the current no-reactivation group than in Hupbach's no-reactivation group, $t(21) = 2.1$, $p = .05$, 95% CI [0.04, 5.38]. Regarding intrusions, no differences were observed between reactivation groups, $t(18) = 1.99$, $p = .06$, 95% CI [-3.83,0.11], nor between no-reactivation groups, $t(16) = 0.88$, $p = .39$, 95% CI [-1.26, 0.52].

The evidence gathered in this study supports the robustness of the asymmetrical intrusion result (i.e., reactivation group present more intrusions than no-reactivation group). It is noteworthy that differences between experimental groups regarding intrusions were significant since the first recall trial and did not increase across trials. The within-group analysis also provides an important result: there is no correlation between correct recall and intrusion rate. The relevance of this result stems in previous memory literature. Earlier studies revealed that if participants adopt a relaxed response criterion (lenient criteria), it is likely to observe an increase both in the number of accurate and inaccurate recalls (Meade & Roediger, 2002; Wright, Gabbert, Memon, & London, 2008; Wright, Startup, & Mathews, 2005). Consequently, our results exclude that the higher intrusion rate in reactivation group could be explained by the adoption of a lenient criterion. Similarly, research has shown that increases in correct recall are often accompanied by increases in false recall of theme-related, critical nonpresented words (McDermott, 1996; Rhodes & Anastasi, 2000; Thapar & McDermott, 2001; Toglia, Neuschatz, & Goodwin, 1999; see also Roediger, Watson, McDermott, & Gallo, 2001). Yet, in other studies, accurate and false recall can vary inversely (McDermott, 1996; McDermott & Watson, 2001; Schacter, Israel, & Racine, 1999; Toglia et al., 1999). Therefore, the negative or positive relation between correct and false recall can be

[5] To compare the current and the previously reported findings, we used a t-test calculator that computes the analysis using sample sizes, means, and standard deviations.

experimentally induced. Our findings constitute a new pattern of results that is not predicted in the field of false memories.

Intrusions' output position analyses revealed that intrusions were evenly distributed across the recall protocol. The rationale for these analyses comes from the idea that reconsolidation process leads to modification in the original memory trace, and from other literature on memory research. Specifically, if intrusions were only observed in the last quartile of the recall protocol, intrusions could be: (1) interpreted as due to the relaxation of the accuracy criterion along the recall test (in that case, intrusions could be mirroring a lenient response criterion rather than an actual memory phenomenon; (Miller & Wolford, 1999), or (2) explained by mechanisms such as response inhibition and output interference. According to this literature, a gradual decline in memory performance is observed as a function of an item's serial position in an output sequence (Anderson et al., 1994; Arbuckle, 1967; Bjork, 1989; Dong, 1972; Roediger, 1973; Roediger & Schmidt, 1980; Smith, D'Agostino, & Reid, 1970; Tulving & Arbuckle, 1963, 1966). False memory research reveals that false memories increase as a function of the serial position in recall protocol, both in the DRM paradigm (McDermott, 1996; Payne, Elie, Blackwell, & Neuschatz, 1996; Roediger & McDermott, 1995), as well as in other paradigms (Schwartz et al., 1998; Sommers & Lewis, 1999). These studies claim that false memories are based on reconstruction and, consequently, they become more probable when the direct access to a memory has been exhausted (for a deeper discussion see Barnhardt, Choi, Gerkens, & Smith, 2006).

Output position analysis seems very pertinent for reconsolidation theoretical discussions. Reconsolidation theory states that reactivating List 1 memory turns its memory trace labile, and susceptible to interfering material (List 2 items), allowing List 2 items to become part of List 1 memory. Therefore, when tested for List 1 memory, participants in the reactivation group would not be accessing the original memory trace, but its updated version. Thus, no specific prediction can be made for the position of intrusions in the recall protocol. Instead, finding intrusions all across the recall protocol would be in line with the reconsolidation account. Our data provided evidence in that sense.

In sum, the free recall protocol analyses considered three axes: mean correct recall and intrusion rate; relationship between correct recall and intrusion rates; and intrusions' output position. Taken together, the results of these analyses showed compelling evidence in favour of reconsolidation phenomenon.

The source recognition test revealed that the vast majority of the items recalled in List 1 test were re-allocated to List 1. Although intrusions were scarce in the no-reactivation group ($M = 0.7$, $SD = 1.3$), more than 50% were correctly assigned to List 2 in the source recognition test. Importantly, this pattern was not observed in the reactivation group, which correctly assigned only 22% of the intrusions to List 2. Reactivation group's consistency between the recall protocol and the recognition test may indicate confidence on considering the recalled items (both correct and intrusions) as belonging to List 1. Critically, this consistency shows that List 1 memory was not recovered in the recognition test. Although our source recognition task cannot be considered as a recovery protocol (e.g., reinstatement, renewal, spontaneous recovery effects), it qualifies as a new opportunity to access to List 1 memory. In this regard, this task constitutes an opportunity for participants to correct their answers. The absence of original memory restore is an important prediction of reconsolidation. However, only few studies explore the recovery effects on reconsolidation paradigms (for a review see Hardwicke, 2016). The few cases available in the human field used fear conditioning paradigms, which makes the comparison with the current paradigm not straightforward. Moreover, the literature is not consistent. Results of those studies vary from finding prevention of fear response re-emergence (Kindt, Soeter, & Vervliet, 2009; Schiller et al., 2010; Thompson & Lipp, 2017) to not finding persistent fear reductions to a conditioned stimulus and even showing recovery effects (Drexler et al., 2014; Fricchione et al., 2016; Kindt & Soeter, 2013; Klucken et al., 2016).

The non-recalled items analysis showed that participants correctly assigned most items to the list they originally belonged to. The reactivation group made more source errors for items that originally belonged to List 1. This outcome could suggest a detrimental effect of List 1 memory trace, or simply a compensation mechanism[6].

The key question of the present study was to explore whether Hupbach's findings could be replicated. In addition, we critically examined the main reconsolidation theoretical assumptions. After this successful replication, we conducted another experiment to address an important prediction of reconsolidation theory: List 2 memory remains unaltered.

[6] A considerable number of items from List 2 were considered as belonging to List 1. Consequently, "List 1" answers were significantly higher than "List 2" answers. If participants realised that difference, they could have started to give more "List 2" answers, leading to higher List 1 source errors.

5.4 Experiment 2

The examination of the detrimental impact of new information on subsequent recall of previously learned information has a long tradition in cognitive psychology (e.g., retroactive interference effect). However, reconsolidation theory claims that the impact of new learning on a previously acquired information critically depends on its reactivation (Agren, 2014; Nader & Hardt, 2009; Tronson & Taylor, 2007).

Following the reconsolidation theory, once a memory is reactivated, it enters in a state of fragility, and the memory trace becomes susceptible to modifications. Considering a reconsolidation paradigm in which new learning is used as a post-reactivation treatment, one should observe: 1) memory modifications in reactivated old information, and 2) no alterations on the memory for the new information. With this premise, Hupbach et al. (2007, Exp. 2) tested if the higher rate of intrusions in reactivation group reflected: 1) an integration of List 2 items into List 1 memory due to reactivation, or 2) an intermix of the two lists related to experimentally-promoted source-monitoring errors. To do so, List 2 (instead of List 1) was tested in Session 3. If the reactivation group showed more intrusions due to source-monitoring difficulties, they would intrude items in Session 3, regardless of the tested List. In contrast, reconsolidation theory predicts that, when List 2 is tested in Session 3, reactivation and no-reactivation groups should have a similar performance. As expected by the reconsolidation theory, results showed that reactivation did not impact memory for List 2 objects, since reactivation and no-reactivation groups did not differ in terms of intrusion rate (List 1 items). Results from a source-monitoring task (Hupbach, Gomez, & Nadel, 2009) revealed that participants in the reactivation group had selective biased misattribution of source towards List 1. Therefore, more evidence was gathered favouring interpretation of results considering reconsolidation theory. In addition, converging evidence has been found in 5-year-old children: they incorporated items from List 2 into memory for List 1, but not vice-versa (Hupbach, Gomez, & Nadel, 2011). Considering the well-documented lack of source-monitoring skills in children (for a review see Foley, 2013), this result is particularly interesting, as it helps to disentangle the asymmetrical pattern of intrusion from an source-monitoring problem.

The above-mentioned studies have provided substantial evidence to validate Hupbach's paradigm as suitable to investigate reconsolidation of episodic memories. However, the reviewed studies have a limitation that is worth further research. In fact, a crucial question was overlooked:

the relative strengths of the original (List 1 items), and newly learned material (List 2 items) after different retention intervals. For instance, in Session 3 of Hupbach's original experiment, participants were asked to recall objects learned 96 hours before (in Session 1). However, in the experiment in which List 2 was tested in Session 3, the targeted memory was only 48 hours old. Retention intervals have a huge impact on humans' ability to recall information. Thus, the absence of intrusions in List 2 test could merely reflect an easier access to List 2 memory, and the intrusions observed in List 1 test could be reflecting a decay of List 1 trace. To overcome this limitation, we conducted a second study in which List 2 memory was tested 96 hours after its acquisition. This manipulation allowed us to make a comparison with the original paradigm, where List 1 is tested 96 hours after its acquisition as well (in Session 3). This way, we could further explore the impact of reactivation in List 2 memory.

5.4.1 Methods

5.4.1.1 Participants

Fifty undergraduate students (46 females and four males; M_{age} = 20.78, SD = 4.20), who had not been included in Experiment 1, took part on the experiment in exchange of course credits. The local Ethical Committee approved this study.

5.4.1.2 Design

As in Experiment 1, the independent variable was the reactivation of List 1 memory in Session 2.

5.4.1.3 Materials and procedure

Materials were identical to those used in Experiment 1. Participants were randomly assigned to each experimental condition: reactivation or no-reactivation. The procedure was similar to Experiment 1 except that: (1) In Session 3, participants were asked to recall List 2 instead of List 1; and (2) Session 3 was delayed 96 hours from Session 2. The experiment was run on Tuesdays (0 hr), Thursdays (48 hr), and Mondays of the following week (96 hr).

5.4.2 Results

5.4.2.1 List 1 and List 2 acquisition

Participants took on average 2.62 trials (SD = 0.73) to reach the learning criterion (recall at least 17 objects) in Session 1, and 2.02 trials (SD = 0.87) in Session 2. There were no significant differences between the reactivation and the no-reactivation groups regarding the necessary

number of trials to reach the learning criterion in Session 1, $t(48) = 0.19$, $p = .85$, $d = 0.05$, 95% CI [-0.37, 0.46]. A significant difference was found regarding the number of trials needed to reach the learning criterion on Session 2, $t(48) = 2.20$, $p = .03$, $d = 0.62$, 95% CI [-0.04, 1.0].

More importantly, regarding the number of recalled objects on the last recall trial, the groups did not differ either on List 1 learning, $t(48) = -0.81$, $p = .42$, $d = 0.23$, 95% CI [-2.22, 0.94], nor in List 2 learning, $t(48) = -1.10$, $p = .28$, $d = 0.31$, 95% CI [-2.37, 0.69]. These analyses show that initial learning was equivalent in reactivation and no-reactivation groups.

5.4.2.2 Free recall task (Session 3)

5.4.2.2.1 *Overall recall performance.* The mean number of items recalled from List 2 (correct recall, averaged over all the four recall trials) and the mean number of items intruded from List 1 (intrusions, averaged over all four recall trials) are presented in Figure 15.

To explore the effect that reactivating List 1 memory had on List 2 memory, we conducted a 2 x 2 mixed ANOVA with Group (reactivation, no-reactivation) as the between-subjects variable and List Recall (List 1; List 2) as the within-subjects variable. The ANOVA revealed a main effect of list, $F(1, 48) = 292.92$, $MSE = 5.61$, $p < .001$, $\eta^2 = .86$, suggesting that participants recalled more items from List 2 (correct recall) than items from List 1 (intrusions). Importantly, neither the main effect of group, $F(1, 48) = 2.57$, $MSE = 3.27$, $p = .12$, $\eta^2 = .05$, nor the interaction, $F(1,48) = 0.90$, $MSE = 5.61$, $p = .35$, $\eta^2 = .003$, reached statistical significance. Together, the results suggest that groups did not differ in terms of correct recall (List 2) and intrusions (List 1).

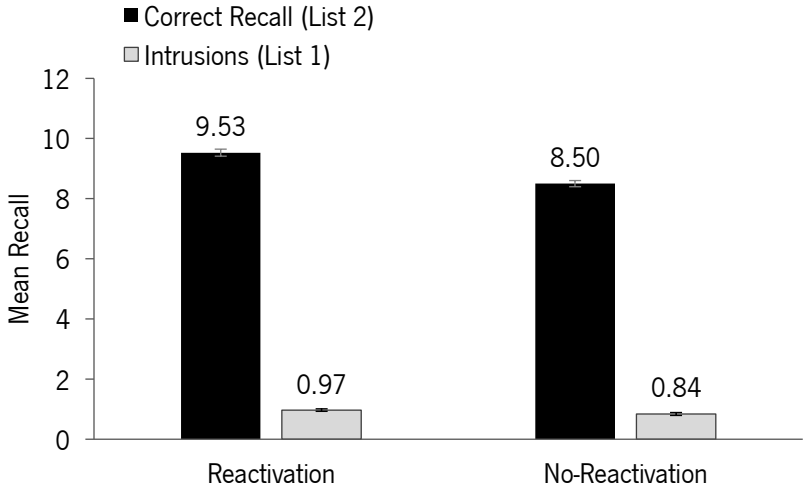


FIGURE 15. Mean number of correctly recalled items (List 2 items) and intrusions (List 1 items) in Session 3 (List 2 free recall test) separated by group. Error bars represent standard errors of the means.

In a Bayesian t-test with mean correct recall (List 2 items) as dependent variable, BF_{01} = 2.18 provided anecdotal evidence for the H0, that is, equivalent List 2 memory in reactivation and no-reactivation. Regarding intrusion rate (List 1 items), the Bayesian t-test revealed BF_{01} = 4.42, moderate evidence for H0, that is, equal intrusions recall in both groups.

5.4.2.2.2 Performance across trials. As in Experiment 1, the number of correctly recalled objects from List 2 were analysed with a 2 x 4 mixed ANOVA with Group (reactivation, no-reactivation) as the between-subjects variable and Trial (1–4) as the within-subjects variable (see Appendix 3 for the descriptive statists). There was a significant effect of trial, $F(2.387, 114.566) = 17.49$, $MSE = 1.37$, $p < .001$, $\eta^2 = .26$, reflecting an increase in correct recall across trials. Neither the main effect of group, $F(1, 48) = 1.76$, $MSE = 30.18$, $p = .19$, $\eta^2 = .04$, nor the interaction Group x Trial, $F(2.387, 114.566) = .89$, $MSE = 1.37$, $p = .43$, $\eta^2 = .01$, were significant. The same analysis was conducted to compare groups across trials regarding intrusions (List 1 items). We found a significant main effect of trial $F(2.335, 112.092) = 11.10$, $MSE = 0.43$, $p < .001$, $\eta^2 = 0.19$, revealing that intrusions increased with trials. The interaction effect between trial and group as well as the main effect of group, did not reach significance, all *F's ≤.90, p*'s > .42.

5.4.4 Discussion

The direct impact on the reactivated memory is an important diagnostic feature of reconsolidation theory. Experiment 2 examined whether the reactivation of List 1 memory before List 2 learning had an impact on memory for List 2. Following reconsolidation theory predictions, we expected a modification of List 1 memory (List 2 items should be incorporated in List 1 memory), whereas List 2 memory should be preserved. As predicted, the results showed that List 1 reactivation had no impact on List 2 memory.

Our findings go in line with previous studies where the updating effect promoted by List 1 reactivation was unidirectional (e.g., Hupbach et al., 2007). Hupbach et al. (2007) considered the absence of List 2 intrusions into List 1 memory as evidence for the unidirectional effect of reactivation. However, we proposed an alternative interpretation. The absence of intrusions in List 2 memory could be reflecting a better memory for List 2 items due to long-term recency effects. To tackle this question, we increased the time between Sessions 2 and 3. In the original paradigm, sessions were separated by 48 hours, so List 1 is tested 96 hours after its encoding. To establish an appropriate comparison with the original paradigm, we used a 96 hours delay between List 2

encoding session (Session 2) and List 2 retrieval session (Session 3). Inevitably, we increased the time interval between Session 1 and Session 3. In our experiment, the time interval between Session 1 and Session 3 was 144 hours, whereas in the original paradigm was 96 hours. Thus, the probability of List 1 interference might be decreased, diminishing its potential impact on List 2 memory (the target memory). However, there are reasonable arguments that help us discarding this hypothesis. For example, the same pattern of results was found when the temporal distance between Session 1 and Session 3 was smaller (96 hours; Hupbach et al., 2007, Exp. 3). The experimental groups performed very similarly in Hupbach et al. (2007, Exp. 3) and in our experiment. Our mean correct recall (List 2 items) was 8.52 for the reactivation group (vs. Hupbach's 9.53), and 9.42 (vs. 8.50) for the no-reactivation group. Our intrusion rate (List 1 items) was 1.08 for reactivation group (vs. Hupbach's 0.97) and 0.34 (vs. 0.84) for no-reactivation group.

Our finding that reactivation uniquely affected the reactivated memory (List 1 memory in Experiment 1), eliminates source-monitoring difficulties as an explanation for the phenomenon observed in the Hupbach's paradigm (Hupbach et al., 2007, 2009, 2011).

5.5 General discussion

Reconsolidation theory postulates that reactivation of an existing memory renders the memory trace labile, susceptible to modifications from new information. This phenomenon of post-reactivation plasticity has been well-supported by animal-research-derived models. Using invasive methods that act at the cellular level, researchers have been able to identify a time-restricted window during which reactivated memories become susceptible to modification. Typically, pharmacological agents that block proteins synthesis are applied in well-defined brain areas that are known to be involved in memory acquisition and consolidation (such as amygdala for fear conditioned memories). The administration of these drugs after memory reactivation results in the disruption of the memory trace. The need for less invasive techniques in the translation for the human field has led to the use of paradigms that raised alternative explanations and brought theoretical ambiguities. However, considering the practical relevance of understanding the memory plasticity underlying mechanisms, efforts are being made to increase knowledge on this topic.

Our studies were conducted to examine the reliability of the existing evidence for episodic memory reconsolidation from a widely cited paradigm. Overall, we found that the presentation of new information after the reactivation of an acquired memory leads to noteworthy modifications on the original memory. We also gathered new information that strengthened the interpretation of results according to the reconsolidation theory.

In Experiment 1 we sought to replicate and extend the reported reconsolidation effect. The first goal was to increase the replicability of the findings. In addition, with the use of new data analysis, we aimed to provide new insights about the data coming from the original paradigm. To achieve the first goal, we provided a clear and detailed description of the instructions and the procedure. Additionally, we increased the sample size, as it affects statistical power and the veracity of the inferences derived from the data. Results revealed a successful replication of an asymmetric pattern of intrusions (reactivation > no-reactivation), suggesting that the impact of a new learning (List 2) on memory for the original information (List 1) depends critically on memory reactivation.

Further data analyses suggested that an accurate accessibility to List 1 memory trace did not prevent the occurrence of intrusions. In this study, List 1 recallers were equally prone to recall intrusions regardless of their accuracy. In other words, correct recall is not related to the intrusion rate. This particular finding highlights a crucial difference with studies in the field of false memories, where typically higher levels of correct recall are related to higher levels of intrusions (Köhnken, Milne, Memon, & Bull, 1999b; Rhodes & Anastasi, 2000; Wright et al., 2008, 2005; but see Roediger et al., 2001).

Moreover, to the best of our knowledge, this is the first reconsolidation study where intrusion output position is analysed. This interesting analysis demonstrated that the intrusions were widespread across the recall protocol. This finding provides further evidence for reconsolidation theory, which predicts similar distributions for List 1 and List 2 items across the recall protocol. Our results seem to strengthen the idea that, in the recall test, participants from reactivation group are accessing a memory trace that has undergone an update (i.e., List 1 memory is now an updated version of List 1 memory that includes List 2 items due to reactivation).

In Experiment 1, after performing the free recall test of List 1, participants were asked to do a source-recognition test. With this task, we examined whether the data would provide support to the reconsolidation theory. On the one hand, reconsolidation theory would expect to find consistency between recall and recognition tasks. On the other hand, modifications (i.e., assigning a previously recalled List 2 item- an intrusion- to List 2 in the recognition test) would be understood

as memory correction. Results agreed with reconsolidation theory's predictions. Participants in the reactivation group were highly consistent in their responses (i.e., intrusions in recall test were re-assigned to List 1 in the recognition task). In other words, in the source-recognition task, the reactivation group was more prone to keep considering intrusions (i.e., List 2 items recalled in List 1 free recall test) as belonging to List 1. In contrast, in the no-reactivation group, 50% of the intrusions were correctly assigned to List 2. This outcome is particularly interesting, as it rules out the hypothesis that the reactivation group were just trying to remain consistent with their previous responses.

In Experiment 2, we tested an important prediction of reconsolidation experiments in which a new learning is used as post-reactivation intervention: only the reactivated memory should show modifications. In the original paradigm, intrusions (i.e., List 2 items recalled in List 1 recall test) in the reactivation group are taken as evidence for memory updating. Since List 1 was reactivated during Session 2, memory for List 1 re-entered a vulnerable state in which new information could be incorporated. The new learning (List 2) is expected to interfere with the original learning (List 1), and not vice-versa. If the memory for new information (List 2) is also altered, the asymmetric pattern of intrusions observed when List 1 is tested could be easily explained by a lack of source monitoring.

To facilitate the interpretation of List 2 memory data, and encouraged by Hupbach and collaborators' findings (2007, Exp. 2), we implemented a variant in the procedure (Experiment 2). Specifically, participants were asked to recall List 2 instead of List 1 and had 96 hours –and not 48 hours– between Session 2 and 3. Results revealed that List 2 memory remained unaltered, and reactivation and no-reactivation groups did not differ in List 2 memory. This unidirectional intrusion effect (List 2 items into List 1 memory, and not vice-versa) suggests that reactivating a memory exclusively targets its original memory trace. These findings deviate from interference explanations and further support the reconsolidation perspective.

Assuming that reactivation of a previously acquired memory enables memory modification in humans entails profound implications at theoretical (Alberini & Ledoux, 2013; Nadel & Land, 2000), clinical (Beckers & Kindt, 2017; Elsey & Kindt, 2017; Lane, Ryan, Nadel, & Greenberg, 2015; Schwabe et al., 2014), and ethical (Hui & Fisher, 2014) levels. This phenomenon is worth additional efforts for its clear understanding, and a considerable amount of manipulations need to be done.

The replication crisis that has been generally observed in Psychology (Ioannidis, 2012, 2014; Maxwell, Lau, & Howard, 2015), and particularly in the reconsolidation field (e.g., Dawson & McGaugh, 1969; Hardwicke et al., 2016), calls into question a defining feature of science: reproducibility. Replication studies should be encouraged and recognized as key for theoretical progress. To stimulate further studies, this paper provides thorough information regarding the procedure of a widely cited paradigm in the field of episodic memory reconsolidation. Combining previous criticisms, and knowledge gathered from different research on cognitive psychology, we contribute with new analyses and new insights on reconsolidation. Taken together, our data provides compelling evidence for the reconsolidation theory.

5.6 References

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Chapter 6. Exploring the role of context on the existing evidence for reconsolidation of episodic memory

6.1 Abstract

Recent research has provided evidence for memory modifications when a post-reactivation treatment (e.g., drugs, new learning) interferes with memory re-stabilization (reconsolidation) process. This finding contradicts the long-standing consolidation theory, and has high practical and theoretical implications. With an object-learning paradigm, Hupbach et al. (2007) showed that episodic memory is highly susceptible to interfering material presented after its reactivation. The reactivation of an original learning (List 1) before a second learning (List 2) led participants to intrude items from List 2 when trying to recall List 1, but not vice-versa. Their work has been widely cited and their findings have been cast in terms of reconsolidation theory. For the first time in literature, we systematically explored the role of the retrieval context as an alternative explanation for Hupbach's results. Our results showed that the intrusion effect occurs independently of the retrieval context (Experiment 3). Additionally, even when the intrusion rate probability is increased (i.e., List 1 memory test is performed in List 2 learning context), groups that did not reactivate the original memory did not commit intrusions (Experiment 4). In sum, we found that the intrusion effect critically depends on the presence of reactivation, discarding alternative interpretations of the results.

Keywords: reconsolidation; episodic memory; memory modification; spatial context.

6.2 Introduction

According to the consolidation theory (Dudai, 2004; McGaugh, 1966, 2000), in long-term memory (LTM), memories remain stable and unsusceptible to modification. Periods of susceptibility are restrictedly associated to the initial phase of memory acquisition. Once memories are stored in LTM, trace modifications are not conceived to exist. In this sense, memory failures are seen as source errors or as difficulties to access an information that is preserved in a storage (LTM). On the contrary, reconsolidation theory (Lewis, 1979; Miller & Matzel, 2000; Nadel & Land, 2000; Nader, Schafe, & LeDoux, 2000b; Sara, 2000) claims that LTM cannot be considered a repository of immutable memory traces. Moreover, it assumes that LTM corresponds to a state in which memory malleability is merely paused. The focus on the "recency of the memory" as the primary determinant of memory fragility was first called into question in the late 60's by researchers who explored the role of memory reactivation (Glickman, 1961; McGaugh, 1966; Misanin, Miller, & Lewis, 1968). It was suggested that, once reactivated, memory re-enters an active state, becoming susceptible to modification. Then, memory is submitted to a "consolidation-like process" (for a review see Alberini, 2005).

In recent years, the reconsolidation phenomenon has been extensively studied and robustly replicated in several species and experimental paradigms (Agren, 2014; Besnard, Caboche, & Laroche, 2012; Nader & Hardt, 2009; Tronson & Taylor, 2007). Most of the evidentiary lines came from animal fear conditioning studies. Researchers were able to induce a selective amnesia effect by injecting protein synthesis inhibitor into the amygdala after reactivating a consolidated fear memory (Nader, Schafe, & LeDoux, 2000a). The long-lasting amnesia caused by a treatment (in this case, pharmacological) administered shortly after memory reactivation is considered a defining feature of memory reconsolidation.

For neuroscientists, reconsolidation theory describes the molecular mechanisms unfolding after reactivation that change memory on the neuronal level (Dudai, 2004). For cognitive psychologists, it offers a new approach to what has been occupying the field for decades: the study of the malleability of memory. In fact, reconsolidation theory provides an explanation for the mechanism that underlies memory distortions, such as the misinformation effect, hindsight bias, and memory interference (Hardt, Einarsson, & Nader, 2010). Due to its undeniable practical (Lane, Ryan, Nadel, & Greenberg, 2015; Nader, Hardt, & Lanius, 2013; Schwabe, Nader, & Pruessner,

2014) and theoretical implications, researchers have been devoting efforts in translating the animal research on reconsolidation to humans (Schiller & Phelps, 2011). One of the main challenges of this translation process is related to the invasive nature of techniques typically employed in animals to interfere with reconsolidation. Therefore, researchers have been working on developing human paradigms to overcome this constraint. Some have resorted to less toxic drugs, such as the beta-blocker propranolol (Brunet et al., 2008, 2014; Kindt, Soeter, & Vervliet, 2009) or controlled electroconvulsive shocks (e.g., Kroes et al., 2014), but the vast majority has used new learning as a post-reactivation intervention (for reviews see Agren, 2014; Lee, Nader, & Schiller, 2017; Schiller & Phelps, 2011). These behavioural interference protocols follow the same canonical structure that commonly defines a reconsolidation paradigm: 1) a well-consolidated memory is reactivated (or not), 2) a new learning moment occurs during the reconsolidation time-window (the period in which the reactivated memory is commonly assumed to be labile), and 3) at least 24 hr later, memory is tested.

Together with supporting evidence for reconsolidation, literature has emerged offering contradictory findings about potential boundary conditions, such as memory age or training strength (Eisenberg & Dudai, 2004; Eisenberg, Kobilo, Berman, & Dudai, 2003; Suzuki et al., 2004; for the counterexamples see Brunet et al., 2008;–Diergaarde, Schoffelmeer, & De Vries, 2006; Wang, de Oliveira Alvares, & Nader, 2009). Plus, other researchers have faced serious difficulties in replicating the phenomenon itself (Dawson & McGaugh, 1969; Hardwicke, Taqi, & Shanks, 2016; van Schie, van Veen, Hendriks, van den Hout, & Engelhard, 2017). These facts advise for a cautious analysis of the existing evidence for the reconsolidation phenomenon. For that reason, in this paper, we will examine Hupbach's work (Hupbach, Gomez, Hardt, & Nadel, 2007), which is acknowledged as the first piece of evidence for reconsolidation of episodic memories.

Hupbach developed an object learning paradigm comprising three sessions, each one separated by 48 hr. In Session 1, participants learn a list of 20 unrelated objects (List 1). In Session 2, memory for List 1 can be reactivated or not, and a new list of unrelated objects is learned (List 2). List 1 memory is reactivated by two contextual components (experimenter and the session's spatial context) and by a reminder question about the procedure of Session 1. Thus, the reactivation group is asked to describe List 1 learning procedure and perform both encoding sessions (1 and 2) with the same experimenter in the same experimental room. On the contrary, the no-reactivation group performs the encoding sessions in different experimental rooms with

different experimenters, and no mention is made to Session 1. Finally, on Session 3, all participants are invited to recall the items learned in Session 1 (List 1 items). In this free recall task, the reactivation group shows significantly more intrusions from List 2 than the no-reactivation group. Results obtained with this paradigm were couched within the theoretical framework of reconsolidation theory as follows: List 1 memory reactivation had rendered memory in an active state, susceptible to the interference of List 2 items. Consequently, after the reconsolidation process is completed (in this case, 48 hour later), the reactivation group does not have access to the original List 1 memory trace. Instead, participants have access to an updated version of the List 1 memory trace, in which List 2 items were incorporated. On a second experiment, Hupbach revealed that this intrusion effect only emerged in a long-term memory test (Session 3), but not immediately after List 2 learning (Session 2). This finding highlighted the time-dependent nature of the intrusion effect (Hupbach et al., 2007, Exp. 2). As predicted by reconsolidation theory, the modifications induced by a post-reactivation treatment (i.e., a second learning) are only expressed after a time interval (at least after 24 hours), rather than immediately. During this time interval reconsolidation processes are thought to take place (Nader et al., 2000a; Strange, Kroes, Fan, & Dolan, 2010; Walker, Brakefield, & Hobson, 2003). Equally important, the so-called updating effect was strictly associated with a modification of the reactivated memory (Hupbach et al., 2007, Exp. 3). In other words, when tested on memory for List 2, participants intruded very few List 1 items, and no differences were found between groups. This result was later supported by a source-monitoring experiment (Capelo, Albuquerque, & Cadavid, 2017; Hupbach, Gomez, & Nadel, 2009).

The memory-updating effect was very compelling and motivated additional research supporting the interpretation of Hupbach's results under the reconsolidation umbrella. Further studies helped to understand which components can trigger memory reactivation (Hupbach et al., 2009), the mnemonic consequences of specific manipulations on the reactivation procedure (e.g., List 1 Subtle reminder vs. List 1 Testing; Hupbach, 2015), and the manipulations to prevent memory update (Hupbach, 2013). The paradigm was also adapted to study the effects of psychosocial stress on episodic memory updating (Dongaonkar, Hupbach, Gomez, & Nadel, 2013).

Hupbach's paradigm has been extensively reported in numerous reconsolidation reviews as evidence of reconsolidation in episodic memories (Agren, 2014; Besnard et al., 2012; Gisquet-Verrier & Riccio, 2012; Hardt et al., 2010; Lane et al., 2015; Lee, 2009; Lee et al., 2017; McKenzie & Eichenbaum, 2011; Nadel, Hupbach, Gomez, & Newman-Smith, 2012; Nader & Hardt, 2009; Sandrini, Cohen, & Censor, 2015; Schiller & Phelps, 2011; Schwabe et al., 2014; Scully, Napper,

& Hupbach, 2017). However, alternative explanations have been proposed to account for the pattern of results found with Hupbach's paradigm (Sederberg, Gershman, Polyn, & Norman, 2011). These go along with an important debate regarding reconsolidation effects' interpretation. According to some authors, the reported phenomenon of memory integration that presumably implies a reconsolidation process could be conceptually formulated in the same terms of extinction. Thereby, results could be a consequence of a process that does not eliminate previous representations, but that creates another representation that competes with the original one (Gisquet-Verrier et al. 2015; Gisquet-Verrier & Riccio 2012; Riccio et al. 2002; Riccio, Millin, et al. 2006). In that sense, these authors have been relying on well-established cognitive mechanisms that operate at memory retrieval, such as context-dependent memory, to approach some of the results that are commonly reported in reconsolidation literature. In fact, literature on context-dependent memory provides an alternative and very straightforward interpretation to Hupbach's data.

An important approach to the role of context can be found in Hupbach, Hardt, Gomez, and Nadel's (2008, Exp. 4) study showing that, when participants recalled List 1 in a new context, only half recalled intrusions. However, the discussion of this result was inconclusive, and the relevance of the inquiry was quite undervalued. Hupbach and her team had then approached the role of experimental context in the intrusion pattern as a component of memory reactivation. They studied the triggers of memory reactivation by isolating the three components that could be operating for that purpose on their previous research: reminder question, spatial context, and experimenter (Hupbach et al., 2008, Exp. 1-3). Results revealed that encoding the interfering material (List 2) in the same experimental room is a sufficient and necessary condition to observe the updating effect. Even in a condition that combined the components "reminder question" and "experimenter", the updating effect was not found.

The hypothesis of context familiarity was later explored in a study with children (Hupbach, Gomez, & Nadel, 2011). Besides replicating the effect on a different population, this study demonstrated that the familiarity with the spatial context modulates the role of spatial context as an effective reminder. In fact, the primary role of spatial context on memory updating was only present when the spatial context was relatively novel. In familiar contexts, other components of memory reactivation –reminder question, experimenter– assumed the role of triggering memory reactivation. In other words, the role of spatial context as reactivation trigger is already accepted. However, the consequences of manipulating the spatial context where memory is retrieved are still

unclear and could call into question the theoretical interpretation of Hupbach's findings.

The matter of the spatial context at retrieval in Hupbach's paradigm should not be dismissed for two reasons. First, a wide number of studies show that manipulations of spatial context affects memory performance (Smith & Vella, 2004). Second, reactivation and no-reactivation groups differ in the extent of association between the context and the two sets of objects (List 1 and List 2). In the reactivation group, both sets of objects are equally related to the retrieval context. Instead, in the no-reactivation group, only the List 1 of objects is related to the retrieval context. In Figure 16.I, Hupbach's paradigm is presented as a function of the context in which each session is conducted. In the reactivation group, the two encoding sessions (Session 1 and 2) are run in the same context (Context A). Thus, Context A is an effective cue for both List 1 and List 2 items. Critically, participants run the retrieval session (Session 3) in that same context (Context A). If participants rely on spatial cues to recall, it is expected to observe the recall of both List 1 and List 2 items (correct recall and intrusions, respectively). Contrarily, participants in the no-reactivation group performed the encoding sessions in two different experimental rooms: List 1 learning in Context A, and List 2 learning in Context B. Consequently, Context A is only linked with items from List 1. At the moment of retrieval, Context A serves as a cue only for List 1 objects, leading to fewer List 2 intrusions. Therefore, the evidence from context-dependent memory in humans can be particularly interesting to account for Hupbach's findings (i.e., higher intrusion rate in the reactivation group). On the one hand, interference reduction paradigm studies suggest that interference is substantially reduced if interfering and target lists are learned in different environments or contexts (e.g., Bilodeau & Schlosberg, 1951; Greenspoon & Ranyard, 1957; Strand, 1970; Zentall, 1970). On the other hand, research on reinstatement effect shows that memory is enhanced when the learning environment is reinstated at test, (e.g., Godden & Baddeley, 1975; Smith, 1979; Smith, Glenberg, & Bjork, 1978; Unsworth, Spillers, & Brewer, 2012; for a review on context-dependent memory effects see Smith & Vela, 2001).

The higher intrusion rate in the reactivation group is also predicted by an interference-based account. Reconsolidation and interference theories differ mainly on considering the intrusion effect as a consequence of processes that operate at encoding (reconsolidation) or at retrieval (interference). According to the reconsolidation theory, in Session 3, only an updated version of the List 1 memory trace exists. However, the interference–based account states that, in Session 3, List 1 and List 2 memory traces are competing for retrieval. In that sense, intrusions (List 2 items) reflect a conflict between competing responses. The disentanglement of these theoretical

approaches mimics the historical and on-going debate on the interpretation of experimental-induced amnesia findings as storage-based impairment or as retrieval deficit (Miller & Matzel, 2006; Nader & Hardt, 2009; Nader & Wang, 2006; Riccio, Millin, & Bogart, 2006c; Sara & Hars, 2006).

The following experiments examine the role of retrieval spatial context in intrusion rate. In the first experiment (from herein Experiment 3), we investigated whether performing the retrieval session in a new experimental room is sufficient to eliminate the intrusion rate elicited by memory reactivation. In a second experiment (from herein Experiment 4), we explored the role of the congruence between encoding context and retrieval context on intrusions rate.

6.3 Experiment 3

In Hupbach and collaborators' previous research, high intrusion rates of post-reactivation learned items are considered as evidence for memory reconsolidation. Criticisms on the paradigm, together with non-conclusive data of an earlier study (Hupbach et al., 2008), led us to examine the retrieval context effect in Hupbach's paradigm. Our question was: Could the asymmetrical intrusion effect be eliminated if List 1 recall task (Session 3) is performed in a totally novel spatial context? According to reconsolidation theory, the manipulation here employed should cause no impact on intrusion rate. In contrast, if the original intrusion effect is a consequence of a context-dependent learning, the present manipulation should lead to a significant decline in intrusion rate.

6.3.1 Methods

6.3.1.1 Participants

Fifty undergraduate students (44 females and six males, M_{age} = 21.10, SD = 4.83) participated in the study in exchange for partial course credits. Only students who had never participated in our lab's reconsolidation studies were admitted in the study. The local Ethical Committee approved this study.

6.3.1.2 Design

The experiment used a between-subject design in which the participants were randomly assigned to one of two experimental groups: reactivation or no-reactivation group. The independent

variable was the reactivation of a previously acquired memory before the presentation of an interfering learning (i.e., reactivation of List 1 memory-trace before List 2 encoding in Session 2). Reactivation of List 1 memory-trace was attained by: (a) spatial context – Session 2 was performed in the same experimental room of Session 1; (b) experimenter – in Session 2 participants met the same experimenter of Session 1; (c) reminder question – participants were asked about the procedure on Session 1.

6.3.1.3 Materials

Two lists of every-day objects were used (List 1: balloon, bow, calculator, toy car, crayon, cup, dice, feather, flash- light, flower, glue, key, sock, sponge, spoon, sunglasses, teabag, tennis ball, toothbrush, whistle; List 2: apple, band-aid, battery, book, cassette tape, cellular phone, comb, dollar bill, elephant, envelope, paper clip, puzzle piece, rock, shovel, straw, thread, tissue, toy pot, watch, zipper). The lists of objects were the same as those used in Hupbach's studies (Hupbach, 2015; Hupbach et al., 2007; Hupbach, Gomez, & Nadel, 2009; Hupbach et al., 2008) and in previous reconsolidation studies conducted in our lab (Capelo, et al., 2017).

6.3.1.4 Procedure

The experiment took place on three sessions, each one separated by 48 hours. Session 1 and 2 were encoding sessions, and Session 3 was a recall session: Session 1, List 1 learning; Session 2, List 2 learning (preceded or not by reactivation); and Session 3, List 1 free recall test. Participants were not aware of this experimental design. Instead, they were informed that their memory for different sets of objects would be tested in each of the three sessions. Data was individually collected.

In Session 1, all participants learned a list of 20 objects (List 1). The experimenter withdrew one object at a time from a bag located on his/her right side, and placed it on the table. Participants had to name the object and to pay close attention to it because their memory was being tested. Once participants named the object, the experimenter placed it on a blue basket located on his/her left side. Once the presentation of the objects had finished, the blue basket containing the objects was hidden. Then, participants were invited to recall as many objects as possible, in any order, without time restrictions. The procedure was repeated until the participants reached the learning criterion (recall at least 17 out of the 20 objects) or a maximum of four learning trials. The learning session took about 20 minutes. This first session took place in an unfamiliar experimental testing room (Context A). The room was on the first floor of the building,

had no windows, and it had noteworthy features: dark green screens in the middle of the room, three computers, and a coat hanger.

In Session 2, all participants learned a new list of 20 objects (List 2). However, memory for Session 1 could be reactivated or not (reactivation and no-reactivation group, respectively). Participants in the reactivation group returned to the Session 1 experimental room (Context A), met the same experimenter, and were reminded about Session 1 procedure. The experimenter showed the blue basket used in Session 1 and asked the participants to describe the procedure of Session 1. Care was taken to avoid any mention of the objects. If participants started to recall the items, the experimenter was ready to stop them (though, no such cases were observed). Participants then learned a new set of objects (List 2). The no-reactivation group learned the new set of objects without previous reactivation of Session 1. These participants met a different experimenter in a different experimental room (Context B) and nothing was mentioned about Session 1. Context B was a meeting room on the ground floor of School of Psychology, with a large window at the back of the room. The learning procedure was the same for all participants. The 20 objects were aligned on a table and participants were instructed to name each object out loud. Once the last object was named, participants had 30 seconds to study the items. Then, objects were covered with a wooden structure and participants had to freely recall the objects. As in Session 1, the procedure was repeated until the learning criterion was met.

In Session 3, all participants had to recall List 1items in a totally new context (Context C). Free recall consisted of four attempts to recall (with no time limit), each one separated by approximately one minute. During that period, participants were engaged in an unrelated conversation with the experimenter (e.g., collect demographic information, talk about other academic issues, etc.). Context C was a professor's office, considerably smaller than Context A or B, with a large desk, a window, and a filled bookshelf on the wall.

All sessions represent a close replication of Hupbach's paradigm, with the exception of Session 3 spatial context (Figure 16.II). To differentiate the present experimental groups from the original paradigm ones, no-reactivation group will be referred as no-reactivation$_{ABC}$ and reactivation group as reactivation$_{AAC}$. The three subscript letters make reference to the context where Session 1, 2, and 3 occurred.

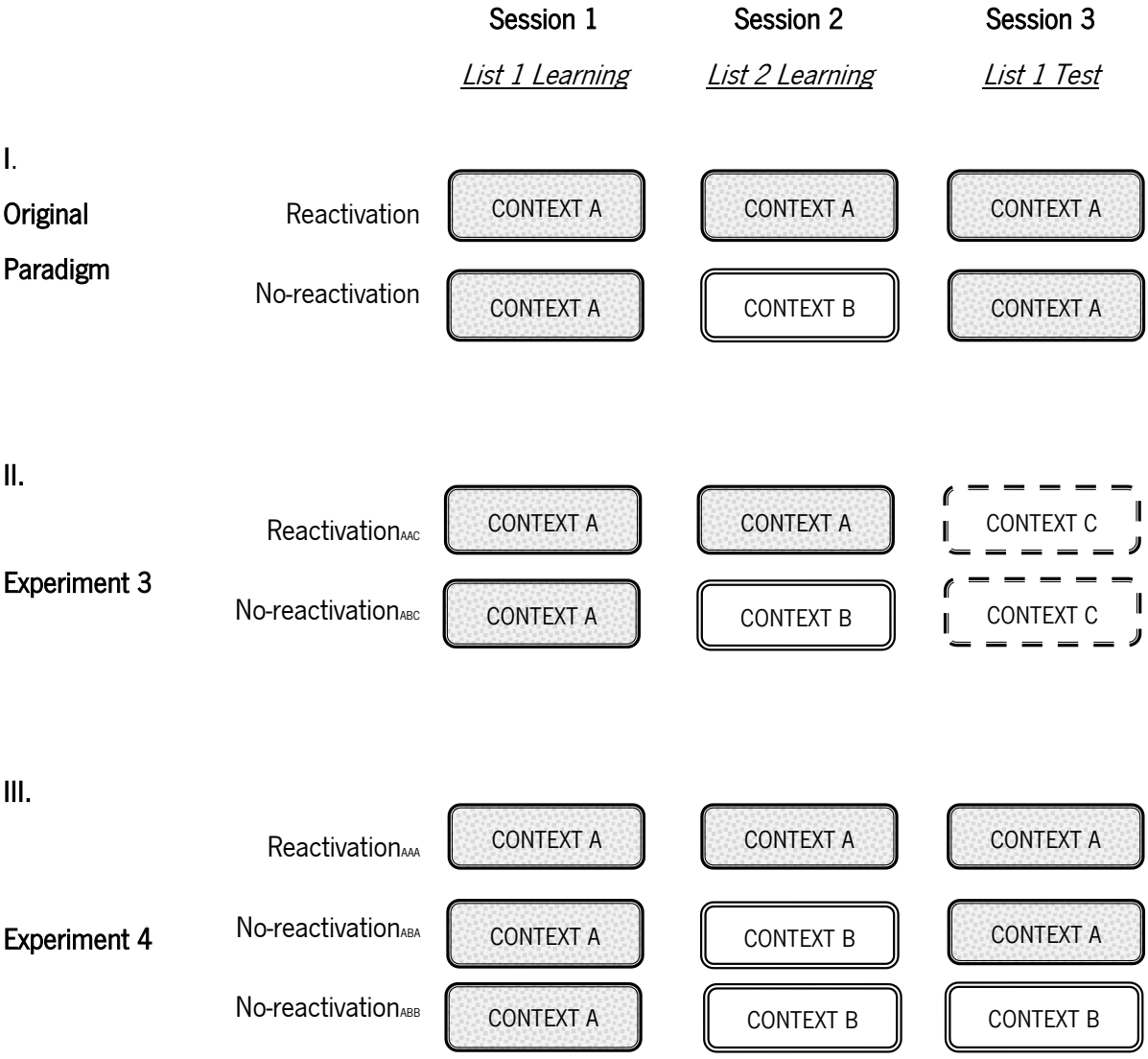


FIGURE 16. Schematic representation of Hupbach's paradigm (I), Experiment 3 (II) and Experiment 4 (III).

6.3.2 Results

6.3.2.1 List 1 and List 2 acquisition

See Table 1.A for the List 1 and List 2 learning performance of each group. In Session 1, participants took on average 2.46 trials (*SD* = 0.76) to reach the learning criterion. The no-reactivation$_{ABC}$ and reactivation$_{AAC}$ groups did not differ in their performance, $t(48) = 0.18$, $p = 0.86$, $d = 0.05$, 95% CI [-0.40, 0.48]. Regarding List 2 acquisition, participants took on average 2.02 trials (*SD* = 0.87) to reach the learning criterion. Groups did not differ in their performance, $t(48) = 0.49$, $p = 0.63$, $d = 0.14$, 95% CI [-0.38, 0.62]. The number of recalled objects on the last recall

trial was also compared between groups. The results show similar List 1 learning among both groups, $t(48) = -0.08$, $p = .94$, $d = -0.02$, 95% CI [-2.23, 2.07], and List 2 learning, $t(48) = -0.45$, $p = .66$, $d = -0.13$, 95% CI [- 0.88, 0.56].

TABLE 1.

Means (and standard deviations) of List 1 and List 2 acquisition. The mean number of trials needed to reach the learning criterion, and the mean number of items that participants recalled in the last trial are presented as a function of condition.

	Number of trials to reach learning criterion				Number of recalled items in the last trial			
	List 1		List 2		List 1		List 2	
A- Experiment 3								
Reactivation$_{AAC}$	2.44	(0.71)	1.96	(0.98)	17.32	(3.77)	17.64	(1.19)
No-reactivation$_{ABC}$	2.48	(0.82)	2.08	(0.76)	17.24	(3.78)	17.48	(1.33)
B- Experiment 4								
Reactivation$_{AAA}$	2.52	(0.82)	1.92	(0.64)	17.84	(1.40)	18.08	(0.86)
No-reactivation$_{ABA}$	2.44	(0.87)	2.08	(0.81)	18.04	(1.02)	17.84	(0.80)
No-reactivation$_{ABB}$	2.88	(1.05)	2.44	(1.26)	17.12	(1.81)	17.68	(1.14)

6.3.2.2 List 1 free recall test (Session 3)

The mean number of items recalled from List 1 (correct recall, averaged over all the four recall trials) and the mean number of items intruded from List 2 (intrusions, averaged over all four recall trials) are displayed in Figure 17.

The main research question was whether the impact of memory reactivation occurs independently of the retrieval context. The performance of both reactivation$_{AAC}$ and no-reactivation$_{ABC}$ group on List 1 memory test was analysed with a 2 (Group: reactivation$_{AAC}$; no-reactivation$_{ABC}$) x 2 (List: List 1; List 2) mixed ANOVA. The ANOVA yielded a main effect of list, $F(1, 48) = 188.51$, $p < .001$, $MSE = 5.94$, $\eta^2 = .76$, revealing that participants recalled more items from List 1 ($M = 8.92$) than from List 2 ($M = 2.25$). A significant main effect of group, $F(1, 48) = 6.77$, $p = .01$, $MSE = 6.20$, $\eta^2 = .12$, was also found. Participants from reactivation$_{AAC}$ group recalled significantly more items ($M = 6.25$) than participants from no-reactivation$_{ABC}$ group ($M = 4.95$). The Group x List

interaction was also statistically significant, $F(1,48) = 13.10$, $p < .001$, $MSE = 5.94$, $\eta^2 = .05$. Specifically, although groups did not differ in terms of List 1 recall, $t(48) = 0.75$, $p = .46$, $d = 0.21$, 95% CI [-0.80, 1.74], participants from the reactivation$_{AAC}$ group recalled significantly more intrusions (List 2 items), $t(48) = -4.04$, $p < .001$, $d = -1.14$, 95% CI [-4.59, -1.54], than participants from the no-reactivation$_{ABC}$ group.

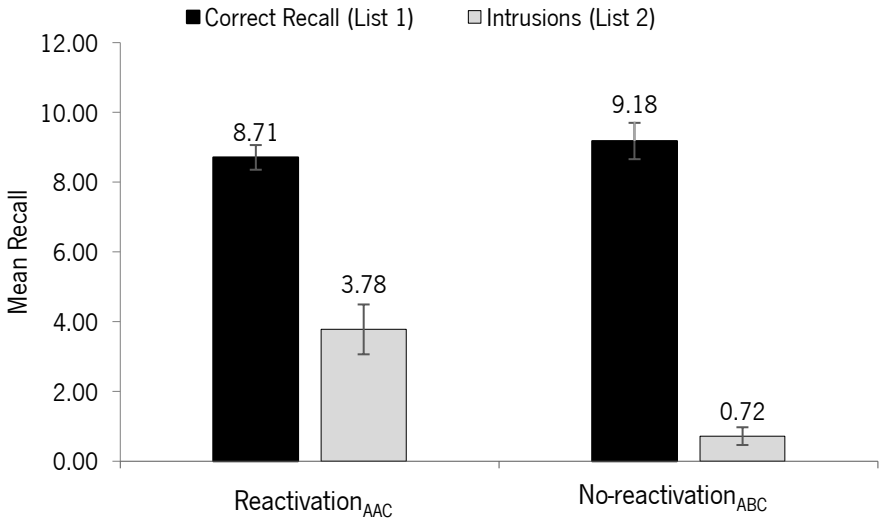


FIGURE 17. Mean number of objects correctly recalled and intruded on Session 3. Data represent means ± standard errors of the means.

Considering the limitations of null-hypothesis significance testing (Dienes, 2011), Bayesian analyses were conducted (Cauchy prior, width 1.0) to examine the evidence in favour of null hypothesis (H0: No differences in performance between no-reactivation$_{ABC}$ and reactivation$_{AAC}$ groups) relative to the reconsolidation hypothesis (H1: no-reactivation and reactivation groups differ in the performance) with the mean correct recall or intrusions as dependent variables (JASP Team, 2016, Version 0.8.0.0). Regarding correct recall (List 1 items), the Bayes factor of $BF_{01} = 3.70$ indicates moderate evidence for the null hypothesis, that is, equivalent correct recall in the no-reactivation$_{ABC}$ and reactivation$_{AAC}$ group. In terms of intrusion rate, the Bayesian *t*-test, $BF_{01} = 0.008$ provided decisive evidence in favour of H1, that stats a difference in intrusion rate between no-reactivation$_{ABC}$ and reactivation$_{AAC}$ groups.

Separate analyses of variance were conducted for correct recall and instrusions to examine the effects of the trial on memory performance in Session 3. We ran two 2 x 4 mixed ANOVAs with group (reactivation$_{AAC}$, no-reactivation$_{ABC}$) as the between-subjects factor and trial as the within-subjects factor (see Table 2.A).

TABLE 2.

Mean number (and *SD*s) of List 1 items that were correctly recalled and List 2 intrusions across the 4 trials of List 1 recall test (Session 3) by group, in Experiment 3 (A) and Experiment 4 (B).

	Trial 1		Trial 2		Trial 3		Trial 4	
	Correct Recall	Intrusions	Correct Recall	Intrusions	Correct Recall	Intrusions	Correct Recall	Intrusions
A. Experiment 3								
Reactivation$_{AAC}$	7.64 (2.25)	3.60 (3.39)	8.40 (1.91)	3.60 (3.58)	9.16 (1.97)	3.88 (3.80)	9.64 (2.18)	4.04 (4.06)
No-reactivation$_{ABC}$	7.88 (2.51)	0.52 (1.16)	8.68 (2.93)	0.68 (1.31)	9.36 (2.98)	0.72 (1.14)	10.80 (2.84)	0.96 (1.70)
B. Experiment 4								
Reactivation$_{AAA}$	8.76 (3.14)	3.12 (2.73)	9.16 (3.51)	3.04 (2.72)	10.04 (2.98)	3.24 (2.89)	10.76 (2.59)	3.00 (3.08)
No-reactivation$_{ABA}$	10.00 (3.76)	0.52 (0.96)	11.00 (3.91)	0.60 (0.87)	11.72 (3.57)	0.72 (1.31)	12.28 (3.23)	0.88 (1.36)
No-reactivation$_{ABB}$	9.80 (3.24)	1.08 (1.85)	10.72 (3.02)	1.20 (1.98)	11.88 (3.33)	1.24 (2.05)	12.28 (2.57)	1.24 (1.98)

In terms of correct recall, there was a main effect of trial, $F(2.406, 115.506) = 34.42$, $p < .001$, $MSE = 1.99$, $\eta^2 = .41$, indicating that accuracy increased over free-recall trials. Both the main effect of group, $F(1, 48) = 0.56$, $p = .46$, $MSE = 19.81$, $\eta^2 = .02$, and the interaction effect Group x Trial, $F(2.406, 115.506) = 1.67$, $p = .19$, $MSE = 1.99$, $\eta^2 = .02$, fell far short of significance.

Regarding intrusions, there was a main effect of group, revealing that participants in reactivation$_{AAC}$ group elicited significantly more intrusions than participants in no-reactivation$_{ABC}$ group, $F(1, 48) = 16.29$, $p < .001$, $MSE = 28.75$, $\eta^2 = .25$. Importantly, there was no main effect of trial, $F(1.893, 90.855) = 2.27$, $p = .11$, $MSE = 1.32$, $\eta^2 = .05$, nor an interaction effect between Group x Trial, $F(1.893, 90.855) = 0.15$, $p = .85$, $MSE = 1.32$, $\eta^2 = .003$.

Considering the floor effect on intrusion rate in no-reactivation$_{ABC}$ group, and the higher variance in reactivation$_{AAC}$ group regarding this variable, we also conducted a non-parametric test with the mean number of intrusion across the four trials as the dependent variable. A Mann-Whitney U-test revealed significant differences between the two groups, $U = 137.5$, $p < .001$, $d = -1.14$, 95% CI [-4.50, -0.50], showing that the intrusion rate is significantly higher in reactivation$_{AAC}$ group.

6.3.3 Discussion

The goal of this study was to address whether the intrusion effect reported in Hupbach's reconsolidation paradigm critically depends on the retrieval context. In that paradigm, memory performances of a group that reactivated a previously acquired memory (List 1 memory) before the encoding of new information (List 2), is compared with a group that does not reactivated the memory. For the reactivation group, all the three sessions (two learning and one retrieval episodes) occur in the same spatial context. For the no-reactivation group, the test session context only matches the context of the target learning episode. The match between List 1 and List 2 learning spatial contexts has already been pointed out as an essential component to observe the intrusion effect (Hupbach et al., 2008). Thus, the critical role of the spatial context on triggering memory reactivation has been identified. However, until now, the potential role of the spatial context in which the memory retrieval is conducted was still unclear. The higher intrusion rate observed in reactivation group has been interpreted accordingly to reconsolidation theory, whereas the apparently obvious analogy to classical context-dependent memory effects (e.g., interference reduction paradigm effects) have been ignored. Clarifying if the spatial context affects remembering was necessary to disentangle the reported intrusion effect from a demonstration of context-dependent memory.

In the present study, all participants were invited to recall List 1 items in a total novel experimental room so that encoding and retrieval contexts did not match in any group. Reconsolidation theory and interference theory predict different outcomes for this manipulation. According to the former, the intrusion rate reflects the access to an updated memory trace. Thus, memory performance in this manipulation should remain similar to the original Hupbach's study: reactivation group should show higher intrusion rates than no-reactivation group. However, according to the latter, intrusion rate is a consequence of a higher interference in reactivation group, in which the encoding and retrieval context match. Therefore, in the current manipulation, reactivation and no-reactivation groups should show similar intrusion rates. As expected by the

reconsolidation theory, our results revealed that the asymmetric intrusion effect occurs independently of the retrieval context. Therefore, the interference account seems to have trouble to accommodate these data.

The available literature on the role of context in episodic memory reconsolidation proposed contradictory hypotheses. On the one hand, previous research conducted in rats pointed the retrieval context as a boundary condition for the updating effect of spatial memory (Jones, Bukoski, Nadel, & Fellous, 2012). The paradigm closely models studies performed in humans, in which spatial context is used as a reminder to reactivate memory. The study replicated Hupbach's findings: when tested for List 1 memories, rats committed intrusions (visits to List 2 feeders), but not when List 2 was tested. Critically, no intrusions occurred when retrieval took place in a new experimental room. On the other hand, Hupbach's studies led us to expect that context would not have an impact on the theoretical interpretation of asymmetrical intrusion pattern. For instance, when List 2 (instead of List 1) was tested, reactivation and no-reactivation groups performed similarly (Hupbach et al., 2007). However, a thorough research was not carried out to explore if the impact of memory reactivation occurs independently of the retrieval context. Our experiment provides a response to this empirical void in episodic memory, by demonstrating that the intrusion pattern withstand the retrieval in a novel context. Thus, our Experiment 3 contributes to the growing body of evidence supporting the idea that there is something special about reactivated memory.

An ultimate test to the reconsolidation theory would need to address whether the scarce intrusions usually reported in the no-reactivation group could be explained by contextual factors. Thus, it would be possible to ascertain whether intrusions (List 2 items) are exclusively dependent on the reactivation of memory.

6.4 Experiment 4

The goal of Experiment 4 was to test whether the reactivation of the initial learning (List 1) before the interfering learning (List 2) was, *per se*, the primary cause for the intrusion of List 2 into List 1 memory. Therefore, we contrasted Hupbach's reactivation and no-reactivation groups with a condition in which the probability of intrusions was enhanced. In this new no-reactivation group, List 2 learning and the List 1 memory test were conducted in the same spatial context (see Figure

16.III).

The rationale for this experiment relies on knowledge gathered from decades of research in episodic memory that could provide alternative explanations for the phenomenon under scrutiny. For instance, the encoding specificity principle states that the information that existed with the target is encoded in an episodic memory trace, and the act of remembering could use that information as a retrieval cue (Tulving & Thomson, 1973). Highly related to that classical principle of episodic memory, there is the reinstatement effect (e.g., Godden & Baddeley, 1975; Smith et al., 1978). The reinstatement paradigm is a widely employed experimental procedure used to assess incidental context-dependent memory. Typically, memory testing occurs either in a context in which the target events were experienced, or in a different context. Results reveal that memory is enhanced when the original context (learning environment) is reinstated at test. The cited literature could explain why Hupbach's no-reactivation group shows a considerable low intrusion rate: learning and retrieval context of the target list matched, whereas the interfering list was learned in a totally different context.

In the current experiment, participants from a modified no-reactivation group were invited to recall List 1 items in the same spatial context in which List 2 learning had occurred (see Figure 16.III). In other words, List 1 items were learned in Context A, whereas List 2 learning and the test session took place in Context B: no-reactivation$_{ABB}$. Of interest was the comparison of this new group with the standard Hupbach's groups. To facilitate the distinction between both no-reactivation groups, we will refer to the standard no-reactivation group as no-reactivation$_{ABA}$, and to the new group as no-reactivation$_{ABB}$. As in Experiment 3, each subscript letter refers to the experimental context of each session. To be consistent with this terminology, reactivation group will be named as reactivation$_{AAA}$.

Considering that the spatial context will be reinstated at test, the literature on context-dependent memory predicts that the new group (no-reactivation$_{ABB}$) will produce a higher rate of intrusions than the no-reactivation$_{ABA}$ group. In this case, the interpretation of Hupbach's intrusion effect as evidence for reconsolidation would be weakened. The same interpretation would be followed if no-reactivation$_{ABB}$ produces as many intrusions as reactivation$_{AAA}$ group. However, if no-reactivation$_{ABB}$ shows fewer intrusions than the reactivation group (and a similar pattern to the original no-reactivation$_{ABA}$ group), reconsolidation hypothesis will be strengthened.

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6.4.1 Methods

6.4.1.1 Participants

A total of 75 students (age: M_{age} = 21.10, *SD* = 3.30), 69 females and six males from University of Minho took part in this study in exchange for course credits. Fifty participants (25 reactivation$_{AAA}$, 25 no-reactivation$_{ABA}$) were randomly selected from a Hupbach's replication study conducted in our lab (Capelo et al., 2017). The other 25 new participants integrated the new experimental condition of interest (no-reactivation$_{ABB}$).

6.4.1.2 Design

A between-subjects experimental design was used with retrieval context as the independent variable. Retrieval context could be: (a) the same in which two different learnings had occured (reactivation$_{AAA}$); (b) a context in which only the targeted memory had been learned (no-reactivation$_{ABA}$); (c) a context in which only the interfering learning had occurred (no-reactivation$_{ABB}$).

6.4.1.1 Materials

Materials were the same as those used in Experiment 3.

6.4.1.2 Procedure

The procedure was similar to Experiment 3, except that there were three (and not two– experimental groups). Two groups were those usually contrasted in Hupbach's paradigm: reactivation$_{AAA}$ and no-reactivation$_{ABA}$. The other condition is a different no-reactivation group. This new no-reactivation$_{ABB}$ group perform the List 1 free recall test in Context B, instead of in Context A (Figure 16.III).

6.4.2 Results

6.4.2.1 List 1 and List 2 acquisition

On average, participants took 2.61 trials (*SD* = 0.93) to reach the learning criterion on Session 1 and 2.15 trials (*SD* = 0.95) on Session 2. In order to explore if the groups matched in the number of trials required to reach the learning criterion, two separate one-way ANOVAs were conducted for List 1 and List 2. The ANOVAs revealed that the groups did not differ significantly on List 1 acquisition, $F(2, 72) = 1.62$, $MSE = 0.85$, $p = .21$, $\eta^2 = .04$, or in List 2 acquisition, $F(2, 72) = 2.00$, $MSE = 0.89$, $p = .14$, $\eta^2 = .05$. (see Table 1.B).

Two additional one-way ANOVAs were conducted to compare the levels of learning of the List 1 and List 2 objects. The total number of items recalled in the last learning trial was the dependent variable. The analyses revealed that groups matched on List 1 initial learning, $F(2, 72) = 2.79$, $MSE = 2.10$, $p = .07$, $\eta^2 = .07$, and List 2 initial learning, $F(2, 72) = 1.13$, $MSE = 0.90$, $p = .33$, $\eta^2 = .03$ (see Table 1.B).

6.4.2.2 List 1 free recall test (Session 3)

The mean number of items recalled from List 1, averaged over all the four recall trials (correct recall), and the mean number of items intruded from List 2 (intrusions rate) are displayed in Figure 18.

The performance on List 1 memory test was analysed by a 2 x 3 mixed ANOVA with list (1 vs. 2) as the within-subjects factor and group (reactivation$_{AAA}$ vs. no-reactivation$_{ABA}$ vs. no-reactivation$_{ABB}$) as the between-subjects factor. The results revealed a main effect of list: all groups recalled more List 1 items than List 2 items, $F(1, 72) = 428.70$, $p < .001$, $MSE = 7.15$, $\eta^2 = .83$. There was no significant main effect of group, $F(2, 72) = 0.38$, $p = .69$, $MSE = 6.01$ $\eta^2 = .01$. There was an interaction effect, $F(2, 72) = 8.10$, $p < .001$, $MSE = 7.15$, $\eta^2 = .03$. Pairwise comparisons between groups for List 1 (correct recall) showed no differences regarding correct recall (List 1 items), all p's ≥ .21. However, regarding the intrusion rate (List 2 items), no-reactivation$_{ABB}$ and no-reactivation$_{ABA}$ groups showed significantly less intrusions (List 2 items) than reactivation group ($p = .02$, and $p = .003$, respectively). Importantly, no differences were observed between the no-reactivation$_{ABB}$ and the no-reactivation$_{ABA}$ groups regarding the intrusion rate ($p = 0.76$).

As in Experiment 4, Bayesian analyses were conducted (Cauchy prior, width 1.0) to examine the evidence in favour of null hypothesis (H0: No differences in performance between groups) relative to the reconsolidation hypothesis (H1: groups differ in the performance) with the intrusions as dependent variable (JASP Team, 2016, Version 0.8.0.0). The present results revealed that reactivation group$_{AAA}$ showed a higher rate of intrusions, and Bayesian analyses provided support for that finding. When reactivation group$_{AAA}$ is compared with no-reactivation group$_{ABB}$, a Bayesian t-test indicated moderate evidence in favour of H1 relative to H0, $BF_{01} = 0.122$. Similarly, the comparison between reactivation group$_{AAA}$ and no-reactivation group$_{ABA}$, held decisive evidence in favour of H1, $BF_{01} = 0.004$. No-reactivation$_{ABB}$ and no-reactivation$_{ABB}$ showed a similar rate of intrusions, and the Bayesian *t*-test revealed anecdotal evidence in favour of H0, $BF_{01} = 2.04$.

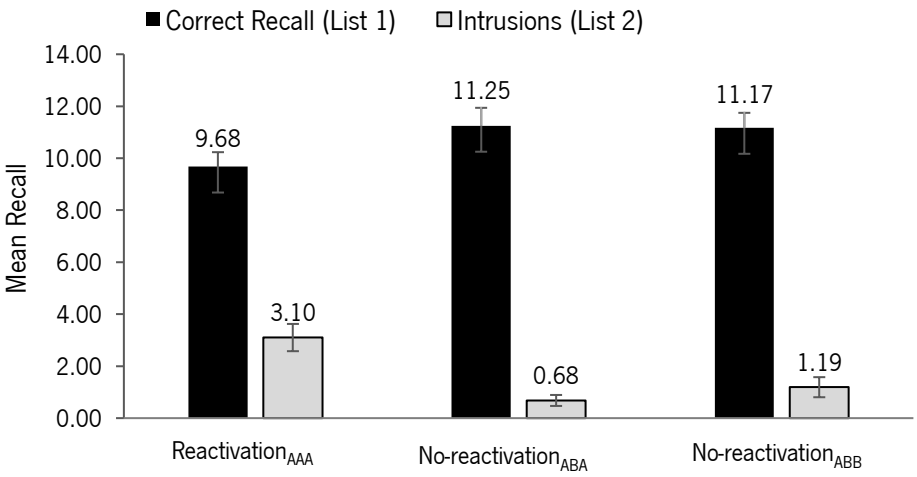


FIGURE 18. Mean number of correctly recalled items (List 1 objects) and intruded items (List 2 objects) in List 1 memory test. Error bars represent standard errors.

To identify any influence of recall trial in performance, we employed a 3 (group: no-reactivation$_{ABB}$, no-reactivation$_{ABA}$, reactivation$_{AAA}$) x 4 (trial: 1–4) analysis (see Table 2.B). Two separate analyses were conducted for correct recall (List 1) and intrusions rate (List 2).

Regarding correct recall, there was a main effect of trial, $F(2.239, 161.203) = 40.43$, $p < .001$, $MSE = 2.46$, $\eta^2 = .36$. There was no main effect of group, $F(2, 72) = 2.11$, $p = .13$, $MSE = 37.04$, $\eta^2 = .06$, or interaction between Trial x Group, $F(4.478, 161.203) = 0.49$, $p = .77$, $MSE = 2.46$, $\eta^2 = .009$.

The 3 x 4 ANOVA conducted for intrusion rate revealed no main effect of trial, $F(1.906, 137.267) = 0.59$, $p = .55$, $MSE = 1.15$, $\eta^2 = .08$, or interaction between Trial x Group, $F(3.81, 137.267) = 0.416$, $p = .78$, $MSE = 1.15$, $\eta^2 = .01$. There was a main effect of group, $F(2, 72) = 10.43$, $p < .001$, $MSE = 15.60$, $\eta^2 = .23$. This outcome is consistent with previously presented analysis: reactivation$_{AAA}$ group recalled significantly more intrusions than no-reactivation$_{ABB}$ and no-reactivation$_{ABA}$ groups, which, in turn, did not differ from each other.

6.4.4 Discussion

With this experiment, we aimed to further evaluate the nature of the reported updating effect (Hupbach, 2015; Hupbach et al., 2007, 2008, 2011). Specifically, we explored the role of spatial context in the intrusions rate. To do so, a modified no-reactivation group was contrasted with the standard no-reactivation and reactivation groups. This modified no-reactivation group (no-reactivation$_{ABB}$) resembles the original Hupbach's no-reactivation group (here referred as

no-reactivation$_{ABA}$) with a crucial difference: in no-reactivation$_{ABB}$, List 2 learning context was reinstated in the retrieval session. Results showed that the reinstatement of List 2 encoding context in the retrieval session did not influence the intrusion rate (i.e., no differences between no-reactivation$_{ABA}$ and no-reactivation$_{ABB}$). Reactivation group elicited significantly more intrusions than both no-reactivation$_{ABA}$ and no-reactivation$_{ABB}$ groups.

An ultimate test to the hypothesized causal relationship between memory reactivation and intrusions should demonstrate that, even when the occurrence of intrusions is favoured by context manipulations, the no-reactivation groups do not elicit intrusions. In this sense, we showed that, even on favourable conditions for intrusions' occurrence, the no-reactivation$_{ABB}$ group recalled significantly fewer intrusions than the reactivation$_{AAA}$ group. Thus, reactivation seems to be a critical ingredient to elicit the intrusion effect.

An extremely important result was that the standard no-reactivation$_{ABA}$ group did not differ from the modified no-reactivation$_{ABB}$ in correct recall, nor in intrusion rate. This suggests that spatial context cues were not being used as a retrieval cue. In other words, in this paradigm, participants do not rely on environmental information to guide recall. Together with Experiment 3, the present experiment discards the role of context in the asymmetric intrusion pattern reported in Hupbach's paradigm, and strengthens the interpretation of the intrusion effect as a reconsolidation phenomenon.

6.5 General discussion

Reconsolidation theory has captured researchers' attention on the last few decades, offering insightful explanations for the malleability of long term memories. However, it has been pointed out that interpretations of the data in the light of other theories (such as interference) have been prematurely put aside for the sake of a reconsolidation interpretation (Gisquet-Verrier et al. 2015; Riccio et al. 2002; Riccio, Millin, et al. 2006; Gisquet-Verrier & Riccio 2012) . In this work, we explored the evidence from a widely cited paradigm (Hupbach et al., 2007) that is considered to provide a compelling demonstration of episodic memory reconsolidation. Specifically, we tackled the role of spatial context, which seems to be a critical test of the reconsolidation hypothesis.

In Hupbach's paradigm, participants learn two sets of objects (List 1 and List 2) on two different sessions. In a third and final session, memory for List 1 is tested. Typically, two groups are contrasted: a group that reactivated memory for List 1 before learning List 2 and a group that does not reactivate memory before List 2 learning. An asymmetrical intrusion rate is found: participants who reactivated memory for List 1 before List 2 learning intruded significantly more List 2 items into the memory of List 1. This result was interpreted in light of the reconsolidation theory. According to this theory, reactivating List 1 memory before List 2 learning destabilizes List 1 memory, turning it susceptible to the interference of List 2 items. Consequently, List 2 items are incorporated in List 1 memory.

The present studies proposed a challenging perspective over Hupbach's paradigm. We followed the claim that the spatial context where the sessions took place could be playing an important role in the reported findings. Hupbach and collaborators expressed the distinction between reactivation and no-reactivation groups in terms of the existence/absence of memory reactivation. We proposed an alternative formulation, based on two different methodological aspects of the paradigm. First, previous studies demonstrated that spatial context is an essential and sufficient component for memory reactivation, and for the asymmetrical intrusions pattern to be observed. Considering the spatial context as a component that triggers memory reactivation has two implications: (a) reactivation group has to perform both encoding sessions (List 1 and List 2 learning) in the same spatial context, and (b) no-reactivation group has to do it in different spatial contexts. Second, in the original paradigm, all groups were tested in the same spatial context of List 1 encoding session. Our claim was that Hupbach's groups differed in terms of retrieval context: whether it is linked only to the target list (no-reactivation group), or whether it is also linked to the interfering list (reactivation group). The finding of more intrusions in the reactivation group could be easily explained by a context-dependent memory approach.

The idea that reconsolidation theory explains the reported finding has very relevant theoretical implications. According to this theory, once reconsolidation is completed, the original memory trace has undergone modifications. Therefore, the subsequent retrieval moments will access a new version of the memory trace. This approach is closely related to the proposal of memory overwriting found in the literature regarding the misinformation effect (Loftus, 1979). On the contrary, alternative explanations deviate from a view of memory impairment, in favour of a retrieval deficit explanations (McCloskey & Zaragoza, 1985). These argue for the existence of memory traces that, at the time of retrieval, compete with each other. In this paper, we tested this

explanation. A diagnostic test for this question had not been conducted until now. Consequently, the interpretation of the asymmetric intrusion pattern as evidence of a reconsolidation phenomenon was not clear yet.

In Experiment 3, we demonstrated that the intrusion effect occurs independently of the retrieval context. An analysis of the original paradigm raised the hypothesis that the higher intrusion rate observed in the reactivation group could be due to the reinstatement of the encoding context at retrieval. Thus, in this experiment, all participants were invited to perform the memory test in a new room (in which no learning had occurred). The asymmetrical pattern of intrusions was found, demonstrating that the reactivation effect generalizes to other retrieval contexts. Therefore, the expression of an updated memory is not bound to the context, contrary to what was reported in rats (Jones et al., 2012).

In Experiment 4, we aimed to understand if the intrusion rate could be mediated by the congruency between encoding and retrieval context, or if it was a consequence of the reminder presence *per se*. For this purpose, we tested if a group that does not reactivate memory, but performs the List 1 memory test in the same spatial context where List 2 items were encoded, is prone to retrieve intrusions (List 2 items). The results revealed that even with this specific manipulation to enhance intrusions, the no-reactivation group did not elicit intrusions. The intrusions' rate critically depended on reactivation.

The results gathered from Experiments 3 and 4 work together for a better understanding of the role of retrieval context in correct recall and intrusion rate. In addition, the comparison between reactivation$_{AAC}$ and no-reactivation$_{ABC}$ groups of Experiment 3 with reactivation$_{AAA}$ and no-reactivation$_{ABB}$ of Experiment 4, provides interesting insights on this issue. It should be noted that what distinguishes these groups is the context of retrieval. When we compared reactivation$_{AAC}$ and reactivation$_{AAA}$ groups, we found that the retrieval context did not influence the correct recall, $t(48) = 1.48$, $p = 0.15$, $d = .42$, 95% CI [-0.35, 2.29], nor the intrusion rate, $t(48) = -0.77$, $p = .45$, $d = -0.22$, 95% CI [-2.46, 1.10]. In contrast, when the no-reactivation$_{ABC}$ and the no-reactivation$_{ABA}$ groups were compared, we found that the retrieval context affected correct recall, $t(48) = 2.40$, $p = .02$, $d = -0.98$, 95% CI [0.33, 3.81]. In other words, when the context of retrieval is the same as the context of encoding, and that context is only associated with one encoding moment, memory is enhanced. This result corroborates the predictions of encoding specificity principle (Tulving & Thomson, 1973) and reinstatement effect (for a review see Smith & Vela, 2001). Importantly, regarding the intrusion rate, there were no differences between the groups, $t(48) = -0.12$, $p = .90$,

d = -0.03, 95% CI [-0.70, 0.62. Thus, these analyses suggest that the observation of such memory effects depended on how many learnings took place in the same context. In the case of the reactivation$_{AAA}$ group, the same context is bound to List 2 and List 1, so when this context is reinstated at the time of retrieval, the performance does not seem to be affected. However, in the case of no-reactivation groups (no-reactivation$_{ABA}$ and no-reactivation$_{ABB}$), learning took place in different contexts. In these groups, memory is enhanced when the learning context of List 1 is reinstated in the List 1 test session (no-reactivation$_{ABA}$). In sum, regarding correct recall, we replicated classic principles of human memory. However, we also demonstrated that intrusion rate cannot be explained by the same principles. Reactivation seems to be promoting a specific memory phenomenon that is generalized across contexts. This phenomenon seems to be determinant to the interference of a second learning on an original memory.

Until now, cumulative evidence has been gathered demonstrating the viability of Hupbach's paradigm to address reconsolidation of episodic memories. The intrusion effect seems to occur independently of the retrieval context (Exp. 1) and the interference of List 2 on List 1 memory seems to depend on reactivation (Exp. 2). Our new findings ensure the interpretation of the asymmetrical pattern of intrusions as evidence for reconsolidation of episodic memories. It is noteworthy that there are still important questions to be answered: what is the role of stimuli? Would the asymmetrical intrusion pattern increase with a higher competition between List 1 items and List 2 items? Under appropriate manipulations that could guide retrieval (e.g., providing stimuli categories or other retrieval cues), would the intrusion effect remain? The paradigm under scrutiny seems to offer an opportunity to conduct further studies that will undoubtedly foster the understanding of the mechanisms responsible for the plasticity of episodic memory.

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PART III

CONCLUDING REMARKS

Chapter 7. Final considerations

We have found it of paramount importance that in order to progress we must recognize the ignorance and leave room for doubt. Scientific knowledge is a body of statements of varying degrees of certainty - some most unsure, some nearly sure, none absolutely certain.

(Feynman, 1999, p. 146)

7.1 Introduction

The main goal of the studies described in this dissertation was to investigate the evidence for reconsolidation of episodic memory. Particularly we were interested in investigating whether a widely cited paradigm (Hupbach, Gomez, Hardt, & Nadel, 2007) would be appropriate for the study of human episodic memory reconsolidation. The need for the present set of studies came from specific concerns related to the paradigm itself, but also from broader theoretical and methodological challenges faced by researchers who study reconsolidation theory's assumptions in humans.

To address this question, we first conducted a replication study to see if the outcomes from our paradigm lead to the results' pattern that is commonly found in the literature (intrusion into a previously reactivated memory). The methodological aspects that initially made us anticipate reproducibility difficulties were exceeded. Although we had successfully replicated the asymmetrical intrusion-effect, we faced this finding with a critical and innovative stance. New data analyses and statistical approaches were used in order to promote new insights on this

topic. Then, our objective was to extend previous results that suggested that the reported effect was unidirectional, and to further explore the role of retrieval context in the paradigm. Our results were very consistent, thus allowing a better understanding of the phenomenon, and providing a humble contribution to this research line.

The following section is devoted to reviewing a central issue of this dissertation: "what is the evidence for episodic memory reconsolidation phenomena in humans?" This section has a main focus on our contributions for answering that question. Then, we discuss the potential implications of reconsolidation theory and finally we explore new insights that could guide future work.

7.2 What is the evidence for episodic memory reconsolidation phenomena in humans?

Since the year 2000, the idea of long-term memory as a stable warehouse of memory traces has been critically challenged by neuroscience community (Dudai, 2000; Nadel & Land, 2000; Nader, Schafe, & LeDoux, 2000; Sara, 2000), and consequently the debates initiated in the 1960s rapidly resurfaced (e.g., Riccio, Millin, & Bogart, 2006; Sara & Hars, 2006). In this sense, the perspective over memory errors claimed by the proponents of consolidation theory as difficulties of accessing a previously stored information was weakened by researchers who examined consequences of memory reactivation. The development of neurobiological research has been providing evidence for the initiation of a labile and active state after the reactivation of a well-established memory. This active state is characterized by a high susceptibility to memory modifications. Moreover, the process of memory re-stabilization that reactivated memories are subjected to, resembles the processes of memory acquisition (in which a newly acquired memory is stored, Alberini, 2005; Dudai, 2004; Rodriguez & Bermúdez, 2007).

Although the study of memory reconsolidation in humans were inspired by the revival of research in non-human animals (Chapter 3), reconsolidation theory directly relates to a rich tradition of research in cognitive psychology demonstrating the malleability of human memory. So, when answering this section's opening question, it is noteworthy that, since 1930, researchers have been gathering evidence in favour of a conceptualization of memory as a

reconstructive process, and a conceptualization of long-term memories as mutable entities. As Bartlett wrote: "(...) the description of memories as 'fixed and lifeless' is merely an unpleasant fiction" (p. 811). Thus, the dynamic nature of human episodic memory caught researchers' attention and fostered numerous studies (e.g., misinformation effect, hindsight bias, flashbulb memory, hypermnesia, reminiscence, and interference). Recently, some authors suggested that reconsolidation theory has brought into light what has long been a subject of study in cognitive psychology, offering neurobiologically plausible mechanisms that might explain the processes that underpin these effects (Hardt, Einarsson, & Nader, 2010). Since reconsolidation theory may provide a framework for well-documented effects on the malleability of memory, efforts have been made to design reconsolidation research paradigms allowing a systematic study of this effect and a clearer comparison with animal models.

However, the translational research on reconsolidation theory faced obstacles from the very beginning (see Chapter 3, section 3.2). Importantly, these early obstacles also reflect current problems, leading us to approach this subject with care, and impartiality.

In this dissertation, we aimed to highlight the inherent complexity of empirical investigations of memory reconsolidation. This complexity is very much related to the reconsolidation interventions and techniques available. For instance, it is currently impossible to demonstrate that a memory trace has been modified or erased as claimed by reconsolidation theory. As Lewandowsky, Ecker, Farrell, and Brown (2012) outlined about consolidation, reconsolidation can also be seen as a "curiously 'invisible' construct" (p. 37), that must rely on indirect inferences (see also Nader, 2006; Tronson & Taylor, 2007). Additionally, the methodological heterogeneity from which reconsolidation has been approached, coupled with a lack of direct replications and a plurality of empirical outcomes of reconsolidation studies, contribute to intensifying the complexity of the discussion of central tenets of the theory.

This dissertation is focused on a widely cited and recognized paradigm, which seemed to be a good candidate for the development of an experimental approach for the exciting and controversial aspect of reconsolidation theory: the idea of a memory updating mechanism (Dudai, 2009; Exton-McGuinness, Lee, & Reichelt, 2015; Lee, 2009). In order to avoid the theoretical confusions that result from the proliferation of ad-hoc hypotheses (Hardwicke, 2016) we conducted critical tests to reconsolidation's hypothesis by means of four different studies.

Our contributions to the field of reconsolidation of episodic memories can be drawn at two different levels, methodological and theoretical.

At a methodological level, Study 1 provides a larger scale and direct replication of Hupbach's original findings. Direct replications are scarce in the field of reconsolidation (Hardwicke et al., 2016), and conceptual replications far more frequent. Conceptual replications refer to studies in which researchers vary parameters or methodological aspects of previous studies, in order to test the generalisability of the theory. In this sense, conceptual replications play a crucial role in the development of a theory or a model (Open_Science_Collaboration, 2012; Schmidt, 2009; Tsang & Kwan, 1999). However, they can be considered a high-risk procedure (Hendrick, 1990), and an unexpected result (replication failure) could be poorly enlightening, especially when conceptual replications are conducted in a non-systematic fashion. In such cases, it would remain unclear if: (a) the results were due to a misconception in the new experimental apparatus; or (b) if the original findings were not replicated because of artefacts, sampling error, fraud, etc. As stated, conceptual replications are necessary, but they have to be conducted systematically, with a clear manipulation of theoretically-relevant parameters (Schmidt, 2009), and still, direct replications should be encouraged. However, this is not always the case, and, consequently, the source of deviations from the original findings is not easy to identify (see Chapter 3, section 3.2). Regarding the paradigm under analysis, only very recently an attempt to replicate it was conducted by Klingmüller and collaborators with unsuccessful results (Klingmüller, Caplan, & Sommer, 2017). The difficulties faced by these authors, highlight the importance of the methodological aspects of Hupbach's paradigm that we had identified as potentials obstacles for a replication study (Chapter 4, section 4.3, Considerations 1-5), and stress the need for clearer methodology.

We resorted to several tools to increase the likelihood of observing the intrusion-effect. For instance, we provided a full description of the procedure and instructions and detailed presentation of stimuli. Additionally, data analysis was complemented with the Bayesian statistical test, the sample size was augmented and, consequently, statistical power was increased.

Regarding our theoretical or conceptual contributions, there are some aspects that merit comment. Our Experiment 1 successfully replicates the asymmetric pattern of intrusions reported by Hupbach and colleagues. Memory for an original learning seems to be affected by the information presented before its reactivation. Thus, when a group of participants, who had reactivated a previously acquired memory before a second learning, is contrasted with a group of participants who did not reactivate the memory, we found that the former intruded significantly

more items from the second learning when recalling the first. The impact of a second learning (List 2) on memory for the original information (List 1) seems to depend on memory reactivation. Our analysEs and experiments intended to submit this interpretation to an experimental test. We were particularly interested in disentangling the results that came from Hupbach's paradigm (which have been couched in terms of reconsolidation theory) from other mnemonic effects that are well documented in memory research. For instance, the analysis of the relationship between correct recall and intrusion rate suggested that an accurate accessibility to the original memory trace did not prevent the occurrence of intrusions. This finding deviates from studies in the field of false memories, where typically higher levels of correct recall are related to higher levels of intrusions (Köhnken, Milne, Memon, & Bull, 1999; Rhodes, Anastasi, & Carolina, 2000; Wright, Gabbert, Memon, & London, 2008; Wright, Startup, & Mathews, 2005; but see Roediger, Watson, McDermott, & Gallo, 2001). Additionally, we were especially concerned in tackling an alternative hypothesis that has been pointed in the reconsolidation research: interference theory. In fact, reconsolidation and interference theory hold on important differences, almost considered as mutually exclusive interpretations. In a broad approach to both theories, one can say that the reconsolidation theory claims for modifications of memory traces (memory overwriting), while interference claims for the existence of multiple memory traces that, at the time of retrieval, compete with each other. Besides this different theoretical stance, considering that the storage failure is almost impossible to demonstrate experimentally (Agren, 2014; Hardt, Nader, & Nadel, 2013; Miller & Matzel, 2006), the implementation of a diagnostic empirical test seems to be a hard task to do. However, we have collected some evidence that may work for that purpose. For instance, the analysis of the recall protocol (the serial order in which items are recalled) revealed that the occurrence of intrusions is widespread across the recall protocol. Our results seem to strengthen the idea that, in the recall test, participants from the reactivation group are accessing a memory trace that has undergone an update (i.e., List 1 memory is now an updated version of List 1 memory that includes List 2 items due to reactivation). Importantly, this finding seems to rule out the explanation of the intrusion rate by different mechanisms from reconsolidation (e.g., response inhibition: Anderson, Bjork, & Bjork, 1994; Bjork, 1989; relaxation of the accuracy criterion: Schwartz, Fisher, & Hebert, 1998). Additionally, the data collected from a source-recognition task after the free recall test was used as an aperture to explore potential recovery effects. According to the reconsolidation theory, intrusions are due to irreversible modifications of the target memory trace (List 1 memory trace). So, the restore (recovery effect)

of an original memory is inconsistent with that specific prediction. In our study, a recovery effect was indexed by modifications in the source identification of an intrusion (a previously incorrectly recalled item from List 2). Our results were in line with reconsolidation hypothesis: in the reactivation group, 75 % of the intruded items were again incorrectly allocated to List 1, see p. 98 for a deeper discussion).

In Experiment 2, we examined an important prediction that could be derived from the reconsolidation theory in studies that use a new learning as post-reactivation intervention: memory modifications (e.g., intrusions) should only be observed in the reactivated memory. In other words, information that is presented after memory reactivation should affect the reconsolidation of the original memory trace, but the memory for the interfering material should not differ between the reactivation and no-reactivation groups. In this experiment, we extended previous findings of Hupbach's lab (no intrusions when List 2 instead of List 1 is tested; Hupbach et al., 2007; Experiment 3), strengthening the idea that intrusion cannot be taken as evidence of source-monitoring problems in reactivation group.

In search of additional evidence that could help us to examine how appropriate was Hupbach's paradigm to observe reconsolidation effect, we conducted two additional studies that tackled an overlooked procedural aspect that could call into question the interpretation of results. Therefore, we tested if the original result could be explained by a context-dependent memory effect (Smith, 1994, 2007). In Experiments 3 and 4, we found compelling evidence that the retrieval context does not play a role in the intrusions rate. Specifically, we found that (a) the intrusion-effect is generalized over a new retrieval context (Experiment 3) and that (b) the intrusion effect critically depends on memory reactivation (Experiment 4).

Altogether, the present set of studies provided solid evidence for the interpretation of the asymmetric pattern of intrusions as evidence for reconsolidation of episodic memory. Considering the potential implications entailed by the reconsolidation theory, this topic should continue to be of intense scientific inquiry.

7.3 Implications

The general finding that reactivation of a previously acquired memory enables memory modification entails profound implications, firstly, at a theoretical level (Alberini & Ledoux, 2013; Nadel & Land, 2000). Reconsolidation theory forces a reconsideration of the long-standing views on the neuronal bases of memory and offers a new framework for the understanding of memory malleability. In fact, reconsolidation theory has opened a door for neuroscientists to study what has been occupying cognitive psychologist for decades: the study of memory malleability. As stated by Nadel and Land (2000), "Psychologists have often argued that memories are dynamic and subject to change, but neuroscientists have tended to shy away from these complexities" (p. 210).

As previously mentioned, the idea that human episodic memory does not represent fixed segments of the past, and it is rather a dynamic and reconstructive process, was apparent in the early psychological theories and memory research. For example, William James (1890) suggested that retrieving in a different context could change the nature of a memory. Nevertheless, the first empirical evidence for the dynamic nature of memory is usually credited to Bartlett's studies with the Indian folktale "The War of the Ghosts". Bartlett (1932) found that recollections of the folktale reflected the participants' interpretations of the stories, suffering the influence of their own cultural and logical expectations. Since this early work, studies on this topic have proliferated (Tulving & Thomson, 1973), implying a reconceptualization of memory as not being a faithful storehouse of experiences. Likewise, in a very influential book on cognitive psychology, Ulric Neisser (1967) argued: "My own view, (...), is that both memory images and percepts are constructed anew on every occasion when they are experienced" (p. 160). In this quote, it is clear that, like Bartlett, Neisser conceptualized memory as a reconstructive process, more specifically as an "anew" construction. The vast literature on memory distortions (e.g., misinformation effect, hindsight bias, flashbulb memory, hypermnesia, reminiscence, and interference) seems to go in line with the idea claimed by the reconsolidation theory: retrieval is more than a passive read-out of memory and may represent an opportunity for change. Although these earlier studies did not use the term "reconsolidation" or do not explicitly resort to reactivation as a precondition for altering memory, some of the proposed theoretical explanations rely on processes that are reminiscent of the reconsolidation theory. In this regard, Hardt and

colleagues (2010) demonstrated that several research traditions on cognitive psychology regarding the malleability of human memory have retrieval as a central component. These authors proposed a new look to those paradigms, emphasizing that some form of reactivation is always included in the procedure. For instance, in the misinformation effect (Loftus, 1979; Loftus, Miller, & Burns, 1978; for a review see Loftus, 2005) participants are asked about aspects of an original experience, and the new misleading information is presented while the original memory is being retrieved. In studies of hindsight bias (Fischhoff, 1975; for a review see Guilbault, Bryant, Brockway, & Posavac, 2004), participants are reminded of a previous experience, and new information is presented. In the interference paradigm (Underwood, 1957; for a review see Wixted, 2004), after learning pairs of stimuli, memory for these pairs is reactivated by re-exposing one of the words, which then appears paired with a new word. All of these experimental paradigms lead to distortions in the original memory. In cases of hypermnesia, (Erdelyi & Becker, 1974; Roediger & Thorpe, 1978) and flashbulb memories (e.g., Brown & Kulik, 1977), which all refer to effects in which it is observed a memory improvement due to repeated testing, reconsolidation theory also offers an explanation. According to it, memory reactivation induces a reconsolidation process, and considering that no new information is presented afterwards, the reactivated memories will be strengthened. This finding has also been reported in reconsolidation studies (Frenkel, Maldonado, & Delorenzi, 2005; Nadel, Hupbach, Gomez, & Newman-Smith, 2012; Tronson, Wiseman, Olausson, & Taylor, 2006). Ultimately, as stated in Chapter 3, the scientific inquiring of the reconsolidation theory could contribute to the restless and historical debate regarding the experimentally-induced amnesia as consequence of storage deficit (disruption of consolidation) or retrieval deficit.

Moreover, researchers have progressively approached some tenets of reconsolidation theory, although without explicitly assuming it. Some authors have been arguing that, in the same way that encoding or learning cause retrieval of related information, retrieval itself may cause the modifications of existing memories. For example, Bjork (1975) expressed his concerns regarding how “retrieval processes modify the long-term state of an item in memory” (p. 136) and found that “the state in memory is modified by its retrieval” (p. 142). It is proposed that test trials can function as learning events, in a sense that “retrieval has the potential to change what is being retrieved” (p. 151, Hardt et al 2010). In a similar vein, Semon (1904; see also Schacter, 2001) suggested that the engram is a product of both encoding (engraphy) and retrieval (ecphory)

processes. Thus, it does not correspond to an actual experience, but also it is also related to other engrams.

The bridge between reconsolidation studies and cognitive traditions could be also beneficial to clarify why under certain circumstances some memory distortions are not observed. For example, in rats, some strong memories (e.g., Wang et al. 2009), do not undergo reconsolidation. Similarly, in humans, it has been found that stronger memories are less susceptible to memory distortions (e.g., Marche, 1999). The identification of such boundary conditions does certainly help to understand memory modifications, but it could also be useful when trying to prevent them.

Overall, reconsolidation theory offers a framework for the understanding of the dynamic nature of memory, and to shed a light on how long-term memories persist over time, and yet, also allowing behavioural flexibility and adaptation to ever-changing environments. The advantages offered by an updatable memory system are undeniable (Bjork, 1978; Dudai, 2009; Kraemer & Golding, 1997). Thus, some authors have been focusing on the adaptive function of retrieval-induced plasticity (Lee, 2009; Lee, Nader, & Schiller, 2017), and its potential practical implications in educational settings (e.g., Hupbach, 2015; for research in related literature on the testing effect see Grimaldi & Karpicke, 2012; Larsen, Butler, & Roediger, 2008; McDaniel et al., 2007).

Nonetheless, the knowledge on retrieval-induced plasticity could be capitalized on helping to ameliorate maladaptive memories and potentiate adaptive behaviours in some clinical conditions. In fact, the practical implications of the reconsolidation theory are very exciting and appealing. Concerning the clinical practice, the finding that memories return to a labile state and have to be restored, has significantly relevant implications as it opens the door to address maladaptive memories that are present in clinical conditions such as PTSD, addiction and obsessive-compulsive disorder (OCD). A better understanding of the mechanisms involved in reconsolidation and memory reactivation, could provide valuable therapeutic tools to successfully manage such conditions. Currently, the challenge of translating basic experimental research into effective clinical interventions is considerable (Elsey & Kindt, 2017). However, studies on this topic have been facing a not surprising growth, which holds the promise that such advances lie ahead.

7.4 Limitations and future directions

The main objective of this dissertation was to study the memory reconsolidation phenomena by examining a widely recognized paradigm and to contribute to developing appropriate experimental paradigms for that propose. Despite the clear contributions of the present work, some shortcomings should be considered. It is noteworthy that, from the replication study until our last study, the experiments follow a consistent line of reasoning, in which the interpretation of the pattern of results was tested. To do so, we conducted systematic manipulations, involving the manipulation of specific variables or methodological aspects, while keeping others constant. For example, methodological aspects as stimuli, learning procedure, spatial contexts (of Session 1 and Session 2), were held constant. In this sense, it would be of significant interest to carry out studies to test the generalizability of our findings. However, the time-consuming nature of the present paradigm may slow the onset of such investigations. In fact, the time cost involved in these experiments is a significant hurdle for the conduction of reconsolidation studies, for which a solution should be found. Intimately related to this, the adaptation of this paradigm to better controlled experimental environments (e.g., in a computer) seems to be the top priority for the following studies[7]. With a successful adaptation of this paradigm to a computer task the data collection will be optimized, thus allowing the efficient conduction of studies, and control of the potential parasite variables that are inherently associated with a face-to-face experiment. If Hupbach's paradigm is suitable for testing the reconsolidation hypothesis, we should be able to replicate it with a computer task. However, we anticipate that the paradigm's adaptation to a digital format may also be challenging. Note that memory reactivation is triggered by spatial context (performing Session 2 and 3 in the same context), so the first challenge will be the effectiveness of context manipulation in a computer. Notwithstanding, some previous studies may inform for such manipulations in digital format (Forcato, Argibay, Pedreira, & Maldonado, 2009), as well as others may inspire on that purpose, with more ecological and immersive manipulations (St. Jacques & Schacter, 2013).

[7] We have developed a preliminary paradigm for online data collection. This will allow the development of a more rigorous and controlled experiments, the optimization of time of data collection and, highly important, a wider access to participants.

It will be of the highest value for future investigations to explore the impact of stimuli manipulations. As discussed previously in this dissertation (see Chapter 4, sections 4.2 and 4.3, Consideration 5) the nature of the stimuli has been pointed out (Hupbach, 2011) as an important factor for the observation of memory update. In other words, the competition between the content of the original memory and the post-reactivation material seems to mediate the impact of the later on correct recall. In this sense, the optimization of the data collection would allow to explore the effect of stimuli competition in a more effective way.

Another aspect that warrants further clarification is the understanding of how reactivation is triggered in the present paradigm. This aspect goes in line with a growing trend in the field of reconsolidation research that calls the attention for the mechanisms of prediction error, or expectancy, to trigger memory reactivation (e.g., Exton-McGuinness et al., 2015; Lee, 2009). Results from a very recent replication attempt conducted by Klingmüller, Caplan, and Sommer (2017)[8] made us curious about exploring this issue in Hupbach's paradigm. In Experiment 3, the authors examined a reconsolidation theory prediction: memory reactivation leads to the re-stabilization of the mnesic trait when no treatment is subsequently applied (Nadel, Hupbach, Gomez, & Newman-Smith, 2012). To test this hypothesis, no interfering learning was performed (List 2), and the memory for the original learning was measured. In the reminder group, participants returned to the same room, were questioned about the procedure of Session 1, and performed a fluid intelligence test (8 min). The no-reminder group did not perform Session 2. No differences were found regarding the number of recalled items. The authors assumed that the absence of a higher recall performance in the reminder group meant that the reactivation was not effective, and consequently, that the results were not compatible with a reconsolidation account. However, this conclusion seems quite premature. Previous studies on this paradigm have shown that (a) the mere re-exposure to the spatial context of the original memory is not sufficient to trigger memory reactivation (when List 2 is learned in a new context; (Hupbach, Hardt, Gomez, & Nadel, 2008, Experiment 3); and (b) being in the same spatial context during the original and new learning is a necessary and sufficient condition to observe the intrusion-effect (Hupbach et al., 2008). So, Klingmüller's experiment disregards the structure of the standard "reactivation session" (which involves the encoding of new material in the same spatial

[8] The fit of Hupbach's paradigm to study reconsolidation was called into question, however their findings should be cautiously analysed. Across the paper, the authors argued as if it failed to replicate the reconsolidation theory central finding. Yet, throughout the experiments, it is clear that the reminder group produces a higher number of intrusions than the no-reminder group (although not significantly).

context), and the potential value of the new encoding task in triggering reactivation. Hupbach's findings go in line with studies on animals, suggesting that post-reminder treatments are effective only when the rat is in an "encoding mode" - when new information is presented or expected during the reactivation phase (Morris et al., 2006). Intimately related to this, the mismatch between what the animal expects and what actually occurs (a factor known as drive encoding; Rescorla & Wagner, 1972), was found to be critical to promote reconsolidation (Pedreira, Pérez-Cuesta, & Maldonado, 2004). Although the gap between animal and human fields is not easily bridged, one may think that the manipulations conducted by Klingmüller and collaborators have failed to trigger the mentioned "encoding mode". In Hupbach's original paradigm, this encoding mode is promoted with the new learning in the reactivation session (i.e., List 2 learning in Session 2). Considering the relevance of the research question raised by Klingmüller and collaborators, future studies could assess the role of expectancy of testing in this paradigm (without the use of a new learning).

Additionally, it would be of significant interest to examine if the intrusion effect persists over time, and how stable is the "updated version" of the original memory. All these future directions will be critically relevant for a broader and more comprehensive view of reconsolidation of episodic memories.

Throughout this dissertation, we explored the complexity behind the study of reconsolidation phenomenon, and more specifically the complexity behind Hupbach's paradigm, which keept us watchful and critical, but motivated to pursue the goal of understanding this exciting mnemonic phenomenon. Our findings provide consistent and solid evidence on the role of memory reactivation in long-term memories fate. We hope that the current findings contribute to a more comprehensive picture of malleable nature of memory. We also hope that the current evidence might instigate novel avenues of research on these complex mechanisms that allow our memory system to undergo constant modifications and still can give rise to apparently stable entities. Ultimately, reconsolidation theory must be approached as an exciting door to integrate the two great research traditions, cognitive psychology and neuroscience, and valued for its potential implications.

As a concluding note, we shall return to William James's exceptionally inspiring writings, who stated in his final considerations about what we experience and what we can remember of it:

> The result is various confused and scattered mysteries and unsatisfied intellectual desires. But why not 'pool' our mysteries into one great mystery, the mystery that brain-processes

> occasion knowledge at all? (...) All that psychology can do is to seek to determine what the several brain-processes are; and this, in a wretchedly imperfect way, is what such writings as the present chapter have begun to do. But of 'images reproduced,' and 'claiming to represent,' and 'put together by a unifying actus,' I have been silent, because such expressions either signify nothing, or they are only roundabout ways of simply saying that the past is known when certain brain-conditions are fulfilled, and it seems to me that the straightest and shortest way of saying that. (James, 1890, p. 689)

More than a century has passed. Despite the undeniable advances in memory research, there are still a considerable amount of *unsatisfied intellectual desires*. However, this disquiet is vital for scientific progression which, to be reached, implies resorting to rigours methods, clear definition of concepts, and impartiality of data interpretation. The present dissertation takes us a little bit away from "roundabout ways" of approaching the fate of long-term memories, and, hopefully, encourages future studies on this enthralling field.

7.5 References

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APPENDIX 1

TABLE.APPENDIX 1. Some of the experimental paradigms and species in which reconsolidation has been reported.

TABLE.APPENDIX 1

Some of the experimental paradigms and species in which reconsolidation has been reported.

Species	Experimental Paradigm	Post-Reactivation Treatment	References
Chick	Passive avoidance	D1R antagonist (SCH23390)	Hale & Crowe, 2003; Sherry, Hale, & Crowe, 2005
		Non NMDA receptor antagonist (CNQX)	Sherry & Crowe, 2008b
		mGluR1 antagonist (LY 367385)	Gieros, Sobczuk, & Salinska, 2012
		mGluR5 antagonist (MPEP)	Gieros et al., 2012; Salinska, 2006
		CDK5 inhibition (Roscovitine)	Sherry & Crowe, 2008a
		Protein synthesis inhibition (Anisomycin)	Anokhin, Tiunova, & Rose, 2002; Salinska, Bourne, & Rose, 2004
		Protein glycosylation inhibition (2-deoxygalactose)	Salinska et al., 2004
		BDNF	Samartgis, Schachte, Hazi, & Crowe, 2012a
		Memantine	Samartgis, Schachte, Hazi, & Crowe, 2012b
Crab	Contextual fear conditioning	NMDA receptor antagonists (MK801)	Pedreira, Pérez-Cuesta, & Maldonado, 2002
		GABAaR agonist/antagonist (Muscimol/bicuculine)	Tano, Molina, Maldonado, & Pedreira, 2009
		IKK inhibition (Sulfasalazine)	Merlo, Freudenthal, Maldonado, & Romano, 2005
		Protein synthesis inhibition (Cycloheximide)	Pedreira & Maldonado, 2003; Pedreira et al., 2002; Pedreira, Pérez-Cuesta, & Maldonado, 2004
	Appetitive conditioning & aversive conditioning	Octopamine receptor antagonist (Mianserin/epinastine	Kaczer, Klappenbach, & Maldonado, 2011
		Dopamine-receptor antagonists (chlorpromazine), fluphenazine, or SCH23390)	Klappenbach, Maldonado, Locatelli, & Kaczer, 2012
Fish	Classical fear conditioning	Transient anaesthesia (MS222)	Eisenberg & Dudai, 2004; Eisenberg, Kobilo, Berman, & Dudai, 2003
Fruit fly	Conditioned-odor aversion	Protein synthesis inhibition (Cycloheximide)	Lagasse, Devaud, & Mery, 2009

TABLE. APPENDIX 1.

Specie	Experimental Paradigm	Post-Reactivation Treatment	References
Honeybee	Appetitive learning	Protein synthesis inhibition (Emetine) -	Stollhoff, Menzel, & Eisenhardt, 2005
Nematode	Habituation	Protein synthesis inhibition (Heat-shock); Non NMDA receptor antagonist (DNQX)	Rose & Rankin, 2006
Rabbit	Appetitive learning	Protein synthesis inhibition (Anisomycin)	Coureaud, Languille, Schaal, & Hars, 2009
Rodent	Spatial learning	NMDA receptor antagonists (MK801 or AP5)	Kim, Moki, & Kida, 2011; Przybyslawski & Sara, 1997
		Protein synthesis inhibition (Anisomycin or Cycloheximide)	Artinian et al., 2008; Flint, Valentine, & Papandrea, 2007; Kim et al., 2011; Morris et al., 2006; Rodriguez-Ortiz, Garcia-DeLaTorre, Benavidez, Ballesteros, & Bermudez-Rattoni, 2008
		β-adrenergic receptor antagonist (Propranolol)	Przybyslawski, Roullet, & Sara, 1999
	Object Identification	NMDA receptor antagonists (AP5 or MK801)	Akirav & Maroun, 2006; Winters, Tucci, & Dacosta-Furtado, 2009
		β-adrenergic receptor antagonist (Propranolol)	Maroun & Akirav, 2008
		Protein synthesis inhibition (Anisomycin)	Akirav & Maroun, 2006; Romero-Granados, Fontán-Lozano, Delgado-García, & Carrión, 2010; Rossato et al., 2007; Winters, Tucci, Jacklin, Reid, & Newsome, 2011
	Conditioned taste aversion	CB1R agonist/antagonist (WIN55,2122/rimonabant)	Kobilo, Hazvi, & Dudai, 2007
		Protein synthesis inhibition (Anisomycin)	Garcia-DeLaTorre, Rodriguez-Ortiz, Arreguin-Martinez, Cruz-Castaneda, & Bermudez-Rattoni, 2009; Gruest, 2004; Rodriguez-Ortiz, De la Cruz, Gutiérrez, & Bermudez-Rattoni, 2005

TABLE.APPENDIX 1.

Species	Experimental Paradigm	Post-Reactivation Treatment	References
Rodent (cont.)	Appetitive learning	NMDA receptor antagonists (MK801)	Lee & Everitt, 2008a, 2008b
		β-adrenergic receptor antagonist (Propranolol)	Diergaarde, Schoffelmeer, & De Vries, 2006; Milton, Lee, & Everitt, 2008
	Contextual fear conditioning	protein synthesis inhibitor anisomycin	Debiec, LeDoux, & Nader, 2002
		inducible and reversible CREB repressor	Kida et al., 2002
		antisense oligodeoxynucleotides	Lee, Everitt, & Thomas, 2004
	Auditory fear conditioning	protein synthesis inhibitor anisomycin	Duvarci & Nader, 2004; Nader, Schafe, & LeDoux, 2000
		inhibition of kinase activity	Tronson, Wiseman, Olausson, & Taylor, 2006
		β-adrenergic receptor antagonist (Propranolol)	Dębiec & Ledoux, 2004
Sea Slug	Pavlovian conditioning	Protein synthesis inhibition (Anisomycin)	Child, Epstein, Kuzirian, & Alkon, 2003
		Cell adhesion molecules inhibition (RGD tripeptide)	Child et al., 2003
		mRNA synthesis inhibition (actinomycin-D)	Child et al., 2003
Slug	Conditioned odor aversion	Cooling	Sekiguchi, Yamada, & Suzuki, 1997
Snail	Operant Conditioning	Cooling	Lukowiak, Fras, Smyth, Wong, & Hittel, 2007; Sangha, Scheibenstock, & Lukowiak, 2003
		mRNA synthesis inhibition (actinomycin-D)	Sangha et al., 2003
	Contextual fear conditioning	Protein synthesis inhibition (Anisomycin)	Gainutdinova et al., 2005
	Conditioned taste aversion	Protein synthesis inhibition (Anisomycin)	Solntseva et al., 2007
		Protein synthesis inhibition (Cycloheximide)	Solntseva et al., 2007

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APPENDIX 2

Instructions and Materials (List 1, List 2 and items used in the source recognition test).

Instructions

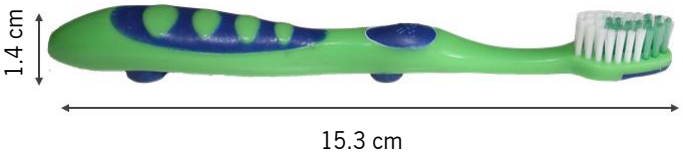
Verbatim instrucions of each session. Reactivation group and No-Reactivation group had the same instrutions in all sessions with the exception of Session 2. In this session participants from Reactivation group were reminded of Session 1 (see reminder instructions), before List 2 learning.

Session	Instructions
Session 1	During this 3 day experiment your memory will be tested for different set of objects. This bag [show the bag] contains all the objects that you will have to memorize. The procedure will be as follows: I will take one object at a time from the bag and I will place it on this table. As soon as I put the object on the table you have to name it out loud. Once you named the object, I will place it in this blue basket. Then I will show you a new object. The procedure will be repeated for all the objects. After the presentation and naming of all the objects, you will have to try to remember, as many as you can, in any order. To begin the recall period I will say: "You can recall", and I will take note of our answers. The recall task does not have a time limit so, when you do not remember any other objects, you should let me know. We want to make sure that you learn the majority of the objects. The procedure could be repeated if your performance does not reach our learning criterion. Any doubt?
Session 2	*Reminder Instructions:* [the experimenter puts the empty blue basket on the table and asks:] -Do you remember this basket and what we did with it? [wait for the answer, and then:] -Could you please describe the procedure of the task that you performed on Monday? *List 2 learning Instructions* Now your memory will be tested for a new set of objects. The procedure will be as follows: the objects will be all arranged on this table. You will have to name each object out loud and try to memorize each one of them. After you have named all the objects you will have 30 seconds to study the set of objects. After this period, the objects will be covered with a wood-made structure and you will have to remember as many objects as you can. You can do it in any order. To begin the recall period I will say: "You can recall", and I will take note of our answers. The recall task does not have a limit of time, so when you do not remember any other objects, you should let me know.

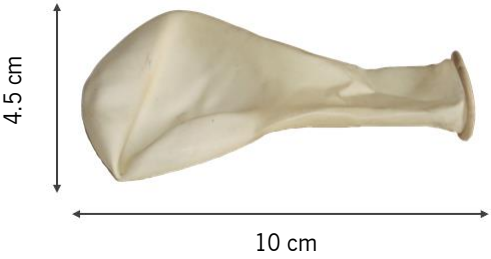
	We want to make sure that you learn the majority of the objects. The procedure could be repeated if your performance does not reach our learning criterion. Any doubt?
Session 3	In this last session I am going to ask you to recall the maximum number of objects of the first set that you learned, on Monday. We will perform four recall attempts regardless of your performance. Try to remember as much as you can. When you do not remember anything else, let me know. We will have a small pause in between each recall attempt. Any doubt?

Materials: List 1 - Set of objects presented on Session 1. Dimensions are displayed along each image, in centimeters.

Toothbrush



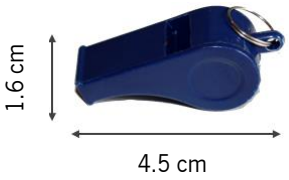
Balloon



Spoon



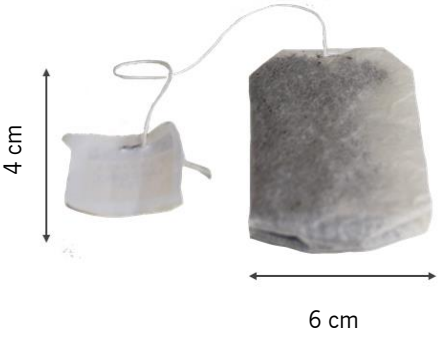
Whistle



Flash-light



Teabag



Sunglasses



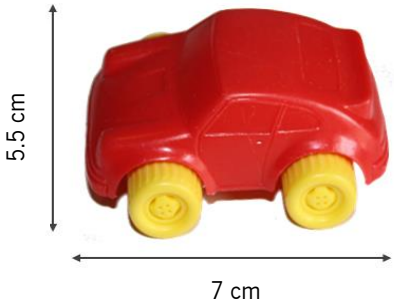
Glue



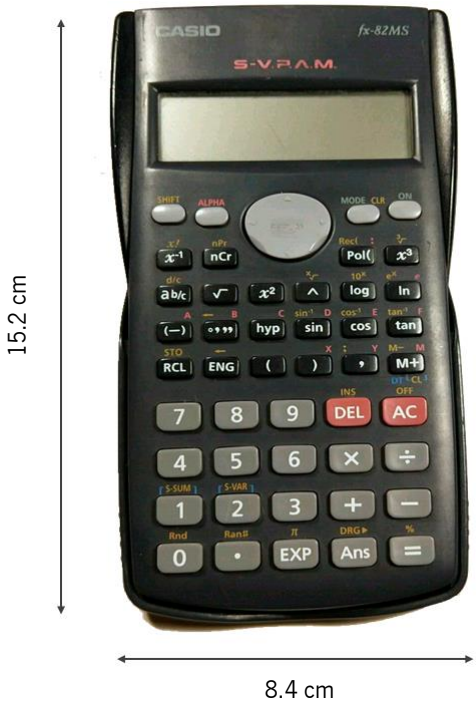
Bow



Toy car



Calculator



Flower



Crayon



Key



Feather



Dice



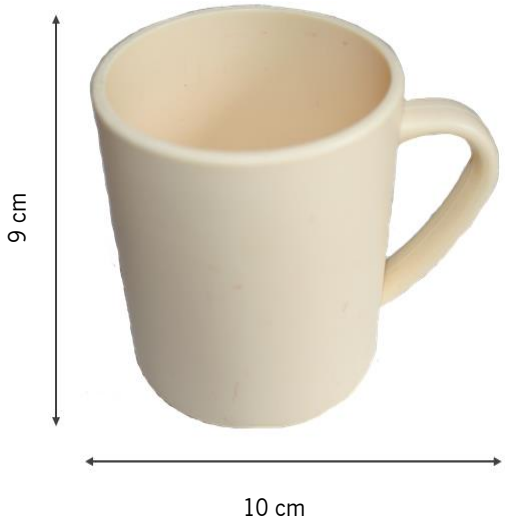
Sock



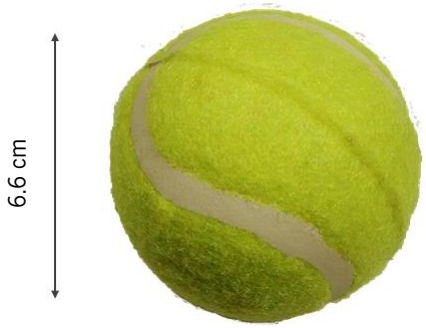
Sponge



Cup

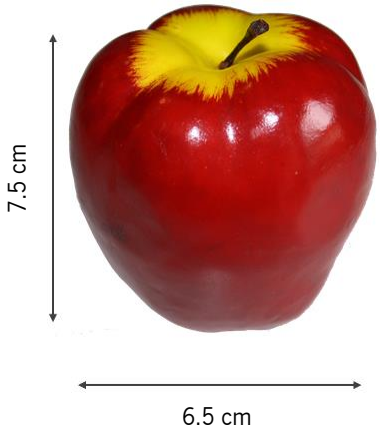


Tennis ball

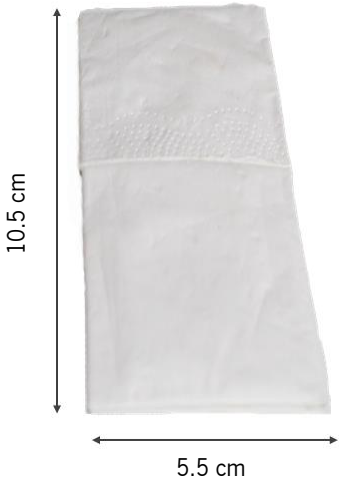


Materials: List 2 - Set of objects presented on Session 2. Dimensions are displayed along each image, in centimeters.

Apple



Tissue



5 euro bill



Thread



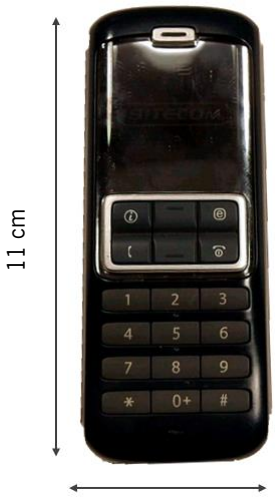
Toy pot



Battery



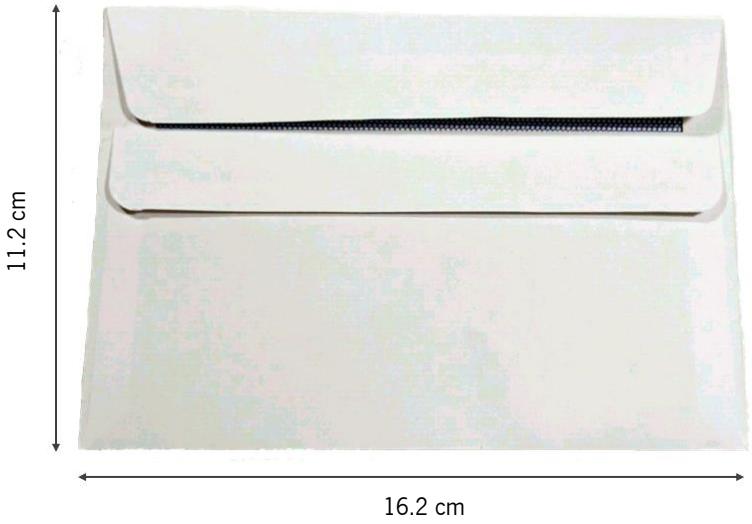
Cellular Phone



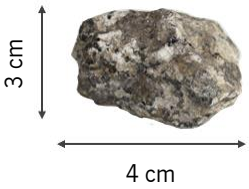
Clip



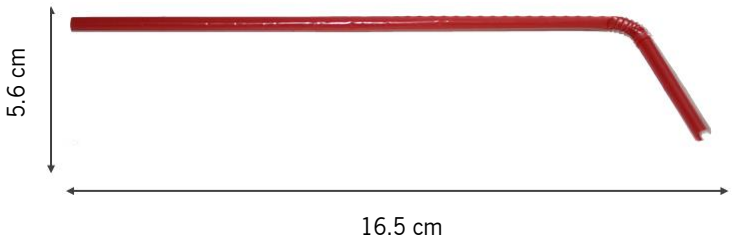
Envelope



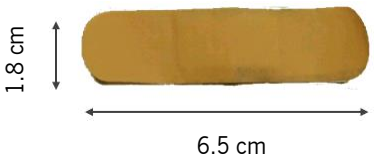
Rock



Straw



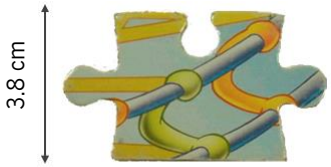
Band-aid



Comb



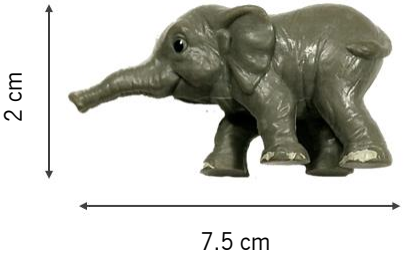
Puzzle piece



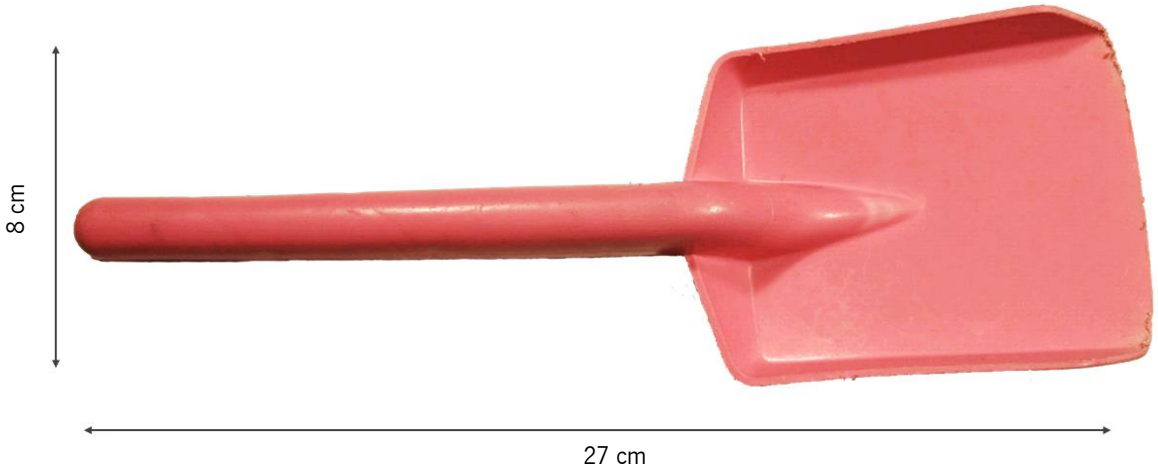
Cassette Tape



Elephant



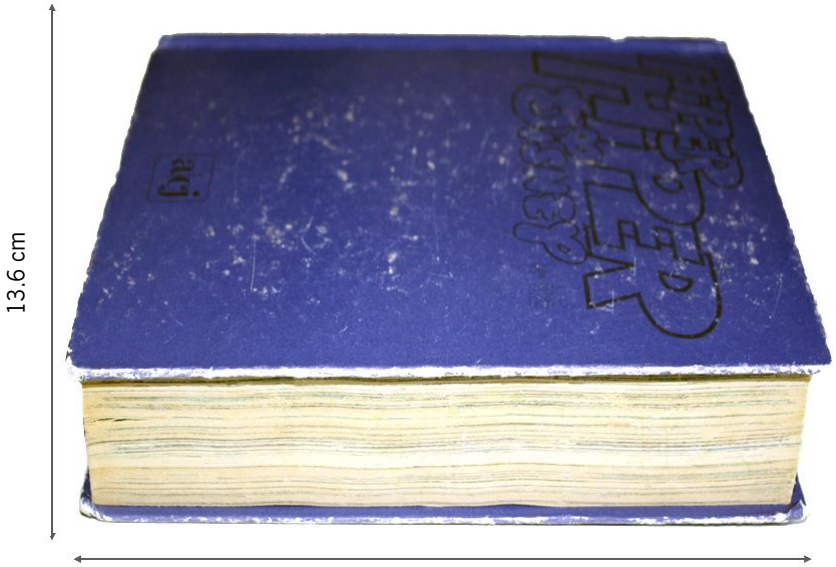
Shovel



Watch



Book



Materials: Source-Recognition Task

List of nonpresented items that were used for the source recognition task performed in Session 1, after the free recall task.

Novel items	
baby bottle	lighter
bag	lipstick
binoculars	magnet
cable	magnifying glass
can opener	match
candle	mirror
candy	nail
clothespin	nail cutter
cube	nail polish
deck of cards	paint brush
earring	pen cap
frame	photographic film
guitar toy	pill
hair tie	screwdriver
hammer	sharpener
hand fan	slingshot toy
head cap	soap
headphones	string
horseshoe	three way plug
hourglass	wine cork

APPENDIX 3

TABLE.APPENDIX 3. Performance across trials in Experiment 1 and Experiment 2. Mean number of correct recall (List 1 items) and intrusions (List 2 items) across the 4 trials of List 1 free recall test as a function of Group (*SD*s in parentheses).

TABLE.APPENDIX 3.

Performance across trials in Experiment 1 and Experiment 2. Mean number of correct recall (List 1 items) and intrusions (List 2 items) across the 4 trials of List 1 free recall test as a function of Group (SDs in parentheses).

	Trial 1		Trial 2		Trial 3		Trial 4	
	Correct Recall	Intrusions	Correct Recall	Intrusions	Correct Recall	Intrusions	Correct Recall	Intrusions
Experiment 1								
Reactivation	10.60 (4.18)	0.47 (0.90)	11.43 (4.21)	0.57 (0.82)	12.20 (4.04)	0.63 (1.22)	12.60 (3.64)	0.77 (1.28)
No-Reactivation	8.77 (3.39)	3.17 (2.98)	9.33 (3.49)	2.77 (2.56)	10.13 (2.90)	2.90 (2.76)	10.93 (2.56)	2.77 (2.87)
Experiment 2								
Reactivation	7.52 (2.71)	0.40 (0.76)	8.40 (2.87)	0.76 (1.27)	8.96 (2.59)	1.12 (1.69)	9.12 (2.74)	1.08 (1.50)
No-Reactivation	8.88 (3.05)	0.68 (1.03)	9.44 (2.84)	0.96 (1.24)	9.64 (3.20)	1.04 (1.17)	10.16 (3.08)	1.20 (1.19)