UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE PSICOLOGÍA
Departamento de Psicología Básica I
(Procesos Cognitivos)

TESIS DOCTORAL

Psicofarmacología de la memoria y emoción en humanos

Psychopharmacology of memory and emotion in humans

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Ana Isabel Galarza Vallejo

Directores

Stephan Moratti
Bryan A. Strange

Madrid, 2018

UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE PSICOLOGÍA

Departamento de Psicología Básica I (Procesos Básicos)

TESIS DOCTORAL

Psicofarmacología de la memoria y emoción en humanos
Psychopharmacology of memory and emotion in humans

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Ana Isabel Galarza Vallejo

Directores

Stephan Moratti
Bryan A. Strange

Madrid, 2017

A mis seres queridos. Mamá, papá, os quiero incondicionalmente. A mi familia y a mis amigos. A los que están, y a los que ya se fueron pero todavía recuerdo.

“Y luego, cuando ante ti se abran muchos caminos y no sepas cuál recorrer, no te metas en uno cualquiera al azar: siéntate y aguarda (…). Quédate quieta, en silencio, y escucha a tu corazón. Y cuando te hable, levántate y ve donde él te lleve.”

Va´dove ti porta il cuore. Susanna Tamaro (1994)

Index

Index of figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Index of tables

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Resumen

El principal propósito de esta tesis ha sido ahondar en el conocimiento del mecanismo neural subyacente a la influencia de la emoción y el sistema motor en la memoria. El primero de los estudios presentados incide sobre la posibilidad de disminuir la memoria episódica, mientras que el segundo estudio presentado incide sobre la viabilidad de aumentarla.

En el primer capítulo, se resumen las principales teorías sobre los procesos de memoria, desde las teorías clásicas a las más actuales. El segundo capítulo repasa los principales sistemas de neurotransmisores del sistema nervioso central y su relación con la emoción y la memoria, presentando los principales estudios en humanos o en animales. En el tercer y cuarto capítulos, se presentan dos estudios novedosos, que son una réplica y ampliación de dos estudios previos.

Las teorías clásicas han considerado la memoria como una facultad monolítica e inmutable de la mente. Sin embargo, las nuevas actualizaciones provenientes de las investigaciones realizadas en las últimas décadas, abren una puerta a la modificación de memorias previamente consolidadas. La teoría de la reconsolidación establece la posibilidad de reactivar de nuevo una memoria mediante la presentación de una "clave" relacionada con la misma. Una vez la memoria es reactivada es susceptible de ser modificada dentro de una ventana de tiempo, mediante la administración de diferentes tipos de manipulaciones, tanto de carácter conductual como farmacológico; necesitando ser consolidada de nuevo después de la reactivación. La reconsolidación de la memoria ha sido observada en diferentes especies animales y en humanos, así como con diferentes tareas y tipos de memoria.

El primer estudio presentado (capítulo 3) se basa en la hipótesis de la implicación del sistema GABAérgico en el deterioro de la reconsolidación de una memoria emocional episódica. Para la realización de este experimento se contó con la participación de pacientes que iban a someterse a una prueba de endoscopia y por lo tanto, recibir una sedación programada. Los resultados obtenidos muestran la disminución de la memoria emocional mediante la administración del agente anestésico propofol, inmediatamente después de la reactivación. Una proporción importante de la población está afectada por trastornos psiquiátricos que tienen en su origen una memoria emocional de carácter traumático o

desadaptativo. La posibilidad de modificar este tipo de memorias, abre un abanico a nuevos tratamientos y terapias coadyuvantes a las ya existentes.

El segundo estudio presenta la relación entre en sistema motor y la memoria. Este estudio analiza cómo realizar una acción motora simple es capaz de aumentar la memoria episódica, al mismo tiempo que, inhibir esa misma acción no la disminuye. El propósito de este estudio fue comprobar la hipótesis de la relación entre estructuras temporo-mediales y el aumento de la memoria episódica mediante la acción de la noradrenalina liberada por el locus coeruleus. La tarea consistía en la realización de una tarea de tipo "Go-NoGo", en la que los participantes han de realizar una acción o inhibirla de acuerdo a una serie de claves previamente aprendidas. Antes del inicio de la prueba, se les administraba a los participantes un fármaco beta-bloqueante (propranolol) o un placebo, en un estudio de diseño doble-ciego. A las 24 horas de la realización de la tarea "Go-NoGo", los participantes regresaban al hospital para realizar una tarea de reconocimiento de memoria sorpresa. No fue posible mostrar una correlación directa entre la manipulación farmacológica y el bloqueo de la mejora de la memoria. Sin embargo, se demostró una correlación entre la excitación (arousal) experimentada por los participantes, traducida en un aumento de presión arterial sistólica y el porcentaje de estímulos correctos recordados.

El principal propósito a la hora de realizar los estudios que se exponen en esta tesis fue siempre las probables implicaciones clínicas. Modificar una memoria, que por exceso, este creando un trastorno y un sufrimiento, ofrece una posibilidad de alivio tanto al paciente como a sus familias. Así mismo, la posibilidad de aumentar la memoria episódica mediante la realización de una acción motora a través del sistema noradrenérgico puede tener potenciales implicaciones clínicas en el tratamiento de las primeras etapas de trastornos degenerativos como el Alzheimer. En este tipo de demencias, el sistema noradrenérgico dependiente del locus coeruleus se halla comprometido desde las primeras etapas.

Ambos estudios tienen, no sólo el objetivo de aumentar el conocimiento y comprensión sobre diferentes enfermedades o trastornos mentales, así como del mecanismo que subyace a las mismas, sino de modificar la percepción y estigmas que la sociedad tiene de las enfermedades que afectan a nuestro sistema nervioso central.

Abstract

The main objective of this thesis has been to deepen the knowledge of the neural mechanism underlying the influence of emotion as well as the motor system in memory. The first of the studies presented focuses on the possibility of decreasing episodic memory, while the second study refers to the feasibility of increasing it.

In the first chapter, the main theories about the processes of memory are summarized, from the classic theories to the more actual ones. The second chapter reviews the main neurotransmitter systems of the central nervous system and its relation to emotion and memory, presenting the main studies in humans or animals. In the third and fourth chapters, two novel studies are presented, which are a replication and extension of two previous studies.

Classical theories have considered memory as a monolithic and immutable faculty of mind. However, new updates from the research carried out in the last decades, opens a door to the modification of previously consolidated memories. The theory of reconsolidation postulates that upon reactivation, memories can become labile and susceptible to manipulation, requiring a new restabilization process in order to maintain them. The reconsolidation of memory has been observed in different animal species and in humans, as well as with different tasks and types of memory.

The first study presented (Chapter 3) is based on the hypothesis of the implication of the GABAergic system in the deterioration of the reconsolidation of an episodic emotional memory. For the accomplishment of this experiment it was counted on the participation of patients who were going to undergo an endoscopy procedure and therefore, to receive a scheduled sedation. The results show the impairment of the emotional memory by the administration of propofol, an anesthetic agent, immediately after the reactivation. A significant proportion of the population is affected by psychiatric disorders that have at their core a traumatic or maladaptive emotional memory. The possibility of modifying this type of memory opens a range to new treatments and adjuvant therapies to those already existing.

The second study presents the relationship between motor system and memory. This study analyzes how performing a simple motor action is able to increase episodic memory, and yet, inhibiting that same action, does not decrease it. The purpose of the study was to test the hypothesis of the involvement of the medial temporal structures in this enhacement of memory by the action of the noradrenaline released from the locus coeruleus. The study consisted of a Go-NoGo task, in which the participants had to perform an action or inhibit it according to a series of keys previously learned. Prior to the performance of the task, a beta-blocker (propranolol) or placebo was administered in a double-blind design study. 24 hours after completing the "Go-NoGo" task, the

participants returned to the hospital to perform a surprise memory test. It was not possible to show a direct correlation between pharmacological manipulation and the blocking of memory enhancement. However, a correlation between the arousal experienced by the subjects, translated in systolic blood pressures and the percentage of correct remembered stimuli was shown.

The main purpose in carrying out the studies that are exposed in this thesis was always the probable clinical implications. Modifying a memory, which by excess, is creating a disorder and suffering, offers a possibility of relief to both the patients and their families. Likewise, the possibility of increasing episodic memory by performing a motor action via the noradrenergic system may have potential clinical implications in the treatment of the early stages of degenerative disorders such as Alzheimer's. In this type of dementia, the noradrenergic system dependent on locus coeruleus is compromised from the early stages.

Both studies have not only the goal of increasing knowledge and understanding about different diseases or mental disorders, and the underlying mechanism, but also to modify the perception and stigmas that society attached at the diseases that affect our central nervous system.

Chapter 1

Memory processes

1.1 Introduction to long-term memory in humans

It is increasingly accepted that memory is not a monolithic faculty (Poldrack & Packard, 2003), but more than a century ago, the divisions and subdivisions of memory, the stages through which the information goes through the brain, and the brain systems that support the different kinds of memory were unknown.

In 1890, William James proposed that memory was not a unitary system, but a double system composed of a primary and a secondary memory, being described primary memory as the one that is held momentarily in consciousness and secondary as the one permanent but unconscious. This was a first approximation of the organization of memory in humans, which Hebb, (1949) converted into a division between short-term memory (STM) and long-term memory (LTM).

Following this assumption the information is transferred from one store (STM) to another (LTM); more than erasing information, it means that the information is "copied without affecting its status in the original store" (Shiffrin & Atkinson, 1969, p.179). The elements are supposed to be attended in order of entrance. If the subject does not attend the item, it would be lost in a short period of time within around 30 seconds, or even less. The control processes, such as for example rehearsal, allow the subject maintain the information in the STM for longer time periods. This STM was also assumed to act not only as an information maintenance store, but also as a working memory (Baddeley, 1992; Shiffrin & Atkinson, 1969), in which manipulations of information may take place on a temporary basis. Once the information is transferred to the LTM, it is supposed to be permanent. The Atkinson-Shiffrin (1965, 1968, and 1969) model about the dissociation between STM and LTM rapidly aroused serious doubts.

In 1974, Baddeley & Hitch replaced the simple unitary STM with a more complex system, that they termed "working memory". Working memory was assumed to comprise an attentional controller, the *central executive*, assisted by two subsidiary systems, the *phonological loop* and the *visuospatial sketchpad*. The phonological (or articulatory) loop is a store that holds memory traces for a few seconds, combined with a sub-vocal rehearsal process. The visuospatial sketchpad (or scratchpad) is supposed to permit the temporary storage and manipulation of visual and spatial information. The third component of the model, the central executive, is assumed to be a system that provides attentional control of

the subsystems of working memory, bind information from a number of sources into coherent episodes, helps to vary the attention between tasks or recovery strategies and coordinates selective attention and inhibition to the stimuli (Baddeley, Kopelman & Wilson, 2002). With the passage of time it became evident that the model did not cover all the needs, and a fourth element was added: the episodic buffer (see Figure 1.1.). The episodic buffer is assumed to be an intermediate storage, prior to LTM, where information is integrated from different modal codes and can be retrieving consciously and manipulated or modified if necessary. It is controlled by the central executive. It is named episodic in the sense that is able to hold episodes where information is integrated (Baddeley, 2000).

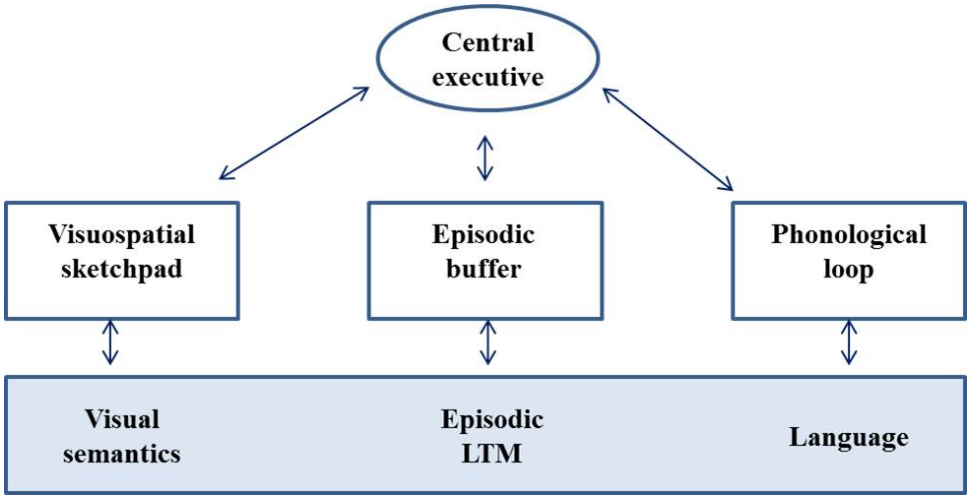

Figure 1.1. The current version of the multimodal working memory model. The episodic buffer is assumed to be capable to integrated information in multiples codes. The buffer is an intermediate store before the LTM, controlled by the central executive. The information that handles is able to be retrieving consciously. (Adapted from Baddeley, 2000)

Even though, Baddeley, among many other authors (see section 1.1.1), helped to build the concept of a memory system, it was not until 1979 that the term "memory system" appears for the first time in the title of a paper. It was an article written by Warrington, (1979), where she made a discussion about the neuropsychological evidence supporting a distinction between short-term and long-term memory systems, and a subdivision of long-term memory system in two: event memory and semantic memory.

1.1.1. Declarative and non-declarative memory

Since the beginning of psychology, different distinctions between different types of memory have been made, according to the predominant zeitgeist. Bergson, Mitchell,

Pearson, & Kolkman, (1911) distinguished between memory and habit; Schactel (1947), formed the terms autobiographical and practical memory; Ryle, (1949), reflected about knowing how and knowing that; Bruner (1969) conceptualized "memory with record" (recollection of the "facts we acquire and events we experience in daily life") and "memory without record" (" some processes that changes the nature of an organism, changes his skills, or changes the rules by which he operates, but are virtually inaccessible in memory as specific encounters") (p.254) ; Winograd, (1975) and Winston, (1977) distinguished between declarative and procedural (the first one using the term "declarative" was Anderson in 1976) (Squire, 1992). These studies among others with healthy populations or amnesic patients (e.g., the ability to resolve stereoscopic images, Benzing & Squire, 1989; cognitive skill learning, Squire & Frambach, 1990; artificial grammar learning, Knowlton, Ramus, & Squire, 1992; and category learning, Knowlton & Squire, 1993) helped to make a distinction between declarative memory and non-declarative memory. Also other terms for similar dichotomies have been used, e.g., explicit (intentional or conscious recollection of past episodes) and implicit memory (unintentional, non-conscious use of previously acquired information) (Graf & Schacter, 1985; Schacter, 1987); or memory and habit (Mishkin, Malamut, & Bachevalier, 1984).

Today, the main differentiation commonly used is between declarative and non-declarative (usually also referred to as explicit (declarative) or implicit (non-declarative), both terms can be used interchangeably) memory. Double dissociations in neuropsychological findings from amnesic patients have mainly formed these concepts (Graf & Schacter, 1985; Squire, 1992; Squire, 2004).

The term declarative (explicit) memory is used in the sense that a person can bring to mind or declare the content of this memory. It also includes memory for faces, spatial layouts, and other material that can be verbalized or that brings an image to the mind; in this sense, declarative memory is considered to be a conscious memory; while the other type or types of memory that are dissociable from this one (non- conscious) are referred to as non-declarative or implicit memories (Squire, 1992) (see Figure 1.2.).

Squire and Zola (1996) consider the episodic and semantic memory as two parallel side-by-side subsystems of a higher division of the declarative memory. The beginning of this fragmentation of the declarative memory goes back to 1966 when Ross Quillian used for

the first time the term “semantic” memory in his doctoral dissertation (Tulving, 1972). Quillian developed a program called TLC (the teachable language comprehender); a series of assumptions to understand how meaning might be stored, using hierarchical organization minimizing the storage demand (Baddeley, 2001). Tulving & Donaldson, (1972) organized a conference where this new line of research was well represented, and led Tulving to make the distinction between “episodic” and “semantic” memory. Previously, psychologists began to use this model to investigate how humans store knowledge, how statements and features of the world can be accessed and verified (Baddeley, 2001).

Tulving (1972) used the term “episodic” to refer to the other kind of memory that was not semantic; suggesting that there were sufficiently fundamental differences between the two forms of memory to consider the two categories separately (Tulving, 1972). According to Tulving (1972), episodic memory receives and stores information about temporally dated episodes or events, and temporal - spatial relations among these events; while semantic memory, reflects a kind of organized knowledge of a person about words and other verbal symbols (such as their meaning and referents, about relations among them, about rules for the manipulation of those symbols, concepts and relations).

In summary, semantic memory is a conscious and propositional memory that can be either true or false. It is based on a recollection of facts and events, fast in acquisition and flexible. It is assumed to reflect our knowledge of the world, holding generic information acquired across different contexts and being able to use it in different situations. In contrast, episodic memory is assumed to recollect personal experiences, specific individual events with spatial-temporal features (Baddeley, 2001).

Non-declarative (or implicit) memory is a non- conscious form of memory. Performance changes as a result of practice and experience, without conscious awareness and usually slows in acquisition (except priming). It refers to a heterogeneous collection of skills, habits, and other dispositions such as simple forms (classical, operant) of conditioning and priming, that are influenced by our behavior and mental life, and are a necessary part of what defines us as individuals (Squire, 2009).

The best understood example of non-declarative memory is simple classical conditioning; specifically delay conditioning that is a simple associative learning and represents the

quintessential paradigm of non-declarative memory. In delay conditioning, the conditioned stimulus (CS), is presented, and then, immediately the unconditioned stimulus (US) is presented; being both stimuli presented at the same time and co-terminate at the same time either (overlap in time, there is no time delay between presentations). Repeated CS-US pairings are learned and the conditioned response (CR) is elicited by the CS in advance of the US (Clark & Squire, 1998). The other form of classical conditioning that obeys to the principles of declarative memory is trace conditioning. It is a different version of classical conditioning in which the "CS is presented and terminated and then a short interval is imposed before the presentation of the US. The name comes from the fact that the CS must leave some trace in the nervous system for a CS-US association to be established" (Clark & Squire, 1998; p.77). The main difference between both conditionings is thought to be that trace conditioning depends on conscious knowledge about the CS-US association, whereas a conscious representation of the CS-US contingency is not necessary in delay conditioning. Nevertheless, in a typical fear conditioning study with humans, participants "may not always acquire a genuine fear response, because the level of aversiveness of the UC is selected by the participant" (Weike, Schupp, & Hamm, 2007; p.170) . In other words, participants may be able to learn that the CS predicts the occurrence of the US, but without learning to "fear" the CS. Participants have the explicit declarative knowledge of the CS-US association [''contingency learning,'' (Rescorla, 1988); or ''propositional learning,'' (Lovibond & Shanks, 2002)], but did not acquire the emotional features in order to activate the fear system in the brain (Weike et al., 2007). Weike, Schupp, & Hamm, (2007) suggested that fear responses can be acquired by implicit learning without necessitating the explicit knowledge of the contingencies (see Öhman & Mineka, 2001). Taken together, their results suggest that in trace conditioning (CS-US presentations are separated in time) the acquisition of declarative knowledge may be a necessary condition for learning, while in delay conditioning, (CS-US presentation overlap in time), the acquisition of a fear response is not related to explicit awareness; being these learnings dependent of different neural circuits (Weike et al., 2007).

Referring to the classification of memory, many of the theories have been elucidated by the study of patients with different types of brain lesions. The term "global anterograde amnesia" was used for referring patients that were no longer able to "learn" more information or to retain new life experiences. Nevertheless, investigators started to see that

these kind of patients were able to retain new experiences of a certain type or in a certain way (Mishkin, Malamut, & Bachevalier, 1984). One of the most important works in this area (memory classification) came from the demonstration by Warrington and Weiskrantz (1968) that these densely amnesic patients were capable of learning (even though, the patients were not aware of their learning) and show that learning, of pictures or words. They showed patients a word or a line drawing, and then asked them to identify a partial or degraded version of the previous word or picture (Warrington & Weiskrantz, 1968). This new form of learning is now known as "perceptual priming", and at the moment of it discovery it was obvious that it was not based on episodic or semantic memory (Schacter & Tulving, 1994), but on "some other, as yet little understood, memory system" (Tulving, Schacter, & Stark, 1932, p.341). Nowadays, priming is a very well-studied form of non-declarative memory, and it is defined as the capacity to improve the perception of stimuli under degraded conditions by prior presentation (Baddeley, 2001).

Skill and habits are two subtypes of a higher subdivision usually known as "procedural" memory, and is a memory acquired by trial and error. Examples of our daily life of procedural memory are: riding a bicycle, typing, reading words… (Mochizuki-Kawai, 2008). This kind of memory involves the acquisition of new behavioral capacities through feed-back guided learning without the mediation of conscious (declarative) memory (Poldrack, Prabhakaran, Seger, & Gabrieli, 1999).

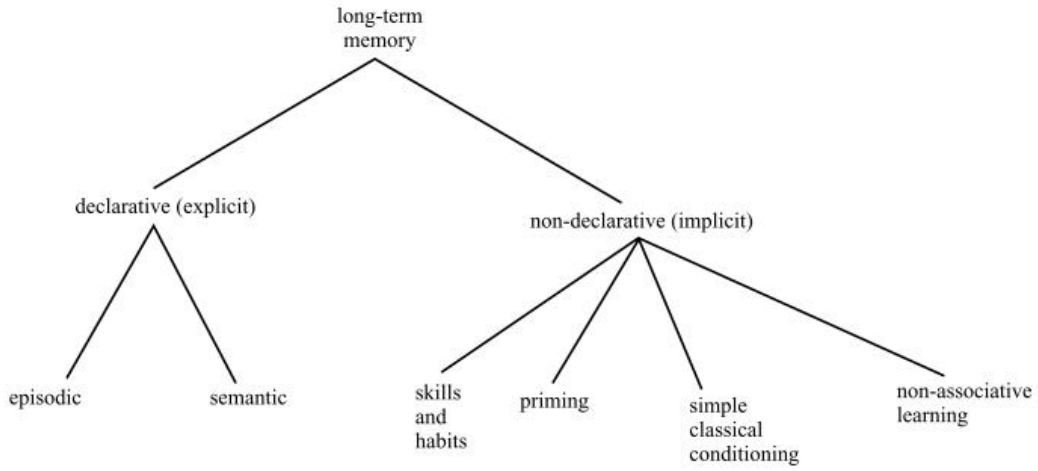

Figure 1.2.Classification of long-term memory. Declarative memory includes memory for facts and events. Non-declarative memory refers to a heterogeneous collection of distinct learning and memory abilities

where performance changes but without affording access to the experience or experiences that caused the change (Reproduce from Zola-Morgan, S., & Squire, L. R., 1990; Squire, 1992)

As Nadel pointed in 1992 on the section "What is a system?" of the book "Memory systems 1994" (Schacter & Tulving, 1994), two criteria are necessary for distinguishing among systems: the length of time the information is stored in them (see section 1.1.) and different neural architectures (Schacter & Tulving, 1994) (see section 1.2.)

1.2. Brain structures

Different types of retention processes imply different storage mechanisms, or even entirely different neural systems (see Figure 1.3.) (Mishkin, Malamut & Bachevalier, 1984).

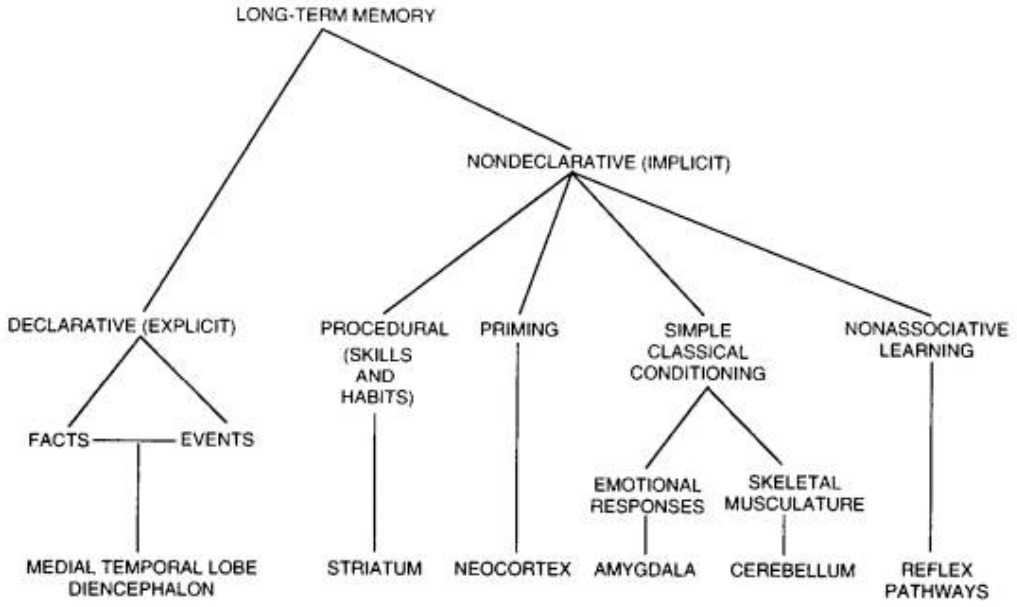

Figure 1.3.The neuroanatomical and behavioral distinctions between declarative and non-declarative memory (Reproduce from Squire, 1992).

1.2.1 The Medial Temporal Lobe

As said before, much of the relevant information of the various kinds of memory and its different stages comes from the study of brain-damaged patients, usually with selective memory impairments (Tulving, 1995). Although Ebbinghaus, William James and many others performed different experimental studies of memory (Dickerson & Eichenbaum, 2010) it was not until the middle 1950s, with the famous studies done by Brenda Milner

(Scoville & Milner, 1957) that the role of the different brain structures and thus the biological substrate of memory came to light.

In 1954, the surgeon Scoville reported a grave impairment of recent memory which he had observed as a sequel to bilateral medial temporal lobe (MTL) resection in two patients, one psychotic patient and one patient with intractable seizures (Scoville, & Milner, 1957). At that time, psychosurgeons used to perform fractional lobotomies on serious ill schizophrenic patients who were resistant to other forms of treatment. The purpose of these fractional lobotomies was to ensure the beneficial effects of a complete frontal lobotomy but also to preserving as much as possible the overall personality. At the age of 27, patient H.M. had a radical bilateral medial temporal lobe resection due to his long history of intractable seizures. The doctors considered justifiable the surgery because the patient was totally unable to lead a normal daily life, due to his seizures. Other justifications for surgery were the known epileptogenic qualities of the uncus and hippocampal complex, and the relative absence of post-operative seizures in other temporal-lobe resections performed before. Among with patient H.M. and the other schizophrenic patient who had the same radical resection, Scoville and Milner in his article published in 1957 analyzed other eight cases who had undergone similar, but less radical, bilateral medial temporal lobe resections. They analyzed all these cases, dividing them into three groups according to different degrees of memory impairment. Group I, was the group of H.M and the schizophrenic patient, both with severe memory impairment. Both patients seemed to forget the incidents of their daily life as fast as they occurred, with no other cognitive impairments; the IQ in the case of H.M. was even higher than preoperative. The resection in these two cases, according to Scoville, was about 8 centimeters (cm) from the midpoints of the tips of the temporal lobes. Among these two patients, in Group I was also another psychotic patient but with a resection of 5.5 cm, showing the same severe memory impairment. Group II was composed of five patients with a moderate to severe memory impairment, with a bilateral medial temporal-lobe resection of about 5 to 6 cm, posteriorly from the temporal tips. These patients were able to recall some impressions of new places and events, but were unable to make any new association such as people´s name. Finally, there was Group III with only two patients diagnosed with a non-persistent memory defect.

The anterograde amnesia of H.M. was profound (Scoville & Milner, 1957), but what was exactly the extension of the damage that caused such a severe memory impairment compared to other medial temporal lobe amnesia with less severe memory deficits? In 1978, a patient known as R.B. had an episode of global ischemia at the age of 52, and developed memory impairment. During the next 5 years that he managed to survive, he had no other cognitive deficits beyond his anterograde amnesia, a less severe amnesia than H.M. After his death, the cerebral histological examination revealed a bilateral lesion involving the entire CA1 field of the hippocampus (Zola-Morgan, Squire, & Amaral, 1986). In the mid-nineties, and for the first time, Corkin and her colleagues, (1997) were able to evaluate the neurosurgical resection in H.M., and to determine precisely which part of the medial temporal lobe were included in his resection and thus may be responsible for his amnesic syndrome. The magnetic resonance imaging (MRI) indicated that the lesion was bilaterally symmetrical, but smaller than Scoville thought (5.4 cm left and 5.1 cm right), and that the severe memory impairment in H.M. compared with that in other amnesic patients with selective hippocampal lesions (R.B), may be related to the inclusion of portions of the entorhinal, perirhinal, and parahippocampal cortices in the medial temporal lobe removal (Corkin, Amaral, González, Johnson, & Hyman, 1997). These studies revealed two main findings. First, that the hippocampus itself is a key component of the MTL memory system; and second, that structures outside the hippocampus must be important for memory, too (Squire & Zola-Morgan, 1991).

The MTL is critical for declarative memory (conscious) and contains structures such as the hippocampus, CA fields, the dentate gyrus, the subicular complex, and the parahippocampal cortex (the adjacent perirhinal, entorhinal and parahippocampal cortices) (Squire, Stark, & Clark, 2004); see also the term “hippocampal region”, Scoville and Milner (1957); see Figure 1.4.).

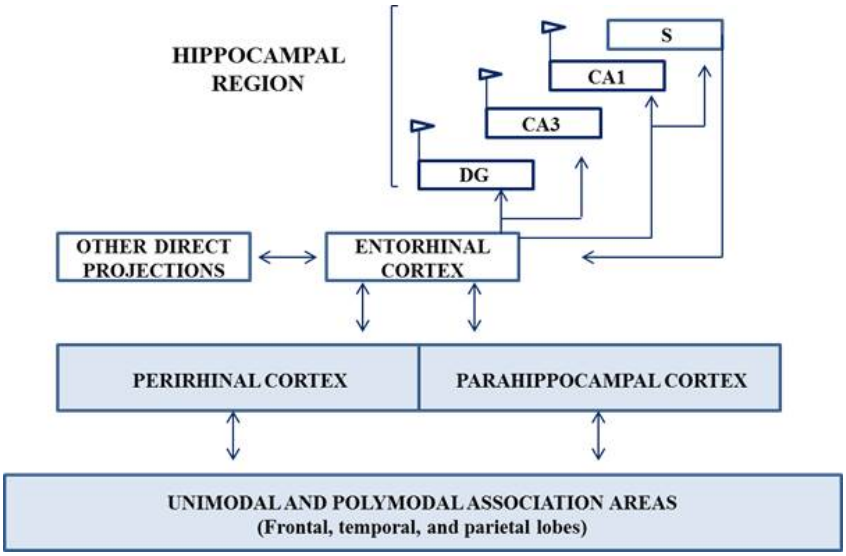

Figure 1.4.The medial temporal lobe structures. S (subicular complex); DG (dentate gyrus); CA1, CA3, the CA fields of the hippocampus. (Adapted from Squire, Stark, & Clark, 2004).

The other conclusion that the work of Milner helped to elucidate was that MTL is only temporary, since the damage in this cerebral area produces temporarily retrograde amnesia (Alvarez & Squire, 1994). This phenomenon was highlighted more than 100 years ago by Theodore Ribot in *The diseases of memory* (1882). Ribot (1882) pointed his famous Ribot´s Law about the temporal gradient, and the extent of retrograde amnesias, ranging from more recent to more remote memory dysfunctions.

In 1968, Milner published an article about the residual learning capacities of patient H.M. He was able to acquire new motor skills, using a mirror drawing task, and also showed some evidence of perceptual learning (Milner, Corkin, & Teuber, 1968). At this time it became increasingly clear that heavily "amnesic patients were able of certain types of learning, including priming, the acquisition of motor skills, classical conditioning and habit learning" (Baddeley, 2001, p.1346); emphasizing a third important dissociation between explicit and implicit memory. These elegant neuropsychological studies of Milner, of the noted amnesic patient H. M., demonstrated convincingly that declarative memory depends on the integrity of the MTL; and also established the fundamental principle that memory could be dissociated from other intellectual functions (Squire, 1992). At that time, and due to the motor skills that H.M. was able to learn even though he denied it, led to the view that motor skills are considered a less cognitive form of memory (Squire, 2004). The subjacent

idea was that motor skills were represented in a different brain area, and the rest of the memory was implemented in another region.

1.2.2. Other brain structures of non-declarative memory in humans

As noted before, the hippocampal function is fundamental for declarative memory, but not for other non-declarative learning (priming, the acquisition of motor skills, classical conditioning and habit learning). By the 80's, studies from animals and amnesic patients started to highlight what other cerebral areas, besides the MTL, were involved in different types of memory.

Another important finding was to discover the role of the neostriatum in feedback-guided learning, a way the brain has to learn how some situations and actions predict positive or negative outcomes (San Martín, 2012) in order to learn an habit. In summary, the neostriatum and its connections with the neocortex form part of a system supporting the incremental learning of habits and reward driven non-motor habits, guiding behavior and cognition (Knowlton, Mangels, & Squire, 1996).

Different studies with amnesic patients have probed that priming is a non-conscious memory process totally independent of the medial temporal lobe (Squire, 2009). Research on this kind of memory came from the observation that amnesic patients could perform as good as control subjects in a sort of memory tests of words where the patients do not have to recall or recognize a previously set of words presented (e.g., TABLE and CHAIR; and they are instructed to complete the stems from English words, e.g., TAB--- and CHA---) (Graf & Mandler, 1984). priming is the facilitation to identify or process stimuli, that have been previously presented (Squire, 2009).

Using electrophysiological recording of neural activity during a very simple and well-characterized form of associative learning, such as paired training trials (delay eyeblink conditioning of the rabbit nictitating membrane, also known as a third eyelid) from different regions of the rabbit´s ipsilateral cerebellum, Thompson et al., (1982) suggested an important role of the cerebellum in coding the learned response. This study demonstrated that the hippocampus is not critical for the acquisition of delay memories, where the conditioned stimulus (CS) and the unconditioned stimulus (US) overlap in time (Beylin et al., 2001). While for trace (eyeblink) conditioning the hippocampus is necessary

for the associative learning of the conditioned (eye-blink) response (Kim, Clark, & Thompson, 1995; Moyer, Deyo, & Disterhoft, 1990).

In relation to other brain structures important for memory, it is necessary to emphasize the role of the amygdala in fear learning (but see section 1.4.)

1.3. Stages of memory

1.3.1. Encoding-Consolidation-Retrieval

"Memory refers to the knowledge that is stored in the brain, and to the processes of acquiring, consolidating and retrieving such knowledge" (Baddeley, Kopelman, & Wilson, 2003, p. 17)

Already in 1859, William Hamilton, made an explicit division of the process of memory into three stages: acquisition, retention and reproduction. Analogous to the classical view of memory formation involving three steps: encoding, consolidation and retrieval (see Figure 1.5.).

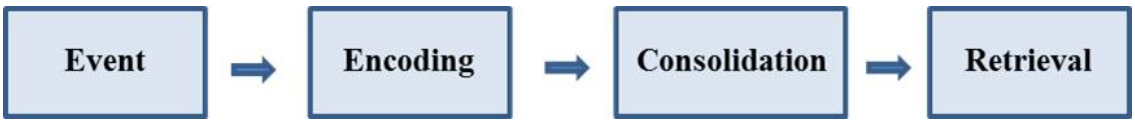

Figure 1.5. Memory encoding, traditional view. Adapted from Nadel, Hupbach, Gomez, & Newman-Smith, (2012).

Encoding can be defined as the processes whereby information is registered. The most typical way of studying this process is by "varying the nature of the material and/or the way that it is processed during learning" (Baddeley, Kopelman& Wilson, 2002; p. 9). The subsequent recall of the information will be affected by the characteristics of the material at the time of the encoding. For example, when processing the visual features of a word, the subsequent recall or recognition will be poorer than if processing that word in terms of meaning (Baddeley, Kopelman & Wilson, 2002).

During the encoding the representations of the different entities involved in the process are activated in the nervous system; mainly in the cortical systems, but also in the hippocampal formation. The hippocampal system encodes spatial and temporal characteristics and also

provides an “index” that allows the retrieval of the information. The discovery of the place cells in the hippocampus by O´Keefe and Dostrovsky in 1971, led to the idea that the hippocampus was in charge of a particular form of memory based on the “representation of experience within a specific context (O´Keefe and Nadel, 1978, p.381). This particular role of the hippocampus in context led to the conclusion of the fundamental role of the hippocampus in representing spatial context (Nadel & Willner, 1980). The hippocampus, as said before, is specialized in the contextual attributes and temporal features. The coding mechanism in the hippocampus allows it to differentiate between close representations; this forms boundaries between similar contexts. Hippocampal dysfunctions provide, among other manifestations, a loss of the ability to encode and discriminate between contexts (Nadel et al., 2012).

The cortical systems are specialized in extracting the semantic characteristics of the entities, their regularities to form categories and concepts. Once the entities have been processed according to their features, there are also linkages between the hippocampus and the cortical systems, for encoding all features of each entity (Nadel et al., 2012).

In 1900, Georg Elias Müller, professor at the University of Göttingen, Germany, and his student Alfons Pilzecker coined the term consolidation in their seminal monograph Experimental Contributions to the Science of Memory. What they proposed was that the learned information does not produce instantaneous, permanent traces of memory, but that time is needed to fix or consolidate that trace. During this necessary time period, memory remains vulnerable to disruption (Lechner, Squire & Byrne, 1999). Memory formation occurs slowly over time, but once consolidation is over, by definition is permanent, unchangeable and the memory trace that results cannot be disrupted in the normal course of events (Nadel, Hupbach, Gomez & Newman-Smith, 2012).

A second important finding is related to Milner et al., (1968) and the proposal that Alvarez and Squire (1994) did about the role of the MTL. It seems clear that the hippocampus and its related cortical structures consolidated memory through a process that is time dependent, but it is not the place where information would remain forever. Ribot (1882) formulated a hypothesis (later confirmed by Squire, Slater, & Chace, (1975) using electroconvulsive therapy) about the susceptibility of a memory; and that this susceptibility to disruption was inversely proportional to the age of the memory. According to this notion, both fact (or

semantic) memory and event (or episodic) memory are impaired together in a graded manner depending on the extent of damage to the hippocampal system as a whole (Knowlton, Squire, & Gluck, 1994). Instead, another proposal stated that the core defect in temporal-lobe amnesia is a loss of context- rich episodic memory, that could be why in some amnesic cases, semantic memory, which is free of context, appears to have been relatively preserved (Tulving, 1995). The debate about if both memories, semantic and episodic, depend on the hippocampus, was open. Vargha-Khadem et al., (1997), provided findings that support the view that only the episodic component of the cognitive memory is fully dependent on the hippocampus. They described three different cases of early bilateral hippocampal pathology (one case at birth, in another by age 4, and in the third at age 9), where despite the pronounced anterograde amnesia for the episodes of everyday life, all three patients attended mainstream schools and attained levels of speech and language competence, literacy, and factual knowledge that are within the average. The findings provide support for the view that the episodic and semantic components of cognitive memory are partly dissociable. In a review of different studies later carried out by Tulving & Markowitsch, (1998), they saw that what Vargha-Khadem et al., (1997) proposed fit perfectly with the episodic theory. Vargha-Khadem et al.,(1997) suggested that the acquisition of factual knowledge can occur independently of the episodic memory, being the neuroanatomical reference for the semantic memory the perihippocampal cortical regions and for the episodic memory the hippocampus. According to this proposal, perhaps only when the hippocampus and underlying cortices are damaged together, as in the famous case of H.M. (Scoville, W. B., & Milner, 1957), does the anterograde amnesia affect both components of cognitive memory equally (Vargha-Khadem et al., 1997).

Squire et al., (1975), measured the temporal gradient of memory loss in retrograde amnesias. Typically, as the interval between learning and amnesic treatment, such as electroconvulsive therapy (ECT) (ECT was used in this study with highly depressed patients) increases, the following amnesia is diminished. This phenomenon has been taken to highlight that the neural substrate of memory changes or consolidates over the time.

There are other brain structures, such as the neocortex, where memory is stored in a slower way, but where it would last longer in a supposedly invariably manner. This idea was proposed by Marr, (1971); he conceived the hippocampus as a temporary “simple” storage

of data, while the neocortex was the permanent store. McGaugh, (1966) pointed the idea that the higher levels of recruitment of neocortical areas during retrieval of remote when compared to recent memories points to the existence of dynamic interactions between the hippocampal formation and cortical areas during the consolidation process. According to more contemporary models of consolidation (McClelland, McNaughton, & O'Reilly, 1995; Squire & Alvarez, 1995), experience is initially encoded in parallel in hippocampal and cortical networks. Then, "reactivation of the hippocampal network reinstates activity in different cortical networks. This coordinated replay across hippocampal–cortical networks leads to gradual strengthening of cortico-cortical connections, which eventually allows new memories to become independent of the hippocampus and to be gradually integrated with preexisting cortical memories" (Frankland & Bontempi, 2005, p.122).

Dudai & Morris, (2000), in order to avoid any confusion with the term consolidation decided to make a differentiation between the memory stabilization process that only takes minutes to hours, what they referred as "synaptic consolidation" and could be assigned to any kind of memories. And the longer process, that may take years, using the term "systems consolidation", which it could only apply to the memories that are initially hippocampus dependent.

However, the neurobiological mechanism that is behind the synaptic consolidation of a memory in the hippocampus and the mechanism that is responsible of transforming that memory into a hippocampus independent one over the time are the same. As outlined before, Müller & Pilzecker, (1900) already noticed that performance can be impaired between two new competing learning events (Gordon & Spear, 1973), if they occur close in time. Also, memory performance can be impaired with invasive treatments such us electroconvulsive shock (Duncan, 1949) or proteins synthesis inhibitors (Flexner, Flexner, & Stellar, 1965) given almost immediately after learning, but not if given after hours. Contrary, retention can be enhanced via administration of different pharmacological compounds, such as strychnine (Gordon, 1977b). These three lines are believed to support the existence of a synaptic consolidation process, that distinct between a short-memory trace that lasts not more than some hours or days and a long- term memory trace that is supposed to be more permanent over time.

The hippocampus is considered to be active during consolidation processes (Dudai, & Morris, 2000), so studies at the cellular level of consolidation includes long-term potentiation (LTP) in this structure. The LTP in hippocampal slice preparations is the "long-lasting enhancement in signal transmission between two neurons following high-frequency stimulation of a chemical synapse" (Nader & Einarsson, 2010, p.28), analogous to the real cellular machinery in the brain. LTP can be divided in two phases, the early transient phase (E-LTP) and the late phase (L-LTP), a more lasting phase, but this line is very abstract. LTP, needs protein synthesis to take place (Bliss & Lømo, 1973; Martin, Grimwood, & Morris, 2000). Also, LTP can be modulated by the action of neurotransmitters, for example, glutamate, through the NMDA receptors activate the LTP process (Bliss & Collingridge, 1993). Dopamine is able to produce an enhancement of the early stages of LTP (Otmakhova & Lisman, 1996); while, GABA agonist (such as benzodiazepines like midazolam) are able to reduce LTP through the action of $GABA_A$ receptors (Evans & Viola-McCabe, 1996).

1.4. Emotional memory

"An impression may be so exciting emotionally as almost to leave a scar upon the cerebral tissues" (James, 1890)

Emotional memory deserves an independent section due to the main topic of this thesis; and because, emotional events usually have a privileged status in memory, and build our personal history (LaBar & Cabeza, 2006). But, what is special about emotional information processing? How emotion influences memory? Which are the neural correlates of that influence? And how may we be able to reduce that influence in pathological memories? It is what is going to be analyzed. Broca named the limbic lobe (hippocampus, the amygdala and the entorhinal cortex) because it forms a rim (in Latin, limbus means "rim") around the corpus callosum. The idea that the limbic lobe was involved in different emotional and viscerosomatic reactions in the mammals was developed by Papez, (1937) as one of the first propositions of the anatomical mechanism of emotion. Papez (1937) in his "Mechanism of emotion", pointed that the structures that may elaborate the emotions in the brain, and may participate in emotional expression were the hypothalamus, the anterior thalamic nuclei, the gyrus cinguli, the hippocampus and their interconnections. At that time,

the main idea was that the hippocampus and the entire limbic lobe were involved in olfactory functions.

1.4.1 The human amygdala

Today, one of the main theoretical frameworks of emotions is a dimensional approach that organizes emotion around two motivational systems: the appetitive and defense systems. These two opposing systems are reflected by the dimension of valence (pleasantness and unpleasantness). Further, arousal is the intensity which with these systems can be activated (Lang, 1995; Lang, Bradley, & Cuthbert, 1990). Arousal can be defined as an emotion´s dimension that oscillates between calm and excitement (LaBar & Cabeza, 2006). In 1990, Cahill & McGaugh proposed for the first time that the amygdala influence on emotional memory is mainly driven by arousal. They hypothesized that the degree of arousal of an emotional stimulus indicated the degree of the amygdala´s involvement in memory storage of that stimulus. The more arousing is the stimulus, more participation of the amygdala, and better subsequent recall. The theory of the main role of arousal, rather than valence, on amygdala activation and later recall was supported by Hamann, Ely, Grafton, & Kilts, (1999). Using Positron Emission Tomography (PET), they showed that bilateral amygdala activity during memory encoding is associated with enhanced episodic recognition memory for both pleasant and aversive stimuli compared to neutral stimuli, and that this relationship is specific to emotional stimuli.

The main studies focusing on the amygdala´s influence of arousal and its interaction with other brain regions such as the hippocampal and medial- temporal lobes were carried out mainly in episodic memory, and in fear conditioning. These studies have showed that amygdala influences memory indirectly, by modulating the activity of the hippocampus and temporal lobes (Hamann et al., 1999; McGaugh, Cahill, & Roozendaal, 1996; Packard & Teather, 1998).

The amygdala comprises about 12 different regions; and each region can be differentiated into several sub-regions. The most relevant areas for fear conditioning and episodic memory are the lateral (LA), basal (B), accessory basal (AB) and central (CE) amygdala, and their interconnections. Usually, the areas lateral and basal are referred together as the basolateral (BLA) amygdala (LeDoux, 2000).

In the fear conditioning paradigm, the conditioned tone (CS) includes projections from the auditory system to the lateral nucleus of the amygdala (LA), and from there, to the central nucleus of the amygdala (CE). In contrast, conditioning to the apparatus or contextual cues that were present at the time when the CS and US are paired, involves the hippocampus for the representation of the context and the projection between the hippocampus and the basal (B) and accessory basal (AB) nuclei of the amygdala, which communicates to CE. For tone conditioning, CE is in charge of the expression of the responses (LeDoux, 2000,)

The knowledge of how emotional memory is based on the integrity of the amygdala comes from studies of patients with amygdala lesions with memory for emotional stimuli disproportionately impaired (Adolphs, Cahill, Schul, & Babinsky, 1997; Babinsky et al., 1993). In humans, brain damage affecting only the amygdala is quite rare (Adolphs et al., 1997). So, the greatest contributions have been made by patients with unilateral damage of the MTL due to lobectomies in intractable epilepsy, or from patients with Urbach-Wiethe syndrome, a rare condition that sometimes can causes bilateral amygdala pathology (Adolphs, Tranel, Damasio, & Damasio, 1995; Hofer, 1972; Strange, Hurlemann, & Dolan, 2003).

Fear conditioning: the role of the amygdala

As Pavlov (1927) have already said, during fear conditioning an initially neutral stimulus [a conditioned stimulus (CS)] can acquire the fear properties after repeated temporal pairings with a biologically significant event [the unconditioned stimulus (US)]. Once the CS-US relation is learned, innate physiological and behavioral responses now occur under the presence of the CS. In animals, for example, if a rat is given a tone (CS) followed by an electric shock (US), after a few tone-shock pair-associations, freezing responses (rat´s defensive response that occurs in the presence of danger) will be elicited by the tone (LeDoux, 2000) (see Figure 1.6.). This form of conditioning is highly conserved across species, including humans (see for reviewLaBar & Cabeza, 2006).

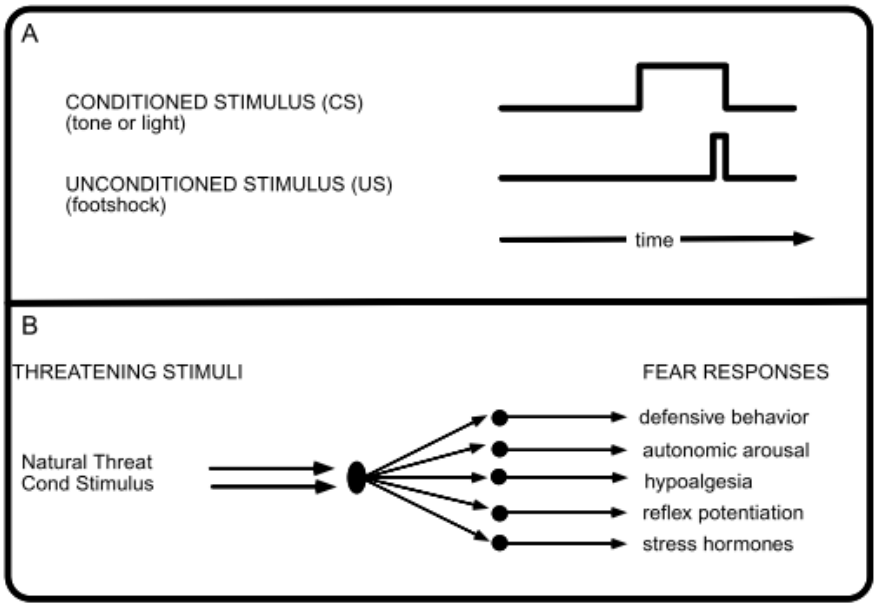

Figure 1.6. Fear conditioning involves the presentation fearful US (footshock), at the end of the occurrence of a neutral CS (a light or a tone), (A). Once the pairing has succeeded, the CS elicits a wide range of behavioral responses that are elicited by the animals in the presence of threatening or fear-arousing stimuli (bottom). Reproduced from LeDoux, (2000).

The amygdala processes the information about the CS and US in conditioned fear, and also controls the fear reactions by it projections to the response control system in the brainstem (an area that is in charge of the autonomic and endocrine response) (LeDoux, 2000). The control of the motor fear responses are in charge of the periaqueductal gray matter (PAG), a neural structure placed in the midbrain that, among other functions, integrates defensive behavior (Graeff, 2004); lesions in the periaqueductal gray it is been showed to interfere with freezing responses in rats (LeDoux, Iwata, Cicchetti, & Reis, 1988) .

Studies with animals with lesions of the BLA and central nuclei of the amygdala have shown the prevention of acquisition of fear cues and environmental contexts; the emotional CS responses can be elicited also by placing the animal in the chamber where the aversive US was previously experienced (Phillips & LeDoux, 1992). Patients with amygdala lesions, similarly as in animals, have impaired fear conditioning and fear-potentiated startle responses (Bechara, Tranel, Damasio, & Adolphs, 1995; LaBar, LeDoux, Spencer, & Phelps, 1995; Peper, Karcher, Wohlfarth, Reinshagen, & LeDoux, 2001). These patients are able to verbalize the reinforcement contingency and can generate unconditioned skin conductance responses (SCRs) to harmful stimuli; this points to an affected implicit

emotional learning mechanism. Instead, amnesic patients with MTL damaged have impaired explicit memories about emotions; but intact implicit emotional memories (LaBar et al., 1995). This dissociation along with neuropsychological data points towards a neural dissociation between the declarative and non-declarative aspects of simple forms of fear learning (LaBar & Disterhoft, 1998).

1.4.2. Memory modulation

Classic theories of memory differentiate between four memory stages (see section 1.4.): encoding, consolidation, storage and retrieval. Psychopharmacological studies have partly elucidated which neurotransmitter systems are involved in these different memory stages (Ferry & McGaugh, 1999; Introini-Collison, Arai, & Mcgaugh, 1989; Oitzl & De Kloet, 1992).

The basolateral amygdala selectively mediates the memory-modulating effects of adrenal stress hormones and different neurotransmitters such as acetylcholine and cortisol (Introini-Collison, Arai, & Mcgaugh, 1989; Oitzl & De Kloet, 1992) . Animal studies have shown that BLA modulates the consolidation of memory via efferent to other brain areas, such as the hippocampus (Beylin & Shors, 2003), the caudate nucleus (Packard & Teather, 1998; Petrovich, Canteras, & Swanson, 2001), nucleus accumbens (Roozendaal & McGaugh, 1996) and the neo-cortex (Power, Thal, & McGaugh, 2002; Price & Amaral, 1981) . Also, human brain neuroimaging studies indicated that subsequent recall of emotionally arousing material (pleasant or unpleasant) is influenced by the degree of activation of the amygdala (Anderson & Sobel, 2003; Small et al., 2003).

Different studies using beta adrenergic drugs have elucidated the role of this neurotransmitter in the amygdala, and in other memory-related regions (see Figure 1.7.). For example, Ferry and McGaugh (1999) showed that the administration of the specific beta-2-adrenergic agonist clenbuterol into the basolateral (BLA) amygdala after training enhances retention in an inhibitory avoidance task. They were able to demonstrate the involvement of the beta-adrenergic system of the BLA in the modulation of memory consolidation for inhibitory avoidance training in rats. On the other hand, post-training infusion in the BLA of beta-adrenergic antagonist blocks the enhancement in memory produced by adrenaline (Liang, Juler, & McGaugh, 1986)

Emotional situations trigger the hypothalamic-pituitary-adrenal axis at central [paraventricular nucleus (PVN) of the hypothalamus (Feldman, Conforti, & Weidenfeld, 1995)]and peripheral [adrenal cortex (Feldman et al., 1995)] sites of action, which activates the adrenergic and glucocorticoid systems. Noradrenaline stimulates the glutamatergic synaptic plasticity in the BLA, a place for learning and memory functions (Wang et al., 1996).

Emotional arousing experiences produce the engagement of stress hormones that can affect both types of memory (emotional and non-emotional forms) in humans (McGaugh & Roozendaal, 2002). The first evidence suggesting the modulatory role on memory by a stress hormones was provided by Gold & Van Buskirk, (1975). During encoding, administration of cortisol or stress-induced endogenous cortisol release generally enhances emotional learning and memory (Buchanan & Lovallo, 2001). Buchanan & Lovallo, (2001) showed that stress-level cortisol treatment in humans enhances memory for emotional material. However, during retrieval, similar manipulations of cortisol, impairs recall for earlier memories (see Chapter 2).

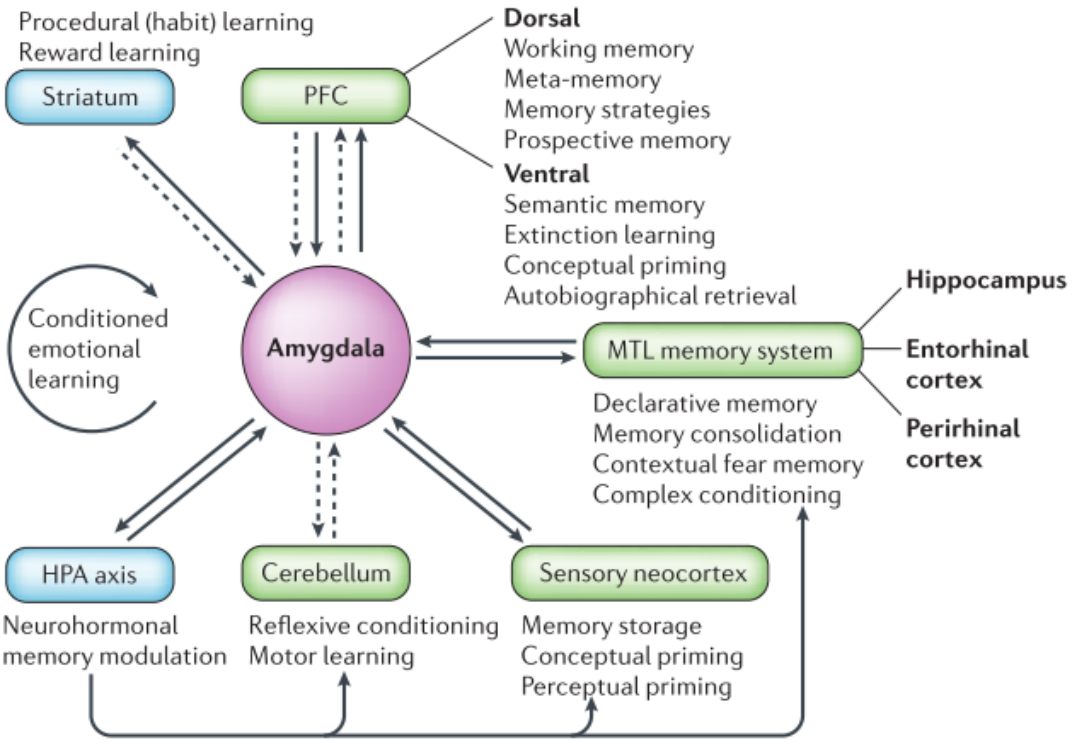

Figure 1.7. The influence of emotional arousal on memory mediates by the amygdala. MTL, medial temporal lobe; PFC, prefrontal cortex. Solid arrows indicate direct connections, dashed arrows indicate

indirect connections and blue labels indicate connections with subcortical structures. Reproduce from LaBar & Cabeza, (2006).

The modulatory effect of the amygdala in emotional memories was summarize in a set of experiments conducted by Strange et al., (2003). They showed that beta adrenergic modulation enhanced recall and forgetting associated with emotional stimuli, and that these enhancements are amygdala dependent.

In summary, BLA adrenergic activity has a key-role in the memory-modulatory effects of adrenal stress hormones released by emotional arousal (Cahill & McGaugh, 1998; McGaugh et al., 1996). Several findings suggest that BLA neuronal activity modulates stress-induced memory consolidation processes in the hippocampus (Cahill & McGaugh, 1998; McGaugh et al., 1996). In another set of experiments, Roozendaal, Nguyen, Power, & McGaugh, (1999) examined whether β –adrenoceptor activation in the BLA allows the facilitation of memory consolidation produced by activation of glucocorticoid receptors (GR) in the hippocampus. Roozendaal et al., (1999) provide further evidence for the mediating stress hormone effects on memory consolidation driven by the β –adrenoceptors in the BLA. They also showed that the BLA modulates the strength of memories in other brain structures, such as the hippocampus, reflecting their emotional significance (Roozendaal et al., 1999).

1.4.3. Context and fear

The amygdala receives information (inputs) from cortical sensory processing regions (see Figure 1.8.) and sends outputs back to those areas as well; these connections allows the amygdala to "know" where the danger is in the sensory world (McDonald, 1998; Turner, Mishkin, & Knapp, 1980). The initial acquisition of fear conditioning cues is driven by the amygdala but other aspects of the conditioning are carried out by the hippocampus, for example contextual cues learning (Kim & Fanselow, 1992; Phillips & LeDoux, 1992) (see Figure 1.9.).

One example of the roles of contextual cues in fear learning is the spontaneous recovery after extinction learning. After acquisition trials (CS-US pairings), the CS is presented alone and the fear response the CS extinguishes over the trials. However, a single presentation of the US after extinction can recover the fear response to the CS (Bouton,

2004; Robbins, 1990). The reinstatement of extinguished fear depends on the context and is a hippocampal-dependent process (LaBar & Phelps, 2005). The suppressed conditioned fear by extinction is very sensitive to contextual cues, so the extinguished responses may "recover" over time [renewed (Rodriguez, Craske, Mineka, & Hladek, 1999) or reinstated (Rescorla & Heth, 1975)], within the context where the CS had been presented (LaBar & Phelps, 2005). Studies in lesioned animals have shown that the contextual recovery of extinguished fear relies on the integrity of the hippocampus (Corcoran & Maren, 2004). Also, studies in humans have confirmed that extinguish fear can be recovered due to the context. This contextual reinstatement of fear is not shown in amnesic patients with hippocampal damage; these patients are able to learn implicitly but are not able to retrieve based on contextual cues (LaBar & Phelps, 2005) . Another region involved in extinction is the ventromedial prefrontal cortex (vmPFC), which is implicated in the storage and recall of extinction memories, probably by inhibiting the CR via suppression of the amygdala. Hobin, Goosens, & Maren, (2003) indicated that the activation of the vmPFC after extinction is context dependent. Kalisch et al., (2006) suggested that the hippocampus sends contextual information to the vmPFC. Both structures, among others, are important in extinction of contextual memories but also, are probably important for the contextual reinstatement of previously extinct memories (Kalisch et al., 2006).

The understanding of how these contextual cues exert their effects on extinguished fear responses is fundamental to also better understand anxiety disorders that are characterized by generalizations of the fear response to other situations due to contextual factors (Mineka, Mystkowski, Hladek, & Rodriguez, 1999). "Flashbacks" in traumatic memories also rely on contextual cues. Due to these implications, the control of the context may be fundamental on the treatment of these disorders (LaBar & Cabeza, 2006).

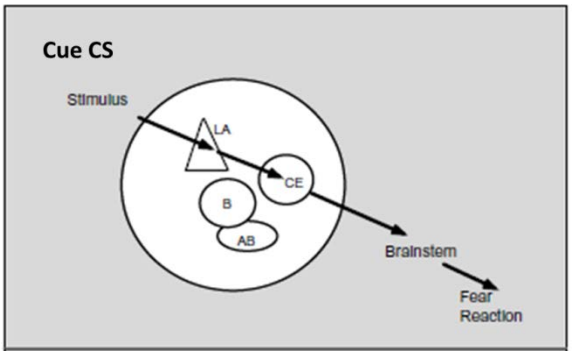

Figure 1.8. Conditioning to a CS implicates projections from the different nucleus of amygdala. In this case, if the CS would be an auditory tone, this would be processed by the lateral amygdala (LA) and project to the central nucleus of the amygdala (CE). Reproduced from LeDoux, (2000).

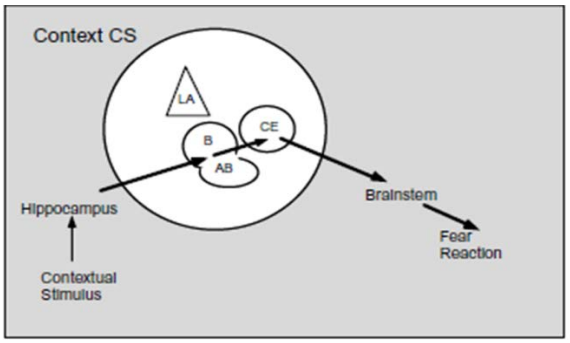

Figure 1.9. Conditioning to other cues, such as the context present when the CS and the US are paired depends on the hippocampus and the basal (B) and accessory basal (AB) nuclei of the amygdala; and the projections to the central nucleus (CE). Reproduced from LeDoux, (2000).

1.4.4. Neuroimaging of fear conditioning

Modern techniques such as event-related fMRI have led to the possibility to study the signal changes during acquisition, without mixing the signals of the CS or the noxious US; revealing activations in a thalamo-amygdalo-cingulate (mainly the anterior cingulate and dorsomedial prefrontal cortex) network (LaBar & Cabeza, 2006). Humans studies with delay (CS-US presentation is overlap in time, non-declarative learning) and trace (the presentation of the CS-US is separated by a gap of time, declarative learning) fear conditioning suggest that the hippocampus codes temporal information during trace conditioning, while other brain regions, important for working memory processes to maintain the CS-US representation during the time interval (Knight, Cheng, Smith, Stein, & Helmstetter, 2004).

One study using event-related fMRI imaging during aversive trace conditioning was able to characterize the brain regions involved in associative learning. Büchel, Dolan, Armony, & Friston (1999) paired neutral auditory tones (CS) with an aversive sound (US). The neural responses evoked by the paired CS, related to conditioning were localized in anterior cingulate and anterior insula, regions associated to delay fear conditioning, too. They observed also activation of the hippocampus and the amygdala (Büchel et al., 1999).

Another study used two angry faces as target visual stimuli, with only one of the faces associated with a burst of white noise during classical conditioning. They also prevented the subjects' knowledge of the angry faces by fast presentation (30 ms) and backward masking them with a neutral face in half of the trials (Morris, Öhman, & Dolan, 1998). The results of this study showed that the subliminal fear conditioned angry face expressions also depend on the amygdala and produce greater functional interactions between the thalamus and superior colliculus than during the "unseen" condition (Morris et al., 1998) .

To better understand fear conditioning, and above all to get better insight in the treatment of fear-related disorders, it is as important to know how the association is learned as how these learned fears are diminished. In another study, the authors used fMRI to examine fear extinction in humans (Phelps, Delgado, Nearing, & Ledoux, 2004). Previous findings in non-human animals have paid attention to two brain regions: the amygdala and the ventromedial prefrontal cortex (vmPFC) (Morgan, Romanski, & LeDoux, 1993; Quirk, Russo, Barron, & Lebron, 2000). In this typical fear-conditioning paradigm studies, extinction happens when a CS is presented alone, without the US pairing, for a number of trials and eventually the conditioned response (CR) is diminished or even, eliminated. Extinction rather than "erased" an old memory, produce a new learning that competes with the old one (Bouton, 2004). This vision of the extinction as a "new" learning is supported by studies showing that after extinction the CR can return in a number of situations, such as after time (spontaneous recovery) (Bouton, 2004; Robbins, 1990), after the presentation of the US alone (reinstatement) (Rescorla & Heth, 1975), or if the animal is placed in the context where the initial CS-US pairing was learned (Phelps, Delgado, Nearing, & Ledoux, 2004).

The first one who mentioned the vmPFC as a neural region implicated in fear extinction was Morgan et al., (1993), by demonstrating that lesions in this area produced an

impairment in extinction. Some years later Quirk et al., (2000), showed that damage in this area result in impairment in the retention of extinction learning over the following days, rather than in an impairment of extinction learning overall.

In 2002, Milad & Quirk, (2002), in a study with rats, demonstrated that if the tone CS is paired with stimulation of the vmPFC, this diminish the expression of the conditioned fear, pointing a role for the vmPFC in the inhibition of the CR. In a recent study Moratti, Giménez-Fernández, Méndez-Bértolo, & de Vicente-Pérez, (2017) showed increased neuromagnetic response in vmPFC during extinction by source localizing real time neural activity as recorded by Magnetoencephalography.

The vmPFC and the amygdala are specific areas for fear conditioning, and are interconnected. The central nucleus (CE) of the amygdala has been related with the physiological expression of conditioned fear, through its connections to the lateral (LA) nucleus of the amygdala. The CE projects to different brain areas, also related with the expression of conditioned fear. The response rate of the CE output neurons can be changed via input from LA by the stimulation of the vmPFC, suggesting that the CE is primarily modulated by the vmPFC (Quirk, Likhtik, Pelletier, & Paré, 2003).

More recent brain imaging studies have examined the mechanisms of fear inhibition but without conditioning. Phelps et al., (2004) did it by presenting negative and neutral scenes and asked subjects to try to diminish their fear responses to the scenes by paying attention to positive or non-emotional aspects of the scene. They showed decreased amygdala activation relating to diminishing negative affect during the re-evaluation of the negative scenes (Phelps et al., 2004). Also, they found that the right lateral PFC was activated when reappraisal succeeds, and that this activation correlated with a reduced amygdala response. This area of the PFC is supposed to have a role in working memory, executive processing, or the active maintenance of online information (Ochsner, Bunge, Gross, & Gabrieli, 2002). The connections between this PFC area and the amygdala are not direct; it happens through the medial PFC regions projections that are more directly connected with the amygdala (Groenewegen, Wright, & Uylings, 1997).

Phelps et al., (2004) found that the predicted CR in acquisition and early extinction involves the amygdala in humans. This finding along with the ones made by Quirk et al.,

(2000) contribute to the idea that the roles of the amygdala and vmPFC are conserved along species.

In summary, the different stages of memory processing are engaged and influenced by emotion; as well as the different brain areas involve in those stages too.

1.4.5. Episodic emotional memory

"Human emotional experience is typically associated with enhanced episodic memory" (Strange & Dolan, 2004; p. 11454).

One of the most cited study with episodic arousal material is the one performed by Cahill (1994). They examined the effect of a beta-adrenergic receptor antagonist (propranolol) or placebo on the memory of an emotionally arousing story accompanied by pictures. Participants that took placebo remembered better the pictures of the emotional part of the story, while participants that were administered with propranolol (beta-adrenergic receptor antagonist) did not show that memory enhancement for the pictures of the emotional part of the story. Another study using PET showed that emotional long-term memory is directly related to the degree of amygdala activation during encoding (McGaugh et al., 1996). As outlined before, the BLA is a location for encoding and memory consolidation, but it is not the actual memory storage. If a BLA lesion is done some time after learning, the retention is not affected; but if the treatment is administrated immediately after learning, LTM is impaired (Liang et al., 1982; Parent, Quirarte, Cahill, & McGaugh, 1995). Also, human amygdala lesions have demonstrated that enhanced memory for emotional events is an amygdala dependent process and involves the beta adrenergic receptor activation (Cahill, Babinsky, Markowitsch, & McGaugh, 1995). These processes seem not to be necessary for non-emotionally arousing material retention (Cahill et al., 1995).

Kleinsmith & Kaplan, (1963) , showed that the effects of emotion on memory retention increase as a function of time between encoding and testing (see also Hu, Stylos-Allan, & Walker, 2006). It has been shown that retention is greater for emotionally arousing compared to neutral words, and that this memory is better if tested after a period of time (1hour to 1 day) rather than if tested immediately (LaBar & Phelps, 1998; Sharot & Phelps, 2004). The facilitation on consolidation by emotional arousal needs time to take place. Several studies have shown that the emotion effects are either absent or much smaller when memory is tested immediately, and they tend to increase in magnitude after a few hours

(Anderson, Yamaguchi, Grabski, & Lacka, 2006; Kleinsmith & Kaplan, 1963; Ritchey, Dolcos, & Cabeza, 2008; Sharot & Phelps, 2004; Sharot & Yonelinas, 2008). This enhanced facilitation process was found to be absent in patients with temporal lobectomy. These patients showed equal forgetting rates for neutral and emotionally arousing words after different time intervals (from immediate to 1 hour).

The time-dependent memory advantage may be due because item–emotion bindings are supported by the amygdala and are forgotten more slowly than item–context bindings supported by the hippocampus (Yonelinas & Ritchey, 2015). The lesion and imaging results show that the amygdala plays a central role in producing the emotion advantage in episodic memory (Mackiewicz, Sarinopoulos, Cleven, & Nitschke, 2006; Ritchey et al., 2008).

Another "benefit" (in terms of higher memory recall) of emotional arousal is the focus of attention on specific stimuli, that can benefit from prioritized processing (Kensinger & Corkin, 2004), in detriment of peripheral information. "Attentional focusing ensures that emotionally salient features of complex events are preferentially retained in memory, which confers evolutionary advantages" (LaBar & Cabeza, 2006; p.55). This beneficial effect is not present in patients with amygdala lesions; but they are able to benefit from the facilitated effect of arousal. This kind of patients remember better words relative to pleasantness and unpleasantness (which are on the valence extremes) but have no the intensity to activate the amygdala because (the words) are low in arousal (a dimension that goes from calm to excitement) when compared to neutral. They are also able to take advantage of neutral words encoded in emotional sentence contexts relative to neutral contexts (Phelps et al., 1998; Phelps, LaBar, & Spencer, 1997) So, it is probable that some emotional advantages can occur besides the amygdala, especially if the lesions occur later in time life. The patients are able to substitute the arousal engaging processes by an emotional valance related cognitive processes (Talmi & Moscovitch, 2004).

All these studies, converged to the conclusion that at the time of encoding, enhanced memory for emotional stimuli may be due by an enhancement of amygdala activation, that also modulates hippocampal processing (Strange & Dolan, 2004). The amygdala facilitates LTM consolidation of emotionally arousing events in other brain structures, and an enhancement in recall of emotional stimuli may reflect amygdala-hippocampal interactions

thanks to the influence of the adrenergic and glucocorticoid systems (Paré, 2003; Roozendaal et al., 1999; Strange & Dolan, 2004).

To summarize all the influences of the amygdala in emotional memory, it can be said that:

- Memories need time to be formed.
- Emotional arousal facilitates the consolidation of episodic memory, and this facilitation effect is mediated by the amygdala.
- This facilitation effect of arousal is mediated by the amygdala through the stress hormones.
- The storage place of emotionally charged episodic memory is not the amygdala, but are more hippocampus-dependent and on cortical regions.
- These modulation effects of the BLA occur in humans.

1.5. Post-consolidation modulation of memory

The classical view of memory formation (see section 1.3.) needs to be updated (Nadel et al., 2012). Apparently it is possible to render labile again an initially fixed memory (Nader, Schafe & Le Doux, 2000). This challenged the consolidation theory from two fronts. From one side, the inability to recall a previous memory imprinted in the brain after the application of different interventions such as electroconvulsive shock (Duncan, 1949) or protein synthesis inhibitors (Flexner et al., 1965). And in the other hand, several studies showing that consolidated memories can become labile again after retrieval, and then re-stabilize (i.e.: Lewis, 1979; but see review by Nader & Einarsson, 2010) (see Figure 1.10.).

During the last decades, the idea that retrieval of a memory can be an opportunity to update or modulate what was originally learned (Monfils, Cowansage, Klann, & LeDoux, 2009) or even erase that memory (Nader, Schafe & Le Doux, 2000), has been receiving increased attention. The term “reconsolidation” refers to the process by which a LTM transiently returns to a labile state and its subsequent stabilization. In order to initiate the process of reconsolidation, it is necessary to activate the target memory again; this process is called reactivation. When the reactivated memory enters in a labile state it becomes vulnerable to change in ways that a non-reactivated LTM cannot be (Nadel et al., 2012). This change can include for example: weakening or even erasure (Nader et al., 2000; Walker et al., 2003), strengthening, or alteration (Hupbach, Gomez, Hardt, & Nadel, 2007).

Three lines of evidence were established to support the existence of a re-stabilization process. First, performance can be impaired if amnesic electroconvulsive shock are given shortly after reactivation (Misanin, Miller, & Lewis, 1968). Second, performance can be impaired if new competing learning occurs shortly after reactivation (Gordon, 1977a). And finally, via administration of different compounds (i.e.: strychnine, highly toxic alkaloid usually used as a pesticide) retention can be enhanced (or impaired) after reactivation (Gordon, 1977b). "Critically, all three manipulations are effective only when given shortly after memory reactivation but not when given after a delay" (Nader & Einarsson, 2010, p.28). These findings, coming from several investigators, in different tasks (Debiec, LeDoux, & Nader, 2002; Nader, Schafe & Le Doux, 2000; Rose & Rankin, 2006) and species (Nader, Schafe & Le Doux, 2000; Rose & Rankin, 2006; Sangha, Scheibenstock, & Lukowiak, 2003), fundamentally support reconsolidation theory as challenge the consolidation one.

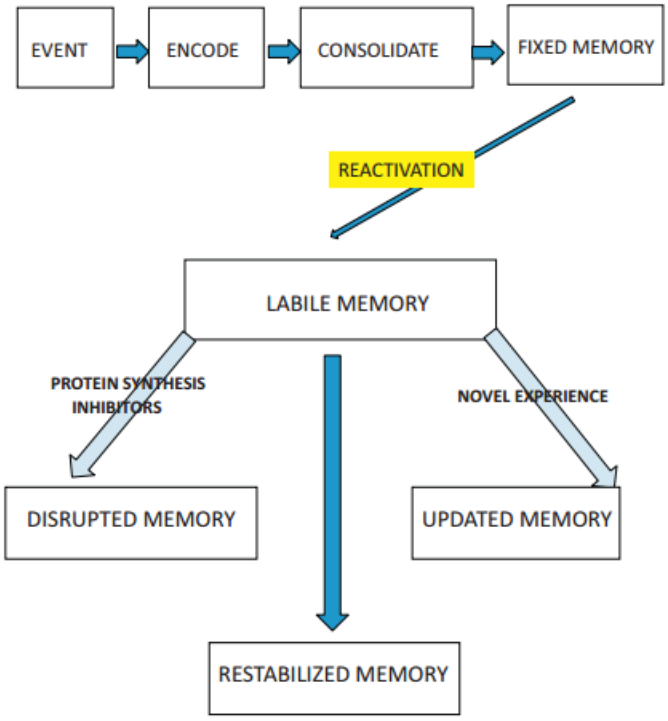

Figure 1.10. Possible effects of reactivating a memory. Reproduced from Nadel et al., (2012).

One of the principal supportive studies of reconsolidation was published in 1979 by Lewis. His paper made a theoretical argumentation based on several findings of other authors, for

example Craik & Lockhart, (1972) or Shiffrin & Atkinson, (1969), about the impossibility that a failure in memory formation (consolidation) between short-term memory (STM) and long- term memory (LTM) could explain the recovery of the memory traces (i.e.: after pharmacological stimulation, Braun, Meyer, & Meyer, 1966), previously disappeared. He concluded that with the lines of evidence that were available at that time was better to make a distinction between active and inactive memory. For Lewis, an active memory (AM) did not occupy a specific site or sites in the brain. He preferred to conceive AM as "a patterned state of neural firing that cannot be localized; different active memories in the brain reflect different densities of firing" (Lewis, 1979, p.1066), and it is totally conscious and accessible no matter if is new or old; while an inactive memory (IM) is not conscious or accessible. Posner (1967) proposed that interference and forgetting would probably take place when the memory is in an active state; giving the understanding that an active memory is not only a new memory, but that an old memory can be reactivated later when the stimuli are presented again (Lewis, 1979). In 1968, Misanin challenged the conception of a consolidated memory as immutable by reporting that using a cue reminder rendered consolidated memories labile again and susceptible to disruption (McKenzie & Eichenbaum, 2011). Using an auditory fear conditioning procedure, they trained rats to associate a conditioned stimulus (a CS tone) to an unconditioned stimulus (US), in this case an electroconvulsive shock (ECS). When the training was followed immediately by the ECS, the memory for the association was disrupted, but if they waited for 24 hours to administer the ECS, nothing happened to the memory for the CS.

Misanin (1968) also performed another experiment, with the same CS-US association, but in this case, the rats that had already learned that association were exposed to the CS before they received ECS, 24 hours after learning. The results were that the memory, measured by the freezing response in rats, for the consolidated tone-shock was disrupted. On the other hand, rats who were not exposed to the CS, and did not activate their memory of the association, showed no memory impairment due to ECS (Misanin et al., 1968).

Misanin and his team, not only demonstrated the distinction between active memory and inactive memory, but also that was possible to disrupt a highly robust fear memory association depending on the state of the memory, active or inactive, at the time of applying an amnesic treatment such as ECS (Misanin et al., 1968).

In 1968, and due to the Zeitgeist, the novel findings of Misanin did not received much attention (Schwabe, Nader, & Pruessner, 2014). Added to this lack of attention, in 1976 a study was published that failed to support the hypothesis of reconsolidation (Squire, Slater & Chace, 1976).Squire results failed to demonstrate the hypothesis that reactivation of previously learned material before convulsive stimulation can cause amnesia (Squire, Slater & Chace, 1976). These negative results helped plunge the theory of reconsolidation into the shadows.

It was not until the year 2000, when this cue-dependent amnesia came into the spotlight of research again with the study of Karim Nader and his colleagues (2000). Using rats with a fear conditioning paradigm, they demonstrated again, that a memory can render labile again and susceptible of disruption by amnesic treatments. They showed that a consolidated fear memory returned to a labile or active state after a reminder and that an infusion of anysomicin, a protein synthesis inhibitor into the basolateral amygdala (BLA), a region implicated in fear learning, produced amnesia of the original US-CS association (Nader, Schafe & Le Doux, 2000). With these set of experiments, they not only showed that a consolidated memory can be susceptible of disruption by amnesic agents, but also they demonstrated for the first time that synthesis of proteins is needed to stabilize again the memory reactivated, and that this is a time dependent process.

After Nader, reconsolidation has been demonstrated in several species with different memory paradigms. In humans, due to ethical reasons, it has been difficult to use invasive treatments such as the ones used in animals. Much of the evidence of human reconsolidation comes from non-invasive techniques that update memory instead of disrupting it during reconsolidation (Schiller & Phelps, 2011).

Even thought, reconsolidation is an accepted stage of memory. Nevertheless, there are some studies that do not support the idea that retrieval after reactivation renders a memory labile again and needs protein synthesis to be fixed in a permanent state again. For example, Lattal & Abel, (2004); Power, Berlau, McGaugh, & Steward, (2006) suggested that the disruption of a memory is transient and fully reversible. The main finding was that they showed impaired behavior caused by systemic injections of anysomicin (a protein synthesis inhibitor) after the acquisition of contextual freezing in rats are maintained over the time, but if the injection of the anysomicin is after retrieval they are not long-lasting

(Lattal & Abel, 2004). Also, the rat´s freezing response was recovered spontaneously after 21 days, although it was not evident in a test after 24 hours retrieval. The finding of this experiment also suggests that the injection of the protein inhibition synthesis has different effects if administered after acquisition of after retrieval (Lattal & Abel, 2004).

Another study with rats showed the hypothesis that complete older consolidated memories are less sensitive to impairment when reactivated. They found that long-lasting memories (1 to 7 days ago; but not 14 or 28 days ago) are able to disrupt processes after reactivation. According to this study, the vulnerability of the memories for having been impaired decreases over the time passed between the original training and the recall. The explanation that the authors gave to their findings was that these recent long-term memories more able to be disrupted by protein synthesis inhibitors were not fully consolidated; so the degree of vulnerability of a reactivated memory changes with the time passed between initial learning and reactivation (Milekic & Alberini, 2002).

Besides the time factor, there are other factors that seem to be important in the possibility to reconsolidate a memory, such as the strength of memory and the strength of the reactivation process (Squire, 2009).

This new era of reconsolidation studies has been based on the findings made in the sixties, which established the basic criteria to be followed to reactivate a memory and manipulate it. In order to asses a successful protocol of reconsolidation; the consolidated memory must be reactivated by a reminder cue (Misanin et al., 1968; Rubin, Fried, & Franks, 1969). Second, the manipulation needed to altering reconsolidation must be administered post-reactivation, rather than prior (Nader, Schafe & Le Doux, 2000); and finally, because reconsolidation is a time dependent process, memory should show the effects of the manipulation after a time-window, allowing reconsolidation to take place (usually tested after 24 hours) (Nader, Schafe & Le Doux, 2000).

Behavioral manipulations of reconsolidation in humans

Extinction

In humans, a behavioral procedure is obviously less invasive than a pharmacological manipulation.

Emotional memory is a crucial kind of memory in this thesis, but also in real life. Almost all experiences that we have during are life-time are coded in way or another by emotional arousal or valence. The autobiographical memories that we recollect along the years can be easily classified between positive or negative experiences. The emotional positive episodic memories are always to be kept and remembered, but negatives are otherwise quite different.

Emotional memories can lead to anxiety disorders. For example, a common anxiety disorder that is linked to traumatic memories is known as post-traumatic stress disorder (PTSD). This disorder and other linked to traumatic or negative memories are fully disturbing of one's life; so an important implication of the findings in impairing memory reconsolidation in animals could be translated to treatments in humans.

Extinction is one of the most successful treatments for anxiety disorders. These kinds of patients associate and act as is a feared stimulus (CS) would be followed by a negative outcome (US). One model, which allows scientist and therapist to study experimentally the acquisition and consolidation of fear memories, is the Pavlovian fear conditioning paradigm, that it has been described earlier. The extinction training repeatedly exposes the patient to the CS but in the absence of the aversive outcome, or in a safe environment. The main problem with extinction is that does not erase the fearful memory, but instead, creates a new competing safe memory, that inhibits the original fearful memory. However, often the fear returns, spontaneously (Bouton, 2004; Robbins, 1990), after presenting the US alone (reinstatement) (Rescorla & Heth, 1975) or by new context (renewal), different from the one that it was extinguished (Rodriguez et al., 1999).

In humans exits the possibility to capitalize on reconsolidation as an update mechanism. Instead of trying to "erased" a memory, maybe it is possible to "re-write" that negative memory with a new memory, more positive, provided at the time of retrieval, and so it may be possible to permanently modify the fearful properties of the old negative memory. But, in animals for example, there is only one demonstration of altering fear memories by introducing non-fearful information. Using rats, Monfils, Cowansage, Klann, & LeDoux, (2009) were able to destabilized a fear memory and reinterpreted as safe with only one trial before extinction, and showed that this behavioral manipulation was able to permanently diminishes the fear memory. Nevertheless, those results were only possible to achieved

using genetically modified mice and optogenetics (Liu et al., 2012; Ramirez et al., 2013).Other studies that tried to modified fear memories with non-fearful information during consolidation have had mixed results (Myers, Ressler, & Davis, 2006; Schiller et al., 2008).

One of the first studies in humans was driven by Walker, Brakefield, & Hobson, (2003), using procedural learning, more specifically a motor skill finger-tapping task. With their study combining sleep and awake states during a 3 day protocol, they were able to showed three different stages of human motor memory after the initial encoding. Their behavioral study showed that waking reactivation is able to turn memory labile again, requiring subsequent reconsolidation. This study has been considered a convincing demonstration of human reconsolidation. However, in four direct replication attempts Hardwicke, Taqi, & Shanks, (2016) did not observe the critical impairment effect that has previously been taken to indicate disruption of an existing motor memory trace. In three additional conceptual replications they explored the broader validity of reconsolidation-updating theory by using a declarative recall task and sequences similar to phone numbers or computer passwords. Rather than inducing vulnerability to interference, memory retrieval appeared to benefit the preservation of existing sequence knowledge relative to a no-retrieval control group. These findings suggest that memory retrieval followed by new learning does not reliably induce human memory updating via reconsolidation (Hardwicke et al., 2016).

One controversial study was the one published by Schiller et al., (2010). They evidenced that old fearful memories can be updated with new non-fearful information after reactivation. They design two experiments using the US-CS association. In one first experiment, they showed that extinction during reconsolidation window prevents spontaneous return of extinguished fear. In order to see if these results would last during time, they performed a second experiment, one year later. In this second experiment, they showed that blockade of the return of fear persists over a year, and that it was specific to the reactivated memories. One main difference with other studies done before with interference paradigm targeting motor or declarative memory was that those other studies showed that new information provided during reconsolidation could affect old memories by modifying or interfering with them, but not blocking them. The authors suggested that these differences could be due to the different nature of the neural systems supporting different

types of memory. Declarative memory has a distributed cortical representation, while conditioned fear memories representation is localized in the amygdala, as mentioned previously.

Due to the importance of being able to reduce emotional memories in humans with a behavioral paradigm, Soeter & Kindt, (2011) tried to replicated Schiller et al., (2010) findings. They tried to demonstrate again that multiple unreinforced presentations allowed for updating of the more cognitive component of emotional memory in humans. Or in other words, an extinction procedure performed within the time-window of reconsolidation turned into the permanent erasure of the skin conductance response (*i.e.*, declarative knowledge).

The results that Soeter & Kindt, (2011) achieved following Schiller´s study (2010) were that a single retrieval trial prior to extinction did not attenuate the recovery of extinguished startle responding, skin conductance response (SCR) or US expectancy ratings. The authors pointed that there were three differences in their study compared to Schiller´s (2010). One, the kind of stimulus used. In Schiller´s (2010), were geometric figures while in Soeter & Kindt, (2011) were fear relevant stimulus (spiders). Second, they employed a different reinforcement scheme during acquisition. Apparently, with their retrieval trial they were not able to activate the process of reconsolidation. And the third difference was the way of measuring the conditioning responses. Schiller assessed the response by subtracting the response to the CS+ (reinforced) and the CS- (not reinforced) while, Soeter & Kindt (2011), inferred the degree of fear from differential responding to the CS+ and CS-. Due to the no difference in responding to the different CS, the authors thought that it could indicate a generalization of fear to the control stimulus.

The failure in replicating Schiller´s study (2010) put at a crossroads a valuable behavioral manipulation. Other experimental group (Oyarzún et al., 2012) decided to try again to reproduce Schiller´s study but with a modified version, using auditory aversive stimulus instead of electroshocks. The CS were geometric figures, but the statistical analysis was a within subjects design (Schiller used a between subjects design) because fewer number of patients are needed and because is more statistically powerful. They used two different auditory tones as US, each of it associated to a specific CS, so the association was stronger. What they found was that only the SCR for the CS that was reactivated before extinction

remained extinguished after reinstatement (re-exposure to the US). Their results supported Schiller´s previous findings, highlighting that extinction within the reconsolidation window can target fearful memories and prevent the reinstatement of fear.

In an attempted to increase the clinical validity of the original study by Schiller (2010), and using a fear conditioning paradigm in two different experiments, one with fear relevant (fearful male faces) and the other with fear irrelevant stimuli (colored squares), Golkar, Bellander, Olsson, & Ohman, (2012), tried to erased fear memories. In order to do so, they designed a three consecutive day protocol, following reconsolidation criteria, where participants went through conditioning (Day 1); reactivation and extinction (Day 2) and reinstatement and re-extinction on Day 3. They used startle response, US expectancy ratings and SCR as dependent measures of fear. The results that this group found were that a single retrieval prior to extinction did not disrupt the recovery of extinguished conditioned fear responses, in line with the results others have obtained with their replication attempts (*i.e.*: Soeter & Kindt, 2011). On the other hand, these findings are contrary to previously published by other authors (Agren, Engman, et al., 2012; Oyarzún et al., 2012; Schiller et al., 2010). Due to the wide range of possible clinical implications, the results of Schiller have received a significant amount of attention; but also, have been very controversial, given the difficulty of an overwhelming replication. One important point that Golkar et al., (2012) highlighted was that previous studies (Agren, Engman, et al., 2012; Oyarzún et al., 2012; Schiller et al., 2010; Soeter & Kindt, 2011) have only included patients that were susceptible of extinction; in other words, they have previously made a selection of the healthy individuals, that may not represent the general population, or at least, not the clinical population. Agren, Furmark, Eriksson, & Fredrikson, (2012) studied the fear reconsolidation and allelic differences in serotonergic and dopaminergic genes in humans. They hypothesized that these contrary results might be due to specific subgroups in which the blocking is effective. Garpenstrand, Annas, & Ekblom, (2001) studied also, the dopaminergic and serotoninergic biological markers in relation to human fear conditioning, founding that 5-HTTLPR is associated with stronger fear acquisition.

Another study that had examined human fear extinction was Klucken et al., (2016). They showed that a single presentation of a conditioned stimulus did not block the return of fear during re-extinction, suggesting that the effect of preventing the return of fear by disrupting

reconsolidation seems to be a more labile phenomenon than previously assumed. They were unable to replicated the results of Agren, Engman, et al., (2012); Agren, Furmark, et al., (2012); Schiller et al., (2010) but supported the results of Golkar et al., (2012); Soeter & Kindt, (2013); Soeter & Kindt, (2011).

Other study combined behavioral and pharmacological manipulations of a differential fear conditioning procedure with three stimuli (CS) and was the one made by Thome et al., (2016) . Two of these CS+ were paired with an electric shock and US expectancy ratings, fear-potentiated startle, and skin conductance response as dependent measures. They observed differential fear responses to the reactivated and non-reactivated CS+ only in the pharmacological (propranolol) condition. Even more, the non-reactivated CS+ elicited stronger fear-potentiated startle-responses compared to the placebo group. Their results showed that none of the interventions prevented the return of the extinguished fear response after re-exposure to the unconditioned stimulus (Thome et al., 2016).

The data of Klucken et al., (2016) and Thome et al., (2016) are in line with other studies mentioned previously that showed that disrupting reconsolidation with extinction does not prevent the return of extinguished fear and that the occurrence of reconsolidation may be constrained by boundary conditions such as differences in experimental manipulations and instructions.

Relative to extinction is important to highlighted what was said before; that the degree of vulnerability of a reactivated memory changes with the time passed between initial learning and reactivation (Milekic & Alberini, 2002). One study performed in animals showed that memory reconsolidation also depends on the strength and age of the memory, such that younger and weaker memories are more easily reconsolidated than older and stronger memories. But, this same study also showed that reconsolidation and extinction are two opposing processes triggered by memory retrieval and so have distinct molecular mechanism (Suzuki et al., 2004). Being different processes made also important take into account that if a reminder (to reactivate a memory) is exposed during a long time could trigger extinction instead of reconsolidation. The duration of the reminders is also a boundary condition depending on its duration (Pedreira & Maldonado, 2003).

Reconsolidation impairment in humans with pharmacological manipulations

As said before, in animals reconsolidation is most usually studied using protein synthesis inhibitors (Alberini, 2005; Duvarci & Nader, 2004; Nader, Schafe & Le Doux, 2000) , which is not practical in humans. But instead, drugs that interact with the release of nor-adrenaline (i.e.: propranolol) in the amygdala could be a successful treatment for disturbing emotional memories (and also, is one of the few drugs that can be used in both, animals and humans).

The most frequently used pharmacological manipulation in human is the administration of the beta-blocker propranolol. Its mechanism of action is through beta- adrenergic receptors that are coupled with the adenylyl cyclase-linked G-protein receptors governing the cAMP cascade that produced protein synthesis-dependent long-term memory formation (Przybyslawski, Roullet, & Sara, 1999).

Kindt et al., (2009), demonstrated that a beta adrenergic receptor antagonist, administered prior to memory reactivation (administered 90 min before due to the pharmacological features of propranolol), erased the startle fear response, while the skin conductance response (SCR) and the unconditioned stimulus (US) expectancy ratings remained invariable. The skin conductance response seems to primarily reflect anticipatory arousal, independently of the valence of the stimulus, while the startle response is considered to be more reliable and specific of fear, and operated aside of the cognitive level of fear learning. In summary, they showed that propranolol prior reactivation of a fear memory is able to diminish the fear memory expression in humans, leaving the declarative memory intact. As said before, there are different neural correlates for the different kinds of memories. So, while declarative memory is based on the hippocampal complex (Squire et al., 2004) the emotional encoding and expression of a fear response requires the amygdala complex (LeDoux, 2000). But, as LaBar & Cabeza, (2006) pointed in their review, both structures interact with each other.

But, what makes a memory labile again? In order to examine this question and the elements needed to return a memory labile again in order to initiate a reconsolidation process, Sevenster, Beckers, & Kindt, (2012) followed the same design from Kindt et al. (2009), but, with the difference that they had one group that received the reactivation (day

2) without the shock electrodes attached. They did this arguing that there was no new information to be learned about the association, so the association between stimulus and shock had no reason to be updated. What they saw, was an increased in the startle response at reactivation, and that the subsequent administration of propranolol did not erased the fear response on day 3.

Following these results, they decided to manipulate the expectancies of the participants by varying the acquisition reinforcement rate between groups (Sevenster, Beckers & Kindt, 2013). So, two groups received complete reinforced differential conditioning and were, in addition, instructed of the contingency. The next day (day 2) the subjects were either shown a reinforced, or an unreinforced stimulus. A third group had acquisition partially reinforced and was shown a reinforced stimulus on day 2, but the complete reinforced group obviously was expecting the shock. Propranolol was administered to all groups on day 2. On day 3, the memory was tested with extinction and reinstatement. Thus, they made a prediction error when they were shown the stimulus without shock on day 2. On day 3, their memory strength was highly impaired by propranolol. The second complete reinforced group, which was shown a reinforced stimulus on day 2, and did not make a prediction error, did not seem to have their memory affected by the propranolol. When the partially reinforced group was shown a reinforced stimulus on day 2, their expectancies of shock increased, they made a prediction error. This group also had their memory decreased by the propranolol. So, according to this study, it seems that prediction error is crucial for reactivating a memory, and also, these findings give support to the idea that reconsolidation may be a process to updated memory.

Impairment of declarative memories

In humans, and in emotional memories, it is being proved that the β adrenergic receptor antagonist propranolol impairs consolidation of declarative memory in humans (see Cahill & McGaugh, 1998) .

Brunet et al., (2008) tested the effect of the β-adrenergic blocker propranolol given within hours after the retrieval of memories of a traumatic event. They based their study on the evidence that indicates that propranolol given after a psychologically traumatic event reduces physiologic responses during subsequent mental imagery of the event.

Their subjects were patients with chronic post-traumatic stress disorder. They made them described their traumatic event during a script preparation session and then received a one-day dose of propranolol or placebo, randomized and double-blind. Seven days later, they made the patients engaged in script-driven mental imagery of their traumatic event while heart rate, skin conductance, and left corrugator electromyogram were measured. Once they took those measures, they found that the physiologic responses were significantly smaller in the subjects who had received post-reactivation propranolol a week earlier. They showed that the physiological responses were decreased in a similar manner after reactivation than after the occurrence of the traumatic event.

Tollenaar, Elzinga, Spinhoven, & Everaerd, (2009) decided to study the effects of propranolol and cortisol on healthy individuals, and how they respond physiologically to emotional (autobiographical) memories. They found no effect on the propranolol group on disrupting reconsolidation in conjunction with a retrieval session. In another study with healthy young men individuals, they found also no effect when the memory of word lists were tested (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009a).

In explanation of these negative outcomes of the memory of emotional scripts the authors suggested that maybe the scripts were no emotionally strong enough to express an effect of propranolol or, maybe the dose was too low (the dose that the authors used in both studies were 80 mg, while in the majority of studies the dose of propranolol is 40 mg), or perhaps was not acting long enough in the body (the times that the authors used in their methods are according with the pharmacokinetics of propranolol; they waited on session 2 , the rigorous 90 minutes, necessary for the amount of propranolol in blood to be at its peak, before doing the script imagery task).

Trying to elucidated how is the brain mechanism underlying emotional memory reconsolidation and the effect of propranolol, Schwabe, Nader, Wolf, Beaudry, & Pruessner, (2012) designed a study with healthy individuals and fMRI. They administered beta adrenergic antagonist receptor propranolol or placebo before the reactivation of a previously learned material (emotional and neutral). During the reactivation time, subjects were at the scan, and so they did too during the memory test. As established in the protocol, on day 3 the memory was tested. They found that for the emotional pictures, propranolol during reactivation diminish subsequent memory, effect that did not appear with the neutral

pictures. The emotional impairment was associated to an increased activity in the amygdala and hippocampus for the remembered pictures at test. Also, the same neural structures were activated during memory reactivation (but not modulated by propranolol). As known before, memory reactivation alone or propranolol without reactivation had no effect on subsequent memory. In other words, their results suggested that the same brain areas that are activated during reactivation undergo changes in activity that is related to subsequent memory recall.

Kroes, Strange, & Dolan, (2010) performed a study using emotionally aversive verbal stimuli (participants were exposed to 360 nouns: 300 neutral, 30 perceptual oddballs and 30 emotionally aversive), a 3-day protocol and administration of propranolol or placebo. On day 2, after the administration of the propranolol/placebo the participants had the memory reactivation, that consisted on the presentation of the first three letters of the nouns encoded on day 1 (240 of the 360 nouns encoded on day 1: 200 neutral, 20 perceptual oddballs, and 20 emotionally negative) and participants had to complete the words. The propranolol group completed fewer emotional nouns on both day 2 and 3. The effect on day 3 cannot be described as reconsolidation effect, because retrieval did not happen on day 2.

All the studies described above, attempt to reactivate a memory in order to destabilize it. But as seen, not all memory types appear to be susceptible and equally affected by reactivation and noradrenergic antagonist administration. In animals studies a single element of the original memory was enough to trigger reactivation, but in humans the matter is considerable different. Dieuwke Sevenster, Beckers, & Kindt, (2013) considered that a prediction error is need it to destabilize a memory, but this prediction error is not always present, as happen for example when reactivating declarative memories. In this order, more knowledge is needed to assort the boundaries conditions of labilization. Despite the evidence that reconsolidation takes place in humans, there is controversy on what instances the labilization and reconsolidation process are triggered. What exactly is needed it to reactivated complex memories, as the ones integrating the PTSD? Is prediction error truly needed it? How long are the effects of reconsolidation and manipulation lasting? Are remote memories equally able to undergo reconsolidation after reactivation? Memories that depend on specific brain regions have the same susceptibility to reactivation? Is the same protocol and susceptibility for all kind of memories?

The other fundamental problem with the pharmacological manipulation of reconsolidation with propranolol is that it must be administered prior to reactivation (60- 90 minutes prior in order to reach its clinical peak), with violates the second criteria of reconsolidation (manipulation must be done after reactivation). If it's given after reactivation the time window that allows these manipulations to take place is close. So, taking into account these boundary conditions in the use of propranolol in humans, is necessary another safe pharmacological manipulation in order to disrupt emotional memories.

Chapter 2

The major neurotransmitters´ systems in the brain

2.1. Psychopharmacology of Human Memory

The first studies analyzing the effects of psychological drugs on memory was driven by Jones, (1909); he "reports introspections obtained on three occasions when chloroform was administered to the author". He identified two stages, first one, loss of sensitivity of the "sense organs"; and the second one, "disappearance of memory, imagery, associational processes, reason and isolated ideas". Another study carried out by Cattell, (1930), showed that 10 g of alcohol enhanced intelligence but impaired associative memory. Few years later, Jones (1933) decided to analyze the effect of the antipyretics on learning due to the huge amount of people taking that drug at that moment, without considering adverse effects. Before Jones, (1933), the relationship between antipyretics and cognitive functions had already been analyzed by Münsterberg, (1892), and later by Macht, Isaacs, & Greenberg, (1918). Both authors found an increase in reaction times, with both, therapeutic doses or with exceedingly large doses of quinine (antipyrin).

During the following years, the effects of the drugs on memory were studied according to the zeitgeist of each moment. Thus, the studies described below analyze the effects of psycho active drugs from a cognitive neuroscientific perspective, focusing on the major neurotransmitters systems of the human brain and their effects enhancing or impairing memory. The current overview of neurotransmitter effects will focus on neurotransmitter effects on fear conditioning and reconsolidation of emotional episodic memories in animal in humans, and in animals when necessary.

The importance to learn that certain environmental stimuli can predict aversive events (Pavlovian fear conditioning) has an evolutionary role for survival, and equips the organism with a flexible association system to deal with changes contingencies between predictor and aversive events (Fanselow, 1994). But above all, disturbances in fear conditioning may play a key-role in disorders related to fear and anxiety in humans, such as panic disorder and specific phobias or post-traumatic stress disorder (Rosen & Schulkin, 1998; Wolpe, 1981).

2.2. GABA

It is well known that γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the vertebrate central nervous system (Brioni, Nagahara, & McGaugh, 1989) and

modulates fear conditioning. It is synthesized primarily from glutamate by glutamate decarboxylase (GAD).

Initially, GABA was found to activate bicuculline-sensitive Cl^- channels, but then, the presence of a novel receptor, insensitive to antagonist such as bicuculline or the majority of the accepted GABA agonist (3-aminopropanesulphonic acid (3-APS) or isoguvacine) led to the actual denomination of the GABA receptors ($GABA_A$, $GABA_B$ and $GABA_C$ receptors) (Bowery et al., 1980). The $GABA_A$ receptor ($GABA_AR$) directly gates a Cl^- ionophore and has modulatory binding sites for benzodiazepines, barbiturates, neurosteroids and ethanol, it is considered an ionotropic receptor (Bormann, 1988). The $GABA_B$ receptor couples to Ca^{2+} and K^+ channels through G proteins and second messengers; baclofen is an agonist, and these receptors are insensitive to the drugs that modulate $GABA_AR$ (Bormann, 1988; Bowery, 1989). Finally, a third ionotropic receptor was discovered due to the cis-4-amino-crotonic acid (CACA), and was designated as $GABA_C$ (Johnston, 1996).

2.2.1. $GABA_A$ receptors

$GABA_A$ receptors are the most abundant of the GABA receptors in the brain. The $GABA_A$ receptors are ion channels that increase membrane permeability for chloride and bicarbonate ions when activated by GABA and the selective agonist muscimol. They can be blocked by bicuculline and picrotoxin, and modulated by benzodiazepines, barbiturates, and other central nervous system depressants that will not be discussed here (see Sieghart, 1995).

In brief, $GABA_A$ receptor activation results in the net entry of anions that trigger processes that make a postsynaptic neuron less likely to generate an action potential, a mechanism known as inhibitory postsynaptic potential (IPSP) (Purves et al., 2008). The enhancement in conductance (that causes shunting of excitatory inputs) and the hyperpolarization (that sums with depolarizations) turns out to be the 'inhibitory' effect of GABA, thereby reducing the probability that an action potential will be initiated (Purves et al., 2008).

$GABA_A$ receptors are pentameric (five protein subunits) assemblies of subunits that form a central ion channel (see Figure 2.1.).

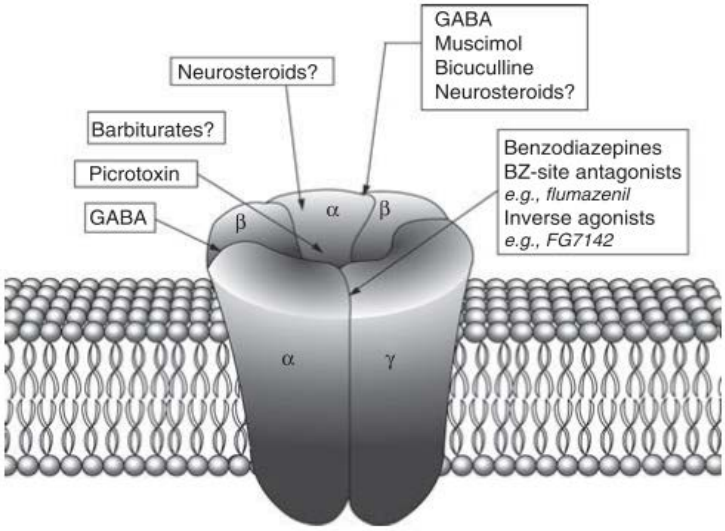

Figure. 2.1. Hypothetical schematic model of the GABAA receptor. Most functional $GABA_A$ receptors are made up of two αsubunits, two β-subunits, and one γ-subunit or alternatively two α-subunits, one β-subunit, and two γ-subunits, which together comprise the central ion channel. Reproduced from (Makkar, Zhang, & Cranney, 2010).

2.2.2. $GABA_A$ receptors and fear conditioning

$GABA_A$ receptors have been related to fear learning, and it has been showed that inhibition of $GABA_A$ receptors facilitates learning; while administration of GABA agonists (*i.e.* benzodiazepines) impair learning (Dickinson-Anson & McGaugh, 1997) (see Table 2.1) by decreasing the expression of the conditioned response (CR) (Dickinson-Anson & McGaugh, 1997). Izquierdo et al., (1990) were able to show that the amnesic effects of administration of GABA agonist at the time of encoding can be reversed after the administration of flumazenil (BZD), which indicates that the effects of BZs are mediated by the specific BZs binding-site in the $GABA_A$ receptors.

GABA receptors and fear learning			
Time of administration	**Action on neurotransmitter**	**Effect on learning**	**Authors**
Pre-training	Agonist	Impairs learning	Dickinson-Anson & McGaugh, 1997; Gafford, Parsons, & Helmstetter, 2005; Izquierdo et al., 1990.
Post-training	Antagonist	Enhances learning	Brioni & McGaugh, 1988; Brioni et al., 1989; Wilensky, A. E., Schafe, G. E., & LeDoux, 2000

Table 2.1. GABA receptors and fear learning.

Regarding to brain areas important for emotional memory; the basolateral amygdala (BLA) (see review LaBar & Cabeza, 2006), mediates the disruptive effects of GABA on the acquisition and consolidation of emotional (fear) memories (Da Cunha, Roozendaal, Vazdarjanova, & McGaugh, 1999) and the hippocampus is important in fear learning, when the CS is a context (Bast, Zhang, & Feldon, 2001; Paul W Frankland & Bontempi, 2006; Kim & Fanselow, 1992). GABA receptors are important for hippocampal-dependent learning (Zarrindast, Bakhsha, Rostami, & Shafaghi, 2002). For example, post-training infusion of midazolam (a GABA agonist) into the hippocampus impairs the retention of contextual fear memory (Gafford, Parsons, & Helmstetter, 2005).

The facilitation of fear learning due to administration of a GABA antagonist is also driven by the increased release of nor-adrenaline (NA) (discussed later) and the associated activation of the β–adrenergic receptors in the BLA. More specifically, there is an interaction between the GABAergic and β-noradrenergic systems in the regulation of memory storage (Introini-Collison, Castellano, & McGaugh, 1994). In order to support this hypothesis, Introini-Collison et al., (1994) demonstrated that the retention-impairing effects of muscimol (a mushroom that actuates as an agonist of the GABAergic system) were reversed by simultaneous administration of NA. The retention-enhancing effects of bicuculline (a GABA antagonist) were blocked by simultaneous administration of the β-

noradrenergic antagonist clenbuterol (decreases NA activation of β-receptors) (Hatfield, Spanis, & McGaugh, 1999). The better understanding of this memory modulation driven by the amygdala and hippocampus (Hatfield et al., 1999; Roozendaal et al., 1999) could help to elucidate the role of anesthesia on the disruption of reconsolidation of emotional episodic memories.

Relative to other times of administration, post-training administration of the GABA agonist muscimol (a type of mushroom) disrupts memory whether given systemically or locally into the amygdala or hippocampus (Ammassari-Teule, Pavone, & Castellano, 1991; Introini-Collison et al., 1994; Tano, Molina, Maldonado, & Pedreira, 2009). While, post-training administration of GABAergic antagonists appears to facilitate memory consolidation (Dickinson-Anson & McGaugh, 1993).

In extinction, administration of $GABA_AR$ agonist would interrupt the formation of the new competing memory, and would leave the original memory intact at the moment of recall (Akirav, 2007; Bustos, Maldonado, & Molina, 2009). Reduced GABA transmission facilitates the storage of the new competing (extinction) memories by enhancing the release of NA and activation of β-receptors (Berlau & McGaugh, 2006). But, if it was co-administrated simultaneously with propranolol (β –blocker), the effect was blocked.

2.2.3. Post-consolidation modulation of memory

GABA transmission is related to anxiety disorders in humans. This may have implications for the treatment of those disorders, particularly the ones associated with maladaptive and intrusive fear memories such as post-traumatic stress disorder (PTSD) or social phobia (Ehlers & Clark, 2000; Hackmann, Clark, & McManus, 2000). GABA agonist (*i.e.:* benzodiazepines), mainly midazolam or diazepam (widely used for the treatment of anxiety symptoms) (Shader & Greenblatt, 1993) , could be administered to the patients immediately after a brief re-exposure to the fear-related stimuli in order to block the reconsolidation of fear memories (Makkar et al., 2010). But, in order to achieve reconsolidation, it is necessary to ensure that the reactivation is brief, and that reduction in anxiety (*i.e.*, within-session extinction) does not occur throughout the re-exposure session (Makkar et al., 2010); otherwise the BZ will disrupt the extinction memory (not the reconsolidation due to the length of the cue exposure), leading to maintenance of fear and anxiety. Also, as mentioned before (see Chapter 1, section 1.5.), there are other conditions that affect the final results of

reconsolidation, such as the age of the fear memory (more age, more time of cue exposure would be need it, risking to not trigger reconsolidation but extinction) (Suzuki et al., 2004) and the drug dosage (that correlates with the age, more age, more drug dosage is need to alter a memory) (Bustos et al., 2009).

Bustos, Maldonado, & Molina, (2006) examined the role of midazolam (MDZ) (GABA agonist) on memory reconsolidation using a contextual fear paradigm and the classical 3-day protocol in rats. MDZ was administered immediately after reactivation, and 24 hours later led to reduced responding (Experiment 1) relative to controls. This impaired responding still evident 10 days later (Experiment 2). Zhang & Cranney, (2008) showed a reconsolidation impairment induced by systemic administration of midazolam right after reactivation. Also, Makkar et al. (2010) showed that administration of MDZ after reactivation produced an impairment of discrete cue auditory fear memory.

As seen above, there are few examples of the use of GABAergic drugs and reconsolidation, and mainly all of them are experimented in animals (Bustos et al., 2006, 2009; Makkar et al., 2010; Zhang & Cranney, 2008). In relation to the study in humans, to my knowledge there is only one study, carried out by Rodríguez et al., (2013) in which it was demonstrated the increase of memory after the reactivation and the administration of a small dose of clonazepam (GABA agonist). The manipulation of reconsolidation through the increase in the GABAergic transmission by propofol administration in humans (described in Chapter 3) would be one of the first attempts to disrupt emotional episodic memories driven by the modulatory interaction effect between the GABA system and the nor-adrenergic system in the brain.

2.2.4. Propofol (“milk of amnesia”)

Many of the therapeutic actions of anesthetics depend on the $GABA_A$ receptors (Barnard et al., 1998). The $GABA_A$ receptors are modulated by general anesthetics of diverse chemical structures including pentobarbital, etomidate, and propofol (Barnard et al., 1998).

One of the novel investigations that conforms this thesis is based on the role of the anesthetic propofol on reconsolidation of emotional episodic memories, so, due to that, there is going to be a major focus on the role of propofol and its interaction with $GABA_A$ receptors.

Propofol (2,6-diisopropylphenol) (to be described in Chapter 3) is an intravenous general anesthetic and hypnotic that is structurally unrelated to other anesthetics. Propofol it is widely used in general anesthesia (GA) due to its clinical benefits: rapid onset, clear emergence, and lack of cumulative effects. Propofol not only potentiates GABA-mediated inhibitory synaptic transmission, but is a direct agonist of $GABA_A$ receptors (Chen, Yang, & Chiu, 1999). The mechanism of action it is not well determined, but it seems that propofol increases the Cl- conductance and enhance the opening probability of GABA-activated channels (Hales & Lambert, 1992). Anterograde amnesia is one of the most important effects of anesthetics. For example, Cheng, (2006) showed that the dose of etomidate that causes amnesia is considerably lower than the dose that causes immobility. Before I highlighted the role of the BLA on emotional memories (see Chapter 1, section 1.4.). The memory modulation effects of the amygdala occur partly through GABAergic mechanisms, for example, systemic administration of diazepam (GABA agonist) fails to cause amnesia if the BLA is lesioned (Tomaz, Dickinson-Anson, & McGaugh, 1992) (similar studies see Alkire, Vazdarjanova, Dickinson-Anson, White, & Cahill, 2001).

The possibility to generalize those findings, or others like the one above to humans have been supported by studies with patients with amygdala damage (Adolphs et al., 1997; Cahill et al., 1995) and healthy subjects with human brain imaging (Cahill et al., 1996; Hamann et al., 1999), that have consistently confirmed the “memory modulation” view of the amygdala derived from the animal studies (McGaugh, 2000).

In order to see the amnesic effects of anesthetic gas such as sevoflurane could block human emotional memory, Alkire et al., (2008) designed a study using their previous findings about the involvement of the BLA in mediating the amnesia caused by the inhalational anesthetic agent sevoflurane through the activation of GABA receptors in an aversive training in rats (Alkire & Nathan, 2005). They showed that sevoflurane blocks the mnemonic boost associated with emotional arousal. Specifically this study reported that structural equation modeling of PET glucose data shows that 0.25% sevoflurane suppresses amygdala to hippocampal effective connectivity. The findings support the hypothesis that the amygdala and GABA receptors are involved in memory modulation by demonstrating that suppressed amygdala effectiveness produces a loss of emotional memory.

2.3. Glutamate

Even though glutamate has been known to have an excitatory action on the mammalian brain since the 50´s (Curtis & Watkins, 1960; Hayashi, 1952), it was not until the 1970s that it did not attain recognition as the major excitatory neurotransmitter of the nervous system (Meldrum, 2000). Since then, glutamate has being on the center of the attention of several researchers due to its role in different processes, such as: neural development, neurotoxicity, synaptic transmission and plasticity (Riedel, Platt, & Micheau, 2003) Almost as the same time (late 70´s), the three postsynaptic ionotropic receptors of glutamate were named based on their preferred agonist: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate (Meldrum, 2000). Given that there are barely few drugs capable of differentiated between AMPA and kainate, they are usually named together as "non-NMDA" receptors (Wong, Mayer, Jane, & Watkins, 1994). NMDA receptor has attracted much attention due to its classical implication in memory (Curran & Weingartner, 2002). NMDA receptor, as the other two, incorporates ion channels, permeable to Na^{+} and Ca^{++}. In the 80´s more types of glutamatergic receptors of another family were proposed, the metabotropic receptors. The metabotropic receptors are couple to a G protein that can act in two ways; first releasing second messengers in the cytoplasm or second, influencing membrane ion channels by the release of G protein subunits (Schoepp & Conn, 1993).

2.3.1. NMDA receptors

Much of the research on NMDA receptors have been done in animals, implicating these receptors in memory. But the research on ketamine in humans has increased due to its strong amnestic effects, because of the possibility to be a putative model of schizophrenia and because of its abuse has expanded (Morgan & Curran, 2006).

In humans, NMDA receptors are mainly localized in the cerebral cortex and hippocampus. In a study (Krystal et al., 1994) with healthy participants using subanesthetics doses of ketamine, which is a non-competitive NMDA antagonist, the authors found, consistently with other studies, that ketamine dose dependently produced psychosis (paranoia, loose associations, tangentiality, ideas of reference and unusual thought content) in the volunteers, and higher doses produced perceptual alterations (relative to the body, time and the environment) and a sense of memory impairment.

Relative to encoding, researchers suggested an impairment of memory for information learnt during the period under the effects of the drug, without impairment of the information learned before the drug administration (intact retrieval). For impairment in recognition memory tasks see Honey et al. (2005) and Hetem et al. (2000); for recall tasks see Morgan et al. (2004); for other memory domains see Table 2.2.

Ketamine (non-competitive NMDA antagonist)	
Memory enhacement	
Memory domain	**Authors**
Verbal	Krystal et al., 1999; Newcomer et al., 1999
Working memory (WM)	Newcomer et al., 1999
Memory impairment	
Memory domain	**Authors**
Episodic	Hetem et al, 2000; Morgan, Mofeez, Brandner, Bromley, & Curran, 2004.
Verbal	Harborne et al, 1996; Krystal et al, 1994; Malhotra et al, 1996.
WM	Adler et al, 1998
Procedural	Morgan, Mofeez, Brandner, Bromley, & Curran, 2004.

Table 2.2. Ketamine and memory effects. Different memory domain affected.

Using functional magnetic resonance imaging with healthy volunteers, Honey et al., (2005) were able to characterize the effects of ketamine on frontal and hippocampal responses to memory encoding and retrieval. A reduce activation in hippocampal and left PFC was observed when information encoded prior to ketamine infusion was retrieved.

To summarize, ketamine has been shown to produce impairments in encoding episodic memory (C. J. A. Morgan & Curran, 2006).

Memantine is a moderate affinity uncompetitive NMDA receptor channel blocker (Kornhuber, Bormann, Retz, Hübers, & Riederer, 1989), that is licensed for severe Alzheimer´s disease.

It has been shown that low doses of the NMDA receptor antagonist memantine enhance learning in animals with inherently poor levels of performance (Mondadori, Weiskrantz, Buerki, Petschke, & Fagg, 1989).

2.3.2. Other glutamate receptors

AMPA receptors (non-NMDA receptors) mediate the fast, immediate postsynaptic response to glutamate release. These receptors were found throughout the brain, with "high expression levels in cerebral cortex, basal ganglia, thalamus and hypothalamus, hippocampus, cerebellum and spinal cord" (Riedel et al., 2003, p.19).

The main problem with AMPA and its analogues is that when injected into the brain, they are neurotoxic, even at very low doses. This effect has prevented their use in behavioural pharmacology.

The metabotropic receptors (mGluRs) appear important for synaptic plasticity but drugs targeting these receptors are currently unavailable for human use.

2.3.4. Post-consolidation modulation of memory

As happens with the GABAergic drugs, the use of glutamatergic drugs in studies targeting reconsolidation in humans is inexistent. In animals is different. Wouda et al., (2010) examine whether alcohol-related memories are susceptible to disruption by the β-adrenergic receptor antagonist propranolol and the NMDA receptor antagonist MK801 following their reactivation. Both propranolol and MK801 administration upon reactivation did not reduce alcohol seeking after the first reactivation test. The authors tried repeated three times the post-reactivation treatments, and found that propranolol diminishes the alcohol seeking conductance. They also found a transient effect of post-reactivation MK801 treatment; alcohol seeking was reduced the following day, but not 7 days after treatment. The effects over time of post-reactivation manipulation of the NMDA receptor are less pronounced than the effects of blockade of β-adrenoceptors. These results and the ones achieved by other investigators such as (Lee & Everitt, 2008; Milton, Lee, Butler, Gardner,

& Everitt, 2008) demonstrated that NMDA receptor plays a (time-limited) role in reconsolidation of memories (Wouda et al., 2010).

2.4. Acetylcholine

In 1914 Dale observed two types of response to acetylcholine, which led to the discovery of the nicotinic and muscarinic receptors (Dale, 1914).

2.4.1 Nicotinic receptors

The nicotinic receptors are ligand gated ion channels (Karlin & Akabas, 1995). There are several subtypes of nicotinic receptors, with different pharmacological properties, and with different distribution through the brain.

In studies with animals, nicotine has been found to improve learning and memory on a variety of tasks. Relative to memory, there are several studies that suggest memory enhancing properties (antagonists of the nicotinic receptors such as mecamylamine impair memory function) (Hasselmo, 2006). The behavioral evidence for this nicotinic enhancement of memory function might come from enhancement of afferent input to cortical structures where memories are encoded (Hasselmo, 2006). In humans, there have being some preliminary studies that have found that some aspects of the cognitive deficit in Alzheimer's disease can be attenuated by nicotine.

2.4.2. Muscarinic receptors

The muscarinic receptors are found in the periphery (muscles) and in the central nervous system of the mammalians, especially in the cortex and hippocampus, where it has been shown that are involved in motor control, temperature regulation, cardiovascular regulation, and memory (Caulfield & Birdsall, 1998).

The muscarinic receptors are transmembrane spanning G-protein metabotropic receptors (M_1- M_5). Their agonists apart from ACh, are carbochol and pilocarpine, and antagonized by scopolamine and atropine.

Drachman et al., (1974) performed one of the first experimental studies in human subjects using scopolamine, methscopolamine bromide (a peripherally acting scopolamine analogue, that does not cross the blood-brain barrier), and physostigmine (a centrally acting anticholinesterase agent) to study the relationship of the cholinergic system of the brain to

memory and cognitive functions. Their results demonstrated that subjects that received scopolamine showed memory encoding impairment and retrieval. Neither methscopolamine nor physostigmine produced any changes in memory or other cognitive functions. (see Table 2.3.)

Scopolamine		
Memory phase	**Effect on memory**	**Authors**
Encoding	Impairment	Drachman et al., (1974); Aigner & Mishkin, 1986; Tang, Mishkin, & Aigner, 1997
Recall	Impairment	Drachman et al., (1974); Crow & Grove-White, 1973; Frith, Richardson, Samuel, Crow, & McKenna, 1984; Ghoneim & Mewaldt, 1975, 1977

Table 2.3. Scopolamine effects on memory phases. Scopolamine is a cholinergic muscarinic antagonist.

The cholinergic muscarinic antagonist scopolamine has been the drug most widely used to induce amnesia in experimental subjects, with a loss of cognitive abilities similar to that observed in old untreated subjects (Blokland, 1996).

2.4.3. The cholinergic Hypothesis of Alzheimer´s disease

Alzheimer's disease (AD) is a progressive neurodegenerative condition. The conclusive diagnostic markers that can be observed in postmortem brains with AD are: intracellular neurofibrillary tangles (paired helical filaments containing the microtubule associated hyperphosphorylated protein tau) and extracellular neuritic senile plaques (with amyloid peptide fibrils in the core, derived from amyloid precursor protein; APP), with seems to drive the primary degenerative effects of the AD (Delacourte & Defossez, 1986). Apart from these pathological markers, in the AD´s brain can be observed also cellular atrophy and cell loss (mainly pyramidal cells), which derivate into a neurochemical abnormal

functioning, with the more severe reduction of activity in the cholinergic system that innervates the cortex and hippocampus (Coyle, Price, & Delong, 1983).

The importance of the cholinergic function in aging and dementia was deduced from the fact that the administration of antagonist (scopolamine) or lesions of the cholinergic nuclei were related to cognitive deficits, similar as those observed in aging and AD (Bartus, 1978). Other findings such as, the reduce choline uptake (Rylett, Ball, & Colhoun, 1983), the impairment in ACh release (Nilsson, Nordberg, Hardy, & Wester, 1986) and the loss of cholinergic cells in the basal forebrain, specifically in the nucleus basalis of Meynert (Whitehouse, Price, Struble, & Clark, 1982); all together led to the development of the cholinergic theory of the Alzheimer´s disease, which attributed the degeneration of the cholinergic pathways from the nucleus basalis of Meynert to the cortex and hippocampus with the cognitive deterioration associated with the AD (Bartus, Dean, Beer, & Lippa, 1982). In addition, clinical studies have reported a positive correlation between the extent of the cholinergic depletion with the number of diffuse plaques in the non-demented elderly (Beach, Honer, & Hughes, 1997).

Since 1997, the acetyl-cholinesterase inhibitors (AChEI) (donepezil, galantamine and rivastigmine) have been the first line pharmacotherapy to treat mild to moderate AD. These drugs produce the inhibition of the breakdown of the ACh by blocking the enzyme acetylcholinesterase (Birks, 2006).

2.5. Dopamine

Dopamine (DA) is the predominant catecholamine neurotransmitter in the mammalian brain. DA has a variety of functions including locomotor activity, cognition, emotion, positive reinforcement, food intake, and endocrine regulation. DA also plays multiple roles in the periphery as a modulator of cardiovascular function, catecholamine release, hormone secretion, vascular tone, renal function, and gastrointestinal motility (Missale, Nash, Robinson, Jaber & Caron, 1998) .

DA has been a subject of intensive research, due to its involvement in several pathological disorders such as Parkinson´s disease, Tourette´s syndrome and psychiatric disorders, like schizophrenia. For example, DA receptor agonist are the reference treatment for

hypokinesia of Parkinson´s disease, or DA antagonist have been proved to be effective blocking hallucinations and delusions in schizophrenic patients (Matthysse, 1973).

In the mammalian CNS, most dopaminergic neurons are found in the substantia nigra (SN), pars compacta, and the ventral tegmental area (VTA). The projections from the SN to the dorsal striatum named the nigro-striatal dopaminergic system; the efferent projections from the VTA to the prefrontal cortex (PFC) named the mesocortical pathway and the projections to the limbic structures mainly, ventral striatum and nucleus accumbens (NAcc) but also to the amygdala and the hippocampus formed the mesolimbic dopaminergic system (Schott & Düzel, 2008).

2.5.1. DA and memory

Although DA has been most studied in the context of reinforcement learning, mesolimbocortical DA has a critical role in episodic learning and memory. It has been observed learning and memory performance deficits in animals with dopaminergic lesions (Missale et al., 1998).

These mesolimbic pathway sends input to the hippocampus (mainly CA1 region and the subiculum), which express DA receptors of the D_1 type (D_1 and D_5) receptors. Long-term potentiation (LTP) at the CA1 region of the hippocampus is an accepted cellular model for hippocampus-dependent memory processes. While the critical step for induction LTP is the activation of NMDA glutamate receptors, dopaminergic receptors seem to have a modulatory role (Huang & Kandel, 1995). The amygdala is a major target of midbrain dopaminergic neurons and is implicated in learning and memory processes. Fried et al., (2001) demonstrated the limbic DA release during associative learning in humans. They did it while carrying out a study with invasive recordings in epileptic patients undergoing pre-surgical evaluation, in order to identify the epileptogenic focus for potential surgical resection.

The main criticism with the Fried et al., (2001) study was the low number of participants. Investigations in healthy humans are restricted to noninvasive approaches, mainly using the effect of pharmacological compounds and its effects. Knecht et al., (2004) gave 100mg of the dopamine precursor levodopa (L-dopa) or placebo to forty healthy individuals. They demonstrated that the precursor L-dopa enhanced significantly the speed, overall success, and long-term retention of newly learned lists of pseudo-words in a dose-dependent

manner. The same group also made a direct comparison between D-amphetamine, DA/noradrenaline reuptake inhibitor and L-dopa, comparing the learning enhancing effects of d-amphetamine with a more selective dopaminergic substance (L-dopa). They found that both pharmacological agents enhanced the associative verbal learning task compared to placebo (Breitenstein, Flöel, et al., 2006); but the administration of pergolide, a DA receptor agonist (D_1/D_2), produced an impairment in performance when compared to placebo (Breitenstein, Korsukewitz, et al., 2006). The explanation of these contradictory results might be due to the tonic DA receptor occupancy which leads to a dulled endogenous DA signal or to the inhibition of endogenous DA release by presynaptic auto inhibitory D_2 DA receptors (Breitenstein, Korsukewitz, et al., 2006). Unreliable results in humans.

2.6. Cortisol

Stress can be defined as a state "in which the individual perceives a real or anticipated challenge to homeostasis, which requires some sort of adaptive response" (Wolf, 2008, p.513). Our brain has the ability to respond to different types of stressors. For example, physical stressors (trauma, cold, injuries) engage the brainstem and hypothalamic regions (de Kloet, Joëls, & Holsboer, 2005), psychological stressors (social interaction, public speak, …), recruit brain regions related to emotion, such as the amygdala and the prefrontal cortex, learning and memory depend on the hippocampus (Newcomer, Craft, Hershey, Askins, & Bardgett, 1994) and decision making relays on the prefrontal cortex (de Kloet et al., 2005; Bruce S McEwen, 2007; McGaugh, 2004b).

The initial response to stress is in neurons in the spinal cord that signal to the adrenal medulla [this sympathetic activation represents the "fight or flight" response (Cannon, 1915)], which release adrenalin and noradrenaline, but these hormones cannot cross the blood barrier easily. The second step of stress leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis resulting in the increased release of hormones, such as corticotropin-releasing hormone (CRH) from the hypothalamus, into the portal circulation. These hormones act on the pituitary to secret adrenocorticotropic hormone (ACTH) that acts on the adrenal cortex to initiate the synthesis and releases of glucocorticoids (GCs), more specifically cortisol (or corticosterone in rodents).

Corticosteroid effects on the brain and cognition can change from adaptive into maladaptive when actions via both receptor types (mineralocorticoid and glucocorticoid) are dysfunctional for a prolonged time (van Stegeren, 2009). Mineralocorticoid receptor (MR) affinity is high enough to activate the receptor for periods of time close to 1 hour, between hormone secretory firings of 20-minutes duration. Glucocorticoid receptor (GR) has less affinity, so this receptor needs time to be activated in a progressive way while stress and circadian-induced increases corticosteroid secretory bursts (van Stegeren, 2009). Low corticosteroid levels are associated with the induction of LTP in the hippocampus, which leads to memory formation (Diamond, Bennett, Fleshner, & Rose, 1992; Martin et al., 2000). By contrast, high levels of corticosteroid, stress or exposure to a new environment have been related to impair LTP and to induce log-term depression (LTD) (Kim & Diamond, 2002; Pavlides, Ogawa, Kimura, & McEwen, 1996).

MRs are implicated in the appraisal process and the onset of the stress response. While, GRs that are only activated by large amounts of cortisol, determinates the stress reactions, mobilizes the energy resources needed for these actions, and facilitates recovery. Relative to memory, GR promotes memory storage in advance of future events (de Kloet et al., 2005).

2.6.1 Cortisol and memory

Classically, the impact of stress on memory has been considered as largely disruptive (Lupien et al., 1994; Newcomer et al., 1994). Exposing subjects directly to cortisol or to psychosocial manipulation like public speaking can be prejudicial to the functioning of the hippocampus resulting in memory deficits (Newcomer et al., 1994; Payne, Nadel, Allen, Thomas, & Jacobs, 2002). In spite of this general vision, other studies demonstrate that elevated levels of stress are able to enhance memory for emotionally arousing experiences (Cahill, Gorski, & Le, 2003; Cahill & McGaugh, 1998).

Emotional information is different than neutral information in terms of processing. As described before (see Chapter 1, see section 1.4.), this facilitation has a survival benefit for the individual, so can remember more easily the relevant information. But this facilitation also can turns from adaptive into maladaptive (psychiatric disorders). Different psychiatric disorders have at their core alterations in emotional memory or emotional learning. BLA and noradrenergic activation (see section 2.6.) is fundamental in this facilitation of

emotional memory to be remembered. It seems that GC-mediated enhanced memory consolidation depends on beta adrenergic activation of the BLA, lesions or administration of beta blockers impair the memory enhancing effects of GC (McGaugh & Roozendaal, 2002). Cortisol and nor-adrenaline interact together in the BLA for enhancing emotional memory (Cahill & McGaugh, 1998; McGaugh, 2000; Roozendaal, 2003). But, elevated levels of cortisol impair the functioning of the hippocampus and prefrontal cortex, key-role structures to memory for neutral materials (Kim & Diamond, 2002).

Buchanan & Lovallo, (2001) administrated cortisol (20 mg) or placebo before participants were exposed to pictures varying in emotional arousal. Memory for the pictures was tested one week later. They showed that elevated cortisol levels during memory encoding enhance the long-term recall performance of emotionally arousing pictures compare to neutral pictures.

Cahill, Gorski, & Le, (2003) administered cold pressor stress (CPS) or a control procedure to participants after they viewed slides of emotional or neutral content, and tested memory one week later. CPS, that elevated salivary cortisol levels, enhances memory for the emotional slides compared with the controls, without affecting memory for the neutral slides. These results are in line with the view that arousal interacts with post-learning stress hormone-related activity at encoding to modulate memory consolidation.

But, it could not be that easy. Other authors have reached the opposite conclusions. Rimmele, Domes, Mathiak, & Hautzinger, (2003) administered hydrocortisone (25mg) or placebo and then presented to the participants either an emotionally arousing or a neutral story. Memory for the story was tested one week later. In all memory tests, the emotionally aspects of the emotional story were remembered better by the subjects who viewed the emotional story; leading to the indication that arousal enhances memory. Also, cortisol enhanced memory for details of the neutral story version, but impaired memory for details of the emotionally arousing version. Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, (2003) also failed to find the interaction between cortisol and arousal in a memory study.

Maheu, Joober, Beaulieu, & Lupien, (2004) in a study with metyrapone (cortisol synthesis inhibitor) with neutral and emotional stories, found that metyrapone decreased long term memory for both types of stories.

Kuhlmann & Wolf, (2006) conducted another study and showed that cortisol enhanced consolidation of emotional stimuli while also impairing consolidation of neutral stimuli, without difference in immediate memory recall performance between the cortisol and the placebo groups. Their data also showed that the cortisol effect increases over time. Therefore, they suggested that memory consolidation of neutral and emotional stimuli are modulated by GR. But the "stress effect on encoding could not be mediated via cortisol since glucocorticoids are secreted with a delay of several minutes after stressor onset but rather via neurotransmitters such as dopamine or nor-adrenaline"(Schwabe & Wolf, 2010a, p.187).

2.6.2. Post – consolidation modulation of memory

Relative to the main topic of this thesis there are few studies analyzing the effect of cortisol on reconsolidation of fear memories or autobiographical memories. The possibility of being able to disrupt or facilitate the reconsolidation of emotional memory by stress exposure has important implications for the treatment of anxiety disorders such as post-traumatic stress disorder and of drug-of-abuse memories. As seen before, the effects of stress (impairment or enhancement) on memory depend on many factors, such as age, gender, features of the stressor (time of exposure, type, duration), the task and the stimuli assessed (see review McEwen, 2007). The role of the neural regions involved in emotional memory in consolidation and reconsolidation has been described already, being the BLA, hippocampus and the PFC the main ones. BLA is a key region that regulates the effects of stress and glucocorticoids on memory formation, consolidation, and reconsolidation. Schwabe & Wolf, (2010a) showed a memory impairing effect of learning under stress in humans. Taubenfeld, Riceberg, New, & Alberini, (2009) have shown that systemic post-reactivation administration of the GR antagonist RU38486 impaired the reconsolidation of inhibitory avoidance. The sum of these results and others such as the ones achieved by Nikzad, Vafaei, Rashidy-Pour, & Haghighi, (2011) indicate that hippocampal GRs are required for reconsolidation of fear-based memory.

Schwabe & Wolf, (2010b) made a study were participants recalled positive, negative and neutral episodes from their recent past and were afterwards exposed to a stressor (the cold pressor test) or to a non-arousing control condition. In this stressor, participants were asked to immerse their right hand up to and including the wrist for 3 min into ice water (0–2 °C). Stress after memory reactivation impaired the memory for the neutral episodes 1 week later, whereas the subsequent memory for the emotional episodes was not affected by stress after reactivation. Reactivation per se or stress without prior memory reactivation had no effect on memory performance. They suggested that these findings showed that the effect of stress on memory reconsolidation is opposite to the stress effect on memory consolidation supporting the view that consolidation and reconsolidation are distinct processes.

2.7. Nor-adrenaline and Adrenaline

Noradrenaline is formed in the body from the amino acid tyrosine, and adrenaline synthesized from nor-adrenaline (Kalat, 1992). Both compounds exert similar pharmacological actions, and are classified as sympathomimetic agents.

Nor-adrenaline, is released either as a hormone from the adrenal medulla into the blood or as a neurotransmitter in the brain (Tully & Bolshakov, 2010). At the level of the CNS, nor-adrenaline neurons can be found through the nervous system, but the majority of these neurons are in the LC (the primary source of nor-adrenaline in the brain) that has projections to the amygdala, hippocampus and neocortex (Vermetten & Bremner, 2002). NA was initially associated with memory processing by Kety, (1972), and has different roles in the CNS: charge of acquire sensory information, and also, modulates and increases the processing of emotional relevant and salient information via its action on sensory, attentional, motor and memory processes (van Stegeren, 2008).

NA activates two major categories of receptors, α (α_1 and α_2) and β (β_1, β_2 and β_3); with subtypes in each group. The mechanism of action of NA is through affecting the excitability by blocking a Ca2+ -dependent K+ current. NA can enhance or reduce excitatory responses to glutamate, depending on its concentration (Sara, 2009; Wikberg, 1982) (see Table 2.4.).

Descriptions for key NA pharmacologic agents				
Drug	**Pharmacological profile**	**Approximate $t_{max}/t_{1/2}$**	**Psychiatric dose range**	**Sample reference**
Clonidine	α_2 -adrenaline receptor agonist	3–5/6–24 h	0.1–1.8 mg	Jakala et al., 1999
Dexmedetomidine	α_2 -adrenaline receptor agonist	0,5h/ 2h	n/a	Aho et al., 1993; Dutta et al., 2000
Metropolol	Centrally active selective to the β_1 receptor antagonist	1-2/3–7 h	50-400 mg	Walker, 1991
Nadolol	Peripheral non selective β- adrenaline receptor antagonist (β-blocker)	4/14-24 h	40-320 mg	Morrison et al., 1998
Propranolol	Centrally active β-adrenaline receptor antagonist (β-blocker)	1–2/3–6 h	5–640 mg	Müller et al., 2005
Reboxetine	Selective noradrenaline reuptake inhibitor (SNRI)	2/13 h	1-4(8) mg	Harmer et al., 2003
Yohimbine	α_2 -adrenaline receptor (adrenoceptor) blocker	0,15/0,5 h	n/a	Swann et al., 2005

Table 2.4. Descriptions for key NA pharmacologic agents. Adapted and reproduced from Chamberlain, Müller, Blackwell, Robbins, & Sahakian, (2006).

Different studies indicate that the brain functioning of NA is via activation of β-adrenoceptors on the ascending vagus nerve that projects to the nucleus of the solitary tract (NTS) (McGaugh & Roozendaal, 2009; Williams & McGaugh, 1993). The NTS has direct and indirect projections to the locus coeruleus that produces that activation of the nor-adrenergic system (McGaugh & Roozendaal, 2002). The results of numerous experiments implicate the amygdala in acquisition and retention of memory for emotionally charged events (see reviews LeDoux, 2000; Maren & Quirk, 2004). Also, it has been showed the involvement of the basolateral amygdala in the regulation of consolidation of memories in other regions of the brain (McGaugh, 2004b; McGaugh et al., 1996). The contribution of the amygdala to modulating memory consolidation critically depends on activation of β-adrenoceptors in the BLA (Ferry & McGaugh, 1999; Power et al., 2002). The activation of

the NA of the BLA via emotional arousal produces posterior induction of cortisol that facilitates memory consolidation, but also interacts with other transmitters and neuromodulators in the amygdala or the hippocampus to facilitate long- term memory formation (for review see McGaugh & Roozendaal, 2009). For example, animals studies evidence the role of drugs that are capable of modulating emotional memory, such as GABAergic agonists and antagonists, by controlling the level of NE within the amygdala (Hatfield et al., 1999; Roozendaal & McGaugh, 1996).

In humans, the facilitating role of NA in consolidation of emotional memories charged with negative (or positive) valence has mostly been attributed to the activation of β -adrenergic receptors. To summarize the effects on consolidation, Cahill et al. (1994) administered propranolol ($\beta_1\beta_2$-antagonist) prior to neutral and emotional stimuli. The prior administration of propranolol is done in order to maximize β-adrenergic blockade at the time of the initial encoding. They showed reduced recognition and recall for the emotional component of the story in the arousal condition after 1 week. These findings have been replicated by several studies (Maheu et al., 2004; Reist, Duffy, Fujimoto, & Cahill, 2001; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998) (see Table 2.5.). So, the hypothesis that enhanced memory associated with emotional experiences involves activation of the β-adrenergic system is being extensively supported by the finding in human subjects that β-adrenergic receptor blockers like propranolol selectively impaired memory for emotional events. Also, it has been found that the effect involved the activation of central β-adrenergic receptors (but not peripheral) (van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998).

Effects of noradrenergic drugs on emotional memory in healthy volunteers				
Authors	**Drug and dose**	**N (females)[per drug condition]/ age (years)**	**Emotional memory task**	**Results and comments**
Cahill et al., 1994; van Stegeren & Cahill, 2003	Propranolol 40 mg/ PLC	36 (19) [8-11]/ 27,4 ± 4,6	Emotional slide story	EM ↓; small sample size
van Stegeren et al., 1998; Cahill & van Stegeren, 2003	Propranolol 40 mg/ Nadolol 40 mg/ PLC	75 (52) [10-15]/ 22,6 ± 0,8	Emotional slide story	EM ↓(after propranolol); EM ↔ (after nadolol)
O´Carroll et al., 1999a	Propranolol 40 mg/ Nadolol 40 mg/ PLC	36 (30) [12]/ 22,6 ± 0,8	Emotional slide story	EM ↔(after both, nadolol y propranolol)
O´Carroll et al., 1999b	Yohimbine 20 mg/ Metoprolol 50 mg / PLC	36 (18) [12]/ ~ 18-31	Emotional slide story	EM ↑ (after yohimbine); EM↓ (after metropolol)
Reist et al., 2001	Propranolol 40 mg / PLC	21 (0) [5-6]/ ~ 35-65 (+17 PTSD patients)	Emotional slide story	EM ↓, similar effects in control and patients; small sample sizes
Papps et al., 2002; O´Carroll and Papps 2003	Reboxetine 4mg - 8 mg/ PLC	36 (10) [12]/ ~ 18-25	Emotional slide story	EM ↓ (dose dependent); inverted U effect?
Southwick et al., 2002	Yohimbine (IV approx 32 mg)/ PLC	30 (9) [14-16]/ 32,4 ± 10,9	Emotional slide story	EM ↔, correlation with plasma MHPG levels; drug adminitration 5 minutes after slide presentation
van Stegeren et al., 2002	Propranolol 40 mg /PLC	60 (46) [15]/ ~ 18-22	Emotional slide story	EM ↔
Cahill & Alkire, 2003	Epinephrine 9,6/ 19,2 (iv)/ PLC	42 (20) [?]/ 21,9 ± 0,7	Emotionally valenced slides	EM ↑ (only primacy recall, slide 1-3); drug administration after slide presentation
Harmer et al., 2003	Reboxetine 4 mg/ PLC	24 (12) [12]/ 20-47	Emotionally valenced word list	EM ↑ (no negative bias)
Strange et al., 2003	Propranolol 40 mg/ PLC	24 (12) [12]/ 19-32	Emotionally valenced word list	EM ↓ after propranolol
Grillon et al., 2004	Propranolol 40 mg/ PLC	30 (?) [15]/ 29 ± 20,8	Cued feared conditioning	EM ↔, emotional arousal ↓
Harmer et al., 2004	Reboxetine (8mg) per day/ Citalopram 20 mg (per day)/ PLC/ 7 days	42 (21) [14]/ 25,0 ± 4,2	Emotionally valenced word list	EM ↑ after both drugs, increased memory for positive stimuli
Maheu et al., 2004, 2005	Propranolol 40/80 mg, metyrapone 2x 750 mg/ PLC	64 (0) [11-14]/ 19-36	Emotional slide story	EM ↓ after high dose of propranolol but not after low dose of metyrapone
Pryor et al., 2004	Dexmedetomidine thipental propofol / PLC	83 (32) [10 dex; variable]/ 18-50	Emotionally valenced slides	EM ↔ (dexmedetomidine) but small N for group
Strange & Dolan, 2004	Propranolol 40 mg /PLC/ fMRI	24 (12) [12]/ 20-39	Emotionally valenced word list	EM ↓ (after propranolol), reduced retrieval activation of amygdala/ hippocampus
van Stegeren et al., 2005	Propranolol 80 mg/ PLC/ cross over design/ fMRI	28/30 (15) [14/15]/18-28	Emotionally valenced slides	EM ↓, less amygdala activation

Table 2.5. Human studies on noradrenergic modulation of emotional memory. Abbreviations: PLC (placebo); EM (emotional memory); iv (intravenous); fMRI (functional magnetic resonance imaging). Adapted and reproduced from Chamberlain, Müller, Blackwell, Robbins, & Sahakian, (2006).

Another study, using similar stimulus material as the one used in Cahill et al. (1994) and the administration of 20 mg yohimbine (which stimulates central noradrenergic activity via

blockade of the α_2-adrenergic autoreceptor) or 50 mg of metoprolol (β_1-receptor blocker) found similar results. Yohimbine significantly elevated, and metoprolol reduced mean heart rate during the slide presentation relative to placebo, thus confirming the efficacy of the pharmacological manipulation. One week later, in a 'surprise' test, memory for the slides was tested. Yohimbine treated subjects recalled significantly more and metoprolol subjects fewer slides relative to placebo. Authors reached to the conclusion that the noradrenergic system results in the enhancement and blockade in a reduction of recall and recognition of emotional material in man (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999). Contradictory results were found in another study using yohimbine, but the dose was administered after slide presentation and not prior (Southwick et al., 2002). Other studies relative to clonidine and working memory: Jäkälä et al., (1999); Coull, Middleton, Robbins, & Sahakian, (1995).

Relative to the studies in humans is important to take gender into account. There are differences driven by gender due to the differential hemispheric amygdala specialization. For example it has been suggested that emotional arousal enhances memory for central story information in men and peripheral details in women (Cahill & van Stegeren, 2003).

Using neuroimaging, there is, for example, one study that used fMRI to investigate the effects of short-term treatment with reboxetine (a NA reuptake inhibitor that blocks the action of the NA transporter), on emotional facial processing in healthy volunteers. Reboxetine was associated with a reduced amygdala response to fearful faces and increased activation to happy *vs* neutral facial expressions in the right fusiform gyrus, compare to placebo treatment and in the absence of changes in mood. These results showed that reboxetine modulates the neural substrates of emotional processing, increasing emotional memory for positively valence stimuli, highlighting a possible mechanism by which drug treatment could compensate negative bias in depression and anxiety (Norbury, Mackay, Cowen, Goodwin, & Harmer, 2007).

More studies using fMRI have shown for example that successful encoding of emotionally aversive nouns activates the left amygdala, and this effect was abolished by administration of propranolol. Recognition of emotional noun words was found to engage the left hippocampus, but this effect was null when β -adrenergic blockade was used at the time of encoding (Strange & Dolan, 2004). In another study, volunteers undertook fMRI while

viewing affective pictures (van Stegeren et al., 2005). Viewing neutral pictures did not increase amygdala activation relative to baseline while emotional pictures did. After receiving 80 mg of propranolol the activation after emotional stimuli was reduced (van Stegeren et al., 2005). These neuroimaging findings are consistent with an important role for NA- mediated modulation of amygdala at the level of encoding, in particular, and during consolidation.

2.7.1. Post – consolidation modulation of memory

From a clinical perspective, the possible applicability of β-blockers for the treatment of PTSD comes from the data suggesting that the β-adrenergic system represents a putative target for the treatment of PTSD (Pitman et al., 2002); therapeutic target that is also supported by neuroimaging evidence (van Stegeren et al., 2005).

For example, Brunet et al., (2008) (see Chapter 1, section 1.5) made one of the first attempts in the evaluation of the effects of reconsolidation in the treatment of psychiatric disorders such us phobias, addictions or PTSD by using propranolol with reactivation of autobiographical trauma memories. After continuing the treatment with propranolol once a week during six weeks, patients in a one week and four-month follow-up did not meet the criteria for PTSD. Also there were no differences observed between physiological responding measured post-treatment (heart rate, skin conductance response and left corrugator electromyogram) and at follow-up (Brunet et al., 2011, 2014).

As a result of these positive results, the possibility of being able to weakening consolidated memories after reactivation by pharmacological agents, extended to another type of disorders in which the emotional memory was in the root of the disease. Soeter & Kindt, (2015) in a double-blind study administered a single dose of propranolol after the reactivation (exposure to a spider) with individuals that have acquired their spider fear outside of the laboratory context, or placebo. According to the authors, the disruption of reconsolidation by propranolol transformed an avoidance behavior into a more approaching behavior in participants with spider phobia, but without affecting the self-declared fear. These results remained during 3 months to 1 year follow-up. Unfortunately, attempts to modify addiction behaviors with propranolol did not have the same success (Lonergan, Saumier, Tremblay, Kieffer, & Brunet, 2016; Pachas, Gilman, Orr, Hoeppner, & Evins, 2015), or they achieved a transient success, as was reported for craving in cocaine-

dependent addicts that benefited from the reduced cue-elicit craving less than a week (Saladin et al., 2013).

Regarding other adrenoceptors, Pussinen & Sirviö, (1998) reported a role of the α1-adrenergic receptor in long-term potentiation induction in animal models. However, the role of the stimulation of this receptor with these memory phases (consolidation/reconsolidation) remains unclear. Few studies have corroborated the participation of α_1Rs in consolidation and reconsolidation of emotional memories (Bernardi, Ryabinin, Berger, & Lattal, 2009; Ferry & McGaugh, 1999). In the case of the α_2-adrenoceptor, Gazarini, Stern, Carobrez, & Bertoglio, (2013) showed that administration of α_2-adrenoceptor antagonist yohimbine was able to potentiate fear memory trace consolidation and reconsolidation in rats; and that the α_2-adrenoceptor agonist clonidine, as opposed to yohimbine, mitigates fear expression by weakening memory consolidation and reconsolidation.

Adding the studies presented in the previous chapter (Chapter 1, section 1.5), to those presented in this section, we can observe that the results of the different studies are confusing as to the feasibility of developing a treatment based on the weakening of episodic emotional memories through the use of different treatments, being the most analyzed, the use of propranolol.

Likewise, there are several conditions that favor the search for another manipulation for episodic memories. These unfavorable conditions are, for example, the fact that β-blockers diminish fear-related responses, leaving basically episodic memory intact, which would be of incredible therapeutic value in the treatment of certain psychiatric disorders such as PTSD or addictions (Kroes, Schiller, LeDoux, & Phelps, 2016). But the fact that episodic memory is left intact can lead to relapses in the underlying disorder. Another factor that argues against the use of propranolol in studies of interruption of reconsolidation of episodic memories is that previously described in section 1.5., Chapter 1. This factor refers to the fact that the use of β-blocker violates two of the basic criteria, which makes it difficult to use for reconsolidation (Kroes et al., 2016). The third factor that makes less acceptable the use of propranolol in this type of studies or future therapies is the fact that its effectiveness has been demonstrated only in studies with memories related to a short period of time, but not with more remote memories (Kroes et al., 2016). Therefore, the study

presented in Chapter 3 is based on the application of anesthetic agents and not on beta blockers in the disruption of emotional episodic memories in humans.

2.7.2. Nor-adrenaline and memory modulation by motor system

Much of the episodic memories we form in our daily life are encoded whilst we are physically interacting with the environment. The idea of voluntary movements being modulating memory processes is in line with recent experiments that increasingly suggest that simulations, situations, and bodily states play central roles in cognition (Rubin, 2006).

Our body is influenced by our mind, and our mind is influenced by our body. This idea has led to the development of a series of studies and experiments showing that different kinds of bodies think differently (Casasanto, 2009, 2011). The several evidence existent about the influence of the motor system on the mind can be integrated as the embodied cognition approach (for review see Rosenbaum, (2005). This approach argues that physical properties of the human body, mainly the perceptual and motor systems, influence cognition (Barsalou, 2008; Fischer & Zwaan, 2008). Cohen, (1981), asked participants to perform a list of actions, to watch someone else performing those actions or to just hear or read the instructions of the actions. In a subsequent test he saw that the ones that perform the actions or saw others doing it had better recall than the ones that simple read or heard the actions. Later those experimental conditions were referred as self- or subject-performed tasks (SPT), experimenter-performed tasks (EPT), and verbal tasks (VT), respectively. Other studies, such as the one driven by Denis, Engelkamp, & Mohr, (1991) observed similar results, better memory for SPT compared to actions that were being imagined. Later, Cohen and Engelkamp joined efforts and began a new field of research: “memory of action events” (see review Engelkamp & Cohen, 1991). “The enactment effect” was one of their first findings, and reflects two main ideas: A) when we perform an action, the underlying mental representation is more complex than verbal phrases, a finding that can be related with the levels of processing proposed by Craik & Lockhart, (1972); and B) enacted actions activates the motor system; while other kinds of encoding are unable to do it.

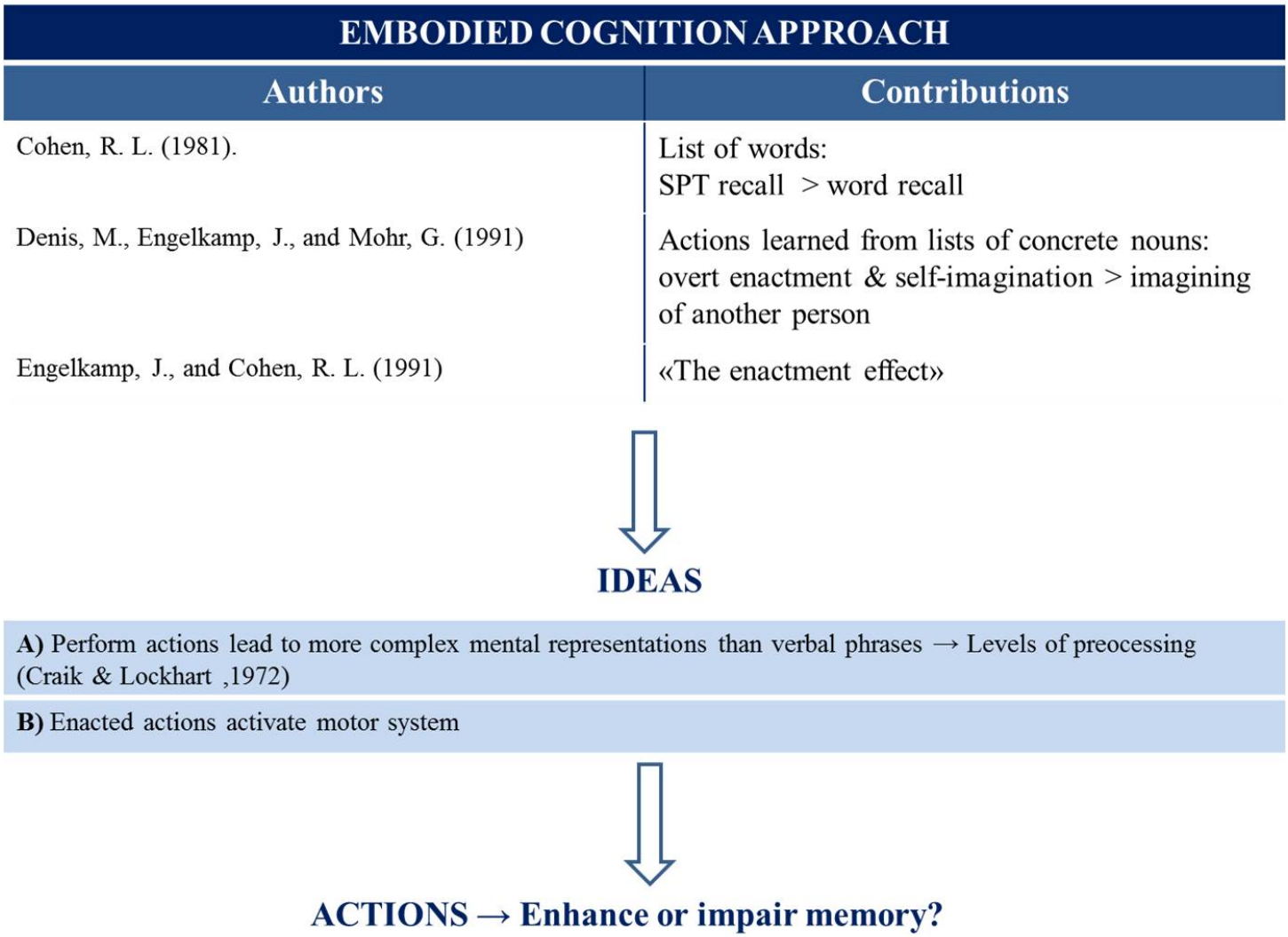

Figure 2.2. Embodied cognition approach. Schematic resume of the embodied cognition approach, authors and contributions.

Remembering a stimulus specifically produces greater activation in modal areas than remembering in generally (Garoff, Slotnick, & Schacter, 2005). Simulating a scene at encoding that extends the boundary of a studied picture produces reconstructive error later at retrieval (Intraub, Gottesman, & Bills, 1998). Pulvermüller, (2005) found that "when participants simply read the word for an action, the motor system becomes active to represent its meaning. More specifically, verbs for head, arm, and leg actions produce head, arm, and leg simulations in the respective areas of the motor system".

The MTL has been related to episodic memory (see Chapter 1, section 1.3). Central regions of the MTL, such as the hippocampus, have been linked to navigation and spatial memory (Maguire et al., 1998; O'keefe & Nadel, 1978). Several findings suggest that hippocampal theta oscillations are engaged during spatial navigation and are supposed to mediate spatial memory formation (Cornwell, Johnson, Holroyd, Carver, & Grillon, 2008). Human hippocampal intracranial recordings have shown increased activity during movement (Caplan et al., 2003; Ekstrom et al., 2005). A more directly link between motor system and hippocampus is been showed in a study using fMRI to measure human cerebral activity associated with motor cognitive processes during the performing of a delayed-associative task (Thoenissen, Zilles, & Toni, 2002). Other area that has been linked to episodic memory-modulation is the locus coeruleus (LC), which is the main source of NA in the brain (LaBar & Cabeza, 2006; Strange & Dolan, 2004; Strange et al., 2003; Tully & Bolshakov, 2010).

Besides the traditional view of the role of the LC activated by emotional arousal which produces NA release to the brain and the subsequent memory enhancement (for Review see Tully & Bolshakov, 2010), other studies have suggested that the LC is active while we take a commitment to act or in goal-directed events (Bouret & Richmond, 2009), regulating the behavioral outcome of decisional processes (Clayton, Rajkowski, Cohen, & Aston-Jones, 2004) Taken into account all these evidences and the contributions of other theoretical approaches, the main subjacent question is if actions enhance or impair memory, and through which neural correlates.

Chapter 3

The effect of sedation on reconsolidation of emotional episodic memory in humans

3.1. Introduction

Upon encoding, memories undergo a time-dependent process known as consolidation (see Chapter 1). Prior to consolidation, memories are sensitive to disruption by, for example, electroconvulsive therapy (ECT) (Duncan, 1949; Glickman, 1961) and protein-synthesis inhibition (Agranoff, Davis, & Brink, 1966; Flexner et al., 1965). Traditionally memories after consolidation have been thought to be relatively insensitive to disruption (McGaugh, 2000). For decades, this has been a central dogma in the neuroscience of memory. However, the concept of reconsolidation challenges this idea (Nader, Schafe, & LeDoux, 2000). Reconsolidation refers to the process of memories changing from a rather fixed to a labile state upon reactivation (*i.e.* what happens during memory retrieval). Therefore, reactivated memories are susceptible to manipulation, once again requiring a time-dependent re-stabilization process (Nader et al., 2000).

Recently, electroconvulsive therapy (ECT) was applied following memory reactivation in patients with therapy-resistant unipolar depression. Results showed a disruption for the reactivated, but not for the non-reactivated memories for an emotional episode (Kroes et al., 2014). Importantly, this effect was observed only for the group that had been tested after 24 h, not for the group tested immediately after ECT recovering.

These findings were important because the ECT study met critical criteria generated from non-human animal studies, thus providing compelling evidence for the reconsolidation phenomena in humans. These criteria consist of: (1) consolidated memories must be reactivated by a reminder cue; (2) the manipulation aimed at altering reconsolidation must be provided post-reactivation, rather than pre-reactivation; and (3) reconsolidation is a time-dependent process and memory should therefore be affected after a time window allowing reconsolidation to take place—usually after 24 h—rather than immediately (McGaugh, 2000; Nader et al., 2000; Williams et al., 2007). Thus, the time-dependence of reconsolidation impairment observed in this previous study, *i.e.* the effect is present at 24 h but not 90 min, is in line with animal studies of reconsolidation suggesting similar neural processes.

Although these results provided evidence for reconsolidation of emotional episodic memories in humans, there is a clear limitation in interpreting these data. ECT comprises the application of both short-acting general anesthesia (GA) and cranial electrical

stimulation to evoke generalized seizure activity. It was simply not possible to elucidate whether reconsolidation impairment was due to the ECT or the general anesthesia. If the GA is responsible, targeted memory disruption in psychiatric patients could be done without ECT, which is an invasive procedure, particularly given recent evidence that frontal ECT alters functional connectivity of the frontal lobes (Perrin et al., 2012).

3.2. Hypothesis

Based on the data available it's hypothesized that the GA impairs the reconsolidation of emotional episodic memories by acting on the GABAergic system.

3.3. Methods and materials

In this section, prior to explaining in detail the procedure followed to engage reconsolidation, the stimulus material for the encoding session, as well as the general anesthetics used at the time of the reactivation session to manipulate memory are going to be described. In order to assess the evaluation of the functioning cognition of the participants, a screening test was administered, the Digit Symbol Substitution Test (DSST), that is described as well in this methods and material section.

3.3.1. Participants

Participants were recruited from the Hospital Clínico San Carlos, Madrid. A total of 50 psychiatrically healthy volunteers (Table 3.1.) from the gastroenterology clinic, with an age range 30-45 years (both ages included), normal or corrected to normal vision and hearing participated in the study. All participants were free of neurological or psychiatric medication, only under stable pharmacological treatment related to gastric ailments (22 out of 50 participants). Participants were asked to join the study since they were undergoing brief general anesthesia (GA) for a routine endoscopy procedure (colonoscopy: 24, gastroscopy: 19 or both procedures: 7). The Ethical committee of the Hospital Clínico San Carlos approved the study and all participants were informed of the procedures to be carried out before they provided written informed consent. Participants were pseudo-randomly assigned to one of the two groups (A and B), matched for age (group A mean age: 38, 88; s.e.m. 0, 90) and group B mean age: 39, 08; s.e.m.: 0, 97), gender (15 men per

group) and educational level (years of education group A mean: 14, 44; s.e.m.: 0, 60 and group B mean: 14, 75; s.e.m.: 0, 53).

		Group A	Group B	Statistics(t, X)	P value
Gender[a]	Female	10	9	$X^2_{(1)}$ =0,32	p=0,86
	Male	15	15		
Age in years[b]	Mean	38,88	39,08	$t_{(47)}$=-0,15	p=0,88
	s.e.m.	0,90	0,97		
Years of schooling[b]	Mean	14,44	14,75	$t_{(47)}$=-0,38	p=0,70
	s.e.m.	0,60	0,53		
Endoscopy procedure[a]	Colonoscopy	13	10	$X^2_{(2)}$=2,97	p=0,23
	Gastroscopy	7	12		
	Both	5	2		
Endoscopy Diagnosis[a]	Not pathological	15	18	$X^2_{(5)}$=2,6	p=0,76
	Inflammatory	4	3		
	Allergy	1	1		
	Vascular	1	0		
	Ulcer	1	0		
	Polyps	3	2		
Propofol in mg/kg[b]	Mean	3,02	2,37	$t_{(47)}$=2,03	p=0,05*
	s.e.m.	0,25	0,19		
Other anesthetics[a]	Yes	13	13	$X^2_{(1)}$=0,023	p=0,88
	No	12	11		
Midazolam in mg[b]	Mean	2,05	1,37	$t_{(14)}$=1,65	p=0,12
	s.e.m.	0,35	0,20		
Alfentanyl in mg[b]	Mean	0,29	0,28	$t_{(12)}$=-0,08	p=0,94
	s.e.m.	0,11	0,10		

Table 3.1. Participant's demographics and clinical details. Twenty five patients per group completed the study. One patient was withdrawn from the study because he was considered an outlier in the performance of the DSST. Groups A and B did not differ in any demographical variable (age, gender, years of schooling or type of endoscopy procedure), or in terms of the amount of other anesthetic (midazolam or alfentanyl) administered. Although, there is a significant difference (* $p<0.05$) in the amount of propofol administered, there is no correlation between this amount (kg/mg) of propofol and the memory scores on both groups. [a] Chi squared, [b] unpaired t-test.

One week after learning two emotionally aversive slide-show story memories (see Figure 3.3) for one of the two stories was reactivated. Immediately following memory reactivation, patients in groups A and B were anaesthetized and had their routine endoscopy procedure. Memory was tested one day after reactivation and anesthesia in group A. In contrast, group B was tested ~27-105 min after reactivation and anesthesia.

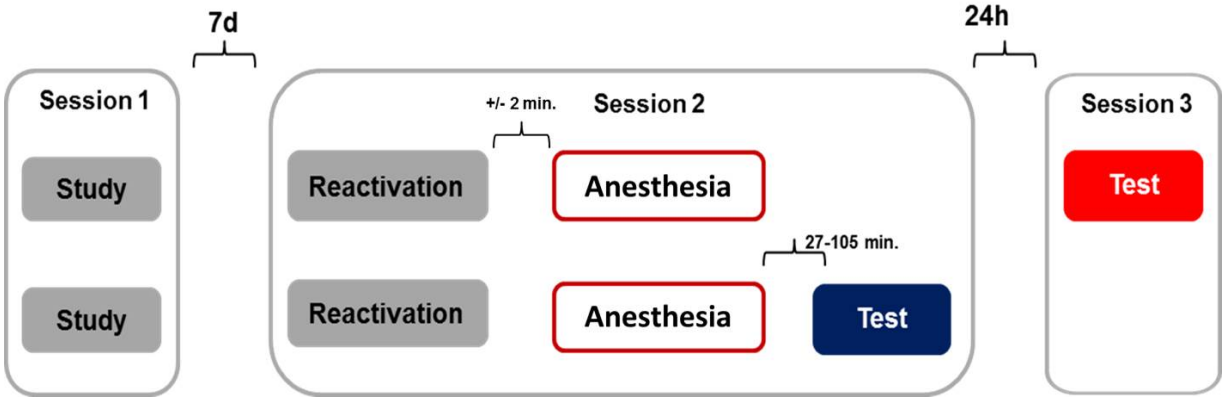

Figure 3.1. Study design. Patients were assigned to one of the two groups (A or B). During a first study session both groups were shown two emotional slide-show stories. During a second session memory for one of the two stories was reactivated. Immediately after memory reactivation patient in groups A and B received anesthesia. In patients of group B memory was tested immediately upon recovery from anesthesia (Test, blue). In patients of group A memory was tested one day after reactivation (Test, red).

3.3.1.1. Exclusion criteria

Subjects were electable because they were undergoing an endoscopy procedure that would need the use of GA. All subjects gave informed consent, but previously participants had to meet none of the exclusion criteria (Table 3.2.). These included that participants were free of neurological or psychiatric history or any anesthesia (propofol, midazolam or alfentanil) contraindications (nevertheless, medical doctors at the hospital were in charge of tested possible contraindications in the used of GA).

Exclusion criteria
- Subjects under (<) 30 years or over (>) 45 years
- Hearing dysfunction
- Previous/current psychiatric disorders
- Previous/current neurological diseases
- Consumption of neurological/psychiatric medication or other (medication) that may affect the CNS
- Consumption of narcotic substances
- Celiac disease

Table 3.2. Exclusion criteria. Participants had to meet none of these exclusion criteria in order to be electable for participate in the study.

3.3.2. Stimulus material

3.3.2.1 Stories

The stimulus material was the same as used in Kroes et al., (2014). During an initial learning session, participants viewed picture series of two high-arousing stories with negative valence on a 16" laptop computer screen. Each story consisted of 11 slides. Each slide was shown for 20 seconds with a total presentation time of 3.6 minutes for each story. Further, each slide was accompanied by an auditory narrative, forming an episode. One of the negative arousing stories was used before by Cahill and colleagues (Cahill & McGaugh, 1994, 1995; note that although a neutral version exists also, we only used the negative arousing version of the Cahill story) , from now on named as the "Story 1", and depicted a mother taking his young son to visit his father at work (see Figure 3.2.a). The second story was developed by Kroes et al. (2014) and involves two sisters that go to a bar, for now on referred as the "Story 2" (see Figure 3.2.b). Story 2 consists of modern digital photographs, whereas Story 1 contained scanned analogue images. To avoid any interference due to the learning of two stories in a short period of time, the narrative in the Story 1 was taped by a male voice, and the story 2 was recorded with a female voice (Kroes et al., 2014). Both

stories were adapted to the Spanish language and were identical in structure (11 sentences, one per slide in both stories), grammar, arousing[($mean_{Story1}$=1,1, s.e.m.= 0,48; $mean_{Story2}$=1,18, s.e.m.=0,55), $t_{(20)}$= -0,13, p=0,90] and neutral words [($mean_{Story1}$= 13,54, s.e.m.= 1,60; $mean_{Story2}$= 14,09, s.e.m.= 1,12), $t_{(20)}$= -0,28, p=0,78], similar in word[($mean_{Story1}$= 14,64, s.e.m.= 1,43; $mean_{Story2}$= 15,27, s.e.m.= 1,39), $t_{(20)}$= -0,32, p=0,75] and syllable count, and voice emphasis[($mean_{Story1}$= 2,64, s.e.m.= 0,58; $mean_{Story2}$= 2,23, s.e.m.= 0,49), $t_{(20)}$=0,48, p=0,64].

Both stories were divided into 3 phases. Phase 1 was composed of slides 1 through 4 and was of emotionally neutral content. Phase 2 was composed of slides 5 to 8, and comprised the negative emotional part of the stories, and Phase 3 consisted of slides 9 to 11 and was again of neutral content.

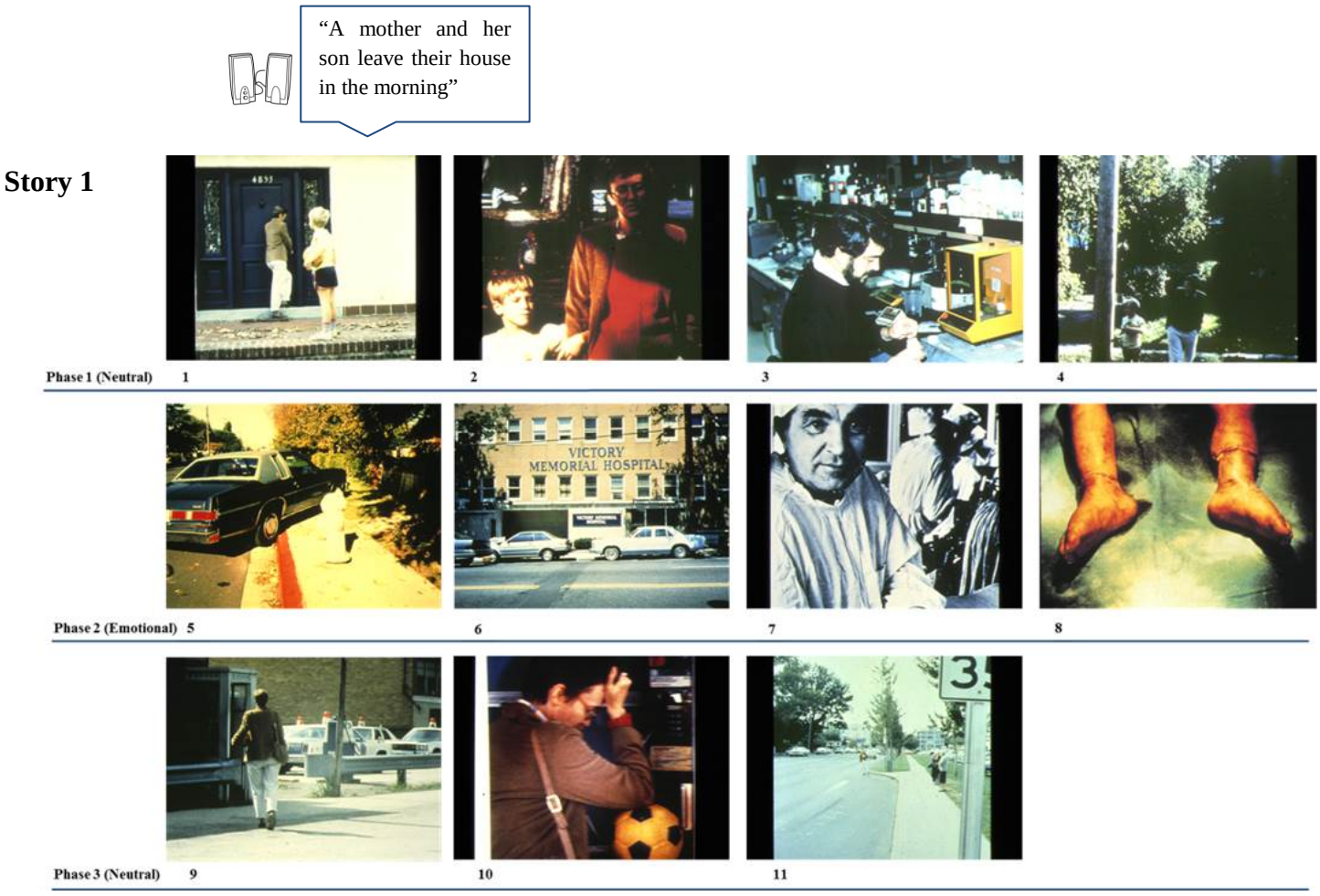

Figure 3.2.a

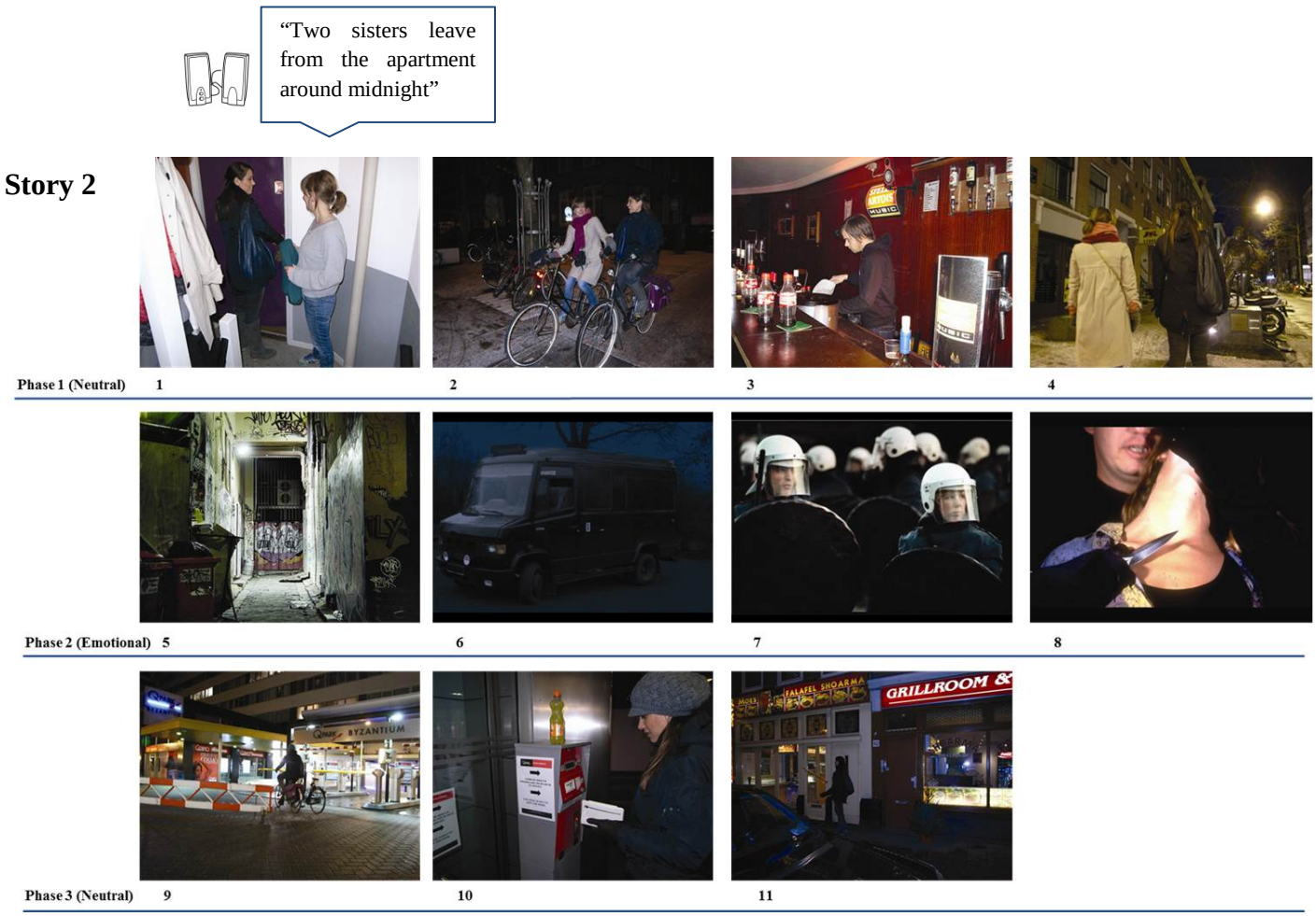

Figure 3.2.b

Figure 3.2. (a and b) Patients were presented with two slide shows that form arousing episodic stories of negative valence. Top: the original Cahill Story now named as "Story 1", bottom: the newly developed story by Kroes et al., (2014), now named as "Story 2". Both stories consist of 11 slides and each slide is accompanied by an auditory narrative presented via computer speakers.

3.3.3 Memory reactivation

Accumulating evidence indicates that consolidated, apparently fixed memories might re-enter a labile state after the presentation of a cue-reminder (process that it is known as reactivation), thus requiring to be re-stabilized again (a process that is known as reconsolidation) (Dudai, 2006; Nadel & Land, 2000; Sara, 2000).

The material used to reactivate a memory where photographs of the first slide of each story. The presentation of one or the other story was balanced across subjects with a 50% of probability of appearance each. Parts of this slide, however, were masked by black-and-

white checkerboard patterns (see Figure 3.3.). Patients were asked three questions on what was visible behind the mask. After the patient answered the question, the related part of the mask was removed, and the entire slide was visible after all three questions were answered.

Reactivation first slide Story 1.

Reactivation first slide Story 2.

Figure 3.3. Reactivation material. Participants were presented with the first slide of one of the two stories, to reactivate memory and initiate reconsolidation. As seen above, the parts of the slide were covered by black and white chessboard patterns. Participants were asked three questions about what was hidden behind the patterns. Once they answered the question, the mask was removed. After all three questions, the entire slide was visible.

3.3.4. Anesthesia

3.3.4.1. Propofol

In the early 1970s, different studies leaded to the development of a new and safe injectable anesthetic, with excellent anxiolytic properties but with no significant analgesic effects (therefore an opioid is usually administered concomitantly) derived from phenol with potent hypnotic properties, the molecule 2,6-di-isopropylphenol (Kay & Stephenson, 1980), chemically unrelated to other anesthetics (Short & Bufalari, 1999). Since then, the use of propofol (2,6-di-isopropylphenol compound) has been extended in clinical practice, as one of the most popular intravenous (IV) anesthetic for the induction and maintenance of

general anesthesia (Short & Bufalari, 1999) and in ambulatory surgeries in outpatients (Trapani, Altomare, Liso, Sanna, & Biggio, 2000). Different studies have shown that propofol possesses antiepileptic properties. Moreover, several studies have shown that propofol may be useful in patients resistant to other antiepileptic drugs such as BDZs, barbiturates, or other epileptic drugs (Al-Hader, Hasan, & Hasan, 1992; De Riu et al., 1992).

Propofol is stable at room temperature and is not light sensitive. The formulation usually consists of 1% propofol in a parental nutritional agent consisting of 10% soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide. It has a pH between 7- 8,5 and appears as a slightly viscous milky white substance (Short & Bufalari, 1999). Propofol is also an agent with antioxidant, anti-inflammatory and bronchodilating properties (Marik, 2004).

3.3.4.1.1 Pharmacodynamics

Propofol was a breakthrough because of its rapid onset of action due to rapid uptake into the central nervous system (CNS), the short duration of action and rapid smooth emergence mainly because of its rapid redistribution, due to its lipophilic nature, from the brain to other tissues and efficient elimination by metabolism (Zoran, Riedesel, & Dyer, 1993) (see table 3.2.). Another property that has made propofol gained a great acceptance is because of the quality and rate of recovery whether it is given by bolus or continuous infusion (Hall & Chambers, 1987).

Propofol is a cardiovascular depressant and also, it is been associated with respiratory depressant effects (reduced tidal volume and apnea), lowered cerebral blood flow that is accompanied by reduced requirement of oxygen and decreased intracranial pressure (ICP) (Bryson, Fulton, & Faulds, 1995). Like other anaesthetic agents, has anticonvulsant (mediated by GABA receptors) and neuroexcitatory activity (unknown origin); also has amnesic properties (less marked that BZDs) (see Table 3.1.) (Bryson et al., 1995).

Propofol also has neuroprotective properties during focal ischemia. Also when administered in large doses produces burst suppression in the electroencephalogram, that is why it is used in neurosurgical procedures for neuroprotection (Miller, Pardo, & Stoelting, 2011).

3.3.4.1.2. Mechanism of action

Some of the pharmacological actions of propofol are mediated by the inhibitory central GABAergic transmission (see Chapter 2). Within the different types of GABA receptors, the most propofol sensitive ones are $GABA_A$ receptors. Another study, reported that the amnesic effect of propofol seems to involve protein expression in the hippocampus, occurring through a network interaction with the BLA; being this key-region responsible of the anesthetic-induced amnesia (Ren, Zhang, Xue, Zhao, & Yu, 2008). Also, animal studies have shown that propofol activates $GABA_A$-receptors present in the locus coeruleus (LC), a small pontine nucleus that contains the major concentration of noradrenergic bodies in the brain, resulting in a decrease firing rate of nor-adrenergic neurons. Peduto, Concas, Santoro, Biggio, & Gessa, (1991) showed that propofol exerts its modulatory action by interacting in a different side from BZDs, at the GABA receptor. The $GABA_A$-receptors of the LC neurons do not contain the γ subunits, which make them insensitive to benzodiazepines, and unable to enhance the propofol-induced responses (Chen et al., 1999) via co-administration of benzodiazepines at the time of anesthesia.

Also, it is been shown that propofol decreased ACh release at the frontal cortex and hippocampus, and that this effect was blocked by bicuculline; on the other hand, release from the striatum was not affected (Kikuchi, Wang, Sato, & Okumura, 1998; Sanna et al., 1999). Excitatory glutamate receptors are also sensitive to propofol, while kainate receptors seem to be insensitive; NMDA receptors are negatively modulated by propofol, but this sensitivity appears to be low (Klein et al., 1993; Orser, Bertlik, Wang, & MacDonald, 1995). Other authors have also suggested that propofol inhibits M1 receptors (Murasaki et al., 2003). Taken into account all these data, it can be inferred that the mechanism of action of propofol is rather complex, and at the clinical level, seems that the general anesthetic action of propofol is the sum of all its interactions with different neurotransmitter systems (Trapani et al., 2000).

There is one factor that not always has been taken into account: gender. Gender appears to be an important factor to count with in recovery from anesthesia. Usually, it is been reported that women experienced more episodes of awareness (three times more frequent in women than in men). Gan et al., (1999) performed a multicenter study, they compared the wake up and recovery times of 274 adults. They found consistently evidence that women woke up faster than men; and that men had significantly prolonged recovery times, without

any differences in the dosage. This factor should be considered with respect to the pharmacodynamics and pharmacokinetic of propofol in the clinical practice.

3.3.4.1.3. Pharmacokinetics

The induction of anesthesia can be achieved by administration of doses of 40 mg every 10 seconds. The dose in adults usually has a range between 2- 2.5 mg/ kg (Langley & Heel, 1988). As said before, propofol can maintain anesthesia through continuous infusion (6 to 12 mg/kg /h) or with bolus injection (20-50mg) (Bryson et al., 1995). The induction of the anesthesia by propofol in combination with tranquilizers, sedatives, or analgesics is a very extensive practice (Morgan & Legge, 1989; Weaver & Raptopoulos, 1990). For example, the co-administration of propofol and midazolam is widely used in pre-anesthesia (Trapani et al., 2000). In order to achieve a total IV anesthesia the combined propofol with opioid agonist such as alfentanil administration is commonly applied in surgical practice (Trapani et al., 2000).

The propofol is characterized by a fast distribution from the blood into tissues and a rapid metabolic clearance that produces a rapid onset and a short duration of action. Propofol is rapidly and extensively distributed to well perfused tissue (including the brain), then to muscle and to fat tissue. It is metabolized primarily in the liver and the half-life is 30 to 60 minutes (Bryson et al., 1995) (see Table 3.3.). Propofol is mainly eliminated by hepatic conjugation to inactive metabolites and excreted by the kidney (Simons et al., 1988).

Pharmacology of propofol
Pharmacodynamics properties of propofol
• Fast action time (approximately 30 seconds). • Decreased blood pressure and heart rate with induction and maintenance of anesthesia. • Ventilatory depression. • Decreased cerebral blood flow. • Decreased intracranial pressure. • Decreased brain metabolism.
Pharmacokinetic properties of propofol
• Rapid distribution time (half-life of 2 to 4 minutes). • Rapid elimination (half-life 30 to 60 minutes). • Extensive distribution. • Fast clearance (1.5 to 2 L / min). • Major hepatic metabolism with urinary formation and excretion of inactive conjugates and quinolones. • Linear pharmacokinetics.

Table 3.3. Pharmacology of propofol. Pharmacodynamics and pharmacokinetic properties of propofol. Adapted from Carrillo-Esper, Garnica-Escamilla, & Bautista-León, (2010).

3.3.4.1.4. Complications associated with the use of propofol

Propofol has been administered successfully to millions of patients, with a remarkably safety record. Even so, there is a very rare but also extremely serious complication known as “propofol infusion syndrome”. This syndrome is associated with a high dose of propofol infusion, and affects the pediatric patients to a greater extent. This syndrome is characterized by a severe metabolic acidosis, Rhabdomyolysis (breakdown of muscle fibers) and cardiovascular collapse frequency leading to death (Vasile, Rasulo, Candiani, & Latronico, 2003).

In 1995, the Centers for Disease Control and Prevention (CDC) were informed of a disproportionate increase in bloodstream infections, surgical site infections, and febrile episodes following surgical procedures in a cohort of 62 patients (Bennett et al., 1995). After an investigation, it was possible to relate the occurrence of this outbreak with contaminated "multipurpose" vials and syringes containing propofol. Subsequently, other outbreaks were reported (Bach & Motsch, 1996; Henry, Plante-Jenkins, & Ostrowska, 2001; McNeil, Lasker, Lott, & Jarvis, 1999). Since then, it is recommended the addition of

a preservative to retard bacterial and fungal growth and to manipulated propofol in sterile conditions (Marik, 2004).

Nevertheless, the most common complaint with the use of propofol is the pain at the injection site, with an incidence range between 28,5% (small veins) to 6% (large veins) of the patients (Mackenzie & Grant, 1987). For other side effects: see Table 3.4.

Propofol side effects		
• Local pain in induction • Hypotension • Bradycardia • Transient apnea during induction • Nausea and vomiting	• Headache • Thrombosis and phlebitis • Epileptiform movements • Rhabdomyolysis (breakdown of muscle fibers). • Pancreatitis	• Postoperative fever • Color changes in uresis • Anaphylaxis • Sexual disinhibition • Pulmonary edema

Table 3.4. Propofol side effects. Adapted from Carrillo-Esper, Garnica-Escamilla, & Bautista-León, (2010).

3.3.4.2. Midazolam

Midazolam is a short-acting BZD with a unique chemical structure that is widely used as a preoperative agent due to its hypnotic, anxiolytic and sedative effects (Miller et al., 2011). MDZ has greater hypnotic effect and is 1,5-2 times as potent as diazepam (Reves, Fragen, Vinik, & Greenblatt, 1985), because interferes with GABA reuptake (Griffin III, Kaye, Bueno, & Kaye, 2013).

3.3.4.2.1. Pharmacodynamics

Midazolam has the properties of BZs: anxiolytic, muscle relaxant, anticonvulsant, sedative, hypnotic, and anterograde amnesia (Miller et al., 2011). BZD receptors have been identified in the heart and skeletal muscle, although the predominance appears to be in the central nervous system (Kanto, Aaltonen, Erkkola, & Äärimaa, 1984), where MDZ´s affinity is approximately twice the affinity of diazepam (Grote, Doenicke, Kugler, Suttmann, & Loos, 1981; Kanto, 1985). BZDs have a low incidence of respiratory depression due to the low concentration of binding sites in the brainstem (J. Kanto et al., 1984).

The maximum clinical effect after IV infusion is reached in approximately 3 minutes (Amrein, Cano, Eckert, & Coassolo, 1980).

3.3.4.2.2. Mechanism of action

As other BZDs, MDZ enhances the inhibitory action of the GABA, by augmenting Cl-; which in turns, prevent the cell to initiate an action potential (see also Chapter 2). There are specific binding sites on the γ-subunit of $GABA_A$ receptors, with the greater density being in the cerebral cortex. Midazolam action can readily be terminated by administration of the BDZ antagonist flumazenil (Miller et al., 2011).

3.3.4.2.3. Pharmacokinetics

After IV infusion, the onset of sedation is quite rapid, with maximum clinical effects seen in approximately 3 min (Amrein et al., 1980). This rapid onset is due to the high lipophilicity of midazolam at physiologic pH (Pieri et al., 1980). This high lipophilicity couple with its fast clearance and elimination, which is the reason of it short time of action (Pieri et al., 1980).

The volume of distribution (Vd) is 1-2.5 L/kg in normal healthy individuals but is greater in women than in men, in the elderly, and during pregnancy (Greenblatt & Abernethy, 1985; Reves et al., 1985), also obese patients have an increased Vd as a result of enhanced distribution to peripheral adipose tissues (Greenblatt & Abernethy, 1985; Reves et al., 1985). The time of action ranges between 60-120 minutes, and the elimination is fast also, with a half –life of 1-4 h (Dundee & Wilson, 1980). MDZ is metabolized in the liver and excreted via the urine (Heizmann & Ziegler, 1980). The total plasma clearance is higher in supine position due to the increase hepatic blood flow by about 40-60% (Daneshmend, Jackson, & Roberts, 1981). The termination of the effect after one single dose of IV administration is fast due to the rapid distribution rate and clearance, and also is due to its lipid solubility, which leads to rapid redistribution from the brain to inactive tissue sites (Miller et al., 2011). Generally, midazolam levels in the circulation are no measurable after 5-6 hours of a single dose (Miller et al., 2011).

3.3.4.2.4. Complications associated with the use of midazolam

The incidence of adverse effects of midazolam is low, and even more in only one dosage treatment. Nevertheless has been associated with respiratory depression, cardiac arrest, and death, particularly when used in combination with opioids. See also Table 3.5.

Midazolam side effects		
CNS disturbances* • Drowsiness • Apathy • Disorientation • Confusion • Headache • Depression • Visual disturbances *After a single dose these residual effects do not last long	Gastrointestinal reactions • Nausea • Constipation • Dry mouth	Cardiovascular disturbances • Tachycardia • Hypotension

Table 3.5. Midazolam side effects. Adapted from Kanto, (1985).

3.3.4.3. Alfentanil

Alfentanil is a synthetic tetrazole (phenylpiperidine), an opiate agonist (Van Bever, Niemegeers, Schellekens, & Janssen, 1975) considered a major component of general anesthesia derivate of fentanyl (Ausems, Hug Jr, & de Lange, 1983; Bovill, Warren, Schuller, van Wezel, & Hoeneveld, 1984; De Lange & De Bruijn, 1982). Alfentanil has a fast onset of action (approx.. 2 minutes), but is about eight times less potent than fentanyl (Howie, McSweeney, Lingam, & Maschke, 1985; White, Coe, Shafer, & Sung, 1986).

3.3.4.3.1. Pharmacodynamics

The binding of alfentanil to the opiate receptors inhibits the activity of adenylcyclase, manifesting itself as a hyperpolarization of the neuron, resulting in the suppression of spontaneous evoked responses. It may interfere with the transport of calcium ions through the membrane, and interfere with the release of neurotransmitters such as acetylcholine, dopamine or noradrenaline. Depression of cholinergic transmission in the CNS may play an important role in the analgesic effect as well as in side effects (Miller et al., 2011). Alfentanil does not alter the responses of the afferent nerve endings to noxious stimuli or alter the conduction of nerve impulses along the peripheral nerves (Stoelting & Hiller, 1991).

3.3.4.3.2. Mechanism of action

Opioids induce anesthesia via interaction with opiate receptors in the CNS, due to a nonspecific mechanism related to the lipid solubility of the opioid (Dodson & Miller,

1985). The opioid receptors are transmembrane proteins whose activation induces reduction of spontaneous neuronal activity. These receptors are mainly found in the central nervous system (the anterior cingulate cortex, the lateral prefrontal cortex and the periaqueductal and periventricular gray matter), but also in other peripheral tissues(Ortiz & Lora-Tamayo, 2009) .

Alfentanil has a small volume of distribution that in addition to its non-ionized form with a physiological pH, allowed it to cross easily the blood-brain barrier (Ortiz & Lora-Tamayo, 2009).

3.3.4.3.3. Pharmacokinetics

Alfentanil is considered as a short-acting drug (Miller et al., 2011). If administered IV, alfentanil has a onset of action that appears in 1-2 min with a peak effect in 1-2 min with a duration of action of around 10-15 min (Ortiz & Lora-Tamayo, 2009).

Alfentanil has a smaller volume of distribution, lower total body clearance, and shorter half-life than fentanyl (Fragen et al., 1983; Hull, 1983; Mather, 1983).

After IV injection, there is a rapid decline of plasma concentration during the first 15 minutes, with almost total elimination from plasma in around 60 minutes (Camu, Gepts, Rucquoi, & Heykants, 1982). The metabolism is through the cytochrome P-450 in the liver, and it is excreted by urine. The mean clearance time for alfentanil is 70 to 98 minutes (Ortiz & Lora-Tamayo, 2009).

3.3.4.3.4. Complications associated with the use of alfentanil

Alfentanil side effects		
Muscle rigidity* • Chest wall rigidity. • Clenching of the jaw. • Flexion of the wrist. *can occur in 50 to 88 percent of patients.	Other side effects • Bradycardia. • Nausea and vomiting. • Pruritis. • Tachycardia. • Hiccup.	• Pain on injection. • Laryngeal spasm. • Dysphagia. • Hypotension/ Hypertension • Dizziness. • Apnea.

Table 3.6. Alfentanil side effects. Adapted from Reitz, (1986)**.**

3.3.5 Digit symbol substitution test (DSST)

DSST (Wechsler, 1997) is a brief cognitive screening test of nine digit-symbol pairs and 115 symbols that all participants had to pass to assess any group differences in general cognitive functioning at the time of story encoding and memory testing (see Figure 3.4.) The performance of the test consists of writing underneath of each symbol the number associated as fast as possible and with less errors as possible. The DSST was administered prior to the initial study session and prior to memory testing.

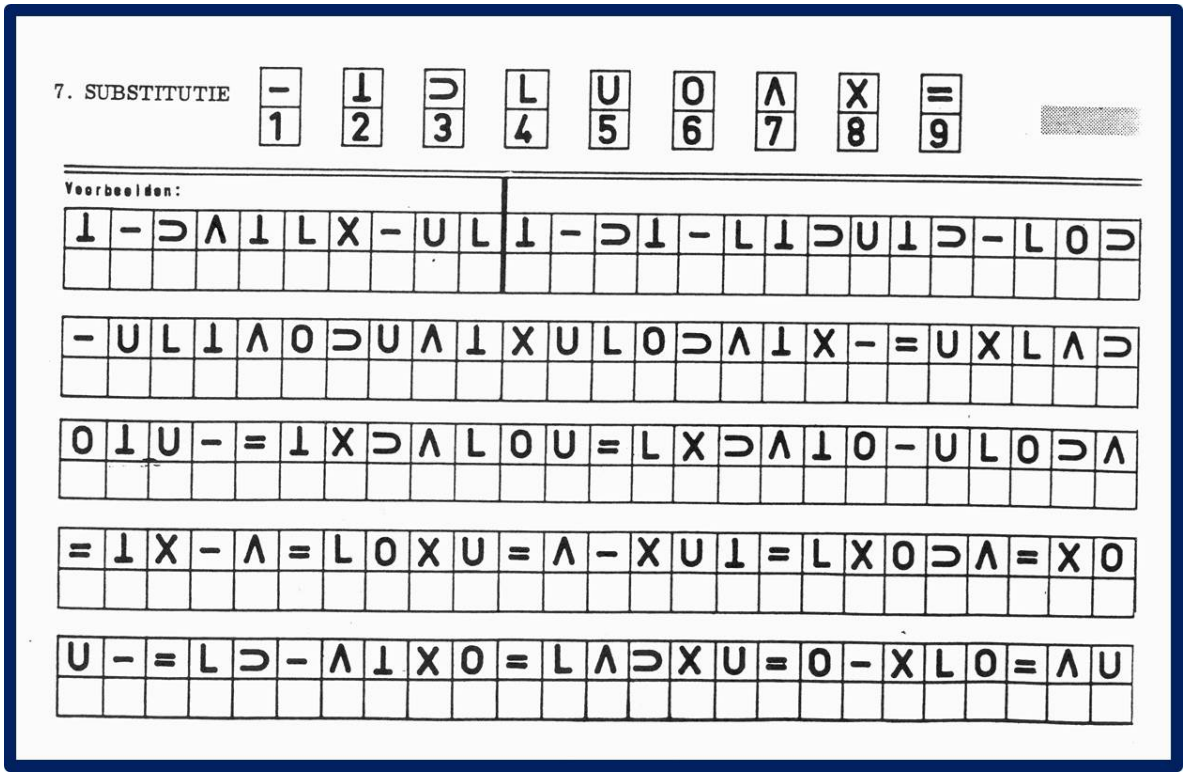

Figure 3.4. Digit Symbol Substitution Test (DSST). Adapted from Wechsler, (1997).

3.3.6. Multiple choice memory test

Following the order of the 11 presented slides; 3–5 multiple-choice questions were posed per slide with 4 answer options. Each story has a total of 40 questions. An example of one of the questions is: “Who is depicted on the slide 2? a) Mother, b) Son, c) Mother and son, d) Mother and son, and another person in the background”. Questions have been selected on the basis of presence of variability and the absence of ceiling or floor effects in pilot studies (Kroes et al., 2014). Scores are expressed as percentage of correct responses. Memory performance on the first slide for both stories has been excluded from the memory

score, as this slide was used for memory reactivation. Testing memory for both stories required approximately 1 h.

3.3.7 Procedures

Once all the methods and material have been disclosure, the descriptions of the different experimental phases are as following:

Experimental Phases:

Emotional Memory Encoding. Once each participant arrived at the hospital, exactly one week before their endoscopy appointment, they were conducted at the consultation room where session 1 and 3 (Figure 3.1.) took place. After given written consent, they performed the Digit Symbol Substitution Test (DSST), a short screening test to avoid any cognitive malfunctioning. Then, all patients were exposed to the two emotionally aversive slide-show stories displayed on a computer screen. The slides were accompanied by the narration presented via computer loud speakers through the integrated device High Definition Audio (mean: 62 dB, in a range between 42-80 dB at 15 cm of distance). For each participant, the order of the two stories was randomized to safeguard against any learning differences due to the order of story presentation. Encoding session of both stories comprised approximately 15 minutes.

Memory Reactivation. This session took place 1 week after the encoding session. Once the participant was supine in the hospital endoscopy room and the intravenous (IV) cannula placed, memory for one of the two stories was reactivated. Which of the two stories was reactivated was counterbalanced across participants within each Group (that is, for 12 subjects in each Group, Story 1 was reactivated). To reactivate the memory and initiate a reconsolidation process, patients were presented with the first slide of one of the two stories. As said in the previous section (section 3.3.3.), parts of this slide, however, were masked by black-and-white checkerboard patterns. Patients were asked three questions on what was visible behind the mask. After the patient answered the question, the related part of the mask was removed, and the entire slide was visible after all three questions were answered. Answers were provided by free recall and recorded with a tape recorder by the investigator. If the patient was unable to answer freely, a two-alternative forced choice question was posed. Reactivation score was calculated as the number of questions answered correctly by free recall × 2 + the number of correctly answered questions by multiple

choice. Immediately following memory reactivation all patients received propofol and underwent their endoscopy. The reactivation session required approximately 1-2 minutes.

General Anesthesia. All participants received propofol (2,6-diisopropylphenon); initial dose: 10-40 mg, additional doses: IV dose of 25-75 mcg/kg per minute; or incremental IV bolus doses of 10-20 mg. Furthermore, 27 of the 50 participants received additional agents, which included midazolam or phenylpiperidine derivatives, (fentanyl, alfentanil or remifentanil).

Memory Testing. Memory for both stories was tested after 24h (Group A) or after 27-105 minutes (Group B) using a multiple choice memory test. Following the order of the 11 presented slides; 3–5 multiple-choice questions were posed per slide with 4 answer options. An example of one of the questions is: "Who is depicted on the slide 2? a) Mother, b) Son, c) Mother and son, d) Mother and son, and another person in the background". Questions have been selected on the basis of presence of variability and the absence of ceiling or floor effects in pilot studies(Kroes et al., 2014). Scores are expressed as percentage of correct responses. Memory performance on the first slide for both stories has been excluded from the memory score, as this slide was used for memory reactivation. Testing memory for both stories required approximately 1 h.

3.3.8. Results

3.3.8.1 Participants

A total of 50 participants completed the study (group A, N=25; group B, N=25). One of the participants of group B was discarded from further analysis because of an atypical difference between the encoding and the memory testing performance in the DSST which could indicate that this patient was still under the influence of the GA. Groups A and B did not differ in any demographical variable (age, gender, years of schooling or type of endoscopy procedure) (see Table 3.1).

3.3.8.2 Anesthesia

There was no group differences in terms of the amount of other anesthetic (midazolam or alfentanil) administered. Although, there is a significant difference (* $p<0.05$) in the amount of propofol administered, there is no correlation between this amount (kg/mg) of

propofol and the memory scores on both groups ($r_{totalReactivated}$=0,17, p=0,25; $r_{totalNonreactivated}$=0,03, p=0,86) (see Table 3.1).

3.3.8.3 Memory reactivation does not differ between groups

Both groups showed memory reactivation being the performance at reactivation above chance level (33%, dashed line). Group A (red) mean: 4.2, s.e.m.: 0.30; group B (blue) mean: 3.87, s.e.m.: 0.34.

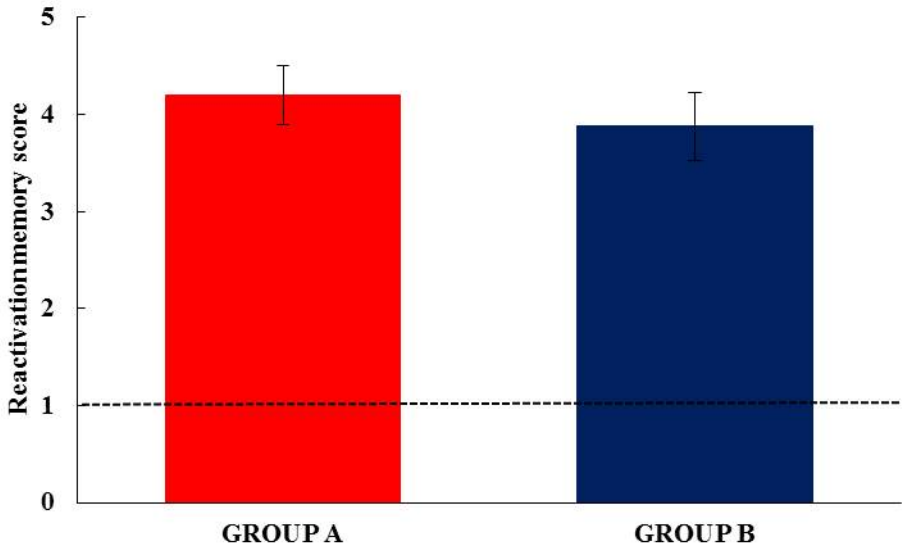

Figure 3.5. Memory reactivation scores for groups A and B. No significant differences between groups. Dashed line indicates chance level (33%).

3.3.8.4. No difference in general cognitive functioning between groups as assessed by the DSST

The DSST was administered two times, one before the encoding of both stories and the other one, before the recognition memory test. There is a significant effect of learning in the performance of the DSST in Group A ($p<0.05$), between the encoding administration and the recognition test administration. For Group B, there is no effect of learning in the performance probably because the participants remained under the effects of GA at the time of the recognition test administration. Between groups there is no difference in general cognitive functioning.

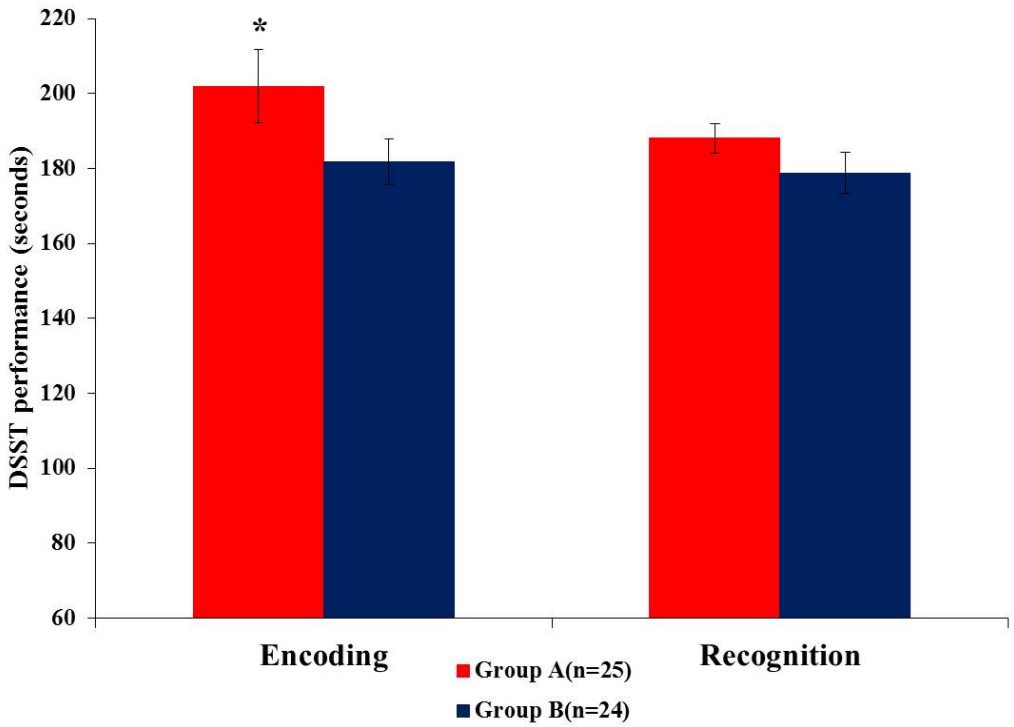

Figure 3.6. Digit Symbol Subsitution Test (DSST) performance for Group A and B. The DSST is a brief screening cognitive test, used in this study to avoid any group differences in general cognitive functioning. Group A (red) has a significant effect of learning (* $p<0.05$), while group B (blue) has not, probably because pacientes remained under the effects of anesthesia.

3.3.8.5 Anesthesia disrupts reactivated emotional memory

Both stories consisted of three phases whereby Phase 1 (slides 1-4) and Phase 3 (slides 9-11) were of neutral content. The middle part of the stories, Phase 2 (slides 5-8), had an emotional content. We first performed a Group (A, B) by Reactivation (yes, no) by Phase (1,2,3) repeated measures ANOVA (rmANOVA). Thereby, the quadratic contrast of Phase entered into the model as we hypothesized a specific memory effect on the emotional part of the stories that would be expressed by a quadratic contrast (phase 1 > phase 2 < phase 3). We observed a three way interaction of Group by Reactivation by quadratic Phase contrast at trend level [$F_{(1,47)}=3.03$, $p=0.09$]. Given our hypothesis, the reactivation-dependent memory effect should be present only in group A and not in group B. Therefore, we fitted an rmANOVA with an interaction term of Reactivation by quadratic Phase contrast for each group separately.

Group A showed a significant Reactivation by quadratic Phase contrast [$F_{(1, 24)} = 6.51$, $p = 0.018$] , whereas this effect was absent in group B [$F_{(1, 24)} < 0$, $p = 0.98$].

For the reactivated story in group A, there is a significant quadratic Phase contrast [$F_{(1,24)}$=5.73, p=0.025] (Figure 3.7); while for the non-reactivated story the quadratic phase contrast is not significant [$F_{(1,24)}$= 5.77, p=0.46] (Figure 3.8). This memory impairment for the emotional part of the story (Phase 2) is further reflected by significant differences between the not reactivated and reactivated versions of the stories [$t_{phase2\ (24)}$= -3.05, p= 0.006]. In contrast, for the neutral parts of the stories (Phases 1&3) reactivation did not result in any memory decline [$t_{\ phase1\ (24)}$= -0.56, p= 0.58; $t_{\ phase3(24)}$= -1.20, p=0.91].

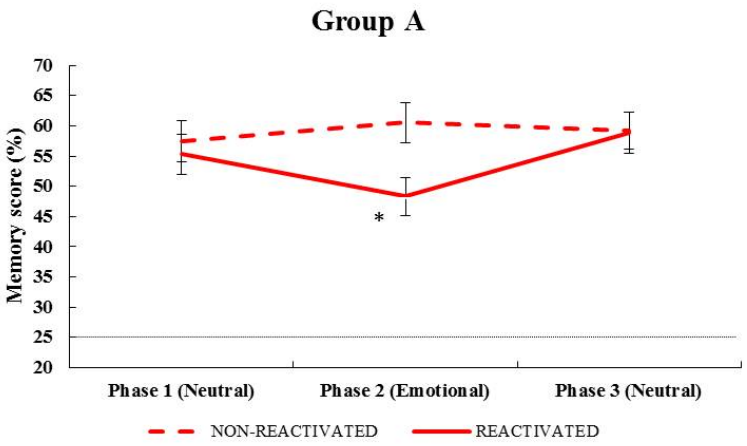

Figure 3.7. Group A (n=25 subjects)

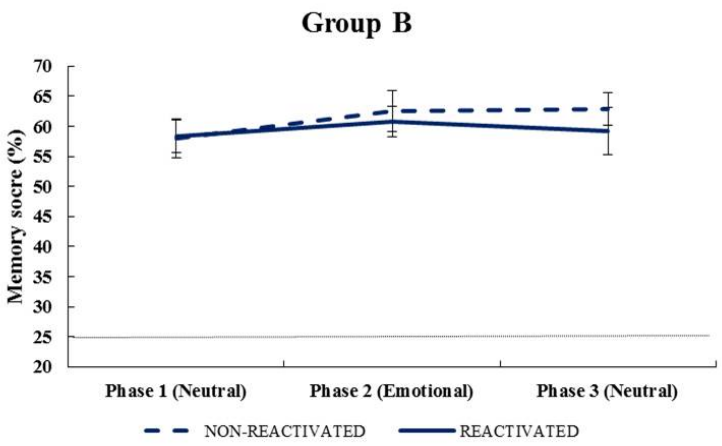

Figure 3.8. Group B (n=24 subjects)

Figure 3.7.Group A (red) (n=25 subjects): General Anesthesia disrupts reconsolidation of the emotional phase (Phase 2) of the reactivated story if tested after 24 hours. Memory scores expressed in percentage correct for the different phases of and the non-reactivated story. There is a significant impairment of the memory of the emotional phase of the reactivated story (* p<0.05). --- Indicates chance level.

Figure 3.8 Group B (blue) (n=24):General anesthesia does not diminish emotional memory of the reactivated Story if tested immediately after recovery of GA. Memory scores expressed in percentage correct for the different phases of the reactivated and the non-reactivated story.

Possible group differences in propofol dose may have contributed to the specific memory effects for group A. Indeed, a two-sample t-test revealed a significant propofol dose difference between groups [$t_{(47)}$=2.04, p= 0.05], group A having received a higher dose (mean= 3.02 mg/ kg, s.e.m.=0.25) than group B (mean=2.37 mg/ kg, s.e.m.=0.19). However, there was no linear association between the dose of propofol and Phase 2 (emotional) recognition scores in group A ($r_{reactivated}$ =0.22; p=0.3; $r_{non\text{-}reactivated}$= -0.007; p=0.97), and in group B ($r_{reactivated}$ =0.12; p=0.56; $r_{non\text{-}reactivated}$=-0.005; p=0.98). Therefore,

the specific memory impairment for the emotional story part in the reactivated group A cannot be accounted for by propofol dose (see Figure 3.9.).

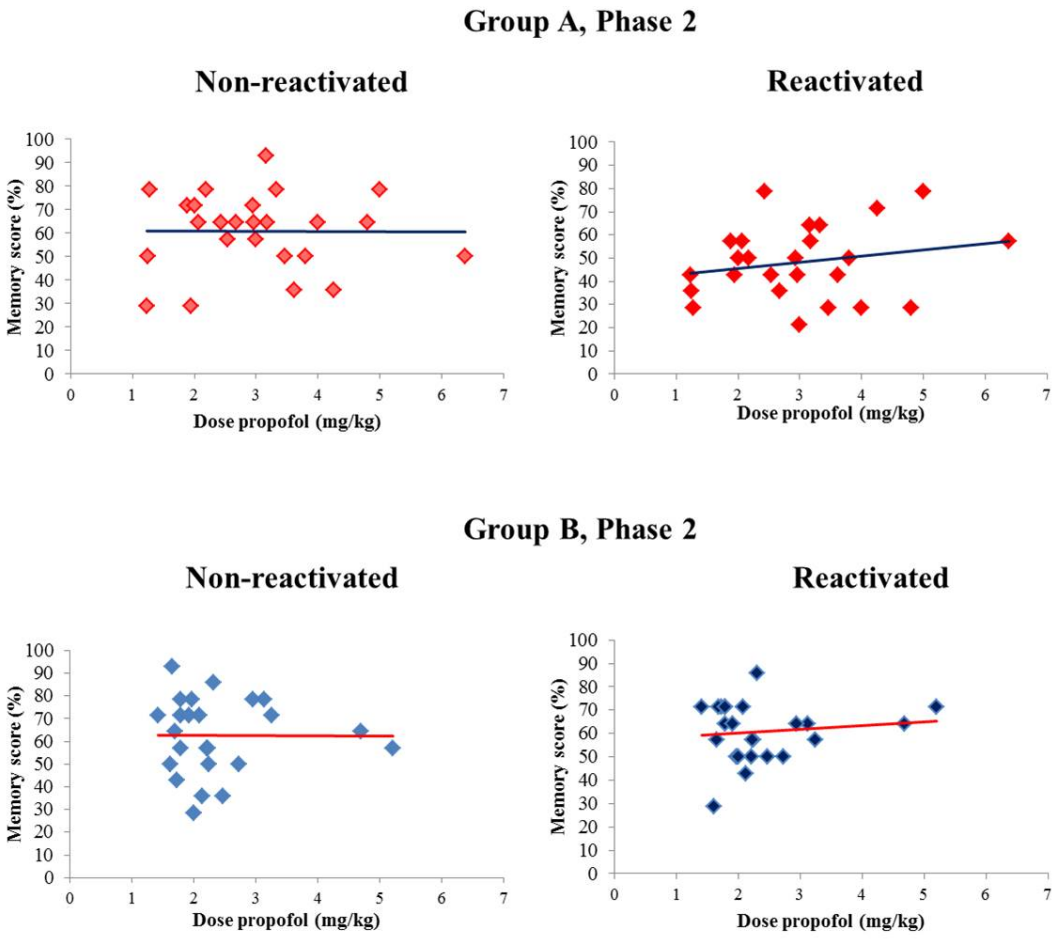

Figure 3.9. Dose of propofol and memory score in phase 2 (emotional) for groups A (red) and B (blue). Linear correlation between the amount of propofol (mg/kg) and the percentage of memory score for Phase 2 (emotional) of the reactivated and no reactivated story, in both groups (A & B). There is no linear relationship between both variables; the memory impairment in Phase 2 in the reactivated story of Group A does not depend on the amount of propofol.

An alternative or additional explanation is that the emotional memory decrease is driven by vagal nerve stimulation. Vagal stimulation can occur either at the time of passing the endoscopy in to oesophagus or the stretching of the sigmoid mesentery during colonoscopy. These effects would be additive in those individuals undergoing both gastro- and colonoscopy. Given that reconsolidation effects in Group A are equivalent across the 3 interventions [$F_{(1,44)}$=1,36; p= 0,26], it is unlikely that vagal stimulation contributes to the memory effects we observe.

3.4. Discussion

This data provides evidence of the disruption of emotional episodic memories by administration of the anesthetic propofol after reactivation. The results satisfy critical criteria for account reconsolidation in humans. Also, it is shown that the memory impairment is not due to any new learning at the time of reactivation that could produce interference at the time of retrieval, but relative to the administration of a GABA agonist such as propofol.

Previously, pharmacological manipulation of reconsolidation in humans has focused on the β-adrenoceptor blocker propranolol. The potential clinical risk of using β-blockers to manipulate reconsolidation is lower than other pharmacological interventions such as the one used in this study (propofol). As mentioned before (see Chapter 1 and 2), memory reactivation and propranolol oral intake are able to affect some threat-related responses (*i.e.:* startle responses), without affecting the conscious knowledge (*i.e.:* episodic memory) of the fear (Kindt et al., 2009). Apart from the benefit of reducing the physical responses related to fear, we should not overlook the fact that many psychiatric disorders (*i.e.:* PTSD, addictions) have episodic memory at their etiological basis. This episodic memory may contribute to the negative symptoms experienced, or to a possible relapse of the physiological fear-related responses. So, it is desirable to alter these episodic memories as well. Several studies have administered propranolol to target reactivated episodic memories. Nevertheless, there are two basic problems when trying to alter memories with propranolol that cannot be ignored. Due to its pharmacological features, propranolol needs approximately 90 minutes to reach its maximum peak in plasma, which forces experimenters to administer the manipulation before reactivation. This prior manipulation violates one of the three critical criteria of reconsolidation, which states that in order to achieve reconsolidation, manipulations have to be done immediately after reactivation. However, as we have pointed out, if the administration of propranolol is performed after manipulation, it takes 90 minutes to reach the maximum effect of the drug, which exceeds the time-window available for the reactivation and manipulation of a memory, thus violating other of the three critical criteria.

Nevertheless, studies with clinical populations (*i.e.:* PTSD), have suggested the use of β-blockers (*i.e.:* propranolol) to block reconsolidation as a novel treatment for PTSD,

characterized by maladaptive emotional episodic memories (Wood et al., 2015). In the Brunet et al., (2008, 2011, 2014) studies using propranolol and a script-driven imagery technique with PTSD patients, the experimenters showed reduced levels of skin conductance response (but not below PTSD cut-off levels) and a reduction of PTSD symptoms. Reductions were maintained over the course of six weeks follow up. However, attempts to replicate these results (Wood et al., 2015) failed to support successful reduction of PTSD symptoms with blockade of reconsolidation, demonstrating the limited success of treating this psychiatric disorder by combining propranolol and memory reactivation.

The oral dose of propranolol that can be well-forward by humans (because of its hypotensive effects) is typically 40-80 mg. this dose may, however, be insufficient to exert a cognitive effect (reconsolidation). However, administration of propranolol that produces no lag in time to peak effect would be intravenous route, but is not possible, since intravenous (IV) administration is only prescribed for patients with life-threatening.

The emotional effect on memory involves the integrity of the basolateral nucleus of the amygdala (Quirarte, Roozendaal, & McGaugh, 1997), which is thought to enhance memory consolidation via interaction with other structures such as the hippocampus (Packard, Cahill, & McGaugh, 1994). The effectiveness of noradrenergic antagonist in reconsolidation of emotional episodic memories is limited (Muravieva & Alberini, 2010).It is unclear, if this limitation is due to the targeted brain regions or to the intrinsic properties of the propranolol, or both.

In a previous study, using ECT with therapy-resistant unipolar depression patients, an impairment of the reactivated episodic memory following the critical criteria of reconsolidation was shown (Kroes et al., 2014). Prior to ECT, an anesthetic, etomidate, was administered, to minimize ECT adverse effects. Nevertheless, it was not possible to elucidate whether reconsolidation impairment was due to the ECT or to the general anesthesia (GA). The hypothesis presented in this thesis was that if the GA was responsible, targeted memory reconsolidation in psychiatric patients could be done without ECT, which is an invasive procedure. Even more, there is recent evidence that frontal ECT alters functional connectivity of the frontal lobes (Perrin et al., 2012). For its part, etomidate is generally used in short surgical procedures due to its benign hemodynamic effects, but suppresses adrenal function transiently, and thereby suppressing cortisol levels,

even after a single bolus (Forman, 2011; Hohl et al., 2010). The adrenal suppression lasts 6-8 hours after a single bolus (Allolio, Stuttmann, Leonhard, Fischer, & Winkelmann, 1984; Fragen, Shanks, Molteni, & Avram, 1984); or more than 24 hours after etomidate infusion (Wanscher, Tønnesen, Hüttel, & Larsen, 1985). Cortisol levels impair memory retrieval at both, very low or very high levels, but not intermediate levels. The shape of the relationship between cortisol levels and memory retrieval is like an inverted-U, and it is originated by the different affinity of the mineralocorticoid receptors (MR) and the glucocorticoid receptors (GR). (Rimmele, Besedovsky, Lange, & Born, 2013). Given this modulatory role of cortisol on memory it is important to control for this.

Thereby, to test the hypothesis, it was decided not to use etomidate, but propofol. Propofol is one of the IV anesthetic of choice in ambulatory procedures for outpatients due to its rapid induction of anesthesia and recovery (Trapani et al., 2000). The mechanism of action is similar to other anesthetic agents (*i.e.:* etomidate), resulting in a positive modulation of the inhibitory function of GABA through $GABA_A$ receptors (Trapani et al., 2000). As described above, we have been able to impair emotional memory with a single dose of propofol, following all critical criteria of reconsolidation.

Animal studies suggest that BLA lesions do not produce memory impairment effects when propofol is administered, demonstrating that BLA is a key brain region that mediates anesthetic-induced amnesia (Alkire, Vazdarjanova, Dickinson-Anson, White and Cahill, 2001). It has also been suggested that anesthetics that act on $GABA_A$ receptors (*i.e.*, propofol) decrease NA from noradrenergic LC neurons (Kushikata, Hirota, Yoshida, & Kubota, 2002; Kushikata, Yoshida, Kudo, Kudo, & Hirota, 2011).

There is increasing evidence that BLA is not a place for storing emotionally modulated memories (Paré, 2003), but may facilitate storage in other regions of the brain, such as the hippocampus through efferent connections. Specifically, there is a study in humans that reported that the structural equation modeling of PET glucose data shows that 0.25% of sevoflurane suppresses the amygdala to effective hippocampal connectivity (Alkire et al., 2008). If a similar mechanism exists for the reconsolidation process, it is possible to infer that the mechanism behind the deterioration of episodic emotional memories by propofol after reactivation is through the BLA and its connections with the hippocampus. Basolateral amygdala is a brain region that is tightly regulated by a small population of GABA

inhibitory neurons (Prager, Bergstrom, Wynn, & Braga, 2016). Moreover, disruptions in GABAergic control of the BLA after trauma results in hyper excitability that manifests itself behaviorally as an increase in anxiety or emotional dysregulation (Prager et al., 2016), and correlates positively with PTSD symptom severity (Shin & Liberzon, 2010). The modulating effect of GABA on the release of NA would specifically affect the reconsolidation of the emotional memories, producing a more evident deterioration of the same memories by the suppression of the connection between BLA and the hippocampus due to the anesthesia.

One of the boundary conditions of reconsolidation pertains to temporal parameters, such as the age of the memory; older memories seem to be more resistant to undergo reconsolidation (Golkar et al., 2012), making the application of reconsolidation difficult to translate to real life clinical therapies. A limitation of this study is that it was not tested if the memory impairment lasts over time. A third experimental group would have been needed, with a longer time interval between the reactivation session and the memory test session (*i.e.:* an interval of one week) to test if our impairment is not temporary, but long-lasting.

A second limitation is that a single dose of propofol affects recent (one week) emotional memories. However, the memories of real life, which underlie psychiatric disorders, are often old. The repetition of the reactivation and the treatment can be beneficial to modify older memories. Addressing the number of sessions required to achieve maximum effectiveness is necessary. That is, for older memories, a certain minimum number of sessions may be necessary, and there may be a maximum number of sessions above which there is no further therapeutic benefit (Brunet et al., 2011, 2014). Another challenge when it comes to reactivating real life memories is to find the right “cue” that would elicit reconsolidation. For this, today it is possible to employ virtual reality. Virtual reality could be a useful tool for reactivating individual memories with a combination of script-driven imaging techniques, making it possible to individualize the process and find the specific cues (in features and time of presentation) to reactivated specific memory real-life trauma.

Future studies are needed to improve the understanding of the reconsolidation process and how it works in real life and to delineate the criteria and critical factors needed to make reconsolidation and the underlying processes in the treatment of clinical populations more

efficient and useful. One further marked question is whether positive valance emotional memories are affected as well.

The results presented in this thesis bring closer the possibility of modifying certain types of memories. Once in their lives a large proportion of the general population is exposed to situations in which their lives or those of others may be endangered. The traumatic experience can leave a memory footprint that entails dysregulated emotional learning that contributes to anxiety disorders (Ressler & Mayberg, 2007; Williams et al., 2007). Anxiety is a frequent response to recalling negative episodic memories (McNally, 2003), and usually it is at the core symptom of certain disorders driven by amygdala-centric fear pathways, such as specific phobias or post-traumatic stress disorder (PTSD) see (Garakani, Mathew & Charney, 2006).The aim of this study was to find a technique to reduce unwanted and maladaptive memories in a relatively non-invasive way, by reactivating these memories before a dose of general anaesthetic is administered. Although the results presented here pertain to decreasing memory in healthy individuals, they provide an empirical basis that a routine anaesthetic procedure, that is available worldwide, could potentially be used to treat or support treatment of disorders such as PTSD, addictions, phobias and obsessive-compulsive disorder. The benefit of the patients could not only be an improvement in their daily life, but also reduce the social stigma attached to mental illness by showing it to be (at least partly) an abnormal memory process that can be treated with the same pharmacological agent you would have if your appendix were to be surgically removed.

3.5. Conclusions

We hypothesized that the impairment of memory shown in our previous work using ECT would be due to the anesthesia and not to the ECT itself, or the posterior seizures (Kroes et al., 2014). Using a single dose of a routine anesthetic, propofol, and following critical criteria of reconsolidation, we have been able to reveal an impairment of memory relative to the emotional phase of the story compared to neutral phases. This memory impairment has been showed only for the reactivated story, and only if tested 24 hours after reactivation (Group A), not after a short period of time (Group B).

Chapter 4

Administration of a β-adrenoceptor antagonist to block the action-induced episodic memory enhancement

4.1. Introduction

To address how movement modulates episodic memory in humans our group (Yebra et al., 2017; submitted) has performed a set of experiments related to the encoding of a visual stimulus in the context of simultaneous voluntary movement in comparison to withholding a movement (a Go-NoGo task, via button press if indicated by contextual cues; described below). The initial behavioural experiments, performed previously by Yebra et al., (2017, submitted), have shown that voluntary movement can enhance memory encoding. Also, it has been described that this mnemonic boost is not regulated by an effect of anticipated financial reward, as should be expected according with recent data suggesting that the expectation of reward influences memory performance, enhancing memory for events that are worth acting for (Koster, Guitart-Masip, Dolan, & Düzel, 2015). Likewise, those previous experiments shown that inhibiting ("NoGo condition") an action does not impair the subsequent episodic memory. To ensure that the memory impairment was not related to inhibitory activity, a variable temporal asynchrony in the presentation of the stimuli was employed. Previous electrophysiological studies (Falkenstein, Hoormann, & Hohnsbein, 1999; Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998; Mecklinger, Parra, & Waldhauser, 2008) of the effect of response inhibition on event related potentials (ERP) have shown changes in the amplitude and topography of different waveforms during response inhibition at ~200-300 ms. So Yebra et al., (2017, submitted) manipulated the stimulus presentation time at different 250 ms time windows. The time windows presentation had 3 different onsets of the stimuli, at 0s, at 250 ms and at 500 ms (0-250, 250-500, 500-750 ms) for both conditions (Go and NoGo). The colored background frame that indicated the instruction to press or not a button was presented from 0 to 750 ms. The results showed no higher memory impairment for the NoGo memory for the 0-250 ms presentation, which would be predicted by a NoGo-induced memory impairment (Falkenstein et al., 1999; Kiefer et al., 1998; Mecklinger et al., 2008).

A range of subsequent experiments were done, in order to assess the underlying neural mechanism behind the memory enhacement including fMRI, pupilometry and manipulation of stimulus arousal. Recent data have linked parahippocampal-locus coeruleus connectivity to memory in healthy individuals (Jacobs et al., 2015). The results obtained in the fMRI study by Yebra et al. (2017, under revision) supported the action-induced memory enhancement associated to an increased LC activity coupled with the parahippocampal

gyrus (PHG). Also, pupilometry data, that associates pupil diameter and neural activity in the LC (Joshi, Li, Kalwani, & Gold, 2016), linked the memory enhancement with LC activation. Thus, both fMRI and pupilometry indicated an underlying noradrenergic mechanism. NA is behind the memory enhacement for emotionally adverse relative to neutral events (LaBar & Cabeza, 2006; Strange & Dolan, 2004; Tully & Bolshakov, 2010). Based on the Yerkes-Dodson law (Yerkes & Dodson, 1908), that establish an inverted-U shaped for the relationship between arousal and cognitive performance, Yebra et al., (2017, submitted) performed a last experiment with emotionally negative and neutral stimuli. It was hypothesized that if during encoding, two features of the stimuli (emotionality and Go cue) that increase NA release happen at the same time, the encoding performance would be predictable due to the influence of the NA. The results indicated that the action-induced episodic memory enhancement was modulated by emotion. All results together provided evidence that the memory enhancement associated to movement (Go-press button) during encoding was associated with increased LC activity, and its interaction to medial temporal structures through a noradrenergic (NA) mechanism. Nevertheless, pharmacological evidence is needed in order to ensure the involvement of NA in the modulation of the episodic memory driven by movement. Propranolol is a non-selective β-adrenergic antagonist. At therapeutic doses, propranolol slightly decreases heart rate (approx. 15%) and the supraventricular conduction of cardiac output (15 to 20%) (Johnson, Roberts, Sobieszek, & Straughan, 1969). Cardiac work, oxygen consumption and secretion of renin (an enzyme that helps to regulate the body's water balance and blood pressure level) are also decreased (Johnson et al., 1969). Propranolol is lipid soluble and also has sodium channel blocking effects. Propranolol crosses easily the blood–brain barrier with effects in the central nervous system, besides its peripheral activity (Steenen et al., 2016).

Propranolol is virtually completely absorbed after oral administration from the gastrointestinal tract (Paterson, Conolly, Dollery, Hayes, & Cooper, 1970). However, after high first pass metabolism and hepatic tissue binding, the total bioavailability is only approx. 30%, and varies greatly between individuals (take into consideration when used in pilot studies with healthy population) (Frishman, 1979; Goodman, 1996). Maximum peak plasma concentrations of propranolol are seen at approximately 90 minutes after oral administration (Lowenthal, Briggs, Gibson, Nelson, & Cirksena, 1974; Parsons, Kaye, Raymond, Trounce, & Turner, 1976; Paterson et al., 1970; Shand & Rangno, 1972).

Administration of food does not significantly change the time to peak levels in healthy individuals (Melander, Danielson, Scherstén, & Wåhlin, 1977).

About 90 to 95 % of the drug is bound to plasma proteins. The volume of distribution (Vd) is 3.9 L/kg, (approximately 200 L in an adult) (Paterson et al., 1970).The plasma half-life ($t_{1/2}$) is 3 to 6 hours. The total body clearance is 800 mL/minute/1.73 m^2. Propranolol is extensively metabolized by the liver, being completely eliminated after oral administration in 48 hours. This hepatic metabolism can be saturated, which would increase the bioavailability when overdoses (Paterson et al., 1970).

4.2. Hypothesis

Taking an action, produces activation of the LC and NA release; if the action-induced memory enhancement is related to the connections between the LC and the parahippocampal gyrus, and modulated by the NA system, then, should be block by the administration of a non-selective central β-adrenergic antagonist.

Our hypothesis was that β-adrenergic blockade would modulate the Go-induced memory enhancement at encoding. For this reason, it was important that the propranolol had washed out before the recognition test. However the prior studies, presented in Yebra et al., (2017, submitted), involved only one hour delay between study and test. We therefore were required to perform pilot studies of the psychological task prior to performing the psychopharmacological study with the 24 hour interval between study and test. The new design of this experiment involves changing the stimulus type, from black and white objects to color pictures taken from the International Affecting Picture System (IAPS) database. Only neutral items from this database were taken. To ensure a correct percentage of correct recognition performance after 24 hour delay we also reduced the number of stimuli from 91 in prior studies by Yebra et al., (2017, submitted) to 68 in the current study. After the first 17 subjects were piloted, we realized that a number of the neutral IAPS stimuli belong to the same semantic category and that this was influencing recognition and false alarms rates. These stimuli were replaced with other stimuli and the pilot continued for a further 8 subjects.

4.3. Methods and materials

In this section, prior to explaining in detail the procedure of the administration of propranolol before the performance of a GoNoGo task, the participants and the stimulus material for the encoding and memory session will be described. In order to ensure maximum safety of the participants, different measures of the blood pressure (BP), as well as an electrocardiogram (ECG) were performed, and will be described as well in this methods and material section.

4.3.1. Participants

Participants were recruited from the Hospital Nacional de Parapléjicos, Toledo. A total of 32 psychiatrically and neurologically healthy volunteers (16 females and 16 males) (Table 3.1.) from the Nursing and Physiotherapy schools of the Universidad de Castilla-La Mancha, with an age range 18-30 years (both ages included) (mean: 21,25, SD: 1,88), normal or corrected to normal vision and hearing participated in the study. All participants were free of neurological or psychiatric medication, or any other medications contraindicated with the use of propranolol (see Exclusion Criteria, section 4.3.2.). Participants were asked to join the study, and gave written informed consent; they all received 40 euros as expenses of transportation at the end of the study (day 2). The Ethical committee of the Hospital Nacional de Parapléjicos approved the study and all participants were informed of the procedures to be carried out before they provided written informed consent. Participants were randomly assigned to one of the two conditions (Placebo or Propranolol) in a double-blind procedure. Randomization was carried out by envelopes balanced for gender and previously randomized. Both groups showed similar age [Placebo group (mean: 21,l2; s.e.m.: 0,45) and Propranolol group (mean: 21,37; s.e.m.: 0,50)], and educational level [years of schooling: placebo group (mean: 14, 56; s.e.m.: 0, 22) and propranolol group (mean: 15,00; s.e.m.: 0, 20)] (see Table 4.1.).

		Placebo	Propranolol	Statistics (t)	P value
Gender	Female	8	8		
	Male	8	8		
Age in years[a]	Mean	21,12	21,37	$t_{(30)}$=-0,37	p=0,71
	s.e.m.	0,45	0,50		
Years of schooling[a]	Mean	14,56	15,00	$t_{(30)}$=-1,48	p=0,16
	s.e.m.	0,22	0,20		
Performance on the task[a]	Correct pressed Go (mean %)	97,42	86,39	$t_{(30)}$=1,67	p=0,10
	s.e.m.	0,92	6,50		
	Correct non-pressed NoGo (mean %)	94,85	90,44	$t_{(30)}$=0,74	p=0,47
	s.e.m.	0,91	5,90		
Blood pressure[a]	1st measure (mmHg) (Baseline) mean (s.e.m.)Systolic	131,81 (3,69)	124,56 (2,48)	$t_{(30)}$=1,62	p=0,114
	1st measure (mmHg) (Baseline) mean (s.e.m.) Diastolic	73,43 (1,98)	68,12 (1,90)	$t_{(30)}$=1,94	p=0,062
	2nd measure (mmHg) (Encoding) mean (s.e.m.) Systolic	127,68 (2,98)	112,81 (2,53)	$t_{(30)}$=3,79	p=0,001*
	2nd measure (mmHg) (Encoding) mean (s.e.m.) Diastolic	74,87 (2,22)	65,44 (1,80)	$t_{(30)}$=3,29	p=0,003*
	3rd measure (mmHg) (Recognition) mean (s.e.m.) Systolic	122,25 (4,57)	123,37 (3,52)	$t_{(30)}$=-0,2	p=0,85
	3rd measure (mmHg) (Recognition) mean (s.e.m.) Diastolic	67,81 (3,19)	70,75 (2,27)	$t_{(30)}$=-0,75	p=0,46
Heart Rate[a]	Baseline mean (s.e.m.)	74,37 (2,50)	65,06 (2,82)	$t_{(30)}$=2,47	p=0,020*
	Encoding mean (s.e.m.)	70,75 (2,57)	53,75 (2,05)	$t_{(30)}$=5,17	p=0,000*
	Recognition mean (s.e.m.)	65,60 (2,70)	65,81 (3,80)	$t_{(30)}$=-0,067	p=0,95

Table 4.1. Participant´s demographics and clinical details. Thirty two participants (sixteen per group) completed the study. Groups were balanced for gender prior to randomization. Placebo group and Propranolol group did not differ in any demographical variable (age or years of schooling). Both groups did not differ in systolic/diastolic BP at the baseline or at the recognition session, but at the time of the encoding task, 90 minutes after pill administration, there is a significant difference in systolic (p=0,001), diastolic (p=0,003) and heart rate (p=0,000) between propranolol and placebo group, evidencing the effectiveness of the pharmacological manipulation. [a] Independent (unpaired) samples t-test.

4.3.1.1. Exclusion criteria

Exclusion criteria
- Subjects under (<) 18 years or over (>) 30 years old.
- Asthma.
- Diabetes
- Pregnancy and lactation
- Hyperthyroidism
- Hypothyroidism
- Pronounced bradycardia
- Manifest heart failure
- Second or third degree heart block
- Severe sinus node disease
- Severe obstructive pulmonary disease
- Hypersensitivity to Hymenoptera toxins (increased risk of anaphylaxis)
- Intake in the last week of drugs that affect the central nervous system (epileptics, antidepressants, antihistamines, anxiolytics, etc.)
- Presence of chronic neuropsychiatric diseases

Table 4.2. Exclusion criteria.

4.3.2. Procedure

Once the participants arrived at the hospital, a baseline electrocardiogram (ECG) and blood pressure (BP) measurements were performed to ensure no contraindication to beta-blockade. This task was carried out in the Internal Medicine Service of the Hospital Nacional de Parapléjicos and was organized by the head of that service. Participants took the pill (propranolol 40mg or placebo) administered by the experimenter in charge of the study at the hospital in a double-blind condition. In view of the kinetics of propranolol's peak plasma concentration (1–2 h), the "Go-NoGo" task started 90 min after drug administration. The surprise memory recognition task of the pictures was performed the

next day (24 hours after), but previously blood pressure was taken again, once the participants arrived at the hospital (see Figure 4.1.; see Table 4.1.).

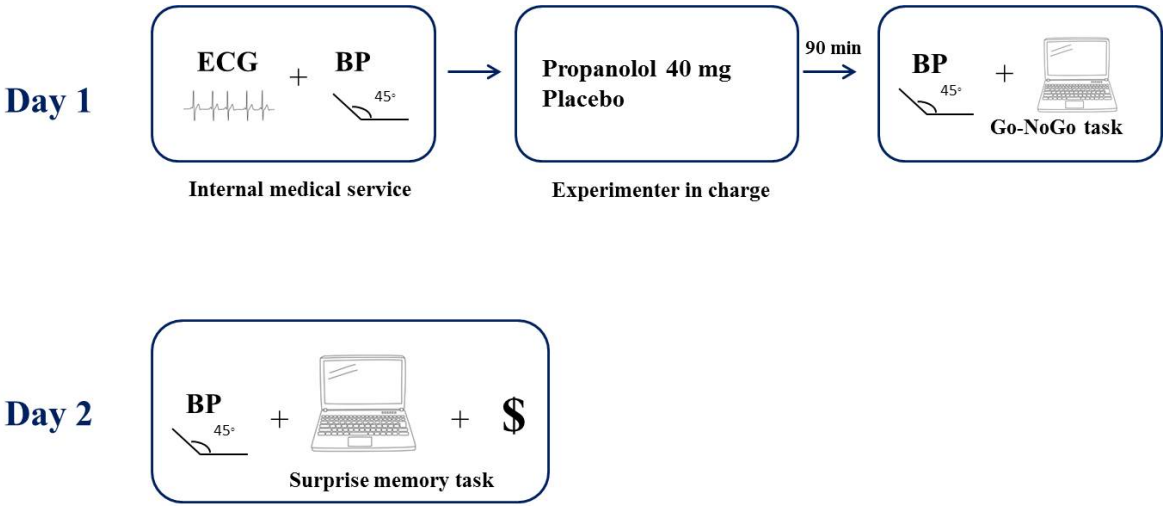

Figure 4.1. Study design. During day 1, once participants arrived at the hospital, ECG (electrocardiogram) and BP (blood pressure) were taken by the internal medical service of the hospital. Once the measurements were taken, the experimenter in charge, in a double-bling design study, gave the participants propranolol 40 mg or placebo. After 90 min, participants performed the computer task. On day 2, BP was taken again, and then a surprise memory task was displayed in the computer. Once participants finished the memory task, they received 40 euros in expenses of transportation and left the hospital. Figure: To take BP, participants were lying on a stretcher with their upper body reclined at a 45-degree tilt.

4.3.3. Experimental Phases

4.3.3.1. "Go-NoGo" task

For the visual stimulus encoding a total of 68 gray-scale photographs of objects (from the International Affective Picture System (IAPS) database) were presented in randomized order. Image presentation time was 250 ms, with a variable ISI (interstimulus interval) from 2.3 to 3.3 seconds. Participants were instructed to press a button ("Go" trials) when the images were presented with a particular color frame (yellow or blue). The condition of the "Go" or "NoGo" was determined by the color of the frame, and this condition was balanced across participants. Both colors of the frame (Go vs NoGo condition) had the same probability of appearance (*i.e.:* both at 50% probability). Participants were instructed to look at the center of the computer screen. Before the task began, the instructions would be displayed at the computer screen, and participants had as much time as they needed to learn the instructions. After, the stimuli presentation would begin. All images would be displayed

with 22-23 degrees of visual angle at a viewing distance of approx. 30-50 cm, on a 16-inch computer screen.

4.3.3.2. Recognition task

Participants returned the following day (24 hours later) to perform a surprise recognition test. A total of 136 images (the 68 that were presented at the time of encoding and 68 new "foils") were presented in randomized order with no frames on a black background. The ISI was from 2.8 to 3.3 seconds. Participants were not aware of this test, since they were told at the time of the instructions that they would repeat the same task as day 1 but without the influence of the drug. The task was carried out in the same room and with the same computer as in the previous day. Participants were required to indicate whether they remember (R), were familiar with (K) or did not remember (forgotten, F) the image from the encoding phase (see Figure 4.2.).

As exclusion criteria, only participants performing over 50% of correct button press for the Go and 50% of correct not- button press for the NoGo condition were included in the study (for exact number of participants, see below).

Figure 4.2. Instructions for the surprise recognition task. The keys corresponding to the Remember condition ("La recuerdo"), Familiarity condition ("Me suena) and the Forgotten condition ("No la recuerdo") instructions were randomized.

4.3.4. Results

4.3.4.1. Participants

A total of 32 participants completed the study (Propranolol group, N=16; Placebo group, N=16). One of the participants from the placebo group (placebo final N=15), and two participants from the propranolol group (propranolol final N=14) were discarded from further analysis because of a low performance (≤ 50%) of correct button press for the Go condition.

4.3.4.2. Propranolol versus placebo

Figure 4.3. shows that the administration of the treatment [propranolol (blue) or placebo (orange)] was effective. The systolic blood pressure (SysBP) (mmHg) at the time of encoding (90 min after the pill intake) of the images is significantly different between both groups [$t_{(27)}$=3,908, *p=0,001] (see Figure 4.3.). In the propranolol group, the difference between systolic BP at the time of encoding is significantly different when compared to baseline [$t_{(13)}$= 5,07; p= 0,000] and when compared to the systolic BP at the time of recognition [$t_{(13)}$= -3,28; p= 0,006]. There was no difference systolic BP at baseline vs at recognition test [$t_{(13)}$= 0,26; p=0,79]. In the placebo group, there was no difference in SysBPs among the 3 measurements.

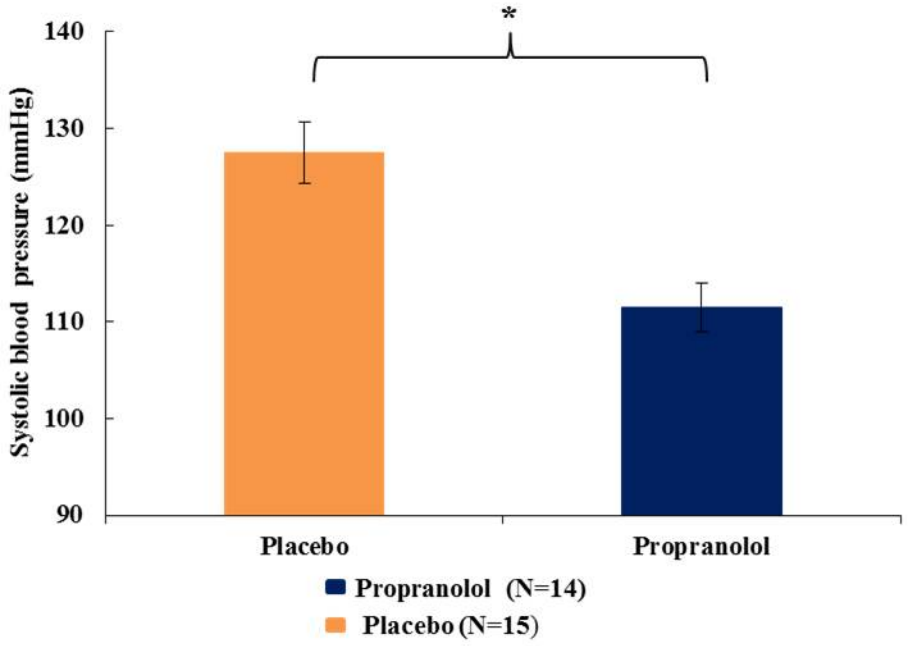

Figure 4.3. Systolic blood pressure (BP) (mmHg) at the time of the encoding. After 90 minutes of the pill intake, there is a significance difference in the systolic BP (mmHg) (*p< 0,001) between the placebo group (orange) and the propranolol group (blue) when performing the encoding task.

4.3.4.3. Performance at the encoding task

There is no significant main effect or interaction of treatment in a rmANOVA (Groups x condition), $F_{(1,27)}$=0,19, p=0,67 (see table 4.3.); (see Figure 4.4.).

Performance at encoding (%)		
	Placebo	**Propranolol**
Correct press Go mean (s.e.m.)	97,84 (0,88)	97,68 (1,03)
Correct non press NoGo Mean (s.e.m.)	95,09 (0,84)	95,79 (1,18)

Table 4.3. Performance at encoding.

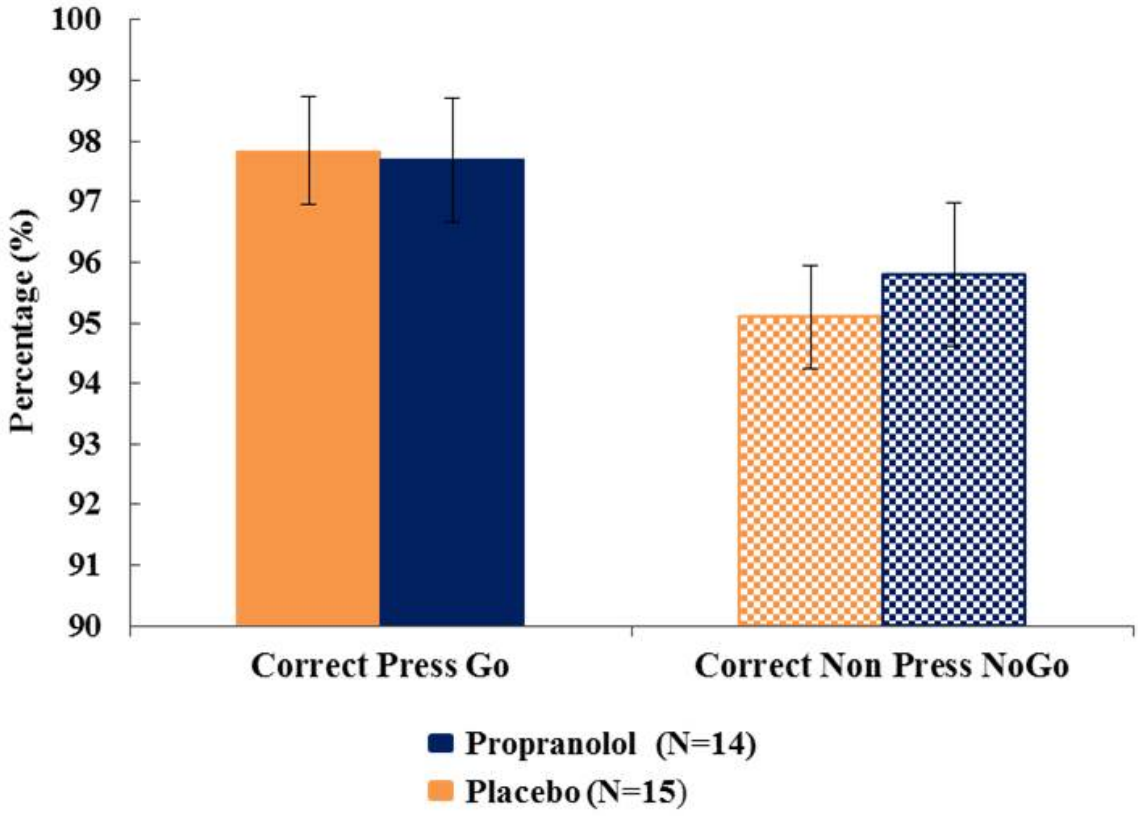

Figure 4.4. Performance at encoding. Percentage of correct press Go and correct Non-press NoGo. There is no significant effect of treatment in the performance of the encoding task (p>0,05). Error bars pertain to the standard error of the mean (s.e.m.)

There is no significant difference between groups in the reaction time (RT) at the encoding, $t_{(27)}$=1,25, p=0,22 (see table 4.4., Figure 4.5.).

Reaction time (ms)		
	Placebo	**Propranolol**
Mean (s.e.m.)	339,16 (36,26)	321,80 (38,86)

Table 4.4. Reaction time at encoding.

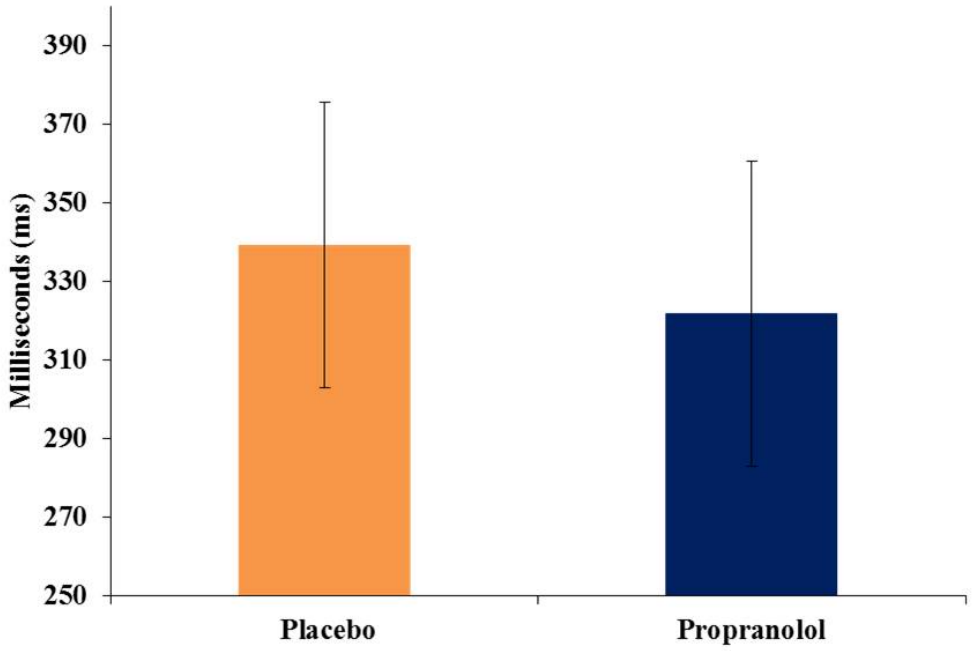

Figure 4.5. Reaction time at encoding. There is no significant difference between placebo and propranolol groups.

4.3.4.4. Recognition main effect of memory does not differ between groups

In an rmANOVA [(Go remembered and NoGo remembered) x (placebo vs. propranolol)] there was no group main effect at the recognition memory test [$F_{(1,27)}$= 0,12; p= 0,74] (see table 4.5.); (see Figure 4.6)

Performance at Recognition		
	Placebo	**Propranolol**
% of Go remembered mean (s.e.m.)	9,77% (3,10)	8,75% (5,01)
% of NoGo remembered mean (s.e.m.)	9,78% (3,12)	7,21% (4,04)

Table 4.5. Performance at Recognition task. Percentage of correct remembered minus false alarms, for the Go and NoGo stimuli.

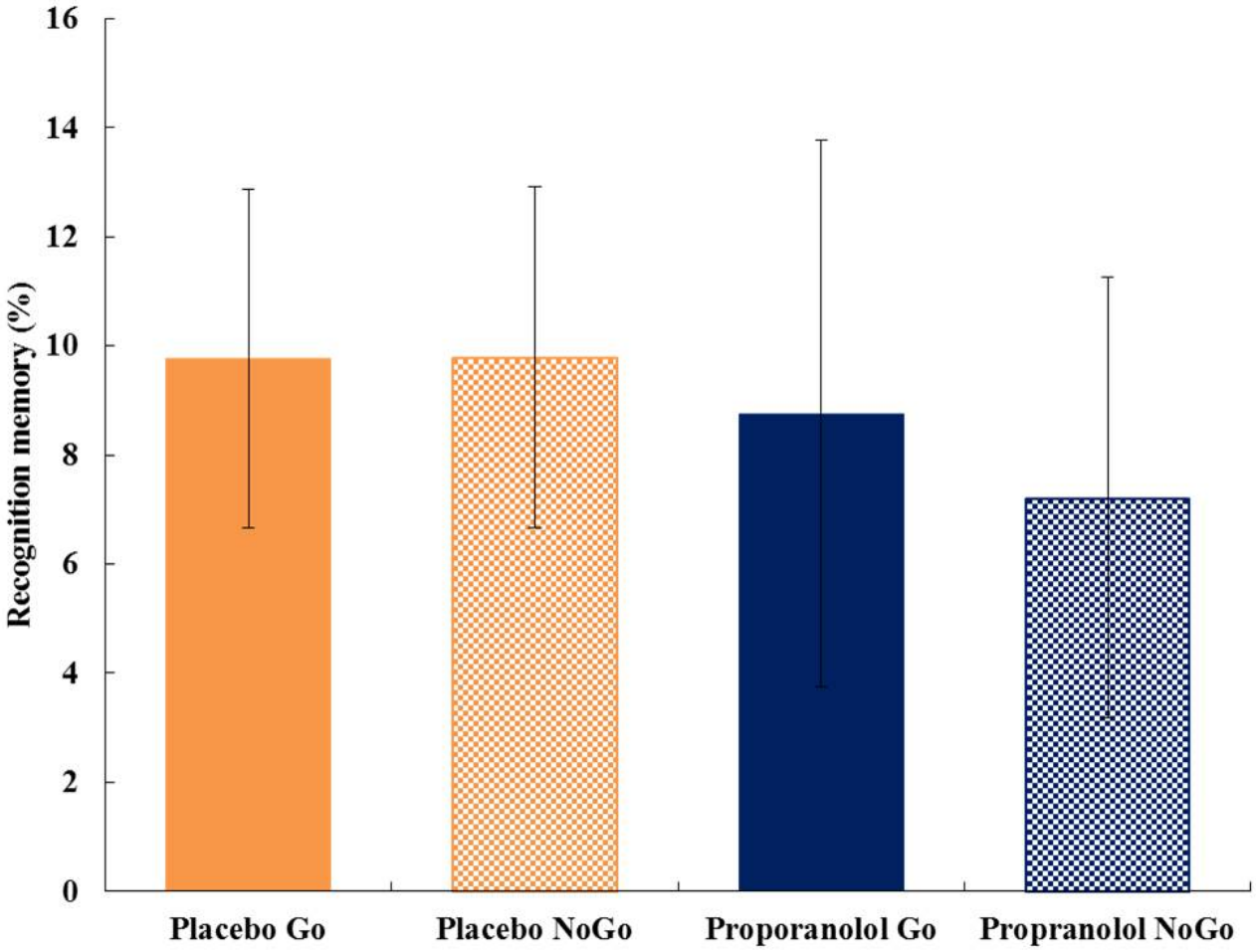

Figure 4.6. Recognition memory test. Recognition memory test (%) (correct hits minus false alarms) for the Go and NoGo condition. There is no significance difference between propranolol-placebo groups (p>0,05) in any of the recognition measures. Error bars pertain to s.e.m.

There is also, no significant difference between groups for the familiarity (K) Go-NoGo memory performance (p>0,05).

4.3.4.5. Significant linear correlation between Systolic BP and Go minus NoGo difference in recognition memory

BP was measured at three different time points. At the baseline measurement, there is no significant difference between both groups (p>0,05). At the time of encoding, 90 minutes after the pill intake, there is a significance difference in systolic BP between both groups (see Table 4.1., Figure 4.3.) (p< 0,001), which indicates that the pharmacological treatment had exerted a hypotensive effect.

However, possible differences in systolic BP, a measure of sympathetic tone, may contribute to the memory effects. Indeed, there is a linear correlation between systolic BP and memory score ("Go minus NoGo" correct remember) (r =0, 38; p =0,042) collapsing across therapeutic groups (see Figure 4.7.). Therefore, the specific memory impairment for the "Go" condition can be accounted for by the BP, but without specific effect of the treatment condition.

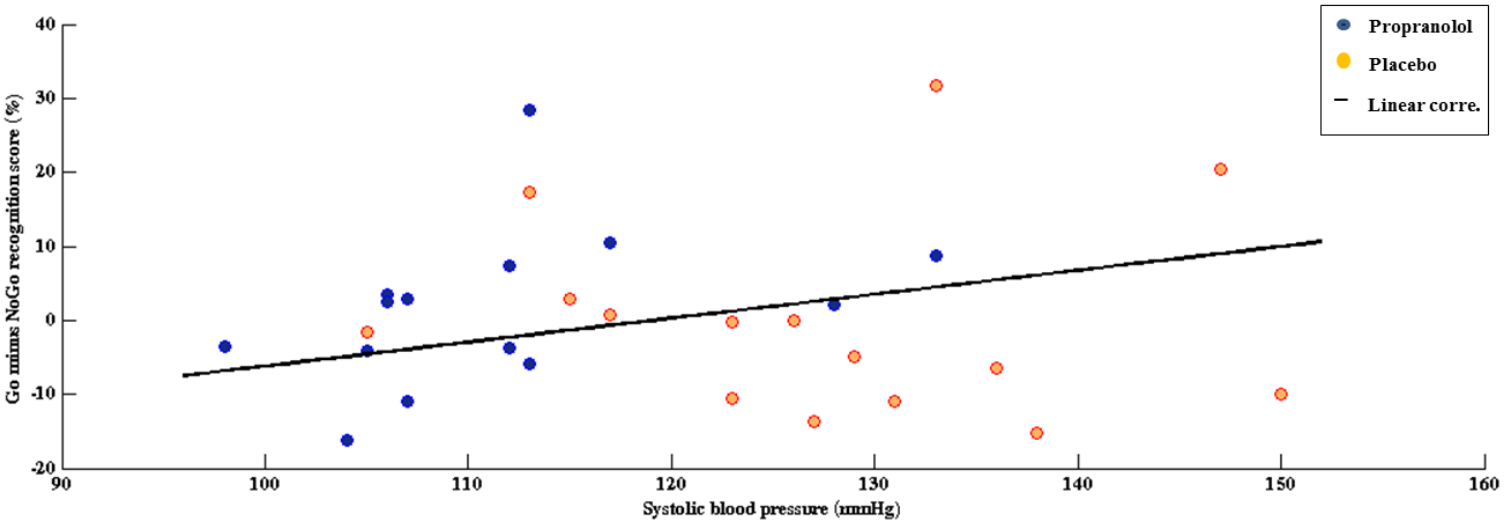

Figure 4.7. Significant linear correlation between the "Go minus NoGo" recognition score and the systolic BP. The lower is the systolic BP, the lower is the "Go" remember percentage. Propranolol group (Blue); Placebo group (orange).

Moreover, the linear correlation between the Go minus NoGo recognition score and the systolic BP at the time of the encoding is significant for the placebo group ($r_{placebo}$= 0,60, p=0,018). While, in the propranolol group, this relationship is not significant

($r_{propranolol}$=0,40, p=0,165) (see Figure 4.8.). Even though the placebo group did not show the expected Go-NoGo effect on memory, there is a significant relationship between the arousal experienced by the participants (higher arousal is indicated by higher systolic BP) and the memory performance; higher arousal is related with better memory for the Go stimuli. In the propranolol group, this relationship between systolic BP at the time of encoding and memory is blocked by the administration of the drug.

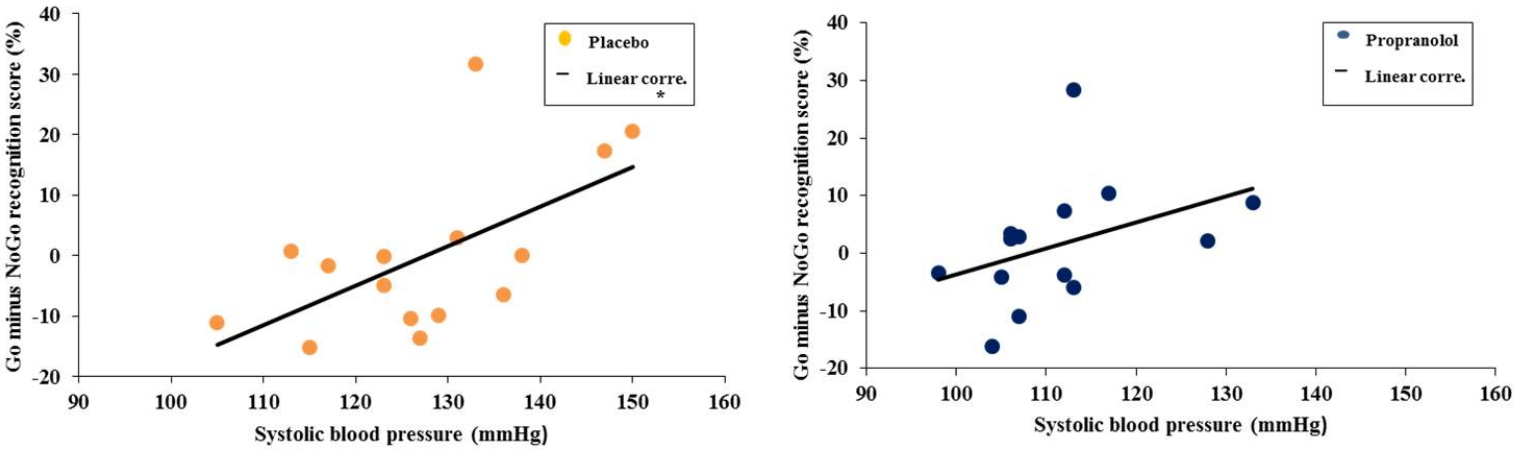

Figure 4.8. Placebo group (orange) Significant linear correlation between the "Go minus NoGo" recognition score and the systolic BP; Propranolol group (blue) non-significant linear correlation between the "Go minus NoGo" recognition score and the systolic BP at the time of encoding .The greater is the systolic BP, the greater is the "Go" remember percentage in the placebo group (*p<0,05).

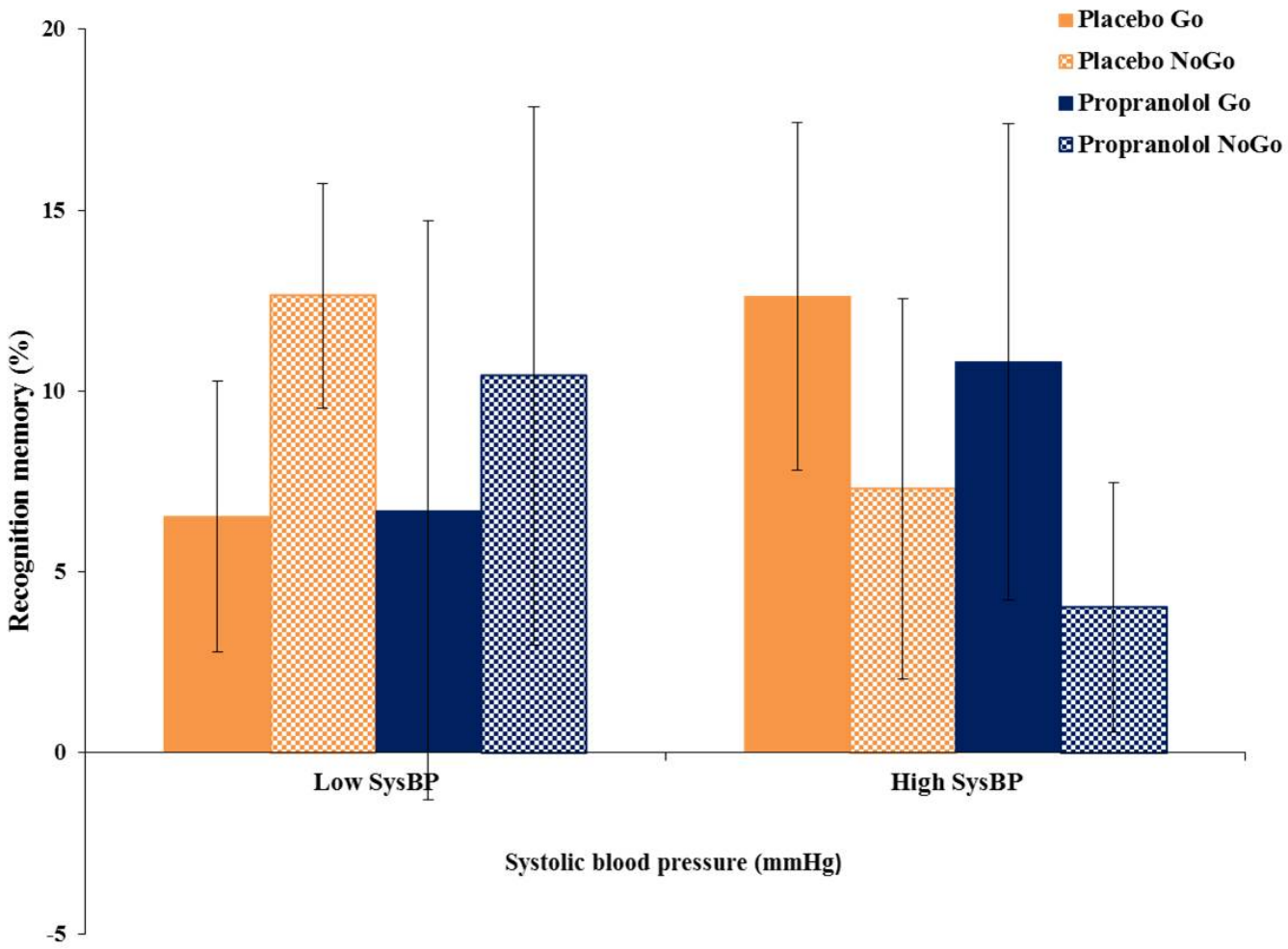

Figure 4.9. Median split of the systolic blood pressure for each group (placebo, orange; propranolol, blue). Median split to separate each group into high and low systolic blood pressure, and the recognition memory (%) for the Go and NoGo stimuli. Higher is the SysBP, higher recognition memory for Go stimuli in both groups (placebo and propranolol). Abbreviations: SysBP, systolic blood pressure.

In order to demonstrate the relationship between higher BP and higher recognition memory (%) for the Go stimuli a median split (to form high and low systolic BP groups, for compare the recognition memory for the Go and NoGo stimuli) was done for each group (see Figure 4.9.). The higher is the SysBP, higher is the recognition memory for the Go stimuli. While the lower is the SysBP, the Go-NoGo effect disappears, and the memory for the Go stimuli is lower than for the NoGo in both groups (placebo and propranolol).

4.4. Discussion

In previous studies (Yebra et al, 2017, submitted) (see also chapter 2, section 2.7.) a consistent boost of memory for the "Go" stimuli has been shown, compared to the "NoGo" condition. This memory enhancement was linked to the action of a button press during the encoding session, and related to an enhacement of NA from the LC. As highlighted before, LC is the major source of NA to the majority of brain regions, including MTL. Besides the facilitation role of the NA in the interaction of different brain structures in charge of different cognitive domains; LC and the related NA released take part in the encoding of relevant events (Cahill, Prins, Weber & McGaugh, 1994). LC is also known to have a key-role in memory consolidation and retrieval (Sara, 2009). Using f-MRI measurements, Yebra et al., (2017, submitted) were able to show a functional relationship between the LC and the parahippocampal gyrus (PHG) during successful encoding of the Go stimuli compared to the NoGo stimuli. PHG is a relevant brain area for episodic memory, related to successful encoding and retrieval (Eichenbaum & Lipton, 2008). This functional connectivity is in line with another study that has related LC and MTL functional association during memory processes for neutral stimuli in healthy individuals (Jacobs et al., 2015). Nevertheless, in order to ensure that the "Go" memory enhacement was related to this functional relationship of the LC and PHG trough the NA released, pupilometry measurements were taken. Pupilometry dilation has been considered as an indirect measure of LC activation (Alnaes et al., 2014; Murphy, O'connell, O'sullivan, Robertson, & Balsters, 2014). With these two independent measures, the relationship between LC-PHG pathway activation by movement and the subsequent memory enhacement, modulated by NA, was set up.

The ultimate measure to probe this memory enhacement pathway was through pharmacological challenge. So, the hypothesis of the memory enhacement for the "Go" stimuli blockade by administration of a β-adrenoceptor antagonist was tested.

The results for the placebo group are not in line with the previous results presented in Yebra et al., (2017, submitted) and that lead to the generation of the tested hypothesis. The placebo group did not show the enhacement effect for the "Go" stimuli due to movement. This in despite a pilot group of subjects with no pharmacological challenge showing a trending towards better Go than NoGo memory on the same version of this task.

Before this study, another experiment using the "Go NoGo" task with neutral or emotional stimuli (Yebra et al., 2017) shown that the memory for the "NoGo" emotional stimuli was higher than for the "Go" emotional stimuli; while for the neutral stimuli results were in the opposite line (better memory for "Go" neutral stimuli than for "NoGo" neutral stimuli). This results concord with inverted-U relationship between arousal (noradrenergic activity) and cognitive performance describe by the Yerkes-Dodson law (Yerkes & Dodson, 1908). Low levels of NA transmission lead to memory (cognitive) impairment. Likewise, very high levels of NA also produce memory impairment; while optimal (medium) NA levels produce memory enhacement (see Figure 4.10.).

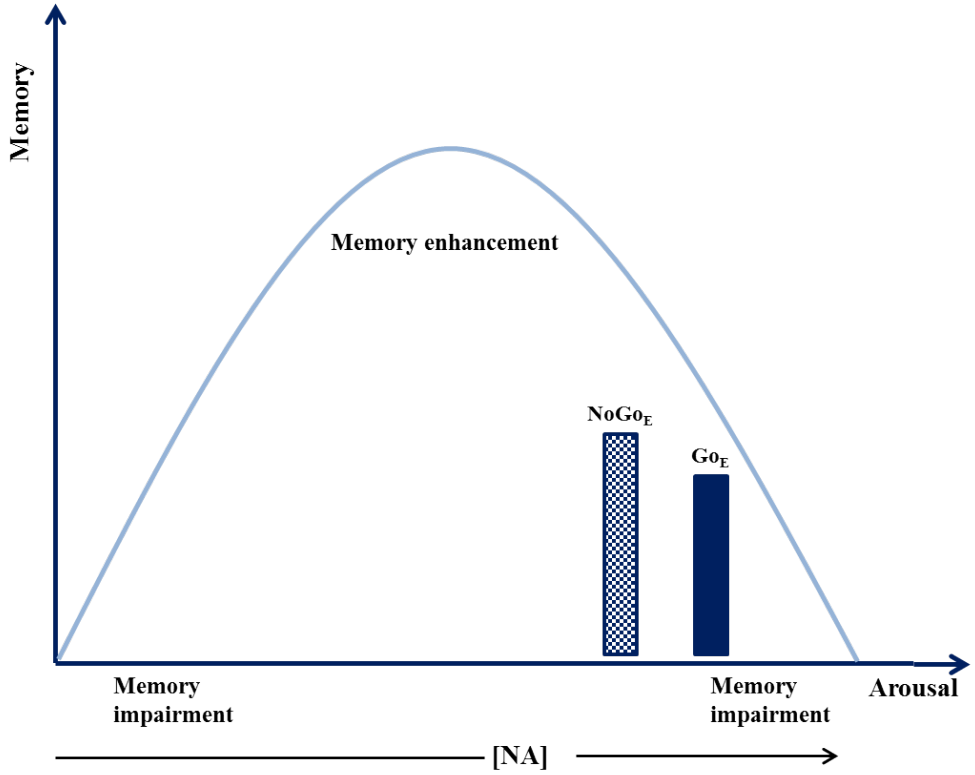

Figure 4.10. Memory enhacement is modulated by emotion. The Yerkes and Dodson law (Yerkes & Dodson, 1908) establish the modulation of memory via NA. The ends of the curve indicate very low or very high NA transmission, which leads to a memory impairment. Medium levels of NA (optimal levels) transmission produce a memory enhacement. Yebra et al. (2017) conducted an experiment with emotional and neutral stimuli presented while performing a "GoNoGo" task. "Go" encoding produces higher released on NA than "NoGo" encoding, which modulates memory in the recognition task. But if the NA released by the "Go" movement is added to the released produce by the encoding of an emotional stimulus, a high amount of NA is released, turning into memory impairment. This addition does not occur in the "NoGo" emotional encoding, which results in better memory for the stimuli. The effect is described as an inverted-U shaped, modulated by

NA levels. Abbreviations: $NoGo_E$ (NoGo emotional); Go_E (Go emotional); [NA] (nor-adrenaline concentration).

If we translate this Yerkes and Dobson law to the study presented in this thesis, participants who received placebo should show increased memory for the "Go" images compared to the "NoGo" images, while for the propranolol group, should not be difference in the memory performance between both conditions, due to the effect of the β-blocker in the release of NA during encoding (see Figure 4.11.). Nevertheless, the results presented showed equal memory performance for the placebo conditions [$t_{(14)}$=-0,005, p=0,99]; while in the propranolol group, the "NoGo" memory has a numerically greater impairment than the memory for the "Go", being that the expectancies were exactly the opposite [$t_{(13)}$=0,54, p=0,60] (see Figure 4.11.) .

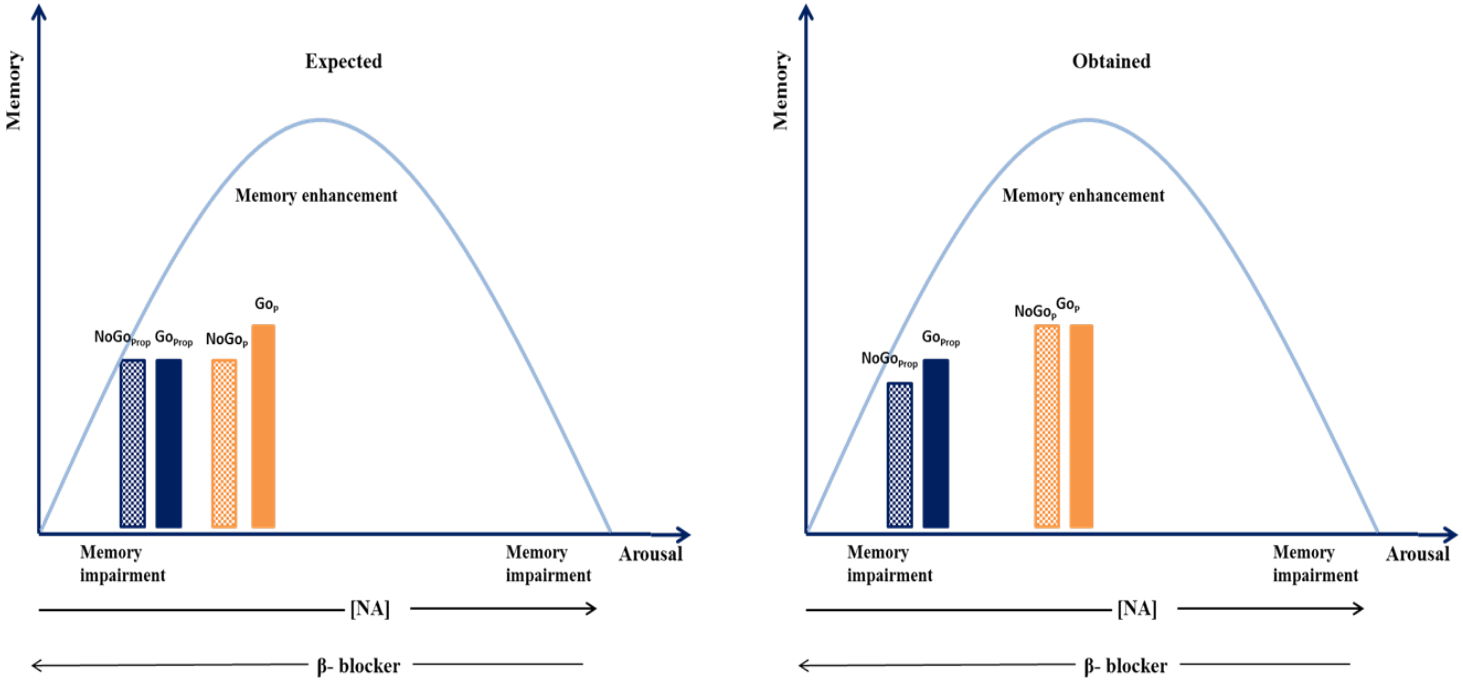

Figure 4.11. (a,b). Memory performance (a) expected and (b) obtained. According to the Yerkes and Dobson law, we should have expected better memory for the Go vs NoGo stimuli in the placebo group; but an impairment in memory for the "Go" condition in the propranolol group (part a of the figure). The results obtained shown equal memory for the placebo group, but memory impairment for the "NoGo" condition vs. the "Go" images (part b of the figure). Abbreviations: $NoGo_P$ (NoGo placebo); Go_P (Go placebo); $NoGo_{Prop}$ (NoGo propranolol); Go_P (Go propranolol).

The fact that healthy subjects with low blood pressures did not participate, made the sample less diverse and representative. This selection bias may be affecting the propranolol group and lessen the effect of the drug on memory performance. While a higher release of NA in the placebo group, may be the underlying reason for the equalization of memory outcomes in both conditions. A possible solution should be to increase the sample as well as the dose of propranolol to correct the bias.

Nevertheless, when analyzing the linear relationship between arousal and memory for both groups separately, the placebo group shown that the higher is the arousal experienced by the participant, the greater is the memory for the Go stimuli, while in the propranolol group this relationship was not present. This experiment has shown evidence of the relationship between action-induced memory and arousal, and that the administration of a β-adrenoceptor antagonist has been able to block this effect of arousal on memory. Nevertheless, in order to avoid some bias and deepen in the knowledge of the relationship between motor and memory system, further studies are needed, with greater sample size.

This first pharmacological attempt of modulating the action-induced memory performance would make closer the possibility of understand the relationship of two different systems in the brain, with the subsequent benefits in the quality of life of many people. Understanding how we are able to enhance memory while making a movement would benefit not only current concepts regarding teaching, but also could benefit different treatment approaches in dementias.

Chapter 5

General discussion

5.1. General discussion

In this thesis, I demonstrate that we can pharmacologically manipulate different memory processes in humans. During the last decades, part of the research in memory has been centred in the viability of modifying memories, enhancing or impairing, in an effective, fast and lasting way. For the sake of scientific completeness the possibility of replication and validation of the achieved findings is mandatory; even more when dealing with humans and with the possibility of improving someone´s daily life.

Pharmacological manipulation is among one of the last frontiers to cross when studying the possibility of a novel treatment for memory. Generally, the less invasive the modification, the less is the risk for the potential patient. Nevertheless, when dealing with neurological and psychiatric disorders, in most cases it is the most effective treatment. Likewise, pharmacological studies are needed in order to confirm a hypothesis, elucidate a neurobiological mechanism, or to continue with the study of novel discoveries.

In this thesis, two replications of two studies have been presented, along with an advance of the underlying mechanism. On one hand, pharmacological manipulation of memory has been tested in order to diminish it; while, on the other hand, a drug has been used to test the reliability of a new pathway to increase memory in humans.

Diminishing disturbing memories

The possibility of offering a different or coadjutant treatment to those already available for disturbing memories opens a window of opportunity for the recovery and reinsertions of patients with psychiatric disorders derived from poorly adaptive or traumatic memories. The disorder that has obtained the most visibility for this type of therapeutic targets has been post-traumatic stress disorder (PTSD). However, the potential benefit in other disorders related to episodic memory such as addiction or phobias, is on the horizon.

One of the principal contributions of this thesis has been to broaden the knowledge about the mechanism underlying the modification of disturbed or maladaptive memories that are at the core of several psychiatric disorders through the investigation of innovative methods. We have focused our attention on PTSD; however, the possibility of transferring these findings to other psychiatric disorders, thus reducing the suffering at a personal, family and social level of many people, makes it necessary to continue investigating the mechanisms

of memory modification described here. The realization of studies with clinical populations should be considered as the next step to help answer all the questions that can be raised now, or in the future.

Augmenting memory

The second study presented in this thesis, measures the influence of the motor system on the episodic memory. Prior to this pharmacological study, a set of experiments had been performed with a Go-NoGo task and its influence in a subsequent recognition task of images. Those experiments highlighted the key-role of the NA system in a subsequent enhancement of memory engaged by taking an action at the time of encoding. Nevertheless, the results obtained opened a series of questions related to the design of the tested paradigm and the drug used to influence the neural mechanism involved in this enhacement of memory.

After summarizing and discussing the findings achieved in the two investigations we have carried out, we will present open questions that can be analysed and answered in future studies.

5.2. Summary of findings

The purpose of this thesis was to amplify the knowledge about the mechanism of how emotion influences memory and how to diminish this influence, contributing to the development of new treatments for psychiatric disorders. Likewise, we have deepened the knowledge regarding the relative mechanism to neural bases that contribute to the memory enhancement following movement.

The first chapter of this thesis describes the classical theories on memory, and how new knowledge acquired recently has transformed and developed them. The second chapter focuses on the major neurotransmitters' systems in the brain and its relationship with memory and emotion, describing the most important human and animal studies when needed. The third chapter is centered in the reconsolidation hypothesis which postulates that upon reactivation, memories can become labile and susceptible to manipulation, requiring a new restabilization process in order to maintain them. We showed evidence of the reconsolidation process using general anesthesia on emotional episodic memories, and

how they can be diminished upon reactivation in a long lasting way, following the reconsolidation criteria.

The fourth chapter analyzed how taking an action enhances episodic memory, but inhibiting action does not impair it; i used a pharmacological manipulation to demonstrate the effect of the motor system on memory. The purpose of the study was to test the hypothesis of the involvement of the medial temporal structures in this enhacement of memory by the action of the NA released from the LC. It was not possible to show a direct correlation between the pharmacological manipulation and the blocking of the memory enhacement; nevertheless, a correlation between the arousal experienced by the subjects, translated in systolic blood pressures and the percentage of correct remembered stimuli was showed.

5.3. Challenging the classical view of memory

Since William Hamilton (1859), the division of the processes of memory formation has included four steps: encoding, consolidation, storage and retrieval. After the initial encoding, the labile and unstable information is set and ceases to be modifiable, in a process known as consolidation. Subsequently, memories are stored in different brain areas as time passes, and can be retrieved at will; but cannot be altered since they are considered immutable. The research presented in this thesis contributes to challenging this classical view of memory by adding new knowledge and evidence against the immutability of memories. After consolidation, a memory can be activated again by presenting a reminder cue, rendering the memory unstable again; susceptible to modification and in need of a restabilization process in order to be maintained.

The work in this thesis contributes to expand the current evidence on the theory of reconsolidation by presenting data showing that, in humans, it is possible to render labile an episodic memory again, and, critically to manipulate it with general anesthesia, reducing the targeted emotional memory traces. Upon reactivation and subsequent manipulation, the memory trace requires a restabilization process, in accordance to the reconsolidation theory.

The special case of emotional memory

When referring to emotional memory, one of the neural structures in charge is the amygdala, and more specifically, the basolateral nucleus of the amygdala (BLA). In addition to the specific role of the BLA in the encoding of emotional arousing material, other brain regions enter in the process, such as the hippocampus. The role of the hippocampus in emotional memories becomes determinant if a context is involved in memory, besides its role in the formation of episodic memory. As it was highlighted in chapter 2, the noradrenaline released from the Locus Coeruleus (LC) modulates the retrieval of emotional memory. Also, NA is thought to be involved in the efferent connection between the amygdala and the hippocampus that contributes to the consolidation of episodic memories.

Anxiety disorders are extremely common amid the general population (Kessler et al., 2005), and they are usually attached to an excessive fear of specific objects or situations (APA, 2000). But among all of them, the best example of a maladaptive emotional memory behind a mental disorder is PTSD.

Individuals, who have been exposed to an event that involved the threat of severe injury or death; or react with intense horror or fear to a specific situation, are vulnerable to developed PTSD (APA, 2000). Among the symptoms, there is the re-experience of the traumatic event across nightmares, intrusive thoughts, flashbacks, distress and excessive physiological arousal (hyper arousal, exaggerated startle, concentration, as well as sleep difficulties) in response to reminders of trauma (APA 2000; Shin & Liberzon, 2010).

Reconsolidation of emotional memories

Since the first demonstration of reconsolidation, emotional memories have been involved. The first attempt of reconsolidation impairment was directed at memories dependent of the amygdala in rats (Nader, Schafe, & Le Doux, 2000; Nader & Hardt, 2009).

Due to NA activity in the brain, the majority of the attempts and demonstrations of blocking reconsolidation in humans have been made using β-blockers; it is been shown that blocking noradrenaline in the amygdala or hippocampus can disrupt memories following reactivation (Dębiec & Ledoux, 2004; Debiec et al., 2002; Lonergan & Pitman, 2013;

Poundja, Sanche, Tremblay, & Brunet, 2012; Saladin et al., 2013; Schwabe et al., 2012). Nevertheless, since the attempts to replicate the findings with clinical populations failed, a different manipulation of the reactivated memories has been suggested (Muravieva & Alberini, 2010). The work presented in this thesis has added knowledge to the understanding of reconsolidation, and has suggested that the interaction between the amygdala and hippocampus is not only regulated by the noradrenergic system, but also by the GABA system.

5.3.1.. Proposal of a different mechanism when blocking reconsolidation

The process behind the amnesia induced by anesthesia remains unclear. The importance of understanding this process is fundamental since amnesia is one of the most important side effects of general anesthesia (Trapani et al., 2000). Classically, it has been supposed that the neural structure behind this amnesia-induced by anesthesia was the hippocampus. In chapter 1, the key role of the hippocampus and other medial temporal lobe structures on memory was presented. Nevertheless, the hippocampus cannot be working alone in the induction of amnesia, and it has been suggested that it works, among others, with the amygdala, and more particularly, with the basolateral nucleus of the amygdala (BLA) (Alkire et al., 2008, 2001; Alkire & Nathan, 2005; Tomaz et al., 1992).

There is plenty of evidence about the modulatory role of the BLA in the consolidation of emotional episodic memories in the hippocampus (McGaugh, 2004b). Findings with posttraining electrical stimulation showed that the amygdala is able to enhance or impair memory, depending on the features and parameters of the stimulation (Gold, Edwards, & McGaugh, 1975); indicating that the amygdala is not a mere place to impair memory, but a neural structure that modulates memory consolidation. This modulatory effect can be exerted because during the consolidation process, there is a time-window during which, memories remain in a labile state; before they are fixed and become invulnerable. Nevertheless the amygdala does not work alone but through its projections (afferent and efferent) to other brain regions: hippocampus, frontal cortex regions (particularly ventral- and dorsal PFC) and LC (Petrovich et al., 2001; Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000; Price, 2003; Rosene & Van Hoesen, 1977). Different neurocircuitry models have linked the amygdala, hippocampus and PFC to the persistence of the traumatic memories in PTSD (Rauch et al., 2000; Rauch, Shin, Whalen, & Pitman, 1998).

For example, several studies have indicated increased amygdala activation in PTSD patients compared to control groups in a script-driven imagery task (Shin et al., 1999, 2004). Supporting this role of the amygdala in PTSD, other studies have showed that amygdala activation correlates positively with PTSD symptom severity (Armony, Corbo, Clément, & Brunet, 2005; Etkin & Wager, 2007). With respect to the hippocampus, humans studies have revealed hippocampal abnormalities in structure (decreased size) and hypoactivation (Bremner et al., 2003; Etkin & Wager, 2007; Geuze, Vermetten, & Bremner, 2005; Nemeroff et al., 2009; Sakamoto et al., 2005); as well as, hypoactivation of the PFC, in traumatic script driven imagery (Bremner et al., 1999; Britton, Phan, Taylor, Fig, & Liberzon, 2005; Etkin & Wager, 2007; Lanius et al., 2001) (see Table 5.1.)

PTSD brain areas		
Brain area	**Functional finding**	**Authors**
Amygdala	Hyperresponsive	Armony, Corbo, Clément, & Brunet, 2005; Etkin, A., & Wager, T. D., 2007.
Hippocampus	Hypoactivation	Bremner et al., 2003; Geuze, Vermetten, & Bremner, 2005; Nemeroff et al., 2009; Sakamoto et al., 2005
PFC	Hypoactivation	Bremner et al, 1999; Britton et al, 2005; Etkin, A., & Wager, T. D. (2007); Lanius et al, 2001

Table 5.1. PTSD brain areas. Brain areas related to PTSD in humans. Abbreviations: PFC, prefrontal cortex.

In relation to neurotransmitters, GABA is the principal inhibitory neurotransmitter in the brain, controlling excitability in several brain regions, including the amygdala (Pitkänen et al., 2000). The GABAergic system it is also implicated in the pathogenesis of anxiety disorders, including PTSD. But even more, low levels of GABA in plasma after a traumatic experience are considered as a predictive factor of developing PTSD (Vaiva et al., 2004). Deficiencies in the GABAergic transmission in the BLA produces the BLA

hyperresponsiveness that is thought to contribute to the development of PTSD (for review see Prager, Bergstrom, Wynn, & Braga, 2016). Likewise, reductions in the GABA content in the hippocampus have been found in animal studies (Harvey, Oosthuizen, Brand, Wegener, & Stein, 2004); findings that have been showed also in PTSD patients (Bremner et al., 2000).

The BLA receives extensive NA innervation from the LC (Pitkänen et al., 2000), and the two neurotransmitter systems (NA and GABA) influence one another in BLA-related memory processes (Li, Nishijo, Ono, Ohtani, & Ohtani, 2002). It has been shown that administration of a $GABA_A$ antagonist enhances NA release in the amygdala, while a $GABA_A$ agonist administration diminishes NA release (Chen et al., 1999; Hatfield et al., 1999). Also, this interaction between both neurotransmitter systems (NA facilitates GABA inhibition transmission) has been shown in other brain regions, such as the hippocampus and neocortex (Bennett, Huguenard, & Prince, 1998; Kawaguchi & Shindou, 1998; Madison & Nicoll, 1986).

In a correctly functioning amygdala, this NA facilitation of GABA would be translated into either suppression of memory formation (by suppressing excitatory activity); or would help an optimal consolidation of a memory trace (by modulating the excitatory activity). Nevertheless, in a hyperresponsive amygdala (as happens in PTSD) the NA facilitation of GABA transmission is blocked, which leads to an enhacement of memory for events with almost no emotional significance, while emotionally charged memories may result in an “overconsolidation” (Braga, Aroniadou-Anderjaska, Manion, Hough, & He, 2004).

Reconsolidation is a process that renders memory labile again. The type of memory affected by the manipulation of reconsolidation is related to the brain area affected, and the dependency of the memory in that particular area would determine the manipulation effect on memory.

Previously, we had hypothesized that the administration of an anesthetic such as propofol would affect the reconsolidation of emotional memories. If the BLA is lesioned, then, the amnesic effect of propofol is not shown (Alkire et al., 2001). Moreover, a study has presented results that indicated that propofol, through the interaction between the BLA and the hippocampus, is able to impair memory consolidation (Ren et al., 2008).

The GA propofol could be exerting its effect on the reactivated memory through the BLA. The impairment of the memory trace could be due to the blockage of the efferent connections between the amygdala and the hippocampus. Likewise, the administration of a $GABA_A$ agonist after the re-activation of an emotional memory (BLA-related memory), may suppress the memory trace formation, due to the suppression of excitation. Both effects, the suppression of the efferent connections between both memory-related structures and the inhibition of the excitation due to the GABA enhacement, may result in a deterioration of the memory traces previously reactivated. Thus, emotional memory will be impaired.

5.4. Relationship between arousal and memory enhancement

In the study presented in chapter 4, a previously tested memory paradigm has been replicated and extended. The parameters of the Go-NoGo task used were set up before by Yebra et al., (2017, submitted). Nevertheless, this study went one step forward, by testing the hypothesis of the blockade via β-adrenoceptor antagonist administration of a novel neurological pathway that results in a boost of episodic memory by performing an action that is unrelated to the encoded material.

Nevertheless, it was not possible to ascertain with the pharmacological manipulation the action-induced episodic memory enhancement driven by the noradrenergic system. But, it was possible to support that action's inhibition did not impair the episodic memory. Previous studies showed an inhibition-induced forgetting (Chiu & Egner, 2014, 2015). Using a Go-NoGo task, Chiu & Egner, (2014) found that NoGo cues were less remembered than Go cues. The interpretation provided was that higher resources demand for response inhibition when the NoGo trials were presented resulted in a higher demand of the NoGo network; which resulted in unsuccessful memory encoding for those stimuli. They attributed the memory impairment to a temporary loss of attention due to a task-set updating (Dreisbach & Wenke, 2011). When replicating their results with fMRI (Chiu & Egner, 2015), the higher resources demand by NoGo-inhibition resulted in a negative correlation with the activity in the brain regions associated to memory encoding. They focused their attention on the ventrolateral prefrontal cortex (VLPFC), as the brain region

responsible for the encoding of the NoGo trials; finding a negative correlation between the activation of this brain area and the inhibitory demand of the NoGo cues.

Nevertheless, as said (chapter 4), there is new evidence of exactly the opposite effect on the memory of the stimuli presented in a Go-NoGo task. Across a series of experiments, Yebra et al., (2017, submitted) showed that the memory for the Go (taken an action) stimuli compared to the NoGo (action inhibition) stimuli, was enhanced. This memory enhacement for the Go condition was thought to involve the noradrenergic mechanism. The involvement of the LC (main source of NA in the brain) was demonstrated by fMRI and pupilometry recordings. To confirm the involvement of the noradrenergic system in the enhacement of memory by taking an action, a final experiment was performed, using emotional and neutral stimuli. The results were as predicted, the emotionally aversive stimuli, which recruit the NE system, modulated the mnemonic enhacement provided by taking an action, when compared to neutral stimuli of the Go condition. The conclusion of the study was that taking action boosts episodic memory encoding via a noradrenergic mechanism. Nevertheless, it is difficult to validate these results with behavioral data and indirect measures of NA alone.

In the pharmacological study presented previously (chapter 4), a non-selective β-blocker (propranolol) was used. The propranolol´s pharmacological features were described previously.

Once the propranolol reached its maximum plasma peak, the experimental group performed the Go-NoGo task. As the experiment was a double-blind design, all participants had to wait 90 minutes after the baseline blood pressure and ECG measures were taken. The results obtained were unable to confirm the main hypothesis of the involvement of the noradrenergic system on the action-induced memory enhancement. Nevertheless, the memory impairment due to action inhibition was not shown either. One interesting result that points toward the noradrenergic mechanism underlying memory enhancement by taking an action was the correlation shown between systolic BP and memory for Go-stimuli. This correlation indicated a possible relationship between arousal and memory. Thus the participants with higher levels of arousal showed better memory for the Go-stimuli compared to the NoGo stimuli. Higher levels of arousal, translated into higher

levels of systolic BP, may indicate a higher release of NA that could be linked to a greater activation of the LC.

The boost of episodic memory driven by a NA mechanism remains a strong hypothesis, but different experimental design issues should be solved in future studies.

NA and memory disorders

Dysfunction of LC is related to different memory disorders, being Alzheimer´s disease (AD) the most widespread worldwide.

As said before (chapter 2), the brainstem nucleus LC is the primary source of NA in the CNS (Berridge & Waterhouse, 2003). LC and its connections to the parahippocampal gyrus (PHG) and amygdala are associated with successful memory performance in encoding and recall in healthy older subjects (Jacobs et al., 2015), but especially when the encoded material is emotional rather than neutral (Sterpenich et al., 2006).

Contemporary theories about AD are linking a reduced functional connectivity between LC and parahippocampal gyrus (PHG) in prodromal (early stages, symptoms) AD patients (Jacobs et al., 2015). Early AD is characterized by LC degeneration which produces NA dysfunction (Grudzien et al., 2007; Missonnier, Ragot, Derouesné, Guez, & Renault, 1999). The LC degeneration and excitability deregulations seem to be related to an abnormal response to stressful stimuli, producing increase in amyloid beta (Aβ) deposition (Ross, McGonigle, & Van Bockstaele, 2015).

Nevertheless, it seems that early AD patients may be able to recruit an existing connection between LC and MTL to maintain memory function (Jacobs et al., 2015). This recruitment is what has been termed a cognitive reserve. A cognitive reserve, as said, is a term that defines the differences between people´s susceptibility to the deficits produced by AD (Stern, 2012). It is possible to differentiate two types: brain reserve, which mentions the differences in brain structure that may help facing the diseased by increasing the tolerance to it; and cognitive reserve, that refers to the lifelong experiences, education, occupation and leisure activities that may help maintaining memory function in prodromal AD (Stern, 2012). Cognitive reserve may be behind the adaptive functional reorganization observed in

AD patients with better memory performance, providing a compensatory mechanism to counteract early AD deficits (Jacobs et al., 2015).

The possibility of boosting episodic memory by taking an action via noradrenergic system may have important implications for potential clinical interventions in the early stages of AD; moreover, understanding the mechanism behind this memory enhacement could provide different pharmacological approaches than those available so far.

5.5. Limitations and outstanding questions

The two studies presented in this thesis have raised questions that need to be answered. As exposed, we have achieved unexpected results, or in future studies we have to deal with some limitations that may be affecting the results.

5.5.1. Reconsolidation of emotional episodic memories using general anesthesia

When talking about amnesia, it remains controversial whether the perceived memory loss is due to a malfunction in the consolidation process (a problem of storage) or to an impaired retrieval (Miller & Springer, 1974; Nader & Wang, 2006). The same diatribe is held when talking about reconsolidation; with the available data at the moment it is not possible to know if the impairment is due to storage or retrieval deficits, since both points of view are able to give an explanation about the recovery or not from amnesia (Miller & Springer, 1974; Nader & Wang, 2006). Nevertheless, some studies have suggested that the recovery from amnesia in new learning is due to storage impairment (Lattal & Abel, 2004; Squire, 2006) but the recovery of the reactivation-induced amnesia is due to retrieval impairment (McGaugh, 2004a; Rudy, Biedenkapp, Moineau, & Bolding, 2006).

One of the limitations of our study is the inability to demonstrate if our memory impairment lasts over time; or if the memory trace would be recovered. Therefore, and as suggested before in chapter 3, another experimental group would be needed, with a longer interval before testing, and a follow up of the results. Another question is if our results would be similar in clinical population. The memory tested here is a memory from an experimental context, and not a real-life memory, from a traumatic experience. When talking about clinical populations, we tend to focus on PTSD. Nevertheless, the application of the results achieved here would be interesting for other mental disorders. But, would GA induced reconsolidation impairment in psychiatric patients? One of the main differences is

that real life memories that are at the core of a disorder such as the PTSD are often old memories that have been reactivated several times, and can be mixed with more than one memory trace. This complexity needs to be examined in order to make an effective treatment.

Many of the so-called 'boundary conditions' that would make reconsolidation unable to take place have been described in chapters 1 and 3 (for review see Tronson & Taylor, 2007).

To make a memory labile again, it is necessary a strong enough cue-reminder, to activate that particular memory trace. But, the complexity of real-life memories makes possible that more than a cue-reminder are able to activate those memories. This characteristic of memory reactivation is called generalization stimuli, and refers to the possibility that cues perceptually or conceptually similar to the cues involved in the real memory can trigger reconsolidation as well. Nowadays, it is possible to solve this limitation of the generalization stimuli, by recreating the original circumstances and the specific cue-reminder of the memory trace with virtual reality. Virtual reality can be a very useful tool that needs to be tested in order to be able to get the most out of it. It is also possible that the appearance of a very strong cue-reminder activates a memory trace that was thought to be impaired. The necessity of analyzing more closely the reminders that can be able to trigger a memory are fundamental if we want to achieve a durable and reliable treatment.

When taking into consideration that real life memories are able to have more than a single memory trace, but an interconnection of different traces, it is possible that reconsolidation only attenuates part of those traces, but not all of them, producing a partial memory trace disruption. In that case, it is necessary to asses if several reactivations and manipulations would add effects and disrupt all the memory traces and the connections. For example propofol could be administered multiple times with multiple reactivations (analogous to repeated ECT sessions in depression or schizophrenia). It is also important to consider than even though a memory trace is not expressed, that does not mean that it does not exist. Recent findings, have been able to demonstrate that a memory that is thought to be erased can be recovered (Gisquet-Verrier et al., 2015). Future studies should focus on memory traces, and its characteristics and properties, to ensure how and what can activate a memory

trace again, and how exactly make a durable disruption, over time and personal circumstances.

Other limitation that would make very complicated to translate reconsolidation from the laboratories to the clinical patients is the resistance that chronic stress-enhanced fear memories, as the ones in PTSD, seem to have (Hoffman et al., 2015). It has been hypothesized that traumatic memories in PTSD are "over consolidated" due to the influenced of stress hormones at the time of the traumatic experience (Pitman, 1989), posing a challenge when targeting this type of trauma-memories. Not every person that experienced a trauma develops PTSD (Breslau, 2001); hence there are individual differences to be taken into account, as well as the possible functional alterations in the fear neurocircuitry that may be supporting and developing PTSD (Hoffman et al., 2015).

If the limitations and boundary conditions can be solved by future research, the possibility of offering a treatment reachable to wide-scale administration would help to redefine not only how general population perceives mental disorders but also the stigma attached to them, by showing that a mental disorder is treatable in the same way as other health diseases affecting other body regions.

5.5.2. Blocking the action induced memory enhancement with β- blockers

Different design problems when trying to block the action-induced memory enhancement with β- blockers were pointed out before. They should be solved in order to be able to increase the validity and reliability of the results obtained in the experiment described in chapter 4. One of the most important limitations of the study was the selection bias described in chapter 4. As said, in order to provide maximum security to the participants involved in the study, participants with low blood pressure (BP) were discarded.

To solve this selection bias, future studies should extend the range of the BP accepted, making the sample more representative of the population. Another possibility could be maintaining the BP range observed in this study, but increasing the amount of the drug.

Another limitation that should be taken into account is the bioavailability of the drug. Bioavailability refers to the percentage of the administered dose of unchanged drug that is able to reach the systemic circulation. As noticed before, after administration, propranolol's total bioavailability is only approximately 30%, and varies greatly between individuals.

This loss in bioavailability is due to the route of administration (oral administration) and first pass metabolism (Frishman, 1979; Goodman, 1996). The only route of administration that would assure 100% of bioavailability is intravenous (IV) administration. However, IV propranolol is not accepted in healthy subjects, only used in case of life-threatening arrhythmias. This bioavailability must be considered when calculating dosages for oral administration.

Adding limitations, a selection bias and the loss of part of the bioavailability due to oral administration, maybe an increase in the dosage of the drug, as well as increasing the size of the sample should be considered, in order to be able to show more clear results when testing the hypothesis.

5.6. Clinical implications

When performing the experiments described in this thesis, clinical implications were always the final goal.

Memory is one the faculties of the brain that makes us who we are. A dysregulation of memory, whether due to a loss or an excess of it, causes severe changes in both, the person suffering and the family, as well as great harm to society, in the forms of productivity losses and healthcare costs.

Both studies presented in this thesis, have the aim to increase the knowledge of the understanding of different diseases that affect our central nervous system. Not only the underlying mechanism but also to change of perception that the general population has over the disorders that affect the brain.

Nowadays, it seems that the percentage of persons affected with a memory disorder, in the form of a psychiatric disorder or a neurodegenerative disorder, is augmenting. It could be related to the society we are integrated in, and to the increase of life expectancy. Whatever it is, the need for a cure is mandatory.

Bibliography

Bibliography

Abercrombie, H. C., Kalin, N. H., Thurow, M. E., Rosenkranz, M. A., & Davidson, R. J. (2003). Cortisol Variation in Humans Affects Memory for Emotionally Laden and Neutral Information. *Behavioral Neuroscience*, *117*(3), 505–516.

Adolphs, R., Cahill, L., Schul, R., & Babinsky, R. (1997). Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learning & Memory*, *4*(3), 291–300.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, a R. (1995). Fear and the human amygdala. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *15*(9), 5879–5891.

Agranoff, B., Davis, R., & Brink, J. (1966). Chemical studies on memory fixation in goldfish. *Brain Research*, *1*(3), 303–309. Retrieved from

Agren, T., Engman, J., Frick, A., Bjorkstrand, J., Larsson, E.-M., Furmark, T., & Fredrikson, M. (2012). Disruption of Reconsolidation Erases a Fear Memory Trace in the Human Amygdala. *Science*, *337*(6101), 1550–1552.

Agren, T., Furmark, T., Eriksson, E., & Fredrikson, M. (2012). Human fear reconsolidation and allelic differences in serotonergic and dopaminergic genes. *Translational Psychiatry*, *2*(2), e76.

Akirav, I. (2007). NMDA Partial Agonist Reverses Blocking of Extinction of Aversive Memory by GABAA Agonist in the Amygdala. *Neuropsychopharmacology*, *32*(3), 542–550.

Al-Hader, A. F., Hasan, M., & Hasan, Z. (1992). The comparative effects of propofol, thiopental and diazepam, administered intravenously, on pentylenetetrazol seizure threshold in the rabbit. *Life Sciences*, *51*(10), 779–786.

Alberini, C. M. (2005). Mechanisms of memory stabilization: Are consolidation and reconsolidation similar or distinct processes? *Trends in Neurosciences*, *28*(1), 51–56.

Alkire, M. T., Gruver, R., Miller, J., McReynolds, J. R., Hahn, E. L., & Cahill, L. (2008). Neuroimaging analysis of an anesthetic gas that blocks human emotional memory.

Proceedings of the National Academy of Sciences of the United States of America, *105*(5), 1722–1727.

Alkire, M. T., & Nathan, S. V. (2005). Does the amygdala mediate anesthetic-induced amnesia? Basolateral amygdala lesions block sevoflurane-induced amnesia. *Anesthesiology*, *102*(4), 754–60.

Alkire, M. T., Vazdarjanova, A., Dickinson-Anson, H., White, N. S., & Cahill, L. (2001). Lesions of the basolateral amygdala complex block propofol-induced amnesia for inhibitory avoidance learning in rats. *Anesthesiology*, *95*(3), 708–715.

Allolio, B., Stuttmann, R., Leonhard, U., Fischer, H., & Winkelmann, W. (1984). Adrenocortical suppression by a single induction dose of etomidate. *Klinische Wochenschrift*, *62*(21), 1014–1017.

Alnaes, D., Sneve, M. H., Espeseth, T., Endestad, T., van de Pavert, S. H. P., & Laeng, B. (2014). Pupil size signals mental effort deployed during multiple object tracking and predicts brain activity in the dorsal attention network and the locus coeruleus. *Journal of Vision*, *14*(4), 1–1.

American Psychiatric Association.APA (2000). (2003). Diagnostic and statistical manual of mental disorders, 4.

Ammassari-Teule, M., Pavone, F., & Castellano, C. (1991). Amygdala and dorsal hippocampus lesions block the effects of GABAergic drugs on memory storage. *Brain Research*, *551*(1), 104–109.

Amrein, R., Cano, J. P., Eckert, M., & Coassolo, P. (1980). Pharmacokinetics of midazolam after iv administration. *Arzneimittel-Forschung*, *31*(12a), 2202–2205.

Anderson, A. K., & Sobel, N. (2003). Dissociating intensity from valence as sensory inputs to emotion. *Neuron*, *39*(4), 581–583.

Anderson, A. K., Yamaguchi, Y., Grabski, W., & Lacka, D. (2006). Emotional memories are not all created equal: evidence for selective memory enhancement. *Learning & Memory* , *13*(6), 711–8.

Armony, J. L., Corbo, V., Clément, M. H., & Brunet, A. (2005). Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. *American Journal of Psychiatry*, *162*(10), 1961–1963.

Ausems, M. E., Hug Jr, C. C., & de Lange, S. (1983). Variable rate infusion of alfentanil as a supplement to nitrous oxide anesthesia for general surgery. *Anesthesia & Analgesia*, *62*(11), 982–986.

Babinsky, R., Calabrese, P., Durwen, H. F., Markowitsch, H. J., Brechtelsbauer, D., Heuser, L., & Gehlen, W. (1993). The possible contribution of the amygdala to memory. *Behavioural Neurology*, *6*(3), 167–170.

Bach, A., & Motsch, J. (1996). Infectious risks associated with the use of propofol. *Acta Anaesthesiologica Scandinavica*, *40*(10), 1189–1196.

Baddeley, A. D., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation*, *8*, 47–89.

Baddeley, A. D., Kopelman, M. D., & Wilson, B. A. (2002). *The handbook of memory disorders.* (John Wiley & Sons., Ed.).

Baddeley, A. D. (1992). Working memory. *Science*, *255*(5044), 556–559. https://doi.org/10.4249/scholarpedia.3015

Baddeley, A. D. (2001). The concept of episodic memory. *Phil. Trans. R. Soc. Lond. B*, *356*, 1345–1350.

Baddeley, A. D. (2000). The episodic buffer : a new component of working memory? *Trends in Cognitive Sciences*, *4*(11), 417–423.

Baddeley, A. D., Kopelman, M. D., & & Wilson, B. A. (2003). *The handbook of memory disorders*. (John Wiley & Sons, Ed.).

Barnard, E. A., Skolnick, P., Olsen, R. W., Mohler, H., Sieghart, W., Biggio, G., … Langer, S. Z. (1998). International Union of Pharmacology. XV. Subtypes of gamma-aminobutyric acidA receptors: classification on the basis of subunit structure and receptor function. *Pharmacological Reviews*, *50*(2), 291–313.

Barsalou, L. W. (2008). Grounded cognition. *Annu. Rev. Psychol*, *59*, 617–645.

Bartus, R. T. (1978). Evidence for a direct cholinergic involvement in the scopolamine-induced amnesia in monkeys: effects of concurrent administration of physostigmine and. *Pharmacology Biochemistry and Behavior*.

Bartus, R. T., Dean, R., Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science*, *217*(4558), 408–414.

Bast, T., Zhang, W. N., & Feldon, J. (2001). The ventral hippocampus and fear conditioning in rats. *Experimental Brain Research*, *139*(1), 39–52.

Beach, T. G., Honer, W. G., & Hughes, L. H. (1997). Cholinergic fibre loss associated with diffuse plaques in the non-demented elderly: the preclinical stage of Alzheimer's disease? *Acta Neuropathologica*, *93*(2), 146–153.

Bechara, A., Tranel, D., Damasio, H., & Adolphs, R. (1995). Double dissociation of conditioning and declarative. *Science*, *269*(5227), 1115.

Bennett, B. D., Huguenard, J. R., & Prince, D. A. (1998). Adrenergic modulation of GABAA receptor-mediated inhibition in rat sensorimotor cortex. *Journal of Neurophysiology*, *79*(2), 937–946.

Bennett, S. N., McNeil, M. M., Bland, L. A., Arduino, M. J., Villarino, M. E., Perrotta, D. M., & Zeitz, P. S. (1995). Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *New England Journal of Medicine*, *333*(3), 147–154.

Benzing, W. C., & Squire, L. R. (1989). Preserved learning and memory in amnesia: intact adaptation-level effects and learning of stereoscopic depth. *Behavioral Neuroscience*, *103*(3), 538.

Bergson, H., Mitchell, A., Pearson, K., & Kolkman, M. (1911). *Creative Evolution*. (University Press of America, Ed.).

Berlau, D. J., & McGaugh, J. L. (2006). Enhancement of extinction memory consolidation: the role of the noradrenergic and GABAergic systems within the basolateral amygdala. *Neurobiology of Learning and Memory*, *86*(2), 123–132.

Bernardi, R. E., Ryabinin, A. E., Berger, S. P., & Lattal, K. M. (2009). Post-retrieval disruption of a cocaine conditioned place preference by systemic and intrabasolateral amygdala b2-and a1-adrenergic antagonists. *Learning & Memory*, *16*(12), 777–789.

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33–84.

Beylin, A. V., & Shors, T. J. (2003). Glucocorticoids are necessary for enhancing the acquisition of associative memories after acute stressful experience. *Hormones and Behavior*, *43*(1), 124–131.

Beylin, a V, Gandhi, C. C., Wood, G. E., Talk, a C., Matzel, L. D., & Shors, T. J. (2001). The role of the hippocampus in trace conditioning: temporal discontinuity or task difficulty? *Neurobiology of Learning and Memory*, *76*(3), 447–461.

Birks, J. S. (2006). Cholinesterase inhibitors for Alzheimer's disease. In J. S. Birks (Ed.), *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd.

Bliss, T. V., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31.

Bliss, T. V., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology*, *232*(2), 331–356.

Blokland, A. (1996). Acetylcholine: A neurotransmitter for learning and memory? *Brain Research Reviews*, *21*(3), 285–300.

Bormann, J. (1988). Electrophysiology of GABA A and GABA B receptor subtypes. *Trends in Neurosciences*, *11*(3), 112–116.

Bouret, S., & Richmond, B. J. (2009). Relation of locus coeruleus neurons in monkeys to Pavlovian and operant behaviors. *Journal of Neurophysiology*, *101*(2), 898–911.

Bouton, M. E. (2004). Context and Behavioral Processes in Extinction. *Learning & Memory*, *11*(5), 485–494.

Bovill, J. G., Warren, P. J., Schuller, J. L., van Wezel, H. B., & Hoeneveld, M. H. (1984). Comparison of fentanyl, sufentanil, and alfentanil anesthesia in patients undergoing valvular heart surgery. *Anesthesia & Analgesia*, *63*(12), 1081–1086.

Bowery, N. (1989). GABAB receptors and their significance in mammalian pharmacology. *Trends in Pharmacological Sciences*, *10*(10), 401–407.

Bowery, N. G., Hill, D. R., Hudson, A., Doble, A., Middlemiss, D. N., Shaw, J., & Turnbull, M. J. (1980). (–) Baclofen decreases neurotransmitter release in the mammalian CNS by an action at a novel GABA receptor. *Nature*, *283*(5742), 92–94.

Braga, M. F. M., Aroniadou-Anderjaska, V., Manion, S. T., Hough, C. J., & He, L. (2004). Stress impairs 1A adrenoceptor-mediated noradrenergic facilitation of GABAergic transmission in the basolateral amygdala. *Neuropsychopharmacology*, *29*(1), 45.

Braun, J. J., Meyer, P. M., & Meyer, D. R. (1966). Sparing of a brightness habit in rats following visual decortication. *Journal of Comparative and Physiological Psychology*, *61*(1), 79.

Breitenstein, C., Flöel, A., Korsukewitz, C., Wailke, S., Bushuven, S., & Knecht, S. (2006). A shift of paradigm: from noradrenergic to dopaminergic modulation of learning? *Journal of the Neurological Sciences*, *248*(1), 42–47.

Breitenstein, C., Korsukewitz, C., Flöel, A., Kretzschmar, T., Diederich, K., & Knecht, S. (2006). Tonic dopaminergic stimulation impairs associative learning in healthy subjects. *Neuropsychopharmacology*, *31*(11), 2552–2564.

Bremner, J. D., Innis, R. B., White, T., Fujita, M., Silbersweig, D., Goddard, A. W., & Baldwin, R. (2000). SPECT [I-123] iomazenil measurement of the benzodiazepine receptor in panic disorder. *Biological Psychiatry*, *47*(2), 96–106.

Bremner, J. D., Narayan, M., Staib, L. H., Southwick, S. M., McGlashan, T., & Charney, D. S. (1999). Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. *Journal of Psychiatry*, *156*(11), 1787–1795.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Staib, L. H., & Charney, D. S. (2003). Neural correlates of declarative memory for

emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. *Biological Psychiatry*, *53*(10), 879–889.

Breslau, N. (2001). The Epidemiology of Posttraumatic Stress Disorder: What Is the Extent of the Problem? *The Journal of Clinical Psychiatry*, *62*(17), 16–22.

Brioni, J. D., Nagahara, A. H., & McGaugh, J. L. (1989). Involvement of the amygdala GABAergic system in the modulation of memory storage. *Brain Research*, *487*(1), 105–112.

Britton, J. C., Phan, K. L., Taylor, S. F., Fig, L. M., & Liberzon, I. (2005). Corticolimbic blood flow in posttraumatic stress disorder during script-driven imagery. *Biological Psychiatry*, *57*(8), 832–840.

Bruner, J. S. (1969). Modalities of memory. *The Pathology of Memory*, 253–259.

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., & Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *Journal of Psychiatric Research*, *42*(6), 503–506.

Brunet, A., Poundja, J., Tremblay, J., Bui, E., Thomas, E., Orr, S. P., … Pitman, R. K. (2011). Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *Journal of Clinical Psychopharmacology*, *31*(4), 547–550.

Brunet, A., Thomas, É., Saumier, D., Ashbaugh, A. R., Azzoug, A., Pitman, R. K., & Tremblay, J. (2014). Trauma reactivation plus propranolol is associated with durably low physiological responding during subsequent script-driven traumatic imagery. *The Canadian Journal of Psychiatry*, *59*(4), 228–232.

Bryson, H. M., Fulton, B. R., & Faulds, D. (1995). Propofol. An update of its use in anaesthesia and conscious sedation. *Drugs*, *50*(3), 513–559.

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology*, *26*(3), 307–317.

Buchanan, T. W., & Lovallo, W. R. (2001). Enhanced memory for emotional material following stress-level cortisol treatment in humans. *Psychoneuroendocrinology*, *26*(3), 307–317.

Büchel, C., Dolan, R. J., Armony, J. L., & Friston, K. J. (1999). Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *The Journal of Neuroscience*, *19*(24), 10869–76.

Bustos, S. G., Maldonado, H., & Molina, V. A. (2006). Midazolam disrupts fear memory reconsolidation. *Neuroscience*, *139*(3), 831–842.

Bustos, S. G., Maldonado, H., & Molina, V. A. (2009). Disruptive Effect of Midazolam on Fear Memory Reconsolidation: Decisive Influence of Reactivation Time Span and Memory Age. *Neuropsychopharmacology*, *34*(2), 446–457.

Cahill, L., & McGaugh, J. L. (1990). Amygdaloid complex lesions differentially affect retention of tasks using appetitive and aversive reinforcement. *Behavioral Neuroscience*, *104*(4), 532–543.

Cahill, L., Prins, B., Weber, M., & McGaugh, J. L. (1994). B- Adrenergic Activation and Memory for Emotional Events. *Nature*, (371), 702–704.

Cahill, L., Babinsky, R., Markowitsch, H. J., & McGaugh, J. L. (1995). The amygdala and emotional memory. *Nature*.

Cahill, L., Gorski, L., & Le, K. (2003). Enhanced Human Memory Consolidation With Post-Learning Stress: Interaction With the Degree of Arousal at Encoding. *Learning &*

Cahill, L., Haier, R. J., Fallon, J., Alkire, M. T., Tang, C., Keator, D. . . ., & Mcgaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proceedings of the National Academy of Sciences*, *93*(15), 8016–8021.

Cahill, L., & McGaugh, J. L. (1994). ß-Adrenergic activation and memory for emotional events. *Nature*.

Cahill, L., & McGaugh, J. L. (1995). A novel demonstration of enhanced memory associated with emotional arousal. *Consciousness and Cognition*.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences*, *21*(7), 294–299.

Cahill, L., & van Stegeren, A. (2003). Sex-related impairment of memory for emotional events with β-adrenergic blockade. *Neurobiology of Learning and Memory*, *79*(1), 81–88. Retrieved from http://www.sciencedirect.com/science/article/pii/S1074742702000199

Camu, F., Gepts, E., Rucquoi, M., & Heykants, J. (1982). Pharmacokinetics of alfentanil in man. *Anesthesia & Analgesia*, *61*(8), 657–661.

Cannon, W. B. (1915). *Bodily changes in pain, hunger, fear and rage. An account of recent researches into the function of emotional excitement. D. Appleton and Co., New York, London*.

Caplan, J. B., Madsen, J. R., Schulze-Bonhage, A., Aschenbrenner-Scheibe, R., Newman, E. L., & Kahana, M. J. (2003). Human θ oscillations related to sensorimotor integration and spatial learning. *Journal of Neuroscience*, *23*(11), 4726–4736.

Carrillo-Esper, R., Garnica-Escamilla, M. A., & Bautista-León, R. C. (2010). Síndrome por infusión de propofol. *Revista Mexicana de Anestesiología*, *33*(2), 97–102.

Casasanto, D. (2009). Embodiment of abstract concepts: good and bad in right-and left-handers. *Journal of Experimental Psychology: General*, *138*(3), 351.

Casasanto, D. (2011). Different Bodies, Different Minds. *Current Directions in Psychological Science*, *20*(6), 378–383.

Cattell, R. B. (1930). The effects of alcohol and caffeine on intelligent and associative performance. *British Journal of Medical Psychology*, *10*(1), 20–33.

Caulfield, M. P., & Birdsall, N. J. M. (1998). International union of pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacological Reviews*, *50*(2), 279–290.

Chamberlain, S. R., Müller, U., Blackwell, A. D., Robbins, T. W., & Sahakian, B. J. (2006). Noradrenergic modulation of working memory and emotional memory in humans. *Psychopharmacology*, *188*(4), 397–407.

Chen, C. L., Yang, Y. R., & Chiu, T. H. (1999). Activation of rat locus coeruleus neuron GABA(A) receptors by propofol and its potentiation by pentobarbital or alphaxalone. *European Journal of Pharmacology*, *386*(2–3), 201–210.

Cheng, V. Y. (2006). Alpha5 GABAA eeceptors mediate the amnestic but not sedative-hypnotic effects of the general anesthetic Etomidate. *Journal of Neuroscience*, *26*(14), 3713–3720.

Chiu, Y. C., & Egner, T. (2014). Inhibition-Induced Forgetting: When More Control Leads to Less Memory. *Psychological Science*, *26*(1), 27–38. Retrieved from

Chiu, Y. C., & Egner, T. (2015). Inhibition-induced forgetting results from resource competition between response inhibition and memory encoding processes. *Journal of Neuroscience*, *35*(34), 11936–11945.

Clark, R. E., & Squire, L. R. (1998). Classical conditioning and brain systems: the role of awareness. *Science*, *280*(5360), 77–81.

Clayton, E. C., Rajkowski, J., Cohen, J. D., & Aston-Jones, G. (2004). Phasic activation of monkey locus ceruleus neurons by simple decisions in a forced-choice task. *Journal of Neuroscience*, *24*(44), 9914–9920.

Cohen, R. L. (1981). On the generality of some memory laws. *Scandinavian Journal of Psychology*, *22*(1), 267–281.

Corcoran, K. A., & Maren, S. (2004). Factors regulating the effects of hippocampal inactivation on renewal of conditional fear after extinction. *Learning & Memory*, *11*(5), 598–603.

Cornwell, B. R., Johnson, L. L., Holroyd, T., Carver, F. W., & Grillon, C. (2008). Human Hippocampal and Parahippocampal Theta during Goal-Directed Spatial Navigation Predicts Performance on a Virtual Morris Water Maze. *Journal of Neuroscience*, *28*(23), 5983–5990.

Coull, J. T., Middleton, H. C., Robbins, T. W., & Sahakian, B. J. (1995). Contrasting effects of clonidine and diazepam on tests of working memory and planning. *Psychopharmacology*, *120*(3), 311–321.

Coyle, J. T., Price, D. L., & Delong, M. R. (1983). Alzheimer's disease: a disorder of cortical cholinergic innervation. *Science*, *219*(4589), 1184–1190.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior*, *11*(6), 671–684.

Curran, H. V., & Weingartner, H. (2002). Psychopharmacology of Human Memory. In A. D. Baddeley, M. D. Kopelman, & B. A. Wilson (Eds.), *The Handbook of Memory Disorders*. John Wiley & Sons.

Curtis, D. R., & Watkins, J. C. (1960). The excitation and depression of spinal neurones by structurally related amino acids. *Journal of Neurochemistry*, *6*(2), 117–141.

Da Cunha, C., Roozendaal, B., Vazdarjanova, A., & McGaugh, J. L. (1999). Microinfusions of flumazenil into the basolateral but not the central nucleus of the amygdala enhance memory consolidation in rats. *Neurobiology of Learning and Memory*, *72*(1), 1–7.

Dale, H. H. (1914). The action of certain esters and ethers of choline and their relation to muscarine. *Wellcome Physiological Research Laboratories*.

Daneshmend, T. K., Jackson, L., & Roberts, C. J. (1981). Physiological and pharmacological variability in estimated hepatic blood flow in man. *British Journal of Clinical Pharmacology*, *11*(5), 491–496.

de Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature Reviews. Neuroscience*, *6*(6), 463–475. https://doi.org/10.1038/nrn1683

De Lange, S., & De Bruijn, N. P. (1982). Alfentanil-oxygen anaesthesia: plasma concentrations and clinical effects during variable-rate continuous infusion for coronary artery surgery. *British Journal of Anaesthesia*, *55*, 183S–189S.

De Riu, P. L., Petruzzi, V., Testa, C., Mulas, M., Melis, F., Caria, M. A., & Mameli, O. (1992). Propofol anticonvulsant activity in experimental epileptic status. *British Journal of Anaesthesia*, *69*(2), 177–181.

Dębiec, J., & Ledoux, J. E. (2004). Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. *Neuroscience*, *129*(2), 267–272. https://doi.org/10.1016/j.neuroscience.2004.08.018

Debiec, J., LeDoux, J. E., & Nader, K. (2002). Cellular and systems reconsolidation in the hippocampus. *Neuron*, *36*(3), 527–538.

Delacourte, A., & Defossez, A. (1986). Alzheimer's disease: Tau proteins, the promoting factors of microtubule assembly, are major components of paired helical filaments. *Journal of the Neurological Sciences*, *76*(2), 173–186.

Denis, M., Engelkamp, J., & Mohr, G. (1991). Memory of imagined actions: Imagining oneself or another person. *Psychological Research*, *53*(3), 246–250.

Diamond, D. M., Bennett, M. C., Fleshner, M., & Rose, G. M. (1992). Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus*, *2*(4), 421–430.

Dickerson, B. C., & Eichenbaum, H. (2010). The Episodic Memory System: Neurocircuitry and Disorders. *Neuropsychopharmacology*, *35*(1), 86–104.

Dickinson-Anson, H., & McGaugh, J. L. (1993). Midazolam administered into the amygdala impairs retention of an inhibitory avoidance task. *Behavioral and Neural Biology*, *60*(1), 84–87.

Dickinson-Anson, H., & McGaugh, J. L. (1997). Bicuculline administered into the amygdala after training blocks benzodiazepine-induced amnesia. *Brain Research*, *752*(1–2), 197–202.

Dodson, B. A., & Miller, K. W. (1985). Evidence for a dual mechanism in the anesthetic action of an opioid peptide. *Anesthesiology*, *62*(5), 615–620.

Drachman, D. A., Leavitt, J., Scoville WB, M. B., Penfield W, M. B., Drachman DA, O.

A., Drachman DA, A. J., … KS, L. (1974). Human Memory and the Cholinergic System. *Archives of Neurology*, *30*(2), 113.

Dreisbach, G., & Wenke, D. (2011). The shielding function of task sets and its relaxation during task switching. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *37*(6), 1540–1546.

Dudai, Y., & Morris, R. G. (2000). To consolidate or not to consolidate: what are the questions. *Brain, Perception, Memory. Advances in Cognitive sciences.Oxford University Press, Oxford.*, 149–162.

Dudai, Y. (2006). Reconsolidation: the advantage of being refocused. *Current Opinion in Neurobiology*, *16*(2), 174–178.

Duncan, C. (1949). The retroactive effect of electroshock on learning. *Journal of Comparative and Physiological Psychology*, *42*(1), 32.

Dundee, J. W., & Wilson, D. B. (1980). Amnesic action of midazolam. *Anaesthesia*, *35*(5), 459–461.

Duvarci, S., & Nader, K. (2004). Characterization of Fear Memory Reconsolidation. *Journal of Neuroscience*, *24*(42), 9269–9275.

Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy*, *38*(4), 319–345.

Eichenbaum, H., & Lipton, P. A. (2008). Towards a functional organization of the medial temporal lobe memory system: role of the parahippocampal and medial entorhinal cortical areas. *Hippocampus*, *18*(12), 1314–1324.

Ekstrom, A. D., Caplan, J. B., Ho, E., Shattuck, K., Fried, I., & Kahana, M. J. (2005). Human hippocampal theta activity during virtual navigation. *Hippocampus*, *15*(7), 881–889.

Engelkamp, J., & Cohen, R. L. (1991). Current issues in memory of action events. *Psychological Research*, *53*(3), 175–182.

Etkin, A., & Wager, T. D. (2007). Functional Neuroimaging of Anxiety: A Meta-Analysis

of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia. *Functional Neuroimaging of Anxiety: A Meta-Analysis of Emotional Processing in PTSD, Social Anxiety Disorder, and Specific Phobia*, *164*(10), 1476–1488.

Evans, M. S., & Viola-McCabe, K. E. (1996). Midazolam inhibits long-term potentiation through modulation of GABAA receptors. *Neuropharmacology*, *35*(3), 347–357.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (1999). ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychologica*, *101*(2), 267–291.

Fanselow, M. S. (1994). Neural organization ofthe defensive behavior system responsible for fear. *Psychonomic Bulletin & Review*, *1*(4), 429–438.

Feldman, S., Conforti, N., & Weidenfeld, J. (1995). Limbic pathways and hypothalamic neurotransmitters mediating adrenocortical responses to neural stimuli. *Neuroscience & Biobehavioral Reviews*, *19*(2), 235–240.

Ferry, B., & McGaugh, J. L. (1999). Clenbuterol administration into the basolateral amygdala post-training enhances retention in an inhibitory avoidance task. *Neurobiology of Learning and Memory*, *72*(1), 8–12.

Fischer, M. H., & Zwaan, R. A. (2008). Embodied language: A review of the role of the motor system in language comprehension. *The Quarterly Journal of Experimental Psychology*, *61*(6), 825–850.

Flexner, L., Flexner, J., & Stellar, E. (1965). Memory and cerebral protein synthesis in mice as affected by graded amounts of puromycin. *Experimental Neurology*, *13*(3), 264–272. Retrieved from

Forman, S. (2011). Clinical and molecular pharmacology of etomidate. *Anesthesiology*, *114*(3), 695–707.

Fragen, R. J., Booij, L. H. D. J., Braak, G. J. J., Vree, T. B., Heykants, J., & Crul, J. F. (1983). Pharmacokinetics of the infusion of alfentanil in man. *British Journal of Anaesthesia*, *55*(11), 1077–1081.

Fragen, R. J., Shanks, C. A., Molteni, A., & Avram, M. J. (1984). Effects of etomidate on

hormonal responses to surgical stress. *Anesthesiology*, *61*(6), 652–656.

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience*, *6*(2), 119–130.

Frankland, P. W., & Bontempi, B. (2006). Fast track to the medial prefrontal cortex, *103*(3), 509–510.

Fried, I., Wilson, C. L., Morrow, J. W., Cameron, K. A., Behnke, E. D., Ackerson, L. C., & Maidment, N. T. (2001). Increased dopamine release in the human amygdala during performance of cognitive tasks. *Nature Neuroscience*, *4*(2), 201–206.

Frishman, W. (1979). Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 1. Pharmacodynamic and pharmacokinetic properties. *American Heart Journal*, *97*(5), 663–70.

Gafford, G. M., Parsons, R. G., & Helmstetter, F. J. (2005). Effects of post-training hippocampal injections of midazolam on fear conditioning. *Learning & Memory*, *12*(6), 573–578.

Gan, T. J., Glass, P. S., Sigl, J., Sebel, P., Payne, F., Rosow, C., & Embree, P. (1999). Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. *The Journal of the American Society of Anesthesiologists*, *90*(5), 1283–1287.

Garakani, A., Mathew, S., & Charney, D. S. (2006). Neurobiology of Anxiety Disorders and Implications for Treatment. *Mount Sinai Journal of Medicine*, *73*(7), 941–950.

Garoff, R. J., Slotnick, S. D., & Schacter, D. L. (2005). The neural origins of specific and general memory: The role of the fusiform cortex. *Neuropsychologia*, *43*(6), 847–859.

Garpenstrand, H., Annas, P., & Ekblom, J. (2001). Human fear conditioning is related to dopaminergic and serotonergic biological markers. *Behavioral Neuroscience*, *115*(2), 358.

Gazarini, L., Stern, C., Carobrez, A. P., & Bertoglio, L. J. (2013). Enhanced noradrenergic activity potentiates fear memory consolidation and reconsolidation by differentially

recruiting α1- and β-adrenergic receptors. *Learning & Memory*, *20*(4), 210–9.

Geuze, E. E. J. D., Vermetten, E., & Bremner, J. D. (2005). MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. *Molecular Psychiatry*, *10*, 160–184.

Gisquet-Verrier, P., Lynch, J. F., Cutolo, P., Toledano, D., Ulmen, A., Jasnow, A. M., & Riccio, D. C. (2015). Integration of new information with active memory accounts for retrograde amnesia: a challenge to the consolidation/reconsolidation hypothesis? *Journal of Neuroscience*, *35*(33), 11623–11633.

Glickman, S. (1961). Perseverative neural processes and consolidation of the memory trace. *Psychological Bulletin*, *58*(3), 218.

Gold, P. E., Edwards, R. M., & McGaugh, J. L. (1975). Amnesia produced by unilateral, subseizure, electrical stimulation of the amygdala in rats. *Behavioral Biology*, *15*(1), 95–105.

Gold, P. E., & Van Buskirk, R. B. (1975). Facilitation of time-dependent memory processes with posttrial epinephrine injections. *Behavioral Biology*, *13*(2), 145–153.

Golkar, A., Bellander, M., Olsson, A., & Ohman, A. (2012). Are fear memories erasable?-reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. *Frontiers in Behavioral Neuroscience*, *6*, 80.

Goodman, L. S. (1996). *Goodman and Gilman's the pharmacological basis of therapeutics*. *New York: McGraw-Hill*.

Gordon, W. (1977a). Similarities of recently acquired and reactivated memories in interference. *The American Journal of Psychology*.

Gordon, W. (1977b). Susceptibility of a reactivated memory to the effects of strychnine: a time-dependent phenomenon. *Physiology & Behavior*.

Gordon, W. C., & Spear, N. E. (1973). Effect of reactivation of a previously acquired memory on the interaction between memories in the rat. *Journal of Experimental Psychology*, *99*(3), 349.

Graeff, F. G. (2004). Serotonin, the periaqueductal gray and panic. *Neuroscience & Biobehavioral Reviews*, *28*(3), 239–259.

Graf, P., & Mandler, G. (1984). Activation makes words more accessible, but not necessarily more retrievable. *Journal of Verbal Learning and Verbal Behavior*, *23*(5), 553–568.

Graf, P., & Schacter, D. L. (1985). Implicit and explicit memory for new associations in normal and amnesic subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *11*(3), 501.

Greenblatt, D. J., & Abernethy, D. R. (1985). Midazolam pharmacology and pharmacokinetics. *Anesthesiology Review*, *12*(3 Suppl.), 17–20.

Griffin III, C. E., Kaye, A. M., Bueno, F. R., & Kaye, A. D. (2013). Benzodiazepine pharmacology and central nervous system–mediated effects. *The Ochsner Journal*, *13*(2), 214–223.

Groenewegen, H. J., Wright, C. I., & Uylings, H. B. M. (1997). The anatomical relationships of the prefrontal cortex with limbic structures and the basal ganglia. *Journal of Psychopharmacology*, *11*(2), 99–106.

Grote, B., Doenicke, A., Kugler, J., Suttmann, H., & Loos, A. (1981). Intramuscular application of midazolam. Its effect upon CNS and respiration. *Arzneimittel-Forschung*, *31*(12a), 2224–2225.

Grudzien, A., Shaw, P., Weintraub, S., Bigio, E., Mash, D. C., & Mesulam, M. M. (2007). Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease. *Neurobiology of Aging*, *28*(3), 327–335.

Hackmann, A., Clark, D. M., & McManus, F. (2000). Recurrent images and early memories in social phobia. *Behaviour Research and Therapy*, *38*(6), 601–610.

Hales, T. G., & Lambert, J. J. (1992). Modulation of GABAA and glycine receptors by chlormethiazole. *European Journal of Pharmacology*, *210*(3), 239–246.

Hall, L. W., & Chambers, J. P. (1987). A clinical trial of propofol infusion anaesthesia in

dogs. *Journal of Small Animal Practice*, *28*(7), 623–637.

Hamann, S. B., Ely, T. D., Grafton, S. T., & Kilts, C. D. (1999). Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neuroscience*, *2*(3), 289–293.

Hardwicke, T. E., Taqi, M., & Shanks, D. R. (2016). Postretrieval new learning does not reliably induce human memory updating via reconsolidation. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(19), 5206–11.

Harvey, B. H., Oosthuizen, F., Brand, L., Wegener, G., & Stein, D. J. (2004). Stress–restress evokes sustained iNOS activity and altered GABA levels and NMDA receptors in rat hippocampus. *Psychopharmacology*, *175*(4), 494–502.

Hasselmo, M. E. (2006). The role of acetylcholine in learning and memory. *Current Opinion in Neurobiology*, *16*(6), 710–715.

Hatfield, T., Spanis, C., & McGaugh, J. L. (1999). Response of amygdalar norepinephrine to footshock and GABAergic drugs using in vivo microdialysis and HPLC. *Brain Research*, *835*(2), 340–345.

Hayashi, T. (1952). A physiological study of epileptic seizures following cortical stimulation in animals and its application to human clinics. *The Japanese Journal of Physiology*, *3*, 46–64.

Hebb, D. . (1949). The Organization of Behavior. A neuropsychological theory. *New York: Wiley*.

Heizmann, P., & Ziegler, W. H. (1980). Excretion and metabolism of 14C-midazolam in humans following oral dosing. *Arzneimittel-Forschung*, *31*(12a), 2220–2223.

Henry, B., Plante-Jenkins, C., & Ostrowska, K. (2001). An outbreak of Serratia marcescens associated with the anesthetic agent propofol. *American Journal of Infection Control*, *29*(5), 312–315.

Hobin, J. A., Goosens, K. A., & Maren, S. (2003). Context-dependent neuronal activity in the lateral amygdala represents fear memories after extinction. *Journal of*

Neuroscience, *23*(23), 8410–8416.

Hofer, P. A. (1972). Urbach-Wiethe disease (lipoglycoproteinosis; lipoid proteinosis; hyalinosis cutis et mucosae). A review. *Acta Dermato-Venereologica. Supplementum*, *53*, 1–52.

Hoffman, A. N., Parga, A., Paode, P. R., Watterson, L. R., Nikulina, E. M., Hammer, R. P., & Conrad, C. D. (2015). Chronic stress enhanced fear memories are associated with increased amygdala zif268 mRNA expression and are resistant to reconsolidation. *Neurobiology of Learning and Memory*, *120*, 61–68.

Hohl, C. M., Kelly-Smith, C. H., Yeung, T. C., Sweet, D. D., Doyle-Waters, M. M., & Schulzer, M. (2010). The Effect of a Bolus Dose of Etomidate on Cortisol Levels, Mortality, and Health Services Utilization: A Systematic Review. *Annals of Emergency Medicine*, *56*(2), 105–113.e5.

Honey, G. D., Honey, R. A. E., O'Loughlin, C., Sharar, S. R., Kumaran, D., Suckling, J., … Fletcher, P. C. (2005). Ketamine disrupts frontal and hippocampal contribution to encoding and retrieval of episodic memory: An fMRI study. *Cerebral Cortex*, *15*(6), 749–759.

Howie, M. B., McSweeney, T. D., Lingam, R. P., & Maschke, S. P. (1985). A comparison of fentanyl-O2 and sufentanil-O2 for cardiac anesthesia. *Anesthesia & Analgesia*, *64*(9), 877–887.

Hu, P. T., Stylos-Allan, M., & Walker, M. P. (2006). Sleep facilitates consolidation of emotionally arousing declarative memory. *Psychological Science*, *17*(10), 891–898.

Huang, Y. Y., & Kandel, E. R. (1995). D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(7), 2446–50.

Hull, C. J. (1983). The pharmacokinetics of alfentanil in man. *British Journal of Anaesthesia*, *55*(Suppl 2), 157S–164S.

Hupbach, A., Gomez, R., Hardt, O., & Nadel, L. (2007). Reconsolidation of episodic memories: A subtle reminder triggers integration of new information. *Learning &*

Memory, *14*(1–2), 47–53.

Intraub, H., Gottesman, C. V., & Bills, A. J. (1998). Effects of perceiving and imagining scenes on memory for pictures. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *24*(1), 186.

Introini-Collison, I. B., Arai, Y., & Mcgaugh, J. L. (1989). Stria terminalis lesions attenuate the effects of posttraining oxotremorine and atropine on retention. *Psychobiology*, *17*(4), 397–401.

Introini-Collison, I. B., Castellano, C., & McGaugh, J. L. (1994). Interaction of GABAergic and β-noradrenergic drugs in the regulation of memory storage. *Behavioral and Neural Biology*, *61*(2), 150–155.

Izquierdo, I., Da Cunha, C., Huang, C. H., Walz, R., Wolfman, C., & Medina, J. H. (1990). Post-training down-regulation of memory consolidation by a GABA-A mechanism in the amygdala modulated by endogenous benzodiazepines. *Behavioral and Neural Biology*, *54*(2), 105–109.

Jacobs, H. I., Wiese, S., van de Ven, V., Gronenschild, E. H., Verhey, F. R., & Matthews, P. M. (2015). Relevance of parahippocampal-locus coeruleus connectivity to memory in early dementia. *Neurobiology of Aging*, *36*(2), 618–626.

James, W. (1890). *The Principles of Psychology*. *Henry Holt and Co* (Vol. 1). New York.

Johnson, E. S., Roberts, M. H., Sobieszek, A., & Straughan, D. W. (1969). Noradrenaline sensitive cells in cat cerebral cortex. *International Journal of Neuropharmacology*, *8*(6), 549–66.

Johnston, G. A. (1996). GABAc receptors: relatively simple transmitter-gated ion channels? *Trends in Pharmacological Sciences*, *17*(9), 319–323.

Jones, E. E. (1909). The waning of consciousness under chloroform. *Psychological Review*, *16*(1), 48.

Jones, J. R. (1933). The influence of some antipyretic drugs on learning. *The Journal of General Psychology*, *9*(2), 472–475.

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron*, *89*(1), 221–234.

Kalisch, R., Korenfeld, E., Stephan, K. E., Weiskopf, N., Seymour, B., & Dolan, R. J. (2006). Context-dependent human extinction memory is mediated by a ventromedial prefrontal and hippocampal network. *Journal of Neuroscience*, *26*(37), 9503–9511.

Kanto, J., Aaltonen, L., Erkkola, R., & Äärimaa, L. (1984). Pharmacokinetics and Sedative Effect of Midazolam in Connection with Caesarean Section Performed Under Epidural Analgesia. *Acta Anaesthesiologica Scandinavica*, *28*(1), 116–118.

Kanto, J. H. (1985). Midazolam: The First Water-soluble Benzodiazepine; Pharmacology, Pharmacokinetics and Efficacy in Insomnia and Anesthesia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *5*(3), 138–155.

Karlin, A., & Akabas, M. H. (1995). oward a structural basis for the function of nicotinic acetylcholine receptors and their cousins. *Neuron*, *15*(6), 1231–1244.

Kawaguchi, Y., & Shindou, T. (1998). Noradrenergic excitation and inhibition of GABAergic cell types in rat frontal cortex. *Journal of Neuroscience*, *18*(17), 6963–6976.

Kay, B., & Stephenson, D. K. (1980). ICI 35868 (Diprivan): a new intravenous anaesthetic. *Anaesthesia*, *35*(12), 1182–1187.

Kensinger, E. A., & Corkin, S. (2004). Two routes to emotional memory: Distinct neural processes for valence and arousal. *Proceedings of the National Academy of Sciences*, *101*(9), 3310–3315.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602.

Kety, S. (1972). *Brain catecholamines, affective states and memory*. (Springer US, Ed.), *The chemistry of mood, motivation, and memory*.

Kiefer, M., Marzinzik, F., Weisbrod, M., Scherg, M., & Spitzer, M. (1998). The time course of brain activations during response inhibition: evidence from event-related potentials in a go/no go task. *Neuroreport*, *9*(4), 765–770.

Kikuchi, T., Wang, Y., Sato, K., & Okumura, F. (1998). In vivo effects of propofol on acetylcholine release from the frontal cortex, hippocampus and striatum studied by intracerebral microdialysis in freely moving rats. *British Journal of Anaesthesia*, *80*(5), 644–648.

Kim, J. J., Clark, R. E., & Thompson, R. F. (1995). Hippocampectomy impairs the memory of recently, but not remotely, acquired trace eyeblink conditioned responses. *Behavioral Neuroscience*, *109*(2), 195.

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience*, *3*(6), 453–462.

Kim, J. J., & Fanselow, M. S. (1992). Modality-Specific Retrograde Amnesia of Fear. *Science*, *256*(5057), 675.

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: erasing human fear responses and preventing the return of fear. *Nature Neuroscience*, *12*(3), 256–8.

Klein, R. L., Sanna, E., McQuilkin, S. J., Sikela, J. M., Whiting, P. J., & Harris, R. A. (1993). 5-HT3 receptor antagonists and GABAA receptors: A functional study. *Soc. Neurosci. Abs*, *19*, 1140.

Kleinsmith, L. J., & Kaplan, S. (1963). Paired-associate learning as a function of arousal and interpolated interval. *Journal of Experimental Psychology*, *65*(2), 190.

Klucken, T., Kruse, O., Schweckendiek, J., Kuepper, Y., Mueller, E. M., Hennig, J., & Stark, R. (2016). No evidence for blocking the return of fear by disrupting reconsolidation prior to extinction learning ScienceDirect. *Cortex*, *79*, 112–122.

Knecht, S., Breitenstein, C., Bushuven, S., Wailke, S., Kamping, S., Flöel, A., … Ringelstein. (2004). Levodopa: Faster and better word learning in normal humans. *Annals of Neurology*, *56*(1), 20–26.

Knight, D. C., Cheng, D. T., Smith, C. N., Stein, E. A., & Helmstetter, F. J. (2004). Neural substrates mediating human delay and trace fear conditioning. *The Journal of Neuroscience*, *24*(1), 218–228.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science (New York, N.Y.)*, *273*(5280), 1399–1402.

Knowlton, B. J., Ramus, S. J., & Squire, L. R. (1992). Intact artificial grammar learning in amnesia: Dissociation of classification learning and explicit memory for specific instances. *Psychological Science*, *3*(3), 172–179.

Knowlton, B. J., & Squire, L. R. (1993). The learning of categories: Parallel brain systems for item memory and category knowledge. *Science-AAAS-Weekly Paper Edition-Including Guide to Scientific Information*, *262*(5140), 1747–1749.

Knowlton, B. J., Squire, L. R., & Gluck, M. A. (1994). Probabilistic Classification Learning in Amnesia, 106–120.

Kornhuber, J., Bormann, J., Retz, W., Hübers, M., & Riederer, P. (1989). Memantine displaces [3H] MK-801 at therapeutic concentrations in postmortem human frontal cortex. *European Journal of Pharmacology*, *166*(3), 589–590.

Koster, R., Guitart-Masip, M., Dolan, R. J., & Düzel, E. (2015). Basal ganglia activity mirrors a benefit of action and reward on long-lasting event memory. *Cerebral Cortex*, *25*(12), 4908–4917.

Kroes, M. C., Schiller, D., LeDoux, J. E., & Phelps, E. A. (2016). Translational approaches targeting reconsolidation. *Translational Neuropsychopharmacology*, 197–230.

Kroes, M. C. W., Strange, B. A., & Dolan, R. J. (2010). Beta-Adrenergic Blockade during Memory Retrieval in Humans Evokes a Sustained Reduction of Declarative Emotional Memory Enhancement. *Journal of Neuroscience*, *30*(11), 3959–3963.

Kroes, M. C. W., Tendolkar, I., van Wingen, G., van Waarde, J. A., Strange, B. A., & Fernández, G. (2014). An electroconvulsive therapy procedure impairs reconsolidation of episodic memories in humans. *Nature Neuroscience*, *17*(2), 204–6.

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., … Charney. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry, 51*(3), 199–214.

Kuhlmann, S., & Wolf, O. T. (2006). Arousal and cortisol interact in modulating memory consolidation in healthy young men. *Behavioral Neuroscience*, *120*(1), 217–223.

Kushikata, T., Hirota, K., Yoshida, H., & Kubota, T. (2002). Alpha-2 adrenoceptor activity affects propofol-induced sleep time. *Anesthesia & Analgesia*, *94*(5), 1201–1206.

Kushikata, T., Yoshida, H., Kudo, M., Kudo, T., & Hirota, K. (2011). Role of coerulean noradrenergic neurones in general anaesthesia in rats. *British Journal of Anaesthesia*, *107*(6), 924–929.

LaBar, K. S., & Cabeza, R. (2006). Cognitive neuroscience of emotional memory. *Nature Reviews Neuroscience*, *7*(1), 54–64.

LaBar, K. S., & Disterhoft, J. F. (1998). Conditioning, awareness, and the hippocampus. *Hippocampus*, *8*(6), 620–626.

LaBar, K. S., LeDoux, J. E., Spencer, D. D., & Phelps, E. A. (1995). Impaired Fear Conditioning Following Unilateral Temporal Lobectomy in Humans. *Journal of Neuroscience*, *15*(10), 6846–6855.

LaBar, K. S., & Phelps, E. A. (1998). Arousal-mediated memory consolidation: Role of the medial temporal lobe in humans. *Psychological Science*, *9*(6), 490–493.

LaBar, K. S., & Phelps, E. A. (2005). Reinstatement of Conditioned Fear in Humans Is Context Dependent and Impaired in Amnesia. *Behavioral Neuroscience*, *119*(3), 677–686.

Lang, P. J. (1995). The emotion probe: Studies of motivation and attention. *American Psychologist*, *50*(5), 372.

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1990). Emotion, attention, and the startle reflex. *Psychological Review*, *97*(3), 377.

Langley, M. S., & Heel, R. C. (1988). Propofol. A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs, 35*(4), 334–372.

Lanius, R. A., Williamson, P. C., Densmore, M., Boksman, K., Gupta, M. A., Neufeld, R. W., & Menon, R. S. (2001). Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *American Journal of Psychiatry, 158*(11), 1920–1922.

Lattal, K. M., & Abel, T. (2004). Behavioral impairments caused by injections of the protein synthesis inhibitor anisomycin after contextual retrieval reverse with time. *Proceedings of the National Academy of Sciences of the United States of America, 101*(13), 4667–4672.

Lechner, H. A., Squire, L. R., & Byrne, J. H. (1999). 100 Years of Consolidation —– Remembering Muller and Pilzecker. *Learning & Memory, 6(2)*, 77–87.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu. Rev. Neurosci., 23*, 155–184.

LeDoux, J. E., Iwata, J., Cicchetti, P. R. D. J., & Reis, D. J. (1988). Different Projections of the Central Amygdaloid Nucleus Mediate Autonomic and Behavioral Correlates of Conditioned Fear. *Journal of Neuroscience, 8*(7), 2517–2529.

Lee, J. L., & Everitt, B. J. (2008). Appetitive memory reconsolidation depends upon NMDA receptor-mediated neurotransmission. *Neurobiology of Learning and Memory, 90*(1), 147–154.

Lewis, D. J. (1979). Psychobiology of active and inactive memory. *Psychological Bulletin, 86(5)*, 1054.

Li, R., Nishijo, H., Ono, T., Ohtani, Y., & Ohtani, O. (2002). Synapses on GABAergic neurons in the basolateral nucleus of the rat amygdala: Double-labeling immunoelectron microscopy. *Synapse, 43*(1), 42–50.

Liang, K. C., Juler, R. G., & McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. *Brain Research, 368*(1), 125–133.

Liang, K. C., McGaugh, J. L., Martinez, J. L., Jensen, R. A., Vasquez, B. J., & Messing, R. B. (1982). Post-training amygdaloid lesions impair retention of an inhibitory avoidance response. *Behavioural Brain Research*, *4*(3), 237–249.

Liu, X., Ramirez, S., Pang, P. T., Puryear, C. B., Govindarajan, A., Deisseroth, K., & Tonegawa, S. (2012). Optogenetic stimulation of a hippocampal engram activates fear memory recall. *Nature*, *484*(7394), 381–385.

Lonergan, M. H., & Pitman, R. K. (2013). Propranolol â€^{TM} s effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants : A meta-analysis. *Journal of Psychiatry & Neuroscience: JPN*, *38(4)*, 222.

Lonergan, M., Saumier, D., Tremblay, J., Kieffer, B., & Brunet, A. (2016). Reactivating addiction-related memories under propranolol to reduce craving: a pilot randomized controlled trial. *Journal of Behavior Therapy and Experimental Psychiatry*, *50*(245–249).

Lovibond, P. F., & Shanks, D. R. (2002). The role of awareness in Pavlovian conditioning: empirical evidence and theoretical implications. *Journal of Experimental Psychology: Animal Behavior Processes*, *28*(1), 3.

Lowenthal, D. T., Briggs, W. A., Gibson, T. P., Nelson, H., & Cirksena, W. J. (1974). Pharmacokinetics of oral propranolol in chronic renal disease. *Clinical Pharmacology & Therapeutics*, *16*(5part1), 761–769.

Lupien, S., Lecours, A. R., Lussier, I., Schwartz, G., Nair, N. P., & Meaney, M. J. (1994). Basal cortisol levels and cognitive deficits in human aging. *Journal of Neuroscience*, *14*(5), 2893–2903.

Macht, D. I., Isaacs, S., & Greenberg, J. (1918). Action of some antipyretic analgesics on psychological reaction time. *Psychobiology*, *1*(4), 327.

Mackenzie, N., & Grant, I. S. (1987). Propofol for intravenous sedation. *Anaesthesia*, *42*(1), 3–6.

Mackiewicz, K. L., Sarinopoulos, I., Cleven, K. L., & Nitschke, J. B. (2006). The effect of anticipation and the specificity of sex differences for amygdala and hippocampus

function in emotional memory. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(38), 14200–5.

Madison, D. V., & Nicoll, R. A. (1986). Actions of noradrenaline recorded intracellularly in rat hippocampal CA1 pyramidal neurones, in vitro. *The Journal of Physiology*, *372*(1), 221–244.

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science*, *280*(5365), 921–924.

Maheu, F. S., Joober, R., Beaulieu, S., & Lupien, S. J. (2004). Differential effects of adrenergic and corticosteroid hormonal systems on human short- and long-term declarative memory for emotionally arousing material. *Behavioral Neuroscience*, *118*(2), 420–8.

Makkar, S. R., Zhang, S. Q., & Cranney, J. (2010). Behavioral and Neural Analysis of GABA in the Acquisition, Consolidation, Reconsolidation, and Extinction of Fear Memory. *Neuropsychopharmacology*, *35*(8), 1625–1652.

Maren, S., & Quirk, G. J. (2004). Neuronal signalling of fear memory. *Nature Reviews. Neuroscience*, *5*(11), 844–852.

Marik, P. E. (2004). Propofol: therapeutic indications and side-effects. *Current Pharmaceutical Design*, *10*(29), 3639–3649.

Marr, D. (1971). Simple Memory: A Theory for Archicortex. *Source: Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *262*(841), 23–81.

Martin, S. J., Grimwood, P. D., & Morris, R. G. M. (2000). Synaptic plasticity and memory: an evaluation of the hypothesis. *Annual Review of Neuroscience*, *23*(1), 649–711.

Mather, L. E. (1983). Clinical Pharmacokinetics of Fentanyl and its Newer Derivatives. *Clinical Pharmacokinetics*, *8*(5), 422–446.

Matthysse, S. (1973). Dopamine and the pharmacology of schizophrenia: the state of the evidence. *Journal of Psychiatric Research, 11*, 107–113.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: *Psychological Review, 102*(3), 419–57.

McDonald, A. J. (1998). Cortical pathways to the mammalian amygdala. *Progress in Neurobiology, 55*(3), 257–332.

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews, 87*(3), 879–904.

McGaugh, J. L. (1966). Time-Dependent Processes in Memory Storage. *Science, 153*(3742), 1351–1358.

McGaugh, J. L. (2000). Neuroscience - Memory - a century of consolidation. *Science, 287*(5451), 248–251.

McGaugh, J. L. (2004a). Memory reconsolidation hypothesis revived but restrained: theoretical comment on Biedenkapp and Rudy (2004).

McGaugh, J. L. (2004b). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci., 27*, 1–28.

McGaugh, J. L., Cahill, L., & Roozendaal, B. (1996). Involvement of the amygdala in memory storage: interaction with other brain systems. *Proceedings of the National Academy of Sciences of the United States of America, 93*(24), 13508–13514.

McGaugh, J. L., & Roozendaal, B. (2002). Role of adrenal stress hormones in forming lasting memories in the brain. *Current Opinion in Neurobiology, 12*(2), 205–210.

McGaugh, J. L., & Roozendaal, B. (2009). Drug enhancement of memory consolidation: historical perspective and neurobiological implications. *Psychopharmacology, 202*(1–3), 3–14.

McKenzie, S., & Eichenbaum, H. (2011). Consolidation and reconsolidation: two lives of memories? *Neuron, 71(2),* 224–233.

McNally, R. (2003). Progress and controversy in the study of posttraumatic stress disorder. *Annual Review of Psychology*, *54*(1), 229–252.

McNeil, M. M., Lasker, B. A., Lott, T. J., & Jarvis, W. R. (1999). Candida albicans Postsurgical. *Journal of Clinical Microbiology*, *37*(5), 1398–1403.

Mecklinger, A., Parra, M., & Waldhauser, G. T. (2008). ERP correlates of intentional forgetting. *Brain Research*, *1255*, 132–147.

Melander, A., Danielson, K., Scherstén, B., & Wåhlin, E. (1977). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clinical Pharmacology & Therapeutics*, *22*(1), 108–112.

Meldrum, B. S. (2000). Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *The Journal of Nutrition*, *130*(4S Suppl), 1007S–15S.

Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*, *420*(6911), 70–74.

Milekic, M. H., & Alberini, C. M. (2002). Temporally graded requirement for protein synthesis following memory reactivation. *Neuron*, *36*(3), 521–525.

Miller, R. D., Pardo, M., & Stoelting, R. K. (2011). *Basics of anesthesia*. Elsevier/Saunders.

Miller, R. R., & Springer, A. D. (1974). Implications of recovery from experimental amnesia. *Psychological Review*, *81*(5), 470.

Milner, B., Corkin, S., & Teuber, H. L. (1968). Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of HM. *Neuropsychologia*, *6*(3), 215–234.

Milton, A. L., Lee, J. L., Butler, V. J., Gardner, R., & Everitt, B. J. (2008). Intra-amygdala and systemic antagonism of NMDA receptors prevents the reconsolidation of drug-associated memory and impairs subsequently both novel and previously acquired drug-seeking behaviors. *Journal of Neuroscience*, *28*(33), 8230–8237.

Mineka, S., Mystkowski, J. L., Hladek, D., & Rodriguez, B. I. (1999). The effects of

changing contexts on return of fear following exposure therapy for spider fear. *Journal of Consulting and Clinical Psychology*, *67*(4), 599.

Misanin, J., Miller, R., & Lewis, D. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science*.

Mishkin, M., Malamut, B., & Bachevalier, J. (1984a). Memories and habits: Two neural systems. *Neurobiology of Learning and Memory*, 65–77.

Mishkin, M., Malamut, B., & Bachevalier, J. (1984b). Memories and habits: Two neural systems. *Neurobiology of Human Learning and Memory*.

Missale, C., Nash, S. R., Robinson, S. W., Jaber, M., &, & Caron, M. G. (1998). Dopamine receptors: from structure to function. *Physiological Reviews*, *78*(1), 189–225.

Missonnier, P., Ragot, R., Derouesné, C., Guez, D., & Renault, B. (1999). Automatic attentional shifts induced by a noradrenergic drug in Alzheimer's disease: evidence from evoked potentials. *International Journal of Psychophysiology*, *33*(3), 243–251.

Mochizuki-Kawai, H. (2008). Neural basis of procedural memory. *Brain and Nerve= Shinkei Kenkyū No Shinpo*.

Mondadori, C., Weiskrantz, L., Buerki, H., Petschke, F., & Fagg, G. E. (1989). NMDA receptor antagonists can enhance or impair learning performance in animals. *Experimental Brain Research*, *75*(3), 449–456.

Monfils, M.-H., Cowansage, K. K., Klann, E., & LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science*, *324*(5929), 951–955.

Moratti, S., Giménez-Fernández, T., Méndez-Bértolo, C., & de Vicente-Pérez, F. (2017). Conditioned inhibitory and excitatory gain modulations of visual cortex in fear conditioning: Effects of analysis strategies of magnetocortical responses. *Psychophysiology*.

Morgan, C. J. A., & Curran, H. V. (2006). Acute and chronic effects of ketamine upon human memory: A review. *Psychopharmacology*, *188*(4), 408–424.

Morgan, D. W., & Legge, K. (1989). Clinical evaluation of propofol as an intravenous anaesthetic agent in cats and dogs. *The Veterinary Record*, *124*(2), 31–33.

Morgan, M. A., Romanski, L. M., & LeDoux, J. E. (1993). Extinction of emotional learning: contribution of medial prefrontal cortex. *Neuroscience Letters*, *163*(1), 109–113.

Morris, J., Öhman, A., & Dolan, R. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature*.

Moyer, J. R., Deyo, R. A., & Disterhoft, J. F. (1990). Hippocampectomy disrupts trace eye-blink conditioning in rabbits. *Behavioral Neuroscience*, *104*(2), 243.

Müller, G. E., & Pilzecker, A. (1900). *Experimentelle beiträge zur lehre vom gedächtniss*. *JA Barth*.

Münsterberg, H. (1892). *Beitraege zur experimentellen Psychologie, Heft 4*.

Murasaki, O., Kaibara, M., Nagase, Y., Mitarai, S., Doi, Y., Sumikawa, K., & Taniyama, K. (2003). Site of action of the general anesthetic propofol in muscarinic M1 receptor-mediated signal transduction. *Journal of Pharmacology and Experimental Therapeutics*, *307*(3), 995–1000.

Muravieva, E. V., & Alberini, C. M. (2010). Limited efficacy of propranolol on the reconsolidation of fear memories. *Learning & Memory*, *17*(6), 306–313.

Murphy, P. R., O'connell, R. G., O'sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Human Brain Mapping*, *35*(8), 4140–4154.

Myers, K. M., Ressler, K. J., & Davis, M. (2006). Different mechanisms of fear extinction dependent on length of time since fear acquisition. *Learning & Memory*, *13*(2), 216–223.

Nadel, L., Hupbach, A., Gomez, R., & Newman-Smith, K. (2012). Memory formation , consolidation and transformation. *Neuroscience & Biobehavioral Reviews*, *36(7)*, 1640–1645.

Nadel, L., & Land, C. (2000). Memory traces revisited. *Nature Reviews. Neuroscience*, *1*(3), 209–212.

Nadel, L., & Willner, J. (1980). Context and conditioning: A place for space. *Physiological Psychology*, *8*(2), 218–228.

Nader, K., Schafe, G. E., & Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*, *406*(6797), 722–726.

Nader, K., & Einarsson, E. (2010). Memory reconsolidation: an update. *Annals of the New York Academy of Sciences*, *1191*, 27–41.

Nader, K., & Hardt, O. (2009). A single standard for memory: the case for reconsolidation. *Nature Reviews Neuroscience*, *10*(3), 224–234.

Nader, K., Schafe, G., & LeDoux, J. (2000). The labile nature of consolidation theory. *Nature Reviews. Neuroscience*, *1*(3), 216–219.

Nader, K., & Wang, S. H. (2006). Fading in. *Learning & Memory*, *13*(5), 530–535.

Nemeroff, C. B., Bremner, J. D., Foa, E. B., Mayberg, H. S., North, C. S., & Stein, M. B. (2009). Posttraumatic Stress Disorder: A State-of-the-Science Review. *Journal of Psychiatric Research*, *40*(1), 1–21.

Newcomer, J. W., Craft, S., Hershey, T., Askins, K., & Bardgett, M. E. (1994). Glucocorticoid-induced impairment in declarative memory performance in adult humans. *Journal of Neuroscience*, *14*(4), 2047–2053.

Nikzad, S., Vafaei, A. A., Rashidy-Pour, A., & Haghighi, S. (2011). Systemic and intrahippocampal administrations of the glucocorticoid receptor antagonist RU38486 impairs fear memory reconsolidation in rats. *Stress*, *14*(4), 459–464.

Nilsson, L., Nordberg, A., Hardy, J., & Wester, P. (1986). Physostigmine restores3H-acetylcholine efflux from Alzheimer brain slices to normal level. *Journal of Neural*.

Norbury, R., Mackay, C. E., Cowen, P. J., Goodwin, G. M., & Harmer, C. J. (2007). Short-term antidepressant treatment and facial processing. Functional magnetic resonance imaging study. *The British Journal of Psychiatry*, *190*(6), 531–532.

O'Carroll, R. E., Drysdale, E., Cahill, L., Shajahan, P., & Ebmeier, K. P. (1999). Stimulation of the noradrenergic system enhances and blockade reduces memory for emotional material in man. *Psychological Medicine*, *29*(5), 1083–1088.

O'keefe, J., & Nadel, L. (1978). *The hippocampus as a cognitive map*. (Oxford: Clarendon Press, Ed.).

Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, *14*(8), 1215–1229.

Öhman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychological Review*, *108*(3), 483.

Oitzl, M. S., & De Kloet, E. R. (1992). Selective Corticosteroid Antagonists Modulate Specific Aspects of Spatial Orientation Learning. *Behavioral Neuroscience*, *106*(1), 62–71.

Orser, B. A., Bertlik, M., Wang, L. Y., & MacDonald, J. F. (1995). Inhibition by propofol (2, 6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. *British Journal of Pharmacology*, *116*(2), 1761–1768.

Ortiz, J. R., & Lora-Tamayo, J. I. (2009). *Anestesia Total intravenosa, Principios básicos.* (L. Aguilera & A. Abad, Eds.). S.A. de Litografía, España 2009.

Otmakhova, N. A., & Lisman, J. E. (1996). D1/D5 Dopamine Receptor Activation Increases the Magnitude of Early Long-Term Potentiation at CA1 Hippocampal Synapses. *Journal of Neuroscience*, *16*(23), 7478–7486.

Oyarzún, J. P., Lopez-Barroso, D., Fuentemilla, L., Cucurell, D., Pedraza, C., Rodriguez-Fornells, A., & de Diego-Balaguer, R. (2012). Updating fearful memories with extinction training during reconsolidation: A human study using auditory aversive stimuli. *PLoS ONE*, *7*(6).

Pachas, G. N., Gilman, J., Orr, S. P., Hoeppner, B., & Evins, A. E. (2015). Single dose propranolol does not affect physiologic or emotional reactivity to smoking cues. *Psychopharmacology*, *232*(9), 1619–1628.

Packard, M. G., Cahill, L., & McGaugh, J. L. (1994). Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proceedings of the National Academy of Sciences, 91*(18), 8477–8481.

Packard, M. G., & Teather, L. A. (1998). Amygdala modulation of multiple memory systems: hippocampus and caudate-putamen. *Neurobiology of Learning and Memory, 69*(2), 163–203.

Papez, J. W. (1937). A proposed mechanism of emotion. *Archives of Neurology & Psychiatry, 38*(4), 725–743.

Paré, D. (2003). Role of the basolateral amygdala in memory consolidation. *Progress in Neurobiology, 70*(5), 409–420.

Parent, M. B., Quirarte, G. L., Cahill, L., & McGaugh, J. L. (1995). Spared retention of inhibitory avoidance learning after posttraining amygdala lesions. *Behavioral Neuroscience, 109*(4), 803.

Parsons, R. L., Kaye, C. M., Raymond, K., Trounce, J. R., & Turner, P. (1976). Absorption of propranolol and practolol in Coeliac disease. *Gut, 17*(2), 139–143.

Paterson, J. W., Conolly, M. E., Dollery, C. T., Hayes, A., & Cooper, R. G. (1970). The pharmacodynamics and metabolism of propranolol in man. *Pharmacologia Clinica, 2*(3), 127–133.

Pavlides, C., Ogawa, S., Kimura, A., & McEwen, B. S. (1996). Role of adrenal steroid mineralocorticoid and glucocorticoid receptors in long-term potentiation in the CA1 field of hippocampal slices. *Brain Research, 738*(2), 229–235.

Payne, J. D., Nadel, L., Allen, J. J., Thomas, K. G., & Jacobs, W. J. (2002). The effects of experimentally induced stress on false recognition. *Memory, 10*(1), 1–6.

Pedreira, M. E., & Maldonado, H. (2003). Protein synthesis subserves reconsolidation or extinction depending on reminder duration. *Neuron, 38*(6), 863–869.

Peduto, V. A., Concas, A., Santoro, G., Biggio, G., & Gessa, G. L. (1991). Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in

the rat brain. *Anesthesiology*, *75*(6), 1000–1009.

Peper, M., Karcher, S., Wohlfarth, R., Reinshagen, G., & LeDoux, J. E. (2001). Aversive learning in patients with unilateral lesions of the amygdala and hippocampus. *Biological Psychology*, *58*(1), 1–23.

Perrin, J., Merz, S., Bennett, D., Currie, J., Steele, D., Reid, I., & Schwarzbauer, C. (2012). Electroconvulsive therapy reduces frontal cortical connectivity in severe depressive disorder. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(14), 5464–8.

Petrovich, G. D., Canteras, N. S., & Swanson, L. W. (2001). Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems. *Brain Research Reviews*, *38*(1), 247–289.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & Ledoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, *43*(6), 897–905.

Phelps, E. A., LaBar, K. S., Anderson, A. K., O'connor, K. J., Fulbright, R. K., & Spencer, D. D. (1998). Specifying the contributions of the human amygdala to emotional memory: A case study. *Neurocase*, *4*(6), 527–540.

Phelps, E. A., LaBar, K. S., & Spencer, D. D. (1997). Memory for emotional words following unilateral temporal lobectomy. *Brain and Cognition*, *35*(1), 85–109.

Phillips, R. G., & Ledoux, J. E. (1992). Differential Contribution of Amygdala and Hippocampus to Cued and Contextual Fear Conditioning. *Behavioral Neuroscience*, *106*(2), 274–285.

Phillips, R. G., & LeDoux, J. E. (1992). Differential Contribution of Amygdala and Hippocampus to Cued and Contextual Fear Conditioning. *Behavioral Neuroscience*, *106*(2), 274.

Pieri, L., Schaffner, R., Scherschlicht, R., Polc, P., Sepinwall, J., Davidson, A., & Keller, H. H. (1980). Pharmacology of midazolam. *Arzneimittel-Forschung*, *31*(12a), 2180–2201.

Pitkänen, A., Pikkarainen, M., Nurminen, N., & Ylinen, A. (2000). Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat: a review. *Annals of the New York Academy of Sciences*, *911*(1), 369–391.

Pitman, R. K. (1989). Post-traumatic stress disorder, hormones, and memory. *Biological Psychiatry*, *26*(3), 221–223.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B., … Orr, S. P. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry*, *51*(2), 189–192.

Poldrack, R. A., Prabhakaran, V., Seger, C. a, & Gabrieli, J. D. (1999). Striatal activation during acquisition of a cognitive skill. *Neuropsychology*, *13*(4), 564–574.

Poldrack, R., & Packard, M. (2003). Competition among multiple memory systems: converging evidence from animal and human brain studies. *Neuropsychologia*, *41*(3), 245–251.

Poundja, J., Sanche, S., Tremblay, J., & Brunet, A. (2012). Trauma reactivation under the influence of propranolol: an examination of clinical predictors. *European Journal of Psychotraumatology*, *3*(2), 1–9.

Power, A. E., Berlau, D. J., McGaugh, J. L., & Steward, O. (2006). Anisomycin infused into the hippocampus fails to block “reconsolidation” but impairs extinction: The role of re-exposure duration. *Learning & Memory*, *13*(1), 27–34.

Power, A. E., Thal, L. J., & McGaugh, J. L. (2002). Lesions of the nucleus basalis magnocellularis induced by 192 IgG-saporin block memory enhancement with posttraining norepinephrine in the basolateral amygdala. *Proceedings of the National Academy of Sciences*, *99*(4), 2315–2319.

Prager, E. M., Bergstrom, H. C., Wynn, G. H., & Braga, M. F. M. (2016). The basolateral amygdala ??-aminobutyric acidergic system in health and disease. *Journal of Neuroscience Research*, *94*(6), 548–567.

Price, J. L., & Amaral, D. G. (1981). An autoradiographic study of the projections of the

central nucleus of the monkey amygdala. *Journal of Neuroscience*, *1*(11), 1242–1259.

Price, J. L. (2003). Comparative aspects of amygdala connectivity. *Annals of the New York Academy of Sciences*, *985*(1), 50–58.

Przybyslawski, J., Roullet, P., & Sara, S. J. (1999). Attenuation of emotional and nonemotional memories after their reactivation: Role of beta adrenergic receptors. *The Journal of Neuroscience*, *19*(15), 6623–6628.

Pulvermüller, F. (2005). Brain mechanisms linking language and action. *Nature Reviews Neuroscience*, *6*(7), 576–582.

Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A.-S., McNamara, J. O., & White, L. E. (2008). *Movement and its central control*. (I. Sinauer Associates, Ed.), *Neuroscience (Fourth Edition)*.

Pussinen, R., & Sirviö, J. (1998). Minor role for α1-adrenoceptors in the facilitation of induction and early maintenance of long-term potentiation in the CA1 field of the hippocampus. *Journal of Neuroscience Research*, *51*(3), 309–315.

Quirarte, G. L., Roozendaal, B., & McGaugh, J. L. (1997). Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences*, *94*(25), 14048–14053.

Quirk, G. J., Likhtik, E., Pelletier, J. G., & Paré, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *The Journal of Neuroscience*, *23*(25), 8800–8807.

Quirk, G. J., Russo, G. K., Barron, J. L., & Lebron, K. (2000). The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *The Journal of Neuroscience*, *20*(16), 6225–6231.

Ramirez, S., Liu, X., Lin, P. A., Suh, J., Pignatelli, M., Redondo, R. L., & Tonegawa, S. (2013). Creating a False Memory in the Hippocampus. *Science*, *341*(6144), 387–391.

Rauch, S. L., Shin, L. M., Whalen, P. J., & Pitman, R. K. (1998). Neuroimaging and the neuroanatomy of posttraumatic stress disorder. *CNS Spectrums*, *3*(S2), 30–41.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., & Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry*, *47*(9), 769–776.

Reist, C., Duffy, J. G., Fujimoto, K., & Cahill, L. (2001). beta-Adrenergic blockade and emotional memory in PTSD. *The International Journal of Neuropsychopharmacology / Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*, *4*(4), 377–383.

Reitz, J. A. (1986). Alfentanil in Anesthesia and Analgesia. *Annals of Pharmacotherapy*, *20*(5), 335–341.

Ren, Y., Zhang, F. J., Xue, Q. S., Zhao, X., & Yu, B. W. (2008). Bilateral Inhibition of gamma-Aminobutyric Acid Type A Receptor Function within the Basolateral Amygdala Blocked Propofol-induced Amnesia and Activity-regulated Cytoskeletal Protein Expression Inhibition in the Hippocampus. *Anesthesiology*, *109*(5), 775–781.

Rescorla, R. A. (1988). Pavlovian Conditioning. *American Psychologist*, *43*(3), 151.

Rescorla, R. A., & Heth, C. D. (1975). Reinstatement of fear to an extinguished conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes*, *1*(1), 88.

Ressler, K., & Mayberg, H. (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nature Neuroscience*, *10*(9), 1116–24.

Reves, J. D., Fragen, R. J., Vinik, H. R., & Greenblatt, D. J. (1985). Midazolam: pharmacology and uses. *Anesthesiology*, *62*(3), 310–324.

Riedel, G., Platt, B., & Micheau, J. (2003). Glutamate receptor function in learning and memory. *Behav.Brain Res.*, *140*(1–2), 1–47.

Rimmele, U., Besedovsky, L., Lange, T., & Born, J. (2013). Blocking mineralocorticoid receptors impairs, blocking glucocorticoid receptors enhances memory retrieval in humans. *Neuropsychopharmacology*, *38*(5), 884–894.

Rimmele, U., Domes, G., Mathiak, K., & Hautzinger, M. (2003). Cortisol has different effects on human memory for emotional and neutral stimuli. *Neuroreport*, *14*(18), 2485–8.

Ritchey, M., Dolcos, F., & Cabeza, R. (2008). Role of Amygdala Connectivity in the Persistence of Emotional Memories Over Time: An Event-Related fMRI Investigation. *Cerebral Cortex*, *18*(11), 2494–2504.

Robbins, S. J. (1990). Mechanisms underlying spontaneous recovery in autoshaping. *lJournal of Experimental Psychology: Animal Behavior Processes*, *16*(3), 235.

Rodriguez, B. I., Craske, M. G., Mineka, S., & Hladek, D. (1999). Context-specificity of relapse: Effects of therapist and environmental context on return of fear. *Behaviour Research and Therapy*, *37*(9), 845–862.

Rodríguez, M. L. C., Campos, J., Forcato, C., Leiguarda, R., Maldonado, H., Molina, V. A., & Pedreira, M. E. (2013). Enhancing a declarative memory in humans : The effect of clonazepam on reconsolidation. *Neuropharmacology*, *64*, 432–442.

Roozendaal, B., & McGaugh, J. L. (1996). The memory-modulatory effects of glucocorticoids depend on an intact stria terminalis. *Brain Research*, *709*(2), 243–250.

Roozendaal, B., Nguyen, B. T., Power, A. E., & McGaugh, J. L. (1999). Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(20), 11642–7.

Rose, J. K., & Rankin, C. H. (2006). Blocking memory reconsolidation reverses memory-associated changes in glutamate receptor expression. *Journal of Neuroscience*, *26*(45), 11582–11587.

Rosen, J. B., & Schulkin, J. (1998). From normal fear to pathological anxiety. *Psychological Review*, *105*(2), 325.

Rosenbaum, D. A. (2005). The Cinderella of Psychology: The Neglect of Motor Control in the Science of Mental Life and Behavior. *American Psychologist*, *60*(4), 308–317.

Rosene, D. L., & Van Hoesen, G. W. (1977). Hippocampal efferents reach widespread areas of cerebral cortex and amygdala in the rhesus monkey. *Science*, *198*(4314), 315–317.

Ross, J. A., McGonigle, P., & Van Bockstaele, E. J. (2015). Locus coeruleus, norepinephrine and Aβ peptides in Alzheimer's disease. *Neurobiology of Stress*, *2*, 73–84.

Rubin, D. C. (2006). The basic-systems model of episodic memory. *Perspectives on Psychological Science*, *1*(4), 277–311.

Rubin, R., Fried, R., & Franks, C. (1969). New application of ECT. *Advances in Behavior Therapy. New York: Academic Press.*, 37–44.

Rudy, J. W., Biedenkapp, J. C., Moineau, J., & Bolding, K. (2006). Anisomycin and the reconsolidation hypothesis. *Learning & Memory*, *13*(1), 1–3.

Ryle, G. (1949). THE CONCEPT OF MIND.

Rylett, R., Ball, M., & Colhoun, E. (1983). Evidence for high affinity choline transport in synaptosomes prepared from hippocampus and neocortex of patients with Alzheimer's disease. *Brain Research*.

Sakamoto, H., Fukuda, R., Okuaki, T., Rogers, M., Kasai, K., Machida, T., & Kato, N. (2005). Parahippocampal activation evoked by masked traumatic images in posttraumatic stress disorder: a functional MRI study. *Neuroimage*, *26*(3), 813–821.

Saladin, M. E., Gray, K. M., McRae-Clark, A. L., LaRowe, S. D., Yeatts, S. D., & Brady, K. T. (2013). A double blind, placebo-controlled study of the effects of post-retrieval propranolol on reconsolidation of memory for craving and cue reactivity in cocaine dependent humans. *Psychopharmacology*, *226*(4), 721–737.

San Martín, R. (2012). Event-related potential studies of outcome processing and feedback-guided learning. *Frontiers in Human Neuroscience*, *6*, 304.

Sangha, S., Scheibenstock, A., & Lukowiak, K. (2003). Reconsolidation of a long-term memory in Lymnaea requires new protein and RNA synthesis and the soma of right

pedal dorsal 1. *Journal of Neuroscience*, *23*(22), 8034–8040.

Sanna, E., Motzo, C., Usala, M., Serra, M., Dazzi, L., Maciocco, E., & Biggio, G. (1999). Characterization of the electrophysiological and pharmacological effects of 4-iodo-2, 6-diisopropylphenol, a propofol analogue devoid of sedative-anaesthetic. *British Journal of Pharmacology*, *126*(6), 1444–1454.

Sara, S. J. (2000). Retrieval and reconsolidation: Toward a neurobiology of remembering. *Learning & Memory*, *7*(2), 73–84.

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience*, *10*(3), 211–223.

Schacter,Daniel L. , Tulving, E. (1994). *Memory Systems 1994*.

Schacter, D. L. (1987). Memory, amnesia, and frontal lobe dysfunction. *Psychobiology*, *15*(1), 21–36.

Schacter, D., & Tulving, E. (1994). What are the memory systems of 1994? In D. L. S. & E. Tulving (Ed.), *Memory systems 1994* (pp. 1–38). Cambridge, MA: MIT Press.

Schiller, D., Cain, C. K., Curley, N. G., Schwartz, J. S., Stern, S. A., LeDoux, J. E., & Phelps, E. A. (2008). Evidence for recovery of fear following immediate extinction in rats and humans. (1). *Learning & Memory (Cold Spring Harbor, N.Y.)*, *15*(6), 394–402.

Schiller, D., Kanen, J. W., LeDoux, J. E., Monfils, M. H., & Phelps, E. A. (2013). Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement. *Proceedings of the National Academy of Sciences*, *110*(50), 20040–20045.

Schiller, D., Monfils, M., Raio, C. M., Johnson, D. C., Ledoux, J. E., & Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*, *463*(7277), 49–53.

Schiller, D., & Phelps, E. A. (2011). Does reconsolidation occur in humans? *Frontiers in Behavioral Neuroscience*, *5*(May), 24. https://doi.org/10.3389/fnbeh.2011.00024

Schoepp, D. D., & Conn, P. J. (1993). Metabotropic glutamate receptors in brain function and pathology. *Trends in Pharmacological Sciences*, *14*(1), 13–20.

Schott, B. H., & Düzel, E. (2008). The multiple roles of dopaminergic neurotransmission in episodic memory. In *Handbook of Behavioral Neuroscience* (Vol. 18, pp. 379–396).

Schwabe, L., Nader, K., & Pruessner, J. C. (2014). Reconsolidation of human memory: brain mechanisms and clinical relevance. *Biological Psychiatry*, *76(4)*, 274–280.

Schwabe, L., Nader, K., Wolf, O. T., Beaudry, T., & Pruessner, J. C. (2012). Neural signature of reconsolidation impairments by propranolol in humans. *Biological Psychiatry*, *71*(4), 380–386.

Schwabe, L., & Wolf, O. T. (2010a). Learning under stress impairs memory formation. *Neurobiology of Learning and Memory*, *93*(2), 183–188.

Schwabe, L., & Wolf, O. T. (2010b). Stress impairs the reconsolidation of autobiographical memories. *Neurobiology of Learning and Memory*, *94*(2), 153–157.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, *20(1)*, 11–21.

Sevenster, D., Beckers, T., & Kindt, M. (2013). Prediction error governs pharmacologically induced amnesia for learned fear. *Science*, *339(6121)*, 830–833.

Sevenster, D., Beckers, T., & Kindt, M. (2012). Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. *Neurobiology of Learning and Memory*, *97*(3), 338–345.

Shader, R. I., & Greenblatt, D. J. (1993). Use of benzodiazepines in anxiety disorders. *New England Journal of Medicine*, *328*(19), 1398–1405.

Shand, D. G., & Rangno, R. E. (1972). The disposition of propranolol. I. Elimination during oral absorption in man. *Pharmacology*, *7*(3), 159–68.

Sharot, T., & Phelps, E. A. (2004). How arousal modulates memory: Disentangling the effects of attention and retention. *Cognitive, Affective, & Behavioral Neuroscience*, *4*(3), 294–306.

Sharot, T., & Yonelinas, A. P. (2008). *Differential time-dependent effects of emotion on recollective experience and memory for contextual information*. *Cognition* (Vol. 106).

Shiffrin, R. M., & Atkinson, R. C. (1969a). Storage and Retrieval Processes in Long-Term Memory. *Psychological Review*, *76*(2), 179–193.

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(1), 169–191.

Shin, L. M., McNally, R. J., Kosslyn, S. M., Thompson, W. L., Rauch, S. L., Alpert, N. M., & Pitman, R. K. (1999). Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. *American Journal of Psychiatry*, *156*(4), 575–584.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., & Alpert, N. M. (2004). Regional cerebral blood flow in the amygdala and medial prefrontalcortex during traumatic imagery in male and female vietnam veterans with ptsd. *Archives of General Psychiatry*, *61*(2), 168–176.

Short, C. E., & Bufalari, A. (1999). Propofol anesthesia. *Veterinary Clinics of North America: Small Animal Practice*, *29*(3), 747–778.

Sieghart, W. (1995). Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes. *Pharmacological Reviews*, *47*(2), 181–234.

Simons, P. J., Cockshott, I. D., Douglas, E. J., Gordon, E. A., Hopkins, K., & Rowland, M. (1988). Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of 14C-propofol. *Xenobiotica*, *18*(4), 429–440.

Small, D. M., Gregory, M. D., Mak, Y. E., Gitelman, D., Mesulam, M. M., & Parrish, T. (2003). Dissociation of neural representation of intensity and affective valuation in human gustation. *Neuron*, *39*(4), 701–711.

Soeter, M., & Kindt, M. (2013). High Trait Anxiety : A Challenge for Disrupting Fear Memory Reconsolidation. *PLoS ONE*, *8(11)*, e75239.

Soeter, M., & Kindt, M. (2011). Disrupting reconsolidation: Pharmacological and behavioral manipulations. *Learning and Memory*, *18*(6), 357–366.

Soeter, M., & Kindt, M. (2015). An abrupt transformation of phobic behavior after a post-retrieval amnesic agent. *Biological Psychiatry*, *78*(12), 880–886.

Southwick, S. M., Davis, M., Horner, B., Cahill, L., Morgan III, C. A., Gold, P. E., & Charney, D. C. (2002). Relationship of enhanced norepinephrine activity during memory consolidation to enhanced long-term memory in humans. *American Journal of Psychiatry*, *159*(8), 1420–1422.

Squire, L. R., Slater, P. C., & Chace, P. M. (1976). Reactivation of recent or remote memory before electroconvulsive therapy does not produce retrograde amnesia. *Behavioral Biology*, *18(3)*, 335–343.

Squire, L. (1992). Memory and the Hippocampus : A Synthesis From Findings With Rats, Monkeys, and Humans. *Psychological Review*, *99*(2), 195–231.

Squire, L. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiology of Learning and Memory*, *82*(3), 171–177.

Squire, L. R. (2006). Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learning & Memory*, *13*(5), 522–529.

Squire, L. R. (2009). Memory and Brain systems:1969-2009. *The Journal of Neuroscience*, *29*(41), 12711–12716. https://doi.org/10.1523/JNEUROSCI.3575-09.2009

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation:a neurobiological perspective. *Current Opinion in Neurobiology PG - 178*, *5*, 183.

Squire, L. R., & Frambach, M. (1990). Cognitive skill learning in amnesia. *Psychobiology*, *18*(1), 109–117.

Squire, L. R., Slater, P. C., & Chace, P. M. (1975). Retrograde amnesia: temporal gradient in very long term memory following electroconvulsive therapy. *Science*, *187*(4171), 77–79.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe*. *Annu. Rev.*

Neurosci., *27*, 279–306.

Squire, L. R., & Zola-Morgan, S. (1991). The Medial Temporal Lobe Memory System. *Science*, *253*(5026), 1380–1386.

Steenen, S. A., van Wijk, A. J., Van Der Heijden, G. J., van Westrhenen, R., de Lange, J., & de Jongh, A. (2016). Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis. *Journal of Psychopharmacology*, *30*(2), 128–139.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology*, *11*(11), 1006–1012.

Sterpenich, V., D'Argembeau, A., Desseilles, M., Balteau, E., Albouy, G., Vandewalle, G., & Maquet, P. (2006). The Locus Ceruleus Is Involved in the Successful Retrieval of Emotional Memories in Humans. *Journal of Neuroscience*, *26*(28), 7416–7423.

Stoelting, R. K., & Hiller, S. C. (1991). Barbiturates. *Pharmacology & Physiology in Anesthetic Practice. 2nd Ed.*, *108*.

Strange, B. A., & Dolan, R. J. (2004). Beta-adrenergic modulation of emotional memory-evoked human amygdala and hippocampal responses. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(31), 11454–8.

Strange, B. A., Hurlemann, R., & Dolan, R. J. (2003). An emotion-induced retrograde amnesia in humans is amygdala-and β-adrenergic-dependent. *Proceedings of the National Academy of Sciences*, *100*(23), 13626–13631.

Suzuki, A., Josselyn, S. A., Frankland, P. W., Masushige, S., Silva, A. J., & Kida, S. (2004). Memory Reconsolidation and Extinction Have Distinct Temporal and Biochemical Signatures. *Journal of Neuroscience*, *24*(20), 4787–4795.

Talmi, D., & Moscovitch, M. (2004). Can semantic relatedness explain the enhancement of memory for emotional words? *Memory & Cognition*, *32*(5), 742–751.

Tano, M. C., Molina, V. A., Maldonado, H., & Pedreira, M. E. (2009). Memory consolidation and reconsolidation in an invertebrate model: the role of the GABAergic system. *Neuroscience*, *158*(2), 387–401.

Taubenfeld, S. M., Riceberg, J. S., New, A. S., & Alberini, C. M. (2009). Preclinical Assessment for Selectively Disrupting a Traumatic Memory via Postretrieval Inhibition of Glucocorticoid Receptors. *Biological Psychiatry*, *65*(3), 249–257.

Thoenissen, D., Zilles, K., & Toni, I. (2002). Differential involvement of parietal and precentral regions in movement preparation and motor intention. *Journal of Neuroscience*, *22*(20), 9024–9034.

Thome, J., Koppe, G., Hauschild, S., Liebke, L., Schmahl, C., Lis, S., & Bohus, M. (2016). Modification of Fear Memory by Pharmacological and Behavioural Interventions during Reconsolidation. *PLOS ONE*, *11*(8).

Thompson, R. F., Berger, T. W., Berry, S. D., Clark, G. A., Kettner, R. N., Lavond, D. G., … Weisz. (1982). *Neuronal substrates of learning and memory: hippocampus and other structures*. (Springer US, Ed.), *Conditioning*.

Tollenaar, M. S., Elzinga, B. M., Spinhoven, P., & Everaerd, W. (2009a). Immediate and prolonged effects of cortisol, but not propranolol, on memory retrieval in healthy young men. *Neurobiology of Learning and Memory*, *91*(1), 23–31.

Tollenaar, M. S., Elzinga, B. M., Spinhoven, P., & Everaerd, W. (2009b). Psychophysiological responding to emotional memories in healthy young men after cortisol and propranolol administration. *Psychopharmacology*, *203*(4), 793–803.

Tomaz, C., Dickinson-Anson, H., & McGaugh, J. L. (1992). Basolateral amygdala lesions block diazepam-induced anterograde amnesia in an inhibitory avoidance task. *Proceedings of the National Academy of Sciences of the United States of America*, *89*(8), 3615–3619.

Trapani, G., Altomare, C., Liso, G., Sanna, E., & Biggio, G. (2000). Propofol in anesthesia. Mechanism of action, structure-activity relationships, and drug delivery. *Curr.Med.Chem.*, *7*(2), 249–271.

Tronson, N. C., & Taylor, J. R. (2007). Molecular mechanisms of memory reconsolidation. *Nature Reviews Neuroscience*, *8*(4), 262–275.

Tully, K., & Bolshakov, V. Y. (2010). Emotional enhancement of memory: how

norepinephrine enables synaptic plasticity. *Molecular Brain*, *3*(1), 15.

Tulving, E. (1972). Episodic and semantic memory 1. Organization of Memory. *London: Academic*, *381*(4), 382–404.

Tulving, E. (1995). Organization of memory: Quo vadis. *The Cognitive Neurosciences*, *839847*.

Tulving, E., & Donaldson, W. (1972). Organization of memory.

Tulving, E., & Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus*, *8*(3), 198–204.

Tulving, E., Schacter, D., & Stark, H. (1932). Priming Effects in Word-Fragment Completion Are "Independent of Recognition Memory. *Learning, Memory*.

Turner, B. H., Mishkin, M., & Knapp, M. (1980). Organization of the amygdalopetal projections from modality-specific cortical association areas in the monkey. *Journal of Comparative Neurology*, *191*(4), 515–543.

Vaiva, G., Thomas, P., Ducrocq, F., Fontaine, M., Boss, V., Devos, P., & Goudemand, M. (2004). Low posttrauma GABA plasma levels as a predictive factor in the development of acute posttraumatic stress disorder. *Biological Psychiatry*, *55*(3), 250–254.

Van Bever, W. F., Niemegeers, C. J., Schellekens, K. H., & Janssen, P. A. (1975). N-4-Substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin. *Arzneimittel-Forschung*, *26*(8), 1548–1551.

van Stegeren, A. H. (2008). The role of the noradrenergic system in emotional memory. *Acta Psychologica*, *127*(3), 532–541.

Van Stegeren, A. H. (2009). Imaging Stress effects on memory: A reviw of neuroimaging studies. *The Canadian Journal of Psychiatry*, *54*(1), 16–27.

van Stegeren, A. H., Everaerd, W., Cahill, L., McGaugh, J. L., & Gooren, L. J. (1998). Memory for emotional events : differential effects of centrally versus peripherally

acting β -blocking agents. *Psychopharmacology*, *138*(3), 305–310.

Van Stegeren, A. H., Everaerd, W., Cahill, L., McGaugh, J. L., & Gooren, L. J. G. (1998). Memory for emotional events: Differential effects of centrally versus peripherally acting ??-blocking agents. *Psychopharmacology*, *138*(3–4), 305–310.

van Stegeren, A. H., Goekoop, R., Everaerd, W., Scheltens, P., Barkhof, F., Kuijer, J. P., & Rombouts, S. A. (2005). Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. *Neuroimage*, *24*(3), 898–909.

Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science (New York, N.Y.)*, *277*(5324), 376–380.

Vasile, B., Rasulo, F., Candiani, A., & Latronico, N. (2003). The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Medicine*, *29*(9), 1417–1425.

Walker, M. P., Brakefield, T., & Hobson, J. A. (2003). Dissociable stages of human memory consolidation and reconsolidation. *Nature*, *425*(October), 616–620.

Wang, S. J., Huang, C. C., Hsu, K. S., Tsai, J. J., Huang, C. C., & Gean, P. W. (1996). Blockade of isoproterenol-induced synaptic potentiation by tetra-9-aminoacridine in the rat amygdala. *Neuroscience Letters*, *214*(2), 87–90.

Wanscher, M., Tønnesen, E., Hüttel, M., & Larsen, K. (1985). Etomidate infusion and adrenocortical function. *Acta Anaesthesiologica Scandinavica*, *29*(5), 483–485.

Warrington, E. K. (1979). Neuropsychological evidence for multiple memory systems. In Amsterdam: Excerpta Medica (Ed.), *Brain and mind: Ciba Foundation Symposium* (pp. 153–166).

Warrington, E. K., & Weiskrantz, L. (1968). A study of learning and retention in amnesic patients. *Neuropsychologia*, *6*(3), 283–291.

Weaver, B. M., & Raptopoulos, D. (1990). Induction of anaesthesia in dogs and cats with propofol. *The Veterinary Record*, *126*(25), 617–620.

Wechsler, D. (1997). *WAIS-III: Wechsler adult intelligence scale*. (T. P. C. San Antonio, Ed.).

Weike, A. I., Schupp, H. T., & Hamm, A. O. (2007). Fear acquisition requires awareness in trace but not delay conditioning. *Psychophysiology*, *44*(1), 170–180.

White, P. F., Coe, V., Shafer, A., & Sung, M. L. (1986). Comparison of alfentanil with fentanyl for outpatient anesthesia. *The Journal of the American Society of Anesthesiologists*, *64*(1), 99–105.

Whitehouse, P., Price, D., Struble, R., & Clark, A. (1982). Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain.

Wikberg, J. E. (1982). Adrenergic receptors: classification, ligand binding and molecular properties. *Journal of Internal Medicine*, *212*(S665), 19–36.

Williams, C. L., & McGaugh, J. L. (1993). Reversible lesions of the nucleus of the solitary tract attenuate the memory-modulating effects of posttraining epinephrine. *Behavioral Neuroscience*, *107*(6), 955.

Williams, J., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., & Dalgleish, T. (2007). Autobiographical memory specificity and emotional disorder. *Psychological Bulletin*, *133*(1), 122–148.

Winograd, T. (1975). Frame representations and the declarative/procedural controversy. *Representation and Understanding: Studies in Cognitive Science*, 185–210.

Wolf, O. T. (2008). The influence of stress hormones on emotional memory: Relevance for psychopathology. *Acta Psychologica*, *127*(3), 513–531.

Wolpe, J. (1981). The dichotomy between classical conditioned and cognitively learned anxiety. *Journal of Behavior Therapy and Experimental Psychiatry*, *12*(1), 35–42.

Wong, L. a, Mayer, M. L., Jane, D. E., & Watkins, J. C. (1994). Willardiines differentiate agonist binding sites for kainate- versus AMPA-preferring glutamate receptors in DRG and hippocampal neurons. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *14*(6), 3881–97.

Wood, N. E., Rosasco, M. L., Suris, A. M., Spring, J. D., Marin, M. F., Lasko, N. B., & Pitman, R. K. (2015). Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: three negative psychophysiological studies. *Psychiatry Research*, *225*(1), 31–39.

Wouda, J. A., Diergaarde, L., Riga, D., van Mourik, Y., Schoffelmeer, A. N. M., & De Vries, T. J. (2010). Disruption of Long-Term Alcohol-Related Memory Reconsolidation: Role of β-Adrenoceptors and NMDA Receptors. *Frontiers in Behavioral Neuroscience*, *4*(11), 179.

Yerkes, R. M., & Dodson, D. (1908). The relation of strength of stimulus to rapidity of habit formation. *Journal of Comparative Neurology and Psycholog*, *18*(5), 459–482.

Yonelinas, A. P., & Ritchey, M. (2015). The slow forgetting of emotional episodic memories: an emotional binding account. *Trends in Cognitive Sciences*, *19*(5), 259–267.

Zarrindast, M. R., Bakhsha, A., Rostami, P., & Shafaghi, B. (2002). Effects of intrahippocampal injection of GABAergic drugs on memory retention of passive avoidance learning in rats. *Journal of Psychopharmacology*, *16*(4), 313–319.

Zhang, S., & Cranney, J. (2008). The Role of GABA and Anxiety in the Reconsolidation of Conditioned Fear. *Behavioral Neuroscience*, *122*(6), 1295.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *The Journal of Neuroscience*, *6*(10), 2950–2967.

Zoran, D. L., Riedesel, D. H., & Dyer, D. C. (1993). Pharmacokinetics of propofol in mixed-breed dogs and greyhounds. *American Journal of Veterinary Research*, *54*(5), 755–760.