UNIVERSIDADE FEDERAL DO RIO DE JANEIRO – UFRJ
CENTRO DE CIÊNCIAS DA SAÚDE – CCS
INSTITUTO DE PSIQUIATRIA – IPUB

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IS PHARMACOLOGICAL INTERVENTION EFFECTIVE IN DISRUPTING FEAR-RELATED MEMORY RECONSOLIDATION?

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Tese de doutorado apresentada ao Programa de pós-graduação em Psiquiatria e Saúde Mental (PROPSAM) do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB-UFRJ), como parte dos requisitos necessários à obtenção do título de Doutor em Ciências – Área de concentração em Psiquiatria.

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Prof. William Berger – Presidente da Banca

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As minhas tão amadas

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ABSTRACT

Background: Dangerous events are deeply memorized to be avoided in future for the aim of animals' survival. Aversive memories seems to be in the heart of fear-related disorders. Nevertheless, memories are not static. Memories are able to be updated with new information in a process called reconsolidation. The reactivation of a previous consolidated long-term memory by retrieval bring this original memory to a labile state until it goes reconsolidation into an updated long-term memory. Thus, reconsolidation process is an outstanding opportunity for updating or modulating maladaptive memories. Hence, considering that emotionally aversive memories play a crucial role in development and symptomatology of fear-related disorders, such as Posttraumatic Stress Disorder (PTSD) and anxiety disorders, the disruption of fear-related memory reconsolidation (FRMR) arises as a remarkable novel treatment mechanism for these psychiatry disorders.

Objectives: To identify the concepts and current knowledge of memory reconsolidation process present in the literature. To verify the effectiveness of pharmacological intervention in disrupting fear-related memory reconsolidation (FRMR) through a systematic review of the literature.

Methods: A computerized systematic literature search of the ISI Web of Science, SCOPUS, PsycInfo and PubMed databases for studies reporting on pharmachological intervention in memory reconsolidation. Original articles investigating interventions that can mitigate fear memory reconsolidation were selected. The selected articles were categorized based on the level of scientific evidence.

Results: 52 articles were selected. Propranolol was the only pharmacological agent categorized with level A of scientific evidence. Cortisol achieved level B of scientific evidence, as well as, doxycycline. Propranolol articles: 22 out of 27 randomized controlled trials (RCT), 3 out of 5 open-label trials and a case report revealed positive results. Cortisol articles: 7 out of 13 studies achieved positive

results using endogenous cortisol in fear-related memory reconsolidation. 2 out 4 trials investigating the use hydrocortisone in disrupting fear memory revealed an enhancing effect of cortisol on reconsolidation of the reactivated memory. Doxycycline attenuated fear-potentiated startle seven days after acquisition in the recall of threat memory. Sirolimus promoted fewer and less intense PTSD symptoms, according to Posttraumatic Civilian List (PCL) and Clinician-Administered PTSD Scale(CAPS) total scores one month after treatment, but the effects did not persisted three months later.

Conclusions: Until now, this is the first systematic review investigating the effectiveness of pharmacological interventions specifically in disrupting fear-related memory reconsolidation. Our results spotlight the beta-adrenergic antagonist, propranolol, which achieved level A of scientific evidence and plays the principal role in memory reconsolidation research until the present date. Besides that, our findings elevate cortisol as an expressive supporting actor in FRMR scenario receiving the level B of evidence. At last, doxycycline raise as a promisor representative of protein synthesis inhibitors in disrupting FRMR.

RESUMO

Introdução: Eventos perigosos são profundamente memorizados para serem evitados no futuro por motivo de sobrevivência dos animais. As memórias aversivas se mostram no centro dos transtornos relacionados ao medo. No entanto, as memórias não são estáticas. As memórias podem ser atualizadas com novas informações em um processo chamado reconsolidação. A reativação de uma memória de longo prazo previamente consolidada, traz novamente esta memória a um estado lábil até que ocorra a reconsolidação da memória atualizada em uma memória de longo prazo. Dessa forma, o processo de reconsolidação é uma excelente oportunidade para atualizar ou modular memórias desadaptativas. Assim, considerando que as memórias emocionalmente aversivas desempenham um papel crucial no desenvolvimento e na sintomatologia dos transtornos relacionados ao medo, como o transtorno de estresse pós-traumático (TEPT) e dos transtornos de ansiedade, o rompimento da reconsolidação da memória relacionada ao medo se apresenta como um incrível mecanismo para o tratamento desses transtornos psiquiátricos.

Objetivos: Identificar na literatura atual os conceitos e o conhecimento existente sobre o processo de reconsolidação de memória. Verificar através de uma revisão sistemática da literatura a eficácia de intervenção farmacológica na interrupção da reconsolidação da memória relacionada ao medo.

Métodos: Uma pesquisa bibliográfica sistemática e computadorizada das bases de dados ISI Web of Science, SCOPUS, PsycInfo e PubMed foi realizada a procura por estudos relatando intervenções farmacológicas na reconsolidação de memória. Foram selecionados artigos originais investigando intervenções a reconsolidação da memória do medo. Em seguida, os artigos selecionados foram categorizados com base no nível de evidência científica.

Resultados: 52 artigos foram selecionados. O propranolol foi o único agente farmacológico categorizado com nível A de evidência científica. O cortisol

atingiu nível B de evidência científica, assim como a doxiciclina. Artigos de propranolol: 22 de 27 ensaios clínicos randomizados (RCT), 3 de 5 estudos abertos e um relato de caso apresentaram resultados positivos. Artigos de cortisol: 7 de 13 estudos obtiveram resultados positivos usando o cortisol endógeno na reconsolidação de memória relacionada ao medo. 2 de 4 estudos que investigaram o uso da hidrocortisona na reconsolidação da memória do medo revelaram efeito positivo do cortisol na reconsolidação da memória. A doxiciclina atenuou os sintomas relacionados ao medo sete dias após a aquisição da memória de medo. O sirolimus promoveu redução dos sintomas de TEPT, de acordo com os escores totais da PCL e da CAPS um mês após o tratamento, mas esses efeitos não continuaram presentes depois de três meses.

Conclusões: Até presente momento, esta é a primeira revisão sistemática investigando a eficácia de intervenções farmacológicas especificamente na interrupção da reconsolidação da memória relacionada ao medo. Nossos resultados destacam o propranolol, que atingiu o nível A de evidência científica e desempenha um papel principal na pesquisa científica sobre reconsolidação da memória. Além disso, nossos achados colocam o cortisol na condição de coadjuvante expresssivo neste cenário, recebendo o nível B de evidência científica. Por fim, a doxiciclina se mostra como um representante promissor dentre os inibidores da síntese proteica na intervenção de reconsolidação de memória do medo.

SUMMARY

LISTA DE SIGLAS

ASI	Anxiety Sensitivity Index
BAI	Beck Anxiety Inventory
BDI-II	Revised Beck Depression Inventory
BLA	Baso-lateral Amygdala
BP	Blood Pressure
CAPS	The Clinician-Administered PTSD Scale
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CNS	Central Nervous System
DASS	Depression, Anxiety and Stress Scales
DRRI	The Deployment Risk and Resilience Inventory-Combat Experiences Scale
DSM	Diagnostic and Statistical Manual
FAS	Fear of Spiders Questionnaire
FRMR	Fear-related Memory Reconsolidation
HPA-axis	Hypothalamus Pittuitary Amygdala – axis
HPP	Hippocampus
HR	Heart Rate
IAPS	International Affective Picture System
IES-R	Impact of Event Scale Revised
LC	Locus coeruleus
MDBF	Multidimensional German Mood Scale
mPC	Medial-precortex
NEO-FFI	Five Factor Inventory

PANAS	Positive Affect and Negative Affect Schedule
PCL	The Posttraumatic Stress Disorder CheckList
PTSD	Posttraumatic Stress Disorder
QIDS-SR	Quick Inventory of Depressive Symptomatology
RCT	Randomized Clinical Trials
SAM	Self-Assessment Mankind
SAM	Subjective Experience of Stress
SCID-IV	The Structured Clinical Interview for DSM-IV
SCL-90	Symptoms Checklist
SECPT	Socially Evaluated Cold Pressor Test
SNAQ	Snake Questionnaire
SPQ	Spider Phobic Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitors
SSNRI	Selective Serotonin and Noradrenaline Reuptake Inhibitors
SUDS	Subjective Units of Distress Scale
TICS	Trier Inventory of Chronic Stress
TSQ	Traumatic Screening Questionnaire
USA	United States of America
VAS	Visual Analog Scales
WAIS-III	Wechsler Adult Intelligence Scale 3rd Edition

I can't remember anything
Can't tell if this is true or dream
Deep down inside I feel to scream
This terrible silence stops me

Now that the war is through with me
I'm waking up, I can now see
That there's not much left of me
Nothing is real but pain now

Hold my breath as I wish for death
Oh please God, wake me

Back in the womb it's much too real
In pumps life that I must feel
But can't look forward to reveal
Look to the time when I'll live

Fed through the tube that sticks in me
Just like a wartime novelty
Tied to machines that make me breathe
Cut this life off from me

Hold my breath as I wish for death
Oh please God, wake me
Now the world is gone I'm just one
Oh God help me
Hold my breath as I wish for death
Oh please God, help me

Darkness
Imprisoning me, All that I see
Absolute horror
I cannot live, I cannot die
Trapped in myself
Body my holding cell

Landmine
Has taken my sight, Taken my speech
Taken my hearing, Taken my arms
Taken my legs, Taken my soul
Left me with life in Hell

One – Metallica

1. INTRODUCTION

Not long time, the Italian philosopher Norberto Bobbio once said, “we are what we remember”. In other words, the memory of an individual is direct linked to his own history of life. Therefore, memory should be considered as a result of reconstructive process in which past experiences are stitched together to form an autobiographic narrative, adding colors inside the lines of life experiences based on their own concepts of the world (Schacter, Guerin, & Jacques, 2011). However not every memory would be healthy.

Based on evolutionary aspects, although is determinant that dangerous events are deeply memorized to be avoided in future for the aim of animals survival (Roger K Pitman et al., 2002), aversive memories seems to be in the heart of fear-related disorders (de Quervain, Schwabe, & Roozendaal, 2017). By the way, emotions presents a quite relationship with memory, enhancing its formation (Mueller & Cahill, 2010).

Nevertheless, memories are not static (M. T. Exton-McGuinness, J. L. Lee, & A. C. Reichelt, 2015). Memories are able to be updated with new information in a process called reconsolidation (Izquierdo, Furini, & Myskiw, 2016). The reactivation of a previous consolidated long-term memory by retrieval bring this original memory to a labile state until it goes reconsolidation into an updated long-term memory. Thus, reconsolidation process is an outstanding opportunity for updating or modulating maladaptive memories (J. L. C. Lee, Nader, & Schiller, 2017; Sandrini, Cohen, & Censor, 2015).

Hence, considering that emotionally aversive memories play a crucial role in development and symptomatology of fear-related disorders, such as Posttraumatic Stress Disorder (PTSD) (van Marle, 2015) and anxiety disorders (Kindt, 2014), the disruption of fear-related memory reconsolidation (FRMR) arises as a remarkable novel treatment mechanism for these psychiatry disorders.

1.1. LITERATURE REVIEW

The first step of the present study is to describe several concepts and structures related to the memory reconsolidation process, specifically fear-related memories reconsolidation, through a brief narrative review of the literature.

The comprehension of the whole processes implicated with fear-related memory is fundamental to understand how novel pharmacological interventions could be an outstanding weapon in the treatment of fear-related disorders.

1.1.1. Evolutionary values of memory

Since *The Expression of the Emotions in Man and Animals*, Darwin have theorized that evolution of emotions was a result of natural selection (Darwin & Prodger, 1998). The notion that emotions drive animals behaviour in search for survival comes also from a long time, supported by evolutionary evidences among different species (Hull, 1943).

Furthermore, animals are capable to make dynamic decisions in the presence of threat which triggers several features correlated to a defensive state (J. E. LeDoux, 2014). This defensive state is intrinsically associated to a multidimensional mechanism that involves hormonal, autonomic and neurotransmitter variables, which is capable to modulate and update memory via a variety of learning processes.

In this scenario, the concept of reconsolidation raise in the memory field. Memory reconsolidation is a neurophysiological process, which a previous consolidated memory turns into a labile state, making possible to be updated through new protein synthesis for once again goes stabilized and storage (Kindt & van Emmerik, 2016).

Among a variety of species, memory reconsolidation is present and seems to be a conserved memory mechanism maintained across them. There are several studies demonstrating memory reconsolidation in nematodes (Rose & Rankin, 2006), honeybees (Stollhoff, Menzel, & Eisenhardt, 2005, 2008), crabs (Marıa Eugenia Pedreira, Luis Marıa Perez-Cuesta, & Hector Maldonado, 2002; Tano, Molina, Maldonado, & Pedreira, 2009), mice (Kranjac et al., 2012; Villain et al., 2016), rats (Nader, Schafe, & Le Doux, 2000; Wu et al., 2014), and human beings. Hence, the ability to respond in a flexible and adaptive manner to continuously changing environments is a crucial evolutionary advantage of memory reconsolidation (Alberini & LeDoux, 2013).

1.1.2. Development of memory concepts

In the early of last century, researchers proposed the term memory consolidation for the first time. The pioneer study of Muller and Pilzecker (Müller & Pilzecker, 1900) investigated verbal learning and retention in human subjects, and concluded that memory formation occurs gradually after acquisition until memory consolidation. In other words, new learned information is labile, but progressively, becomes stable and resistant to disruption, and finally, storage as long-term memory, consolidated (McGaugh, 2000). In addition, early studies indicated that memory consolidation involves proteins synthesis in neurons (Davis & Squire, 1984; Flexner, Flexner, & Stellar, 1965; Goelet, Castellucci, Schacher, & Kandel, 1986).

Nevertheless, experiments demonstrated that memories are susceptible to disruption to be back to labile state. In animal models, researchers demonstrated that electroconvulsive shock (ECS) administered just after reminder session disrupts memory and promotes amnestic effects of original learning (Misanin, Miller, & Lewis, 1968; Schneider & Sherman, 1968). Since these findings, scientific attention come over the memory consolidation mechanism.

The primordial model of memory formation after a new learning consists in the transition from a short-term, an unstable state, to a long-term, stable form of this memory (McGaugh, 2000). This process received the name of consolidation. Memory consolidation states as protein synthesis dependent process (Kandel, Dudai, & Mayford, 2014). However, as already said above, a previous consolidated memory can be brought into a labile state by reactivation under certain conditions, during which the memory trace can be modified or even disrupted, to once again go stabilized (Nader et al., 2000). This process is called memory reconsolidation, and is protein synthesis de novo dependent.

The interference in memory reconsolidation process is best known as disruption of memory. Disruption aims to module the original memory, in its labile state, during the reconsolidation process. It is a time-dependent process and the result of modulating reconsolidation is present only after the reconsolidation process is completed (Agren, 2014).

In connection with memory disruption, retrieval is the process of recollecting previously stored information. Thus, a cue from the environmental setting or a fear reminder retrieve memories to a labile state, susceptible to alteration by a process known as reconsolidation (Nader et al., 2000; Przybyslawski, Roullet, & Sara, 1999). During “reconsolidation window”, molecular mechanisms of plasticity and memory stability can interferes updating, enhancing or disrupting memories (Cogan, Shapses, Robinson, & Tronson, 2018; Tronson, Wiseman, Olausson, & Taylor, 2006) through new protein synthesis. Therefore, since reconsolidation is not a simple reinstatement of consolidation, but a different phenomenon, the expression “reconsolidation” itself would not be the best one to describe the complexity of it mechanism (Izquierdo et al., 2016). Reconsolidation elucidates diverse aspect of memory processes and features, such as its dynamic nature of storage, behavioral flexibility and adaptation to environmental changing, likewise ameliorate maladaptive memories and potentiate adaptive behaviors in psychopathology.

In parallel, memory extinction arises as a concurrent phenomenon to memory reconsolidation process (Merlo, Milton, Goozee, Theobald, & Everitt, 2014). Early last century researches stated that memory extinction is a form of

learning in which animals learn to inhibit retrieval (Pavlov, 2010). Thus, memory extinction process not erase the original fear memory, but promotes its inhibition by new learned memory (Bouton, 1991; Dachowski & Flaherty, 2013), competing against the original one. In other meaning, extinction is the process during which conditioned responses to a stimulus previously paired with an aversive event suffers diminishing, when the stimulus is presented repeatedly without the aversive event (Bouton, 2002; Quirk & Mueller, 2008).

Furthermore, extinction of fear during memory retrieval could operate as a boundary condition for memory reconsolidation (M. G. N. Bos, Beckers, & Kindt, 2012). Previous studies postulated that reconsolidation and extinction are processes that brain chooses after retrieval depending on boundary conditions (Merlo et al., 2014; Nader et al., 2000). In other words, chooses between the disappearance of a learned response to a fear conditioned stimulus, the enhancement, or update of the original memory (Forcato, Argibay, Pedreira, & Maldonado, 2009; Forcato, Rodríguez, Pedreira, & Maldonado, 2010; Daniela Schiller et al., 2010; Daniela Schiller, Raio, & Phelps, 2012).

Hence, the fundamental key that wheels brain choices not seems to be the retrieval itself, but what is interpreted during the conditioned stimulus representation in retrieval (de Carvalho Myskiw, Furini, Schmidt, Ferreira, & Izquierdo, 2015; Santoyo-Zedillo, Rodriguez-Ortiz, Chavez-Marchetta, Bermudez-Rattoni, & Balderas, 2014).

1.2. BIOLOGICAL BASIS OF FEAR MEMORIES

Fear is the most studied emotion, which seems to be a result of neurophysiological associations triggered by exposure to real or imagined threats (Costanzi, Cannas, Saraulli, Rossi-Arnaud, & Cestari, 2011). However, what humans call fear today may be not the same emotion evoked when animals are exposed to comparable threats (J. LeDoux, 2012; J. E. LeDoux, 2014).

The ability to learn how to predict aversive events through environmental stimuli is crucial to the survival throughout the animal kingdom including human beings. By now, the classical Pavlovian fear-conditioning paradigm is an exemplar of this form of learning present in rodents and humans (Pavlov, 2010). Under an evolution shelter, this form of learning is an essential component of mammalian defensive behaviour system in face of present threats and future ones (Fanselow & LeDoux, 1999).

1.2.1. The Pavlovian fear conditioning

The Pavlovian fear conditioning, the classical paradigm, is well stablished as a reactivation protocol that aims to induce memory changes. This paradigm consists at first in presenting a neutral conditioned stimlulus (CS) contingently paired to an aversive event, unconditioned stimulus (US), like an electric shock, and another conditioned stimulus with different cue of original memory trace. Then, reactivates the original memory by representing the same CS, without the US paired before.

Differently to rodent species, fear-conditioning protocol in humans does not elicit overt behavioural responses to the CS. Usually, fear-conditioning uses readouts from the autonomic nervous system, such as skin conductance response (SCR) (D. R. Bach, Daunizeau, Friston, & Dolan; Staib, Castegnetti, & Bach, 2015) or its interaction with an innate startle response (D. R. Bach, 2015), to quantify its effectiveness.

Additionally, there is evidence that the formation and storage of CS-US associations during Pavlovian fear conditioning takes place in the amygdala (Maren, 2001), a limbic system structure. Electrophysiological recordings of amygdaloidal neuronal activity support a critical role for the amygdala in encoding and storing fear associations.

Therefore, understanding the neural features of a rapidly acquired and adaptive form of associative learning and memory in mammals, Pavlovian fear

conditioning has proved to be an illuminating translational model for comprehension and treating fear-related disorders, such as posttraumatic stress disorder (PTSD), phobic and anxiety disorders.

1.2.2. Fear-related memory reconsolidation (FRMR)

Maladaptive memories are at the bottom of fear-related disorders, such as Posttraumatic Stress Disorder (PTSD), phobic and anxiety disorders. The memory for a trauma becomes so disturbing as to disrupt ordinary functioning

This phenomena requires a conditioned stimulus quite similar to the original or sufficient intense to turn consolidated memory into labile state for memory reconsolidation. In contrary, a new different memory is formed and consolidated in long-term memory for storage.

Boundary conditions on destabilization and reconsolidation bases on an important observation in the study of reconsolidation is that memories are not always destabilized by simple retrieval, consistent with the apparent parallelism of expression and destabilization. Furthermore, the parameters of a reactivation session may cause the formation of a new memory, instead of updating the old one. Thus, it appears memories will only destabilize and undergo reconsolidation under certain conditions; successful reactivation and subsequent destabilization of the consolidated trace is prerequisite to permit the updating of the memory. It may be hypothesized that all memories can potentially undergo reconsolidation.

However, the reconsolidation process appears to be constrained by several boundary conditions. These include the existing strength of a memory (Suzuki et al., 2004; Reichelt & Lee, 2012), the age of a memory (Suzuki et al., 2004) and the competition between reconsolidation and extinction (Eisenberg et al., 2003; Merlo et al., 2014). The reconsolidation process appears to update the original memory (Lee, 2010), while extinction forms a new inhibitory memory trace (Bouton, 2002). In order to explain the outcome of this competition it was

suggested that short extinction sessions typically engage reconsolidation, while longer sessions lead to extinction (Reichelt & Lee, 2013).

A consolidated fear memory can enter a transient labile phase upon its reactivation. Pharmacological blockade of the subsequent protein synthesis dependent restabilization (reconsolidation) produces a memory deficit in both animals (Nader et al., 2000) and humans (Kindt et al., 2009). However, an independent measure for memory destabilization, other than the occurrence of reconsolidation itself, is not yet available.

1.2.3. Prediction error hypothesis

An important hypothesis in FRMR field is the Prediction Error (PE). Mainly studies on human and animals models argued that a consolidated memory, long-term memory, requires specific conditions to destabilization into a labile state for manipulation during reconsolidation process signal. However, retrieval of the original long-term memories not always lead to destabilization and then reconsolidation (Dieuwke Sevenster, Beckers, & Kindt, 2012). Then, there are certain boundary conditions determining that reconsolidation will only occur when updating of a memory is required (M. T. J. Exton-McGuinness, J. L. C. Lee, & A. C. Reichelt, 2015).

PE hypothesis postulates that there is a discrepancy between what is expected based on previous experiences of consolidated long-term memory and what is experienced during the reactivation process that triggers the original memory destabilization (Rescorla & Wagner, 1972). Thus, memory reactivation will lead to memory destabilization only if the animal new experiences present a prediction error (D. Sevenster, Beckers, & Kindt, 2014).

Recently, there are several studies supporting the PE hypothesis, in both humans and rats (Corlett & Fletcher, 2015; Fernandez, Boccia, & Pedreira, 2016; Krawczyk, Fernandez, Pedreira, & Boccia, 2017; Li et al., 2017; Dieuwke Sevenster et al., 2012). Different predict error types of predict errors were

induced in these experiments, varying the amount of CS or the response to exposure, or the temporal expectation of the US (M. T. J. Exton-McGuinness et al., 2015; Dieuwke Sevenster et al., 2012; D. Sevenster, Beckers, & Kindt, 2013; D. Sevenster et al., 2014).

In one hand, the authors demonstrated that a retrieval of memory followed by an asymptomatic learning episode or an omission of a predicted reinforcement during reactivation may destabilize a consolidated memory, but would leave the original memory intact. In other hand, if memory retrieval follows a symptomatic learning episode or a similar reinforced reminder, it should generate additional learning to the original memory via reconsolidation.

Therefore, considering that memory reconsolidation functional role is to update memories with new learning and destabilization occurs in response to a PE signaling, PE raise as an remarkable driven process of reconsolidation. (Finnie & Nader, 2012; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Dieuwke Sevenster et al., 2012). Hence, PE should provide a clear guide for developing treatments searching for permanent reduce of fear-related memories expression.

1.2.4. Fear generalization theory

A less investigated phenomenon, Fear Generalization (FG) theory advocates that a previously acquired physiological response to a specific threat should be transferred to a similar (Lopresto, Schipper, & Homberg, 2016). FG have a sophisticated charge in adaptive animal survival, since it promotes fast reactions to new environment stimuli judging it related to a previous learned fear-related experience and having the same consequences (Ghosh & Chattarji, 2015; Lissek et al., 2014).

Nevertheless, this dynamic mechanism could be maladaptive, when stimuli do not represent a real threat, but it is recognized as a dangerous one. Therefore, the occurrence of fear response in inappropriate circumstances may

produce a pathological cycle of functioning that predisposes the development of fear-related disorders, such as PTSD and anxiety disorders (Rajbhandari, Zhu, Adling, Fanselow, & Waschek, 2016).

In addition, exposure to stress presents a major risk factor for fear-related disorders, whereas it influences different phases of fear memory consolidation (Bender, Otamendi, Calfa, & Molina, 2018). Indeed, PTSD patients present an hyperactivity in response to numerous neutral stimuli far from the original traumatic event, even in safe contexts (Duits et al., 2015; Dunsmoor, Mitroff, & LaBar, 2009). Thus, FG have a great importance in PTSD etiological basis and pathological mechanism comprehension, as far as, the spread of anxiety cues signals through the individual's environment increases and maintain the anxiety symptoms, like positive feedback of fear response (Lissek et al., 2014)

1.3. FEAR-RELATED DISORDERS

According to DSM-5, stress exposure is a major risk factor for the occurrence of anxiety disorders (Association, 2013). The anxiety related disorders are among the most common psychiatric disorders, with a lifetime population prevalence about 29% in the USA (Kessler & Wang, 2008). The pathogenesis of fear-related disorders resides on the formation of a strong fear memory after experiencing an aversive event, depending on a associative learning or conditioning of this maladaptive memory trace (de Quervain et al., 2017).

Additionally, an optimal stress level facilitates long-term memory and stimulates cognitive performance by promoting consolidation, what is essential for long-term memory formation allowing adaptation to new environment changes. However, exposure to extreme, traumatic or chronic stress may lead to cognitive impairments and psychopathological disorders such as PTSD and anxiety disorders (Alberini & LeDoux, 2013).

Hence, stress is closely involved in the aetiology, exacerbation and treatment of affective psychopathology (Raio & Phelps, 2015). At first, exposure to acute stress immediately exerts effects on different brain regions intrinsically involved in the regulation of fear responses. Then, chronic exposure to stress increases systemic neuroendocrine changes possibly leading to dysfunctional regulation of the HPA-axis.

1.3.1. Posttraumautic stress disorder (PTSD)

The proposal that PTSD is primarily a disorder of memory seem quite stablished in the literature (Brewin, Kleiner, Vasterling, & Field, 2007; McNally, 2005; Van der Kolk & Fisler, 1995; van Marle, 2015). PTSD is a chronic and debilitating psychiatric disorder precipitated by exposure to severe traumatic event. In general population, there is a life time prevalence of approximately 7.2% (Kessler et al., 2005). In addition, the severity of PTSD symptomatology drastically impacts quality of life of the patients, even in the presence of other psychiatric disorders (Pagotto et al., 2015).

Emotion enhances memory encoding and facilitates later recall. During the traumatic event exposure, stress hormones are released and promote a deeply consolidation of the traumatic memory. Over time, the remembrance of the traumatic unwanted memories are quite frequently and intense, promoting the sense that the traumatic event is happening repeatedly, and then re-experiencing the trauma memory. Thus, contextual tracks related to the traumatic event easily reactivates the memory of trauma, causing hyperactivity of PTSD symptoms and avoidance of trauma reminders, until runs reconsolidation (Brunet et al., 2008; Roger K. Pitman, 2011). Subsequently, the extensively repeated reactivation of the traumatic memory in PTSD patients may lead to strengthening of the traumatic memory (Brunet et al., 2014; Dębiec, Bush, & LeDoux, 2011)

In PTSD traumatic memory machinery, the fear generalization theory could take a part. PTSD patients continue to perceive threat even when circumstances were different from the traumatic setting. Thereby it produces inappropriate fear responses to conditions that are no longer appropriate (Milad & Quirk, 2012).

1.3.2. Phobic and anxiety disorders

Fear memory lies at the root of anxiety disorders (Kindt, 2014), since their aetiology involves maladaptive learning and memory processes (Zlomuzica et al., 2014). As well as PTSD, phobic and anxiety disorders are intrinsically related to maladaptive fear generalization. Although, a fast response to a novel potential threat condition promoted by fear generalization is functional, it could become a maladaptive fear response when a neutral stimuli or contexts are inadequately considered harmful, likewise in anxiety disorders.

In FRMR researches in anxiety disorders, the Pavlovian fear-conditioning paradigm is the most used instrument. Despite this paradigm observations unveiled the neurobiology processes of fear learning and memory, neither in animals nor in humans can be directly translated to anxiety and related disorders. However, this limitation do not underestimate the paradigm empirical utility in anxiety disorders comprehension (Kindt, 2014).

1.4. ANATOMICAL STRUCTURES OF FRMR

The multiple processes of FRMR described above involves activity in different brain regions. In this context, there are several structures mutually implicated in central nervous system (CNS) that directly participate to FRMR (Kandel et al. 2014). Therefore, researches seek to find targets along the CNS

susceptible to pharmacological agents in disrupting fear-related memories among psychiatric disorders.

Among brain structures, the hippocampus, the amygdala and the Pre-Frontal Cortex specifically implicated with FRMR (Bolkan & Lattal, 2014; Dębiec, Díaz-Mataix, Bush, Doyère, & LeDoux, 2010; Mamiya et al., 2009; Prager, Bergstrom, Wynn, & Braga, 2016; Rajbhandari et al., 2016; A. M. Wells et al., 2011). Additionally, the acquisition of conditioned fear memory seems to be dependent on both hippocampus and amygdala (Maren, 2008).

1.4.1. Hippocampus

The capacity to modulate aspects of fear learning spotlights hippocampus in FRMR hall (Maren, 2001; Rossato, Köhler, Radiske, Bevilaqua, & Cammarota, 2015). One of the most plastic regions in the brain, hippocampus is essential to the perception and recognition of environmental stimuli, likewise, to spatial and contextual-based learning, and required for the acquisition of new episodic and declarative memories (Corcoran, Desmond, Frey, & Maren, 2005; Orsini & Maren, 2012).

However, memories do not remain in hippocampus. Time after time, memory are stored in frontal cortex, thus brain damage of the hippocampus cannot disrupts a memory once established (Taylor & Torregrossa, 2015).

The majority of studies investigating hippocampus mechanisms for disrupting fear memory reconsolidation focused in dorsal hippocampal activity. The dorsal hippocampus seems to wheel new protein synthesis required for memory reconsolidation, but coordinated by the amygdala (Ramirez et al., 2009; Audrey M Wells et al., 2011). In contrary, ventral hippocampus has even more intrinsic relationship with other brain regions involved in emotional regulation than dorsal hippocampus, what would better explain hippocampus regulation of fear-related memories. Hence, hippocampus malfunctioning

possibly correlates to fear memories disorders, like PTSD or anxiety disorders (Alberini & LeDoux, 2013).

1.4.2. Amygdala

The amygdala is a key structure for the FRMR (Nader, 2015). There are evidence that amygdala actively participates enhancing memory consolidation of emotionally arousing experiences, as well as, the GABAergic system present in the amygdala is the principal component involved in the modulation of emotional reactions to stressful stimuli (Prager et al 2016).

The emergence of amygdala, as a central character in regulating acquisition and expression of fear learning, started with investigations that used avoidance tasks in animal models to assess emotional behavior (Hitchcock & Davis, 1986; Slotnick, 1973). Since then, researches showed that amygdala extensively and intrinsically connects to cortical and subcortical regions (McDonald, 1998; Sah, Faber, Lopez de Armentia, & Power, 2003). There are multiple connections between the amygdala and medial prefrontal cortex (mPFC) that are crucial for the Pavlovian fear conditioning paradigm (Sotres-Bayon & Quirk, 2010). Amygdala also influences activity in the hippocampus by signaling for contextual fear memory reconsolidation (Taylor & Torregrossa, 2015).

Specifically, the Basolateral Amygdala (BLA) is critically implicated in the formation of fear-related memories and in coordinating appropriate response to environmental threats (Espejo, Ortiz, Martijena, & Molina, 2017). Moreover, the GABAergic signalling in BLA plays a pivotal role in the emergence of fear memory (Wolff et al., 2014) and in the promoting influence of stress on fear memory consolidation, since stress attenuates GABAergic inhibitory control in the BLA, thereby facilitating excitatory transmission which enhanced fear memory formation (I. D. Martijena & V. A. Molina, 2012). In rodents,

experiments have revealed that the Basolateral Amygdala (BLA) is an essential structure in FRMR mediating the update of the original fear-related memories.

The BLA is the primary sensory input zone of the amygdala, while the Central Amygdala (CeA) is the primary output structure that initiates physiological fear responses (Pape & Pare, 2010). The BLA is around 80% formed by glutamatergic principal neurons and the remaining cells are GABAergic interneurons (Spampanato, Polepalli, & Sah, 2011). The glutamatergic neurons in the BLA ascends to CeA and downstream connections to initiate the physiological fear responses (Ehrlich et al., 2009). In contrast, the CeA is a striatal-like structure that formed by GABAergic neurons

1.4.3. Frontal cortex

The PFC seems to have limited participation in FRMR. For instance, trace fear conditioning does not undergo protein synthesis-dependent reconsolidation in the medial PFC (Blum, Runyan, & Dash, 2006) and it shown more involvement in fear memory extinction than reconsolidation (Peters, Kalivas, & Quirk, 2009).

However, the inhibition of protein synthesis or the blockade of NMDA receptors in the ventromedial PFC hinders reconsolidation of an object recognition memory (Akirav & Maroun, 2006). Additionaly, the infusion of prazosin, an alpha-1-adrenergic receptor antagonist, in the prelimbic PFC inhibited reconsolidation of an olfactory-fear memory (Do Monte, Souza, Wong, & de Padua Carobrez, 2013).

1.4.4. Other structures

Locus coeruleus (LC) has a regulatory charge in aversive memory learning mediated by noradrenaline (NE), since LC arborizes dendritic

projections to all the other structures of hypothalamus-hypophysis-adrenal axis (HPA axis) (Arnsten, 2015). This regulation functioning is based on stress levels. Therefore, under higher stress level, LC increases NE levels in the amygdala enhancing its activity in cued fear learning while diminishes the prefrontal cortex (PFC) function. In contrast, under low stress levels, LC improves PFC function to promote inhibition of the amygdala and extinction of cued fear. In addition, LC exerts influence specifically the alfa1 and beta-adrenergic receptors in the BLA, modulating levels of fear and hindering new learning.

The nucleus accumbens has implications in FRMR. Glutamatergic inputs from the amygdala, hippocampus, and PFC and projects achieve the nucleus accumbens. Moreover, by its turn, nucleus accumbens GABAergic outputs to structures related to behavioural motor skills. There is less evidence that the nucleus accumbens is important for the reconsolidation of fear-associated memories.

1.5. PHYSIOLOGICAL MECHANISMS FOR FRMR DISRUPTION

There are three major mechanisms highlighted in the literature investigating pharmacological intervention in memory reconsolidation: the adrenergic blockade, the glucocorticoid-modulating role, and the protein synthesis inhibition.

In the next section, they are individually described. Each process are depicted and discussed through the FRMR perspective. Other mechanisms, involving NDMA receptors and GABAergic signaling, are briefly summarized.

1.5.1. Adrenergic blockade mechanism

The adrenergic activity strengthens memory consolidation and fear conditioning in the amygdala (McGaugh, 2004; Roozendaal, McEwen, & Chattarji, 2009). Researchers postulated that an adrenergic blockade promoted by pharmacological agents would abolish these effects (Brunet, Orr, Tremblay, Nader, & Pitman, 2005; Dębiec et al., 2011; Roger K Pitman et al., 2002).

Noradrenaline actively participates in the formation and the retrieval of emotional memories. Therefore, pharmacological manipulation that interferes in noradrenaline should be extremely important in fear-related disorders. For instance, studies have indicated that noradrenaline system may be dysregulated in PTSD (Tawa & Murphy, 2013).

Manipulations of adrenergic signalling are probably the most commonly studied mechanism of memory reconsolidation (Lim et al., 2018; Littel et al., 2017; Visser, Kunze, Westhoff, Scholte, & Kindt, 2015). Research on mechanisms of fear memory consolidation established that stimulation of beta-adrenergic receptors during conditioning can strengths fear memories. In contrary, disruption of adrenergic signalling during fear conditioning can make fear memories weaker (Dębiec & LeDoux, 2006).

Furthermore, stressful situations activates the sympathetic nervous system to noradrenaline release that is directly associated with the arousal and frightening degree. Thus, it is hypothesized that adrenergic signalling is responsible for the strength of fearful memories, so that the most arousing and dangerous experiences are remembered best and avoided in the future (McGaugh, 2013). Yet, researchers identified that adrenergic signalling influences not only the initial fear conditioning and consolidation, but also fear memory reconsolidation.

With regard to fear-related memories, systemic beta-adrenergic receptor blockade shows to inhibit reconsolidation of auditory fear conditioning (Debiec & Ledoux, 2004; Muravieva & Alberini, 2010) and inhibitory avoidance as described above (Przybyslawski et al., 1999). Other studies found that propranolol reduces a post-retrieval remote fear memory, thus providing evidence for its potential therapeutic utility (Debiec & Ledoux, 2004).

1.5.2. Glucocorticoid modulating role

The more stressful and emotionally arousing a memory trace is, the more vividly this memory trace will be remembered (Kuhlmann, Piel, & Wolf, 2005). There is evidence in the literature indicating that emotionally arousing information is especially sensitive to the memory-modulating effects of stress through glucocorticoids (GC) (Wolf, Hamacher-Dang, Drexler, & Merz, 2015). Thus, the combination of GR and adrenergic receptor stimulation in arousal situations strongly encodes memory consolidation.

The GC effects in memory implies the activation of the hypothalamus–pituitary–adrenal (HPA) axis, which powerfully modulates memory processes of encoding, consolidation, and retrieval (S. M. Drexler, Merz, Hamacher-Dang, Tegenthoff, & Wolf, 2015). However, GCs presents paradox properties over memory modulation. In one hand, GC enhance the consolidation of new memories under stress conditions (Buchanan & Lovallo, 2001). On the other hand, GC can reduce the retrieval of information that has already been stored, which means that a reduced memory retrieval would be helpful to hinder behaviours that are no more relevant or even maladaptive, such as happens in fear-related disorders (Wolf, Atsak, de Quervain, Roozendaal, & Wingenfeld, 2016; Zhou, Kindt, Joels, & Krugers, 2011).

Cortisol, a GC hormone, physiologically released in response to stress, have been widely investigated in disrupting memory reconsolidation. Elevated cortisol levels strongly impair memory retrieval (Aerni et al., 2004; S. M. Drexler, Merz, Hamacher-Dang, & Wolf, 2016; Schwabe & Wolf, 2010). Experiments

using cortisol have been reported to reduce general feelings of fear, and the reduction in fear is maintained when subjects are exposed to the phobic stimulus (Dominique et al., 2011; Soravia et al., 2006). Taken together these studies suggest that cortisol can reduce fear-related maladaptive memories. Thus, cortisol seems to interfere with memory retrieval rather than inhibiting reconsolidation.

The clinical relevance of the effects of exogenous GC administration is highlighted by the description of patients with anxiety disorders who demonstrate an enhancement of extinction-based therapies by GC treatment (Wolf et al., 2016). Moreover, GC acute administration reduces recall of trauma-related memory in PTSD and enhances fear extinction in patients with PTSD and phobic disorders (de Quervain et al., 2017).

The clinical interventions with GCs have special interest because unlike the most other drugs used to memory interference, GCs affect distinct memory processes that can synergistically contribute to a reduction of fear-related symptoms, reducing aversive-memory retrieval and enhancing fear extinction (de Quervain et al., 2017). Thus, cortisol stands as a great agent against the pathological cycle of fear-related memory reconsolidation.

However, while GCs strengths memory consolidation, there are also reports of acute stress or GC inhibiting memory, particularly post-retrieval manipulations that presumably affect reconsolidation processes. In contextual fear conditioning paradigms, acute post-retrieval administration of GC or stress exposure, impairs subsequent expression of fear (Cai, Blundell, Han, Greene, & Powell, 2006; Yang et al., 2013).

1.5.3. Protein synthesis inhibition

The inhibition of protein synthesis is an outstanding mechanism of action in animal models research of fear-related memory reconsolidation. It is well established that memory reconsolidation can be disrupted by either intracranial

or systemic administration of protein synthesis inhibitors (Nader et al., 2000; M. E. Pedreira, L. M. Perez-Cuesta, & H. Maldonado, 2002). Considering the reconsolidation protein synthesis dependence, the availability of agents that could block protein synthesis presents an outstanding advance in fear-related disorders treatment. Therefore, protein synthesis inhibitors should prevent the expression of long-term memory when administered shortly after learning (Schafe & LeDoux, 2000).

However, pharmacological manipulation of threat memories in humans has been difficult. The general agents investigated in animal models until the present have a higher toxicity for humans, what limits clinical investigation of this process. For instance, anisomycin, a protein synthesis inhibitor that shows successful results in blocking processes necessary for memory reconsolidation is prohibit for human use due to its toxicity (Blundell, Kouser, & Powell, 2008; Duvarci, Nader, & LeDoux, 2005; S. H. Lee et al., 2008; Santini, Ge, Ren, Peña De Ortiz, & Quirk, 2004).

Nevertheless, rapamycin or sirolimus, a protein kinase mTOR pathway, which regulates dendritic protein synthesis in the amygdala and dorsal hippocampus, was evaluated in several animal studies (Blundell et al., 2008; Duvarci et al., 2005; S. H. Lee et al., 2008; Santini et al., 2004). The administration of rapamycin hindered fear-related reconsolidation in animal models.

In this context, sirolimus, the rapamycin for human use appears to be an alternative protein synthesis inhibitor for clinical research. Originally developed as antifungal, sirolimus is approved for prevention of organ rejection in transplanted patients as immunosuppressant agent (Helmstetter, Parsons, & Gafford, 2008). Suris and colleagues conducted an innovator experiment administering sirolimus immediately after script-driven imagery protocol in combat veterans diagnosed with PTSD (Suris, Smith, Powell, & North, 2013).

Another protein synthesis agent investigated in clinical research is the metalloproteinase doxycycline. The authors hypothesized that the synaptic remodelling needed for learning threat conditions involves the extracellular

enzyme matrix metalloproteinase (MMP), and that extracellular activity gives safety in human use (D. Bach, Tzovara, & Vunder, 2017). Results indicated impairment in threat memory measured by increased surprisingly behaviour to the CS in the re-learning session.

1.5.4. NDMA Receptors

NDMA receptors promotes a bidirectional signalling depending on the type of pharmacological agent employed. Both, D-cycloserine, a partial N-methyl-D-aspartate agonist, and ketamine, a NDMA antagonist seems to be involved in fear memory manipulation.

DCS may be effective as a cognitive enhancer only within the context of high levels of fear, such as those found in clinical anxiety disorders (Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007; Kalisch et al., 2008). Majority of studies investigated the DCS enhance effects associated with cognitive behavioural therapies based on the hypothesis that its use before therapy sessions could abbreviate the number of sessions and anticipate patients recover (Norberg, Krystal, & Tolin, 2008; Otto et al., 2010; Ressler et al., 2004). This feature would aids an extra weapon among the new arsenal of pharmacological agents involved in memory processes to fear-related disorder treatments.

The blockade of NMDA receptors was effective in attenuating reconsolidation in multiple models of fear conditioning. (Akirav & Maroun, 2006; J. L. C. Lee & Everitt, 2008). Among the NDMA receptor antagonists, ketamine is the most investigated agent. In mice, researchers demonstrated that ketamine intervention promoted enhancement in resilience to a stress exposure reducing fear behaviours. Therefore, the authors advocated that ketamine treatment would be implemented like vaccine in high-risk groups (Brachman et al., 2016; McGowan et al., 2017). Moreover, the administration of ketamine in trauma focused psychotherapies for PTSD during reconsolidation and extinction

learning seem to be a promising approach, whereas NMDA-receptor functioning is essential (Duclot, Perez-Taboada, Wright, & Kabbaj, 2016).

1.5.5. GABAergic mechanism

The gamma-amino butyric acid (GABA) is the primary inhibitory neurotransmitter. Hence, GABA signalling could interfere with the activity of cells necessary for retrieving and reconsolidating maladaptive memories.

A number of reports have revealed that a single stressful experience, prior to fear learning, promotes the emergence of robust emotional memories (Cordero et al., 2003; Rodriguez Manzanares et al., 2005). Moreover, a similar manipulation results in a memory trace resistant to the reconsolidation process (Bustos et al., 2010, Espejo et al., 2016) and retards the formation of the extinction memory (Akirav et al., 2009). At the neurobiological level, the behavioral sequelae of stressful experiences are closely linked to a reduced central GABAergic neurotransmission in the basolateral amygdala complex (BLA) (Martijena and Molina, 2012). In fact, it has been observed that the decrease in the inhibitory GABAergic control in the BLA has a major role in the stress-induced promoting influence on both formation of fear memory and induction of long-term potentiation in the BLA (Rodriguez Manzanares et al, 2005). Studies conducted with midazolam, a GABA receptor agonist, systemically administered during the post-retrieval session of a contextual fear memory protocol, disrupted reconsolidation of fear-related memory (Bustos, Maldonado, & Molina, 2006; Zhang & Cranney, 2008).

Hence, GABAergic neurotransmission in the BLA could serve as a dynamic gating mechanism, adjusting fear memory encoding according to the emotional state at the moment of the fear learning process (I. Martijena & V. Molina, 2012).

1.6. FRMR RESEARCH FEATURES

Generally, studies centered in FRMR use a 3-day experimental design (Figure 1). The experiments starts with an encoding of new memory, on the first day. Then, in the second experiment day, takes place the memory reactivation, turning the long-term memory to a labile state in purpose to manipulation.

In parallel, normally a control group do not receive the manipulation, or receive the manipulation after a period that reconsolidation process is supposed to be concluded, or “the window of reconsolidation” is already closed. Likewise, to emphasize the necessity of reactivation to manipulation of the original memory happens, a control group do not receive a reactivation.

Finally, on the third day of the experiment, there is a variety of outcomes measurement instruments used to verify the manipulation effectiveness in the experiment. There are studies that conducts further follow up tests.

In clinical studies, similar design is used when the subject are healthy volunteers. Nonetheless, studies investigating interventions in disrupting FRMR in patients with fear-related disorders are slightly different. In these studies, the experimental day 1 consists in obtaining measurements a varietal of instruments accessing the original fear-related memories and disorders, and then the subjects proceed directly to second day of the experiment.

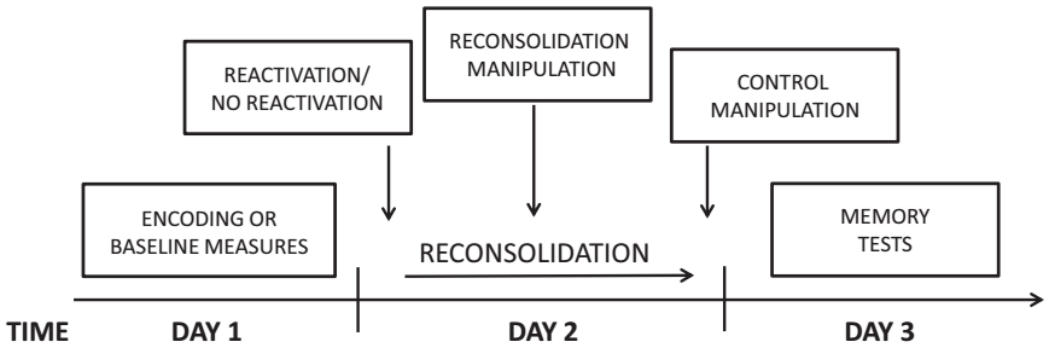


Figure 1 – FRMR experimental design.

1.6.1. FRMR research protocols

Generally, the protocols employed in the fear-related reconsolidation studies are the Pavlovian fear conditioning, script-driven imagery and declarative memory tasks. In spite of fear conditioning and declarative memory tasks involve different neurophysiological mechanisms to memory intervention, there is a previous review in the literature proposing that both mechanisms relates to emotional memories and have potential subject to reconsolidation blockade (D. Schiller & Phelps, 2011). Therefore, to spell out the results of each experiment selected for this review, here we depicted the three fear-related memory reconsolidation protocols mentioned above.

Fear conditioning paradigm

Even though already described in early sessions of this study, here the Pavlovian fear conditioning get back from where it once belonged. In this paradigm, a neutral stimulus, the conditioned stimulus (CS), is paired with a fear stimulus until presentation of the CS alone elicits the fear response. Commonly, one day after the baseline learning, the pharmacological intervention takes place time before the retrieval session of the fear-related memory, depending on the drug peak of action. Fear memory reaches reactivation by presentation of the CS, reactivation cue. Then, fear-related memory reconsolidation is tested for physical and/or psychological outcomes after the intervention agent washout period about 1 up to 7 days, or even 1 up to 12 months of follow-up.

Script-driven imagery tasks

In this protocol, participants write down a script or report orally one or more emotionally aversive memories in details during a first session. Trial

conducted with PTSD patients, the traumatic experience evoked. In a second session, participants receive the pharmacological agent before listening to an audiotaped recording of their script, which serves as the reactivation cue. During the second session protocol, psychophysiological responses are recorded. Third session takes place after washout period depending the characteristics of the intervention drug. Once again, participants listen to their script while their psychophysiological responses are recorded one more time, but without receiving any intervention at this session, thus measuring the outcomes for reconsolidation blockade.

Declarative memory tasks

This paradigm consists in participant's learning of a list of emotionally valence and neutral words or textual material, at the first experiment session. In the same way to earlier protocols described, the subjects also receive the drug intervention before participating a cued recall memory task. In next day session, at least 24 hours after due to washout period, subjects participate the same cued recall task, which serves also as the reconsolidation blockade test.

1.6.2. FRMR pharmacological agents

The close relationship between fear and anxiety in human beings provides insight into the biological nature of fear-related disorders.

By now, the cognitive behavioural therapy, such as exposure therapy, currently the most widely recognized evidence based research treatment for PTSD and anxiety disorders, suggests that a huge percentage of patients may fail to achieve significant improvements, as well as, a great number of patients successfully treated, further presents relapses (Elsey & Kindt, 2017). In the same way, the ISSR or ISSNR, the first line drugs used in treatment for PTSD and anxiety disorders shows also limited effects across the patients. Even the

combination of cognitive therapies with the conventional pharmacological agents, shows limitations in treating fear-related disorders (Tawa & Murphy, 2013).

In this scenario, considering limitations of conventional treatments, the rationales of labile state of memory observed during FRMR open a window of opportunity allowing novel pharmacological agents to strike fear-related disorders (M Kindt, M Soeter, & D Sevenster, 2014; Lars Schwabe, Karim Nader, Oliver T Wolf, Thomas Beaudry, & Jens C Pruessner, 2012b). Therefore, novel pharmacological agents that disrupts FRMR claim for a pivotal role.

Adrenergic agents

The most commonly adrenergic agent used in humans to disrupt memory reconsolidation is propranolol, a beta-adrenergic receptor antagonist that easily crosses the blood–brain barrier. Propranolol exerts peripheral effects on the noradrenergic system as well as central inhibitory effects on protein synthesis, and seems to induce emotional memory impairment through altered activity in the amygdala and hippocampus based on neuroimaging (Lars Schwabe, Karim Nader, Oliver T. Wolf, Thomas Beaudry, & Jens C. Pruessner, 2012a). This characteristic confers propranolol a decreasing emotional charge of memories (Debiec & Ledoux, 2004; Nader et al., 2000; Przybyslawski et al., 1999). In addition, propranolol is a well-tolerated pharmacological agent, vastly used in clinical practice for multiple purposes, such as migraine, tachycardia and performance anxiety (Brantigan, Brantigan, & Joseph, 1982; Diener et al., 2002; Holroyd, Penzien, & Cordingley, 1991).

At first, Pitman and colleagues investigated the effects of propranolol in PTSD prophylaxis in a pilot RCT study. Results suggested that propranolol acute administration immediately after the traumatic event may have a preventive effect on subsequent PTSD (Roger K Pitman et al., 2002). Although, this study concerns about consolidation of traumatic memory, or fear-related memory, proportionated further investigations in this area.

Consecutively, Brunet and collaborators conducted a pioneer study with propranolol investigating particularly the reconsolidation process in PTSD patients (Brunet et al., 2008). Their results suggest that propranolol significantly impaired FRMR measuring physiologic responding during mental imagery of the traumatic event.

Other adrenergic agents have been studied, since propranolol initial positive effectiveness in memory field. Nadolol is also a beta-adrenergic receptor antagonist, but crosses the blood–brain barrier to a much lesser extent than propranolol. It was studied in crossover trial with propranolol, but as a peripheral beta-adrenergic antagonist, nadolol administered before memory reactivation showed no effect on subsequent fear responding.

Conversely, an alpha2-adrenergic receptor antagonist, yohimbine was administered before a learning session to strength fear memory consolidation in healthy subjects experiment (Marieke Soeter & Merel Kindt, 2012). The authors originally hypothesized that noradrenergic strengthening of fear memory should not impair the disruption of reconsolidation mediated by propranolol. Results indicated that excessive release of noradrenaline during memory formation not only delayed the process of extinction, but also triggered fear generalization. However, propranolol administration before reconsolidation session selectively blocked fear-arousing aspects of the noradrenergic-strengthened memory and undermined the generalization of fear.

Furthermore, antagonists there are open-label studies verifying the protective properties of the beta-adrenergic receptors administered in hazardous clinical conditions for PTSD development. In a retrospective pilot study, patients who experienced an intracardiac defribrillator (ICD) discharge while continuously taking a lipophilic beta-blocker reported less severe PTSD symptoms related to the ICD discharge event a month later evaluation, compared to patients who had been taking a hydrophilic beta-blocker (Bhuvaneswar, Ruskin, Katzman, Wood, & Pitman, 2014). In a cohort study conducted in patients suspected for acute coronary syndrome from an emergency department suggested that general beta-blockers administration had a protective effect for later psychological health, producing lower PTSD

rates a month later evaluation (Meli et al., 2017). Nevertheless, propranolol administered for victims of burnt showed no protective effect for PTSD compared with those that not received propranolol.

Glucocorticoid agents

The hydrocortisone and cortisol are principal characters in glucocorticoid modulating mechanism cast. Moreover, other agents that are able to interfere in glucocorticoid formation and release claims for a supporting role in the present group. Several studies investigated the effectiveness of these agents in FRMR.

Cortisol given during reactivation of a fear memory trace leads to a substantial and specific strengthening of the reconsolidated memory trace, and became apparent during reinstatement testing 24 h after reconsolidation manipulation (S. M. Drexler et al., 2015)

The clinical relevance of the effects of exogenous GC administration is highlighted by the description of patients with anxiety disorders who demonstrate an enhancement of extinction-based therapies by GC treatment (Wolf et al., 2016).

Protein synthesis inhibitors

Several pharmacological agents with property to direct inhibit protein synthesis, and consequently disrupt of FRMR would be the first line of investigations. However, due to its cellular toxic effects, clinical investigations of these agents are limited, even when there are positive results in animal models studies.

In a clinical experiment, the administration of sirolimus do not replicate the previous findings of rapamycin in animal models. However, in specific analyses with the post-Vietnam subsample sirolimus group reported significantly fewer and less intense PTSD symptoms (PCL and CAPS total

score and group D symptom score) at a month posttreatment, but not three months later follow-up.

At this knowledge, a determinant role is the learning US predictions which that demands a synaptic reconfiguration leading to long-term potentiation of the amygdala to converge CS and US input. Then, doxycycline, the metalloproteinase inhibitor, aimed to block human fear memory through an extracellular signalling pathway inhibiting this synaptic reconfiguration in clinical researches.

NDMA receptors agents

The dissociative anaesthetic drug, ketamine, acts on the CNS through n-methyl-d-aspartate (NMDA) receptor antagonism. Recently, ketamine has attracted attention as a rapid-acting anti-depressant (Iadarola et al., 2015) and should be employed also in resistant depression and PTSD (Krystal et al., 2017; Serafini, H Howland, Rovedi, Girardi, & Amore, 2014). However, there is a lack of investigations about the effects of ketamine in FRMR. Despite investigations, using ketamine in addiction memory reconsolidation shows promisor findings (Ezquerra-Romano, Lawn, Krupitsky, & Morgan, 2018), it presented negative effects in FRMR, strengthening the aversive memory (Corlett et al., 2013).

In contrast, d-cycloserine (DCS), an N-methyl-D-aspartate partial agonist, demonstrates enhanced core learning processes. Considering this effect, studies used DCS in association to cognitive behavioural therapy CBT attempting to improve the efficacy of this strategy, and showed promising results for aiding in the treatment of anxiety disorders (Hofmann, Wu, & Boettcher, 2013). Yet, as already reported, DCS effects seem to be more related to memory extinction as reconsolidation.

2. OBJECTIVES

The objectives of the present thesis is to identify the concepts and actual knowledge of memory reconsolidation process present in the literature to verify the effectiveness of pharmacological intervention in disrupting fear-related memory reconsolidation (FRMR).

3. METHODS

3.1. SEARCH STRATEGY

We performed a computerized systematic literature search of the ISI Web of Science, SCOPUS, PsycInfo and PubMed databases for studies reporting on pharmachological intervention in memory reconsolidation until September 5th 2018, without language or time period restrictions and combining the following terms: memor* AND reconsolidat* AND (“protein synthesis inhibitor*” OR “protein synthesis antagonist*” OR sirolimus OR proteinase OR anti-bacterial* OR antibacterial* OR toxin* OR antifungal* OR anti-fungal* OR *adrenergic* OR propranolol OR yohimbine OR *cycloserine OR cortisol OR *cortisone OR glucocorticoid* OR mifepristone OR andosol OR atenolol OR pindolol OR prazosin) on “topic”, “title, abstract, keywords”, “any field” and “all fields”, respectively in databases.

An asterisk before or after a term means that all terms that end or begin with that root were included in the search. As each database has a specific thesaurus system, we employed the following search strategy with respect to controlled vocabularies: (1) ISI Web of Science, we used the field “topic”, which includes title, abstract, and keywords; (2) SCOPUS, “title, abstract, keywords”; (3) PsycInfo, “any field”; and (4) Medline, “All fields”.

The protocol of this systematic review was registered in advance at the international prospective register of systematic reviews (PROSPERO), registration number 39418, and was performed following the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

3.2. STUDY SELECTION

The inclusion and exclusion criteria were set a priori. Inclusion criteria were original articles investigating pharmacological interventions that can influence fear memory reconsolidation. Exclusion criteria were papers which investigated memory consolidation or extinction rather than reconsolidation, included subjects under 18 years and over 65 years old, animal samples, non-peer-reviewed (including theses, dissertations, conferences, book chapters, letters, comments, editorials), theoretical articles, reviews and meta-analysis.

In a first screening of titles and abstracts of all identified papers, the first author (L.F.P.) excluded duplicated studies retrieved from more than one database, reviews and metanalysis papers.

In a second screening, abstracts were reviewed independently by two authors (L.F.P. and M.L.) who scrutinized the full text of the remaining studies.

The remaining studies were selected based on the two authors (L.F.P. and M.L.) consensus following these criteria: 1) original articles investigating pharmacological intervention in fear-memory reconsolidation; 2) randomized controlled trials; 2) open-label studies; 3) series of cases or case report. If a criterion was not met because not enough information was provided, the abstract was set aside for further evaluation. At last, if consensus still not reached, the study was set aside for further evaluation and disagreements were discussed with a third author (W.B).

In addition to the computer search of databases, we reviewed the reference lists of all articles selected and specialized textbooks available in the literature (cross-references). Besides that, we examined the full texts of potentially interesting studies in pharmacological interventions in memory reconsolidation and contact five authors and experts on memory reconsolidation.

3.3. SCIENTIFIC EVIDENCE CATEGORIZATION

We categorized the pharmacological agents used in disrupting FRMR according to the methodology level of scientific evidence and clinical relevance (Services, 1993), as described below:

Level A of evidence: multiple double blind placebo-controlled trials with positive results and a confirmatory metanalysis (in addition to level B of evidence);

Level B of evidence: at least one double-blind placebo-controlled trial with positive results (in addition to level C of evidence);

Level C of evidence: anecdotal reports, case series and open trials with positive results, in addition to expert endorsement or consensus;

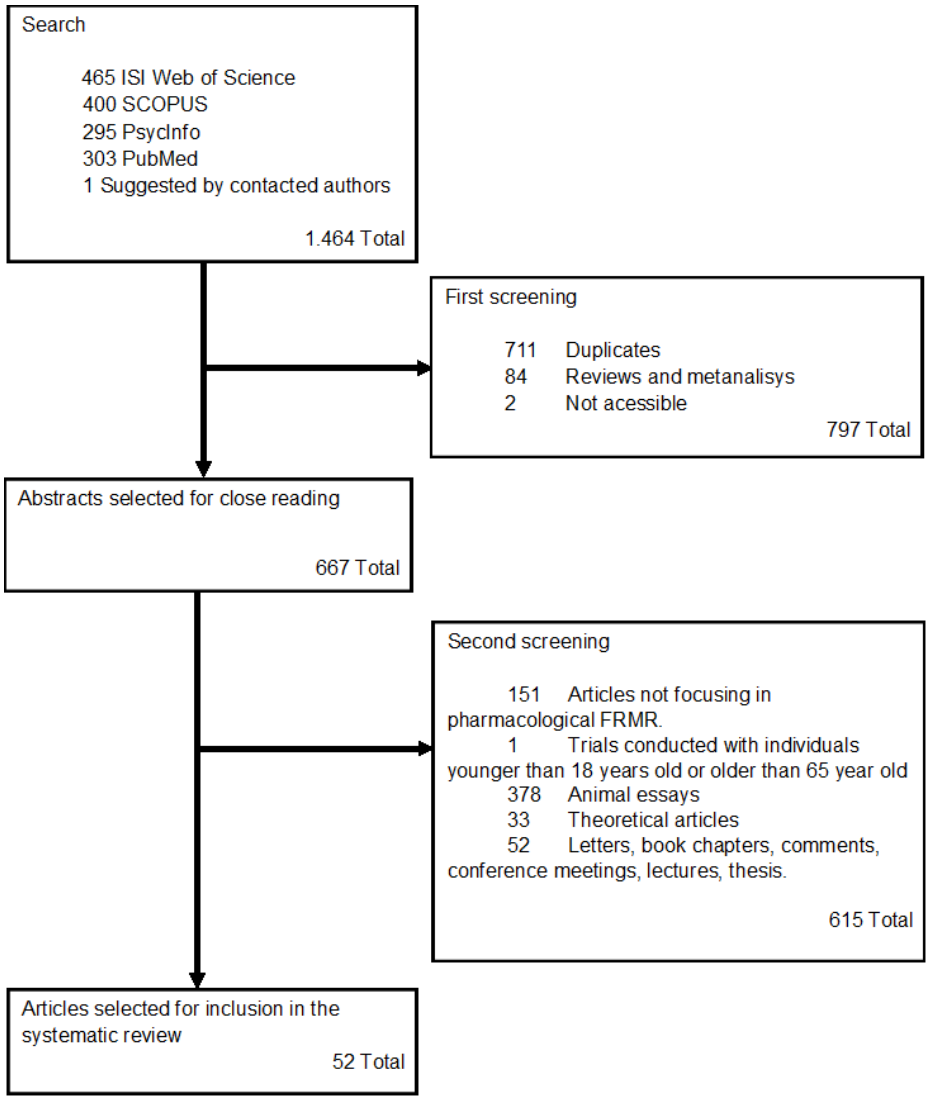
Level D of evidence: Few case reports with positive results, however without any expert panel endorsement.

4. RESULTS

We screened 1464 abstracts published in the last 45 years, among the four database researched, ISI Web of Science, SCOPUS, PsycInfo, and Medline, and an extra article were included suggested by contacted authors.

The first screening of titles and abstracts of all identified papers, excluded 711 duplicated studies retrieved from more than one database, 84 reviews and metanalysis papers, and two articles that we could not access for technical purposes. The second screening of abstracts selected for close reading excluded: abstracts not focusing in pharmacological FRMR; a trial conducted with individuals younger than 18 years old or older than 65 year old; animal essays; theoretical articles; papers between letters, book chapters, comments, conference meetings, lectures and thesis. Finally, after the second screening applying the exclusion criteria, 52 articles were selected. The results of our search are depicted in Figure 2.

Figure 2 – Systematic review flow chart results.



The main characteristics (type and dosage of drugs, sample size, instruments employed, etc) of each RCTs selected, considering the critical relevance of RCTs for the advancement of scientific knowledge in disrupting memory reconsolidation, in Table 1. Studies using less accurate methods, such as open label trials and case report, had their summaries in the text below. The results according to the level of scientific evidence in Table 2.

The present systematic review succeed to classify in level A of scientific evidence criteria a single pharmacological agent. The beta-adrenergic receptor antagonist, propranolol, showed an amount of positive results in randomized controlled trials investigating its effectiveness in disruption of fear-related memory reconsolidation. In addition, there were a previous metanalysis study verifying the effects of propranolol in memory reconsolidation (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013).

Cortisol is the following agent enrolled in this list considering scientific evidence. Although, there is no metanalysis study, endogenous cortisol and hydrocortisone RCTs demonstrate effectiveness in disrupting fear-related memory reconsolidation. Thus, cortisol achieved level B of scientific evidence.

Likewise, doxycycline stands also with level B of scientific evidence. Despite there is only one RCT conducted with this protein synthesis inhibitor, doxycycline use appear to be a promisor intervention in fear-related memory reconsolidation disruption.

Table 1 - Summary of randomized controlled trials for FRMR disruption.

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Adrenergic agents							
Brunet et al. (2008)	Civil (19) PTSD patients	Propranolol 40mg (short action) + 60mg (long action)	Script-driven imagery	None	HR Skin conductance	SCID-IV	Yes
Kindt et al. (2009)	Civil (60) Healthy volunteers	Propranolol 40mg	Pictures (spiders - IAPS) Electric shock	None	EMG	None	Yes
Kroes et al. (2010)	Civil (24) Healthy volunteers	Propranolol 40mg	Nouns (neutral and aversive)	None	None	STAI BDI-II	Yes
Soeter et al. (2010)	Civil (60) Healthy volunteers	Propranolol 40mg	Pictures (spiders - IAPS) Electric shock	None	Saliva BP EMG Skin conductance	SPQ STAI ASI	Yes
Soeter et al. (2011)a	Civil (40) Healthy volunteers	Propranolol 40mg	Pictures (spider and gun - IAPS) Electric shock	None	Saliva BP EMG Skin conductance	STAI SPQ ASI SAM	Yes
Soeter et al. (2011)b	Civil (40) Healthy volunteers	Propranolol 40mg	Pictures (spider and gun IAPS) Electric shock	None	Saliva EMG Skin conductance	STAI SPQ ASI SAM	Yes

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Soeter et al. (2012)	Civil (24) Healthy volunteers	Propranolol 40mg	Pictures (spider and gun - IAPS) Electric shock	None	Saliva BP EMG Skin conductance	STAI SPQ ASI	Yes
Soeter et al. (2012)b	Civil (40) Healthy volunteers	Propranolol 40mg	Pictures (fear-relevant) Electric shock	None	Saliva BP	STAI SPQ ASI	No
Schwabe et al. (2012)	Civil (52) Healthy volunteers	Propranolol 40mg	Pictures (aversive - IAPS)	None	HR	Memory recall test	Yes
Sevenster et al. (2012)	Civil (60) Healthy volunteers	Propranolol 40mg	Pictures (spiders - IAPS)	None	Skin conductance	SPQ	No
Soeter et al. (2013)	Civil (107) Healthy volunteers	Propranolol 40mg	Pictures (spider and gun - IAPS) Loud noise Electric shock	None	Saliva BP EMG Skin conductance	STAI ASI	Yes
Schwabe et al. (2013)	Civil (48) Healthy volunteers	Propranolol 40mg	Pictures (aversive - IAPS)	None	HR	Memory recall test	Yes
Kindt et al. (2014)	Civil (not informed) Healthy volunteers	Propranolol 40mg	Pictures (aversive – IAPS) Electric shock	None	HR BP	STAI ASI SPQ	Yes

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Soeter et al. (2015)a	Civil (30) Healthy volunteers	Propranolol 40mg	Pictures (spiders and snakes - IAPS)	None	BP	STAI ASI SPQ SNAQ	No
Soeter et al. (2015)b	Civil (45) Specific phobic patients	Propranolol 40mg	Baby tarantula exposition	None	Saliva BP	STAI SPQ ASI BDI SCID-DSM-IV	Yes
Wood et al. (2015)a	Military (18) PTSD patients	Propranolol 10mg	Personal trauma script	None	HR Skin conductance EMG	IES-R CAPS-DX SCID DSM-IV	No
Thomas et al. (2016)a	Civil (36) Healthy volunteers	Propranolol 40mg (after recall session)	Slides Narratives (neutral and negative)	None	HR Skin conductance EMG	Memory recall test	No
Thomas et al. (2016)b	Civil (51) Healthy volunteers	Propranolol 40mg (before recall session)	Slides Narratives (neutral and negative)	None	HR Skin conductance EMG	Memory recall test	Yes
Thome et al. (2016)	Civil (80) Healthy volunteers	Propranolol 40mg	Pictures (spider and snake - IAPS)	None	BP	STAI FAS SNAQ	No

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Mahabir et al. (2016)	Civil (41) PTSD patients	Propranolol 1 mg/kg	Traumatic experiences	None	HR BP	WAIS IES-R CAPS	Yes
Littel et al. (2017)	Civil (56) Healthy volunteers	Propranolol 40mg	Personal aversive memories	EM Task	HR Skin conductance	VAS	Yes
Brunet et al. (2018)	Civil (30) PTSD patients	Propranolol 0.67 mg/kg short action + 1mg/kg long action	Personal trauma script	None	None	CAPS PCL-S	Yes
Kindt et al. (2018)b	Civil (20) Healthy volunteers	Propranolol 40mg	Pictures (spider and gun - IAPS)	None	Eye-blink startle reflex EMG	Não houve	Yes
Kindt et al. (2018)c	Civil (20) Healthy volunteers	Propranolol 40mg	Pictures (spider and gun - IAPS)	None	Eye-blink startle reflex EMG	Não houve	Yes
Tolenaar et al. (2009)	Civil (85) Healthy volunteers	Propranolol 80mg	Words (neutral and emotional)	None	HR BP Saliva (cortisol)	STAI-Trait SCL-90 BDI-II	No
Tolenaar et al. (2009)	Civil (79) Healthy volunteers	Propranolol 80mg	Personal trauma script	None	HR Skin conductance	STAI-Trait SCL-90 BDI-II	No

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Glucocorticoid Agents							
Tolenaar et al. (2009)	Civil (79) Healthy volunteers	Hydrocortisone 35mg	Words (neutral and emotional)	None	HR BP Saliva (cortisol)	STAI-Trait SCL-90 BDI-II	Yes
Tolenaar et al. (2009)	Civil (79) Healthy volunteers	Hydrocortisone 35mg	Personal trauma script	None	Skin conductance HR	STAI-Trait SCL-90 BDI-II	No
Drexler et al. (2015)	Civil (40) Healthy volunteers	Hydrocortisone 30mg	Electric shock	None	Skin conductance	None	Yes
Drexler et al. (2016)	Civil (67) Healthy volunteers	Hydrocortisone 30mg	Electric shock	None	Skin conductance	None	No
Schwabe et al. (2008)	Civil (96) Healthy volunteers	Endogenous cortisol	Words (neutral, negative and positive)	Cold pressor test	Saliva cortisol HR ECG BP	Recall test	Yes
Tollenaar et al. (2008)	Civil (65) Healthy volunteers	Endogenous cortisol	Words (neutral and negative emotion)	Trier social stress task	None	Recall test	No
Schiller et al. (2009)a	Civil (43) Healthy volunteers	Endogenous cortisol	Coloured squares	Electric shock	Skin conductance	None	Yes

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Schwabe et al. (2010)	Civil (64) Healthy volunteers	Endogenous cortisol	Autobiographic memories (positive, neutral and negative)	Cold pressor test	Saliva (cortisol) BP	Recall test MDBF	No
Bos et al. (2014)	Civil (51) Healthy volunteers	Endogenous cortisol	Words (negative) with background pictures	Maastricht acute stress test	Saliva cortisol HR BP	SAM STAI-T ASI BDI PANAS WAIS	No
Bos et al. (2014)	Civil (66) Healthy volunteers	Endogenous cortisol	Words (neutral, positive and negative)	Cold pressor test	Saliva (cortisol) BP HR	WAIS-R ASI BDI PANAS	Yes
Schwabe et al. (2014)	Civil (120) Healthy volunteers	Endogenous cortisol	Words (neutral and negative)	Cold pressor test	Saliva (cortisol) BP	Recall test (memory performance)	Yes
Steinfurth et al. (2014)	Civil (79) Healthy volunteers	Endogenous cortisol	Coloured squares	Electric shock	None	Recall test	Yes
Cheung et al. (2015)	Civil (63) Healthy volunteers	Endogenous cortisol	Trauma film	Cold pressor test	Saliva (cortisol)	DASS 2 TSQ IES	No
Drexler et al. (2017)	Civil (45) Healthy volunteers	Endogenous cortisol	Geometrical figures Electric shock	Cold pressor test	Saliva (cortisol) BP Skin conductance	NEO-FFI STAI-T TICS ASI	Yes

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Li et al. (2017)	Civil (92) Healthy volunteers	Endogenous cortisol	Cold and warm coloured solid figures	Electric shock	Skin conductance	None	Yes
Thompson et al. (2017)	Civil (25) Healthy volunteers	Endogenous cortisol	Pictures (spider, snake and coloured squares)	Electric shock	Skin conductance	None	Yes
Sheldon et al. (2018)	Civil (44) Healthy volunteers	Endogenous cortisol	Aversive autobiographical memory	Stress test	Saliva (cortisol)	None	No
Wood et al. (2015)	Civil (43) PTSD patients	Mifepristone 1800mg	Script-driven imagery	None	HR Skin conductance EMG	IES-R CAPS SCID DSM-IV	No
Rimmele et al. (2015)	Civil (18) Healthy volunteers	Metyrapone 1mg	Emotional texts and pictures	None	Cortisol, ACTH concentration Plasma epinephrine and norepinephrine	PANAS WAIS	No
Protein Synthesis Inhibitors							
Suris et al. (2013)	Military (51) PTSD patients	Sirolimus 15mg	Script-driven imagery	None	HR CP EMG	CAPS PCL QIDS-SR	No
Bach et al. (2017)	Civil (76) Healthy volunteers	Doxycycline 200mg	Electric shock	N-back task d2 test	EMG	STAI BDI	Yes

Study (year)	Sample (N)	Intervention drug (mg)	Aversive stimulus	Task	Outcome measures		Was effective in disrupting FRMR?
					Physiological	Psychological	
Protein Synthesis Inhibitors							
Suris et al. (2013)	Military (51) PTSD patients	Sirolimus 15mg	Script-driven imagery	None	HR CP EMG	CAPS PCL QIDS-SR	No
Bach et al. (2017)	Civil (76) Healthy volunteers	Doxycycline 200mg	Electric shock	N-back task d2 test	EMG	STAI BDI	Yes
Other Agents							
Litz et al. (2012)	Military (26) PTSD patients	D-cycloserine 50mg	Exposure therapy	None	None	SCID CAPS PCL BDI-II DRRI SUDS	No
Wood et al. (2015)	Civil (21) PTSD patients	D-cycloserine 100mg + mifepristone 1800mg	Script-driven imagery	None	HR Skin conductance Facial corrugator muscle	IES CAPS SCID-IV	No
Corllet et al. (2018)	Civil (18) Healthy volunteers	Ketamine 200 ng/ml	Pictures (spiders – IAPS)	None	Skin conductance	None	No

The Clinician-Administered PTSD Scale (CAPS); The PTSD Checklist (PCL); Quick Inventory of Depressive Symptomatology (Self-report) (QIDS-SR); The Structured Clinical Interview for DSM-IV (SCID-IV); Revised Beck Depression Inventory (BDI-II); heart rate (HR); blood pressure (BP); Spider Phobic Questionnaire (SPQ); The Deployment Risk and Resilience Inventory-Combat Experiences Scale (DRRI); Subjective Units of Distress Scale (SUDS); Anxiety Sensitivity Index (ASI); Self-Assessment Mankind (SAM); Fear of Spiders Questionnaire (FAS); Snake Questionnaire (SNAQ); Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III); Impact of Event Scale Revised (IES-R); Subjective Experience of Stress (SAM); Positive Affect and Negative Affect Schedule (PANAS); Depression, Anxiety and Stress Scales (DASS); Traumatic Screening Questionnaire (TSQ); Multidimensional German Mood Scale (MDBF); Five Factor Inventory (NEO-FFI); Trier Inventory of Chronic Stress (TICS); Symptoms Checklist (SCL-90); Visual Analog Scales (VAS); Socially Evaluated Cold Pressor Test (SECPT).

Table 2 – Evidence of Scientific Level of Pharmacological Interventions

Intervention	RCTs	Open-label studies	Case reports	Total	Evidence Level
Adrenergic agents					
Propranolol	26	9	1	36	A
Nadolol	0	1	0	1	D
Corticosteroid agents					
Hydrocortisone	4	0	0	4	B
Endogenous cortisol	13	0	0	13	B
Mifepristone	1	0	0	1	C
Metyrapone	1	0	0	1	C
Protein synthesis inhibitors					
Doxycycline	1	0	0	1	B
Sirolimus	1	0	0	1	D
Other agents					
D-cycloserine	2	0	0	2	D
Ketamine	1	0	0	1	D

4.1. ADRENERGIC AGENTS

4.1.1. Propranolol: Level of evidence A

Randomized controlled trials with fear conditioning protocol

The present systematic review highlights the propranolol effectiveness in disrupting fear-related memory reconsolidation. Twenty-two out of 27 randomized controlled trials (RCT), as well as, 3 out of 5 open-label trials and a case report revealed positive results of propranolol use in distinct paradigms experiments investigating fear-related memory reconsolidation.

The majority of RCTs, 18 out of 27, employed propranolol in disrupting fear-related memories used fear conditioning protocols. Thirteen studies paired an electrical shock to an aversive or a neutral picture in the experiments. Eleven out of 13 found that propranolol is effective in disrupting fear-related memory reconsolidation (Kindt & Soeter, 2018; M. Kindt, M. Soeter, & D. Sevenster, 2014; Kindt, Soeter, & Vervliet, 2009; Marieke Soeter & Kindt, 2010, 2011; M. Soeter & M. Kindt, 2012; M. Soeter & Kindt, 2013; Marieke Soeter & Kindt, 2015b).

The remained two studies which not associated an electrical shock to aversive and neutral stimulus to their trials, also found positive results, but using emotional and neutral images paradigm.

Two RCRs failed to replicate beneficial effects of propranolol intervention in fear-related memory reconsolidation. Sevenster and collaborators did not find significant differences among propranolol group in reported spider fear, anxiety sensitivity or trait anxiety, from the propranolol no-shock group and the placebo group (Dieuwke Sevenster et al., 2012). Thome, by his turn, reported difficulties in triggering reconsolidation process implicating in no significant effects of propranolol intervention in fear-related memory reconsolidation (Thome et al., 2016).

A RCT evaluated the noradrenergic blockade promoted by 40 mg propranolol in 45 patients diagnosed with specific phobia of spider exposed to a baby tarantula (Marieke Soeter & Kindt, 2015a). The authors found positive results with noradrenergic blockade in disrupting FRMR, transferring avoidance behaviour into approach behaviour in participants who received propranolol.

Randomized controlled trials with script-driven imagery protocol

We found four experiments employing personal trauma script-driven as aversive stimulus in PTSD patients. Three of them reached positive results with propranolol administration in disrupting fear-related memories. Brunet and colleagues conducted a pioneer study in this field, with 19 participants diagnosed with PTSD (Brunet et al., 2008). The subjects were divided in propranolol and placebo groups. Participants of each group had to hear their two worst personal trauma script-driven in activation and reactivation sessions. The general physiologic responding to mental imagery of the traumatic event was significantly smaller in the PTSD subjects who had received propranolol a week earlier compared to those who had received placebo. The same research group conducted a newer study with PTSD patients (Brunet et al., 2018). Nevertheless, this time the authors evaluated the PTSD symptoms by CAPS and PCL scores finding substantial decrease in symptom ratings compared with placebo.

Despite the fact that Mahabir and colleagues examined propranolol's acute effect on cognitive performance in PTSD participants, the authors used physiological measurements and psychological instruments to evaluate propranolol effects far beyond cognitive performance (Mahabir, Ashbaugh, Saumier, & Tremblay, 2016). Their results evidenced significant HR and BP reduction, but no difference change an in symptom severity post-intervention between groups.

At last, Wood failed to replicate Brunet findings in PTSD patients (Wood et al., 2015). In contrast to the previous study that used a post-reactivation propranolol administration, Wood employed pre-reactivation intervention.

Thomas and collaborators investigated the propranolol effects in fear-related memory reconsolidation when administered after and before reactivation session

(Thomas, Saumier, Pitman, Tremblay, & Brunet, 2016). First, 36 healthy participants listened to three parts of an emotional story with a neutral and a negative final while watching a slideshow. Immediately after recall session, participants received 40 mg propranolol or placebo. The second experiment had the same aversive stimulus design, but this time 51 healthy subjects took propranolol or placebo 90 minutes before the recall session. The authors measured heart rate, peak skin conductance, and peak left corrugator and left frontalis facial muscles activity in both essays. Just the second experiment succeed in disrupting fear-related memory reconsolidation.

Littel and collaborators verified the blockade of noradrenergic neurotransmission promoted by propranolol abolishing the effects of eye movement desensitization and reprocessing (EMDR) in 56 healthy participants in a RCR mixed factorial design (Littel et al., 2017). The outcome measures evaluated were heart rate and blood pressure, as well as, the intensity of vivid negative memories. The results showed reduction of HR and BP, but no difference in vividness of negative memories.

Other RCR investigated the propranolol versus hydrocortisone effects in 79 healthy male participants (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009b). The aversive stimulus elected for this study was negative disturbing memory script. The subjects were evaluated a week and eight months later. The experiment failed to achieve differences among propranolol, hydrocortisone and placebo groups.

Randomized controlled trials with declarative tasks protocol

Kroes and collaborators investigated immediate and persisted effects of propranolol in an emotional memory recall test using 360 nouns, including 30 aversively emotional oddballs on day 2 and day 3 (Kroes, Strange, & Dolan, 2010). Twenty-four healthy subjects received 40 mg propranolol before recall session in day 2, but not in day 3. The authors' findings indicated that the beta-adrenergic blockade at retrieval abolishes the declarative memory enhancement for emotionally aversive nouns. Besides that, results showed a sustained reduction of emotional item recall in day 3, even 24 h after propranolol administration

Tollenaar and colleagues compared propranolol and hydrocortisone effects in fear-related memory reconsolidation in placebo-controlled study (Tollenaar, Elzinga, Spinhoven, & Everaerd, 2009a). Eight five healthy volunteers were asked to retrieve previously learned emotional and neutral information after ingestion of 35 mg cortisol, 80 mg propranolol or placebo. One week later, the participants passed through a recall session. Propranolol showed no immediate or prolonged effects on memory retrieval, despite significant reductions in sympathetic arousal.

Open label studies with fear conditioning protocol

There were two open-label trials using aversive pictures as conditioned stimulus. Mahabir and colleagues found positive results administrating 1mg/Kg propranolol before reactivation session evaluated through fMRI in a PTSD patient's sample (Mahabir, Tucholka, Shin, Etienne, & Brunet, 2015). Images of faces with negative, positive and neutral expressions were showed during acquisition, reactivation sessions. Participants with chronic PTSD reported significantly decreased symptom severity after reconsolidation impairment using propranolol, in agreement with a decrease in CAPS scores. In contrast, other research groups found no impairment in fear memory by 40 mg propranolol administration in reactivation session (Schroyens, Beckers, & Kindt, 2017). The aversive stimulus adopted in this study was spider and gun pictures from IAPS.

Spring and colleagues, tested the efficacy of propranolol in blocking reconsolidation of conditioned fear in healthy young adults (Spring et al., 2015). The authors used videos of tarantulas as aversive stimulus. Despite the strong differential conditioning observed among a screened subset of participants during acquisition, measured by skin conductance, subsequent propranolol failed to reduce reactivity to the reactivated conditioned stimulus.

Open label studies with script-driven imagery protocol:

Two open-label studies used personal trauma script as aversive stimulus in samples composed by PTSD patients. Both studies reached positive results in use of propranolol in disrupting fear memory reconsolidation. Poundja and collaborators administrated propranolol before trauma recall in 33 subjects one time week along six weeks (Poundja, Sanche, Tremblay, & Brunet, 2012). After these six weeks, patients showed an important decrease in symptom ratings measured by CAPS, PCL, BDI and WHOQOL.

In accordance, to the previous study described above, Brunet reached similar results but in psychophysiological responses (heart rate, skin conductance and left corrugator muscle EMG) (Brunet et al., 2014). The majority of the 22 participants were classified as non-PTSD after propranolol intervention, and 96% at follow-up, based on their physiological responses during trauma-related imagery.

Case report with script-driven imagery protocol:

Matuskey described the effects of administration of 40mg propranolol in a 47-year-old man diagnosed with intermittent explosive disorder, polysubstance dependence, and mild mental retardation intermittent explosive disorder, five hours after a burst of aggression episode in which he was restrained (Matuskey & Sondik, 2015). The author reported a tremendous reduction in burst of aggression episodes during the subsequent weeks.

4.1.2. Nadolol: Level D of evidence

Open-label study with Fear conditioning protocol:

An open-label study evaluated the effects between propranolol and nadolol in fear memory reconsolidation (Kindt & Soeter, 2018). The participants were divided in two groups receiving an electrical shock as aversive stimulus. After fear learning, activation and reactivation sessions, results corroborated author's hypothesis that propranolol fear-erasing effect is centrally mediated. In contrast, administration of the peripheral beta-adrenergic receptor antagonist, nadolol, before memory reactivation, shows no effect on subsequent fear responding.

4.2. GLUCOCORTICOID AGENTS

4.2.1. Endogenous cortisol: Level B of evidence

The present review found eight RCTs investigating the effects of endogenous cortisol released after stress task in disrupting fear-related memory reconsolidation. Cold pressor test was the most used protocol to increase cortisol levels in the participants (Bullinger et al., 1984). In this test, participants have to immerse the nondominant hand in ice water for one minute. Besides cold pressor test, social stress The Trier Social Stress Test (STSS) was the most used test to trigger (Kirschbaum, Pirke, & Hellhammer, 1993). In STSS design, participants must prepare and give a presentation and perform an arithmetic task in front of an audience. Similar social stress tests were also used in experiments, such as the Maastricht Acute Stress Test (Smeets et al., 2012).

Randomized controlled trials with fear conditioning protocol:

Studies using geometrical figures paired to electric shock inducing cortisol release produced the most impressive results. Four trials out of five studies achieved positive results using endogenous s cortisol in fear-related memory reconsolidation (Shira Meir Drexler & Wolf, 2017; Li et al., 2017; D. Schiller et al., 2010; Steinfurth et al., 2014). Thompson and colleagues achieved success using aversive pictures as stimulus and electric shock to induce stress (Thompson & Lipp, 2017).

Randomized controlled trials with declarative tasks protocol:

Three out of five RCTs reached positive results using other paradigm (M. G. Bos, Jacobs van Goethem, Beckers, & Kindt, 2014; M. G. Bos, Schuijer, Lodestijn, Beckers, & Kindt, 2014; Schwabe, Bohringer, Chatterjee, & Schachinger, 2008; Schwabe & Wolf, 2014; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2008). The trial employed emotional words as aversive stimulus and cold pressor tests or stress tasks to promote release of cortisol before reactivation sessions.

Randomized Controlled Trials with Script-driven Imagery protocol:

In contrast to these previous studies, endogenous cortisol not showed significant effect for autobiographical negative memories (Schwabe & Wolf, 2010; Sheldon, Chu, Nitschke, Pruessner, & Bartz, 2018) or a trauma film (Cheung, Garber, & Bryant, 2015).

4.2.2. Hydrocortisone: Level B of evidence

There are four RCTs investigating the effects of orally administration of hydrocortisone in disrupting FRMR.

Randomized controlled trials with fear conditioning protocol:

Drexler and collaborators conducted other two trials investigating the use hydrocortisone in disrupting fear memory. Forty healthy male volunteers was exposed to electric shock session learning fear. Then, the participants received 30mg of hydrocortisone before reactivation session. The study results revealed an enhancing effect of cortisol on reconsolidation of the reactivated memory. The reinstatement of the reactivated group was significantly higher compared with the non-reactivated group. Subsequently, the authors repeated the same procedure in a sample composed by 67 healthy female volunteers. The results not confirmed the original hypothesis. There were no differences among the three experimental groups. Hydrocortisone with reactivation did not enhance fear reconsolidation.

Randomized controlled trials with declarative task protocol:

Tollenaar and colleagues conducted two trials comparing intervention with 35mg hydrocortisone, 80mg propranolol and placebo using different types of aversive stimulus in 79 healthy volunteers' civil sample. The authors used words emotionally valence or neutral as aversive stimulus evaluating physical features (blood pressure and heart rate), as well as psychometric measurements (STAI-Trait, SCL-90, BDI-II) (Tollenaar et al., 2009a). Memory retrieval of neutral and emotional information was impaired by a single dose of hydrocortisone compared to placebo and remained after a week later.

Randomized controlled trials with script-driven imagery:

In this experiment, the authors prepared a script of a negative disturbing memory of each subject as aversive stimulus. Similar to the previous study, the authors evaluated heart rate and skin conductance as physical features, and STAI-Trait, SCL-90, BDI-II as psychometric measurements (Tollenaar et al., 2009b). However, no diminishing effect of either propranolol or hydrocortisone was achieved on psychophysiological responding to the script-driven imagery of emotional memories.

4.2.3. Mifepristone: Level D of evidence

There is a single RCT investigating the use of mifepristone, a glucocorticoid receptor antagonist, which failed to show significant differences in memory reconsolidation blockage among mifepristone reactivation, mifepristone no-reactivation and placebo groups (Wood et al., 2015). Wood and colleagues administrated 1800mg of mifepristone before reactivation sessions in PTSD patients from civil sample.

The same study made a subsequent experiment associating mifepristone and D-cycloserine (DCS) versus placebo in 21 PTSD patients after those finding above. Authors hypothesized that DCS, a partial N-methyl-D-aspartate (NMDA) receptor agonist, may destabilize fear memory and mifepristone would blockade the memory reconsolidation in a trauma script-driven paradigm. Yet this trial also found no significant difference between the group receiving DCS plus mifepristone and the placebo control group.

4.2.4. Metyrapone: Level D of evidence

There is a RCT conducted to verify the effects of glucocorticoid suppression in a civil sample, promoted by metyrapone (Rimmele, Besedovsky, Lange, & Born, 2015). In this trial, 18 healthy volunteers took 1 mg metyrapone before retrieval sessions of emotional text and negative pictures recall, as well as one week later.

In addition, suppression of the morning cortisol by metyrapone significantly impaired free recall of emotional texts, but not recall of neutral texts or emotional and neutral pictures. These findings suggest that inhibition of cortisol synthesis persistently weakens emotional memories possibly promoted by affecting re-encoding of these emotional memories.

4.3. PROTEIN SYNTHESIS INHIBITORS

4.3.1. Doxycycline: Level B of evidence

The antibiotic doxycycline, a metalloproteinase inhibitor, was employed in an attempt to impair fear memory reconsolidation in a Pavlovian fear conditioning paradigm by Bach and colleagues (D. Bach et al., 2017). Doxycycline 200mg dose was administered to 38 healthy volunteers versus 38 from placebo group, before reactivation session. The results revealed that 60% in individuals that received doxycycline presented attenuated fear-potentiated startle seven days after acquisition in the recall of threat memory.

4.3.2. Sirolimus: Level D of evidence

There was one RCR investigating sirolimus (Suris et al., 2013), or rapamycin, a dendritic protein synthesis regulator in amygdala and hippocampus, that showed reduction of fear memory in mammalian animal model (Smolewski, 2006). Sirolimus is a protein synthesis inhibitor commonly prescribed as antifungal for immunosuppressed patients. The authors aimed to verify the effects of sirolimus administration in reconsolidation of traumatic memories in veteran PTSD patients (Suris et al., 2013).

The subjects were evaluated through physiological measurements, such as HR and EMG response, and for PTSD symptoms, using CAPS, PCL and QIDS-R. No significant differences were found for any of the PTSD symptoms or physiologic measures when the entire veteran sample was evaluated. However, the analyses of the post-Vietnam subgroup alone, indicated that sirolimus group reported significantly fewer and less intense PTSD symptoms, according to PCL and CAPS total scores one month after treatment, but the effects did not persisted three months later.

4.4. OTHER AGENTS

4.4.1. D-cycloserine (DCS): Level D of evidence

Previous studies hypothesized that DCS, a partial NMDA receptor agonists, enhances extinction of fear-related memory, which has been linked to NMDA glutamatergic receptor activity in the basolateral amygdala (Norberg et al., 2008). Furthermore, bidirectional manipulations of NMDA receptor activity affected reconsolidation and extinction in diverse ways when applied to a short or long reactivation protocol, respectively (Merlo et al., 2014).

There are two RCT investigating de effectiveness of DCS in disrupting fear-related memory reconsolidation. First, Litz (Litz et al., 2012) examined the effects of DCS administered before exposure therapy session, along six weeks in veterans with PTSD patients. In contrast to previous trials using DCS to enhance exposure therapy (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012), Litz results indicated that PTSD veterans experienced significantly less symptom reduction than those in the exposure therapy plus placebo condition throughout the treatment.

The second trial investigated the effects DCS in association with mifepristone, a powerful glucocorticoid antagonist. Wood and colleagues (Wood et al., 2015) hypothesized that PTSD patients who underwent memory reactivation preceded first by DCS (memory destabilizer) and second by mifepristone (reconsolidation blocker) would show smaller physiological responses during script-driven imagery testing a week later compared to those who received two placebos. However, their results showed no significant difference between the group receiving DCS plus mifepristone and the placebo control group.

4.4.2. Ketamine: Level D of evidence

The present review found a single RCT investigating the effectiveness of ketamine, a non-competitive NMDA receptor antagonist, in disrupting fear-related memory reconsolidation. Corlett and collaborators (Corlett et al., 2013) administered ketamine in a Pavlovian fear conditioning model in healthy volunteers, verifying ketamine influence on reactivated aversive memories.

The study used spider pictures as aversive stimulus and the representation of a training aversive cue under ketamine or placebo. Results indicated that ketamine correlates to elevated ratings of unpleasantness in the following day. Besides that, representation of the conditioned stimulus under ketamine led to a stronger subsequent memory than under placebo.

5. DISCUSSION

Until now, this is the first systematic review investigating the effectiveness of pharmacological interventions specifically in disrupting fear-related memory reconsolidation. Our results spotlight the beta-adrenergic receptor antagonist, propranolol, which achieved level A of scientific evidence and plays the principal role in memory reconsolidation research until the present date. Besides that, our findings elevate cortisol as an expressive supporting actor in FRMR scenario receiving the level B of evidence. At last, doxycycline raise as a promisor representative of protein synthesis inhibitors in disrupting FRMR.

There is strong evidence indicating that propranolol administration just before retrieval in protocol models compounded by aversive pictures paired to electric shock in healthy participants. This result is in accordance to those of previous studies in the literature, in spite of precedent investigations not only specifically refers to fear-related memory reconsolidation, but general reconsolidation and consolidation memory (Lonergan et al., 2013; D. Schiller & Phelps, 2011). Moreover, they also obtained the most expressive results. Protocols elected pictures of spiders, snakes, guns or other aversive imagery themes from the as the aversive stimulus in each experiment. In addition, two different models of propranolol administration reported reduction in the subsequent memory for emotional pictures during reactivation associated with significantly increased activity in the amygdala and the hippocampus (Schwabe et al., 2012a). The second trial conducted by the same research group, reinforced the previous findings of propranolol administration before memory reactivation reduced specifically the memory accuracy and the subjective sense of remembering associated with emotional pictures, suggesting that propranolol disrupted the reconsolidation of emotional episodic memories (Schwabe, Nader, & Pruessner, 2013).

Despite these positive findings, a similar trial conducted with spider pictures from International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1997) paired with electrical shock did not achieve the same results (Dieuwke Sevenster et

al., 2012). However, this experiment highlights the prediction error hypothesis, since the administration of prior to reactivation did not affect the startle fear response 24h later, when the outcome of the reminder trial was perfectly predictable, no prediction error. In contrast, the noradrenergic blockade hindered the startle fear response on day 3, when there was something new to be learned during the reactivation session prediction error. The boundary conditions regarding to reactivation and reconsolidation were also discussed in other trials collected for this systematic review (Schroyens et al., 2017; Wood et al., 2015).

Additionally, Thome and colleagues did not replicate the erasure of fear by propranolol administration (Thome et al., 2016). Interestingly, their experiment calls attention to the presence of a similar fear response during retention and reinstatement testing for all stimulus types, suggesting a generalization of fear to the neutral control stimulus. Fear generalization theory refers to an excessive fear response to dissimilar conditioned stimuli, most of time neutral or never presented before (C. L. Bender, A. Otamendi, G. D. Calfa, & V. A. Molina, 2018). There are evidence in the literature concerning about overgeneralization of cues, in clinical population (Kaczkurkin et al., 2016; Lissek et al., 2014) and non-clinical population with higher state anxiety (Dibbets & Evers, 2017) or trait anxiety (Dibbets, van den Broek, & Evers, 2015).

Furthermore, propranolol showed to be also effective in disrupting traumatic event memories among PTSD patients in script-driven imagery protocols. Nonetheless, Wood and collaborators did not replicate the previous findings (Brunet et al., 2008; Wood et al., 2015). Although, the experiment recruited combat-veterans diagnosed with PTSD, an incentive of a participation fee was given, differing from a treatment-seeking population. Persons with the most severe PTSD may be hesitant to volunteer for research studies. Besides that, not always the script-driven imagery of the traumatic event is sufficient to reactivate the original memory and reconsolidation.

Surprisingly, a case report underlines propranolol application in a patient diagnosed with intermittent explosive disorder and polysubstance abuse promoting important reduction in frequency and intensity of behavioral incidents.

Not so far, cortisol follows or even walk side-by-side propranolol through a diversity of studies investigating its effects in memory reconsolidation mechanism. The limitation to cortisol achieve level A resides on the fact that there is no meta-analysis about its use in memory reconsolidation. Maybe, it is due to the lack of protocol unification in studies investigating cortisol effects in memory reconsolidation. Endogenous cortisol released after cold pressor test or stress tasks achieved significant results in paradigms using geometrical figures paired with electric shock. Hence, studies that evaluated cortisol intervention in memory reconsolidation through learning negative or emotionally words versus neutral or positive material reinforce its importance in this field.

Moreover, in a RCT comparing propranolol and placebo to hydrocortisone, a single dose of the GC was sufficient to impair emotional memory retrieval, even a week follow-up (Tollenaar et al., 2009a). In addition, the results presented in this systematic review are similiar to those of other reviews investigating the effects of GC in patients with PTSD and phobic disorders which demonstrated that GC treatment reduced the retrieval of aversive memories (Aerni et al., 2004; Soravia et al., 2006; Yehuda et al., 2015). By the way, suppression of the morning cortisol by metyrapone significantly impaired free recall of emotional texts, but not recall of neutral texts or emotional and neutral pictures. These findings suggest that inhibition of cortisol synthesis persistently weakens emotional memories possibly promoted by affecting re-encoding of these emotional memories

The research of protein synthesis inhibitors in clinical trials is limited by the toxicity the toxicity of the agents employed in previous animal studies. Doxycycline opens a new perspective for future studies due to its positive results as well as its characteristics of extracellular action. The authors confirmed their original hypothesis of inhibiting synaptic remodeling by targeting an extracellular signaling pathway.

Furthermore, sirolimus, other protein synthesis antagonist, showed hopeful reduction in posttraumatic symptoms in a sample subgroup compound by Vietnan veterans, but not sustained these positive effects in a three months follow-up. These limited results may suffered influence of the time of traumatic memories, since stronger or older memories appear to be relatively resistant to undergoing reconsolidation. However, there is evidence in the literature considering boundary

conditions to reactivate and promotes reconsolidation of strengthened and older fear-related memories through specifically protocols (Elsey & Kindt, 2017a). The single dosage administered in this trial should also limited its effect in follow-up outcomes. Possibly, a repeatedly administration through more reactivation sessions would achieve different results.

These findings described in this systematic review have some limitations. The fear conditioning protocols used in studies may be inadequate to address the real menace responsive behavior in a dynamic fear environment. Additionally, the majority of the studies investigated FRMR in healthy volunteers who acquired the new aversive information in a safe laboratory, which is too far from a real traumatic event in PTSD patients, or even, in patients with specific phobic disorders, for instance. At last, the different paradigms used to study the effects of drugs in FRMR precluded us to synthesize the data into a meta-analysis. We did not permorm a quality check of the studies included in this review.

6. CONCLUSION

The present systematic review aimed to verify if pharmacological interventions disrupts FRMR. Considering this purpose, the answer is yes. However, the complexity of the processes involved with FRMR disruption, the multiple neurophysiologic pathways and the variety of features that possibly influences the outcomes of manipulation represent a long road to ride.

In sum, some features might guide future researches in FRMR disruption. It is clearly that time matters when talking about disrupting reconsolidation. The window of opportunity to target fear-related memory is small, thereby it is preceded and followed by phases that may leave unaffected the original memory. This condition poses a challenge for clinical practice. An independent prediction error index may contribute to decide whether an intervention to change maladaptive emotional memories has the potential to be effective. Thus, the success of the manipulation depends on subtle differences in the reactivation procedure.

Another challenge in this area, the precisely comprehension of the interactions between glucocorticoids and noradrenergic activation in fear-related memory processes seems to be essential for future researches. The glucocorticoid actions associated with noradrenaline promotes increase in glutamate transmission and strengthens memories of the stressful experience. As soon as glucocorticoid levels are elevated, retrieval processes are impaired, possibly to avoid interference and protect the consolidation of the stressful event for survival purposes.

Therefore, drugs capable to disrupt FRMR should revolute the treatment of severe and debilitating disorders such as PTSD and phobias.

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