

Pharmacological interventions during the process of reconsolidation of aversive memories: A systematic review



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ABSTRACT

Reconsolidation is the return of a memory to a transient state of lability, following memory consolidation, that can occur when memories are evoked. During the process of reconsolidation, memories may be modified by different means, including the administration of drugs, during a period called the "reconsolidation window". This process has been widely studied in animals, but human studies are limited and include several methodological pitfalls. Our objective was to conduct a systematic review of the literature that utilizes pharmacological interventions during the process of reconsolidation of aversive memories in humans, with a critical analysis of the methodologies used. Searches were made in the electronic databases PubMed, Scopus, Web of Science and SciELO using the following search terms: (memory) AND (consolidation OR reconsolidation) AND (pharmacological manipulation OR pharmacological intervention). We found 294 references and ten (3.4%) were included in the review, based on preestablished eligibility criteria. All studies were randomized, double-blind clinical trials. The most commonly studied drug was propranolol. Two studies used a protocol involving autobiographical aversive memories, while in the remaining aversive memories were produced in the laboratory. The timing of pharmacological interventions is a controversial issue in the field, as drug activity must occur within the reconsolidation window. The small number of studies and some methodological difficulties of this type of research highlights the need for studies that individually evaluate some of the issues discussed, particularly the timing of pharmacological interventions and the duration of reconsolidation windows.

1. Introduction

Memory is the faculty of the brain by which one acquires, trains, preserves, and retrieves information. Memories are not stored in their final form, undergoing periods of instability in which they are susceptible to modifications (Izquierdo, 2011). In 1900, Muller and Pilzecker proposed the theory of memory consolidation based on studies with human subjects. When acquired, information requires time to be fixed, or consolidated. During this period, protein synthesis occurs in different brain regions, including the dorsal hippocampus, amygdala nuclei, and neocortex, inducing the synaptic plasticity necessary for the formation and maintenance of memory (McGaugh, 2000; Rodriguez-Ortiz and Bermúdez-Rattoni, 2007). While this process is taking place, memories are in a labile state and are susceptible to interference from other memories, drugs, or other treatments (Dudai, 2004; Izquierdo, 1989). Studies demonstrating that consolidated memories, when reactivated, can return to a transitory labile state followed by re-stabilization have challenged the notion that consolidation transforms short-term memories into long-term memories, insensitive to modification. This process is known as 'reconsolidation' (Agren, 2014; Einarsson and Nader, 2012; Rodriguez-Ortiz and Bermúdez-Rattoni, 2007). Memories become active at times near their acquisition and when reactivated through recovery (Lewis, 1979).

Memories can be improved or weakened throughout reconsolidation by the same factors involved in the original process of consolidation. It has been suggested that the two processes involve different mechanisms, brain areas, and temporal dynamics (Agren, 2014; Schwabe et al., 2014). The consolidation of memories always encompasses a period of lability during which they can be modified. However, a memory is not necessarily induced to a labile state when evoked and reactivated (Rodriguez-Ortiz and Bermúdez-Rattoni, 2007; Schwabe et al., 2014). The critical issue in reconsolidation studies consists of the circumstances under which memories can be induced to a labile state (Agren, 2014).

It is important to differentiate reconsolidation from extinction, particularly in the face of an aversive stimulus. Extinction is a process by which the repeated exposure of the subject to the conditioned stimulus, in the absence of the unconditioned stimulus, causes the fear response to become less frequent (National Collaborating Centre for Mental Health, 2005). In extinction, this repeated exposure in the absence of the unconditioned stimulus leads to the learning of a new behavior, which does not affect the association between the aversive stimulus and the original behavior, thus allowing the behavior to re-occur (Catania, 1999). As in consolidation, interference in memory after the recall of a given event creates a period that is called the "reconsolidation window," during which the quality of memories can be

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modified or interrupted by interference in the synthesis of proteins. During the reconsolidation window, the use of pharmacological agents such as beta-adrenergic antagonists, including propranolol or protein synthesis inhibitors, may lead to the loss or weakening of an existing memory (Exton-McGuinness et al., 2015). Thus, reconsolidation may serve as an adaptive updating mechanism, allowing new information to be added to the existing representation (Schiller et al., 2010). This process is important for mitigating maladaptive memories that affect daily life, such as those associated with anxiety disorders and drug addiction.

In contrast to animal studies, studies about pharmacological interventions during the process of memory reconsolidation in humans are scarce. A review of the literature (Schiller and Phelps, 2011) found 300 animal studies, compared to only 13 human studies over a period of 10 years prior to its publication. Among the obstacles to studies with human samples in this area are methodological difficulties related to the reproduction of procedures used in animal studies.

The objective of this study was, therefore, to conduct a systematic review of the literature regarding the use of pharmacological interventions during the process of reconsolidation of aversive memories in humans and to perform a critical analysis of the methodologies used in these studies.

2. Method

We conducted a systematic review consisting of a bibliographical survey on pharmacological interventions during the process of reconsolidation of aversive memories in humans following the guidelines of the PRISMA initiative (Moher et al., 2009). PRISMA aims to improve the transparency of systematic reviews by providing recommendations for authors to report the research methods and findings. It presents a flowchart divided into four phases of the studies reviewed, namely identification, screening, eligibility, and included. The PRISMA diagram is not designed to evaluate the methodological quality of the studies (Moher et al., 2009).

2.1. Selection of articles

The searches were carried out in the electronic databases PubMed, Scopus, Web of Science, and SciELO. Multiple searches with several descriptors were made in order to ensure that as many references as possible were identified. The following descriptors were established: [(memory) AND (consolidation OR reconsolidation) AND (pharmacological manipulation OR pharmacological intervention)]. The last searches were conducted on July 27, 2018, using the same descriptors in English and Portuguese. The filter "humans" was used in the PubMed database. In addition to the electronic searches, the reference lists of the selected articles were manually checked for further relevant references.

2.2. Eligibility criteria

The review only included original articles published in English or Portuguese that reported the results of human pharmacological interventions during aversive memory reconsolidation. Exclusion criteria included studies with animals, literature reviews, studies that did not deal with reconsolidation of aversive memories, and studies with no pharmacological interventions (e.g. behavioral interventions), however, there were no exclusion criteria based on age of the study. We excluded the systematic reviews by selecting only the complete articles with detailed methodology, which allowed for a critical analysis of the methods used in each study.

2.3. Procedure

The first step in the selection of articles for the review consisted of reading the titles and abstracts of the references found through the

electronic databases in accordance with the pre-established eligibility criteria. In a case of uncertainty about the inclusion or exclusion of any given article, the reference was independently evaluated by two reviewers. After the pre-selection described above, the studies were read in full and underwent a new analysis in order to be included in the systematic review.

3. Results

The electronic searches returned a total of 294 references. Three additional references were included from the reference lists of the selected articles. Duplicated results between databases resulted in the exclusion of 65 references (22.1%). Eligibility criteria led to the exclusion of 223 articles (96.12%), resulting in an inclusion of ten studies. All studies included in the review were randomized, double-blind clinical trials. Flowchart 1 illustrates the process of article search and selection.

3.1. Main characteristics of the samples

The main characteristics of the selected studies were recorded for analysis, including study design, sample size, participants, interventions performed, and main results. Table 1 summarizes the main characteristics of the samples in the studies reviewed as well as the year of publication, country of origin, groups, sex, and age.

The articles included in the review were published between 2008 and 2017. Taken together, a total of 538 subjects were randomized into placebo groups and groups receiving medication. It should be noted that in one study (Brunet et al., 2008) the sample consisted of subjects with posttraumatic stress disorder (PTSD), while the samples of all the remaining studies included only healthy subjects (Kindt et al., 2009; Tollenaar et al., 2009; Soeter and Kindt, 2010, 2012; Marin et al., 2011; Schwabe et al., 2012; Drexler et al., 2015, 2016; Thomas et al., 2017). Three studies included only male participants (Tollenaar et al., 2009; Marin et al., 2011; Drexler et al., 2015) and one study included only female participants (Drexler et al., 2016), whereas the remaining included both male and female volunteers (Brunet et al., 2008; Kindt et al., 2009; Marin et al., 2011; Schwabe et al., 2012; Soeter and Kindt, 2010, 2012). All participants in the studies reviewed were at least 18 years old. In respect to recruitment procedures, three studies selected volunteers from the general population (Brunet et al., 2008; Schwabe et al., 2012; Thomas et al., 2017) and seven recruited their participants among university students (Tollenaar et al., 2009; Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Marin et al., 2011; Drexler et al., 2015, 2016).

Two studies (20%) used memory reactivation in all subjects following randomization to the drug or placebo groups (Brunet et al., 2008; Soeter and Kindt, 2010). Six studies (60%) (Tollenaar et al., 2009; Kindt et al., 2009; Soeter and Kindt., 2010; Marin et al., 2011; Schwabe et al., 2012; Drexler et al., 2015, 2016) randomized their samples into three groups, two memory reactivation groups that received the test drug or placebo and one group that received the drug but was not exposed to memory reactivation. One study (10%) (Schwabe et al., 2012) divided their sample into four groups (either drug or placebo x with or without memory reactivation), whereas one other study (10%) (Thomas et al., 2017) divided their sample into three groups; a control group who received a placebo during both the memory consolidation and reconsolidation, the second group who received the drug during consolidation and placebo during reconsolidation and, the third group who received the drug during reconsolidation and placebo during consolidation.

3.2. Experimental protocols

Propranolol was used as the only pharmacological intervention in six studies (60%) (Brunet et al., 2008; Kindt et al., 2009; Soeter and

Table 1
Characteristics of the samples of analyzed studies.

Study	Year	Country	Sample Size (N)	Subject type	Groups (N)	Number of groups (Division of groups for reactivation of memory)		Sex (N)	Age Interval or Mean (SD)
						Drug/Placebo	Male/Female		
Brunet et al., 2008	2008	Canada	19	Patient with PTSD*	9/10	2 (Drug + Reat ^a ./Plac ^b + Reat)	9/10	34.9 (± 10.2)	
Kindt et al. (2009)	2009	Netherlands	60	Healthy	40/20	3 (Drug + Reat ^a /Plac ^b + Reat ^a /Drug - Reat ^a)	17/43	18 to 28	
Tollenaar et al. (2009)	2009	Netherlands	79	Healthy	53/26	3 (Drug + Reat ^a ./Plac ^b + Reat ^a /Drug - Reat ^a)	79 men	18 to 35	
Soeter and Kindt (2010)	2010	Netherlands	60	Healthy	40/20	3 (Drug + Reat ^a /Plac ^b + Reat ^a /Drug - Reat ^a)	15/45	18 to 46	
Marin et al., 2011	2011	Canada	33	Healthy	22/11	3 (Drug + Reat ^a /Drug + Drug + Reat ^a /Pla ^b + Reat ^a)	33 men	18 to 35	
Soeter and Kindt, 2012	2012	Netherlands	40	Healthy	20/20	2 (Drug + Reat ^a ./Plac ^b + Reat ^a)	10/30	18 to 26	
Schwabe et al. (2012)	2012	Canada	52	Healthy	26/26	4 (Drug + Reat ^a /Plac ^b + Reat ^a /Drug/Reat ^a /Plac ^b -Reat ^a)	26/26	18 to 30	
Drexler et al., 2015	2014	Germany	42	Healthy	28/14	3 (Drug + Reat ^a /Plac ^b + Reat ^a /Drug - Reat ^a)	42 men	18 to 35	
Drexler et al. (2016)	2016	Germany	67	Healthy	45/22	3 (Drug + Reat ^a /Plac ^b + Reat ^a /Drug - Reat ^a)	67 women	18 to 34	
Thomas et al. (2017)	2017	Canada	87	Healthy	28/46	2 (Drug + Reat ^a ./Plac ^b + Reat ^a)	20/16 16/34	32.6 (11.7) 25.4 (7.8)	

^a Reactivation.

^b Placebo.

Kindt, 2010, 2012; Schwabe et al., 2012; Thomas et al., 2017). Three studies (30%) used cortisol (Tollenaar et al., 2009; Drexler et al., 2015, 2016), one of which (10%) also used propranolol (Tollenaar et al., 2009), and one study (10%) (Marin et al., 2011) used metyrapone, a cortisol inhibitor.

Aversive memories were the only memory type assessed in the studies reviewed and were divided into autobiographical (Brunet et al., 2008; Tollenaar et al., 2009) and laboratory learned (Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Marin et al., 2011; Schwabe et al., 2012; Drexler et al., 2015, 2016; Thomas et al., 2017). Table 2 shows the different methodologies used as well as their main outcomes.

The two studies that assessed autobiographical memories (Brunet et al., 2008; Tollenaar et al., 2009) both used the protocol proposed by Pitman et al. (1987), one using two days and with the other using three days. This protocol consists of reporting the traumatic event description, while being recorded. Later the subjects should listen to the audio recording and imagine their own report as vividly as possible. For the study with the two-day experimental protocol (Fig. 1A) (Brunet et al., 2008), the first day of the test was characterized by the synthesis of two scripts, which reported events that triggered the PTSD. The second day occurred one week following the first day, during which the researcher read to the research subjects each "script" and asked the subject to imagine the traumatic event for 30 s. The physiological responses during the hearing and the imagination of the traumatic event were evaluated by subtracting the mean response from the first day to the second day. In the three-day protocol (Tollenaar et al., 2009) (Fig. 1B), the first day was used for the preparation of scripts containing memories of fear, anger, or anxiety, and the researcher recorded this memory in audio form for approximately one minute. The second day occurred one week after day one, during which the participants ingested a capsule of propranolol, cortisol, or placebo and 75 min later listened to the audio recorded by the researcher. The third day was similar to the second day, but was without the pharmacological intervention. The BDI II (Beck et al., 1996), the STAI-trait (Spielberger, 1983), and SCL-90 (Arrindell et al., 1986) questionnaires were administered on day two and day three.

The similarities between the two protocols are the methodology to assess autobiographical memory, the time interval between the pharmacological interventions and the memory test (seven days), and that neither studies report the time interval between the traumatic experience and the remembrance of the traumatic experience. However, they differ in the fact that in only one study (Brunet et al., 2008) is the traumatic event in agreement with the criterion for a PTSD diagnosis. Another difference is the moment of pharmacological administration, being before (Tollenaar et al., 2009) or immediately after (Brunet et al., 2008) the recall of the traumatic event.

The studies that assessed healthy subjects submitted to fear conditioning employed two types of experimental protocols (Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Marin et al., 2011; Schwabe et al., 2012; Drexler et al., 2015, 2016; Thomas et al., 2017). The first, used in five studies (Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Drexler et al., 2015, 2016), consisted of typical Pavlovian fear conditioning; whereas the second protocol, used in three studies (Marin et al., 2011; Schwabe et al., 2012; Thomas et al., 2017), was based on declarative memory tasks containing aversive and neutral memories. Despite the type of protocol, these studies used similar pharmacological interventions (before the recollection of the traumatic memory) and had the same duration of the experimental protocol (three days). The time interval between the pharmacological intervention and the memory tests ranged from 24 h to seven days, and in one study the pharmacological intervention occurred both before and after the recollection of aversive memories.

A summary of the experimental protocol used in the studies on the manipulation of autobiographical memories and laboratory-produced memories are shown in Figs. 1 and 2, respectively.

Table 2
Methodologies and main outcomes.

Study	Drug (doses)	Type of Memory	Time of pharmacological intervention	Time between memory learning and pharmacological intervention	Time between pharmacological intervention and memory test	Measures	Outcomes
Brunet et al., 2008	Propranolol (40 mg e 60 mg)	Autobiographical	Immediately after reconsolidation	Not reported (Min 3 months)	7 days	HR ^a , SC ^b , EMG ^c	Subjects who received propranolol after remembrance showed typical physiological responses (FC ^c , CP ^d) of trauma victims without PTSD. EMG ^c was below for both groups. Propranolol prior to the activation of a fear memory resulted in a substantial weakening of the fear response. No effect was found on the reduction of psychophysiological responses or subjective experience of either propranolol or cortisol to the script of emotional scripts. In the propranolol group, PS, EMG, and AS decreased compared to the placebo group, comparing day 1 to day 3. Propranolol before reconsolidation resulted in the erasure of the fear startle response 24h later. This effect persisted in one month follow-up.
Kindt et al., 2009	Propranolol (40 mg)	Created in the laboratory	70min before reconsolidation	24h	24h	BP ^d , IDATE-E and T	
Tollenaar et al. (2009)	Propranolol (80 mg)	Autobiographical	90min before reconsolidation	Not reported	7 days	HR ^a , SC ^b , SS ^e	
Soeter et al. (2010)	Cortisol (35 mg) Propranolol (40 mg)	Created in the laboratory	90min before reconsolidation	24h	24h	SC ^b , EMG ^c , BP ^d , SS ^e	
Marin et al., 2011	Metirapona (750 mg/2x)	Created in the laboratory	90min before reconsolidation.	3 days	4 days	SS ^e	Double dose of metirapona significantly decreases the recovery of emotional memory.
Soeter et al. (2012)	Yohimbine Propranolol (40 mg)	Created in the laboratory	Before and after reconsolidation	24h	24h	^b ^{sc}	I: the administration of propranolol reduced the startle of fear 48h later. II: propranolol after reactivation also eliminated the fear response of startle 48h after acquisition.
Schwabe et al. (2012)	Propranolol (40 mg)	Created in the laboratory	60min before reconsolidation	24h	24h	Remember of figures	Propranolol before reactivation reduced memories for emotionally unpleasant photos; Neutral images remained unchanged.
Drexler et al., 2015	Cortisol (30 mg)	Created in the laboratory	30min before reconsolidation	24h	24h	SC ^b	Cortisol improved the reconsolidation of original fear memory, leading to a more pronounced reestablishment of fear.
Drexler et al., 2016	Cortisol (30 mg)	Created in the laboratory	30min before reconsolidation	24h	24h	SC ^b	In the group which had received cortisol before reactivation, the reinstatement of the reactivated CS1 + was significantly higher compared with the non-reactivated CS2 +.
Thomas et al., 2017	Propranolol (0.67 mg/kg)	Created in the laboratory	Experiment 1: Immediately after learning Experiment 2: 60–75 min before recall	7 days	7 days	HR ^a , SC ^b , EMG ^c	Experiment 1: propranolol administered immediately after learning or immediately after retrieval, the impairment of emotional memory is not reliably achieved. Experiment 2: the consolidation as well as the reconsolidation of emotional memory can be impaired when propranolol is given 60–75 min before learning or retrieval.

^a Heart rate (HR).^b Skin Conductance (SC).^c Electromyography (EMG)^d Blood Pressure (BP).^e Sample of Saliva (SS).

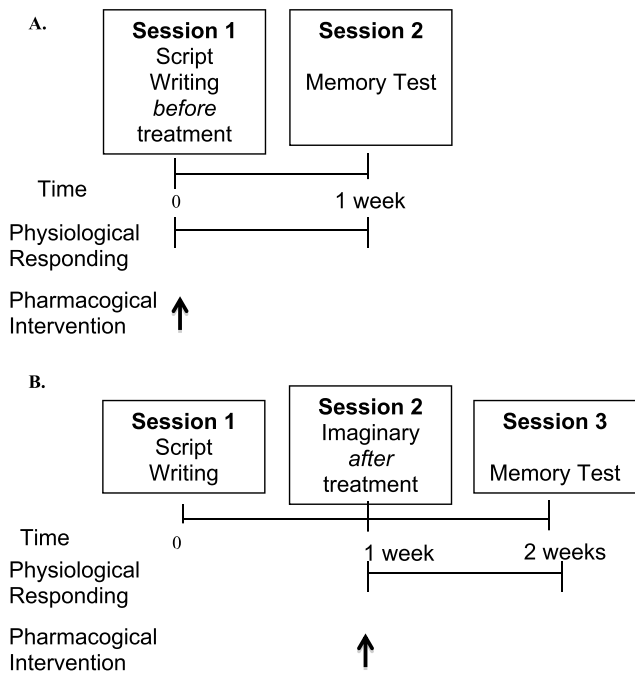


Fig. 1. Experimental protocol for the study of autobiographical memories. (A) Traumatic memories are in agreement with the criterion of PTSD diagnostic. (B) Traumatic memories occur in the subject without the diagnosis of PTSD.

3.3. Main outcomes

The outcome measures for the assessment of psychological and psychophysiological responses in the studies reviewed included blood pressure (BP), heart rate (HR), skin conductance (SC) level, electromyography (EMG) results, anxiety level (IDATE), cortisol level (CL), and number of remembered figures. The physiological measures were

used as a correlate of anxiety level.

Among the investigations on autobiographical memories (Fig. 1A and B), the outcome measures of one study (Brunet et al., 2008) consisted of the differences in BP, HR, and EMG results between baseline, before recollection of the traumatic event, and after recollection of the traumatic event. In this study, the subjects presented psychophysiological responses typically seen in victims of trauma without PTSD on the day of the test. As for the other study on autobiographical memories (Tollenaar et al., 2009), the outcome measures analyzed were CL, BP, and SC. Responses were calculated by comparing the measures recorded on day two (traumatic event imagery and pharmacological intervention) and day three (recollection test). No significant results were found regarding the reduction of anxiety responses in that study.

SC, HR, and measures of startle were used as outcome measures in articles that dealt with healthy subjects submitted to fear conditioning, studies involving typical Pavlovian conditioning (Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Drexler et al., 2015, 2016) (Fig. 2A). The analyses were conducted to determine the difference between those measures over the three days of the experiment. All the articles described a decrease in fear responses on the day of the memory test (day three).

Studies that used pictures related to emotionally negative and neutral memories (Marin et al., 2011; Schwabe et al., 2012; Thomas et al., 2017) (Fig. 2B) assessed the retrieval memory in two different ways. One way is based on a paradigm proposed by Cahill et al. (1994) that presents pictures accompanied by the narration of stories neutral or emotionally negative. A blind rater evaluated the memory performance according to a coding scheme (Marin et al., 2011; Thomas et al., 2017). The other protocol (Schwabe et al., 2012) used a set of 25 neutral and 25 emotionally negative pictures during the learning session and retested with the same images mixed with two new sets of neutral and negative pictures during the memory test. The primary outcome measures were the number of emotionally negative or neutral figures that participants remembered on the memory test. In the memory test (day three), the studies showed that the administration of drugs prior to memory reactivation (day two) decreased the emotional

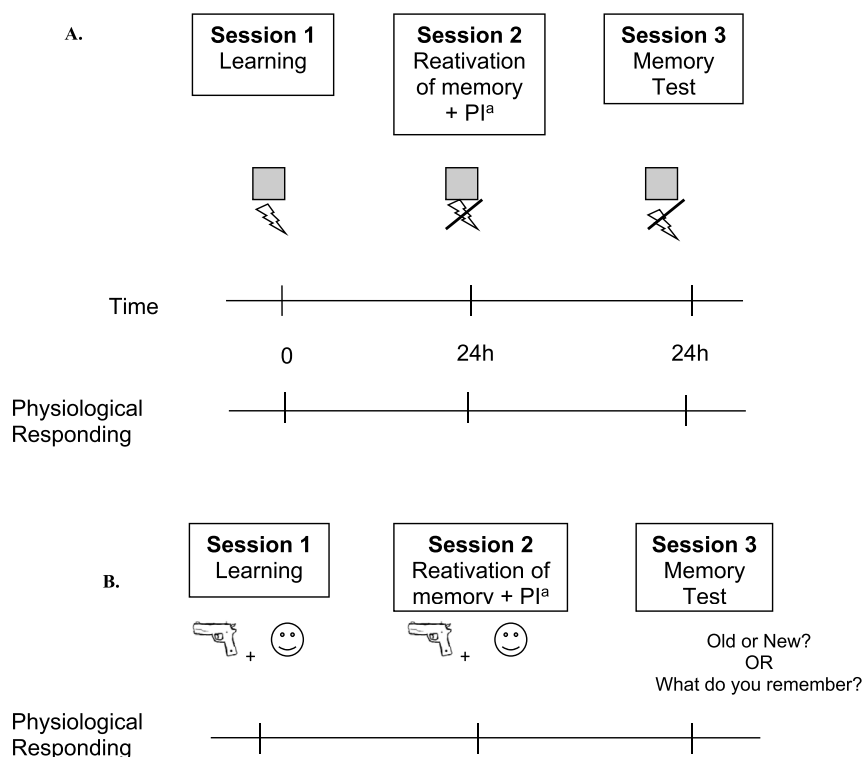
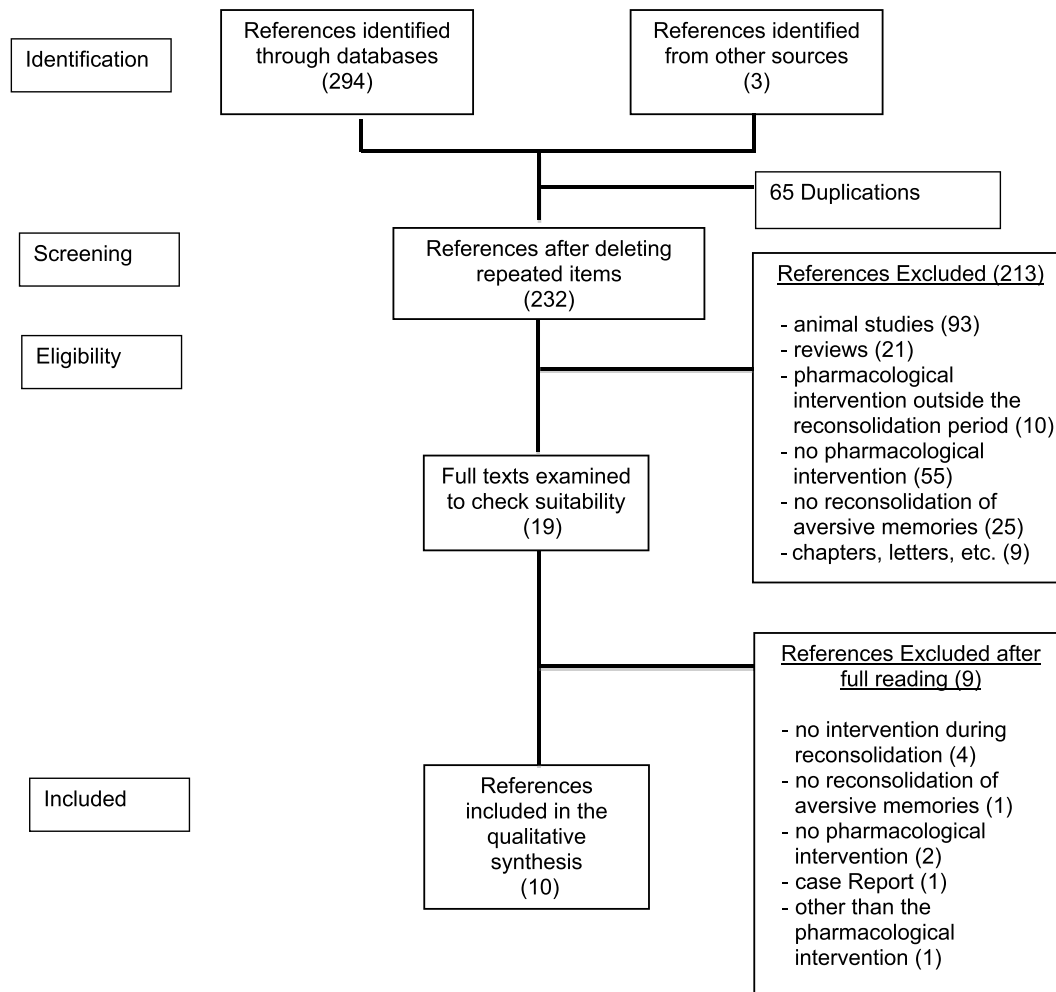


Fig. 2. Experimental protocol of studies of memories produced in laboratories. (A) Protocol of Pavlovian Conditioning. (B) Protocol of Aversive image pairing and Neutral images. PI^a: Pharmacological Intervention; □ Unconditioned stimuli; ◻ Conditioned stimuli.



Flowchart 1. Selection process of the studies (Moher et al., 2009).

memory enhancement observed in the learning process (day one).

4. Discussion

A critical analysis of the methodologies used in pharmacological interventions studies that utilize the process of reconsolidation of aversive memories in humans is discussed below.

4.1. Article selection and characteristics of the samples

The vast majority of the articles found using the selected search terms still concentrate on animal studies, consonant with previous data (see Flow chart 1) (Schiller and Phelps, 2011). Even when the filter "humans" was used in the PubMed database, several references to animal studies were still found (93/232). While animal studies use well-established experimental paradigms such as conditioning, studies with humans are very heterogeneous, ranging from healthy subjects submitted to fear conditioning to using subjects' own autobiographical memories (Buchanan, 2007).

Several studies found in the searches (55/232) did not use pharmacological interventions, but instead used behavioral interventions such as the extinction paradigm. This mechanism is widely used in studies on the attenuation of fear responses (Schiller et al., 2010; Agren et al., 2012; Oyarzún et al., 2012).

4.2. Drugs

Most of the studies (70%) (Brunet et al., 2008; Kindt et al., 2009; Tollenaar et al., 2009; Schwabe et al., 2012; Soeter and Kindt, 2010, 2012; Thomas et al., 2017) used propranolol to interfere in the process of memory reconsolidation. Probably, this predominance of studies with propranolol is because there is a rational justification for this effect, based on a possible mechanism of action, accompanied by satisfactory results in animal reconsolidation models. Memory reconsolidation involves a new synthesis of proteins and propranolol may indirectly impair this. This drug could interfere in the molecular cascade that regulates the genetic transcription necessary for the consolidation and reconsolidation of memory through the downstream beta-adrenergic receptor/PKA/CREB (Thonberg et al., 2002). The interference of propranolol in animal reconsolidation models has been demonstrated since 1999 (Przybylski et al., 1999) and replicated several times (Debiec and LeDoux, 2004; Abrari et al., 2008; Muravieva and Alberini, 2010; Schneider et al., 2014). In human studies the propranolol was administered in oral doses of 40 mg (Brunet et al., 2008; Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Schwabe et al., 2012), and in some studies (Brunet et al., 2008; Soeter et al., 2012) was followed by doses of 60 mg of propranolol and 20 mg of yohimbine, respectively. The remaining studies used metyrapone, a cortisol inhibitor (750 mg) (Marin et al., 2011) and hydrocortisone, a glucocorticoid (30 mg) (Drexler et al., 2015, 2016). One study (Tollenaar et al., 2009) used both propranolol (80 mg) and cortisol (35 mg), while another study (Thomas et al., 2017) used propranolol at the dose of 0.67 mg/kg.

All medications were given orally.

In the studies examined in this review, propranolol produced a decrease in fear responses even when fear acquisition was pharmacologically enhanced (Soeter and Kindt, 2012). Animal studies indicate that the administration of stress hormones such as epinephrine and corticosterone improves the consolidation of aversive memories (McGaugh, 2004). Thus, propranolol, which blocks beta-adrenergic receptors, could prevent or hinder the consolidation (Cahill et al., 2000; Ferry and McGaugh, 1999; Kroon and Carobrez, 2009) and reconsolidation (Debiec and LeDoux, 2004; Abrari et al., 2008; Muravieva and Alberini, 2010; Schneider et al., 2014) of aversive memories. Thus, we can say that propranolol is a well-studied drug in both the consolidation and reconsolidation of aversive memories in animals and a meta-analysis showed a reduction of aversive memories in healthy subjects (Lonergan et al., 2013). Given that protein synthesis is required both in consolidation and reconsolidation (Nader et al., 2000) and that propranolol is one of the substances that produce inhibition reduction of aversive memories, this may be one of the mechanisms involved in the effect on consolidation and reconsolidation (Guiustino et al., 2016). Another, interference in reconsolidation is the anxiolytic effect (Brandigan et al., 1982) that can be attenuated the stress induced by the fear memory.

Similar trials have been performed with the drugs metyrapone and hydrocortisone. Metyrapone and hydrocortisone both interfere with glucocorticoids, which play a key role in the response to stressors (Buchanan, 2007; Drexler et al., 2015) and may mediate the consolidation of emotional events (de Quervain et al., 2009). In this review, metyrapone, which inhibits the secretion of glucocorticoids, impaired the recovery of emotional memory. Conversely, the administration of cortisol led to inconsistent results in both improvement (Drexler et al., 2015) and lack of interference (Tollenaar et al., 2009; Drexler et al., 2016) in memory reconsolidation.

The effects of cortisol on the reconsolidation of aversive memories may, indeed, depend on the sex of the participants. Two studies used similar experimental protocols, with the only difference being that in one study (Drexler et al., 2015) the participants were exclusively male and in another study (Drexler et al., 2016) the participants were exclusively female. In the first one, there were significant cortisol results in the reconsolidation of aversive memories and, on the other, absence of results. Differences between the sexes may explain this discrepancy.

Studies on the differences in cortisol modulation in learning are quite heterogeneous, with surveys pointing to the absence of differences in fear conditioning between the sexes (Zorawski et al., 2005) and a superior conditioning response in women compared to men (Guimarães et al., 1991). Nonetheless, cortisol interferes with the secretion of sex hormones, which interfere with emotional learning and extinction (Milad et al., 2009, 2010; Moreira et al., 2005; Drexler et al., 2016).

Other safe drugs for use in humans have been tested in animals but have not been studied in humans. Among them the cannabidiol (CBD), a component of Cannabis sativa free of the psychoactive effects of the plant, that presents several pieces of evidence of blocking the consolidation or reconsolidation of an aversive memory in a context-based fear paradigm in rodents (Stern et al., 2012, 2014; 2015, 2018; Gazarini et al., 2014; Rossignoli et al., 2017). Although CBD is a safe drug for use in humans (Bergamaschi et al., 2011), we did not find studies that directly evaluate its effect on reconsolidation and only one study in which it improved the extinction task of fear conditioning (Das et al., 2013). Some difficulties in the study with CBD could explain this lack of studies in humans, among them: not knowing exactly which of its multiple actions would be involved in the effect on reconsolidation; have an inverted U-dose response effect making it difficult to determine the appropriate dose; and the low bioavailability of CBD by oral ingestion requiring higher doses (Ney et al., 2019). Others safe drugs were less studied, such as clonidine (Gamache et al., 2012), Delta-9 tetrahydrocannabinol (Stern et al., 2012), and midazolam (Bustos et al.,

2009).

4.3. Experimental protocols

Different experimental protocols have been used in the studies included in this systematic review. We can divide the studies by type of aversive memories; those that investigated "natural" memories, that is, autobiographical memories, and those that investigated healthy subjects submitted to fear conditioning.

The two autobiographical studies reviewed used the same seven day interval between the pharmacological interventions and memory tests. The methodologies were also similar in respect to the lack of information about the learning time of aversive memories; however, one study recruited subjects with a diagnosis of PTSD (Brunet et al., 2008) and the other recruited subjects who had memories of fear, anger or anxiety (Tollenaar et al., 2009). The decision to use autobiographical memories in this type of investigation provides a more realistic situation, which increases the clinical relevance of findings for the treatment of subjects with anxiety disorders and posttraumatic stress.

Contrary to the study of patients with PTSD (Brunet et al., 2008), Tollenaar et al. (2009) demonstrated unsatisfactory results in terms of the decrease in emotionally negative responses. The study used two types of drugs, propranolol and cortisol, but neither had significant effects. One possible reason for this difference is that the memories reported by these participants may not have been as intense as those of the participants diagnosed with PTSD. Another explanation refers to the dose of propranolol used. In the study with PTSD patients (Brunet et al., 2008), volunteers received an initial dose of 40 mg, complemented by an additional dose of 60 mg two hours later if there was no reduction in blood pressure, while participants in the study with healthy volunteers (Tollenaar et al., 2009) received a dose of 80 mg.

It is also possible that the age of memories may interfere, to a certain degree, with reconsolidation. Unfortunately, this is not able to be examined directly with these studies, as neither study reported the duration between the event being remembered and the study protocol. One study with healthy volunteers (Wichert et al., 2011) showed that interferences after memory recovery could modify original memories depending on the age of these memories. In a test to determine whether the possibility of changing retrieved memories is dependent on their age, participants learned a set of emotional and neutral images and were asked to recall the images after one, seven, and 28 days since learning. Immediately after the recollection, participants learned a second set of images. The results showed that the effect of reconsolidation appeared for memories with seven days of age, but not for memories of 28 days. Most authors agree that it is still a challenge to determine the exact conditions in which memory reconsolidation can occur (Schiller and Phelps, 2011; Schwabe et al., 2014; Wichert et al., 2011).

Contrary to the studies with autobiographical memories, all studies using healthy subjects submitted to fear conditioning (Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Marin et al., 2011; Schwabe et al., 2012; Drexler et al., 2015, 2016; Thomas et al., 2017) (Fig. 2), employed an experimental protocol of three test days. According to Agren (2014), the process of reconsolidation is typically studied in an experimental protocol of three days, in which participants learn the aversive memories on the first day, perform recall tasks on the second day, at which time pharmacological interventions occur (before or after recall), and complete memory tests and psychophysiological measures on the third day. Some studies (Kindt et al., 2009; Tollenaar et al., 2009; Soeter and Kindt, 2010; Marin et al., 2011; Drexler et al., 2015) assessed a third group in addition to the drug and placebo groups, which received the drug intervention but did not perform recall tests.

One study (Schwabe et al., 2012) employed rigorous methodological control and included four groups of participants: drug and memory reactivation, placebo and memory reactivation, drug without memory reactivation, and placebo without memory reactivation,

demonstrating that for memory to be modified, pharmacological interventions alone are not enough, as there is still the need for memories to be reactivated.

Studies that investigated aversive memories in health volunteers can be divided according to the type of experimental protocol used: studies involving typical Pavlovian conditioning (Kindt et al., 2009; Soeter and Kindt, 2010, 2012; Drexler et al., 2015, 2016) (Fig. 2A) and studies in which aversive memories were presented concomitantly with neutral, or declarative (Agren, 2014) memories (Marin et al., 2011; Schwabe et al., 2012; Thomas et al., 2017) (Fig. 2B). Studies using Pavlovian conditioning attempt to reproduce protocols, and therefore resemble, protocols used in animal studies through the creation and manipulation of memories in the laboratory (Schiller and Phelps, 2011). It is noteworthy that in all these studies, the results were satisfactory in respect to the decrease of emotionally negative responses following a pharmacological intervention. In studies involving declarative memory tasks (Marin et al., 2011; Schwabe et al., 2012, 2014; Thomas et al., 2017), participants were initially instructed to learn a list of neutral and negative words or figures. On the second day, participants were administered either active drugs or placebo and completed memory recall tasks. On the third day, memory recall tests were repeated and psychophysiological measures were recorded. A literature review suggested that both types of memories (aversive due to Pavlovian conditioning and declarative memories) are referred to as emotional memories and could be subject to rebinding blockade (Schiller and Phelps, 2011).

4.4. Timing of pharmacological interventions

Another aspect examined in this review was the timing of pharmacological interventions during the reconsolidation of aversive memories, namely, whether interventions occurred before or after recollection of the traumatic event. Per the original experimental model (Lewis, 1969; Misanin et al., 1968), the administration of the treatment to alter reconsolidation should be performed following memory reactivation, not before (Schiller and Phelps, 2011). Only one of the studies included in this review followed this protocol strictly. In that study (Brunet et al., 2008), the memories were reactivated through scripts executed by the participants themselves and the pharmacological intervention occurred immediately after the recollection of the scripts. Most of the studies reviewed (Kindt et al., 2009; Tollenaar et al., 2009; Soeter and Kindt, 2010; Marin et al., 2011; Schwabe et al., 2012; Drexler et al., 2015), however, performed pharmacological interventions before the recollection of traumatic events, in an attempt to match peak plasma concentrations of the drug administered with the time of recollection. This protocol makes it impossible to exclude the potential influence of the drug itself on the process of memory recollection. This is a matter of paramount importance in reconsolidation studies, since drugs administered prior to reactivation may affect the recall and, conversely, if the drug is administered after reactivation, the peak of drug activity may occur outside the reconsolidation window (Schiller and Phelps, 2011; Schwabe et al., 2012).

Soeter and Kindt (2012) administered yohimbine, an alpha-2 adrenergic self-receptor antagonist that stimulates noradrenergic activity, prior to the acquisition of aversive memories in humans and performed two types of experiments. In the first, either propranolol or a placebo were administered 90 min prior to memory reactivation, while in the second, the administration of either propranolol or a placebo occurred immediately after memory reconsolidation. The authors reported that propranolol can disrupt the reconsolidation of fear memories, even when fear acquisition is pharmacologically enhanced by yohimbine. In addition, the effect of propranolol remains if the drug is given after reactivation, thus excluding the possibility that propranolol may affect reactivation of a fear memory rather than reconsolidation.

4.5. Reconsolidation window

A key issue in human memory reconsolidation studies is to establish the period of instability or labile state, known as the reconsolidation window. Previous animal studies have demonstrated that the reconsolidation window persists for six hours. Indeed, animal experiments in which pharmacological interventions occurred outside the labile period showed no interference in reconsolidation (Monfils et al., 2009).

In humans, the duration of the reconsolidation window is not yet clear, but can last for several hours after recall. One study on behavioral interventions during the reconsolidation of aversive memories in humans (Schiller et al., 2010) demonstrated that individuals who were submitted to extinction training ten minutes following recollection of the traumatic event did not present spontaneous recovery of fear memories, suggesting an interference in reconsolidation, with results persisting for at least one year. Conversely, individuals who were submitted to extinction training six hours after recollection or who were only asked to recollect the event and did not were submitted to extinction training presented spontaneous recovery of fear memories, suggesting that there was no interference in reconsolidation. This suggests that the reconsolidation window may occur sometime between ten minutes and 6 h.

5. Conclusion

The present systematic review critically examined ten articles that evaluated the effects of pharmacological interventions during the reconsolidation process of aversive memories. The most commonly used drug was propranolol, and the most commonly used protocol was aversive memory in health subjects submitted to fear conditioning. The timing of pharmacological interventions is a controversial issue in the field, as it must be ensured that drug activity occurs within the reconsolidation window. The results of this review suggest that some pharmacological interventions may affect the reconsolidation of aversive memory, although there are methodological difficulties involved in this type of study. However, the issues raised in this review remain open, given the small number of human studies and the need for studies that specifically evaluate some of the issues discussed.

Conflicts of interest

The authors declare no conflicts of interest.

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