

Review

The role of glucocorticoids in emotional memory reconsolidation



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ABSTRACT

Glucocorticoids are secreted following exposure to stressful events. Their modulating role on memory reconsolidation, a post-retrieval process of re-stabilization, has been investigated only recently, at times with conflicting results. The goal of this review is twofold. First, to establish the modulating role of glucocorticoids on memory reconsolidation. Second, to point the potential factors and confounds that might explain the seemingly paradoxical findings. Here we review recent pharmacological studies, conducted in rodents and humans, which suggest a critical role of glucocorticoids in this post-retrieval process. In particular, the activation of glucocorticoid receptors in the amygdala and hippocampus is suggested to be involved in emotional memories reconsolidation, pointing to a similarity between post-retrieval reconsolidation and initial memory consolidation. In addition, based on the general reconsolidation literature, we suggest several factors that might play a role in determining the direction and strength of the reconsolidation effect following glucocorticoids treatment: memory-related factors, manipulation-related factors, and individual differences. We conclude that only when taking these additional factors into account can the paradox be resolved.

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Abbreviations: BLA, basolateral amygdala; GAD, generalized anxiety disorder; GCs, glucocorticoids; GR, glucocorticoid receptors; HPA, hypothalamus-pituitary-adrenal; MR, mineralocorticoid receptors; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder.

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1. Introduction

Glucocorticoids (GCs; cortisol in humans, corticosterone in rodents) are secreted from the adrenal cortex following the activation of the hypothalamus-pituitary-adrenal (HPA) axis. GCs reach peak concentrations after an exposure to a stressful event. Following stress exposure, they promote an adaptive response to environmental challenges by modulating physiological and behavioral processes, such as learning and memory (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006). While GCs enhance the consolidation of memory, especially for emotional stimuli or in arousing contexts (Maroun & Akirav, 2008; Roozendaal, 2000), they impair the retrieval of information that was previously acquired (Buchanan, Tranel, & Adolphs, 2006; Wolf, 2009). In other words, GCs promote a 'memory consolidation mode' on the expense of retrieval (Joels et al., 2006; Roozendaal, 2000).

The timing of stress exposure/GCs secretion is, therefore, a major factor determining the direction of the effect (i.e. enhancement or impairment) on the memory process. Yet additional learning- and stress-related factors interact in affecting the memory process (Sandi & Pinelo-Nava, 2007). Among them are the memory type, stress intensity, source and duration. For instance, fear memories are more strongly consolidated than neutral memories. This results from GCs and noradrenaline interaction in the basolateral amygdala (BLA) following an exposure to a stressful event (Roozendaal, 2000; Roozendaal, Portillo-Marquez, & McGaugh, 1996). Stress intensity has different effects on various memory types. For fear memory consolidation, a linear or linear-asymptotic dose-response curve was suggested (i.e. stronger memories following higher GCs levels) (Sandi & Pinelo-Nava, 2007). For spatial memory, in contrast, an inverted U-shaped curve was demonstrated, with moderately elevated GCs levels acting as memory facilitators while too high or too low levels impair it (Joels, 2006). The source and duration of stress also play a role. Whereas intrinsic stressor (i.e. related to the cognitive task) may enhance memory consolidation, the effects of extrinsic stress (i.e. unrelated to the task) are more heterogeneous (Sandi & Pinelo-Nava, 2007). Moreover, while acute stress may have various effects on memory, chronic stress is likely to impair it (McEwen, 2004; Sapolsky, 1999).

In the traditional memory research, memory consolidation was thought to be a one-time event. According to this view, after an initial fragile period the memory trace becomes stable (McGaugh, 1966). Yet already in the late 1960s, Misanin, Miller, and Lewis (1968) challenged this idea, suggesting that retrieval can reactivate the memory, rendering it fragile again. The post-retrieval lability period, later demonstrated to last up to 6 h after retrieval (Kindt, Soeter, & Vervliet, 2009; Schiller et al., 2010), was suggested to serve as an adaptive update mechanism (Alberini, 2011; Rodriguez-Ortiz, De, Gutierrez, & Bermudez-Rattoni, 2005; Sara, 2000). In the last fifteen years, various pharmacological agents and behavioral manipulations have been found to affect reactivated memories, thereby revealing the mechanisms mediating the reconsolidation of memory. For instance, Nader, Schafe, and

LeDoux (2000) demonstrated that memory reconsolidation is a protein-synthesis dependent process, while Kindt et al. (2009) revealed that emotional memory reconsolidation depends on noradrenergic activity. These findings suggest a similarity between reconsolidation following retrieval and initial consolidation, a protein-synthesis process (Kandel, 2001) that benefits from noradrenergic activity (Roozendaal, Okuda, Van der Zee, & McGaugh, 2006).

Even though timing plays a critical role in determining the effect of stress and GCs on memory processes (see Fig. 1), GCs modulation of memory reconsolidation has been investigated only recently. As reviewed by Akirav and Maroun (2013), the results are often conflicting, as animal studies reported an impairing effect of stress (Wang, Zhao, Ghitza, Li, & Lu, 2008), GCs administration (Yang et al., 2013) but also GCs antagonists (Pitman et al., 2011) on reactivated memories. Human studies, usually involving stress induction as opposed to a pharmacological intervention, demonstrate either an impairing (Schwabe & Wolf, 2010; Zhao, Zhang, Shi, Epstein, & Lu, 2009) or enhancing (Bos, Schuijjer, Lodestijn, Beckers, & Kindt, 2014; Cocoz, Maldonado, & Delorenzi, 2011; Cocoz, Sandoval, Stehberg, & Delorenzi, 2013) effect of stress on memory reconsolidation, with conflicting results with regard to the susceptibility of strong emotional memories. Others (Wood et al., 2015) reported no effect. This is not surprising, as GCs modulation of learning and memory processes depends on additional factors other than timing of intervention (e.g. post-retrieval) alone (Sandi & Pinelo-Nava, 2007). Yet while the literature offers a clearer understanding of the way some factors interact in modulating memory consolidation (Joels, 2006) and retrieval (Buchanan & Lovallo, 2001), this is not the case for the emerging field of reconsolidation. In this field, conflicting results are sometimes regarded as a paradox or, more often, are accepted without a more thorough explanation. The goal of this review is thus twofold. First, to establish the modulating role of GCs for memory reconsolidation. Second, to point to potential factors (and possible confounds) that might interact in determining these effects.

To achieve this, here we review studies that investigated GCs effects on the reconsolidation of memories. The review is limited to pharmacological studies only. As opposed to stress induction, which leads to the secretion of GCs and additional stress modulators, such as noradrenaline (Joels et al., 2006), pharmacological manipulation allows to focus on the GCs system and to determine the role of its specific receptors. Most of the studies presented here are rodent studies, yet the translational and clinical value of these studies is discussed by presenting data from the (limited) human literature, including patients. Aversive memories are the focus of the majority of the studies we present, but appetitive memories are presented when possible. These findings are discussed and compared to the broader literature on memory reconsolidation.

2. Glucocorticoid involvement in memory reconsolidation

GCs are lipophilic and therefore easily enter the brain (McEwen, Weiss, & Schwartz, 1968) where their activation is mediated by

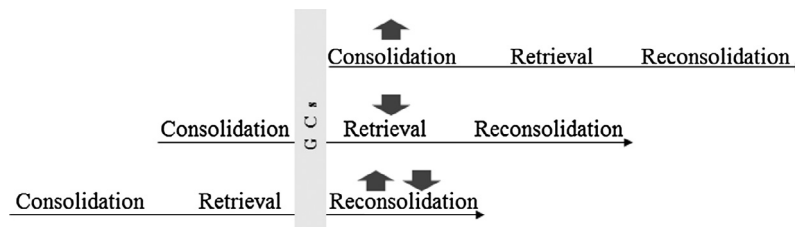


Fig. 1. The time-dependent effects of glucocorticoids (GCs) on memory processes. Consolidation: upwards arrow indicates overall enhancing effects. Retrieval: downwards arrow indicates overall impairing effects. Reconsolidation: both upwards and downwards arrow represents conflicting results.

two receptors types: mineralocorticoid (MR) and glucocorticoid (GR) receptors. The two receptor types differ in affinity and distribution (Joels, 2006). The MR are of higher affinity, mostly saturated under basal conditions. They are mainly present in limbic areas and mediate the initial response to stress, such as information appraisal and response selection (Lupien & McEwen, 1997; Oitzl & de Kloet, 1992). The GR are of lower affinity, thus becoming occupied during the circadian peak or following stress exposure. They contribute to the secession of the stress response by acting on the HPA negative feedback loop, and mediate the beneficial effects of stress on memory consolidation (de Kloet, Vreugdenhil, Oitzl, & Joels, 1998). Both MR and GR were previously thought to primarily exert their effects through gene expression. More recent evidence, however, has shown that membrane-bound variants of both receptor types can alter neuronal functions via non-genomic pathways (i.e. within minutes) (Joels & Karst, 2012; Joels, Karst, DeRijk, & de Kloet, 2008; Roozendaal et al., 2010).

In this section we present animal studies that used specific MR and GR antagonists as reconsolidation manipulation, mainly post-retrieval. This will allow to establish the involvement of GCs and their specific receptor types in the process of memory reconsolidation.

2.1. Mineralocorticoid receptors

Only two rodent studies used MR antagonist as post-retrieval manipulation (Achterberg, Trezza, & Vanderschuren, 2014; Vafaei, Pakdel, Nikzad, & Rashidy-Pour, 2011). However, the two studies differed significantly in methodology. They examined tasks of different emotionality (aversive vs. appetitive tasks), used different learning paradigms, treatment doses and administration methods. They can thus provide an initial view on MR involvement in memory reconsolidation.

Post-retrieval treatment with the MR antagonist spironolactone was found to be inefficient in affecting memory reconsolidation. This was the result for both aversive and appetitive memories, using both systemic or intra-hippocampal injection with various doses. Vafaei et al. (2011) investigated the effects of spironolactone on memory reconsolidation using the inhibitory avoidance paradigm, in which the animal learns to avoid a context that was previously associated with an aversive event (e.g. shock). This is, in fact, an instrumental manifestation of the Pavlovian fear memory. In this paradigm, re-entry to the previously dangerous compartment is considered to be a retrieval session, and is then followed by treatment. A thorough investigation of various doses administered either systemically (5, 25, 50 or 100 mg/kg) or intra-hippocampally (0.3, 3, 30 or 100 ng/ μ l) could not demonstrate any effect on the reactivated memory. Similar findings were reported by Achterberg et al. (2014) with an appetitive task of social reward memory. In that study, post-retrieval systemic administration of an intermediate dose of spironolactone (50 mg/kg) could not affect the reactivated memory. Thus, both studies – covering different tasks, doses and administration methods – suggest that the MR antagonist spironolactone has no effect on reactivated memories.

2.2. Glucocorticoid receptors

In contrast to the lack of effect of MR antagonism reported above, several animal studies used the GR antagonist mifepristone and suggested a key role of GR in the reconsolidation of emotional memories.

Post-retrieval systemic injection of mifepristone (20–30 mg/kg) was found to impair fear memory reconsolidation in the inhibitory avoidance (Nikzad, Vafaei, Rashidy-Pour, & Haghghi, 2011; Taubenfeld, Riceberg, New, & Alberini, 2009) and the cued fear con-

ditioning paradigms (Pitman et al., 2011). For instance, Pitman et al. (2011) trained male and female rats to associate a cue with a footshock. After the reactivation of the conditioned memory (i.e. by an unreinforced re-exposure to the conditioned cue), mifepristone was systemically administered to the animals. The result was a reduction in the conditioned fear, as evident by a shorter duration of freezing to the cue. This effect was relatively long-lasting (lasting 10 days after treatment) and was dependent on memory reactivation (i.e. was absent following mifepristone administration alone), suggesting it resulted from a disruption to the reconsolidation process. Comparable results were demonstrated by Achterberg et al. (2014), who showed the impairing effects of mifepristone on the reconsolidation of appetitive (i.e. social reward) memories. In this study, however, only pre-retrieval (as opposed to post-retrieval) administration led to an effect, probably due to the longer duration of a reactivation session in this paradigm relative to the fear conditioning based paradigms (Achterberg et al., 2014). Other studies have demonstrated the critical role of GR in the BLA and hippocampus in the reconsolidation of emotional memories. Two studies reported an impairment of fear memory reconsolidation following post-retrieval mifepristone administration to the BLA (Jin, Lu, Yang, Ma, & Li, 2007; Tronel & Alberini, 2007). The effect was dose-dependent, seen only following the administration of the higher mifepristone dose while the lower concentrations produced no effect. A dose-dependent effect was also demonstrated by Nikzad et al. (2011), where post-retrieval mifepristone administration to the hippocampus led to a more pronounced reduction of fear using the higher (3 ng/ μ l) compared with the lower (0.3 ng/ μ l) dose.

2.3. Conclusion

Mifepristone, a GR antagonist, was demonstrated to be an efficient pharmacological agent for the disruption of emotional memory reconsolidation. Although the literature provides only scarce data on MR antagonists, the results suggest they do not play a critical role in this process. The involvement of GR activation in the consolidation of newly acquired emotional memories is well established (Roozendaal, 2000; Roozendaal & Mcgaugh, 1997). The above studies suggest that GR activation, in the BLA and hippocampus in particular, is also involved in the reconsolidation of emotional memories after retrieval.

3. The paradox: the consequences of systemic glucocorticoid administration

The studies reviewed in Section 2 suggest that GCs activation, mediated by GR, is necessary for the reconsolidation of emotional memories. These results point to a similarity between memory reconsolidation and initial consolidation of memory (Roozendaal, 2000). Indeed, the rise in GCs concentrations following stress is positively correlated with an improved memory consolidation in both rodents (Cordero, Merino, & Sandi, 1998; Sandi, Loscertales, & Guaza, 1997) and humans (Cahill, Gorski, & Le, 2003). Consolidation enhancement can also be achieved by post-training GCs administration, as demonstrated by Sandi et al. (1997). Blocking GR activity, either pharmacologically in rats (Cordero & Sandi, 1998; Oitzl & de Kloet, 1992) or genetically in mice (Oitzl, Reichardt, Joels, & de Kloet, 2001), prevents this enhancement of initial consolidation. Following this, one could expect that pharmacological elevations of GCs (e.g. via systemic administration) following memory retrieval would lead to enhancement of memory reconsolidation (i.e. the opposite effect of GR antagonists).

Several rodent studies have investigated the effects of systemic corticosterone on memory reconsolidation (Abrari, Rashidy-Pour,

Semnanian, & Fathollahi, 2008; Amiri et al., 2015; Cai, Blundell, Han, Greene, & Powell, 2006; Yang et al., 2013). All studies used a systemic administration of corticosterone (by an injection) with doses ranging from 0.3 mg/kg to 10 mg/kg. The memory tasks were all fear-dependent, using either the contextual fear conditioning (i.e. a Pavlovian conditioning task) or the inhibitory avoidance (i.e. instrumental conditioning) paradigm. In contrast to the arguably expected enhancing effect of GCs activation, the studies demonstrated an impairing effect of corticosterone administration on memory reconsolidation. This effect was suggested to be dose-dependent, resulting from post-retrieval intermediate (3 mg/kg) corticosterone treatment and was absent following lower doses (0.3–1 mg/kg) (Abrari et al., 2008; Amiri et al., 2015; Cai et al., 2006). Conflicting results emerged following the use of higher corticosterone concentrations (10 mg/kg). While two reported an impairment (Cai et al., 2006; Yang et al., 2013), one study (Abrari et al., 2008) reported no effect.

The human literature on the consequences of GCs administration on memory reconsolidation is very limited. Sharing a similar 3-day reconsolidation design, two studies from our laboratory investigated the effects of systemic cortisol administration on fear memory reconsolidation in men (Meir Drexler, Merz, Hamacher-Dang, Tegenthoff, & Wolf, 2015) and women (Meir Drexler, Merz, Hamacher-Dang, & Wolf, 2016). On the first day, the participants were conditioned to two stimuli that were associated with an electric shock. On the second day, one of the conditioned stimuli was reactivated (i.e. presented but was not followed by a shock) after hydrocortisone (30 mg) or placebo pill intake. The return of fear after reinstatement shocks was assessed on the third day. The results showed that in men, cortisol facilitated the reconsolidation of the fear memory, but in women it had no effect.

Thus, while the GR antagonist-dependent memory impairment (Section 2.2.) suggested that GCs are critical in the reconsolidation of emotional memories, systemic administration of GCs led to conflicting results. In humans, oral administration of hydrocortisone indeed enhanced reactivated fear memories in men, yet it had no effect in women. In animals, corticosterone injection was demonstrated to impair reactivated fear memories. This effect was suggested to be dose-dependent. A more thorough investigation of the methodological aspects of the reviewed studies might provide an explanation to these seemingly paradoxical findings. This could be a key step in portraying the potential factors that determine GCs modulation of emotional memory reconsolidation.

4. Understanding glucocorticoids effects on memory reconsolidation

The studies reviewed in the previous sections have demonstrated impairing, enhancing or no effect of both GCs agonists and antagonists on emotional memory reconsolidation. These conflicting results are not unique to memory reconsolidation, and are also seen in memory consolidation studies (Akirav & Maroun, 2013). For instance, while acute GCs administration enhances memory consolidation for spatial and contextual learning in various appetitive and aversive tasks (Cordero et al., 1998; Roozendaal, 2002), the use of GR antagonists can also enhance memory consolidation. GR antagonists were found to improve the performances of chronically corticosterone-exposed rats in a contextual fear conditioning task (Conrad et al., 2004). In addition, chronic (but not acute) administration of GR antagonists led to facilitation of spatial memory processes in a dose-dependent manner (Oitzl, Flutterm, Sutanto, & de Kloet, 1998). Clearly, the effects of GCs on memory processes, reconsolidation included, cannot be simply classified as impairing or enhancing (Akirav & Maroun, 2013), without taking additional factors into account.

Table 1

Factors determining the strength/direction of an effect in reconsolidation studies.

Factor	Findings (References)
Memory-related factors	<p>Memory type and strength</p> <p>Reconsolidation effects were found for:</p> <ul style="list-style-type: none"> • Fear memories (Kindt et al., 2009; Nader et al., 2000) • Declarative memories (Schwabe et al., 2012) • Appetitive memories (Achterberg et al., 2014; Corlett et al., 2013) • Procedural memories (Walker et al., 2003) • Phobia and drug-related memories (Soeter & Kindt, 2015; Zhao et al., 2009) <p>Mixed results:</p> <ul style="list-style-type: none"> • Well-learned instrumental memories (Exton-McGuinness, Patton, Sacco, & Lee, 2014; Hernandez & Kelley, 2004) • Posttraumatic memories (Brunet et al., 2008; Suris et al., 2010)
	<p>Memory age</p> <p>Mixed results:</p> <ul style="list-style-type: none"> • Recent memories might be more susceptible than older memories (Boccia, Blake, Acosta, & Baratti, 2006; Suzuki et al., 2004) • Yet even older memories can be affected (Debiec & LeDoux, 2004; Wichert, Wolf, & Schwabe, 2011)
Manipulation-related factors	<p>Reactivation</p> <ul style="list-style-type: none"> • Availability of new information (Rodriguez-Ortiz et al., 2005, 2008), e.g. a prediction error (Almeida-Correa & Amaral, 2014; Sevenster et al., 2013) is required to destabilize the memory. Contextual settings (Chan, Leung, Westbrook, & McNally, 2010; Meir Drexler et al., 2014; Monfils et al., 2009) and length of retrieval (Merlo et al., 2014) might play a role in creating the 'right' amount of novelty • Timing of retrieval: pre- or post-treatment (Achterberg et al., 2014; Kindt et al., 2009)
	<p>Treatment</p> <ul style="list-style-type: none"> • Pharmacological agents vs. behavioral interventions (Kindt & Soeter, 2013) • Dose-dependency of treatment (Jin et al., 2007; Tronel & Alberini, 2007)
Individual differences	<ul style="list-style-type: none"> • Trait anxiety (Soeter & Kindt, 2013) • Sex and sex hormones (Meir Drexler et al., 2015, 2016)

Conflicting findings are thus not paradoxical, they are only partially explained.

The general reconsolidation literature identifies multiple factors that determine the strength and direction of a reconsolidation effect. Among them are memory-related factors, manipulation-related factors, and individual differences (Akirav & Maroun, 2013; Sandi & Pinelo-Nava, 2007; Soeter & Kindt, 2013) (see Table 1). Their potential influence is discussed next with respect to the current literature on GCs modulation of emotional memory reconsolidation.

4.1. Memory-related factors

Memory-related factors include the type, age and strength of the memory trace. Not all memories are equally susceptible to post-retrieval manipulations. Therefore, a similar post-retrieval manipulation may lead to different results, based on the nature of the targeted memory (Akirav & Maroun, 2013). Fear memories were shown to be susceptible to post-retrieval behavioral (Monfils, Cowansage, Klann, & LeDoux, 2009; Schiller et al., 2010) and pharmacological (Kindt et al., 2009; Nader et al., 2000) manip-

ulations. Significant effects were also seen in declarative memories (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2012), appetitive memories (Corlett et al., 2013) and procedural (Walker, Brakefield, Hobson, & Stickgold, 2003) memories. In contrast, some suggest that well-learned instrumental memories do not undergo reconsolidation when retrieved (Hernandez & Kelley, 2004). Indeed, the age and strength of memories may play an important role, as some studies suggest that older and stronger memories are less susceptible to interruption (Schwabe & Wolf, 2009; Suzuki et al., 2004; Wichert, Wolf, & Schwabe, 2013). However, others have found that even old and strong memories may become susceptible post-retrieval (Debiec, LeDoux, & Nader, 2002; Soeter & Kindt, 2015).

The GCs reconsolidation literature focuses on emotional memories only, almost exclusively aversive ones. All studies but one employed the fear conditioning paradigm (either classical or instrumental), as only Achterberg et al. (2014) examined appetitive memories. The studies suggest that GCs are potent modulators of the reconsolidation of emotional memories, even when the memories are relatively old and strong (Jin et al., 2007; Taubenfeld et al., 2009). Therefore, memory-related factors, albeit critical in other reconsolidation studies, do not seem to provide an explanation to the conflicting results in the GCs reconsolidation literature.

4.2. Manipulation-related factors

4.2.1. Reactivation

The term 'reconsolidation' might wrongly suggest that this post-retrieval process involves the exact re-occurring of the initial consolidation process. This is inaccurate, as reconsolidation is an update mechanism (Rodriguez-Ortiz, Garcia-DeLaTorre, Benavidez, Ballesteros, & Bermudez-Rattoni, 2008; Rodriguez-Ortiz et al., 2005) occurring following the destabilization of the memory trace. As such, it is triggered by the availability of new information that was not present during initial consolidation.

Detecting prediction errors (i.e. a mismatch between expected and current events) is a general coding strategy by which memories are acquired and updated. A prediction error can be negative (a non-reinforced trial) or positive (a learning trial) (Fernandez, Boccia, & Pedreira, 2016). A reminder cue (e.g. a light associated with a shock), which had led to a prediction error (e.g. no shock was actually given), can trigger two different processes: reactivation (followed by reconsolidation and update of the original memory), or creation of a new memory (e.g. extinction memory) (Merlo, Milton, & Everitt, 2015; Merlo, Milton, Goozee, Theobald, & Everitt, 2014). Not all reminder cues or retrieval protocols are equally effective in destabilizing the memory and initiating the reconsolidation process. To successfully trigger the reconsolidation process, the reactivation (retrieval) experience has to be similar, but not identical, to the original learning experience (Sevenster, Beckers, & Kindt, 2013). The right degree of novelty can be manipulated, for instance, by changing the length of the retrieval session. Merlo et al. (2014) demonstrated that repeated unreinforced presentations of the conditioned stimulus create a new extinction memory, while a short unreinforced exposure triggers memory destabilization and the subsequent reconsolidation process. Yet the definitions of a 'brief' exposure may vary between studies. Successful reconsolidation effects were seen following stimulus presentations that lasted 4 s, same as acquisition (Schiller et al., 2010) or 2 min, significantly longer than the original acquisition presentation (Agren et al., 2012).

Even though brain activation patterns (e.g. in the hippocampus) may differ in response to unpredictable vs. predictable cues (the former more related to memory reactivation than the latter) (Forcato et al., 2016), there is currently no objective measure of a successful reactivation. Thus, interrupting the effects of a post-

retrieval behavioral or pharmacological manipulation might be difficult, as it may not be clear which of the processes was triggered by the retrieval protocol: memory reconsolidation, or creation of a new memory.

The same pharmacological treatment can lead to opposite effects, depending on whether reconsolidation or extinction were triggered (Merlo et al., 2015). Abrari et al. (2008) showed that corticosterone administration after memory retrieval produced a deficit in memory, suggesting a GCs-dependent disruption in memory reconsolidation. Yet this deficit was transient, and a reminder shock led to the return of fear. Transient effects were also seen in the rodent study of Cai et al. (2006). As a reconsolidation effect is thought to influence the original memory, it should resist relapse paradigms such as reinstatement (Debiec et al., 2002). This led Cai et al. (2006) to favor extinction over reconsolidation as an explanation to the observed results, stating that GCs promoted a very strong extinction memory, even after a single trial. The systemic corticosterone studies, discussed in Section 3, shared a very similar method to that of Cai et al. (2006). If extinction, as opposed to reconsolidation, was triggered using this method in those studies, it could explain how GCs led to a lower fear response: not by impairing reconsolidation, but by enhancing extinction. Due to their role as consolidation enhancers, GCs are indeed efficient in enhancing the consolidation of newly acquired extinction memories, leading to a reduced fear response (de Quervain & Margraf, 2008). However, if that is the case, it remains unclear why extinction learning, and not reconsolidation, was triggered by this paradigm. A similar (brief and unreinforced) presentation of the conditioned stimulus was found to be sufficient to trigger (and disrupt) reconsolidation processes using other post-retrieval treatments, such as protein-synthesis inhibitors and noradrenergic β -blockers (Kindt et al., 2009; Nader et al., 2000).

4.2.2. Treatment

Even if reconsolidation was successfully triggered in all of the above studies, the difference in the post- (or less commonly, pre-) retrieval treatment may explain some of the conflicting results. All animal studies presented here used a corticosterone injection as a mean of systemic administration. A systemic injection procedure is a stressor by itself, as even a vehicle injection can lead to corticosterone response (Atsak et al., 2016). This adds to the possible adversity of the reactivation session (Yu et al., 2015), creating an aversive experience in the animals studies. The intensity, source and duration of stress can affect its modulation of memory processes (Sandi & Pinelo-Nava, 2007). Stress can impair the initial consolidation of memories when it is too intense (or too weak, functioning in an inverted U-shaped curve) (Joels, 2006) or out of the learning context (Joels, 2006; Sandi & Pinelo-Nava, 2007), and was also suggested to impair the reconsolidation of emotional memories (Zhao et al., 2009). In contrast, the usual practice in humans is oral administration of a hydrocortisone pill, a less stressful experience (Meir Drexler et al., 2015, 2016). Thus, the intense stress, which impaired memory reconsolidation in the animal studies, was presumably not part of the manipulation in the human studies, thus allowing GCs to exert their memory enhancing properties. Future investigations into the noradrenergic and GCs activity around the time of reactivation in different human and animal paradigms might help support this explanation.

4.2.3. Individual differences

Certain traits may render the individual's sensitivity to the behavioral and neurobiological effects of stress and influence learning and memory abilities (Salehi, Cordero, & Sandi, 2010). For instance, trait anxiety was demonstrated to have a modulating role on memory in both rodents (Herrero, Sandi, & Venero, 2006; Sandi et al., 2008) and humans (Soeter & Kindt, 2013). Individual

differences can also explain inconsistencies (e.g. lack of effects) often seen in reconsolidation studies. Soeter and Kindt (2013) demonstrated that the successful reduction of fear using a post-retrieval propranolol (a noradrenergic β -blocker) depends on anxiety traits. The higher the anxiety, the lower the fear reduction. High trait anxiety individuals often utilize a better safe-than-sorry strategy when facing ambiguous situations. In that case, a single unreinforced reactivation trial may be insufficient to create a prediction error that destabilizes the fear memory trace (Soeter & Kindt, 2013). Thus, high trait anxiety individuals may need higher dosage of propranolol or a different reactivation protocol to successfully target and change fear memories.

Sex might be an additional factor (Merz & Wolf, 2015). While cortisol was found to enhance fear memory reconsolidation in healthy men (Meir Drexler et al., 2015), it had no effect on women (Meir Drexler et al., 2016). This could be a result of alternating concentrations of sex hormones during the different phases of the female menstrual cycle or following oral contraceptive use. These factors were found to affect emotional learning and memory processes in humans and other animals (Ferree, Kamat, & Cahill, 2011; Milad, Igoe, Lebron-Milad, & Novales, 2009; Milad et al., 2006) as well as the severity of symptoms in clinical populations after trauma exposure (Ferree, Wheeler, & Cahill, 2012). Yet even though males and females may respond differently to emotional tasks (Milad et al., 2010) or GCs treatment (Merz et al., 2012), the majority of studies are still conducted on male animals and human males (Beery & Zucker, 2011; Saldin & Mattison, 2009). This is true for the majority of studies that investigated GCs modulation of reconsolidation as well. As sex and sex hormones might interact with GCs modulation of memory reconsolidation, further investigations in females are of great theoretical and clinical importance.

5. Implications and limitations

5.1. Theoretical implications and limitations

The main brain areas that underlie the effects of stress and GCs on initial memory consolidation are the BLA, hippocampus and prefrontal cortex (Rooszendaal, McEwen, & Chattarji, 2009). The role of GR in that process is well documented (Rooszendaal, 2000). GR antagonism (e.g. by mifepristone) (Yang, Chao, & Lu, 2006) or inhibition of corticosterone synthesis (e.g. by metyrapone) (Blundell, Blaiss, Lagace, Eisch, & Powell, 2011) were found to disrupt memory consolidation. In contrast, systemic corticosterone (Blundell et al., 2011) or GR agonists (e.g. dexamethasone) administration (Ninomiya et al., 2010; Yang et al., 2006) facilitate memory consolidation (for a review of consolidation enhancers, also used as extinction-learning facilitators, see: Singewald, Schmuckermair, Whittle, Holmes, & Ressler, 2015). GR can induce genomic responses by binding to GCs responsive elements within promoter regions of responsive genes, and act as transcription factors that induce gene expression (Singewald et al., 2015). They can induce additional genomic changes via activation of signaling cascades such as the ERK/MAPK pathway (Reul, 2014) and affect other neurotransmitter systems, such as the noradrenergic (Rooszendaal, 2000) and glutamatergic (Reul, 2014) systems. In addition, membrane-bound GR can induce non-genomic actions, such as the synthesis of endocannabinoids (Di, Malcher-Lopes, Halmos, & Tasker, 2003) relevant for learning and memory. The reconsolidation of memory after retrieval is not identical to initial consolidation, yet both processes share similar mechanisms. Both depend on protein synthesis and cell firing in specific brain areas such as the amygdala (Nader et al., 2000) and the hippocampus (Lux, Masseck, Herlitze, & Sauvage, 2015), and are facilitated by noradrenergic activity (Kindt et al., 2009; Mahabir, Tucholka, Shin,

Etienne, & Brunet, 2015) during a limited time-window (Kindt et al., 2009). In a similar manner, the studies reviewed here demonstrate that GR activation, in the BLA and hippocampus in particular, is also critical for the reconsolidation of emotional memories, both appetitive and aversive, after retrieval. The mechanism of this post-retrieval process, and its similarity to initial GCs-dependent facilitation of memory consolidation, is yet to be determined.

GCs modulation of memory reconsolidation cannot be simply classified as impairing or enhancing, as it is mediated by additional factors (Akirav & Maroun, 2013). The general reconsolidation literature identifies various factors that determine the strength and direction of a reconsolidation effect. Among them are memory-related factors, manipulation-related factors, and individual differences (Akirav & Maroun, 2013; Sandi & Pinelo-Nava, 2007; Soeter & Kindt, 2013). This review, aiming to settle some of the conflicting findings in the field, is a view on the ways these factors might influence GCs modulation of memory reconsolidation. Future studies are needed to further support and elaborate these conclusions. Many open questions remain. Some are more specific, for instance, the question of GCs involvement in the reconsolidation of neutral memories. Others are shared with the general reconsolidation literature, such as the possible adversity of a retrieval session in a fear conditioning paradigm, and the role of individual and sex differences in achieving reconsolidation effects.

5.2. Clinical implications and limitations

Pathologic fear and anxiety characterize a range of psychiatric conditions, including phobias, panic disorder, obsessive-compulsive disorder (OCD), generalized anxiety (GAD) and post-traumatic stress disorder (PTSD) (Singewald et al., 2015). Fear memory formed by the fear conditioning paradigm might be similar to these memories (Cordero, Kruyt, Merino, & Sandi, 2002; Yehuda & Antelman, 1993). Reward memories, on the other hand, can serve as a model for drug-seeking behavior and other addictions (Achterberg et al., 2014; Wang et al., 2008). Disruption of maladaptive emotional memories by blocking reconsolidation can thus be a possible therapeutic tool (Merlo et al., 2015). Relapse is not uncommon in patients, even after successful extinction-based ('exposure') treatments (Bouton, 2014; Craske, 1999; Singewald et al., 2015). Yet due to the impact of reconsolidation-based manipulations on the original memory trace itself, the effect is suggested to be resistant to relapse (but see: Gisquet-Verrier et al., 2015; Ryan & Tonegawa, 2016 for alternative explanations). The reconsolidation literature points to the noradrenergic β -blocker propranolol as a potent pharmacological agent, capable of disrupting strong emotional memories (Kindt et al., 2009; Sevenster et al., 2013), even in sub-clinical populations (Soeter & Kindt, 2015). Noradrenergic activity in the amygdala is necessary for emotional memories to reconsolidate after retrieval (Debiec & LeDoux, 2004; Schwabe et al., 2012), and so disturbance to this process can disrupt the memory trace from reconsolidating. The role of GCs in memory consolidation is well documented (Rooszendaal, 2000; Wolf, 2009) and due to their facilitative effect on extinction memory consolidation they can be used in treatment (de Quervain & Margraf, 2008). Recent evidence, reviewed here, reveal that GCs may serve as an additional target for future reconsolidation-based therapies.

Mifepristone has been widely used as GR antagonist for the study of the role of GR in memory consolidation in the hippocampus and amygdala (Oitzl, Flutterm, & de Kloet, 1998; Rooszendaal & Mcgaugh, 1997). This is currently the only suitable GR antagonist approved for human use. It is safe and effective to use in patients with psychotic depression and bipolar disorder (DeBattista & Belanoff, 2006; Flores, Kenna, Keller, Solvason, & Schatzberg,

2006). Here, we reviewed the consequences of systemic mifepristone administration (Nikzad et al., 2011; Pitman et al., 2011; Taubenfeld et al., 2009), revealing its disrupting effects on the strength of reactivated conditioned fears. Until recently, it remained unclear whether acute dose of this antagonist can indeed affect traumatic memories in clinical populations. Wood et al. (2015) investigated the effects of mifepristone, given in proximity to reactivation of traumatic memories, on PTSD symptoms and physiological response in patients (both men and women). Yet even though the treatment dose given to patients corresponded to a successful treatment dose in rodents (30 mg/kg), no significant reduction in either symptoms or physiological response was found. This demonstrates the difficulty in translating successful results from animal model to patients. However, as even propranolol could not lead to a reconsolidation disruption in the study of Wood et al. (2015) (but see: Mahabir et al., 2015), the lack of the effect might be attributed to memory-related factors, as opposed to the post-reactivation treatment itself. Maladaptive memories in sub-clinical phobic populations (Soeter & Kindt, 2015) and even in abstained drug-addicts (Zhao et al., 2009) might be easier to successfully target in a reconsolidation-based treatment, compared with the more complex multiple memory traces in PTSD patients (Suris, North, Adinoff, Powell, & Greene, 2010).

6. Conclusions

GCs modulation of emotional memory reconsolidation has been investigated only recently, often with conflicting, 'paradoxical' results. In this review we presented animal and human studies that suggest a critical role for GCs in this post-retrieval process. We pointed to mediating factors that affect the strength and direction of GCs effects on memory reconsolidation, demonstrating that the so-called 'paradox' can be solved once additional factors are taken into account. We conclude that GR activation in the amygdala and hippocampus is involved in emotional memory reconsolidation. This demonstrates a similarity between post-retrieval reconsolidation and initial memory consolidation. In addition, it suggests the use of GR antagonists (e.g. mifepristone) as possible adjuvants in future reconsolidation-based therapies.

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