How stress and glucocorticoids timing-dependently affect extinction and relapse

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ABSTRACT

In recent years, various research groups aimed to augment extinction learning (the most important underlying mechanism of exposure therapy) using glucocorticoids (GCs), in particular the stress hormone cortisol. In this review, we introduce the STaR (Stress Timing affects Relapse) model, a theoretical model of the timing-dependent effects of stress/GCs treatment on extinction and relapse. In particular, we show that (1) pre-extinction stress/GCs promote memory consolidation in a context-independent manner, making extinction memory more resistant to relapse following context change. (2) Post-extinction stress also enhances extinction consolidation, but in a context-bound manner. These differences may result from the timing-dependent effects of cortisol on emotional memory contextualization. At the neural level, extinction facilitation is reflected in alterations in the amygdala-hippocampal-prefrontal cortex network. (3) Stress/GCs before a retrieval test impair extinction retrieval and promote relapse. This may result from strengthening amygdala signaling or disruption of the inhibitory functioning of the prefrontal cortex. The STaR model can contribute to the understanding and prevention of relapse processes.

1. Introduction

Extinction learning can occur when a previously learned association is no longer valid. For instance, if a dog attack led a child to associate dogs with danger, leading to a fear response, repeated neutral encounters with dogs in the future might promote the extinction association that dogs are not necessarily dangerous and should not be feared. Extinction is nowadays most commonly viewed as new learning, forming an inhibitory memory trace that does not directly affect the older, original memory trace but competes with it (Bouton et al., 2006). Following extinction, the relative strength and retrieval availability of both memories determine the response in a given situation (Bouton, 2004; Vervliet et al., 2013b). However, these two memories are usually not of equal strength. The original memory, in particular when it is fear-related, is often robust and context-independent, and may thus easily generalize (Bouton, 2002; Onat and Büchel, 2015). Extinction, as the second association that is learned about a conditioned stimulus, is presumably encoded as a conditional exception to the rule (Bouton, 2002), and is thus more context-specific (Vervliet et al., 2013a).

The differences in strength and context-dependency of the original memory and the extinction memory give rise to various relapse phenomena after extinction. A 'renewal' of the original memory can occur following a change in context after extinction (Bouton, 2004, 2014). Relapse might also occur by the passage of time ('spontaneous recovery') or after exposure to an aversive stimulus ('reinstatement') (Brooks and Bouton, 1993; Rescorla and Heth, 1975). These additional relapse phenomena are context-dependent as well, at least to some extent (e.g., relapse is stronger when reinstatement and test occur in the same context: Haaker et al., 2014; Vervliet et al., 2013a), and might themselves represent a form of relapse caused by variations in context (e.g., contextual changes across time promote spontaneous recovery, Bouton, 2004).

Extinction learning is one of the most important underlying mechanisms of exposure therapy, a technique in cognitive-behavioral psychotherapy commonly used for the treatment of posttraumatic stress disorder (PTSD) and anxiety disorders (Craske et al., 2018; Marks, 1979). Relapse poses a significant challenge for the long-term success of these interventions (Craske, 1999). For example, even if the fear of dogs (i.e., fear previously acquired in context A) subsided following exposure therapy (i.e., extinguished in context B), the context-dependency of the extinction memory might lead to a recovery of fear outside this context, e.g., when the patient faces a dog in the original learning context (A) or a novel context (C) (Bouton, 2014).

1.1. Optimizing exposure therapy

In recent years, several research groups have investigated the augmentation of extinction learning or exposure therapy by the use of cognitive/behavioral modifications (e.g., expectancy violation, multiple contexts exposure, or reconsolidation manipulation: Craske et al., 2014; Schiller et al., 2010; Shiban et al., 2013), brain stimulation techniques (e.g., by transcranial direct current stimulation, or tDCS: Dittert et al., 2018), and pharmacological adjuvants (de Bitencourt et al., 2013; Fitzgerald et al., 2014; Hofmann et al., 2015). For instance, the partial N-methyl-D-aspartate (NMDA) receptor agonist D-cycloserine (DCS) was shown to enhance exposure therapy in patients with anxiety disorders (Hofmann et al., 2013; Ressler et al., 2004). Similar beneficial effects were found using endocannabinoid agonists (de Bitencourt et al., 2013).

Glucocorticoids (GCs: mainly cortisol in humans, corticosterone in rodents) have also been a major target in the extinction augmentation research (Bentz et al., 2010; de Quervain and Margraf, 2008; de Quervain et al., 2017). Promising findings demonstrate the beneficial use of GCs in the treatment of PTSD (Aerni et al., 2004; Yehuda et al., 2015), social phobia, phobia of spiders (Soravia et al., 2006, 2014), and of heights (de Quervain et al., 2011). The results of these studies show improved treatment retention as well as a reduction in symptoms.

1.2. How do glucocorticoids augment exposure therapy?

GCs are the end products of the hypothalamus-pituitary-adrenocortical (HPA) axis. They are secreted in a circadian rhythm (Pruessner et al., 1997; Sherman et al., 1985) and following exposure to stressful events (Joëls and Baram, 2009). GCs promote the adaptive physiological and behavioral response to the stressor as well as the return to homeostasis (McEwen, 2004). Importantly, GCs are potent modulators of learning and memory processes, thereby affecting the adaptive response to future events (de Kloet et al., 1999; Sandi and Pinelo-Nava, 2007). Following exposure to stress, GCs promote a 'memory consolidation mode', during which the consolidation of (mainly emotional) memories is enhanced while the retrieval of previously consolidated memories is impaired (Buchanan et al., 2006; de Quervain et al., 1998; Roozendaal, 2002; Smeets, 2011). This effect is modulated by the interaction of noradrenaline (one of the end products of the sympathetic nervous system, or SNS) and GCs in the amygdala, hippocampus and prefrontal cortex (Diamond and Zoladz, 2016; Roozendaal, 2000; Roozendaal et al., 2006). The same properties, which in extreme cases may lead to the fear- and trauma-related memories seen in phobias and PTSD (Maren and Holmes, 2016; Merz et al., 2016), can also account for the improved treatment retention in GCs-augmented exposure therapy.

Like other types of learning and memory processes, both fear and extinction memories can be subdivided into encoding, consolidation, and retrieval (Quirk and Mueller, 2008). According to de Quervain and Margraf (2008), the beneficial effects of GCs on exposure therapy stem from both the prevention of fear memory retrieval during exposure and the enhancement of extinction memory consolidation after exposure (de Quervain et al., 2011, 2017). Indeed, stress induction enhances memory consolidation (Roozendaal, 2000; Sandi and Rose, 1994) and impairs retrieval (Buchanan et al., 2006; Smeets, 2011) in various other tasks. Pharmacological administration of cortisol often mimics these effects (consolidation: Buchanan and Lovallo, 2001; retrieval: de Quervain et al., 2000). However, previous studies on GCs augmentation of extinction or exposure could not clearly separate the discrete effects of GCs on these processes. This was due to chronic cortisol treatment (e.g., daily dose, regardless of exposure sessions or lack thereof; Aerni et al., 2004; de Quervain and Margraf, 2008), or, more commonly, the lack of variation in the timing of cortisol treatment, with the majority of studies including pre-extinction/pre-exposure cortisol, thus theoretically affecting both the encoding and consolidation of the extinction

memory (de Quervain et al., 2011, 2017; de Quervain and Margraf, 2008; Soravia et al., 2006, 2014; Yehuda et al., 2015). Data on how post-extinction cortisol affects extinction memory consolidation in humans was not available at the time our review was prepared. Moreover, since these studies did not include contextual manipulations, the potential use of GCs for preventing context-dependent relapse has remained largely unclear.

2. The effects of GCs and stress on extinction and relapse are timing-dependent

In the last several years, our group has been investigating the timing-dependent effects of stress and GCs on extinction memory and extinction retrieval (for a summary of these studies and a comparison to findings from other groups, see Table 1). We have been using two paradigms: the (contextual) fear conditioning paradigm (a model of fear- and anxiety-related disorders; see Milad et al., 2007, 2009), and the predictive learning task (a declarative task of contingency learning that shares similarities with classical conditioning; see Hamacher-Dang et al., 2013a; Üngör and Lachnit, 2006). Stress or cortisol administration were applied either before extinction training (i.e., to affect extinction encoding/consolidation), after extinction training (i.e., to affect extinction consolidation) or before a retrieval test. Since context change after extinction can lead to a renewal of extinguished associations in the fear conditioning paradigm (Bouton and Bolles, 1979; Milad et al., 2005) and the predictive learning task (Rosas et al., 2001; Üngör and Lachnit, 2006), we focused in particular on the effects of the manipulation on the context-dependency of extinction and its retrieval. Our results reveal a critical role of timing on the effects of stress/GCs on extinction memory and relapse. The STaR (Stress Timing affects Relapse) model, presented in Fig. 1, summarizes these findings.

In the following sections, we will discuss the consequences of stress/GCs exposure at each of the time points on extinction and extinction retrieval.

2.1. Before extinction: Effects on extinction learning and consolidation

We have recently tested the effects of exposure to stress before extinction training on the strength and context-dependency of extinction memory (Meir Drexler et al., 2018) using the contextual fear conditioning paradigm, adapted from Milad et al. (2007, 2009) for a three-day design. On the first day, the participants learned to associate certain stimuli (i.e., pictures of a lamp in a specific color, here the conditioned stimuli, or CS) within a context (i.e., a picture of a room) with the occurrence of an unpleasant electrical stimulation (the unconditioned stimulus, or UCS). On the second day, the participants were either exposed to stress (the SECPT, socially evaluated cold-pressor test; see: Schwabe et al., 2008) or a control condition. Twenty-five minutes later, at peak cortisol levels (Dickerson and Kemeny, 2004), extinction training took place. Critically, extinction training was performed in a different context (i.e., a picture of a different room) to simulate the context change under real-life treatment conditions (Craske et al., 2018). On the third day, participants were presented with the CS in both contexts to test for renewal. Our findings revealed no group differences in fear response (measured by skin conductance response, or SCR) over the course of extinction itself (day 2). Nonetheless, a significant group difference emerged in the renewal test (day 3). While a renewal effect was seen in the control group as the CS was presented again in the acquisition context compared to the extinction context, no renewal was seen in the stress group. These findings suggest that exposure to stress before extinction training leads to a stronger, less context-bound extinction memory, which can be generalized to the acquisition context.

Indeed, in a previous study (Meir Drexler et al., 2017) we found similar effects of pre-extinction stress using the neutral predictive learning task. In this paradigm, participants learn (and then extinguish)

Table 1

A summary of our studies, which demonstrate a timing-dependent effect of stress/glucocorticoids (GCs) on extinction and extinction retrieval, and a comparison to selected findings from other studies in humans. Only studies that targeted a specific memory phase were included. CPT, Cold pressor test; SECPT, Socially-evaluated cold pressor test; vmPFC, ventromedial prefrontal cortex.

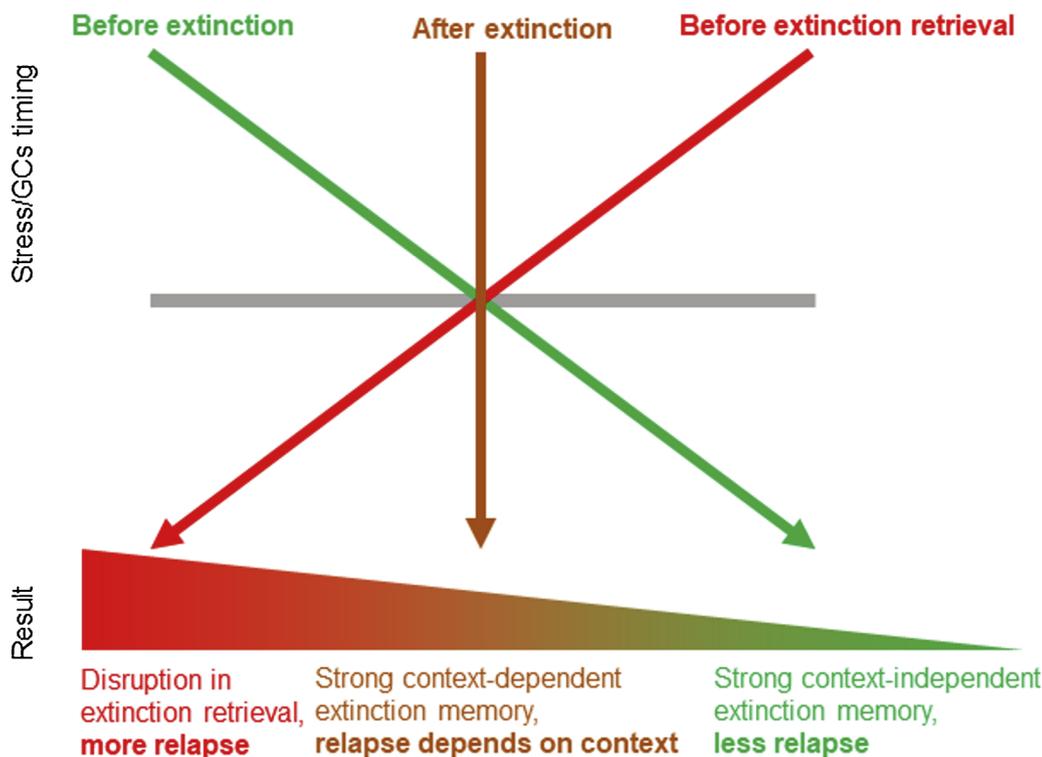| Timing of GC/stress	Findings from extinction/exposure studies	Selective findings from other studies
Before learning	• SECPT (20–25 min before learning) leads to **stronger, context-independent extinction** in the predictive learning task (Meir Drexler et al., 2017) and the contextual fear conditioning paradigm (Meir Drexler et al., 2018). CPT (20 min before extinction) leads to **reduction in expectancy ratings**; possible sex differences (e.g., Bentz et al., 2013). • 30 mg hydrocortisone (50 min before learning) leads to **stronger, context-dependent extinction** in a contextual fear conditioning paradigm. The treatment led to alterations in the network amygdala-hippocampus-vmPFC (Merz et al., 2018a). Discrepancy may be related to the prolonged cortisol response in this pharmacological treatment. • 10–30 mg hydrocortisone (20–60 min before exposure) **improves extinction learning or leads to greater reduction in symptoms**: PTSD (Yehuda et al., 2015); spider phobia (Soravia et al., 2006, 2014); phobia of heights (de Quervain et al., 2011). Contextual factors were not examined. • SECPT (immediately after extinction) leads to **context-dependent extinction:** predictive learning task (Hamacher-Dang et al., 2013a); contextual fear conditioning (Hamacher-Dang et al., 2015). • Post-extinction hydrocortisone (20 mg) **has no augmenting effect** on exposure in spider phobia (Raeder et al., 2019).	• Stress/GCs in proximity (before/after) a learning task **strengthens emotional memory consolidation** (Buchanan and Lovallo, 2001); there are possible sex differences, e.g. in fear conditioning (Stark et al., 2006; Zorawski et al., 2006). • GC/stress before a learning task **disrupts contextualization** during fear acquisition (McGlade et al., 2019), object location (Schwabe et al., 2009), and verbal memory tasks (van Ast et al., 2013). • GCs/stress after learning **improves contextualization** of verbal memory (van Ast et al., 2013).
After learning	(see above, bulleted items continue)	
Before retrieval test	• 30 mg hydrocortisone (40 min before test) **disrupts extinction retrieval** (i.e., more relapse) in the predictive learning task (Kinner et al., 2016) and the contextual fear conditioning paradigm (Kinner et al., 2018). At the neural level, this treatment led to disruption in vmPFC functioning and connectivity (predictive learning task) and enhanced amygdala activation (fear conditioning). • SECPT/CPT (15–20 min before test) leads to more relapse in the predictive learning task (Hamacher-Dang et al., 2013b) and in the fear conditioning paradigm (Raio et al., 2014) but to **disruption in fear memory retrieval** (i.e., less relapse) in the contextual fear conditioning paradigm (Merz, Hamacher-Dang, et al., 2014). Discrepancy may be related to the type of relapse test.	• Stress/GCs **impair retrieval** of declarative memories (Buchanan et al., 2006; de Quervain et al., 2000; Smeets, 2011).

Fig. 1. The STaR (Stress Timing affects Relapse) model represents the timing-dependent modulation of extinction and relapse by stress/glucocorticoids (GCs). Stress/GCs before extinction promote memory consolidation in a context-independent manner, making extinction memory more generalized and thus resistant to relapse following context change. Stress/GCs after extinction also enhance extinction consolidation, but in a context-bound manner, not generalizing to other contexts. Stress/GCs before extinction retrieval test impair extinction retrieval and promote relapse.

associations between stimuli (i.e., a picture of a type of food) within a context (i.e., a picture of a specific restaurant) with a specific outcome (i.e., stomach trouble). Pre-extinction stress in this task, like in the fear conditioning paradigm, led to a stronger, more generalized extinction memory that extended from the extinction context to the acquisition context.

In an imaging study (Merz et al., 2018a), using pre-extinction cortisol administration instead of stress, the cortisol treatment reduced conditioned SCRs, attenuated the activation of the amygdala-hippocampal complex, and enhanced the connectivity of the para-hippocampal gyrus (PHG) with the ventromedial prefrontal cortex (vmPFC) during early extinction learning. The interactions between these areas reflect the balance between processes underlying fear and extinction memories (Joëls and Baram, 2009), and their modulation using cortisol presumably led to less fear retrieval and enhanced inhibitory control. After one week, the cortisol group responded to the extinguished stimuli with increased hippocampal activation and hippocampal-vmPFC connectivity, indicating retrieval of the extinction memory trace and suppression of the fear memory trace (see Fig. 2 for illustration). However, in contrast to our previous findings using pre-extinction stress induction (Meir Drexler et al., 2017, 2018), in this study, extinction was indeed enhanced yet it remained context-bound. This finding might be a result of the pharmacological intervention, which led to higher and more prolonged elevation in cortisol, which was not limited to the pre-extinction phase but extended post-extinction. As we will discuss in the next section, post-extinction cortisol might enhance the context-dependency of the extinction memory, thus leading to these conflicting results.

These findings are largely in agreement with the model suggested by de Quervain and Margraf (2008), which emphasized the role of GCs in enhancing extinction memory consolidation. In addition, our results reveal the critical role of GCs timing in promoting the generalization of extinction memory to additional contexts. They are in line with findings from other labs, which showed that exposure to stress or GCs before a learning task could disrupt contextualization and promote generalization in various tasks, e.g., in the acquisition of fear (McGlade et al., 2019) as well as in an object location (Schwabe et al., 2009) or verbal

memory tasks (van Ast et al., 2013). Our model, however, is at odds with de Quervain and Margraf's predictions (2008) and with some additional findings that suggest that GCs augment extinction learning itself, e.g., leads to accelerated extinction (Bentz et al., 2013, 2010; de Bitencourt et al., 2013; de Quervain et al., 2011, 2017). In contrast, in a study by Soravia et al. (2014), the administration of cortisol before exposure therapy resulted in a reduction in fear of spiders only at follow-up, but not immediately post-treatment. The findings from our lab mostly support a long-term (i.e., on memory consolidation), but not immediate effect (Meir Drexler et al., 2017, 2018). The different findings on immediate GCs effects might be accounted by variations in manipulations (endogenous alterations in cortisol concentrations, e.g., Lass-Hennemann and Michael, 2014; cortisol administration vs. stress manipulation, cf. Schmidt et al., 2010), sample population (patients or healthy participants), and paradigms (Merz et al., 2018a) between the studies.

2.2. After extinction: Effects on extinction consolidation

Post-extinction stress was found to be critical for the consolidation of contextual information (Hamacher-Dang et al., 2013a, 2015), albeit in the opposite direction to that of pre-extinction stress. In the predictive learning task (Hamacher-Dang et al., 2013a), we exposed participants to stress after extinction and tested them 24 h later for retrieval in both the acquisition and extinction contexts. The stress group exhibited a reduced recovery of conditioned responding (i.e., demonstrating a strong extinction memory), but only in the extinction context, suggesting that the extinction memory was not generalized. We found similar results using the fear conditioning paradigm (Hamacher-Dang et al., 2015). Thus, while pre-extinction stress disrupted the contextualization of extinction, creating an enhanced context-independent extinction memory (Meir Drexler et al., 2017, 2018), post-extinction stress enhanced extinction memory in a context-dependent way, which did not lead the extinction memory to generalize to other contexts.

Our post-extinction studies used a behavioral intervention (SECPT as a stressor), yet they are in line with some pharmacological studies that showed that post-learning GCs contribute to the consolidation of
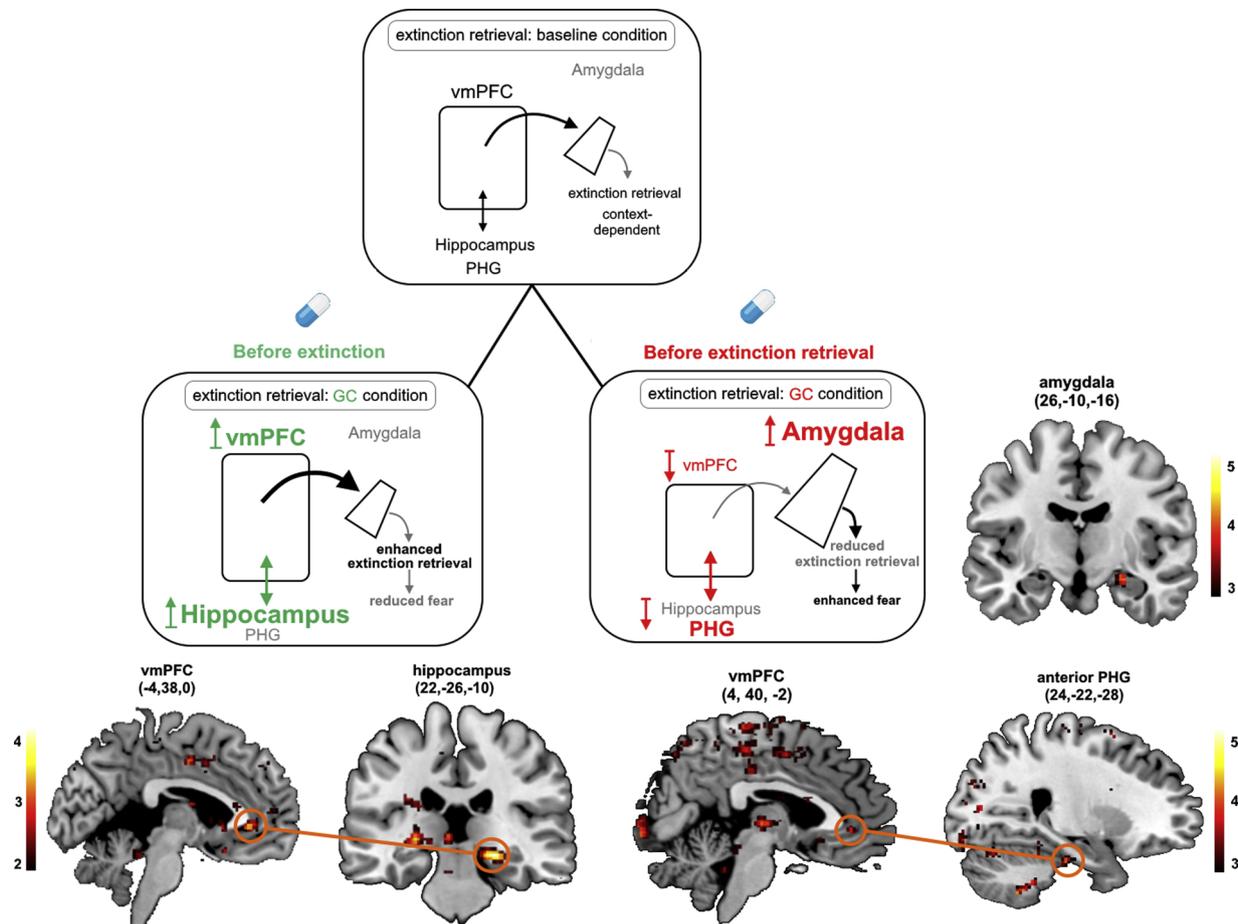
Fig. 2. Simplified scheme of the neural network mediating extinction retrieval under baseline conditions (upper panel) and the proposed neural mechanisms underlying the effects of glucocorticoids (GC) on this network, when administered before extinction learning (lower left panel, Merz et al., 2018a) or before extinction retrieval (lower right panel, Kinner et al., 2016, 2018). Neural activation and functional connectivity are additionally shown for the comparison between conditioned stimuli in the respective brain regions.
Under baseline conditions, the ventromedial prefrontal cortex (vmPFC) is activated together with hippocampal regions to context-dependently express extinction memory. When cortisol was administered before extinction, activity in the hippocampus and its functional connectivity to the vmPFC were enhanced during extinction retrieval, resulting in less fear. In contrast, cortisol administration before extinction retrieval suppresses vmPFC activation and its functional connectivity with the parahippocampal gyrus (PHG) and boosts activation in the amygdala, leading to an impairment of extinction retrieval and enhanced fear. The size of the structures indicate activation dominance. The colors of the arrows depict the proposed modulating influence (black = modulation; grey = reduced modulation by GCs; green = enhancing GC effects; red = impairing GC effects).

contextual representations in other tasks, such as in the acquisition of fear. Pugh et al. (1997) tested the role of corticosterone on contextual fear acquisition and found impaired contextual fear responses at a later retrieval test in adrenalectomized rats compared to controls. Importantly, these effects were selectively long-term – the rats showed no contextual conditioning impairment immediately, but only 24 h later – and were reversed when corticosterone replacement was given after fear acquisition. In agreement with these findings, van Ast et al. (2013) reported enhanced memory contextualization (i.e., less generalization) when cortisol was administered after an emotional memory task, and impaired contextualization (i.e., more generalization) when the treatment was given pre-encoding. Interestingly, neutral memory contextualization remained unaffected by the timing of treatment, suggesting that this effect depends on arousal and is probably mediated by noradrenaline. Indeed, post-learning noradrenaline in the amygdala has a significant role in promoting the accuracy of remote contextual memories, as recently described by Atucha et al. (2017).

2.3. Before extinction retrieval: Effects on extinction retrieval

According to de Quervain's model (de Quervain et al., 2017), some of the beneficial effects of GCs on exposure therapy result from

disrupting the retrieval of the original emotional (e.g., fear or trauma) memories. In contrast, other studies show a positive relationship between stress and relapse in alcohol and drug dependency (Breese et al., 2005) and between stress and the return of fear in phobias (Jacobs and Nadel, 1985) and generalized anxiety disorder (Francis et al., 2012). These findings suggest that stress may result in a disruption of extinction memory retrieval (going hand in hand with an increased fear retrieval), which is also mostly supported by our findings.

In four studies, we examined the effects of stress or cortisol administration on the retrieval of extinction memory in the predictive learning task (Hamacher-Dang et al., 2013b; Kinner et al., 2016) or the fear conditioning paradigm (Kinner et al., 2018; Merz et al., 2014b). In these experiments, the participants were trained in both the learning task and the subsequent extinction without any treatment, and were then exposed to stress/cortisol shortly before (i.e., 20 min for SECPT, 30–40 min for pill intake) the retrieval test, which took place 24 h after extinction. When the retrieval of extinguished associations was tested in the predictive learning task in both the acquisition and extinction context (Hamacher-Dang et al., 2013b), all participants demonstrated the expected renewal effect (i.e., stronger recovery of conditioned responding in the acquisition compared to the extinction context). The stress group, however, showed an even stronger recovery of responding

in the acquisition context, indicating that the acute stress led to either an enhancement of original memory retrieval, deficit in extinction memory retrieval, or both. In an imaging study using the same paradigm (Kinner et al., 2016), we showed that cortisol substantially disrupts vmPFC functioning and its communication with PHG, anterior cingulate cortex (ACC) and cerebellum. This suggests a cortisol-induced impairment in the retrieval of the extinguished association even in the extinction context.

More recently, we investigated the neural correlates of cortisol effects on extinction retrieval in the fear conditioning paradigm as well (Kinner et al., 2018). Here, cortisol administration promoted the return of fear after reinstatement, as measured by enhanced SCR and amygdala signaling in response to the extinguished stimulus (see Fig. 2 for illustration). Indeed, it was previously found that acute stress impairs fear extinction retrieval and leads to re-emergence of conditioned fear responses (Deschaux et al., 2013; Raio et al., 2014). In rodents, elevated concentrations of corticosterone strengthen amygdala functioning and reduce activity in fear-inhibitory regions such as the PFC (Akirav and Maroun, 2007). In contrast, in another study using a similar paradigm, acute stress was shown to abolish fear renewal (Merz, Hamacher-Dang, et al., 2014). It is likely that the effects of stress on the retrieval of original vs. extinction memories are affected by the intensity of the procedure itself (e.g., reinstatement or renewal test) and the manipulation (stress vs. cortisol). Since both reinstatement and renewal are clinically relevant phenomena, more studies are needed to reveal these potential modulating factors.

3. Discussion

3.1. Timing is everything

The timing of exposure to stress/GCs in relation to the memory phase of encoding (Buchanan and Lovallo, 2001; Schwabe et al., 2009), consolidation (Cahill et al., 2003; Roozendaal, 2000), retrieval (Merz, Hamacher-Dang, et al., 2014; Smeets, 2011) or reconsolidation (Maroun and Akirav, 2008; Meir Drexler and Wolf, 2017, 2018) is a significant factor in determining its effects in various tasks (for a review on stress effects on episodic memory, see Shields et al., 2017). Our StaR model (Fig. 1) schematically presents the findings from last years, showing that stress and GCs have similar timing-related effects on extinction as well.

First, pre-extinction stress or GCs promote extinction memory consolidation (Meir Drexler et al., 2017, 2018, cf. de Quervain et al., 2017; Soravia et al., 2006, 2014; Yehuda et al., 2015) in a context-independent manner (Meir Drexler et al., 2017, 2018), making extinction memory more resistant to relapse following context change (cf. GCs-related contextual disruption in other tasks: McGlade et al., 2019; Schwabe et al., 2009; van Ast et al., 2013). In contrast, post-extinction stress enhances consolidation in a context-dependent manner (Hamacher-Dang et al., 2013a, 2015), making extinction retrieval stronger only in the context in which it had been learned (cf. GC-related context dependency in other tasks: van Ast et al., 2013). Finally, in contrast to de Quervain and Margraf's model (2008), when exposure to stress/GCs takes place shortly before retrieval (Hamacher-Dang et al., 2013b; Kinner et al., 2016, 2018) extinction retrieval is impaired, and relapse is likely to occur (cf. GCs-related retrieval deficit in other tasks: Buchanan et al., 2006; Smeets, 2011).

The timing-dependent effects of stress/GCs on extinction memories are modulated by alterations in the amygdala, hippocampal complex, and PFC (Kinner et al., 2016, 2018; Merz et al., 2018a) and their communication with additional brain regions, which are critical for fear extinction (Kinner et al., 2016, 2018; Maren et al., 2013). The amygdala has a central role in the acquisition of fear and extinction memories (Quirk and Mueller, 2008). The hippocampus is critical for contextualization, and it encodes the relations between stimuli in a given context. For instance, high activation of the hippocampus during

extinction learning was previously shown to be related to a stronger renewal effect (i.e., context encoding was improved and therefore extinction was more context-bound), and vice versa (Lissek et al., 2016). Contextual disruption following pre-learning stress might result from the rapid non-genomic effects of GCs, while contextual enhancement following post-learning stress can be a result of its slower genomic effects (van Ast et al., 2013); noradrenergic activation plays a timing-dependent role as well (Atucha et al., 2017). After learning has been completed, excitatory input from the dorsal ACC and inhibitory input from the vmPFC modulate the expression of fear memories via the amygdala (Graham and Milad, 2011). This circuit receives contextual information from the hippocampus (Maren et al., 2013; Milad et al., 2007). The disruption of the vmPFC activity, its communication with other extinction-related structures, and the enhanced amygdala signaling under stress/high GCs concentrations (Akirav and Maroun, 2007; Kinner et al., 2016, 2018) might thus favor the retrieval of the original memory trace over the extinction memory trace, and thus promote relapse (see Fig. 2).

3.2. Understanding and treating fear- and stress-related disorders

Exposure to a stressful event activates the SNS and the HPA axis and leads to physiological, cognitive and behavioral changes (Joëls et al., 2006). The response to stress results in a restricted attention to contextual cues (Schwabe et al., 2009; Schwabe and Wolf, 2013) and to an enhanced emotional memory consolidation (Roozendaal, 2000; Sandi and Rose, 1994; Wolf, 2008). This can explain the strength and generalization of emotional memories. However, the same properties that lead to robust and persistent emotional memories can also be used for the benefit of extinction learning (de Quervain & Margraf, 2008; de Quervain et al., 2017) and to promote its generalization across contexts (Meir Drexler et al., 2017, 2018). Our STaR model presents further support for the use of GCs in psychotherapy (Bentz et al., 2010; de Quervain et al., 2017). The results suggest that exposure to stress/GCs should be promoted 20–25 min before, and avoided after extinction-based psychotherapy, as the latter might increase the probability for relapse outside the therapeutic context. Indeed, in a recent study with spider-phobia patients, post-treatment cortisol did not promote the reduction of behavioral, psychophysiological or subjective symptoms more than placebo, and led to a greater fear renewal in the long-term (Raeder et al., 2019). Our findings might inspire the incorporation of additional behavioral interventions, such as mild stress (or alternatively, very low cortisol doses), into psychotherapy, as this manipulation might provide the rapid and time-limited cortisol response required for designing a pre-extinction-only GC session (cf. Meir Drexler et al., 2017, 2018; Merz et al., 2018a). In addition, due to the circadian rhythm of cortisol, treatment might profit from time-of-day alterations (Lass-Hennemann and Michael, 2014; Meuret et al., 2015, 2016), such as performing exposure sessions in the morning (when cortisol levels are elevated due to the circadian rhythm) and not later during the day (when cortisol levels are lower). This may promote the desired cortisol pattern (i.e., higher cortisol pre-extinction, cortisol levels decline during the session, and are low post-extinction). Additional adjustments should be considered for people who show alterations in the circadian rhythm of cortisol (e.g., in its timing or amplitude) or in the cortisol response to stress (e.g., enhanced or blunted response) as a result of shift work, fatigue, chronic stress (Chida and Steptoe, 2009; Golombek et al., 2013), health status (Fries et al., 2009), or (in women) hormonal contraceptive use (Kirschbaum et al., 1999). For instance, chronic stress can lead to an impairment in the retrieval of extinction memories (Miracle et al., 2006), and should thus be mitigated prior and during exposure-based treatments.

In order to avoid detrimental consequences of GCs administration in treatment, it is critical to remember that both extinction and reconsolidation (i.e., the process of restabilization of memory after retrieval) can be triggered by exposure to conditioned cues (Merlo et al.,

2014). While a brief presentation can trigger reconsolidation of the aversive memory, repeated presentations usually lead to the formation of a new extinction memory. Manipulating extinction or reconsolidation using the same pharmacological or behavioral treatment may lead to opposite consequences. For instance, DCS enhances exposure therapy and thus reduces fear (Ressler et al., 2004). However, it can also enhance fear responses if administered following a brief exposure, presumably due to its enhancing effects on fear memory reconsolidation (Lee et al., 2006). Similarly, cortisol, as a facilitator of extinction learning, can reduce fear (de Quervain et al., 2011; Meir Drexler et al., 2017, 2018), but might lead to unwanted effects after brief exposure that triggers reconsolidation of the original memory (Meir Drexler et al., 2015). Thus, based on these findings, it is advisable to administer GCs at the beginning of a prolonged exposure session in order to achieve a stronger and more generalized extinction memory.

The results on the timing-dependent effects of GCs raise questions regarding the context-dependency of exposure enhancement in general. DCS, for instance, has been shown to reduce spontaneous recovery when no context change occurred between extinction learning and test (Vervliet, 2008), yet it did not affect the renewal of fear when testing took place in the acquisition context (Bouton et al., 2008). Similarly, the extinction enhancing effects of the α2-adrenergic receptor antagonist yohimbine are context specific (Morris and Bouton, 2007). These findings indicate the importance of considering timing when studying the effects of GCs, DCS, yohimbine, and possibly other adjuvants, on extinction. In contrast, the dopamine precursor L-dopa, administered after extinction, was found to reduce the renewal effect (Haaker et al., 2013), suggesting an enchantment of extinction independent of context. Additional research is needed to support these findings.

3.3. Is timing really everything? Several open questions

Timing, as discussed above and presented in our StaR model, is critical in determining the effects of stress/GCs on extinction and relapse, but other factors also play a role. For instance, memory domain (declarative memory vs. fear conditioning), experimental manipulation (cortisol administration vs. stress), the retrieval test procedure (renewal, reinstatement, or spontaneous recovery), and the sex of the participants. Many of the studies reported here examined only men (Hamacher-Dang et al., 2015; Meir Drexler et al., 2018; Merz et al., 2018a, 2014) or demonstrated effects only in men but not in women (Kinner et al., 2016, 2018). Women are more susceptible to anxiety and stress-related disorders than men (Kessler et al., 2005; Maeng and Milad, 2015), and there are pronounced sex differences in fear acquisition, extinction, and reconsolidation after stress exposure/GCs administration (Meir Drexler et al., 2016; Merz and Wolf, 2017; Shors, 2004; Stark et al., 2006). For instance, low concentrations of estradiol, either endogenously during the menstrual cycle or following the use of hormonal contraceptives, are associated with increased fear retrieval in women (Graham and Milad, 2013; Merz et al., 2018b; Milad et al., 2010; Stockhorst and Antov, 2016; Zeidan et al., 2011). Future experiments should take the possible interaction between stress, sex and sex hormones, and fear extinction into account.

Moreover, additional indices for learning should be used. In the fear conditioning studies described above, SCR was used almost exclusively as a measure of fear (except for the imaging studies investigating neural correlates). SCR represents autonomic arousal in response to a stimulus and contingency knowledge, and is somewhat similar to expectancy ratings (van Dooren et al., 2012). Fear-potentiated startle, on the other hand, provides an index of affective state (Grillon, 2002). Sometimes, the two indices are affected differently by the same manipulation (e.g., Kindt et al., 2009). Thus, future studies should investigate whether the effects shown here, using SCR, can also be found using additional indices, such as expectancy ratings, fear ratings, or the startle response, bearing in mind the challenges with concurrent measurement (Lonsdorf et al., 2017).

4. Conclusion

The effects of exposure to stress/GCs on learning and memory processes depend, to a large extent, on timing: the consequences significantly differ when the exposure is done either before learning (i.e., affecting encoding, consolidation), after learning (i.e., affecting consolidation), or before retrieval. As depicted in our STaR model, stress timing affects extinction learning and memory in a rather similar way to its effects on other memory types. While pre-extinction stress disrupts contextual encoding and enhances extinction memory consolidation, post-extinction stress enhances context-dependent (i.e., more accurate) extinction memory consolidation. When applied as part of exposure therapy, both interventions may thus prevent relapse, yet their context-dependency might differ. Pre-retrieval stress, on the other hand, is likely to disrupt extinction retrieval and thereby promote relapse. Taken together, our model will help in understanding the mechanisms underlying various relapse phenomena and in developing more efficient interventions.

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