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How stress hormones shape memories of fear and anxiety in humans

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ABSTRACT

Stress hormones influence the processing of fear, anxiety, and related memory mechanisms. For example, they modulate consolidation and retrieval processes associated with emotional episodic memory, fear and extinction learning. In this review, we summarize recent laboratory findings on the timing-dependent effects of stress on extinction learning and extinction retrieval. Furthermore, we relate these experiments to clinical intervention approaches relying on extinction processes such as exposure therapy, for which beneficial effects of the administration of the stress hormone cortisol have been observed. The modulation of extinction-based interventions differs from findings obtained with reconsolidation manipulation procedures utilizing the restabilization of retrieved (or reactivated) memories. In this case, blockade of adrenergic beta-receptors during reconsolidation of the fearful stimulus might represent a promising intervention. The substantial progress made in the understanding of the interaction of stress hormones with memory processes associated with fear and anxiety has the potential to enhance therapeutic success and prevent relapse in the long run.

1. Introduction

Fear[1] and **anxiety** prominently trigger **stress** responses, including the release of **(nor)epinephrine** and **glucocorticoids** (mostly **cortisol** in humans; McEwen et al., 2015; McEwen et al., 2012; cf. Fig. 1). These stress hormones directly or indirectly travel to the brain, where norepinephrine binds to alpha- and beta-receptors and glucocorticoids to mineralocorticoid and glucocorticoid receptors. Critically, (nor) epinephrine and glucocorticoids influence learning and memory processes (Roozendaal et al., 2009) and are involved in the initiation and maintenance of fear and anxiety. In particular, stress hormones modulate **episodic memory**, **fear conditioning,** and fear **reconsolidation** (Meir Drexler et al., 2020, 2019; Merz and Wolf, 2017; Schwabe et al., 2022; Shields et al., 2017). Additionally, in recent years, different stress hormone-related approaches have been tested in enhancing intervention strategies, such as **exposure therapy** (de Quervain et al., 2019, 2017) or reconsolidation-based approaches (Elsey et al., 2018; Kroes et al., 2016a).

The current review aims to provide a brief update of the relevant literature covering critical experimental (Section 2) and applied (i.e., clinical) findings (Section 3) regarding the differential impact of (nor) epinephrine and glucocorticoids on fear and extinction memories, reconsolidation, and related interventions. We focus on the effects of acute stress in humans, for a review on chronic stress, we refer to McEwen (2004).

1.1. A shared neural circuitry for fear, anxiety, and stress

The amygdala complex including the bed nucleus of the stria terminalis is a central hub for both fear and anxiety to elicit stress responses (Fox and Shackman, 2019; Gungor and Paré, 2016; Hur et al., 2020; Tovote et al., 2015). Vice versa, a stressor activates the amygdala to elicit fear and anxiety (Daviu et al., 2019). On the one hand, distinct fearful stimuli or situations immediately lead to a phasic amygdala response (Davis et al., 2010). In particular, stress hormones exert fine-tuned regulatory effects on amygdala activation and its network connectivity (Henckens et al., 2012, 2010). On the other hand, rather unspecific, unpredictable, or distant threats trigger anxiety via the bed nucleus of the stria terminalis (Davis et al., 2010; Lebow and Chen, 2016), which is also modulated by stress hormones (Daniel and Rainnie, 2016). Stress directly engages corticotropin-releasing hormone projections from the amygdala to the locus coeruleus, which support increased tonic activity of norepinephrine neurons to directly induce anxiety (Daviu et al., 2019; McCall et al., 2015). The slow release of

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[1] Terms defined in the glossary (Section 5) are marked in bold.

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glucocorticoids counteracts this rapid stress response (Hermans et al., 2014; Joëls et al., 2011); for example, cortisol administration can reduce negative affect (Het and Wolf, 2007; Reuter, 2002), phobic fear (Soravia et al., 2006) and the related amygdala activation (Nakataki et al., 2016), and posttraumatic stress symptoms (Aerni et al., 2004; de Quervain et al., 2009; Schelling et al., 2004). Thus, stress, fear, and anxiety recruit a partially overlapping microcircuitry (Gilpin et al., 2015; Shin and Liberzon, 2010; Tovote et al., 2015) securing adaptation or even survival (McEwen et al., 2012; Rodrigues et al., 2009).

1.2. Emotional learning and memory paradigms

Emotional learning and memory paradigms have been developed to test the interplay between stress, fear, and anxiety such as fear conditioning and episodic memory paradigms. Fear conditioning is part of non-declarative or implicit long-term memory and typically measured with various outcome variables such as skin conductance responses, fear potentiated startle responses, heart rate, pupillary responses, or functional neuroimaging (Lonsdorf et al., 2017). Additionally, expectancy ratings of the unconditioned stimulus can be evaluated or measures of contingency awareness. Thus, fear conditioning can also incorporate episodic memory processes as evident in partially overlapping neural circuits, while methodological approaches are different (Dunsmoor and Kroes, 2019).

Episodic memory tests encompass an encoding phase, in which participants either intentionally or incidentally learn a certain number of stimuli (images, words, numbers, stories etc.) for a later retrieval test. Retrieval can consist of a free recall, cued recall and/or a recognition test of the stimuli encoded before. Episodic memory is part of declarative or explicit long-term memory, for which the hippocampus and prefrontal cortex are critically involved in encoding, consolidation and retrieval (Dunsmoor and Kroes, 2019; Moscovitch et al., 2016). Additionally, the amygdala is engaged in episodic memories encompassing emotional content, making them quite comparable with memories established by fear conditioning paradigms (Dunsmoor and Kroes, 2019).

1.3. Stress hormone effects on emotional learning and memory

What we know about the effects of stress hormones on those learning and memory processes involved in fear and anxiety is mainly based on fear conditioning research. Human imaging and animal behavioral or molecular experiments indicate that norepinephrine increases synaptic excitability and long-term potentiation. This facilitates the encoding of emotionally arousing material (for a review, see Joëls et al., 2011) as occurring during **fear learning** (for a review: Rodrigues et al., 2009). Glucocorticoids (either systemic cortisol administration or exposure to stress before **fear acquisition training**) seem to reduce fear learning as evident in amygdala or hippocampus responding (for reviews: Merz and Wolf, 2017; Peyrot et al., 2020).

In episodic memory, increases in stress hormones strengthen memory encoding, particularly for memories essentially linked to the stressful event itself (Bierbrauer et al., 2021; Wiemers et al., 2013). Thus, stress close to or during, but also immediately after episodic memory encoding creates stronger memories by strengthening encoding and consolidation processes (cf. Fig. 1; for a review: Roozendaal et al., 2009). In particular, systemic manipulations increasing norepinephrine enhance amygdala-hippocampus interactions to facilitate memory accuracy. Systemic glucocorticoid administration, in contrast, supports the integration of a new memory into neocortical networks, promoting memory generalization (for a review: Bahtiyar et al., 2020).

Overall, memories established in the same context as stress can be preferentially accessed during later retrieval (Joëls et al., 2006; Sazma et al., 2019). This account might thus explain the discrepancy in stress hormone effects on fear learning vs. encoding of episodic memories. In these kind of experiments, cortisol administration or stress induction is conducted in a different room with a certain delay regarding the onset of fear acquisition training (e.g. Merz et al., 2013; Merz et al., 2012, 2010).

Furthermore, and in contrast to its primarily beneficial effects on encoding and consolidation, exposure to stress or systemic cortisol administration exert detrimental effects on episodic memory retrieval (for reviews: Schwabe et al., 2022; Shields et al., 2017; Wolf et al., 2016; cf. Fig. 1). For example, this stress-hormone induced retrieval deficit is relevant for exams or witness statements.

2. Stress hormone effects on extinction and reconsolidation

While it is essential to understand stress hormone effects on how fear is acquired (fear learning), it is equally important to know their impact on how safety is acquired (extinction learning) and how they modulate extinction learning-based treatments such as exposure therapy (Milad and Quirk, 2012).

Extinction learning depends on forming a new inhibitory memory

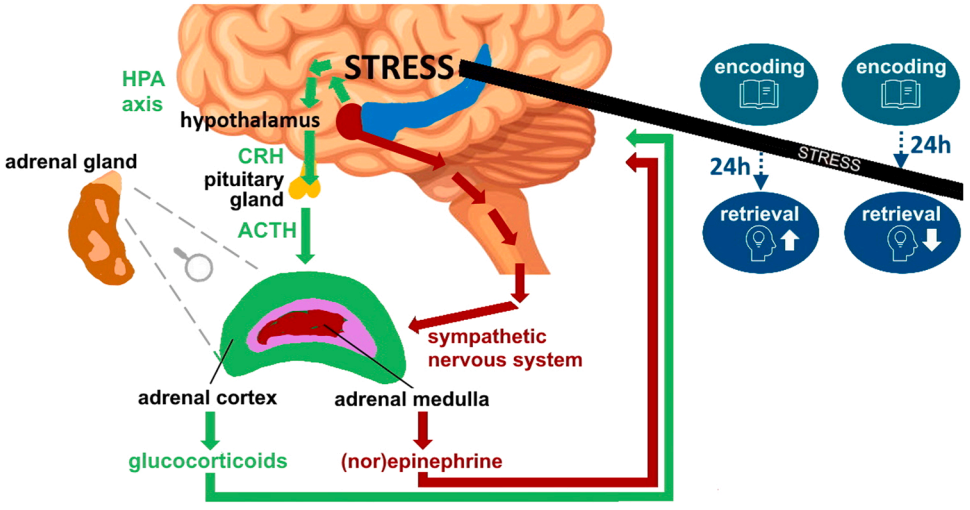

Fig. 1. Orchestration of the neurobiological stress response and its impact on consolidation and retrieval of episodic memories. On the one hand, stress rapidly activates the sympathetic nervous system to initiate a quick increase of (nor)epinephrine from the adrenal medulla and sympathetic nerves. On the other hand, stress activates the hypothalamus-pituitary-adrenocortical (HPA) axis: the hypothalamus releases corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH). Travelling via the bloodstream, ACTH stimulates the adrenal cortex to release glucocorticoids. Norepinephrine and glucocorticoids directly or indirectly stimulate a wide range of brain regions expressing alpha- and beta-receptors (norepinephrine), as well as mineralocorticoid and glucocorticoid receptors (glucocorticoids) involved in learning and memory processes.
Stress after encoding of episodic memories typically enhances retrieval (e.g. examined 24 h later), thus, consolidation is facilitated by stress. Stress before retrieval typically reduces memory retrieval.

trace and does not erase the originally learned fear memory trace. Thus, following extinction learning, the initial fear memory trace and the newly established extinction memory trace co-exist and might both influence behavior. The original fear memory trace is often relatively robust, context-independent, and tends to generalize. In contrast, the extinction memory trace is typically stored as a conditional event dependent on the specific context (Bouton, 2004; Podlesnik et al., 2017; Vervliet et al., 2013a). As a result, a return of fear may occur in situations where the fear memory trace is more likely to be retrieved than the extinction memory trace. These situations encompass a temporal delay (spontaneous recovery) or a context change (**renewal**) between **extinction training** and retrieval, as well as re-exposure to the unconditioned stimulus before retrieval (reinstatement; cf. Fig. 2; Bouton, 2004; Lonsdorf et al., 2017; Myers and Davis, 2002; Quirk and Mueller, 2008). In the last few years, a systematic characterization of the influence of stress hormones on these phenomena has started.

In rodents, pharmacological (systemic and local administration of agonists and antagonists) and optogenetic approaches have shown that norepinephrine enhances extinction learning, consolidation, and retrieval. This process likely involves beta- rather than alpha-receptors and is supported by the infralimbic cortex (for reviews: Bierwirth and Stockhorst, 2022; Mueller and Cahill, 2010; Stockhorst and Antov, 2016). In contrast to these experiments employing a delayed extinction design (extinction training taking place at least 24 h after fear acquisition training), high norepinephrine levels after fear learning impair immediate extinction as evident in reduced extinction retrieval. This immediate extinction deficit was observed in rodents (for reviews: Bierwirth and Stockhorst, 2022; Giustino and Maren, 2018; Maren, 2014) and recently replicated in humans (Sperl et al., 2022). Additionally, high norepinephrine levels after delayed extinction training led to increased fear-related activation during retrieval in healthy men (Lonsdorf et al., 2014). However, further studies revealed no consistent picture in humans so far (for reviews: Bierwirth and Stockhorst, 2022; Stockhorst and Antov, 2016): for example, the beta-receptor blocker propranolol was shown to impair (Bos et al., 2012), but also to enhance extinction learning (Kroes et al., 2016b). More experiments are needed to disentangle the exact role of norepinephrine in extinction learning and extinction retrieval in humans.

Regarding cortisol, we have developed the STaR model (Stress Timing affects Relapse) to describe the impact of timing of stress induction on the strength and context-dependency of extinction learning (Meir Drexler et al., 2020, 2019). The model is based on research in which we used laboratory stressors or cortisol administration at different time points, either before extinction training, after extinction training, or before extinction retrieval (cf. Fig. 2).

Cortisol administration before extinction training reduced conditioned skin conductance responses and activation of the amygdala-hippocampus complex and increased its functional connectivity to the ventromedial prefrontal cortex (vmPFC; Merz et al., 2018). One week later, during extinction retrieval, a higher hippocampus activation and functional connectivity of the hippocampus with the vmPFC was observed in the cortisol relative to the placebo group hinting at beneficial cortisol effects on extinction consolidation. Similarly, exposure to stress before extinction training led to reduced expectancy of the unconditioned stimulus during extinction training and retrieval on the next day (Bentz et al., 2013). Apparently, stress made the extinction memory trace less context-dependent, indicated by a diminished renewal effect (Meir Drexler et al., 2018, 2017), a desirable outcome from a clinical perspective. In contrast, stress or cortisol administration after extinction training promoted extinction memory consolidation (Brückner et al., 2019) but also increased the context-dependency of the extinction memory trace (Hamacher-Dang et al., 2015, 2013a). This increased

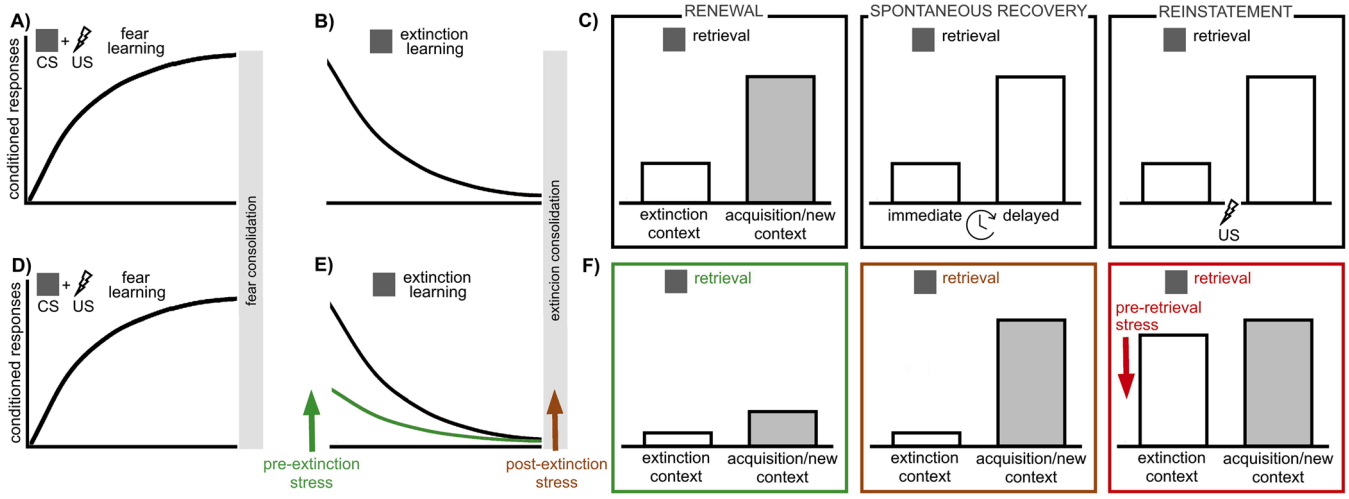

Fig. 2. A-C) Illustration of the fear conditioning design and D-F) the impact of stress hormones on extinction learning, consolidation and retrieval as proposed by the Stress Timing affects Relapse (STaR) model (Meir Drexler et al., 2020, 2019). **A) + D)** During fear acquisition training, a conditioned stimulus (CS, e.g. a visual cue of a geometric shape) is paired with an aversive unconditioned stimulus (US; e.g. an electrical stimulation). This procedure results in fear learning indicated by increased conditioned responses. This fear memory is stabilized during subsequent fear consolidation. **B)** During extinction training, the CS is presented in the absence of the US. This procedure leads to extinction learning indicated by decreased conditioned responses. This extinction memory is stabilized during subsequent extinction consolidation. **C)** During retrieval, the CS is presented again in the absence of the US. Different recovery phenomena needs to be distinguished which are associated with a return of conditioned responses. During **renewal**, conditioned responses are low when the CS is shown in the extinction context (extinction retrieval), but high in the original fear acquisition or a new context (fear retrieval). **Spontaneous recovery** reflects the phenomenon that conditioned responding returns as a function of time: immediate retrieval (relative to extinction training) evokes low conditioned responses, delayed retrieval leads to high conditioned responses. **Reinstatement** refers to high conditioned responses occurring after unsignaled exposure to the US initially paired with the CS or any other aversive US. **E) Pre-extinction stress induction or cortisol administration** (illustrated in green) reduces conditioned responses at the beginning of extinction training and also strengthens extinction consolidation as evident during retrieval: **F)** Conditioned responses are reduced in the extinction as well as in the fear acquisition or a new context indicating a context-independent extinction retrieval. **E) Post-extinction stress induction or cortisol administration** (illustrated in brown) selectively enhances extinction consolidation as seen during retrieval: **F)** Extinction memory retrieval is enhanced indicated by reduced conditioned responses in the extinction context. However, conditioned responses in the fear acquisition or a new context are not affected by post-extinction stress. **F) Pre-retrieval stress induction or cortisol administration** (illustrated in red) impairs extinction memory retrieval as indicated by increased conditioned responses in the extinction context.

context-dependency when stress hormones are high after extinction training is mirrored during retrieval in the extinction context only. However, this effect does not typically generalize to other contexts. These experimental findings shed light on how high pre-exposure cortisol concentrations might boost therapeutic success (cf. Fig. 2; see Section 3).

However, stress or cortisol administration before retrieval impaired extinction retrieval, thus, eliciting a return of fear (in other words, a return of the initially acquired memory trace; Hamacher-Dang et al., 2013b; Kinner et al., 2018; Kinner et al., 2016; Merz et al., 2020; Raio et al., 2014; but see Merz et al., 2014). On the neural level, cortisol administration before retrieval reduced vmPFC activation and increased amygdala responding (Kinner et al., 2018, 2016). Importantly, these retrieval findings might explain how stress after an initially successful exposure therapy can cause symptom relapse (Francis et al., 2012; Jacobs and Nadel, 1985). In a recent study, we tested whether stimulus-based extinction generalization training could prevent the stress hormone-induced return of fear. During stimulus-based extinction generalization training, we presented one conditioned stimulus of the same size as during fear acquisition training. We compared it to another conditioned stimulus shown in different sizes to create a more generalized extinction memory trace. While extinction generalization effectively reduced amygdala responding during retrieval, cortisol administration before retrieval abolished this beneficial effect (Hagedorn et al., 2021). Future studies should test other learning theory-based behavioral interventions aimed at reducing the impairing effects of stress hormones on extinction retrieval (Craske et al., 2018, 2014; Weisman and Rodebaugh, 2018).

In sum, laboratory-based findings helped to understand further the critical conditions in which stress or cortisol administration can increase therapeutic success (when administered before extinction training/exposure; see Section 3) and, simultaneously, characterize the mechanisms underlying the stress-induced return of fear.

Reconsolidation blockade has been proposed as a potentially more efficient and enduring alternative to extinction training (Nader and Hardt, 2009). After targeted reactivation of the fear memory trace, pharmacological and behavioral interventions may reduce or even prevent reconsolidation of the fear memory trace in laboratory studies. In their seminal study, Nader et al. (2000) could demonstrate that administration of the protein synthesis inhibitor anisomycin after fear memory reactivation blocked fear reconsolidation in rodents. In humans, Kindt and colleagues (2009) reported that administration of the beta-blocker propranolol in combination with fear reactivation prevented fear reconsolidation as measured with the fear-potentiated startle (cf. Fig. 3). Interestingly, beta-blockade did not affect the explicit memory of the fear associations learned before as measured with expectancy ratings of the unconditioned stimulus. Still, beta-blockade hindered this intact explicit memory to produce an effect in fear-potentiated startle. In the meantime, some boundary conditions underlying this initial finding were characterized such as age and strength of fear-related memories, (un)expected change in contingencies or surprising or novel content included during memory reactivation (for a review: Elsey et al., 2018).

In contrast, cortisol administration enhanced reconsolidation, which corresponds with its effects on episodic memory consolidation and extinction consolidation (see above; Meir Drexler et al., 2020; Meir Drexler et al., 2015; Meir Drexler and Wolf, 2016; Roozendaal et al., 2009). Supporting this observation, cortisol suppression with metyrapone administration during reactivation impaired reconsolidation (Antypa et al., 2019). Consequently, the usage of beta-blockers, but not cortisol, might exert beneficial effects in the context of reconsolidation-based interventions, as outlined in the next section.

3. Stress hormones effects on extinction- and reconsolidation-based therapies

Since stress hormones promote extinction learning, the question arose if these promising findings could be translated into extinction-based treatments such as exposure therapy. During exposure therapy, patients are confronted with their phobic stimuli or situations until fear decreases (Craske et al., 2022, 2014).

Indeed, exposure therapy elicits stress responses, as shown in increased (nor)epinephrine levels and verbal reports (Curtis et al., 1978, 1976). However, exposure therapy often does not increase cortisol concentrations (cf. Fig. 4A; Curtis et al., 1978; Curtis et al., 1976; Diemer et al., 2016; Lass-Hennemann and Michael, 2014; Schumacher et al., 2015; but see Alpers et al., 2003; Schumacher et al., 2014). Moreover, patients with anxiety disorders also do not always show an adequate cortisol response to stress in general (Garcia-Leal et al., 2005; Petrowski et al., 2021, 2013, 2010; but see Klumbies et al., 2014; Martel et al., 1999). Interestingly, an absent cortisol response during exposure therapy appears to reduce treatment success (Fischer et al., 2021; Fischer and Cleare, 2017; Siegmund et al., 2011). As mentioned above, cortisol typically inhibits retrieval and facilitates consolidation (de Quervain et al., 2017; Meir Drexler et al., 2019; Shields et al., 2017). Thus, on the one hand, patients not adequately responding with cortisol increases cannot profit from the additional, beneficial cortisol effects on reducing fear retrieval when confronted with their phobic stimuli or situations.

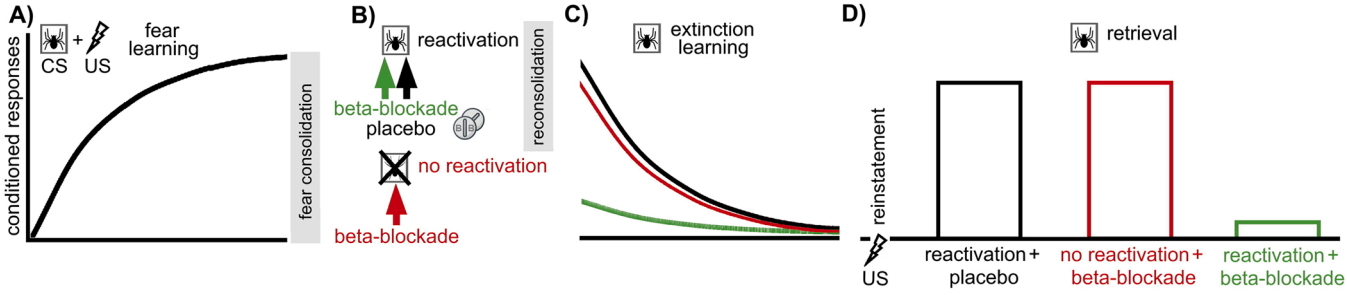

Fig. 3. Illustration of a pharmacological reconsolidation study according to Kindt and colleagues (2009). **A)** During fear acquisition training on day 1, a conditioned stimulus (CS, picture of a spider) was paired with an aversive unconditioned stimulus (US; electrical stimulation). This procedure resulted in fear learning indicated by increased conditioned responses. This fear memory was stabilized during subsequent fear consolidation. **B)** During reactivation on day 2, a single CS was presented in the absence of the US. This procedure led to subsequent reconsolidation. Reconsolidation took place either under beta-blockade (administration of the beta-blocker propranolol 90 min before reactivation) or under placebo treatment. The beta-blocker propranolol was administered to a further control group, without reactivation of the CS. **C)** During extinction training on day 3, the CS was presented in the absence of the US. This procedure led to extinction learning indicated by decreased conditioned responses. Reactivation + beta-blockade only reduced conditioned responses already at the beginning of extinction learning, but not reactivation + placebo or no reactivation + beta-blockade. **D)** Subsequent unsignaled exposure to three US during reinstatement on day 3 led to high conditioned responses towards the CS for both, the reactivation + placebo and the no reactivation + beta-blockade group, but not for the reactivation + beta-blockade group. Thus, disrupting fear memory reconsolidation with beta-blockade prevented the return of fear.

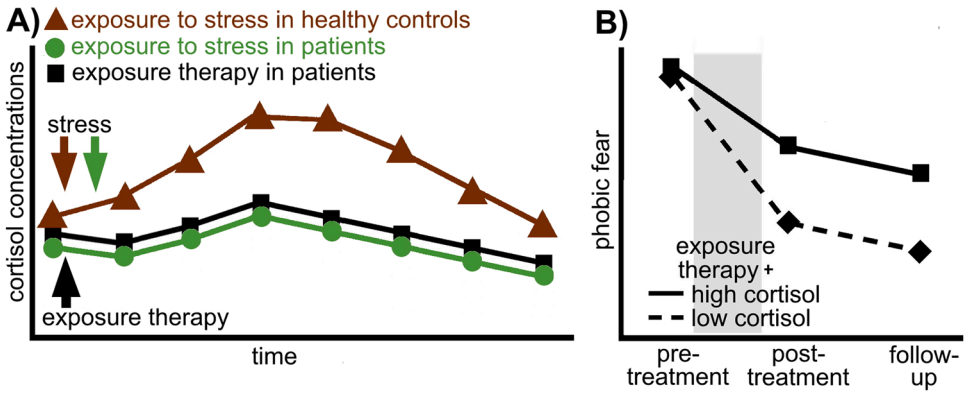

Fig. 4. Illustration of findings from cortisol research in patients with anxiety disorders. **A)** Exposure to stress increases cortisol concentrations in healthy controls, but patients with anxiety disorders do not always mount an adequate cortisol response towards stress. In addition, exposure therapy does not necessarily lead to cortisol increases in patients with anxiety disorders. **B)** Exposure therapy in patients with anxiety disorders is more successful under conditions of high cortisol concentrations (cortisol administration or exposure therapy conducted in the morning) compared to low cortisol concentrations (placebo administration or exposure therapy conducted in the evening).

On the other hand, the consolidation of their new, corrective experiences made during exposure therapy is not supported by increased cortisol levels.

Based on these insights, one central idea to augment exposure therapy was to increase cortisol during exposure therapy (cf. Fig. 4B; Bentz et al., 2010; de Quervain et al., 2019; de Quervain et al., 2017). Indeed, cortisol administration before (not necessarily after; Raeder et al., 2019) exposure therapy enhanced therapeutic success in patients with spider phobia, social phobia, or acrophobia (de Quervain et al., 2011; Soravia et al., 2014, 2006). Furthermore, exposure therapy sessions conducted in the morning (associated with high cortisol levels) reduced fear more in patients with spider phobia than exposure sessions in the evening (low cortisol levels; Lass-Hennemann and Michael, 2014). Similarly, a higher cortisol awakening response and higher absolute cortisol concentrations during exposure sessions were linked to better exposure therapy success in patients with panic disorder and agoraphobia (Meuret et al., 2015). All these fear-alleviating cortisol effects might be related to the ability of cortisol to restore the reduced activation of the salience and default mode networks in phobic patients (Soravia et al., 2018). Additionally, cortisol can reduce subjective phobic fear and associated amygdala activation to a level similar to healthy participants (Nakataki et al., 2016). Future studies should explicitly test the context-dependency of the observed cortisol effects since the STaR model (Meir Drexler et al., 2020, 2019) predicts pre-exposure cortisol to enhance exposure therapy success context-independently, while post-exposure cortisol should enhance exposure therapy success context-dependently.

Another idea to increase exposure therapy success was to raise norepinephrine signaling, as suggested by animal work on extinction learning (for reviews: Bierwirth and Stockhorst, 2022; Mueller and Cahill, 2010; Stockhorst and Antov, 2016). Indeed, the first studies revealed norepinephrine to improve the outcome of exposure therapy in patients with claustrophobia (Powers et al., 2009), social anxiety disorder (Smits et al., 2014) and posttraumatic stress disorder (Tuerk et al., 2018), but not in patients with fear of flying (Meyerbröker et al., 2018, 2012). More studies in clinical populations are needed to disentangle the exact role of norepinephrine in exposure therapy.

The beneficial effects of cortisol (but not necessarily norepinephrine) on extinction-based therapies have been established over the last few years. What about reconsolidation-based therapies? As mentioned before, cortisol does not seem to exert beneficial effects on reconsolidation processes (Meir Drexler et al., 2020; Meir Drexler and Wolf, 2016), but beta-blockers effectively reduced fear reconsolidation (Elsey et al., 2018; Kindt et al., 2009; Kroes et al., 2016a). On the one hand, the first translation attempts to the clinic revealed that spider fearful participants profited from the beta-blocker/reactivation approach (Soeter and Kindt, 2015). On the other hand, attempts to reduce posttraumatic stress disorder symptoms by combining a beta-blocker with reactivation have been less successful (Raut et al., 2022; but see Brunet et al., 2018). Thus, the success of reconsolidation blockade in the clinical context might be restricted to relatively focused and specific fears (e.g., spider phobia). The complex and often spontaneously reactivated memories at the core of posttraumatic stress disorder might be more challenging to modify using reconsolidation-based approaches. A critical, mechanistic review on the potential of beta-blockers for reconsolidation-based treatments is provided by AlOkda and colleagues (2019).

In summary, therapies based on reconsolidation blockade are conceptually very attractive, but the supporting empirical evidence is still somewhat preliminary. Moreover, some of the hallmark findings in the reconsolidation field have been hard to replicate (Chalkia et al., 2020a, 2020b; Cox et al., 2022; Stemerding et al., 2022). Beta-blocker administration or behavioral interventions after reactivation (e.g., interference, extinction training) appear to be the most promising (Astill Wright et al., 2021).

4. Conclusion and outlook

First, the present review illustrated the influence of stress hormones on fear and extinction memories as well as reconsolidation in experimental settings (Section 2). Second, different parts of the stress response can support therapy success: while cortisol administration should promote extinction-based interventions (Bentz et al., 2010; de Quervain et al., 2017), beta-blockade might exert beneficial effects on reconsolidation-based interventions (Section 3; cf. Fig. 5; (AlOkda et al., 2019; Astill Wright et al., 2021; Elsey et al., 2018)). However, contextual features seem to limit cortisol effects depending on the exact timing (pre- versus post-exposure) of the intervention (Meir Drexler et al., 2020, 2019). In the future, different recovery phenomena commonly tested in extinction research, such as renewal or reinstatement should be more closely investigated in human reconsolidation studies.

Obtained results hold great clinical potential; still, additional translational research is needed. Large randomized clinical trials should establish the effectiveness of cortisol administration before exposure therapy and beta-blockade during reconsolidation-based interventions. Moreover, non-pharmacological interventions aimed at raising cortisol levels before or during extinction-based treatment (e.g. stress induction (Meir Drexler et al., 2018), physical exercise (Keyan and Bryant, 2019) or circadian rhythm variations (Lass-Hennemann and Michael, 2014)) should be explored in the laboratory but also the clinical context. Finally, a characterization of specific patient characteristics predicting a beneficial response to the modulation of stress hormones during therapy would be desirable. For example, stress hormone effects in different domains do not universally occur in all participants. In particular, women taking hormonal contraceptives seem to show dampened, absent, or even reversed effects on memory processes in the face of stress (Jentsch et al., 2022; Merz and Wolf, 2017; Shields et al., 2017).

The substantial progress made during recent years in stress, learning, and memory may pave the way to more successful and personalized

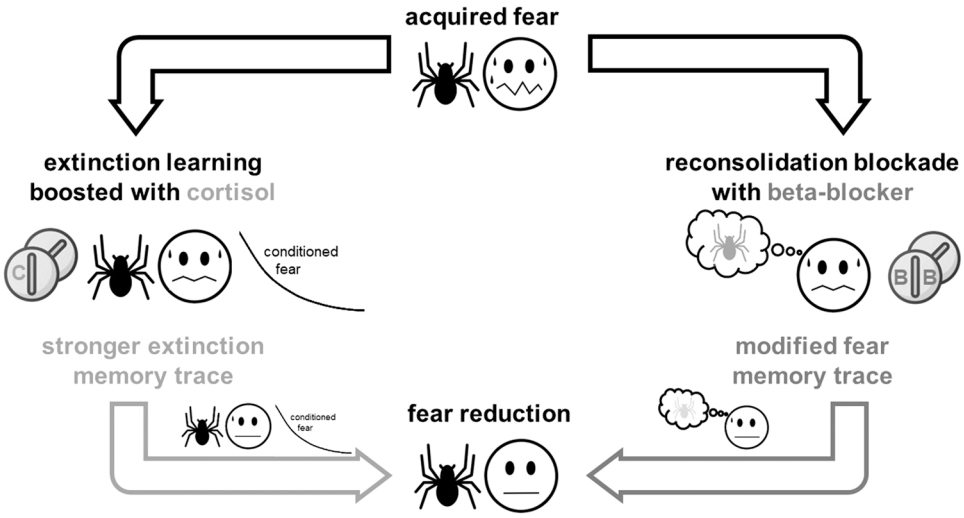

Fig. 5. Two possible routes to fear reduction of initially acquired (pathological) fear involving different stress hormone manipulations. One route involves high cortisol concentrations (realized by cortisol administration, stress induction, physical exercise, or circadian rhythm) in combination with extinction learning leading to a stronger consolidation of the inhibitory, extinction memory trace. The other route encompasses administration of a beta-blocker to block fear reconsolidation processes when confronted with the feared stimulus, thus modifying the initially acquired fear memory trace. Both possible routes are based on laboratory findings and first clinical investigations but await further confirmation particularly in randomized clinical trials across different fear- and anxiety-related mental disorders.

interventions for patients suffering from fear- and anxiety-related symptoms.

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Declaration of interest

None.

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Glossary

Anxiety: Sustained defensive state towards a potential, unspecific and anticipated threat in the future involving sustained arousal, vigilance, and apprehension. The distinct bed nucleus of the stria terminalis and amygdala circuits and subnuclei, cortico-hippocampal inputs to the amygdala, and the septohippocampal system play a critical role in conveying anxiety responses (Davis et al., 2010; Fox and Shackman, 2019; Gungor and Paré, 2016; Hur et al., 2020; Tovote et al., 2015; Walker et al., 2009). The anxiety circuitry is more complex than the fear circuitry, but both networks share substantial overlaps.

Episodic memory: Tulving (2002) initially defined episodic memory as containing information about a specific event (context, time, participants, known as the "what--when-where" criterion). Nowadays, the idea of episodic memory retrieval as a mental time travel in the past has gained acceptance. Episodic memory retrieval is a constructive process during which the gist stored in an episodic memory trace is enriched with semantic information (Cheng et al., 2016).

Exposure therapy: During exposure therapy, patients are repeatedly and systematically exposed to their specific fearful stimuli or situations in a safe environment which should lead to a decrease of their phobic fear (Öst, 1997). Extinction learning comprises one important mechanism underlying exposure therapy as also outlined in the inhibitory retrieval model (Craske et al., 2022, 2014).

Extinction learning: Process referring to the decrease in conditioned responses as a result of extinction training (Lonsdorf et al., 2017).

Extinction training: Procedure involving the repeated exposure to the conditioned stimulus (e.g. tone or visual cue) in the absence of the unconditioned stimulus (e.g. electrical stimulation; Lonsdorf et al., 2017).

Fear: The individual's conscious emotional experience in response to an acute and discrete threat (LeDoux, 2014). Fear conditioning serves as the most prominent and translational paradigm to investigate the fear circuitry and fear responses. Important parts of the fear network comprise distinct amygdala subnuclei, the hippocampus, insula and parts of the prefrontal cortex, including the dorsal anterior cingulate cortex (Davis et al., 2010; Maren and Quirk, 2004; Shin and Liberzon, 2010; Tovote et al., 2015).

Fear acquisition training: Procedure involving pairings of the conditioned stimulus (e.g. tone or visual cue) with an aversive unconditioned stimulus (e.g. electrical stimulation; Lonsdorf et al., 2017).

Fear conditioning: Fear conditioning is used as an umbrella term to cover the different stages of a fear conditioning experiment: fear acquisition training, extinction training and retrieval.

Fear learning: Fear learning describes changes in conditioned responses (e.g. increases in skin conductance or startle responses) as a result of fear acquisition training (Lonsdorf et al., 2017).

Glucocorticoids (Cortisol): Steroid hormones belonging to the class of corticosteroids. Stress activates the hypothalamus-pituitary-adrenocortical-axis initiating the release of corticotropin-releasing hormone from the hypothalamus, which stimulates the pituitary gland to secrete adrenocorticotropic hormone eventually leading to the release of glucocorticoids from the adrenal cortex (Joëls and Baram, 2009). In humans, the main glucocorticoid is cortisol, in most rodents, the main glucocorticoid is corticosterone. Glucocorticoids influence a variety of organ systems including the cardiovascular, metabolic, immune, and nervous system (Kadmiel and Cidlowski, 2013).

(Nor)epinephrine: The catecholamines norepinephrine and epinephrine act as hormones as well as neurotransmitters. Stress activates the sympathetic nervous system to initiate a quick increase of (nor)epinephrine from the adrenal medulla and sympathetic nerves (Joëls and Baram, 2009). In the brain, norepinephrine is secreted from the locus coeruleus and brainstem sites.

Reconsolidation: Post-retrieval process of restabilization of retrieved (or reactivated) memories (Nader and Hardt, 2009). Retrieval (or reactivation) of a memory renders the respective memory trace susceptible for new information. Pharmacological or behavioral manipulations within this reconsolidation window can alter the reconsolidation process (Elsey et al., 2018).

Renewal: Phenomenon describing that conditioned responses reoccur during retrieval when retrieval is tested in a context different from extinction training (Bouton et al., 2021; Bouton, 2004; Vervliet et al., 2013b). Different designs serve to test for the renewal effect: In an ABA design, fear acquisition training and retrieval share the same context (A), while extinction training is conducted in a different context (B). In an ABC design, each experimental phase is conducted in a new context. In an AAB design, fear acquisition and extinction training share the same context (A) and only the context during retrieval is different (B). The renewal effect reflects the ideas that extinction learning is context-dependent and different memory traces exist during retrieval: the excitatory fear memory trace acquired during fear acquisition training as well as the inhibitory extinction memory trace acquired during extinction training.

Stress: Rather loosely defined concept which is almost excessively used nowadays (for an extensive discussion: Cohen et al., 2016; Kagan, 2016a, 2016b; McEwen and McEwen, 2016). Stress occurs when an individual is confronted with a stressor, causing a stress response. The acute stress response is typically associated with affective, physiological and neuroendocrine changes (see glucocorticoids (cortisol) and (nor)epinephrine). Goldstein and McEwen p. 56) (2002) define stress from a neuroscientific perspective: "Stress occurs when the organism senses a disruption or a threat of disruption of homeostasis, leading to a compensatory reaction. The sensation requires a comparative process, where the brain compares available information with setpoints for responding". A stronger focus on psychological mechanisms is put forward by Lazarus and Folkman p. 19) (1984): "Psychological stress is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being". For humans, situations characterized by uncontrollability and social evaluative threat are especially potent in inducing a neuroendocrine stress response (Dickerson and Kemeny, 2004; Mason, 1968).