Impact of Stress and Exercise on Fear Extinction

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Abstract This chapter reviews the literature on the impact of stress and exercise on fear extinction. Given that key brain regions of the fear circuitry (e.g., hippocampus, amygdala and frontal cortex) can be modulated by stress hormones, it is important to investigate how stress influences this process. Laboratory-based studies performed in healthy adults have yielded mixed results, which are most likely attributable to various methodological factors. Among these factors, inter-individual differences modulating the stress response and timing of stressor administration with respect to the task may contribute to this heterogeneity. Given that fear is a core manifestation of various psychopathologies and that exposure-based therapy relies on fear extinction principles, several studies have attempted to assess the role of stress hormones

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on exposure-based therapy in patients suffering from post-traumatic stress disorder or anxiety disorders. These studies tend to suggest a beneficial impact of stress hormones (through either natural endogenous variations or synthetic administration) on exposure-based therapy as assessed mostly by subjective fear measures. Similar to stress, exercise can have an impact on many physiological and biological systems in humans. Of note, exercise modulates biomarkers such as brain-derived neurotrophic factor (BDNF) and anandamide (EAE) that act on brain regions implicated in the fear circuitry, supporting the importance of studying the impact of exercise on fear extinction. Overall, the results converge and indicate that fear extinction (tested in the laboratory or via exposure-based therapy in clinical populations) can be enhanced with exercise. Further research is needed to understand the mechanisms by which stress and exercise modulate fear learning and extinction processes, as well as to maximize the applicability to clinical contexts.

Keywords Exposure-based therapy · Extinction recall · Fear conditioning · Fear extinction · Laboratory-based experiments · Physical exercise · Sex differences · Stress

In this chapter, we will discuss the literature regarding the impact of stress and exercise on fear extinction. Several experimental and clinical studies have already addressed these issues. However, before diving into the heart of the matter, it is important to understand the mechanisms underlying the stress response and the context in which the various experimental and clinical studies have been conducted.

1 The Stress Response: Mechanisms and Brain Regions

The stress response is essential for human survival. Stress is a psychobiological response that is triggered when the brain perceives a stimulus as a threat (Mason 1975; Selye 1950). Physiologically, this leads to an important cascade involving several brain regions and the synthesis and release of several hormones. The stress response unfolds via two different hormonal cascades (see Fig. 1): (1) activation of the sympathetic-adrenal-medullary (SAM) axis (Sapolsky et al. 2000), which occurs rapidly and leads to adaptive physiological responses to a stressor and (2) activation of the hypothalamic-pituitary-adrenal (HPA) axis (Sapolsky et al. 2000), a much slower process that persists longer across time. When an individual perceives a threat in their environment, the SAM axis commences with a distress signal sent from the amygdala and hypothalamus that activate the sympathetic nervous system, leading to the secretion of adrenaline (A) and noradrenaline (NA) by the adrenal medulla (Cannon 1915). The secretion of these catecholamines is followed by the activation of multiple brain regions such as the hippocampus, amygdala, and cingulate, insular, and frontal cortices (Reznikoff et al. 1986). It is important to note that these regions are also implicated in fear circuitry and are characterized by their abundance of

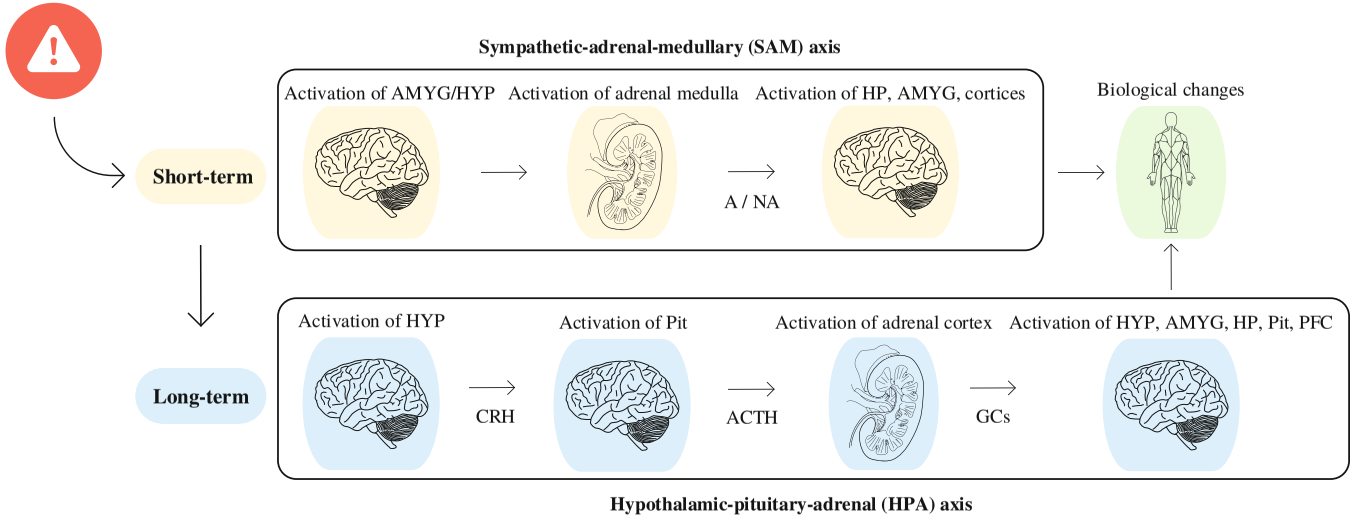

Fig. 1 Schematic representation of the two axes involved during a stress response. *AMYG* amygdala, *HYP* hypothalamus, *HP* hippocampus, *Pit* pituitary, *PFC* prefrontal cortex, *CRH* corticotropin-releasing hormone, *ACTH* adrenocorticotropic hormone, *GCs* glucocorticoids, *A* adrenaline, *NA* noradrenaline

adrenaline receptors (Reznikoff et al. 1986). The activation of the SAM axis in response to a stressor results in the following biological changes: increased blood pressure, heart rate, and respiration (Cannon and Lissák 1939; Selye 1950). The second cascade begins with the activation of the hypothalamus. This brain structure secretes corticotropin-releasing hormone (CRH), which leads to the activation of the pituitary gland. The latter secretes adrenocorticotropic hormone (ACTH), which is then released into the bloodstream. ACTH activates the cortex of the adrenal glands, resulting in the production of glucocorticoids (GCs), where cortisol is the principal GC in humans (for reviews, see Gunnar and Vazquez 2015; Heim et al. 1997; López et al. 1999). GCs can cross the blood–brain barrier and thereafter bind to corticosteroid receptors in the hypothalamus, amygdala, hippocampus, pituitary, and prefrontal cortex (Joëls and Baram 2009; Lupien et al. 2009; Mcewen et al. 1968). These brain regions play an important role in various cognitive processes, notably memory consolidation and retrieval. In general, it has been shown that stress promotes memory consolidation (Beckner et al. 2006; Cahill et al. 2003; for reviews, see de Quervain et al. 2017; Marin et al. 2019; Schwabe et al. 2012), notably for emotional information (Maheu et al. 2004; Payne et al. 2007; for a review, see Marin et al. 2019), but impairs memory retrieval (Buchanan et al. 2006; Buchanan and Tranel 2008; de Quervain et al. 1998; Tollenaar et al. 2009; for reviews, see Het et al. 2005; Marin et al. 2019). Rich in stress hormone receptors, these regions are also implicated in the fear circuitry (for a review, see Shin and Liberzon 2010). The binding of GCs to corticosteroid receptors leads to a decrease in the production of CRH and ACTH, allowing for a gradual cessation of the stress response (de Kloet et al. 2008; McEwen et al. 2016). As noted, several regions are involved in both the stress and fear response. Thus, stress seems to have a considerable influence on brain regions involved in fear processes. Furthermore, as noted and discussed in subsequent chapters in this book, dysregulation of this stress response has a significant impact on the brain circuits involved in emotion regulation and in turn is heavily intertwined with the etiology of certain psychopathologies.

2 Different Ways to Induce Stress in a Laboratory Setting

To investigate the effects of stress and its mechanisms in the laboratory, researchers can induce stress in participants in a variety of ways (see Fig. 2). First, the physiological aspects of a stress response can be targeted via the administration of synthetic hormones. For example, yohimbine (a compound that increases catecholamine concentrations; Powers et al. 2009; Smits et al. 2014) can be used to target the SAM axis, whereas synthetic GCs (e.g., hydrocortisone; Merz et al. 2014; Tabbert et al. 2010; de Quervain et al. 2011) can be used specifically for the HPA axis. Second, stress can be induced in participants using a physical stressor such as the Cold Pressor Test (CPT; Hines and Brown 1936). The CPT requires participants to submerge one of their hands in ice water for a variable short period of time. This test induces an aversive sensation that generates a stress response (Bentz et al. 2013). A

Methods used to administer stress	Advantages	Disadvantages
Synthetic hormone administration	1. Easily target a specific stress axis 2. Activates stress axis regardless of individual interpretation of the situation	1. Lack of subjective (i.e., psychological) stress component 2. More invasive than psychological protocols
Cold Pressor Test (CPT)	1. Easy administration 2. Participant is passive	1. Unable to target specific stress axis 2. Induces physical pain 3. Lack of subjective (i.e., psychological) stress component
Trier Social Stress Test (TSST)	1. Can be used to induce subjective (i.e., psychological) and objective (i.e., physiological) stress	1. Unable to target specific stress axis 2. Not universally stressful for all (individual interpretation)
Socially Evaluated Cold Pressor Test (SECPT)	1. Can be used to induce subjective (i.e., psychological) and objective (i.e., physiological) stress	1. Unable to target specific stress axis 2. Induces physical pain

Fig. 2 Advantages and disadvantages of methods used to administer stress in laboratory settings

third way to induce stress is via exposure to a psychosocial stressor such as the Trier Social Stress Test (TSST; Kirschbaum et al. 1993). The TSST consists of an oral presentation and mental arithmetic task (total of 10 min), all while the participants believe they are being filmed and evaluated by a committee of experts (Kirschbaum et al. 1993). Finally, a stressor consisting of both a physical and psychosocial component (e.g., Socially Evaluated Cold Pressor Test; SECPT; Schwabe et al. 2008) can be used to induce a stress response. Although this method is quite similar to the CPT, participants undergoing the SECPT are filmed while their hand is submerged in ice water. For the social component of this task, participants are told that their reactions are being observed by an experimenter (Meir Drexler et al. 2017). Importantly, the latter stressor type and psychosocial stressor types involve an important psychological and anticipation component (i.e., judgment from others) that can foster negative mood (Kirschbaum et al. 1993; Schwabe et al. 2008). In contrast, the administration of synthetic stress hormones does not involve these components. Moreover, the CPT and SECPT also induce physical pain in participants (Hines and Brown 1936; Schwabe et al. 2008). Therefore, pain is an important confound in these studies. For this reason, it can be difficult to generalize the effects found in CPT studies to those involving painless stressors (Antov et al. 2013). Finally, a portion of the aforementioned methods used to induce stress act on the SAM axis (Hines and Brown 1936; Smits et al. 2014), others on the HPA axis (de Quervain et al. 2011; Merz et al. 2014; Tabbert et al. 2010), whereas other methods can act on both axes (Hines and Brown 1936; Kirschbaum et al. 1993; Schwabe et al. 2008).

3 Impact of Stress on Fear Extinction

3.1 Impact of Stress-Related Synthetic Hormones in Men

As mentioned above, many stress-related synthetic hormones can be used to evoke a stress response in experimental settings. Several studies utilizing the administration of hydrocortisone before fear extinction have produced varying findings (Merz et al. 2014, 2018). Merz et al. (2014) first showed an alteration in extinction, with higher differential skin conductance responses (SCR) and lower differential activation of key fear circuitry regions (amygdala, nucleus accumbens, and medial prefrontal cortex), especially during the late extinction phase. Another study reported that hydrocortisone administration had an enhancing effect on fear extinction, as evidenced at the beginning of extinction learning by reduced SCR, lower activation of the amygdala-hippocampal complex, and enhanced functional connectivity between the vmPFC and anterior parahippocampal gyrus (Merz et al. 2018). Furthermore, when the latter study tested extinction recall 1 week later, the cortisol group still exhibited greater hippocampal-vmPFC connectivity to the extinguished cue and lower activation of the insular cortex to the non-extinguished cue compared to the placebo group.

Importantly, the main difference between these two studies lies in the delay between conditioning and extinction. In the first study, fear conditioning and extinction occurred on the same day and hydrocortisone was administered immediately after fear conditioning (45 min before fear extinction; Merz et al. 2014). In the second study, fear extinction occurred 24 h after fear conditioning. The delay between conditioning and extinction phases could modulate the direction of the effect that cortisol has on fear extinction. Based on the consolidation hypothesis, stress hormones (such as cortisol and NA) act on the amygdala during memory consolidation processes (for a review, see McGaugh 2000). That said, hydrocortisone administration immediately after the conditioning phase (and thus, during the consolidation of fear memory) may enhance fear memory consolidation and lead to higher resistance to extinction learning. With this, the enhancing effect of stress on extinction learning may require a consolidation period between conditioning and extinction learning (i.e., absence of any experimental manipulation; Merz et al. 2018). However, the time window needed to assess this effect is not known yet. Another hypothesis could be that when both threat- and safety-related information are presented on the same day (and thus, both memories are modifiable), cortisol may promote the consolidation of threat-related information by default, making the fear memory stronger and preventing any enhancing effect on fear extinction. This would explain findings on the enhancing effects of cortisol on extinction learning (safety learning) only when fear conditioning (threat learning) was already consolidated (occurring 24 h before).

3.2 Impact of Stress-Related Synthetic Hormones in Women

Most of the studies involving stress and fear extinction were performed solely in men (Merz et al. 2014, 2018). However, Tabbert et al. (2010) investigated the phenomenon in women taking oral contraceptives using hydrocortisone administration 45 min before conditioning and immediately followed by fear extinction. During conditioning (CS+ vs. CS− contrast), the cortisol group exhibited greater activation in the left ACC and left hippocampus, as well as trends in the left insula, right ACC, and right thalamus responses compared to the placebo group. The cortisol group also showed higher SCR during the entire extinction learning process (but not during conditioning) compared to the placebo group and this, irrespective of CS type. Interestingly, a group difference was found in the CS+ vs CS− contrast during extinction in the following regions: right hippocampus and right thalamus, with trends in the bilateral amygdala, right ACC, and right insula. This difference was driven by higher activation in these brain regions for the cortisol group toward the CS− compared to the CS+. According to previous research, this neural differentiation (greater activation to CS− than the CS+) in the hippocampus and amygdala is known to be involved in fear extinction learning (Knight et al. 2004; Phelps et al. 2004). Indeed, Phelps et al. (2004) reported a positive correlation between the neural differentiation in the amygdala and success in fear extinction (as indexed with SCR).

Therefore, increases in cortisol levels may enhance neural differentiation between the two stimuli and this could contribute to the enhancement of extinction learning (Tabbert et al. 2010). Greater responses to the CS− (compared to the CS+) during extinction have also been observed in other studies using fear-potentiated startle responses (FPS; Norrholm et al. 2006, 2008). To make sense of these results, the authors suggested either a generalization effect between the CSs at the beginning of extinction learning (Norrholm et al. 2006) or the anticipation of an additional conditioning phase involving reversed CS-US contingency (Norrholm et al. 2008). Given that few studies have been conducted in women and the small sample size of oral contraceptive users in the study by Tabbert et al. (2010), more studies are needed to understand the mechanisms by which synthetic stress hormones impact fear extinction in women.

3.3 Impact of SAM Axis Modulation

Finally, few studies in humans have explored the impact of catecholamines (particularly A and NA) on fear extinction. In a study conducted by Bos et al. (2012), participants received either propranolol (a β-adrenergic receptor antagonist) or a placebo pill before extinction learning (day 2), which was performed 24 h after fear conditioning (day 1). Their results showed that propranolol administration led to impaired extinction learning (as assessed by subjective ratings of US expectancy) that persisted during the test of extinction recall and reinstatement phase. As no impact of propranolol administration was observed on the SCR and FPS during extinction, the authors of the study concluded that the effects of propranolol on fear extinction seem to be limited to a cognitive level, as physiological measures of fear were unaffected. In another study, Lonsdorf et al. (2014) administered either reboxetine (a selective NA reuptake inhibitor that increases NA levels in the frontal cortex and hippocampus in an animal model; Hajós et al. 2004) or a placebo pill to men immediately after extinction learning (occurring 24 h after the fear conditioning phase). Based on fear ratings and SCR, results showed no impact of reboxetine administration on the consolidation of fear extinction learning. However, following reinstatement (1 week after extinction learning), the reboxetine group exhibited greater activation in the amygdala and posterior hippocampus, but lower activation in the vmPFC and anterior hippocampus relative to the placebo group. These results suggest that reboxetine-treated participants had greater activation in brain regions known to promote fear expression compared to placebo participants (who displayed greater activation in regions known to promote fear inhibition). Taken together, the results of these studies suggest that enhancement or blockade of NA may not be a promising avenue to facilitate fear extinction, at least at the physiological and neural levels.

3.4 Impact of Physical Stressors

Beyond the use of pharmacological protocols, researchers have also administered different types of stressors (physical and psychological) to study the effects of stress hormones on fear learning and extinction mechanisms. To assess the effects of the first hormonal cascade (SAM axis) on fear extinction, Antov et al. (2013, 2015) exposed male participants to either the CPT or a control condition (warm water) before fear conditioning (which occurred only 18 min before extinction learning; Antov et al. 2013) or immediately after fear conditioning, but right before fear extinction (Antov et al. 2015). In both studies, although the CPT group showed increased activity of the SAM axis, salivary cortisol concentrations remained stable (while they decreased in the control group). For this reason, we cannot rule out the possibility that the task also influenced HPA axis activity. During both the early and late phases of fear extinction learning in the first study, the CPT group exhibited a greater fear response to the CS+ compared to the CS− (when differentiation between CS+ and CS− should be minimal or absent). Again, exposure to a stressor before the conditioning phase seemed to enhance fear extinction resistance by promoting the consolidation of the fear memory (Antov et al. 2013). In the second study, no Group x Time interaction for the differential SCR during extinction was found. This suggests that no reduction of fear was observed in the latter. Of note, however, separate analyses for each group revealed a significant fear reduction in the CPT group during extinction (a result that was not found in the control group). In the latter study only, extinction recall was tested 24 h after extinction learning and led to a significantly better extinction retention index in the CPT group compared to controls. This points to a delayed beneficial effect of stress on extinction (Antov et al. 2015).

Finally, Bentz et al. (2013) exposed participants to a conditioning phase (day 1) and administered CPT (or a control condition) 20 min before fear extinction learning (day 2). On day 3, extinction memory recall was tested. When relying on the subjective measure of US expectancy, the authors observed a successful fear acquisition, but no apparent extinction of fear for both groups. However, at the beginning of days 2 and 3, men exposed to the CPT showed lower US expectancy than the control group. This suggests that stress induces lower explicit fear memory. This effect was not found in women. The authors noted that the observed sex differences may be due to lower cortisol responses in women in the CPT group compared to men in the same group (Bentz et al. 2013).

These three studies reached different conclusions while using diverse measures of fear (neural, SCR, subjective US expectancy) and sex distributions. Moreover, these studies utilized various methodologies regarding the timing of CPT administration and had certain limitations (e.g., non-successful conditioning and/or extinction in the control group). It is also important to remember that these three studies reported a potential impact of the CPT on the HPA axis, which ultimately prevented the researchers from isolating the effects of the SAM axis on fear extinction processes. Taken together, these differences and limitations across studies rendered it difficult

to draw definitive conclusions about the effects of physical stressors on extinction learning.

3.5 *Impact of Psychosocial and Combined Stressors*

The studies summarized thus far have had mixed results. Studies employing psychological stressors are no exception regarding the impact of stress on fear extinction (Antov and Stockhorst 2014; Jackson et al. 2006; Simon-Kutscher et al. 2019). In these studies, participants were exposed to a variant of the TSST or control condition before the conditioning phase, which was immediately followed by extinction learning. However, only Antov and Stockhorst (2014) tested extinction memory recall.

To begin, Simon-Kutscher et al. (2019) reported a resistance effect of stress on fear extinction as seen by no reduction of SCR to the CS+ during extinction. The authors argue that the results obtained during extinction learning may be explained by an increased fear memory during acquisition due to TSST exposure, which could have promoted extinction resistance in that group. Given that cortisol levels were similar for both groups (i.e., stressed and controls) during extinction (but that SCR differed), cortisol may have promoted fear memory and in turn led to deficits in extinction through enhanced extinction resistance mechanisms. Similarly, Jackson et al. (2006) reported larger SCR to the CS+ during fear acquisition in stressed men only, where this effect was maintained during early and late trials of extinction learning. However, Antov and Stockhorst (2014) failed to find an impact of psychosocial stress on fear extinction learning in both men and women. In their study, the effects of stress were found during extinction recall as a function of participants' estradiol profiles. Specifically, stressed women in the early follicular phase of their menstrual cycle (low estradiol levels) showed greater fear recovery than their non-stressed counterparts. The opposite was found in mid-cycle women (high estradiol levels). Thus, although extinction retention in women seems to be modulated by stress when administered before fear conditioning, this effect varies according to estradiol levels. As the other studies did not test extinction recall, no study so far has replicated the results obtained by Antov and Stockhorst (2014).

Finally, only one study in the literature utilized the SECPT (Schwabe et al. 2008) to explore the impact of stress on fear extinction (Riggenbach et al. 2019). Here, stress was induced before the fear conditioning phase, 24 h before extinction learning, and 48 h before extinction memory testing. Despite a lack of evidence found for an effect of stress on extinction learning assessed by FPS, results showed that the reduction of threat expectancy for the CS+ was slower in stressed participants compared to controls. These findings reflect a resistance effect of fear extinction after exposure to the SECPT. In addition, extinction recall showed that stressed participants expressed greater FPS for both the CS+ and CS−. The authors also reported that cortisol responses to the SECPT were positively correlated with CS discrimination during extinction learning and recall. Again, stress exposure before

fear conditioning seems to promote fear memory and alter fear extinction processes (Riggenbach et al. 2019).

As summarized above, the literature contains mixed findings regarding the impact of stress on fear extinction in a laboratory setting, such that stress can alter, enhance, or have no impact on fear extinction (for a summary of the studies conducted in laboratory settings discussed in this chapter, see Fig. 3). First, individual differences (e.g., personality traits, sex, and early life events) may influence how a person responds to stress on neuroendocrine, emotional, and physiological levels (Bangasser and Wicks 2017; Childs et al. 2014; Meaney et al. 1993; Orem et al. 2019). These inter-individual differences may contribute to the mixed findings regarding the impact of stress on fear extinction. Second, beyond the fact that these differences can also be partially explained by statistical power, stressor types, or population characteristics (such as sex), many studies have noted the importance of considering when the stressor is presented and the delay between conditioning and extinction phases (timing; Henckens et al. 2010, 2011, 2012; Meir Drexler et al. 2019). To have a better understanding of the effect of stress on fear extinction, it would be relevant to isolate each phase of the fear conditioning protocol by separating the phases by at least 24 h. This would reduce the chances of contamination between phases or the stressor acting on multiple phases. Together, this would allow researchers to isolate the effects of stress on the different phases and ultimately reach clearer conclusions.

4 Impact of Stress Hormones on Exposure Therapy

As mentioned in the opening of this chapter, studies examining the impact of stress hormones on fear extinction can be conducted in clinical settings. Several of these studies use the synthetic hormone administration techniques explained above to modulate stress hormone levels in patients and assess their impact on exposure-based therapy.

4.1 In Populations with Anxiety Disorders

Studies have exposed individuals with phobic disorder to exposure-based therapy sessions. In these studies, half of the participants were administered cortisol or yohimbine (to evaluate the influence of the HPA or SAM axis, respectively) 1 h before each session, whereas the remainder of the samples received a placebo. Three studies reported a greater decrease in subjective fear levels or phobic symptoms in the cortisol group over the course of exposure therapy compared to the placebo group (Soravia et al. 2006; de Quervain et al. 2011; Smits et al. 2014). For the SAM axis, a similar significant reduction in phobic fear in both groups (placebo vs. yohimbine) was found after therapy (Powers et al. 2009). Importantly,

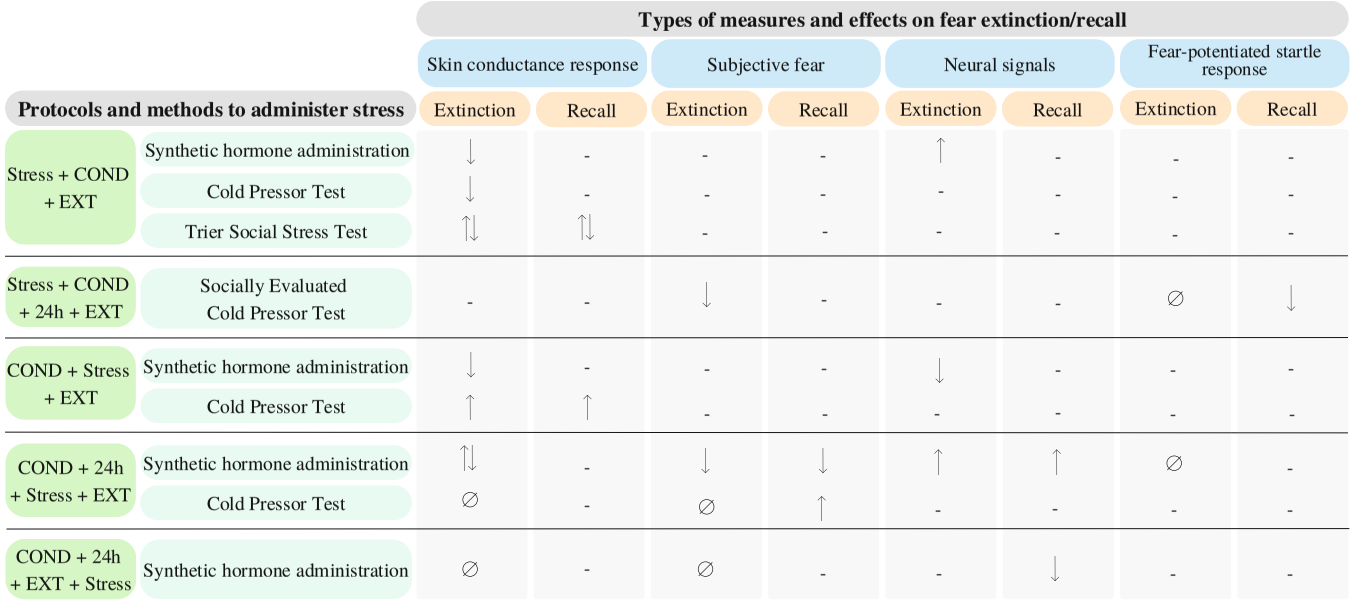

Fig. 3 Effects of different protocols and methods of administering stress on fear extinction and recall in laboratory settings as quantified by physiological, subjective, neural, and fear-potentiated startle response measures. *COND* fear conditioning, *EXT* fear extinction, *24 h* delay of 24 h, ↑ enhanced effect, ↓ hindered effect, ↑↓ mixed results, Ø null effect, - no studies available

all studies showed a long-lasting effect of stress on exposure therapy as seen by lower fear levels at the last session and follow-ups (2-week and 1-month). With this, as the effect of stress remained at the follow-up session (where no drugs were administrated), it seems that modulation of the stress systems not only acts by blocking fear memory retrieval during therapy but most likely facilitates the consolidation of the safety-memory trace formed during exposure-based therapy (Soravia et al. 2006; Powers et al. 2009).

Collectively, these results converge to suggest an enhancing role of synthetic stress hormones (that act on either the SAM or HPA axes) in exposure-based therapy in phobic individuals. Importantly, one of these studies showed that endogenous cortisol released during exposure therapy by participants in the placebo group negatively correlated with fear ratings, suggesting that even endogenous cortisol may contribute to reduced fear symptoms in individuals suffering from specific phobia (Soravia et al. 2006). Similarly, higher endogenous cortisol elevation during exposure therapy also led to greater symptom improvement, as measured by subjective ratings, in individuals suffering from agoraphobia or panic disorder (Meuret et al. 2015).

Most of these effects are based on self-reports. Although de Quervain et al. (2011) also found beneficial effects of cortisol administration on physiological fear levels, more studies are needed to confirm whether the positive effects of synthetic and endogenous stress hormones on self-reported fear translate to physiological fear levels.

4.2 In Populations with Post-Traumatic Stress Disorder (PTSD)

To the best of our knowledge, only two studies explored the combination of stress hormone administration with exposure-based therapy in PTSD patients. A case study in two veterans with PTSD showed that the veteran who received a combination of hydrocortisone and exposure therapy exhibited a greater and faster decline in PTSD symptoms compared to the veteran who was given a placebo (Yehuda et al. 2010). Due to their intriguing findings, the research group conducted the same experiment in 24 veterans with PTSD. Half of the sample received hydrocortisone before exposure therapy, whereas the other half was given a placebo. As they were able to replicate the findings of their original study, hydrocortisone may enhance retention during exposure-based therapy and in consequence lead to a greater reduction in PTSD symptoms (Yehuda et al. 2015).

In addition, another study showed that higher endogenous cortisol levels may be an important biomarker for treatment responsiveness in populations with PTSD (van Gelderen et al. 2020). Here, salivary cortisol levels were measured before and after each therapy session, as well as in the afternoon following each session. Results showed that responders to treatment had higher pre- and post-session salivary

cortisol levels relative to non-responders, which predicted greater improvements in PTSD symptoms. As cortisol levels in the hours following the treatment session did not differ between the responders and non-responders, the authors suggested that the beneficial effects of cortisol on exposure-based therapy are not attributable to higher basal cortisol levels, but rather to a higher anticipatory response before the therapy session (van Gelderen et al. 2020). Thus, endogenous cortisol responses to the therapy may have beneficial treatment outcomes.

In sum, the literature reviewed in this chapter suggests that fear extinction processes can be influenced by both exogenous and endogenous stress hormone modulation. The direction of the effects depends on various methodological factors. Overall, conclusions resulting from studies using laboratory-based protocols are mixed. However, stress hormone administration and endogenous stress hormone levels both seem to facilitate exposure-based therapy in clinical populations (for a review, see McGuire et al. 2014). This highlights the need for further well-controlled experimental studies to identify the mechanisms that promote such an effect.

As with stress, exercise can have an impact on numerous physiological and biological systems in humans (Cotman and Berchtold 2002; Nowakowski Sims 2015; for a review, see Tanner et al. 2018). Thus, it is relevant to explore the modulatory effects of exercise on fear extinction in both experimental and clinical settings.

5 The Influence of Physical Exercise

Exercise is known to improve physical health, sleep, mood, energy levels, and emotions, among others (Nowakowski Sims 2015). Exercise may also prevent, promote, and maintain good mental health (Saxena et al. 2005) and lead to various immediate physical changes including faster heart rate and respiration. Moreover, it has been shown that exercise can alter neurochemical processes, such as modulation of brain-derived neurotrophic factor (BDNF) levels (Cotman and Berchtold 2002) and anandamide (AEA; Crombie et al. 2018, 2019). On the one hand, BDNF is essential for the development and differentiation of neurons in several brain regions (for a review, see Notaras and van den Buuse 2020) that form the fear circuitry, including the hippocampus (Cotman and Berchtold 2002; Greenwood et al. 2009; Neeper et al. 1995), amygdala (Greenwood et al. 2009), and prefrontal cortex (Aksu et al. 2012; for a review, see Notaras and van den Buuse 2020). In addition, BDNF plays a role in adaptive plasticity, where the latter is important for learning, memory, and fear processes (for a review, see Notaras and van den Buuse 2020). Interestingly, animal studies have also reported that a lower natural BDNF concentration was associated with greater difficulty in extinguishing fear, whereas an increase in BDNF concentration appeared to prevent extinction failure (Peters et al. 2010). On the other hand, AEA is one of the important endocannabinoid (eCB) system biomarkers (Katona and Freund 2012) that modulate fear and extinction processes. This biomarker acts on the amygdala, hippocampus, and frontal cortex, among others

(Katona and Freund 2012; Lafenêtre et al. 2007; Lutz et al. 2015). Again, these three brain regions are highly important in fear extinction mechanisms (for a review, see Shin and Liberzon 2010). Therefore, given that exercise modulates biomarkers that are involved in both neural plasticity and fear-related circuitry, researchers have investigated the impact of exercise on fear extinction.

5.1 Impact of Exercise on Fear Extinction

The few human studies that have investigated this topic were initiated following results obtained from animal research. In general, animal studies have reported that aerobic exercise (e.g., running or walking) may enhance fear extinction when exercise is done after fear extinction learning, but not before (Jacquart et al. 2017; Roquet and Monfils 2018). The human literature has built on these findings to assess the impact of exercise on fear extinction.

In an experimental study, Keyan and Bryant (2019) exposed healthy young adults to a fear conditioning protocol and thereafter, randomly assigned them to either an exercise or control condition immediately after the fear extinction phase. Results showed that participants in the exercise group exhibited lower FPS to the CS+ than the control group during extinction recall, suggesting an enhancing effect of exercise on fear extinction processes. These effects may be due to the modulation of BDNF levels, although the latter was not quantified in this study. However, it is well-documented that the influence of BDNF could be modulated by genetic factors, such as the Val66Met polymorphism (Egan et al. 2003). For this reason, the authors tested whether the effect of exercise on fear extinction memory was moderated by this polymorphism. Although fear recovery and exercise condition were not associated with the Val homozygote carriers, the Met allele carriers showed greater fear recovery 24 h after fear extinction learning in the exercise group. The authors suggest that these individuals may have experienced higher exercise-induced stress without the beneficial effects of BDNF, therefore compromising fear extinction (Keyan and Bryant 2019). Due to the limited number of studies exploring this question, this remains speculative and requires further experimental studies to test this hypothesis.

Further, Crombie et al. (2021a, b) explored the impact of exercise on fear extinction in samples of women with PTSD. In their study, they sought to establish the nature of the influence of exercise on fear extinction (Crombie et al. 2021b) and better understand the underlying mechanisms (Crombie et al. 2021a). Although this study was conducted in a clinical sample, the researchers used a laboratory protocol in which the feared stimulus was unrelated to the participants' PTSD (Crombie et al. 2021a, b). Participants were randomly assigned to either the exercise or control condition immediately after the extinction learning phase (which occurred 24 h after conditioning). To assess AEA and BDNF concentrations, a subset of the participants provided blood samples before and after the exercise/control condition (Crombie et al. 2021a).

First, compared to the control group, the exercise group reported less threat expectancy to both CS+ and CS− after reinstatement. As no effect of exercise was identified during the initial fear recall test, researchers proposed that the potentiating effect of exercise on fear extinction consolidation may only be observed when later confronted with the feared stimulus. As such, greater extinction consolidation would protect the individual from fear reinstatement (Crombie et al. 2021b). Second, compared to the control condition, the exercise group showed a statistical trend toward increased AEA concentrations after the exercise protocol (Crombie et al. 2021a). Moreover, a trend revealed that the increases in AEA were negatively associated with lower threat expectancy after reinstatement. Compared to controls, participants in the exercise condition also showed the same negative association between BDNF concentrations and threat expectancy after reinstatement. Therefore, exercise may improve the consolidation of fear extinction learning in women with PTSD, where this effect seems to be mediated by AEA and BDNF concentrations (Crombie et al. 2021a).

6 Impact of Physical Exercise in Clinical Samples

As they rely on fear extinction mechanisms, a few studies have begun to explore the impact of exercise on exposure therapies that are commonly used in the treatment of PTSD and anxiety disorders (Jacquart et al. 2017; McInerney et al. 2021; Powers et al. 2015).

Powers et al. (2015) conducted the first pilot study in individuals diagnosed with PTSD to investigate the effect of BDNF concentrations on the influence of exercise on exposure therapy. While participants in the exercise condition exhibited higher BDNF concentrations and fewer PTSD symptoms at the end of the last session than participants in the control condition (Powers et al. 2015), two similar studies using virtual reality exposure therapy with participants with acrophobia did not observe an effect of exercise on therapy outcomes (Jacquart et al. 2017; McInerney et al. 2021). First, one noted that their divergent results could be explained by the nature of the participants' diagnoses in each study (PTSD vs. acrophobia) and the small sample used in the pilot study (Jacquart et al. 2017). Second, though only the participants in the exercise condition demonstrated a high heart rate during therapy, both groups demonstrated considerable fear reduction following exposure therapy, with no added value of exercise in the study conducted by McInerney et al. (2021). From this, the authors inferred that virtual reality exposure therapy alone may be sufficient to treat height phobias and that increased physical arousal through exercise appeared to have no additional effect.

In summary, this chapter aimed to explore the influence of stress and exercise on fear extinction. First, we highlighted the mixed nature of the literature regarding the effect of stress on fear extinction in experimental settings, where stress can reduce, enhance, or have no effect on fear extinction learning and recall. One major consideration for future studies pertains to the timing at which the modulation of

the stress systems occurs with regard to the various phases of the protocol (i.e., conditioning, extinction). The limited number of studies targeting this question, individual differences in stress responses, different methods, diverse study populations, and small sample sizes may also account for some of these diverging results in the studies conducted thus far. Therefore, further studies are required to better understand how stress mechanisms impact extinction learning, consolidation, and retention. However, the studies performed in clinical populations tend to suggest a beneficial impact of stress hormone administration, and to some degree endogenous stress hormone levels, on exposure therapy assessed principally by subjective measures. More studies using physiological fear responses and neuroimaging techniques are still needed. Second, human studies investigating the impact of exercise on fear extinction (or exposure therapies) remain scarce. Though, overall results indicate an effect of exercise on enhancing fear extinction consolidation. These positive results were obtained in both experimental and clinical settings. In light of the limitations reported in the literature, future research is required to better understand the mechanisms underlying the impact of exercise on fear extinction. Important considerations for future studies include recruiting larger samples, targeting varying populations, examining genetic predispositions, considering the timing of exercise, measuring physiological fear responses, and using neuroimaging techniques. Overall, the modest literature suggests beneficial effects of both exercise and stress hormone modulation on exposure-based therapy in clinical populations. More fundamental and translational research is however necessary to tackle the mechanisms by which these effects occur and maximize its utility in clinical settings.

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