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# Aerobic exercise in the treatment of PTSD: an examination of preclinical and clinical laboratory findings, potential mechanisms, clinical implications, and future directions

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## Abstract

Posttraumatic stress disorder (PTSD) is associated with heightened emotional responding, avoidance of trauma related stimuli, and physical health concerns (e.g., metabolic syndrome, type 2 diabetes, cardiovascular disease). Existing treatments such as exposure-based therapies (e.g., prolonged exposure) aim to reduce anxiety symptoms triggered by trauma reminders, and are hypothesized to work via mechanisms of extinction learning. However, these conventional gold standard psychotherapies do not address physical health concerns frequently presented in PTSD. In addition to widely documented physical and mental health benefits of exercise, emerging preclinical and clinical evidence supports the hypothesis that precisely timed administration of aerobic exercise can enhance the consolidation and subsequent recall of fear extinction learning. These findings suggest that aerobic exercise may be a promising adjunctive strategy for simultaneously improving physical health while enhancing the effects of exposure therapies, which is desirable given the suboptimal efficacy and remission rates. Accordingly, this review: 1) encompasses an overview of preclinical and clinical exercise and fear conditioning studies which form the basis for this claim, 2) discusses several plausible mechanisms for enhanced consolidation of fear extinction memories following exercise, and 3) provides suggestions for

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future research that could advance the understanding of the potential importance of incorporating exercise into the treatment of PTSD.

**Keywords**

fear extinction; exposure therapy; behavioral tagging; pattern separation; endocannabinoid system; brain derived neurotrophic factor

## Introduction

Regular engagement in physical activity (including aerobic exercise activities such as walking or jogging) is associated with substantial physical and mental health benefits, including reductions in: all-cause mortality (Arem et al., 2015; Saint-Maurice et al., 2019; Wang et al., 2021), cancer-related mortality (Li et al., 2016), metabolic syndrome (i.e., co-occurrence of cardiovascular disease and type 2 diabetes risk factors such as insulin resistance, obesity, dyslipidemia, hypertension), cardiovascular-related events, mortality, and disease development (e.g., coronary heart disease, type 2 diabetes)(Wahid et al., 2016), and the onset of dementia and Alzheimer's disease (Laurin et al., 2001; Scarmeas et al., 2009), anxiety (Firth et al., 2020; Schuch et al., 2019), depression (Firth et al., 2020; McDowell et al., 2018), and posttraumatic stress disorder (PTSD)(Firth et al., 2020; Schuch et al., 2019). Unfortunately, approximately 80% of Americans are insufficiently active – that is to say, they fail to meet the *U.S. Department of Health and Human Services Physical Activity Guidelines for Americans*, which recommends engaging in the equivalent of at least 150 minutes of moderate-intensity physical activity (e.g., walking at a brisk pace or jogging) per week, in addition to engaging in muscle-strengthening activities (involving all major muscle groups) of at least moderate-intensity on 2 or more days per week (Piercy et al., 2018). This level of inactivity is common among individuals with PTSD (Vancampfort et al., 2016), who in addition to experiencing PTSD-specific symptoms and other comorbid mental health concerns (e.g., substance use disorder, anxiety, depression, poor sleep quality)(Brown et al., 2001; Gould et al., 2021; Kessler et al., 2005; Pietrzak et al., 2011), have approximately 2–3x the risk of developing metabolic syndrome or cardiovascular disease risk factors (Bartoli et al., 2015; Kibler et al., 2009; Rosenbaum et al., 2015), type 2 diabetes (Roberts et al., 2015; Vancampfort et al., 2017), cardiovascular disease (Ebrahimi et al., 2021; O'Donnell et al., 2021; Vancampfort et al., 2016), and all-cause mortality (Roberts et al., 2020; Xue et al., 2012) compared to those without PTSD.

Given these increased risk and high prevalence rates for physical health problems in PTSD (38.7%, 10%, and 6.8% for metabolic syndrome, T2D, and CVD, respectively) (Rosenbaum et al., 2015; Vancampfort et al., 2017, 2016) and considerable physical benefits of physical activity (i.e., any bodily movement that results in muscle contraction and substantial increases in energy expenditure) and exercise (i.e., any type of physical activity that involves planned, structured, repetitive bodily movement done to maintain or improve one or more component of physical fitness), it is not controversial to suggest that it would be beneficial for health care providers, including psychologists, social workers, counselors, and psychiatrists, to adequately prescribe regular participation in physical activity (e.g.,

aerobic exercise) for at-risk patients with PTSD. In addition to aerobic exercise serving as an important component for improving physical health outcomes among those with PTSD, emerging evidence from preclinical and clinical fear conditioning and extinction studies (Bouchet et al., 2017; Crombie et al., 2021b; Jacquart et al., 2017; Keyan and Bryant, 2019; Mika et al., 2015; Moya et al., 2020; Roquet and Monfils, 2018; Siette et al., 2014; Tanner et al., 2018) suggests that there is potential for administering aerobic exercise in conjunction with certain types of individual therapy sessions (i.e., exposure-based sessions) for PTSD. More specifically, precisely timed bouts of aerobic exercise around the time of a psychotherapy treatment session (e.g., exercise after psychotherapy sessions) could improve treatment outcomes, while simultaneously improving physical health (see Figure 1).

Given the increased interest in this domain, a major impetus for this review was to not only summarize the findings and discuss potential mechanisms, but also to discuss some of the limitations of prior work (e.g., failure to assess or report data on exercise stimulus parameters) that need to be addressed in future research to propel the field forward. In line with this, we utilize a narrative review approach in order to afford a more specific focus on particularly noteworthy studies that highlight major findings, key methodological strengths, and/or key methodological considerations that need to be addressed in future research. Accordingly, this review will 1) encompass an overview of the findings from preclinical and clinical exercise and fear conditioning and extinction studies which form the scientific rationale for this claim; 2) discuss potential mechanisms responsible for enhanced memory consolidation of fear extinction memories following exercise, and 3) provide suggestions for future research that could advance the understanding of the potential importance of incorporating exercise into the treatment of PTSD.

## Fear Extinction as a Laboratory Model of Exposure-Based Therapies

Exposure-based therapies, such as Prolonged exposure (PE) are among the most commonly administered and best supported psychotherapeutic treatment options for PTSD. Although the efficacy of these treatments has been demonstrated in multiple randomized controlled trials, there is room for improvement because remission rates range from ~53–60% (Resick et al., 2002; Schnurr et al., 2007; Vervliet et al., 2013). Exposure-based therapies are based on a fear extinction model whereby the trauma cue is conceptualized as a conditioned stimulus (CS+) that triggers anxiety responses (conditioned responses) due to its association with the traumatic event (the unconditioned stimulus). Repeated exposure to the trauma cue (CS+) in a safe context is theorized to weaken the predictive threat value of the trauma cue and thereby weaken its ability to elicit distress (conditioned response)(Cisler et al., 2014; Craske et al., 2008; Crombie et al., 2021a). In other words, exposure-based therapies aim to reduce anxiety symptoms toward trauma reminders by enabling therapeutic safety learning. Given that fear extinction learning is regarded as a core principle underlying exposure therapy, fear conditioning paradigms are widely used as a laboratory model of exposure therapy in both animal models and clinical research. Importantly, recent research supports this theoretical conceptualization as the degree of safety learning during laboratory fear extinction tasks (e.g., those with stronger prediction error-related signaling in ventromedial prefrontal cortex [vmPFC] during extinction learning) predicts the magnitude of symptom

reduction during exposure therapy among individuals with a specific phobia (Lange et al., 2020).

Fortunately, fear conditioning and extinction paradigms are well established (Vervliet and Boddez, 2020), which has allowed researchers to examine the effect of various experimental manipulations (i.e., potential treatment approaches) on relevant cognitive processes and treatment targets (e.g., memory consolidation and extinction recall); see (Lonsdorf et al., 2017) for comprehensive overview of fear conditioning paradigms and procedures and Figure 2 for a general overview of an experimental design. In other words, manipulations that enhance extinction processes in the laboratory setting, may prove to be promising candidates for improving exposure-based treatments. Initially, experimental pharmacological manipulations (e.g., D-cycloserine, methylene blue, yohimbine) were examined as adjuncts to enhance extinction learning and/or exposure-therapy (see Ebrahimi et al., 2020; Inslicht et al., 2021; Smits et al., 2014, 2013; Zoellner et al., 2017 for comprehensive overviews). While there are certainly a number of viable pharmacological manipulations that target specific neurochemical pathways, there are limitations to these approaches. First, though a strength of a pharmacological manipulation can be relatively clean probe of a relatively specific neural system, this is also a potential limitation as there is an abundance of evidence demonstrating that multiple neural systems mediate fear extinction learning, consolidation, and recall. Second, these pharmacological manipulations do not necessarily address the significant physical health problems associated with PTSD reviewed above. Third, prescribing pharmacological interventions as an augmentation strategy of psychotherapy can present implementation challenges, as many providers cannot prescribe medications and some patients prefer care that does not involve medications (McHugh et al., 2013). As such, a behavioral approach that can engage multiple neural systems involved in extinction at once and also concurrently address physical health concerns, such as aerobic exercise, has significant potential both experimentally and clinically (see Figure 1).

## Overview of Preclinical and Clinical Aerobic Exercise and Fear Extinction Findings

The majority of investigations examining the effects of exercise on fear extinction have focused on acute bouts of aerobic exercise, which is the focus of this section given the translational potential for administering acute bouts of aerobic exercise in conjunction with therapy sessions (see (Tanner et al., 2018) for a comprehensive discussion of the effects of chronic exercise and extinction outcomes). One of the earliest preclinical investigations found that 3 hours of access to a running wheel immediately prior to or following cued fear extinction learning resulted in improved fear extinction recall (i.e., reduced freezing behavior) during an extinction memory recall test 24 hrs later in comparison to rats that either were not provided with running wheel access or were not given access until 6 hours following extinction training (Siette et al., 2014). Additionally, another group found that rats that exercised using a freely mobile running wheel during cued fear extinction training (but not before) demonstrated reduced fear during an extinction recall test administered one week after the fear extinction training session was paired with exercise (Mika et al., 2015).This finding was supported by an investigation that found that acute bouts of voluntary wheel running administered after contextual fear extinction training and again after a proximal memory test (24hrs later; i.e., an additional extinction training session), resulted in enhanced

extinction recall when tested during a distal extinction memory test (10 days later)(Bouchet et al., 2017). Additionally, several null findings (Jacquart et al., 2017; Tanner et al., 2018) suggest important methodological parameters required for exercise-induced enhancement of extinction learning and recall. Indeed, a meta-analysis of the preclinical literature was able to statistically demonstrate that timing of exercise (i.e., whether delivered before, during, or after extinction) was a statistically significant methodological moderator of enhanced extinction (Roquet and Monfils, 2018). These preclinical investigations highlighted the importance of timing of acute exercise bouts relative to fear extinction training and suggest that aerobic exercise does not likely influence the acquisition of fear extinction learning but can limit the return of fear (i.e., enhance memory consolidation and extinction recall, reduced renewal) if administered either during or after extinction learning (Roquet and Monfils, 2018; Tanner et al., 2018).

Recent investigations in humans have begun to expand upon and translate the aforementioned preclinical findings (see Table 1). The first human trial examined a non-clinical sample of adults that exercised on a cycle ergometer for 20 minutes following extinction training, which resulted in significantly lower fear responding (fear-potentiated startle) to the CS+ (but not the CS-) when tested 24 hours later compared to a light-intensity exercise control condition (Keyan and Bryant, 2019). However, this study involved a 2-day design in which fear conditioning and extinction occurred on the same day, with extinction recall occurring 24hrs later. Given that extinction training occurred shortly after conditioning in this study, it is difficult to determine if exercise enhanced extinction or if the consolidation of conditioning was blocked (see Avenues for Future Research section for discussion on 2-day vs 3-day study designs). More recently, our group expanded upon these findings and implemented a three-day fear acquisition, extinction, and extinction recall protocol to examine whether moderate-intensity aerobic exercise (30 minutes at 70–75% age-adjusted maximum heart rate) administered after an extinction learning task improved the consolidation of fear extinction learning (i.e., enhanced extinction recall) compared to a light-intensity aerobic exercise control condition in a clinical population of women with interpersonal violence (i.e., physical and or sexual assault) related PTSD. There were no differences in fear responding between groups during the initial extinction recall test; however, participants from the moderate-intensity exercise group exhibited significantly reduced threat expectancy ratings following a fear reinstatement procedure (i.e., single presentation of the unconditioned stimulus) relative to the initial extinction recall test and to those in the light-intensity group (Crombie et al., 2021b). These results suggest that the beneficial effect of exercise may be subtle and unobservable until an individual experiences an external reinstatement event, during which stronger consolidation of the extinction memory protects against return of the original fear memory (Crombie et al., 2021b).

Collectively, the preclinical and clinical aerobic exercise and fear extinction investigations suggest that exercise enhances the consolidation of newly formed extinction memories and reduces the return of fear, particularly when administered during or after fear extinction training (although more research specifically examining timing effects is warranted in human studies). These findings may present significant implications for improving the efficacy of exposure-based treatments for anxiety- and trauma-related disorders such as PTSD (see Figure 1).

## Overview of Aerobic Exercise and Exposure Therapy Findings

There have been several initial attempts to translate the lab-based fear extinction findings to the clinical setting by examining the effects of exercise on exposure therapy or therapy analogue outcomes (see Table 1). Most studies have reported non-significant differences between exercise with exposure and control conditions or findings have been difficult to interpret. Mixed and null findings are likely due to testing unrepresentative samples and methodological inconsistencies and experimental designs that are inconsistent with effective preclinical parameters outlined above; namely, most studies have administered exercise before exposure.

Despite clear trends in the pre-clinical data, only three studies have examined the effects of aerobic exercise *after* exposure (Bryant et al., 2023; Voorendonk et al., 2021; Weisman and Rodebaugh, 2020). Voorendonk et al. reported a significant reduction in trauma-related distress and vividness ratings (but not freezing or emotional regulation ratings) for individuals that exercised after a single PE session in comparison to individuals that exercised before a single PE session (Voorendonk et al., 2021). The decision to have participants engage in exercise at different time-points in conjunction with the PE sessions (prior to and following) is a strength. Unfortunately, there are several limitations that dampen enthusiasm. For instance, the exercise stimulus consisted of light to moderate-intensity walking outdoors in a forest in a group setting involving 8–10 participants. It is not clear the degree to which the group setting alters the basic processes of exposure therapy. Additionally, this study did not collect data on exercise intensity (e.g., heart-rate, ratings of perceived exertion), and instead simply reported that participants walked approximately 3km in 60-minutes.

In another study, a sample of non-clinical undergraduates who reported high levels of anxiety related to public speaking were randomized to either 30-minutes of aerobic exercise or quiet rest immediately following a brief speech exposure trial and then completed memory and speech anxiety testing on week later (Weisman and Rodebaugh, 2020). Contrary to the investigator's hypotheses, no significant group differences in memory or speech anxiety were detected. Participants were instructed to exercise between 40–60% of their heart rate reserve, but no heart rate data was provided. However, the authors did report a mean (but no standard deviation) perceived exertion rating (RPE) for participants, and indicated that those that reported higher RPE ratings reported greater increases in anxiety scores during the second speech. Given this finding, the inclusion of additional data pertaining to the exercise parameters would have been beneficial. It is also important to note that the exposure used in this study was so brief that it may not have actually functioned as a clinical exposure session.

Bryant et al. conducted the most recent study to test the effects of aerobic exercise after individual exposure therapy sessions (Bryant et al., 2023). In this single-blind, parallel randomized controlled trial, Australian adult men and women (N=130) with a clinical diagnosis of PTSD were randomized to either receive nine, 90-min individual exposure therapy sessions followed by either aerobic exercise (approximately 10-min warm up to reach target heart rate followed by 10-min of aerobic exercise at 65–85% MHR) or passive stretching (20-minutes of slow and non-strenuous stretching of limbs). Results revealed that

exposure therapy plus aerobic exercise group exhibited a significant reduction in PTSD symptom severity (past week CAPS scores) at the 6-month follow-up compared to the exposure therapy plus passive stretching group. Additionally, the exposure therapy plus aerobic exercise group exhibited a small effect size improvement (albeit non-significant) in PTSD symptom severity (past week CAPS scores) at 1-week following the intervention compared to the exposure therapy plus passive stretching group.

The strengths of this study include a large sample size of men and women with a clinical assessment of PTSD. Although these results appear promising, there are several limitations (i.e., lack of sufficient reporting surrounding exercise stimulus parameters) that dampen enthusiasm. First, few details pertaining to the exercise stimulus administered as part of the intervention were reported. The authors described that participants were instructed to run on a 15-cm high stepper exercise platform until they reached their target heart-rate (65–85% MHR) at which point they were to continue maintaining that intensity for 10-minutes. The authors note this entire process took approximately 20 minutes. However, the authors did not report data regarding the exercise stimulus (e.g., means and standard deviations of exercising heart rate throughout exercise bout and time to reach target heart rate). This is problematic as it is likely that participants received different exercise stimuluses (e.g., one participant could have gotten to target heart rate in 5 minutes, while one participant may have been exercising close to the target range [e.g., 60% MHR] for 10-minutes prior to reaching target heart rate) and may have exercised at vastly different exercise intensities (e.g., one participant may have exercised at 65% MHR, while another exercised at 85% MHR). Additionally, there appears to be some equivocal reporting regarding the calculation of target heart rate. Additionally, it is interesting to note that the exposure therapy plus passive stretching group actually had a similar (slightly higher) reported target heart rate (110.00 ± 22.10 beats per minute) compared to the exposure therapy plus exercise group (104.60 ± 23.30 beats per minute). The manuscript states that exertion was assessed in the passive stretching group (unreported), although it is unclear if there was a prescribed intensity for the actual stretching component (Bryant et al., 2023). The authors should be credited with measuring self-reported past-week physical activity levels at the follow-up time points. However, a stronger approach (although undoubtedly more difficult) would have been to measure physical activity levels via activity monitors at more regular intervals throughout the follow-up time period (i.e., a more objective approach), which would have allowed the authors to determine if participants from the exercise group started exercising more (and when) after the intervention, possibly due to experiencing some sort of benefit during the intervention period. Overall, the inclusion of the aforementioned data would have been beneficial for improving our understanding of the effects of administering aerobic exercise after individual exposure therapy sessions. While this study is an important contribution to the literature and suggests the clinical viability of using exercise to enhance exposure therapy outcomes, the limitations we mention here preclude strong inferences regarding whether or how exercise enhances these outcomes.

Four studies have examined the effects of exercise before exposure, none of which reported statistically significant group differences between exercise before exposure and control condition(s). Powers et al. conducted the first investigation in this area (Powers et al., 2015). They randomized nine individuals to a treatment-as-usual group that received only

individual PE for 12 weeks or acute 30-minute bouts of moderate-intensity aerobic exercise prior to PE sessions. Although this study was too small to conduct inferential statistics, participants from both groups reported reductions in PTSD symptoms from pre- to post-intervention. Specifically, mean PTSD symptom scores on the PTSD Symptom Scale were decreased from 37.00 to 8.25 in the PE only group, and 42.00 to 5.20 in the aerobic exercise prior to PE group. This investigation was arguably the most translatable investigation conducted to date as they administered exercise sessions in conjunction with each therapy session and tested a PTSD population in which psychotherapy regularly includes exposure therapy. Future investigations are needed to replicate these findings in a larger sample. Further, based on our understanding of the effects of exercise on fear extinction memory and relapse detailed above, it will be important to compare the effects of aerobic exercise administered before or after exposure therapy sessions.

A recent study among active duty service members (primarily male, noncommissioned Army officers) with PTSD symptoms found that although aerobic exercise in conjunction with five imaginal exposure therapy sessions over 8 weeks decreased PTSD symptom severity (from pre- to post-intervention), there were no significant differences compared to an exercise alone condition, an imaginal exposure alone condition, and a no-treatment control condition (Young-McCaughan et al., 2022). Similar to Voorendonk et al., this study did not report on exercise intensity data (e.g., heart rate, ratings of perceived exertion), and instead simply reported that participants were instructed to engage in preferred aerobic exercise activity for 20–25 minutes at > 60% of their heart rate reserve, while listening to their imaginal exposure audio recordings. The lack of reporting is unfortunate as 1) participants were required to keep HR logs and 2) it is plausible that participants engaged in different intensities of exercise (which could differentially influence engagement of neurobiological targets) given that the authors reported that any difficulties exercising or exercising at the prescribed intensity were problem-solved with an exercise specialist.

Two studies failed to detect statistically significant differences between moderate- to high-intensity aerobic exercise and light-intensity aerobic exercise or control conditions administered before exposure-based therapy/therapy analogues (Bischoff et al., 2018; Jacquart et al., 2017). Bischoff et al. administered 30-minutes of moderate-intensity (70% $VO_{2max}$) or light-intensity (30% $V0_{2max}$) treadmill exercise prior to five exposure sessions within a standardized seven-week exposure-based cognitive behavioral therapy program for adults diagnosed with panic disorder or agoraphobia. Results revealed that both groups reported significant improvements in their primary outcomes of anxiety severity, with a trend for the moderate-intensity group to experience a greater reduction (i.e., Hamilton Anxiety Rating Scale mean reduction of 11.4 vs 8.0 for the moderate – and light-intensity groups, respectively) (Bischoff et al., 2018). Jacquart et al. reported that although a 30-minute bout of high-intensity aerobic exercise (80% maximum heart rate) prior to a single-session virtual reality exposure therapy protocol resulted in large effect size reductions in participant's self-reported fear of heights (at 1- and 2-weeks following exposure), there was no significant difference in comparison to a quiet-rest condition (Jacquart et al., 2017).

Collectively, these investigations highlight that greater methodological consideration surrounding the experimental design as well as exercise prescription parameters is needed to

translate the promising exercise and fear extinction findings and further our understanding of the potential for aerobic exercise to enhance the efficacy of exposure therapies. Unfortunately, the absence of data on exercise parameters (e.g., exercise intensity), in addition to not collecting blood to assess candidate biomarkers renders it difficult to extend our understanding and determine if the exercise stimuli administered were able to elicit engagement of several neuromodulatory systems and targets thought to be involved in exercise-induced enhancement of several cognitive effects (e.g., extinction learning). Although the Powers et al. (Powers et al., 2015) study collected peripheral blood samples to measure brain derived neurotrophic factor (BDNF), the decision to collect at baseline (prior to first exercise session) and following the last exercise session at the end of the intervention complicates the interpretation of the data. Accordingly, it is imperative for future studies to address the aforementioned limitations (and those discussed in the Avenues for Future Research section) and implement experimental designs that incorporate our knowledge of the specific exercise parameters (e.g., frequency, intensity, time, and type of exercise stimulus) reported to enhance extinction learning.

**Potential Mechanisms—**Although more research is warranted, particularly in translating the promising fear extinction findings to exposure therapy designs, an important simultaneous step is to also elucidate potential mechanisms responsible for exercise-induced enhancement of fear extinction learning. Understanding mechanisms is not only important for fundamental knowledge, it will also help researchers determine precisely how exercise exerts its effect, and shed light on individual differences to help characterize which individuals will benefit from exercise, and may pave the way for alterative interventions to target these mechanisms. Although not exclusive, the following section discusses a number of plausible mechanisms. However, it is important to note that acute bouts of aerobic exercise likely recruits numerous other systems/targets capable of enhancing fear extinction and reducing relapse that are not reviewed herein (e.g., central norepinephrine, irisin (Islam et al., 2021; Nicastro and Greenwood, 2016)).

## Exercise-induced Increases in Neurotransmitters, Neurotransmitter Modulators, and Engagement of Pathways that Boost Extinction Consolidation

It is plausible that exercise-induced increases in several neurotransmitters, neurotransmitter modulators, and peptides (i.e., transient neurochemical events) may exert an influence on the molecular processes in key neural pathways underlying enhanced consolidation of extinction learning. Four of the more widely implicated mechanisms include the endocannabinoid (eCB) system, dopaminergic signaling, BDNF, and the mammalian target of rapamycin (mTOR).

Emerging evidence suggests that the eCB system (particularly increases in N-arachidonoylethanolamine [Anandamide, AEA; a primary eCB] signaling) may be one pathway through which aerobic exercise enhances the consolidation of extinction learning. The eCB system primarily consists of receptors (cannabinoid type-1 [CB1R] and type-2 [CB2R]) endogenous ligands known as eCBs (AEA and 2-arachidonoylglycerol, 2-AG), and enzymes involved in the synthesis and degradation of eCBs, such as fatty acid amide hydrolase (FAAH; primary degrading enzyme of AEA)(Katona and Freund, 2012). Seminal

studies elucidating the role of the eCB system in fear extinction learning revealed that adequate extinction learning is dependent on eCB/CB1R signaling; administration of CB1R antagonists or genetic deletion of CB1Rs resulted in impaired extinction learning and increased anxiety-like behaviors (Marsicano et al., 2002). Relatedly, healthy adults with elevated AEA exhibit enhanced regulation of the amygdala by the vmPFC, which is in contrast to adults with PTSD who typically exhibit impaired extinction learning and altered fear extinction neurocircuitry such as amygdala hyperreactivity and vmPFC and hippocampal hyporeactivity. Recent attempts to increase AEA levels (e.g., via acute and chronic administration of FAAH inhibitors or CB1R agonists) has resulted in enhanced extinction learning and long-term consolidation of extinction memories in animal models and in humans without a clinical anxiety disorder, and led to greater vmPFC and hippocampus activation during extinction recall in healthy adults (Mayo et al., 2022, 2020a, 2020b; Morena et al., 2018, 2014; Rabinak et al., 2020, 2014, 2013). Therefore, exercise-induced enhancements of AEA-mediated signaling following extinction learning may correct neurocircuitry deficits critical for enhanced consolidation of extinction memories.

Given that the eCB system is a neuromodulatory system (i.e., regulates the release of other neurotransmitters upon binding of eCBs to CB1Rs), if the eCB system even partially explains the pro-cognitive effect of exercise on enhanced consolidation of extinction learning, it is fundamentally necessary for other signaling systems (e.g., dopaminergic system) to also play a role (Ney et al., 2022, 2021). For instance, rodent models have demonstrated that pharmacological administration of dopamine agonists (specifically those that target D1/D5 dopamine receptors) in conjunction with extinction learning results in decreased fear responding during extinction recall tests (Abraham et al., 2016; Haaker et al., 2013). Additionally, recent human studies reported enhanced consolidation of fear extinction memories following administration of a dopamine precursor (L-DOPA) in non-clinical (Haaker et al., 2013) and a clinical PTSD population (Cisler et al., 2020). Importantly, recent models based on animal research suggest that exercise produces a hyperdopaminergic state (Greenwood, 2019) that engages dopamine projections from the substantia nigra and ventral tegmental area to the striatum, which in turn has dense projections to other structures linked to fear extinction learning (e.g., basolateral amygdala, medial prefrontal cortex)(Mika et al., 2015; Tanner et al., 2018). Relatedly, stimulation of substantia nigra dopaminergic neurons, which are classically associated with regulation of locomotion, similarly mirror the effects of acute exercise on enhanced extinction recall and reduction in fear renewal (Bouchet et al., 2018).

Related work also demonstrates a critical role of BDNF signaling as a mechanism of enhanced extinction consolidation following aerobic exercise. BDNF is a neuropeptide that supports neuronal survival and growth and promotes synaptic plasticity (upon binding to its receptor [tyrosine receptor kinase B]), which highlights the relevance of BDNF to adequate memory consolidation, particularly extinction learning (Kaplan and Miller, 2000; Lu et al., 2008; Notaras and van den Buuse, 2020; Patapoutian and Reichardt, 2001). Moreover, causal manipulations that increase or decrease BDNF in the hippocampus and amygdala has been shown to either enhance or impair extinction learning, respectively (Chhatwal et al., 2006; Peters et al., 2010). Importantly, exercise is widely documented to increase circulating BDNF concentrations and central BDNF expression in the hippocampus and prefrontal

cortex (Baranowski et al., 2021; Kallies et al., 2019; Neeper et al., 1995; Rasmussen et al., 2009; Walsh and Tschakovsky, 2018; Wrann et al., 2013), which has direct relevance to the mechanisms of fear extinction learning. However, although there is evidence that BDNF can cross the blood-brain barrier (Pan et al., 1998), the relationship of circulating plasma concentrations of BDNF to BDNF activity in the central nervous system remains obscure in clinical populations.

Finally, the mammalian target of rapamycin (mTOR) has recently emerged as a potential contributing factor to enhanced consolidation of extinction learning following aerobic exercise (Moya et al., 2020). mTOR is a translation regulator and serine/threonine protein kinase involved in synaptic plasticity, cell motility, and cell proliferation, and is sensitive to many exercise signals such as monoamines, growth factors, and cellular metabolism (Hall, 2008). Generally speaking, mTOR regulates translation initiators (e.g., 4E-BP1 and S6 kinases) involved in neuronal plasticity, which indicates a role of mTOR in memory consolidation (Moya et al., 2020). Additionally, a link between mTOR and fear extinction learning has been documented in investigations with and without exercise manipulations. For instance, inhibition of mTOR in the medial prefrontal cortex prevented enhanced extinction memory consolidation observed following administration of ketamine in the absence of mTOR inhibition (Girgenti et al., 2017). Moya and colleagues (2020) were the first to use exercise as a non-pharmacological approach to examine the role of mTOR in fear extinction learning, and demonstrated that intracerebral-ventricular administration of rapamycin (an mTOR inhibitor) in rats prevented enhanced extinction memory consolidation regularly observed following aerobic exercise. Importantly, this study elegantly demonstrated that administration of the mTOR inhibitor did not influence voluntary exercise behavior or alter fear extinction behavior in rats not provided a running wheel (Moya et al., 2020).

## Behavioral Tagging Hypothesis

A description of long-term potentiation (LTP) and the synaptic tagging and capture process (Frey and Morris, 1997) is necessary prior to discussing the behavior tagging hypothesis. In humans, LTP is the primary cellular model of memory, and is a process that involves increased synaptic strength following repeated stimulation between neurons in regions involved in memory storage and retrieval. Initial encoding of a memory (i.e., early LTP) occurs independent of protein synthesis, which is in contrast to persistent long-term memory formation (i.e., late LTP) which requires gene transcription and is dependent on protein synthesis in the postsynaptic cell (mainly in the cell body). As such, the process of memory consolidation is thought to require the release of neuromodulatory factors in close temporal proximity to the initial encoding. Interestingly, seminal work also demonstrated that two processes (weak tetanic stimulation or repeated tetanization with protein-synthesis inhibitors) that typically do not result in protein-synthesis dependent long-term memory formation (i.e., late LTP), can achieve such a result if repeated tetanization is previously applied to another input to the same population of neurons (Frey and Morris, 1997). This finding formed the basis of the synaptic tag and capture hypothesis, which suggests that early LTP initiates the creation of a short-lasting protein-synthesis-independent “synaptic

tag" at the potentiated synapse which can then result in late LTP if the relevant proteins are "captured" by the tag (Frey and Morris, 1997).

The behavioral tagging hypothesis is an extension of the synaptic tagging and capture process, and suggests that synthesized proteins from a behavioral experience performed in close temporal proximity of a "weak" learning experience (for which a tag is set) can be captured resulting in late LTP (i.e., enhanced long-term memory formation). Support for the behavioral tagging phenomenon was initially based on pre-clinical findings of enhanced extinction learning following a mobility-based behavioral task (i.e., novel open-field exploration) administered immediately following the extinction learning task (de Carvalho Myskiw et al., 2014, 2013). As such, given that aerobic exercise increases plasticity related proteins (see section above), it is plausible that aerobic exercise administered shortly after extinction learning serves as a component of the "strong event" to enhance the consolidation of weak learning, due to increases in relevant proteins that get captured by the initial LTP tag at hippocampal synapses (engaged during extinction) involved in long-term memory formation (see Figure 3). In fact, recent research provides indirect support for this hypothesis because exercise-induced increases in both AEA and BDNF mediated the relationship between moderate-intensity aerobic exercise and enhanced extinction recall in adult women with PTSD (Crombie et al., 2021c).

## Episodic Memory/Pattern Separation

The human brain is constantly tasked with processing and interpreting various types of stimuli, and as a result, it is impossible to focus on every trivial detail. However, when a particularly salient emotional event occurs (e.g., trauma exposure), it is advantageous for humans to remember specific details surrounding the event, as retrieval of such information can be used to predict and navigate one's environment in the future. For instance, consider the unfortunately common experience of an individual who experiences a physical and/or sexual assault and later goes on to develop PTSD. Remembering specific details about the event (i.e., episodic memory) will ideally aid in distinguishing safety from threat in the future as one navigates their environment (under similar and dissimilar circumstances). Unfortunately, this process of differentiating among similar experiences in an effort to keep stored memories distinct from one another (i.e., pattern separation) is often easier said than done, which is why a considerable amount of time in exposure-based psychotherapy is devoted to forming new safety memories that "over-power" or inhibit the old trauma memories in order to help individuals distinguish safety from threat and limit avoidance behaviors.

Interestingly, initial evidence suggests that aerobic exercise is capable of improving pattern separation (Déry et al., 2013; Suwabe et al., 2018, 2017) and more broadly speaking, episodic memory (Marin Bosch et al., 2020; van Dongen et al., 2016). In rodents, exercise enhances discrimination between similar but distinct stimuli and contexts (Bolz et al., 2015; Creer et al., 2010; Greenwood et al., 2009; Islam et al., 2021; Wu et al., 2015). In humans, although stronger methodological designs with larger and more representative clinical populations are needed, both greater aerobic fitness and an acute bout of moderate-intensity aerobic exercise have been reported to enhance discrimination between highly

similar objects during mnemonic discrimination tasks (Déry et al., 2013; Suwabe et al., 2018, 2017). In addition to pattern separation, prior work has demonstrated that, compared to a no-exercise control group, 35-minutes of aerobic exercise (i.e., submaximal interval training involving 5 sets of 4 minutes of stationary cycling at 80% MHR followed by 3 minutes at a lower load allowing participants HR to decrease naturally) administered after encoding of a declarative memory task, resulted in greater retention of picture-location associations and increased hippocampal pattern similarity for correct responses when tested 48 hrs after the encoding plus exercise session (van Dongen et al., 2016).

It is plausible that aerobic exercise exerts an effect on pattern separation and episodic memory due to its influence on hippocampal functioning. For instance, considerable evidence purports the hippocampus (more specifically the dentate gyrus) as playing an important mediating role in pattern separation, and in encoding and storing episodic memory representations (Leal and Yassa, 2018). Additionally, regular participation in moderate-intensity aerobic exercise has been shown to increase hippocampal volume (Erickson et al., 2011) and induce vascular plasticity in the hippocampus (Maass et al., 2015). A recent study also demonstrated that improved aerobic fitness was positively related to improved performance on a complex spatial object recognition memory test – an effect that was modulated by hippocampal perfusion (Maass et al., 2015). Regular exercise also promotes neurogenesis (Cotman and Berchtold, 2002), which has been shown to contribute to enhanced pattern separation (Aimone et al., 2011; Creer et al., 2010; Sahay et al., 2011). Although the signals for enhancing cell proliferation and survival may be increased by an acute bout of aerobic exercise, given that the new neurons aren't immediately incorporated into the dentate gyrus granule cell layer, we argue that neurogenesis cannot explain the aforementioned acute exercise and extinction findings. As such, it may be the case that aerobic exercise promotes enhanced discrimination of similar but importantly different stimuli (e.g., CS+ in acquisition context vs extinction context) by improving dentate-gyrus mediated pattern separation. Such an effect may not only explain enhanced consolidation of newly formed extinction and safety memories reported in the aforementioned lab-based exercise studies, but could also explain how exercise paired with exposure therapy may promote the important distinction between similar but distinct safety and threat cues in the real-world.

## Avenues for Future Research

Although initial findings are promising, additional research is needed, especially in clinical anxiety populations for which understanding the potential of aerobic exercise to enhance extinction learning, and ultimately exposure therapy, is most relevant. Moving forward, we recommend that future investigations examining the efficacy of aerobic exercise to enhance extinction learning or augment exposure therapy 1) continue to systematically manipulate and evaluate the precise exercise parameters needed to influence relevant outcomes, 2) sufficiently report on the relevant parametric data from the administered exercise sessions, such as exercise duration, intensity (e.g., percent of maximum heart-rate or % of $VO_2$ max), and time of administration relative to safety learning (e.g., prior to or following extinction learning or exposure paradigm), and 3) collect blood samples before and after exercise manipulations to aid in determining the mediating role of candidate biomarkers and

to serve as a manipulation check allowing researchers to verify whether various different neuromodulatory targets were actually engaged during exercise. It is also important for future research to consider other relevant therapeutic mechanisms that exercise may engage beyond enhancing extinction learning. This could include, but is not limited to self-efficacy, distress tolerance, anxiety sensitivity, and engagement in therapy (Jacquart et al., 2019). Addressing these concerns would significantly advance the existing literature (especially among studies attempting to elucidate mechanisms) which often neglect to report on the parameters of the exercise sessions and simply extrapolate from prior investigations in purporting that various different neuromodulatory targets were engaged without actual data to support their claims. Relatedly, future trials should consider examining additional potentially relevant outcomes, including but not limited: participant's physical activity and exercise history, motivation for physical activity/exercise, and potential expectancy/placebo effects (Lindheimer et al., 2020). In the event that these (or other) outcomes prove to be important, clinicians will need to assess and address these outcomes in their clinical practice in order to successfully translate the lab-based findings into practice. Finally, it is important for future investigations to examine other modalities of exercise (e.g., resistance training), which have been understudied at this point. For instance, future studies could investigate the degree to which resistance training versus aerobic exercise engages candidate mechanisms (e.g., enhanced extinction learning, increased concentrations of BDNF, eCBs, etc.).

In addition, we recommend that future exercise and fear conditioning investigations incorporate the following methodological approaches, including: 1) the utilization of designs with fear conditioning, extinction, and recall occurring on separate days, 2) the use of generalized stimuli (ideally trauma-related) as conditioned stimuli, and 3) examining the effect of exercise on enhanced extinction learning and recall at intervals beyond 24–48 hours. Experimental fMRI designs that separate fear acquisition, extinction, and extinction recall phases across three separate days will allow researchers to more clearly define the impact of exercise on the consolidation of extinction learning, which is currently impossible with 2-day designs where acquisition and extinction phases alternate on the same day. Additionally, in contrast to lab-based fear extinction studies, exposure therapy rarely (if ever) uses the exact stimuli from an individual's actual learning history. The exclusion of such stimuli is due to the fact that reproducing the exact conditions is thought to be difficult or dangerous and contradictory to the goals of exposure therapy. Rather, exposure therapy for PTSD primarily focuses on stimuli that are perceptually or conceptually related to the individual's trauma history (i.e., generalization stimuli). Moreover, exposure therapy for PTSD aims to allow individuals to accurately distinguish between actual threatening and dangerous events (e.g., experiencing sexual assault), and situations, contexts and stimuli that may remind them of the actual dangerous event (e.g., being in a crowd, unfamiliar men, TV series or movies, etc.). In other words, the goal of exposure therapy for PTSD is not to reduce fear responding to the original traumatic event/stimuli (which might remain an actual threat), but rather to reduce fear responding to generalized stimuli that are non-dangerous or threatening (Dunsmoor et al., 2022). Although extinction to the original CS is the standard in laboratory protocols, exposure to GSs in the absence of an aversive outcome is a better analogue of clinical exposure therapy, and therefore should be incorporated in future trials, including those examining the role of exercise (see Figure 4). Finally, administering aerobic

exercise in conjunction with extinction learning and observing a significant effect in a laboratory setting when tested 24 hrs later is important advancement, but the field must also consider the importance of demonstrating an effect when tested several days to weeks later and in different contexts. After all, individuals with PTSD are continually tasked with distinguishing safety from threat as they navigate their environment. It is imperative that our experimental designs adequately reflect and model this notion.

## Conclusion

Collectively, this review highlighted preclinical and clinical evidence that supports the notion that precisely timed administration of aerobic exercise (i.e., evidence to date suggests administration of exercise during or after extinction training) enhances the consolidation of fear extinction learning, which improves its subsequent recall. Several plausible mechanisms (potentially synergistic in nature) for this pro-cognitive effect of exercise were discussed, along with potential future research avenues needed in order to propel the field forward. Ultimately, the goal of enhancing laboratory fear extinction (or exposure therapy analogues) is to inform methods to enhance exposure therapy used in the clinic. Accordingly, after sufficient data is gathered allowing the mechanisms to be fully elucidated, future research should then begin to translate the laboratory findings into the clinic by systematically examining aerobic exercise in conjunction with exposure-based therapies. If these eventual trials extend upon the promising results obtained from lab-based fear conditioning studies, aerobic exercise has the potential to be a safe, cost-effective, and readily accessible treatment component for improving physical health outcomes and enhancing the efficacy of exposure-based therapies.

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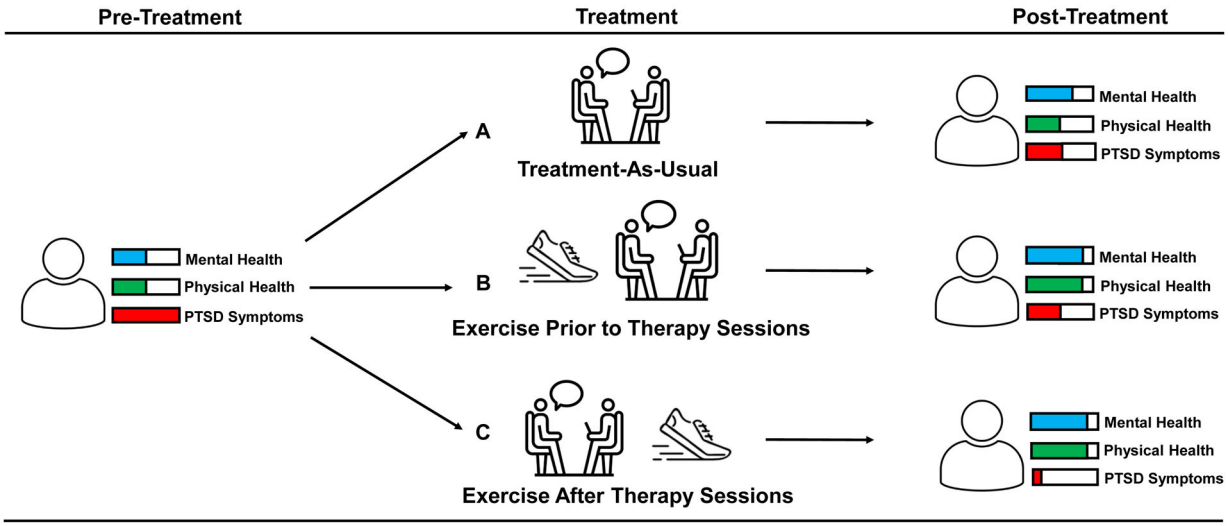


**Figure 1.**

Theoretical schematic of the influence of administering aerobic exercise in conjunction with individual exposure based therapy (e.g., prolonged exposure) sessions for adults with PTSD. Prior to treatment, the individual has suboptimal mental and physical health, with a high level of PTSD symptoms. In example A, the individual completes a conventional gold standard psychotherapy program (treatment-as-usual, TAU), which does not involve the administration of aerobic exercise in conjunction with the individual therapy sessions and does not address physical health concerns in any way. At post-treatment, this individual will see an improvement in overall mental health and a reduction in PTSD symptoms. In example B, the individual completes a conventional gold standard psychotherapy program and is administered aerobic exercise prior to each individual therapy session. At post-treatment, the individual will see an improvement in overall mental health (beyond the improvement seen with TAU) and physical health due to regular engagement in aerobic exercise throughout the treatment program. The individual will also see a similar reduction in PTSD symptoms as TAU, as the exercise may not have an effect on the consolidation of the learning that occurs during the individual therapy sessions (due to timing of exercise administration occurring prior to therapy sessions [i.e., pro-cognitive effects of exercise may not linger into consolidation window]). In example C, the individual completes a conventional gold standard psychotherapy program and is administered aerobic exercise following each individual therapy session. At post-treatment, the individual will see an improvement in overall mental health (beyond the improvement seen with TAU) and physical health due to regular engagement in aerobic exercise throughout the treatment program. The individual will also see the greatest reduction in PTSD symptoms (compared to TAU and exercise prior to TAU) due to timing of exercise administration (i.e., during consolidation window) which will promote enhanced consolidation of learning that just occurred during the individual therapy sessions. It is important to note that the hypothesized timing effects are based on the available evidence to date. Further human trials (examining effects of exercise on extinction learning and exposure therapy outcomes) should continue to examine timing effects. Additionally, it may be the case that exercise prior to therapy may be beneficial for

other therapies that are not primarily based on the principles of extinction learning (e.g., cognitive processing therapy).

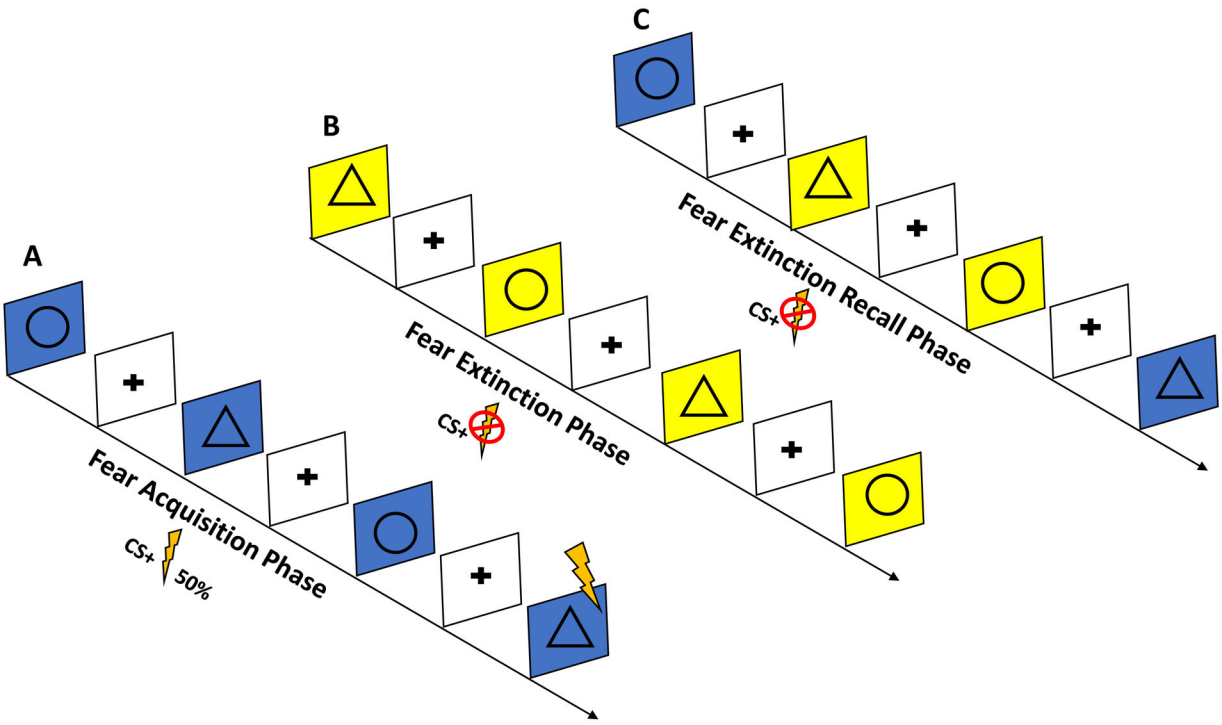


**Figure 2.**

Overview of a typical laboratory-based task assessing fear acquisition (A), extinction (B), and extinction recall (C). During the fear acquisition phase (A), participants are trained to associate the presentation of a specific stimulus (i.e., conditioned stimulus, CS+; depicted here as a triangle) with the occurrence (which varies but is often times a 50% reinforcement rate) of an aversive outcome (e.g., electric shock [as depicted]; burst of air). Conditioned stimuli (CS+ and CS-; depicted here as circles and triangles) during the day 1 fear acquisition task are typically provided against a colored background (depicted here as a blue background), which is referred to as the acquisition context. During the fear extinction phase (B), the CS+ and CS- are presented in a new context (depicted here as a yellow background) and aversive outcomes no longer follow presentation of the CS+, which ideally results in the participants learning that the CS+ is no longer threatening in the extinction context. During the fear extinction recall phase (C), the CS+ and CS- are presented (ideally in a pseudorandomized order) in both the fear acquisition and fear extinction contexts, in the absence of any aversive outcomes. During this phase, researchers will often conduct two runs, with the administration of an experimental procedure (e.g., single presentation of aversive outcome) in between runs in an effort or promote reinstatement. This fear extinction recall phase allows researchers to assess several outcomes including: spontaneous recovery (increased fear responding following passage of time), renewal (increased fear responding in a context that is the same or similar to the one in which the fear memory was originally acquired), and reinstatement (increased fear responding following exposure to the unconditioned stimulus that instantiated the original fear memory). Fear responding throughout the task is most commonly assessed via physiological (e.g., skin conductance responses) and cognitive (e.g., threat expectancy ratings) indices. For a complete and

comprehensive overview of fear extinction protocols and experimental considerations, readers are encouraged to consult (Lonsdorf et al., 2017).

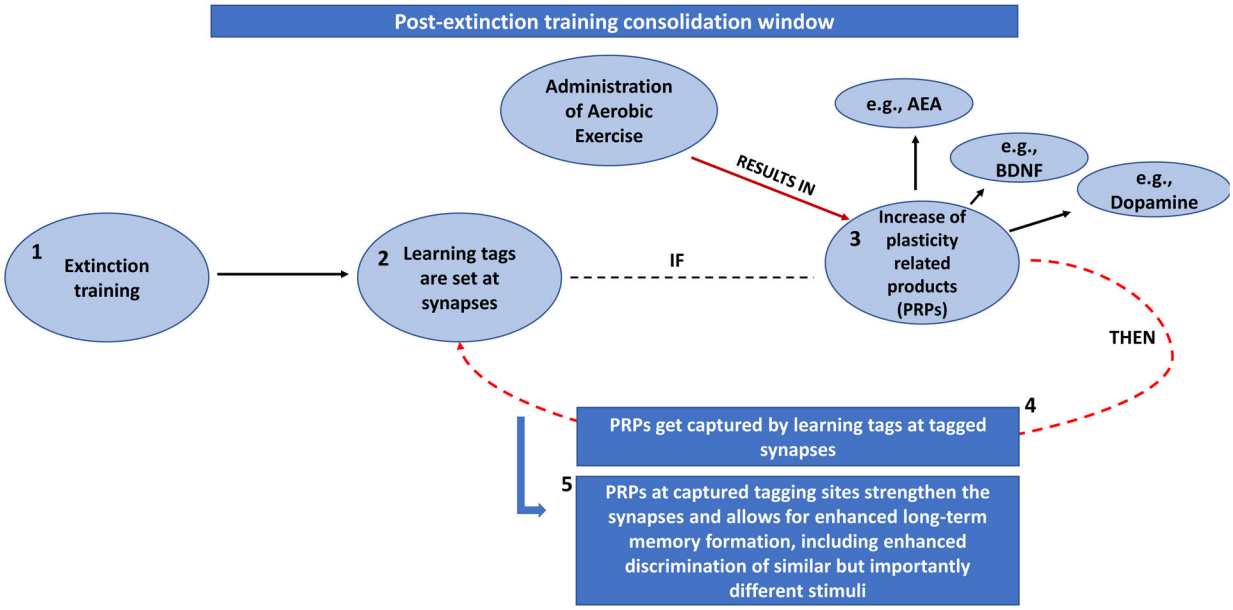


**Figure 3.**

Conceptual model of potential synergistic mechanisms (e.g., behavioral tagging hypothesis, engagement of neurotransmitter and neuromodulatory systems, enhanced pattern separation) responsible for exercise-induced enhancement of fear extinction learning. Extinction training produces tags at weak early long-term potentiation hippocampal synapses (1&2). Aerobic exercise administered during the post-extinction consolidation window following extinction learning results in exercise-induced synthesis of plasticity related products (3), which get captured by the tags (4) which then strengthen the synapses that generated the tags (5). As a result of this, enhanced long-term potentiation occurs, which results in enhanced memory consolidation and extinction recall upon exposure to subsequent fear reminders.

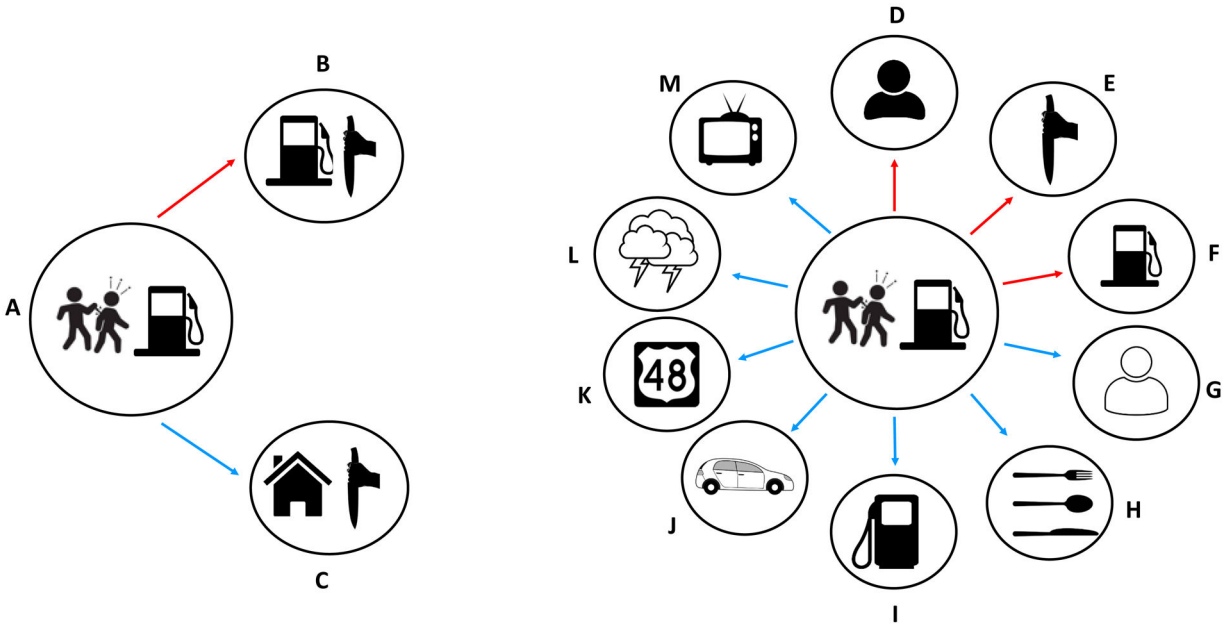


**Figure 4.**

A schematic depicting the translational promise of fear conditioning protocols that use generalized as opposed to standard stimuli. A standard fear conditioning protocol promotes an individual to learn that a given stimuli is likely to lead to an aversive outcome in one context, yet that same stimuli predicts safety in another context. However, consider a hypothetical example where an individual was exposed to a traumatic event in which they were stabbed by someone with a knife while pumping gas. Conceptually, given that extinction to the original conditioned stimuli is the standard in laboratory protocols, a standard fear conditioning protocol attempting to model the hypothetical scenario would assume that the knife poses a threat to the individual if they are at a gas station, but not at their home (see panels A-C). However, in the real-world, it is adaptive for an individual to continue fearing certain elements of the traumatic event (e.g., the man that committed the assault [D], someone holding a knife as a weapon [E], and the same gas station where the attack and several others occurred [F]), but not to generalized stimuli such as other men that did not commit the assault (G), a butter knife and other silverware (H), other gas stations (I), cars (J), traveling/commuting (K), weather similar to the day of the attack (L), television shows (M), etc. In fact, it is explicitly not the goal of exposure therapy to reduce fear responding to the original traumatic stimuli (which might remain an actual threat), but rather reduce fear to non-dangerous stimuli to which the fear has generalized. As such, although standard fear conditioning protocols have and continue to be instrumental for our understanding of the etiology, maintenance, and treatment of mental health disorders with learning and memory components (e.g., PTSD), the continued implementation of generalized stimuli during fear extinction tasks in the laboratory may prove to be a better analogue of exposure-based therapies administered in clinical settings. See (Cooper et al., 2022; Dunsmoor et al., 2022; Hennings et al., 2022, 2020) for additional information on fear generalization paradigms.

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**Table 1:**

**Overview of clinical studies examining role of exercise on fear extinction or exposure therapy/analogue outcomes**

| First author (year) | Population Characteristics | Type of Study | Exercise Timing | Exercise Stimulus | Control Condition | Main outcome |
|---|---|---|---|---|---|---|
| Powers (2015) | Adult men and women (N=9; 8 women) with community-based PTSD | Exposure therapy (12 weeks) | Prior to each PE session (12 weekly sessions) | 30-min on treadmill at 70% AAMHR | TAU (12 weekly sessions of PE) | EX resulted in greater reduction in PTSD symptoms compared to TAU |
| Jacquart (2017) | Adult men and women (N=59; 69.5% women) with significant fear of heights | Exposure Analogue (single session) | Prior to a single session of virtual reality exposure therapy | 30-min on treadmill at 80% AAMHR | Time-matched seated rest (while watching comedy television show) | EX group reported large effect size reductions in fear of heights (1- and 2-wks later), although there was no significant group difference |
| Bischoff (2018) | Adult men and women (N=77; 63.6% women) with clinical diagnosis of panic disorder or agoraphobia | Exposure therapy (7 weeks) | Prior to five PE sessions (over course of 7 weeks) | 30-min on treadmill at 70% VO2max | 30-min on treadmill at 30% VO2max | Both groups reported significant reduction in anxiety (HAM-A) with trend favoring greater reductions in EX group |
| Keyan (2019) | Adult men and women (N=70) without a clinical diagnosis | Fear extinction | After extinction learning | 20-min of stationary cycling at maximal resistance (e.g., 129.16 ± 36.37 watts) while still maintaining a cadence of 60–70 RPM | 20-min of stationary cycling at 60–70 RPM with no resistance (e.g., 0 watts) | EX group exhibited significantly lower fear responding (fear-potentiated startle) to the CS+ compared to light-intensity CON group |
| Weisman (2020) | Non-clinical undergraduates (N=84; 64.3% women) with high self-reported levels of public speaking anxiety | Exposure Analogue (single session) | Following a brief speech exposure | 30-min on stationary cycle at 40–60% HRR while maintaining 70–80 RPM | Time-matched seated rest (while reading choice of magazine) | No significant group differences in speech anxiety at 1-week follow-up |
| Voorendonk (2021) | Adult men and women (N=93; 75.27% W) with community-based PTSD | Exposure therapy (single session) | Prior to vs following a single PE session | Light- to moderate-intensity walking outdoors in a forest in a group of 8–10 participants | N/A | EX after PE session resulted in significant reduction in trauma-related distress and vividness ratings (but not freezing or emotional regulation ratings) compared to EX prior to PE session |
| Crombie (2021) | Adult women (N=35) with interpersonal violence related PTSD | Fear extinction | After extinction learning | 30-min on treadmill at 70–75% AAMHR | 30-min on treadmill at <55% AAMHR | EX enhanced cognitive indices of extinction recall following reinstatement (i.e., EX group reported reduced threat expectancy ratings following a reinstatement procedure) compared to light-intensity CON group |
| Young-McCaughan (2022) | Active duty service men and women (N=72; 92% men) with PTSD symptoms | Exposure therapy (five imaginal exposure sessions) | During imaginal exposure | 20–25 min of preferred aerobic exercise activity (e.g., cycling, treadmill) at > 60% HRR | EX only (no imaginal exposure); imaginal exposure only (no EX); no EX & no imaginal exposure | All groups reported a decrease in PTSD symptom severity from pre- to post-intervention |
| Bryant (2023) | Adult men and women (N=130; 61.00% women) with clinical diagnosis of PTSD | Exposure Therapy (nine, 90-min weekly individual sessions) | After exposure therapy sessions | 10-min of aerobic exercise (65–85% MHR) - participants instructed to run on a 15cm-high stepper exercise platform. Took approximately 10 mins for participants to get to desired target heart rate | 20-mins of passive stretching, involving slow and non-strenuous stretching of limbs | Exposure + EX showed significantly greater reductions in PTSD symptom severity (past week CAPS scores) at 6-month follow-up compared to exposure + passive stretching group. Exposure + EX showed a small effect size improvement in PTSD symptom severity (past week CAPS |

| First author (year) | Population Characteristics | Type of Study | Exercise Timing | Exercise Stimulus | Control Condition | Main outcome |
|---|---|---|---|---|---|---|
| | | | | | | scores) at 1-week post treatment compared to exposure + passive stretching group. |

Note. PTSD = posttraumatic stress disorder; PE = prolonged exposure; AAMHR = age-adjusted maximal heart rate; TAU = treatment-as-usual; EX = exercise group; HAM-A = Hamilton Anxiety Rating Scale; RPM = revolutions per minute; CON = control group; HRR= heart rate reserve