



Effects of acute exercise on fear extinction in rats and exposure therapy in humans: Null findings from five experiments



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ABSTRACT

Background: Exposure therapy is an established learning-based intervention for the treatment of anxiety disorders with an average response rate of nearly 50%, leaving room for improvement. Emerging strategies to enhance exposure therapy in humans and fear extinction retention in animal models are primarily pharmacological. These approaches are limited as many patients report preferring non-pharmacological approaches in therapy. With general cognitive enhancement effects, exercise has emerged as a plausible non-pharmacological augmentation strategy. The present study tested the hypothesis that fear extinction and exposure therapy would be enhanced by a pre-training bout of exercise.

Methods: We conducted four experiments with rats that involved a standardized conditioning and extinction paradigm and a manipulation of exercise. In a fifth experiment, we manipulated vigorous-intensity exercise prior to a standardized virtual reality exposure therapy session among adults with fear of heights.

Results: In experiments 1–4, exercise did not facilitate fear extinction, long-term memory, or fear relapse tests. In experiment 5, human participants showed an overall reduction in fear of heights but exercise did not enhance symptom improvement.

Conclusions: Although acute exercise prior to fear extinction or exposure therapy, as operationalized in the present 5 studies, did not enhance outcomes, these results must be interpreted within the context of a broader literature that includes positive findings. Taken all together, this suggests that more research is necessary to identify optimal parameters and key individual differences so that exercise can be implemented successfully to treat anxiety disorders.

1. Introduction

Exposure-based therapy is an established intervention for treating anxiety disorders (Deacon & Abramowitz, 2004; Hofmann & Smits, 2008; Hofmann, Smits, Asnaani, Gutner, & Otto, 2011); however, there is room for improvement, as non-response rates average nearly 50% (Loerinc et al., 2015). Because exposure therapy is grounded in fear extinction and inhibitory learning principles (Craske et al., 2008; Davis, Ressler, Rothbaum, & Richardson, 2006), it may be prudent to develop and test exposure augmentation strategies that can enhance the acquisition and retention of extinction memories formed during exposure therapy. Support for this approach comes from ongoing research examining the efficacy of a variety of cognitive enhancing drugs shown to

augment exposure based therapies (Singewald, Schmuckermair, Whittle, Holmes, & Ressler, 2015). For example, following early work relating the N-methyl-D-aspartate (NMDA) receptor to fear extinction retention (Davis et al., 2006; Walker, Ressler, Lu, & Davis, 2002), experiments in rodents and clinical trials in humans have since shown that, when administered prior to a training or therapy session, the NMDA receptor partial agonist d-cycloserine (DCS), can facilitate extinction retention and symptom improvement (Mataix-Cols et al., 2017; Otto et al., 2016; however see Guastella, Dadds, Lovibond, Mitchell, & Richardson, 2007). However even with these promising research findings, patients seeking care for anxiety disorders generally prefer psychosocial, over pharmacological, approaches (Arch, 2014; McHugh, Whittton, Peckham, Welge, & Otto, 2013). Thus, justifying the

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development and evaluation of non-pharmacological strategies that can facilitate fear extinction and, by extension, may have the potential to augment exposure therapy outcomes.

Aerobic exercise emerges as one plausible non-pharmacological candidate because it has been shown to broadly affect learning and memory processes, in both acute and chronic forms (Chang & Etnier, 2009; Chang, Labban, Gapin, & Etnier, 2012; Coles & Tomporowski, 2008; Lambourne & Tomporowski, 2010; Perini, Bortoletto, Capogrosso, Fertonani, & Miniussi, 2016; Pesce, Crova, Cereatti, Casella, & Bellucci, 2009; Smith et al., 2010), possibly through a brain-derived neurotrophic factor (BDNF)-dependent mechanism. BDNF has been shown to enhance synaptic plasticity and neuronal excitability (Gomez-Pinilla & Hillman, 2013) as well as mediate extinction memory consolidation (Bramham & Messaoudi, 2005; Chen, Bambah-Mukku, Pollonini, & Alberini, 2012; Peters, Dieppa-Perea, Melendez, & Quirk, 2010; Rattiner, Davis, French, & Ressler, 2004; Schulz-Klaus, Lessmann, & Endres, 2013). Both chronic and acute aerobic exercise have been shown to increase the availability of BDNF in rats and humans (Church et al., 2016; Huang et al., 2006; Marquez, Vanaudenaerde, Troosters, & Wenderoth, 2015; Soya et al., 2007; Szuhany, Bugatti, & Otto, 2015). These increases in BDNF have been associated with exercise training-induced improvements in learning and cognitive abilities in humans (Kimhy et al., 2015; Vaughan et al., 2014; Winter et al., 2007), as well as increases in human hippocampal adult-neurogenesis (Erickson et al., 2011; Pereira et al., 2007). Accordingly, since exercise has been shown to facilitate learning and memory broadly and has been shown to engage a putative partial mediator of fear extinction retention (i.e., BDNF), acute exercise may have the potential to enhance fear extinction retention and exposure therapy outcomes.

A few studies have tested these hypotheses. For example, Siette, Reichelt, and Westbrook (2014) showed that rats with voluntary wheel access for 3-h immediately before or after fear extinction training showed less freezing at a long-term memory test compared to rats with wheel access 6-h following extinction training or no wheel access. Moreover, the distance run was correlated with extinction retention. On the other hand, Mika et al. (2015) found that four days of 12-h wheel access prior to extinction (including the night following conditioning) did not enhance extinction learning or relapse. But, when voluntary wheel access *during* the extinction session was available, outcomes improved on a relapse test. In humans, a pilot study of nine participants with post-traumatic stress disorder (PTSD) found that 30-min of moderate-intensity aerobic exercise immediately before each of the 12 sessions of Prolonged Exposure Therapy (PE) resulted in significantly greater increases in pre- to post-treatment peripheral BDNF levels and greater reductions in PTSD symptoms, compared to PE alone (Powers et al., 2015).

Building upon the aforementioned research, we aimed to provide a comprehensive test of the potential efficacy of acute pre-training administration of aerobic exercise for augmenting exposure therapy. Following a stepped approach to translational research on exposure therapy (see Vervliet, Craske, & Hermans, 2013), we conducted both a test of the augmentation strategy in rats, focusing on the putative behavioral mechanism (i.e., fear extinction retention), and a test of the augmentation strategy in adult humans with acrophobia, focusing on improved symptom reduction (Rodebaugh, Levinson, & Lenze, 2013).

Specifically, we conducted four separate experiments using rats to determine if exercise timing or exercise duration would augment extinction learning or memory. First, using previous data on the time course of the upregulation of BDNF after 30-min of low-intensity forced exercise (Soya et al., 2007), we examined a 30-min bout of voluntary wheel running both 2-h and 1-h before cued extinction training targeting extinction acquisition and consolidation (experiments 1 and 2, respectively). We hypothesized that a 30-min bout of exercise prior to extinction training would reduce freezing in a subsequent memory test, long-term memory, and decrease relapse of fear responding after

reinstatement procedures. Second, because memories are comprised of multiple features including both explicit cue information as well as information about the context in which the learning occurred, we examined an extended, 3-h bout of wheel access immediately prior to both cued and contextual fear extinction training sessions (experiments 3 and 4). We hypothesized that we would replicate previous findings indicating an effect of voluntary exercise on extinction retention in contextually conditioned rats (Siette et al., 2014) and that these results would extend to a cued fear paradigm. Third, we enrolled humans with height phobia in a single session of virtual reality exposure therapy (VRET) for fear of heights and randomly assigned them to either 30-min of aerobic exercise or 30-min of rest prior to the VRET session (experiment 5). We hypothesized that participants assigned to aerobic exercise would experience greater symptom reduction compared to those assigned to rest and, following recent findings (Smits et al., 2013, 2014; Telch et al., 2014), that fear level at the end of the VRET session would moderate the relationship between exercise and exposure therapy response.

2. Methods

2.1. Experiments 1–3: effects of exercise prior to cued extinction training on extinction learning and memory

The aim of experiments 1–3 was to test if an acute bout of voluntary wheel running prior to extinction training could enhance extinction learning or subsequent memory tests across discrete cue based conditioning. The memory tests included a test of long-term memory (LTM; i.e. memory retention from learning that occurred during the extinction training session) and of reinstatement (i.e. how much freezing behavior is reinstated by exposure to the unconditioned stimulus [US] alone without presentation of the conditioned stimulus [CS] after extinction has occurred; Rescorla & Heth, 1975). We hypothesized that an acute bout of exercise prior to extinction would enhance extinction memories as indexed by reduced levels of freezing at LTM and/or reinstatement tests. We tested three variants of exercise administered prior to extinction, Experiment 1 consisted of 30-min of exercise 2-h prior to extinction, Experiment-2 consisted of 30-min of exercise 1-h prior to extinction and Experiment 3 consisted of 3-h of exercise immediately prior to extinction. For full details of methodology including equipment, housing and full procedures see Supplemental materials.

2.1.1. Subjects

A total of 102 male Sprague-Dawley albino rats (Harlan Laboratories) weighing 275–300 g were ordered for the three experiments (34 rats Experiment 1, 32 rats Experiment 2 and 36 rats Experiment 3). They were housed in pairs throughout the entirety of each experiment. Power analyses conducted in G*Power (Faul et al., 2007; Faul, Erdfelder, Lang, & Buchner, 2007) indicated that we would have greater than 0.80 power to detect an effect size as small as $f = 0.4$ (a large effect size). All experiments were designed to run 8–12 rats per group (for individual group sizes per experiment see Supplemental Table 1 [S1]). All procedures in all of our experiments were conducted in compliance with the National Institutes of Health Guide for the Care and Use of Experimental Animals and were approved by the University of Texas at Austin Animal Care and Use Committee (IACUC).

2.1.2. Procedures

For experiment specific timelines see Fig. 1A. Across all cued fear experiments, rats initially went through a conditioning session during which there were three pairings of a 20-s tone cue co-terminating with a foot shock. The following day rats in the exercise condition were exposed to a bout of voluntary wheel running prior to extinction training, whereas control rats remained sedentary (for full details of individual experimental procedures, see Table S1). Note that in experiments 1 and 2, prior to conditioning and throughout the entirety of the experiment,

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