Published in final edited form as:
Expert Rev Neurother. 2012 August ; 12(8): 1011–1022. doi:10.1586/ern.12.73.

Exploring exercise as an avenue for the treatment of anxiety disorders

Lindsey B DeBoer[1], **Mark B Powers**[1], **Angela C Utschig**[2], **Michael W Otto**[2], and **Jasper AJ Smits**[*,1]

[1]Southern Methodist University, 6116 N. Central Expressway, Ste. 1100, Dallas, TX 75206, USA

[2]Boston University, Boston, MA, USA

Abstract

Anxiety disorders constitute a significant public health problem. Current gold standard treatments are limited in their effectiveness, prompting the consideration of alternative approaches. In this review, we examine the evidence for exercise as an intervention for anxiety disorders. This evidence comes from population studies, studies of nonclinical anxiety reduction, as well as a limited number of studies of clinically anxious individuals. All of these studies provide converging evidence for consistent beneficial effects of exercise on anxiety, and are consistent with a variety of accounts of the mechanism of anxiety reduction with exercise. Further study of clinical populations is encouraged, as are studies of the mechanism of change of exercise interventions, which have the potential to help refine exercise intervention strategies. Likewise, studies that identify moderators of treatment efficacy will assist clinicians in deciding how and for whom to prescribe exercise.

Keywords

anxiety; anxiety disorders; exercise; intervention; physical activity; treatment

Among psychological disorders, anxiety disorders are the most common [1,2] and are associated with the most impairment across various domains of functioning [3], including significant impairment of relationships, care giving and job productivity [4–7]. The current gold standard treatments for anxiety disorders are cognitive-behavioral therapy (CBT) and pharmacotherapy [8–11]. Though efficacious, 14–43% of anxiety disorder patients do not respond to treatment [12–16] and 18–48% relapse within 6 months [12,15]. Furthermore, well over half of those suffering with anxiety do not initiate or receive adequate treatment [17,18] due to lack of access to empirically supported treatments [19–21], stigma or subcultural disapproval of psychotherapy and psychotropic medication [22,23], and aversive medication side effects [24–27]. Together, these findings call for the consideration of

[*]Author for correspondence: Tel.: +1 214 768 4125, Fax: +1 214 594 5520, jsmits@smu.edu.

Disclaimer

The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse (NDA) or the NIH.

Financial and competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

augmentation and alternate complementary or stand-alone approaches to the treatment of anxiety disorders.

The purpose of this paper is to review the potential of exercise as an intervention for the treatment of anxiety disorders. The authors begin by reviewing research on potential biological, behavioral and psychological mechanisms by which exercise may have an effect on anxiety disorders. Then, the authors review studies examining the effects of exercise on anxiety and discuss potential moderators of these effects. Together, these findings form the basis of the last section, in which the authors provide a number of future directions for research in this area.

Potential change mechanisms

Neurotransmitter functioning

Animal studies have demonstrated that exercise produces similar alterations in neural systems, such as the serotonergic [28–31] and noradrenergic systems [32–36], which are presumed to underlie pharmacologic treatments for depression and anxiety. For example, treadmill running appears to increase blood free (i.e., not bound to albumin) tryptophan, thereby causing tryptophan (the precursor to serotonin) to enter the brain at an increased rate, resulting in increased serotonin (5-hydroxyindoleacetic acid [5-HT]) synthesis in rats [37]. Exercise has also been associated with increased 5-HT turnover in the mediobasal hypothalamus of rats [38]. Initial work from Broocks *et al.* has extended this work to humans by demonstrating that the anxiolytic effect of exercise is correlated with a downregulation of postsynaptic serotonin receptors, specifically the 5-HT_{2C} receptors [39,40]. In two studies [39,40], the authors examined the effects of meta-chlorophenylpiperazine (m-CPP), a 5-HT_{2C} partial agonist, in physically trained versus untrained participants. Administration of m-CPP produces psychological and physiological anxiogenic symptoms, including increases in plasma cortisol, thought to be mediated by m-CPP's effects on 5-HT_{2C} receptors [39]. It has thus been frequently used as a gauge of serotonergic functioning in humans. Broocks *et al.* found that endurance athletes showed a diminished cortisol response to m-CPP relative to sedentary controls [39]. In a later study, the authors found a similar blunted cortisol response to m-CPP after 10 weeks of moderate-intensity aerobic exercise among previously sedentary participants [40]. These data support the hypothesis that chronic exercise results in a reduced hormonal reaction to m-CPP, and suggest that the anxiolytic effects of exercise may be mediated by repeated stimulation of central serotonin turnover, ultimately resulting in downregulation of 5-HT_{2C} receptors [40].

Exercise may also affect noradrenergic neurotransmission, which has been implicated in the etiology of panic disorder [32–36]. Support for this hypothesis comes from studies showing that increased physical activity in rats is associated with increased noradrenaline turnover in the mediobasal hypothalamus, which appears to cause a downregulation of α_2-adrenergic receptors [41,42]. To our knowledge, this finding in rats has not yet been translated to humans. Indeed, Sommer *et al.* examined the psychological and physiological effects of intravenous yohimbine administration in endurance athletes versus sedentary controls [43]. Yohimbine is an anxiogenic herbal supplement that acts as an α_2-adrenergic antagonist, leading to increased neuronal firing and turnover of noradrenaline in the locus coeruleus [14]. Contrary to hypothesis, the authors found no differences between athletes and controls in plasma cortisol increases, heart rate, blood pressure, or self-reported anxiety symptoms in response to yohimbine [43]. This study therefore failed to show evidence for a downregulation of central noradrenergic neurotransmission associated with chronic exercise.

Given the efficacy of benzodiazepines for reducing anxiety, exercise-induced changes in GABA functioning have also been examined as a mediator of the effects of exercise on

anxiety. Injections of GABA into the nucleus accumbens septi and ventral posterior globus pallidus attenuate open-field locomotion (a common index of fear and anxiety in rats [44–46]), whereas injection of picrotoxin, a $GABA_A$ receptor antagonist, increases locomotion [47,48]. Jones *et al.* concluded that GABA receptors of the nucleus accumbens septi and ventral posterior globus pallidus directly impact locomotion in rats [47,48]. Given that exercise also increases open-field locomotion in rats [49,50], Dishman *et al.* posited that exercise may reduce anxious behavior in rats by increasing GABA concentrations, thereby downregulating $GABA_A$ receptors (i.e., decreasing $GABA_A$ receptor density) in the corpus striatum [51]. They found that voluntary exercise on an activity wheel, but not forced treadmill exercise, increased open-field locomotion and decreased other anxiety-related behaviors with a corresponding $GABA_A$ downregulation [51]. Both activity wheel exercise and treadmill exercise resulted in increased GABA levels, suggesting that the decreases in anxiety behavior resulted from chronic downregulation of $GABA_A$ receptors and not acute increases in GABA. Whether exercise-related anxiolysis in humans can be accounted for by $GABA_A$ downregulation remains unclear. Interestingly, recent work by Streeter *et al.* has demonstrated that anxiety reductions achieved with yoga are associated with increased thalamic GABA levels [52,53]. Specifically, they found that a 12-week yoga intervention produced greater anxiolytic effects and increases in acute thalamic GABA levels than a metabolically matched walking intervention, suggesting that the GABA-mediated anxiolytic effects may be specific to yoga and not generalize to other forms of exercise [53].

Atrial natriuretic peptide

Atrial natriuretic peptide (ANP) is a peptide hormone that inhibits hypothalamic pituitary adrenocortical activity and may have anxiolytic properties [54]. Ströhle *et al.* showed that both central and peripheral administration of atriopeptin reduced fear responding in rats as well as among individuals with panic disorder [55,56]. As submaximal and maximal exercise bouts significantly increase ANP concentrations [57], Ströhle *et al.* examined the effects of exercise on ANP and response to panic provocation [54]. They found that exercise (30 min of 70% of maximum heart rate on a treadmill) significantly increased plasma ANP and reduced anxious responding to CCK_4. Importantly, the magnitude of the reduction in anxiety was directly associated with the increase in plasma ANP.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in brain neuroplasticity, differentiation and survival of neurons in both the central and peripheral nervous system [58,59]. Adequate BDNF levels appear to be an important factor in the maintenance of normal cognitive function and mood [58,59], whereas impairments have been associated with reduced memory/learning [60–62] and depressive symptoms [63–65]. Similarly, reduced BDNF levels have been associated with both increased general anxiety [66] and anxiety disorders [64,67]. In addition, baseline serum BDNF levels among persons with panic disorder have been shown to be predictive of response to exposure-based treatment, such that those with higher serum BDNF levels show greater response compared with those with lower serum BDNF levels [68]. Thus, interventions that increase BDNF levels may have clinical implications for treatment of individuals with anxiety disorders [59].

Acute aerobic exercise has been shown to significantly increase BDNF levels in normal controls [67,69–71] and individuals with neurological/psychiatric conditions [70–72]. For example, Ströhle *et al.* compared individuals with panic disorder to normal controls before and after a 30-min bout of moderate-intensity exercise [67]. The authors found that patients with panic disorder had significantly reduced BDNF concentrations relative to normal controls at baseline. Moreover, 30 min of moderate-intensity exercise significantly increased

BDNF concentrations in these individuals with panic disorder, whereas no changes in BDNF concentrations were observed in the normal controls. In addition, there appears to be a dose–response relationship; the increase in BDNF levels tend to be greater following high compared with low aerobic exercise intensity [69,73–76]. These initial findings prompt the need for follow-up studies examining whether BDNF concentrations normalize with exercise training programs and whether this change indeed guides anxiety symptom reduction.

Endorphins

A popular hypothesis is that endorphins, endogenous peptides that act as opioid receptor agonists, mediate exercise-induced anxiety reduction [77]. However, evidence to support this hypothesis is mixed [77]. Multiple studies have demonstrated that acute exercise results in decreased anxiety regardless of whether participants were administered naltrexone, an opioid receptor-blocking medication, or placebo (e.g., [78,79]). Furthermore, Galiano and colleagues observed that larger increases in β-endorphin during exercise were associated with increases in state anxiety, as opposed to decreases (unpublished observation noted in [79]). Although β-endorphin is released into the bloodstream during stress, including physiological stressors such as exercise, there is limited evidence that β-endorphin crosses the blood–brain barrier during or after exercise, and peripheral β-endorphin is therefore unlikely to directly influence anxiety or mood [80]. A recent study was the first to demonstrate increases in central endogenous opioid binding following prolonged vigorous exercise among trained athletes [81]. Furthermore, the authors of this study also found that opioid binding in the frontolimbic brain regions was associated with self-reported euphoria, suggesting that opioidergic effects of exercise may indeed mediate anxiolysis following prolonged physical exertion [81]. However, these data may not explain the anxiolytic effects of less strenuous exercise (see the following paragraphs).

Adenosine

Adenosine is an inhibitory neuromodulator that influences synaptic transmission of dopamine and glutamate. Adenosine A_1 and A_{2A} receptors, the receptors responsible for controlling neurotransmission, are implicated in anxiety etiology [82]. Although there is evidence that exercise impacts central neurotransmitter systems, including adenosine-modulated dopamine and glutamate [83], the authors are not aware of any studies that have examined the effects of exercise on adenosine in humans. In animal work, one of the first studies to examine the effects of exercise (8 weeks of 20-min moderate-intensity treadmill running) on adenosine A_1 and A_{2A} receptors in rats found that all training frequencies (1, 3 and 7 days per week) reversed the typical age-related increases in A_{2A} receptors in the hippocampus [84]. However, only the once-weekly exercise protocol was found to attenuate age-related anxiety behavior, with anxious behavior increasing following the other exercise frequencies in both adult and middle-aged rats [84]. These results suggest that A_{2A}-mediated anxiolysis following exercise training may be limited to moderate-intensity exercise at low frequencies among middle-aged rats [84]. The finding that most frequencies of moderate-intensity exercise increased anxiety behavior was unexpected, but may be due to the 48-h exercise abstinence prior to assessing anxiety behavior or to the forced nature of treadmill exercise in rats [84]. Indeed, the anxiolytic effects of exercise are less consistent in rats than in humans, and the impact of exercise on adenosine receptors and subsequent changes in anxiety thus needs to be tested in humans.

Electrocortical changes

Electrocortical changes, specifically increased in EEG-α wave frequency band, following exercise have also been proposed as a mechanism of action [85]. Specifically, increases in the EEG-α frequency band, particularly in the frontal anterior regions of the brain, are

thought to be associated with relaxation and decreased anxiety. Studies have shown that the EEG-α frequency band does increase during and after exercise; however, no more than other frequency bands [85]. Furthermore, there are no significant differences in the EEG-α frequency band increases across brain regions [85]. In their meta-analysis, Crabbe and Dishman also found that increased frontal alpha activity and interhemispheric asymmetry after exercise was not reliably associated with decreases in anxiety [85].

Core body temperature

Core body temperature increases with exercise and core temperature has been found in some studies to be associated with exercise-induced decreases in anxiety [86]. The thermogenic hypothesis states that the increase in core body temperature that results from exercise may be responsible for reductions in anxiety by way of reducing muscular tension and altering neuron activity [87–89]. This hypothesis has been largely unsupported in empirical work [90]. For example, several studies have found a positive rather than an inverse relationship between body temperature and anxiety ratings when experimentally manipulating body temperature changes during exercise [90–92]. Petruzzello *et al.* found that self-reported anxiety immediately following exercise was higher among those randomized to a warm running condition that induced higher body temperatures than those who exercised in neutral or cool conditions [91]. No condition differences in anxiety were found throughout a 30-min recovery phase, and the temperature manipulation explained only little variance in anxiety ratings, such that the authors concluded that the thermogenic hypothesis was unsupported [91]. Another study found that reductions in anxiety occurred when body temperature was prevented from rising during exercise [86]. The mixed support for the thermogenic hypothesis may have resulted from methodological inconsistencies across studies [86]. Researchers have proposed that exercise-induced changes in anxiety may result from increases in brain (specifically hypothalamus) temperature rather than body temperature and that using tympanic temperature is preferable to the more commonly used rectal temperature [86,91].

Extinction learning

Anderson and Insel have highlighted the promise of fear extinction research in animals and humans for improving psychosocial interventions and especially exposure-based treatments for anxiety disorders [93]. Indeed, the procedures for fear extinction training in animals are very similar to exposure therapy procedures in humans with anxiety disorders [93–95]. That is, animals display extinction learning following repeated exposure to feared stimuli in the absence of associated negative outcomes [95,96] and humans with anxiety disorders display fear reduction following (repeated or prolonged) exposure to feared stimuli in the absence of negative outcomes [97,98]. This extinction model may also be useful for explaining why and how exercise reduces fear among anxiety disorder populations. For example, if completed in situations where other people are present (e.g., gyms, classes, research studies and so on), exercise provides exposure to feared stimuli (e.g., to having visible signs associated with anxiety while with others who may notice and negatively evaluate them) for people with social anxiety. Similarly, for individuals with contamination concerns, using sweaty, warm gym equipment that is shared by others may provide exposure to feared contaminants.

The extinction model for explaining the effect of exercise for anxiety disorders appears particularly apt for panic and related disorders [99]. Central to the onset and maintenance of panic and related disorders is elevated anxiety sensitivity, or the fear of anxiety and related sensations [100]. Anxiety sensitivity is an established cognitive risk factor for panic attacks and panic disorder [100], and psychological interventions that effectively reduce anxiety sensitivity are associated with panic prevention or amelioration [101,102]. The key component to these psychological interventions is interoceptive exposure, or the repeated

induction of bodily sensations (e.g., running in place, hyperventilation [103]). Accordingly, because exercise can produce many of the stimuli that are feared by individuals with panic and related disorders (e.g., increased heart rate, increased cardiac stroke volume, increased perspiration, elevated respiration rate), exercise could be viewed as a vehicle for interoceptive exposure.

Consistent with this hypothesis, three studies have documented significant changes in anxiety sensitivity with programmed exercise. In the first trial, Broman-Fulks *et al.* randomly assigned 54 participants with high levels of anxiety sensitivity to either six 20-min high-intensity (60–90% maximal heart rate) or a low-intensity (below 60% of maximal heart rate) aerobic exercise program [104]. The high-intensity intervention was associated with significantly greater reductions in anxiety sensitivity compared with the low intensity intervention. In a second study, Broman-Fulks and Storey compared six sessions of aerobic exercise to a no-exercise comparison condition in 24 participants with high anxiety sensitivity [105]. Anxiety sensitivity decreased significantly in the aerobic exercise condition, with no significant change in the control condition. In a third study, Smits *et al.* compared 20-min high-intensity exercise sessions (six sessions over a 2-week period, delivered either alone or with cognitive restructuring) to a waitlist control in 60 participants with high anxiety sensitivity [103]. The two exercise conditions were found to be equally efficacious in reducing anxiety sensitivity and markedly better than the waitlist condition. In addition, the exercise conditions were associated with significant reductions in overall anxiety compared with the waitlist condition.

Emotional action tendencies

Modifying emotional action tendencies – that is, self-perpetuating behavioral patterns in affective disorders (e.g., avoidance in anxiety, social withdrawal and inaction in depression) – is a fundamental therapeutic strategy shown to be efficacious for treating anxiety disorders [106]. Exercise may be useful in the treatment of anxiety disorders because it requires enduring negative physical and emotional states in order to remain engaged in the activity [107]. Specifically, exercise involves an action (i.e., approach) that is inconsistent with the natural action tendencies associated with anxiety (i.e., avoidance). Similar to behavioral activation treatments for depression [108,109], persisting in exercise whereas experiencing the physiological and psychological symptoms of exertion (which, as discussed above, mimic anxiety symptoms) may also have more general effects on restoring participants to adaptive activity [107].

Self-efficacy

Exercise may also alleviate anxiety, in part, by enhancing perceived coping ability or self-efficacy. McAuley *et al.* have described a reciprocal relationship between self-efficacy and physical activity whereby higher levels of self-efficacy lead to greater initiation and maintenance of exercise, and exercise results in increased self-efficacy [110]. Self-efficacy also appears to be correlated with the impact of exercise on anxiety [108,111]. For example, Steptoe and colleagues observed parallel decreases in perceived coping deficits and anxiety among healthy adults who participated in a 10-week moderate-intensity exercise program [108]. Neither the control groups nor the exercise group experienced decreases in anxiety or perceived coping deficits. Another study of older adults found that anxiety on the State Anxiety Inventory (STAI-S [112]) was significantly decreased at all levels of exercise intensity (i.e., light, moderate and maximal) when items assessing arousal were removed (total STAI-S score increased following high-intensity exercise due to increases in arousal [111]). Similar to the Steptoe and colleagues' findings [108], exercise-induced increases in self-efficacy were associated with decreases in state anxiety following only moderate-intensity exercise [111]. These data are also consistent with the effects of higher intensity

exercise on mood during exercise; mood ratings decrease during exercise when exercise is of higher intensity (i.e., tend to decrease when the ventilatory threshold is reached [113]), even though mood improves after exercise. In the same way, high-intensity exercise seems to take its toll on self-efficacy, perhaps simply because of the degree of effort required for high-intensity workouts.

Not only does exercise intensity appear to influence self-efficacy and related decreases in anxiety, but other conditions may also enhance or detract from the effects of exercise on self-efficacy and subsequent decreases in anxiety. For example, female participants given false negative feedback about their exercise performance experienced decreases in self-efficacy relative to those who received positive feedback [114]. Self-efficacy mediated levels of postexercise state anxiety such that those who received positive feedback had significantly lower levels of anxiety [114]. Thus, it appears that a supportive exercise environment may enhance the meditational effects of self-efficacy. Furthermore, exercise interventions that specifically target self-efficacy [115] and particular forms of exercise that target self-efficacy may be particularly effective in reducing anxiety. For example, 45 min of martial arts was associated with greater decreases in state anxiety and increases in positive affect than 45 min of exercise on a stationary bicycle [109]. Hence, when it comes to changes in self-efficacy, the socially constructed meaning of exercise and whether certain performance criteria were met appear to have an influence over and above other influences of exercise.

Distraction

Others have proposed that the anxiolytic effects of exercise are due to exercise serving as a distraction or ‘time-out’ from worries and concerns. For example, Bahrke and Morgan found significant reductions in state anxiety following 20 min of exercise (at 70% maximal heart rate), meditation or rest, suggesting that exercise may be one of several forms of distraction that can decrease anxiety [116]. A more recent study tested the time-out hypothesis among college females high in trait anxiety [117]; specifically, they examined within-subject differences in anxiety following four conditions: exercise-only (low intensity); exercise-while-studying (i.e., exercise in which a time-out is prevented); study only and resting control condition. Anxiety was reduced only after the exercise-only condition, supporting the hypothesis that exercise decreases anxiety because it provided a time-out from daily concerns.

Summary of mechanisms of action: a broad spectrum of effects

As evident from the preceding review, there is no shortage of viable mechanisms for the effects of exercise on anxiety. Multiple neurotransmitter, neuromodulator and psychological mechanisms of action have received support, with insufficient evidence at present for the selection of one account over the others. As such, we are faced with the interim conclusion that there are multiple reasons why exercise should act as an anxiolytic. We now turn to the evidence on how consistently and strongly it does act in this capacity.

Evidence for the efficacy of exercise for anxiety disorders

Population-based studies have provided reliable evidence of fewer anxiety symptoms, lower stress and greater well-being among individuals who engage in regular physical activity [62,118]. Likewise, individuals who exercise regularly are significantly less likely to meet diagnostic criteria for panic disorder, agoraphobia, social phobia, generalized anxiety disorder (GAD) or specific phobias [119,120]. Furthermore, among those who do have anxiety disorders, higher physical activity is associated with better social functioning and vitality [121].

A series of laboratory challenge studies have extended these findings by demonstrating that acute exercise confers antipanic and anxiolytic effects. For example, Esquivel *et al.* found that 12 min of exercise (bicycle ergometer with increasing workload to reach >6 mmol/l of blood lactate concentration) prior to a single vital capacity inhalation of 35% CO_2/65% O_2 was associated with significantly decreased fear reactivity, demonstrated by fewer panic symptoms, compared with minimal exercise (cycling on the ergometer with continuous [low] workload) in 20 healthy adults [122]. Similarly, Ströhle *et al.* randomized 15 healthy participants to either 30 min of treadmill exercise at 70% of maximum oxygen consumption or 30 min of quiet rest prior to a biological challenge using an injection of 50 μg of CCK_4 [123] and found moderate to large between-group differences with respect to CCK_4-induced panic attacks, panic symptoms and anxiety [123]. Smits *et al.* documented that healthy participants who engaged in 20 min of moderate-intensity treadmill exercise (i.e., 70% of maximum heart rate; n = 46) reported less anxiety reactivity prior to a single vital capacity inhalation of 35% CO_2/65% O_2 (n = 46) relative to participants who rested prior to challenge [124].

Particularly important for the treatment of anxiety disorders are two studies that have documented similar effects of acute exercise on biological challenge reactivity among individuals with anxiety disorder diagnoses. First, Esquivel *et al.* found that moderate to hard exercise (i.e., up to 15 min of cycling at 80–90% of maximum heart rate) was associated with reduced reactivity to CO_2 challenge, demonstrated by fewer panic attacks and symptoms and less anxiety, in comparison with very light exercise in individuals suffering from panic disorder [125]. Similarly, Ströhle *et al.* found that individuals with panic disorder who engaged in 30 min of aerobic exercise (70% of VO_2 max) were less likely to have a panic attack in response to a CCK_4 challenge as compared with those who did not exercise beforehand [126].

This evidence that acute bouts of vigorous exercise have anxiolytic effects, along with extant work specifically examining the blood lactate–anxiety relationship (e.g., [127–129]), is in opposition to the Pitts and McClure hypothesis that excessive lactate production in response to exercise (and other stressors) may be responsible for producing panic attacks [130,131]. This hypothesis was in part based on the observation that injections of sodium $_{DL}$-lactate produced panic attacks in the majority of a sample with ‘anxiety neurotics’ and that anxiety patients produced greater levels of blood lactate following exercise. By contrast, Garvin *et al.* found no correlation between changes in blood lactate and anxiety ratings following acute bouts of aerobic and anaerobic exercise at 70% maximal capacity [127]. Anxiety significantly decreased 1 h following aerobic exercise and there were no increases in anxiety in the anaerobic condition despite larger increases in blood lactate [127]. In a review of the relation between exercise and panic attacks among patients with panic disorder, O’Connor *et al.* argued that Pitts and McClure’s conclusions were based on inaccurate interpretations of prior work, a misunderstanding of the physiological effects of exercise-induced lactate increases versus injections of sodium $_{DL}$-lactate, and the failure to consider alternative explanations (e.g., associations between exercise-induced lactate and anxiety symptoms could be due to anxiety patients’ relative lack of fitness) [129]. They found no evidence that acute bouts of exercise induce panic attacks (and indeed they co-occur only rarely and by chance [129]). On the contrary, the evidence suggests that exercise benefits patients with panic disorder [129].

In addition to single bouts of exercise, exercise programs have also caused relief from anxiety symptoms. For example, a meta-analysis of 49 randomized controlled trials of primarily nonpsychiatric populations (e.g., studies of the general population, the elderly or medically ill samples) revealed a moderate effect size for the advantage of exercise interventions over the control conditions on the self-report of anxiety symptoms [132]. As

applied to anxiety disorders, studies are few in number and have involved small sample sizes. For example, Broocks and associates examined the relative efficacy of aerobic exercise, clomipramine and pill placebo in a randomized trial of 46 patients with panic disorder [133]. The exercise intervention was a 10-week program that asked patients to find and complete a 4-mile route (forest or park) that was easily accessible from their home at least three times a week. At treatment end point, both active treatments resulted in equal reductions in anxiety and outperformed placebo at post-treatment; however, clomipramine yielded greater changes in global improvement ratings compared with aerobic exercise.

Similarly, there is initial support of the efficacy of exercise as an adjunctive intervention for group CBT. Specifically, Merom *et al.* randomized anxiety patients – including those with panic disorder, generalized anxiety disorder and social phobia – to adjunctive treatment with either an exercise condition (with the group therapists recommending working up to a goal of 150 min of exercise spread across five sessions per week) or to a healthy eating educational control group [134]. These interventions were initiated during the beginning of an 8- to 10-week program of group CBT. Across treatment, significantly lower levels of depression, anxiety and stress were reported by patients who underwent the exercise intervention. Notably, the effects were most prominent for patients being treated for social phobia.

Another trial similarly examined exercise as an adjunctive intervention for anxiety patients (again represented by those with panic disorder, generalized anxiety disorder and social phobia), but targeted patients in an inpatient setting [135]. In this trial, 8 weeks aerobic exercise (walking or running at 70% maximal aerobic capacity) was compared with an anaerobic training program. Both groups improved significantly, allowing no firm conclusions about the role of exercise in these gains.

In addition to these findings from randomized trials, a number of open trials in other anxiety disorders suggest both feasibility and potential efficacy for exercise interventions. For example, in an open trial examining the efficacy of aerobic exercise as an adjunctive intervention to regular care for obsessive-compulsive disorder, Brown *et al.* examined a 12-week moderate-intensity group exercise program [136]. Significant changes in obsessive and compulsive symptoms were evident at post-treatment, and continued to be evident at a 6-month follow-up assessment. Likewise, two small studies of inpatient adolescents with post-traumatic stress disorder (PTSD) utilized a multiple baseline design to examine within-subject changes in PTSD symptom severity following three sessions per week of aerobic exercise [137,138]. In both studies, PTSD symptoms decreased following the exercise intervention. No studies have yet examined the efficacy of exercise in treating specific phobias.

Potential moderators of the effects of exercise on anxiety

Research on the acute effects of exercise suggests that the efficacy and utility of exercise interventions for anxiety disorders may vary by exercise modality. Specifically, reductions in anxiety occur immediately and up to 120 min following aerobic exercise [116,139,140], whereas resistance training has been found to result in a temporary increase in anxiety immediately following exercise but then returns to baseline levels 20–60 min following exercise [141,142]. An earlier study found no decreases in state anxiety after one 50-min session of self-selected resistance training [143]. However, long-term resistance training programs are associated with anxiety reduction [144– 146]. For example, 12-week resistance training programs consisting of three weekly sessions at both high and low intensity showed significant and comparable reductions in tension and trait anxiety at post-treatment relative

to a no-treatment control group [146]. Similar effects were observed following a 24-week weight machine intervention consisting of three weekly sessions [144].

Overall, there is limited extant work comparing different forms of exercise, with treadmill walking/running and resistance training the most commonly examined. Recently, yoga and tai chi have shown promise as interventions for anxiety. Field *et al.* found that a 20-min class combining tai chi movements and yoga postures produced significant reductions in state anxiety from pre- to post-exercise among healthy participants [147]. Another study compared the effects of a 12-week yoga intervention (three 60-min sessions per week) compared with a metabolically matched walking control condition among healthy participants [53]. Those in the yoga condition showed significantly greater improvements in state anxiety, tranquility and revitalization at post-treatment relative to those in the walking condition. Together, these results suggest that a range of exercise modalities may be beneficial in treating anxiety disorders, which is important for individuals unable to participate in particular forms of exercise (e.g., vigorous or high-impact exercise such as running). It is unclear at this time whether a particular form of exercise produces greater anxiolytic effects than others.

Few studies have examined the dose–response relationship of exercise and anxiety reduction. Therefore, little is known about the effects of exercise program length, session duration, session frequency and exercise intensity on anxiety. It appears that the length of the exercise intervention may have a linear relationship to the magnitude of anxiolytic effects [148]. In a meta-analysis, programs lasting 16 weeks or longer produced the largest reductions in trait anxiety, and meaningful reductions in anxiety were found only in programs lasting 10 weeks or longer [148]. In another meta-analysis, Wipfli *et al.* found that exercise frequency of three to four times per week elicited larger anxiolytic effects than less or more frequent regimens [149]. Exercise session duration may also affect the magnitude of anxiety reductions, with activity sessions lasting 21–30 min potentially providing the most anxiety reduction [148]. However, another review suggests that session duration does not predict degree of anxiety reduction beyond the effects explained by the degree of exercise intensity [113]. Although several studies have shown no effect of exercise intensity, others have suggested that greater intensity increases state anxiety and decreases positive affect during and immediately following acute bouts of exercise [113]. One study suggests that the positive relationship between exercise intensity and anxiety may be stronger for men than for women [150]. Unfortunately, studies that have carefully manipulated the exercise dose by varying intervention length, session duration, intensity and frequency are lacking.

In addition to certain exercise intervention parameters, there may be person variables associated with the efficacy of exercise for anxiety disorders. For example, recent work suggests that two specific anxiety vulnerability factors – anxiety sensitivity and social physique anxiety – may influence the degree to which individuals can tolerate exercise interventions. That is, these variables are negative affective responses to exercise, and they may reduce satisfaction with exercise and potentially prevent continued adherence to an exercise program. Indeed, affective responses to exercise are related to total time spent in physical activity during 6- and 12-month follow-up periods [151], and affective responses to exercise appear to be critically linked to exercise motivation [152,153]. Smits *et al.* observed that anxiety sensitivity and BMI interacted to predict fear during moderate-intensity exercise, such that those with both high BMI and high anxiety sensitivity reported the greatest levels of fear [154]. Social physique anxiety (i.e., anxiety about the evaluation of one's physical appearance by others) is also associated with reduced physical activity [155], and appears to explain at least in part negative affective responses to exercise among obese women [156].

Person variables that potentially affect the utility of exercise interventions for anxiety disorders may also include biological markers. For example, physical activity was found to be a protective factor for depression only among adolescent girls with a *BDNF* met allele at the val66met polymorphism [157]. Similarly, Toups *et al.* recently found that depressed adults with high serum BDNF experienced more rapid improvements in depressive symptoms after a 12-week aerobic exercise intervention relative to those with lower BDNF levels [158]. Thus, the met allele may not only identify individuals most at risk for depression, but also identify a subgroup of individuals for whom exercise interventions would have the most ameliorative effects [157].

Expert commentary

In this article, we have reviewed the findings from a wide range of studies that, collectively, support a role for exercise interventions for the treatment of anxiety disorders. Both population-based studies and large-scale, well-controlled clinical trials demonstrating the efficacy of exercise as a stand-alone or augmentation intervention for depression justify using exercise as an intervention for improving emotional well-being [152]. Support for considering exercise as an intervention specifically for the treatment of anxiety disorders comes from studies linking exercise to behavioral, cognitive and neural processes theorized to operate in anxiety reduction, as well as from the increasing body of research demonstrating that both acute exercise and more extensive exercise programs reduce anxiety [152]. At this time, however, there have been few randomized controlled trials of exercise involving anxiety disorder samples. Initial trials for panic disorder and related core fears have indicated that exercise can be a powerful intervention. Much less research has been conducted involving other anxiety disorders, but preliminary work indicates that exercise is a feasible intervention for those in inpatient or outpatient settings, and that it has the potential to enhance outcome for established treatments such as CBT.

Five-year view

Establishing exercise as an empirically supported intervention for the anxiety disorders requires randomized controlled trials involving anxiety disorder samples. Here, there is sufficient rationale to examine exercise as a stand-alone intervention or as an augmentation strategy to established interventions such as CBT and pharmacotherapy [8,159]. Confidence in the effects of exercise can be enhanced when these studies utilize appropriate comparator interventions such as wellness education [160] or supportive treatment [161]. In addition to examining the specificity of exercise, future studies should attend to the examination of mediators and moderators of exercise efficacy. Regarding the study of mediators, it is important to include multiple measures of multiple plausible mediators (e.g., self-efficacy, extinction learning and so on) and anxiety severity throughout the intervention period [162,163]. This allows for both establishing temporal precedence (i.e., mediator to anxiety and anxiety to mediator effects) and testing of specificity of meditational effects (i.e., ruling out third variable explanations). Identifying mediators will help increase the understanding of the mechanism of change of exercise intervention, thus enabling the refinement of exercise intervention strategies. Much like the identification of mediators, the study of moderators will help determine the utility of exercise interventions for the anxiety disorders. Here, it is important to consider the influence of intervention parameters (e.g., dose, resistance vs cardio and so on) and person variables (age, sex and so on) as well as their interaction on the strength of the exercise–anxiety effect. Such findings will ultimately help clinicians decide how and for whom to prescribe exercise.

In conclusion, the extant research highlights the potential of exercise as a stand-alone or complementary intervention for anxiety disorders. Previous work on potential mechanisms

of the anxiolytic effects of exercise has demonstrated that exercise is associated with physiological, psychological and behavioral processes theorized to operate in anxiolysis. Furthermore, several initial randomized controlled trials have revealed reductions in anxiety following both acute bouts of exercise and programmatic exercise.

Acknowledgments

LB DeBoer, AC Utschig and MB Powers report no financial relationships with commercial interests. In the last 3 years, MW Otto has received consulting and research support from Organon/Schering-Plough (now Merck), royalties for use of the SIGH-A from Lilly, and book royalties from Oxford University Press. In the past 3 years, JAJ Smits has received grant support from Organon/Schering-Plough (now Merck) and receives book royalties from Oxford University Press. JAJ Smits is currently supported by National Institutes of Health (NIH) Grants R01DA027533 and R34DA031038.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry. 2005; 62(6):617–627. [PubMed: 15939839]
2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry. 2005; 62(6):593–602. [PubMed: 15939837]
3. Buist-Bouwman MA, De Graaf R, Vollebergh WA, Alonso J, Bruffaerts R, Ormel J. ESEMeD/MHEDEA 2000 Investigators. Functional disability of mental disorders and comparison with physical disorders: a study among the general population of six European countries. Acta Psychiatr. Scand. 2006; 113(6):492–500. [PubMed: 16677226]
4. Greenberg PE, Sisitsky T, Kessler RC, et al. The economic burden of anxiety disorders in the 1990s. J. Clin. Psychiatry. 1999; 60(7):427–435. [PubMed: 10453795]
5. Leon AC, Portera L, Weissman MM. The social costs of anxiety disorders. Br. J. Psychiatry. Suppl. 1995; (27):19–22. [PubMed: 7794589]
6. Schneider S, Houweling JE, Gommlich-Schneider S, Klein C, Nündel B, Wolke D. Effect of maternal panic disorder on mother-child interaction and relation to child anxiety and child self-efficacy. Arch. Womens Ment. Health. 2009; 12(4):251–259. [PubMed: 19396526]
7. Zaider TI, Heimberg RG, Iida M. Anxiety disorders and intimate relationships: a study of daily processes in couples. J. Abnorm. Psychol. 2010; 119(1):163–173. [PubMed: 20141253]
8. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J. Clin. Psychiatry. 2008; 69(4):621–632. [PubMed: 18363421]
9. Powers MB, Emmelkamp PM. Virtual reality exposure therapy for anxiety disorders: a meta-analysis. J. Anxiety Disord. 2008; 22(3):561–569. [PubMed: 17544252]
10. Powers MB, Halpern JM, Ferenschak MP, Gillihan SJ, Foa EB. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin. Psychol. Rev. 2010; 30(6):635–641. [PubMed: 20546985]
11. Powers MB, Sigmarsson SR, Emmelkamp PMG. A meta-analytic review of psychological treatments for social anxiety disorder. Int. J. Cognitive Ther. 2008; 12:94–113.
12. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive–behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA. 2000; 283(19):2529–2536. [PubMed: 10815116]

13. Borkovec TD, Newman MG, Pincus AL, Lytle R. A component analysis of cognitive-behavioral therapy for generalized anxiety disorder and the role of interpersonal problems. J. Consult. Clin. Psychol. 2002; 70(2):288–298. [PubMed: 11952187]
14. Davidson JR, Foa EB, Huppert JD, et al. Fluoxetine, comprehensive cognitive-behavioral therapy, and placebo in generalized social phobia. Arch. Gen. Psychiatry. 2004; 61(10):1005–1013. [PubMed: 15466674]
15. Foa EB, Liebowitz MR, Kozak MJ, et al. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. Am. J. Psychiatry. 2005; 162(1):151–161. [PubMed: 15625214]
16. Marks I, Lovell K, Noshirvani H, Livanou M, Thrasher S. Treatment of posttraumatic stress disorder by exposure and/or cognitive-restructuring: a controlled study. Arch. Gen. Psychiatry. 1998; 55(4):317–325. [PubMed: 9554427]
17. Wang PS, Demler O, Kessler RC. Adequacy of treatment for serious mental illness in the United States. Am. J. Public Health. 2002; 92(1):92–98. [PubMed: 11772769]
18. Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch. Gen. Psychiatry. 2005; 62(6):629–640. [PubMed: 15939840]
19. Becker CB, Zayfert C, Anderson E. A survey of psychologists' attitudes towards and utilization of exposure therapy for PTSD. Behav. Res. Ther. 2004; 42(3):277–292. [PubMed: 14975770]
20. Freiheit SR, Vye C, Swan R, Cady M. Cognitive–behavioral therapy for anxiety: is dissemination working? Behav. Ther. 2004; 27(2):25–32.
21. Rosen CS, Chow HC, Finney JF, et al. VA practice patterns and practice guidelines for treating posttraumatic stress disorder. J. Trauma. Stress. 2004; 17(3):213–222. [PubMed: 15253093]
22. Hunter LR, Schmidt NB. Anxiety psychopathology in African American adults: literature review and development of an empirically informed sociocultural model. Psychol. Bull. 2010; 136(2): 211–235. [PubMed: 20192561]
23. Overton SL, Medina SL. The stigma of mental illness. J. Couns. Dev. 2008; 86(2):143–151.
24. Choy Y. Managing side effects of anxiolytics. Prof. Psychol. 2007; 14(7):68–76.
25. Golden RN. Making advances where it matters: improving outcomes in mood and anxiety disorders. CNS Spectr. 2004; 9 Suppl. 4(6):14–22. [PubMed: 15181381]
26. Mavissakalian M, Perel J, Guo S. Specific side effects of long-term imipramine management of panic disorder. J. Clin. Psychopharmacol. 2002; 22(2):155–161. [PubMed: 11910260]
27. Rivas-Vazquez RA. Benzodiazepines in contemporary clinical practice. Prof. Psychol: Res. Pr. 2003; 34(3):324–328.
28. Broocks A, Bandelow B, George A, et al. Increased psychological responses and divergent neuroendocrine responses to m-CPP and ipsapirone in patients with panic disorder. Int. Clin. Psychopharmacol. 2000; 15(3):153–161. [PubMed: 10870873]
29. Kahn RS, Asnis GM, Wetzler S, van Praag HM. Neuroendocrine evidence for serotonin receptor hypersensitivity in panic disorder. Psychopharmacology (Berl.). 1988; 96(3):360–364. [PubMed: 2906153]
30. Kahn RS, Wetzler S, van Praag HM, Asnis GM, Strauman T. Behavioral indications for serotonin receptor hypersensitivity in panic disorder. Psychiatry Res. 1988; 25(1):101–104. [PubMed: 3217461]
31. Lesch KP, Mayer S, Disselkamp-Tietze J, Hoh A, Schoellnhammer G, Schulte HM. Subsensitivity of the 5-hydroxytryptamine1A (5-HT1A) receptor-mediated hypothermic response to ipsapirone in unipolar depression. Life Sci. 1990; 46(18):1271–1277. [PubMed: 1971701]
32. Albus M, Zahn TP, Breier A. Anxiogenic properties of yohimbine. I. Behavioral, physiological and biochemical measures. Eur. Arch. Psychiatry Clin. Neurosci. 1992; 241(6):337–344. [PubMed: 1504110]
33. Albus M, Zahn TP, Breier A. Anxiogenic properties of yohimbine. II. Influence of experimental set and setting. Eur. Arch. Psychiatry Clin. Neurosci. 1992; 241(6):345–351. [PubMed: 1504111]
34. Charney DS, Heninger GR. Abnormal regulation of noradrenergic function in panic disorders. Effects of clonidine in healthy subjects and patients with agoraphobia and panic disorder. Arch. Gen. Psychiatry. 1986; 43(11):1042–1054. [PubMed: 3021083]

35. Charney DS, Woods SW, Goodman WK, Heninger GR. Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. Am. J. Psychiatry. 1987; 144(8):1030–1036. [PubMed: 3037926]
36. Yeragani VK, Tancer M, Uhde T. Heart rate and QT interval variability: abnormal alpha-2 adrenergic function in patients with panic disorder. Psychiatry Res. 2003; 121(2):185–196. [PubMed: 14656453]
37. Chaouloff F. Effects of acute physical exercise on central serotonergic systems. Med. Sci. Sports Exerc. 1997; 29(1):58–62. [PubMed: 9000156]
38. Broocks A, Schweiger U, Pirke KM. The influence of semistarvation-induced hyperactivity on hypothalamic serotonin metabolism. Physiol. Behav. 1991; 50(2):385–388. [PubMed: 1720894]
39. Broocks A, Meyer T, George A, et al. Decreased neuroendocrine responses to meta-chlorophenylpiperazine (m-CPP) but normal responses to ipsapirone in marathon runners. Neuropsychopharmacology. 1999; 20(2):150–161. [PubMed: 9885795]
40. Broocks A, Meyer T, Gleiter CH, et al. Effect of aerobic exercise on behavioral and neuroendocrine responses to meta-chlorophenylpiperazine and to ipsapirone in untrained healthy subjects. Psychopharmacology (Berl.). 2001; 155(3):234–241. [PubMed: 11432685]
41. Broocks A, Liu J, Pirke KM. Semistarvation-induced hyperactivity compensates for decreased norepinephrine and dopamine turnover in the mediobasal hypothalamus of the rat. J. Neural Transm. Gen. Sect. 1990; 79(1–2):113–124. [PubMed: 2297396]
42. Morishima M, Harada N, Hara S, et al. Monoamine oxidase A activity and norepinephrine level in hippocampus determine hyperwheel running in SPORTS rats. Neuropsychopharmacology. 2006; 31(12):2627–2638. [PubMed: 16421512]
43. Sommer M, Braumann M, Althoff T, et al. Psychological and neuroendocrine responses to social stress and to the administration of the alpha-2-receptor antagonist, yohimbine, in highly trained endurance athletes in comparison to untrained healthy controls. Pharmacopsychiatry. 2011; 44(4): 129–134. [PubMed: 21710402]
44. Dishman RK, Armstrong RB, Delp MD, Graham RE, Dunn AL. Open-field behavior is not related to treadmill performance in exercising rats. Physiol. Behav. 1988; 43(5):541–546. [PubMed: 3200908]
45. Morgan WP, Olson EB Jr, Pedersen NP. A rat model of psychopathology for use in exercise science. Med. Sci. Sports Exerc. 1982; 14(1):91–100. [PubMed: 7070264]
46. Royce JR. On the construct validity of open-field measures. Psychol. Bull. 1977; 84(6):1098–1106.
47. Jones DL, Mogenson GJ. Nucleus accumbens to globus pallidus GABA projection subserving ambulatory activity. Am. J. Physiol. 1980; 238(1):R65–R69. [PubMed: 7356049]
48. Jones DL, Mogenson GJ, Wu M. Injections of dopaminergic, cholinergic, serotoninergic and GABAergic drugs into the nucleus accumbens: effects on locomotor activity in the rat. Neuropharmacology. 1981; 20(1):29–37. [PubMed: 6261181]
49. Tharp GD, Carson WH. Emotionality changes in rats following chronic exercise. Med. Sci. Sports. 1975; 7(2):123–126. [PubMed: 1171347]
50. Weber JC, Lee RA. Effects of differing prepuberty exercise programs on the emotionality of male albino rats. Res. Q. 1968; 39(3):748–751. [PubMed: 5246982]
51. Dishman RK, Dunn AL, Youngstedt SD, et al. Increased open-field locomotion and decreased striatal $GABA_A$ binding after activity wheel running. Physiol. Behav. 1996; 60(3):699–705. [PubMed: 8873239]
52. Streeter CC, Jensen JE, Perlmutter RM, et al. Yoga Asana sessions increase brain GABA levels: a pilot study. J. Altern. Complement. Med. 2007; 13(4):419–426. [PubMed: 17532734]
53. Streeter CC, Whitfield TH, Owen L, et al. Effects of yoga versus walking on mood, anxiety, and brain GABA levels: a randomized controlled MRS study. J. Altern. Complement. Med. 2010; 16(11):1145–1152. [PubMed: 20722471]
54. Ströhle A, Feller C, Strasburger CJ, Heinz A, Dimeo F. Anxiety modulation by the heart? Aerobic exercise and atrial natriuretic peptide. Psychoneuroendocrinology. 2006; 31(9):1127–1130. [PubMed: 17010527] • Exercise increased plasma atrial natriuretic peptide and reduced anxious responding.

55. Ströhle A, Jahn H, Montkowski A, et al. Central and peripheral administration of atriopeptin is anxiolytic in rats. Neuroendocrinology. 1997; 65(3):210–215. [PubMed: 9088002]
56. Ströhle A, Kellner M, Holsboer F, Wiedemann K. Anxiolytic activity of atrial natriuretic peptide in patients with panic disorder. Am. J. Psychiatry. 2001; 158(9):1514–1516. [PubMed: 11532742]
57. Mandroukas K, Zakas A, Aggelopoulou N, Christoulas K, Abatzides G, Karamouzis M. Atrial natriuretic factor responses to submaximal and maximal exercise. Br. J. Sports Med. 1995; 29(4): 248–251. [PubMed: 8808538]
58. Kaplan GB, Vasterling JJ, Vedak PC. Brain-derived neurotrophic factor in traumatic brain injury, posttraumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment. Behav. Pharmacol. 2010; 21(5–6):427–437. [PubMed: 20679891]
59. Nagahara AH, Tuszynski MH. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nat. Rev. Drug Discov. 2011; 10(3):209–219. [PubMed: 21358740]
60. Cirulli F, Berry A, Chiarotti F, Alleva E. Intrahippocampal administration of BDNF in adult rats affects short-term behavioral plasticity in the Morris water maze and performance in the elevated plus-maze. Hippocampus. 2004; 14(7):802–807. [PubMed: 15382250]
61. Egan MF, Kojima M, Callicott JH, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003; 112(2): 257–269. [PubMed: 12553913]
62. Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol. Psychiatry. 2007; 12(7): 656–670. [PubMed: 17264839]
63. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int. J. Neuropsychopharmacol. 2008; 11(8):1169–1180. [PubMed: 18752720]
64. Dell'osso L, Carmassi C, Del Debbio A, et al. Brain-derived neurotrophic factor plasma levels in patients suffering from posttraumatic stress disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2009; 33(5):899–902. [PubMed: 19409951]
65. Piccinni A, Marazziti D, Catena M, et al. Plasma and serum brain-derived neurotrophic factor (BDNF) in depressed patients during 1 year of antidepressant treatments. J. Affect. Disord. 2008; 105(1–3):279–283. [PubMed: 17553570]
66. Chen ZY, Jing D, Bath KG, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 2006; 314(5796):140–143. [PubMed: 17023662]
67. Ströhle A, Stoy M, Graetz B, et al. Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. Psychoneuroendocrinology. 2010; 35(3):364–368. [PubMed: 19682803] • Exercise increased brain-derived neurotrophic factor concentrations in panic disorder patients.
68. Kobayashi K, Shimizu E, Hashimoto K, et al. Serum brain-derived neurotrophic factor (BDNF) levels in patients with panic disorder: as a biological predictor of response to group cognitive–behavioral therapy. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2005; 29(5):658–663. [PubMed: 15905010]
69. Goekint M, Heyman E, Roelands B, et al. No influence of noradrenaline manipulation on acute exercise-induced increase of brain-derived neurotrophic factor. Med. Sci. Sports Exerc. 2008; 40(11):1990–1996. [PubMed: 18845978]
70. Gold SM, Schulz KH, Hartmann S, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J. Neuroimmunol. 2003; 138(1–2):99–105. [PubMed: 12742659]
71. Gustafsson G, Lira CM, Johansson J, et al. The acute response of plasma brain-derived neurotrophic factor as a result of exercise in major depressive disorder. Psychiatry Res. 2009; 169(3):244–248. [PubMed: 19729204]
72. Laske C, Banschbach S, Stransky E, et al. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. Int. J. Neuropsychopharmacol. 2010; 13(5):595–602. [PubMed: 20067661]

73. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. Med. Sci. Sports Exerc. 2007; 39(4):728–734. [PubMed: 17414812]
74. Schiffer T, Schulte S, Sperlich B, Achtzehn S, Fricke H, Strüder HK. Lactate infusion at rest increases BDNF blood concentration in humans. Neurosci. Lett. 2011; 488(3):234–237. [PubMed: 21094220]
75. Rojas Vega S, Strüder HK, Vera Wahrmann B, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. Brain Res. 2006; 1121(1):59–65. [PubMed: 17010953]
76. Winter B, Breitenstein C, Mooren FC, et al. High impact running improves learning. Neurobiol. Learn. Mem. 2007; 87(4):597–609. [PubMed: 17185007]
77. Dishman RK, O'Connor PJ. Lessons in exercise neurobiology: the case of endorphins. Ment. Health Phys. Act. 2009; 2(1):4–9.
78. Farrell PA, Gustafson AB, Garthwaite TL, Kalkhoff RK, Cowley AW Jr, Morgan WP. Influence of endogenous opioids on the response of selected hormones to exercise in humans. J. Appl. Physiol. 1986; 61(3):1051–1057. [PubMed: 3759744]
79. Markoff RA, Ryan P, Young T. Endorphins and mood changes in long-distance running. Med. Sci. Sports Exerc. 1982; 14(1):11–15. [PubMed: 7070250]
80. Sforzo GA. Opioids and exercise. An update. Sports Med. 1989; 7(2):109–124. [PubMed: 2537995]
81. Boecker H, Sprenger T, Spilker ME, et al. The runner's high: opioidergic mechanisms in the human brain. Cereb. Cortex. 2008; 18(11):2523–2531. [PubMed: 18296435]
82. Cunha RA, Ferré S, Vaugeois JM, Chen JF. Potential therapeutic interest of adenosine A2A receptors in psychiatric disorders. Curr. Pharm. Des. 2008; 14(15):1512–1524. [PubMed: 18537674]
83. Meeusen R, Piacentini MF, De Meirleir K. Brain microdialysis in exercise research. Sports Med. 2001; 31(14):965–983. [PubMed: 11735681]
84. Costa MS, Ardais AP, Fioreze GT, et al. Treadmill running frequency on anxiety and hippocampal adenosine receptors density in adult and middle-aged rats. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2012; 36(1):198–204. [PubMed: 22064330]
85. Crabbe JB, Dishman RK. Brain electrocortical activity during and after exercise: a quantitative synthesis. Psychophysiology. 2004; 41(4):563–574. [PubMed: 15189479]
86. Koltyn KF, Schultes SS. Psychological effects of an aerobic exercise session and a rest session following pregnancy. J. Sports Med. Phys. Fitness. 1997; 37(4):287–291. [PubMed: 9509828]
87. deVries, HA. Tension reduction with exercise. In: Morgan, WP.; Goldston, SE., editors. Exercise and Mental Health. Washington, DC, USA: Hemisphere Publishing Corp.; 1987. p. 99-104.
88. Morgan, WP.; O'Connor, PJ. Exercise and mental health. In: Dishman, RK., editor. Exercise Adherence: Its Impact on Public Health. IL, USA: Human Kinetics; 1988. p. 91-121.
89. Raglin JS, Morgan WP. Influence of vigorous exercise on mood state. Behav. Ther. 1985; 8:179–183.
90. Koltyn KF, Morgan WP. Influence of wet suit wear on anxiety responses to underwater exercise. Undersea Hyperb. Med. 1997; 24(1):23–28. [PubMed: 9068152]
91. Petruzzello SJ, Landers DM, Salazar W. Exercise and anxiety reduction: examination of temperature as an explanation for affective change. J. Sport Exercise Psy. 1993; 15:63–76.
92. Reeves DL, Levinson DM, Justesen DR, Lubin B. Endogenous hyperthermia in normal human subjects: experimental study of emotional states (II). Int. J. Psychosom. 1985; 32(4):18–23. [PubMed: 3865910]
93. Anderson KC, Insel TR. The promise of extinction research for the prevention and treatment of anxiety disorders. Biol. Psychiatry. 2006; 60(4):319–321. [PubMed: 16919521]
94. Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. Biol. Psychiatry. 2002; 52(10):976–986. [PubMed: 12437938]
95. Myers KM, Davis M. Mechanisms of fear extinction. Mol. Psychiatry. 2007; 12(2):120–150. [PubMed: 17160066]

96. Pavlov, IP. Conditioned Reflexes. London, UK: Oxford University Press; 1927.

97. Foa EB, Chambless DL. Habituation of subjective anxiety during flooding in imagery. Behav. Res. Ther. 1978; 16(6):391–399. [PubMed: 736873]

98. Watson JP, Gaind R, Marks IM. Physiological habituation to continuous phobic stimulation. Behav. Res. Ther. 1972; 10(3):269–278. [PubMed: 5047683]

99. Smits JAJ, Powers MB, Berry AC, Otto MW. Translating empirically supported strategies into accessible interventions: the potential utility of exercise for the treatment of panic disorder. Cogn. Behav. Pract. 2007; 14(4):364–374. •• Reviews literature examining utility of exercise for panic disorder.

100. McNally RJ. Anxiety sensitivity and panic disorder. Biol. Psychiatry. 2002; 52(10):938–946. [PubMed: 12437935]

101. Gardenswartz CA, Craske MG. Prevention of panic disorder. Behav. Ther. 2001; 32:725–737.

102. Smits JA, Powers MB, Cho Y, Telch MJ. Mechanism of change in cognitive-behavioral treatment of panic disorder: evidence for the fear of fear mediational hypothesis. J. Consult. Clin. Psychol. 2004; 72(4):646–652. [PubMed: 15301649]

103. Smits JA, Berry AC, Rosenfield D, Powers MB, Behar E, Otto MW. Reducing anxiety sensitivity with exercise. Depress. Anxiety. 2008; 25(8):689–699. [PubMed: 18729145]

104. Broman-Fulks JJ, Berman ME, Rabian BA, Webster MJ. Effects of aerobic exercise on anxiety sensitivity. Behav. Res. Ther. 2004; 42(2):125–136. [PubMed: 14975776]

105. Broman-Fulks JJ, Storey KM. Evaluation of a brief aerobic exercise intervention for high anxiety sensitivity. Anxiety. Stress. Coping. 2008; 21(2):117–128. [PubMed: 18350391]

106. Barlow DH, Allen LB, Choate ML. Toward a unified treatment for emotional disorders. Behav. Ther. 2004; 35:205–230.

107. Stathopoulou G, Powers MB, Berry AC, Smits JAJ, Otto MW. Exercise interventions for mental health: a quantitative and qualitative review. Clin. Psychol. Sci. Pr. 2006; 13(2):179–193.

108. Moses J, Steptoe A, Mathews A, Edwards S. The effects of exercise training on mental well-being in the normal population: a controlled trial. J. Psychosom. Res. 1989; 33(1):47–61. [PubMed: 2926699]

109. Bodin T, Martinsen EW. Mood and self-efficacy during acute exercise in clinical depression. A randomized, controlled study. J. Sport. Exercise Psy. 2004; 26:623–633.

110. McAuley E, Doerksen SE, Morris KS, et al. Pathways from physical activity to quality of life in older women. Ann. Behav. Med. 2008; 36(1):13–20. [PubMed: 18677453]

111. Katula JA, Blissmer BJ, McAuley E. Exercise intensity and self-efficacy effects on anxiety reduction in healthy, older adults. J. Behav. Med. 1999; 22(3):233–247. [PubMed: 10422616]

112. Spielberger, CD.; Gorusch, RL.; Luschene, R.; Vagg, PR.; Jacobs, GA. Manual for the State-Trait Anxiety Inventory. CA, USA: Consulting Psychologists Press; 1983.

113. Ekkekakis P, Petruzzello SJ. Acute aerobic exercise and affect: current status, problems and prospects regarding dose–response. Sports Med. 1999; 28(5):337–374. [PubMed: 10593646]

114. Marquez DX, Jerome GJ, McAuley E, Snook EM, Canaklisova S. Self-efficacy manipulation and state anxiety responses to exercise in low active women. Psychol. Health. 2002; 17(6):783–791.

115. McAuley E, Courneya KS, Rudolph DL, Lox CL. Enhancing exercise adherence in middle-aged males and females. Prev. Med. 1994; 23(4):498–506. [PubMed: 7971878]

116. Bahrke MS, Morgan WP. Anxiety reduction following exercise and meditation. Cognitive Ther. Res. 1978; 2(4):323–333.

117. Breus MJ, O'Connor PJ. Exercise-induced anxiolysis: a test of the 'time-out' hypothesis in high anxious females. Med. Sci. Sports Exerc. 1998; 30(7):1107–1112. [PubMed: 9662680]

118. Hassmén P, Koivula N, Uutela A. Physical exercise and psychological well-being: a population study in Finland. Prev. Med. 2000; 30(1):17–25. [PubMed: 10642456]

119. Goodwin RD. Association between physical activity and mental disorders among adults in the United States. Prev. Med. 2003; 36(6):698–703. [PubMed: 12744913]

120. Ströhle A, Höfler M, Pfister H, et al. Physical activity and prevalence and incidence of mental disorders in adolescents and young adults. Psychol. Med. 2007; 37(11):1657–1666. [PubMed: 17579930]

121. Schmitz N, Kruse J, Kugler J. The association between physical exercises and health-related quality of life in subjects with mental disorders: results from a cross-sectional survey. Prev. Med. 2004; 39(6):1200–1207. [PubMed: 15539056]

122. Esquivel G, Schruers K, Kuipers H, Griez E. The effects of acute exercise and high lactate levels on 35% CO_2 challenge in healthy volunteers. Acta Psychiatr. Scand. 2002; 106(5):394–397. [PubMed: 12366475]

123. Ströhle A, Feller C, Onken M, Godemann F, Heinz A, Dimeo F. The acute antipanic activity of aerobic exercise. Am. J. Psychiatry. 2005; 162(12):2376–2378. [PubMed: 16330604]

124. Smits JA, Meuret AE, Zvolensky MJ, Rosenfield D, Seidel A. The effects of acute exercise on CO(2) challenge reactivity. J. Psychiatr. Res. 2009; 43(4):446–454. [PubMed: 18603261]

125. Esquivel G, Díaz-Galvis J, Schruers K, Berlanga C, Lara-Muñoz C, Griez E. Acute exercise reduces the effects of a 35% CO_2 challenge in patients with panic disorder. J. Affect. Disord. 2008; 107(1–3):217–220. [PubMed: 17727960] • Exercise intensity is positively related to decreased anxious responding in panic patients.

126. Ströhle A, Graetz B, Scheel M, et al. The acute antipanic and anxiolytic activity of aerobic exercise in patients with panic disorder and healthy control subjects. J. Psychiatr. Res. 2009; 43(12):1013–1017. [PubMed: 19289240]

127. Garvin AW, Koltyn KF, Morgan WP. Influence of acute physical activity and relaxation on state anxiety and blood lactate in untrained college males. Int. J. Sports Med. 1997; 18(6):470–476. [PubMed: 9351695]

128. Grosz HJ, Farmer BB. Blood lactate in the development of anxiety symptoms. A critical examination of Pitts and McClure's hypothesis and experimental study. Arch. Gen. Psychiatry. 1969; 21(5):611–619. [PubMed: 5823483]

129. O'Connor PJ, Smith JC, Morgan WP. Physical activity does not provoke panic attacks in patients with panic disorder: a review of the evidence. Anxiety, Stress Coping. 2000; 13(4):333–353.

130. Pitts FN Jr. The biochemistry of anxiety. Sci. Am. 1969; 220(2):69–75. [PubMed: 4886147]

131. Pitts FN Jr, McClure JN Jr. Lactate metabolism in anxiety neurosis. N. Engl. J. Med. 1967; 277(25):1329–1336. [PubMed: 6081131]

132. Wipfli BM, Rethorst CD, Landers DM. The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose–response analysis. J. Sport Exerc. Psychol. 2008; 30(4):392–410. [PubMed: 18723899] •• Meta-analysis revealing a moderate effect for exercise over control conditions.

133. Broocks A, Bandelow B, Pekrun G, et al. Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder. Am. J. Psychiatry. 1998; 155(5):603–609. [PubMed: 9585709] • 10-week exercise program outperformed placebo at post-treatment in anxiety reduction.

134. Merom D, Phongsavan P, Wagner R, et al. Promoting walking as an adjunct intervention to group cognitive–behavioral therapy for anxiety disorders – a pilot group randomized trial. J. Anxiety Disord. 2008; 22(6):959–968. [PubMed: 17988832] •• Exercise augmention to cognitive-behavioral therapy outperformed active placebo in anxiety disorder patients.

135. Martinsen EW, Hoffart A, Solberg ØY. Aerobic and nonaerobic forms of exercise in the treatment of anxiety disorders. Stress. Med. 1989; 5(2):115–120.

136. Brown RA, Abrantes AM, Strong DR, et al. A pilot study of moderate-intensity aerobic exercise for obsessive-compulsive disorder. J. Nerv. Ment. Dis. 2007; 195(6):514–520. [PubMed: 17568300]

137. Diaz AB, Motta R. The effects of an aerobic exercise program on posttraumatic stress disorder symptom severity in adolescents. Int. J. Emerg. Ment. Health. 2008; 10(1):49–59. [PubMed: 18546759]

138. Newman CL, Motta RW. The effects of aerobic exercise on childhood PTSD, anxiety, and depression. Int. J. Emerg. Ment. Health. 2007; 9(2):133–158. [PubMed: 17725082]

139. Hale BS, Raglin JS. State anxiety responses to acute resistance training and step aerobic exercise across eight weeks of training. J. Sports Med. Phys. Fitness. 2002; 42(1):108–112. [PubMed: 11832884]

140. Raglin JS, Wilson M. State anxiety following 20 minutes of bicycle ergometer exercise at selected intensities. Int. J. Sports Med. 1996; 17(6):467–471. [PubMed: 8884424]

141. Bibeau WS, Moore JB, Mitchell NG, Vargas-Tonsing T, Bartholomew JB. Effects of acute resistance training of different intensities and rest periods on anxiety and affect. J. Strength Cond. Res. 2010; 24(8):2184–2191. [PubMed: 19834350]

142. Raglin JS, Turner PE, Eksten F. State anxiety and blood pressure following 30 min of leg ergometry or weight training. Med. Sci. Sports Exerc. 1993; 25(9):1044–1048. [PubMed: 8231773]

143. Koltyn KF, Raglin JS, O'Connor PJ, Morgan WP. Influence of weight training on state anxiety, body awareness and blood pressure. Int. J. Sports Med. 1995; 16(4):266–269. [PubMed: 7657422]

144. Cassilhas RC, Antunes HK, Tufik S, de Mello MT. Mood, anxiety, and serum IGF-1 in elderly men given 24 weeks of high resistance exercise. Percept. Mot. Skills. 2010; 110(1):265–276. [PubMed: 20391891]

145. Tsutsumi T, Don BM, Zaichkowsky LD, Takenaka K, Oka K, Ohno T. Comparison of high and moderate-intensity of strength training on mood and anxiety in older adults. Percept. Mot. Skills. 1998; 87(3 Pt 1):1003–1011. [PubMed: 9885072]

146. Tsutsumi T, Don BM, Zaichkowsky LD, Delizonna LL. Physical fitness and psychological benefits of strength training in community dwelling older adults. Appl. Human Sci. 1997; 16(6): 257–266.

147. Field T, Diego M, Hernandez-Reif M. Tai chi/yoga effects on anxiety, heartrate, EEG and math computations. Complement. Ther. Clin. Pract. 2010; 16(4):235–238. [PubMed: 20920810]

148. Petruzzello SJ, Landers DM, Hatfield BD, Kubitz KA, Salazar W. A meta-analysis on the anxiety-reducing effects of acute and chronic exercise. Outcomes and mechanisms. Sports Med. 1991; 11(3):143–182. [PubMed: 1828608]

149. Wipfli BM, Rethorst CD, Landers DM. The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose–response analysis. J. Sport Exerc. Psychol. 2008; 30(4):392–410. [PubMed: 18723899]

150. O'Connor PJ, Raglin JS, Morgan WP. Psychometric correlates of perception during arm ergometry in males and females. Int. J. Sports Med. 1996; 17(6):462–466. [PubMed: 8884423]

151. Williams DM, Dunsiger S, Ciccolo JT, Lewis BA, Albrecht AE, Marcus BH. Acute affective response to a moderate-intensity exercise stimulus predicts physical activity participation 6 and 12 months later. Psychol. Sport Exerc. 2008; 9(3):231–245. [PubMed: 18496608]

152. Otto MW, Smits JAJ. Exercise for Mood and Anxiety: Proven Strategies for Overcoming Depression and Enhancing Well-Being. 2011NY, USAOxford University Press •• Reviews evidence for exercise interventions for anxiety.

153. Dishman RK. Increasing and maintaining exercise and physical activity. Behav. Ther. 1991; 22(3):345–378.

154. Smits JA, Tart CD, Presnell K, Rosenfield D, Otto MW. Identifying potential barriers to physical activity adherence: anxiety sensitivity and body mass as predictors of fear during exercise. Cogn. Behav. Ther. 2010; 39(1):28–36. [PubMed: 19675961]

155. Atalay A, Gençöz T. Critical factors of social physique anxiety: exercising and body image satisfaction. Behav. Change. 2008; 25(3):178–188.

156. Ekkekakis P, Lind E, Vazou S. Affective responses to increasing levels of exercise intensity in normal-weight, overweight, and obese middle-aged women. Obesity (Silver Spring). 2010; 18(1): 79–85. [PubMed: 19556979]

157. Mata J, Thompson RJ, Gotlib IH. BDNF genotype moderates the relation between physical activity and depressive symptoms. Health Psychol. 2010; 29(2):130–133. [PubMed: 20230085]

158. Toups MS, Greer TL, Kurian BT, et al. Effects of serum Brain-Derived Neurotrophic Factor on exercise augmentation treatment of depression. J. Psychiatr. Res. 2011; 45(10):1301–1306. [PubMed: 21641002]

159. Otto MW, Smits JAJ, Reese HE. Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults: review and analyses. Clin. Psychol- Sci. Pr. 2005; 12:72–86.

160. Marcus BH, Albrecht AE, King TK, et al. The efficacy of exercise as an aid for smoking cessation in women: a randomized controlled trial. Arch. Intern. Med. 1999; 159(11):1229–1234. [PubMed: 10371231]

161. Smits JA, Hofmann SG. A meta-analytic review of the effects of psychotherapy control conditions for anxiety disorders. Psychol. Med. 2009; 39(2):229–239. [PubMed: 18466666]

162. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu. Rev. Clin. Psychol. 2007; 3:1–27. [PubMed: 17716046]

163. Smits JA, Rosenfield D, McDonald R, Telch MJ. Cognitive mechanisms of social anxiety reduction: an examination of specificity and temporality. J. Consult. Clin. Psychol. 2006; 74(6): 1203–1212. [PubMed: 17154749]

Key issues

- Current gold standard treatments for anxiety disorders are limited in their effectiveness, necessitating the study of treatment augmentation strategies and alternative approaches to anxiety treatment.
- Studies linking exercise to processes theorized to operate in anxiety reduction provide theoretical support for exercise interventions.
- Potential mechanisms of change include extinction learning; modulation of neurotransmitter functioning, atrial natriuretic peptide and brain-derived neurotrophic factor; and modification of emotional action tendencies and self-efficacy.
- Research demonstrating anxiety reduction following both acute bouts of exercise and programmatic exercise have provided initial support for the potential of exercise as stand-alone or complementary intervention for anxiety disorders.
- Few trials have examined exercise intervention efficacy among individuals suffering from an anxiety disorder, but initial trials have shown promise.
- More randomized controlled trials of other anxiety disorders are needed.
- Future work should examine mediators in order to increase understanding of the mechanism of change of exercise intervention and thus, enable the refinement of exercise intervention strategies.
- The identification of moderators, including possible exercise intervention parameters and person factors, will help assist clinicians in deciding how and for whom to prescribe exercise.