Exercise Augmentation of Exposure Therapy for PTSD: Rationale and Pilot Efficacy Data

Mark B. Powers¹, Johnna L. Medina¹, Stephanie Burns¹, Brooke Y. Kauffman¹, Marie Monfils¹, Gordon J.G. Asmundson², Allison Diamond¹, Christa McIntyre³, and Jasper A.J. Smits¹

¹Department of Psychology, Institute for Mental Health Research, The University of Texas at Austin, Austin, TX, USA
²Department of Psychology, University of Regina, Regina, Canada
³School of Behavioral Health and Brain Sciences, The University of Texas at Dallas, Dallas, TX, USA

Abstract

Brain-derived neurotrophic factor (BDNF) is associated with synaptic plasticity, which is crucial for long-term learning and memory. Some studies suggest that people suffering from anxiety disorders show reduced BDNF relative to healthy controls. Lower BDNF is associated with impaired learning, cognitive deficits, and poor exposure-based treatment outcomes. A series of studies with rats showed that exercise elevates BDNF and enhances fear extinction. However, this strategy has not been tested in humans. In this pilot study, we randomized participants (N = 9, 8 females, M_Age = 34) with posttraumatic stress disorder (PTSD) to (a) prolonged exposure alone (PE) or (b) prolonged exposure + exercise (PE + E). Participants randomized to the PE + E condition completed a 30-minute bout of moderate-intensity treadmill exercise (70% of age-predicted HR_max) prior to each PE session. Consistent with prediction, the PE + E group showed a greater improvement in PTSD symptoms (d = 2.65) and elevated BDNF (d = 1.08) relative to the PE only condition. This pilot study provides initial support for further investigation into exercise augmented exposure therapy.

Keywords

exercise; augmentation; exposure therapy; BDNF; anxiety disorders; pilot data; CBT

Introduction

Exposure therapy has demonstrated clear efficacy for the anxiety disorders, offering clinically meaningful advantages over psychological placebo conditions and showing improvements in symptoms comparable to established pharmacotherapies (Barlow, Gorman,

¹Correspondence address: Mark B. Powers, Department of Psychology, Institute for Mental Health Research, The University of Texas at Austin, Austin, TX, USA. mbpowers@utexas.edu.

Disclosure statement: The authors have declared that no conflict of interest exists.
Shear, & Woods, 2000; Blanco et al., 2010; Goodson et al., 2011; Hofmann & Smits, 2008; Powers & Emmelkamp, 2008; Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010; Powers, Sigmarsson, & Emmelkamp, 2008; Simpson et al., 2013). However, many patients who receive exposure therapy either fail to respond or continue to experience some residual symptoms following treatment discontinuation (Barlow et al., 2000; Blanco et al., 2010; Hofmann & Smits, 2008; Simpson et al., 2013). Large clinical trials of exposure-based treatment efficacy for the various anxiety disorders have yielded non-optimal response rates of up to 49% for social anxiety disorder (Davidson et al., 2004), 38% for obsessive-compulsive disorder (Foa et al., 2005), 36% for panic disorder (Barlow et al., 2000), and 44% for PTSD (Foa, Rothbaum, Riggs, & Murdock, 1991). Accordingly, the agenda for exposure therapy research has shifted to the development of strategies to enhance the efficacy of exposure therapy. Augmentation strategies that reduce anxiety during exposure therapy (breathing retraining, anxiety reducing drugs/benzodiazepines, and use of safety behaviors) have failed to enhance outcome (Otto, Hong, & Safren, 2002; Powers, Smits, & Telch, 2004; Powers, Smits, Whiteley, Bystritsky, & Telch, 2008; Schmidt et al., 2000); however, strategies that enhance the learning that takes place during exposure therapy appear more promising (Powers, Smits, Leyro, & Otto, 2007; Powers, Vervliet, Smits, & Otto, 2009). One such augmentation strategy to enhance exposure learning is physical exercise.

The primary aims of this article are to detail the rationale for use of exercise as an augmentation strategy for exposure therapy and to present findings from a small-scale randomized study that tested the efficacy of exercise as an aid to exposure therapy in adults suffering from PTSD. PTSD is most similar to the translational research on extinction research given there is a definitive conditioning event (the trauma). We have organized the article into three sections. In the first section, we present a rationale for using exercise as an augmentation strategy, focusing specifically on the capacity of exercise to manipulate a key molecular mediator of fear extinction. In the second section, we describe the methodology and findings of the pilot study. In the third and final section, we provide directions for future research in this area.

Rationale

Fear extinction as a model for exposure therapy

Emphasizing the current priority of the National Institute of Mental Health to support translational research, Anderson & Insel (2006) discussed the promise of fear extinction research, particularly that which examines fear extinction retention, for improving treatment outcome for people with anxiety disorders. As others have asserted (Bouton, 2002; Myers & Davis, 2007), Anderson & Insel (2006) draw parallels between the procedures employed in animal and human studies of extinction learning and those used in exposure therapy. Specifically, extinction training and exposure therapy involve repeated exposure to feared cues without the associated negative outcome (Pavlov, 1927). Extinction retention has been associated with greater symptom reduction following exposure therapy (Berry, Rosenfield, & Smits, 2009); hence, parameters of fear extinction training related to greater consolidation of fear extinction learning may guide the development of strategies that can augment the
efficacy of exposure therapy (Berry et al., 2009; Ledgerwood, Richardson, & Cranney, 2004; Myers & Davis, 2007; Santini, Ge, Ren, Penza de Ortiz, & Quirk, 2004).

Converging evidence from studies of extinction in human and non-human animals indicates that the same structures implicated in the maintenance of PTSD are involved in extinction of conditioned fear. In particular, hyperreactivity is seen in the amygdala (Nutt & Malizia, 2004) and decreased activity is exhibited in the ventromedial prefrontal cortex (vmPFC; Etkin & Wager, 2007) in individuals suffering from PTSD. Hippocampal volume and metabolic rate are also reduced in PTSD (Smith, 2005). Both human and animal studies implicate the amygdala in fear conditioning (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; LeDoux, Sakaguchi, & Reis, 1984), indicating that the function of the amygdala is conserved across species and hyperactivity in the amygdala may contribute to enhanced recall of traumatic memories in PTSD (Pitman, Shin, & Rauch, 2001). Anatomical studies show that the vmPFC projects to the amygdala, predominantly to inhibitory neurons in the intercalated region (intercalated cells are important for inhibitory control over the amygdala), suggesting that vmPFC activity may suppress amygdala activity. Quirk and colleagues (Quirk, Russo, Barron, & Lebron, 2000) reported evidence indicating that lesions of the infralimbic region (IL) of the rodent vmPFC impaired extinction of conditioned fear. The authors proposed that the IL interacts with the amygdala to enable the extinction of conditioned fear, a finding that is now supported by further studies in rats (Mueller, Bravo-Rivera, & Quirk, 2010; Quirk, Likhtik, Pelletier, & Paré, 2003) and in humans (Linnman et al., 2012; Phelps, Delgado, Nearing, & LeDoux, 2004). One of the limitations of exposure therapy is the return of fear that occurs after the conditioned response appears to be extinguished. The hippocampus plays a role in gating of extinction to a specific conditioned stimulus, thus preventing generalization of extinction to multiple contexts (Ji & Maren, 2005). Inactivation of the hippocampus prevents the return of fear in rats exposed to the conditioned cue in a new context (Ji & Maren, 2005); however, inactivation of the hippocampus during extinction training impairs extinction recall the following day, indicating that the hippocampus is necessary for the consolidation of extinction learning (Corcoran, Desmond, Frey, & Maren, 2005).

Fear extinction research can guide the development of strategies to enhance exposure therapy: a successful example of translational research

As described in the previous section, animal research on fear extinction has helped delineate core mechanisms and structures involved in the extinction of conditioned fear. The last decade has illustrated how this basic and mechanistic research can help identify treatment targets and corresponding interventions for enhancing exposure therapy outcomes. Specifically, in their animal research, Davis and colleagues first demonstrated that extinction learning is modulated by activity of the glutamatergic N-methyl-D-aspartate receptor (NMDA-R) in the amygdala (Davis, Ressler, Rothbaum, & Richardson, 2006). They showed that inhibitors of this activity blocked the retention of extinction learning (Falls, Miserendino, & Davis, 1992) and, likewise, partial agonists, such as d-cycloserine (DCS), enhance the consolidation of this learning (Ledgerwood, Richardson, & Cranney, 2003; Walker, Ressler, Lu, & Davis, 2002). Teaming up with clinical researchers, Davis and colleagues then translated these preclinical findings, demonstrating that the acute pre-session
administration of DCS facilitated reductions in fear of heights with exposure therapy. Since then, a number of clinical trials (e.g. Hofmann et al., 2013; Smits et al., 2013; Smits et al., 2013; Tart et al., 2013) have replicated and extended these findings to other anxiety disorder samples (Rodrigues et al., 2014). This translational research success supports a continued focus on fear extinction and its core mechanisms for developing augmentation interventions for exposure therapy (Anderson & Insel, 2006).

**BDNF: a key mechanism underlying fear extinction**

One key target for augmentation of exposure therapy is brain-derived neurotrophic factor (BDNF). BDNF is a member of the neurotrophins—a family of structurally related proteins that promote neuronal differentiation and survival during development (Barde, 1994; Levi-Montalcini, 1987)—and has been implicated in a host of pathological conditions. BDNF is also a potent modulator of synaptic plasticity (Arancio & Chao, 2007; Bramham & Messaoudi, 2005; Schinder & Poo, 2000) and much effort has been devoted to studying its role in the hippocampus, a structure traditionally associated with learning and memory.

These sets of studies suggest that BDNF plays a role in hippocampal long-term potentiation (LTP) and learning. Initial work showed deficits in early LTP (E-LTP) in BDNF knock-out mice that could be rescued by exogenous administration of BDNF (Korte et al., 1995; Patterson et al., 1996). Intrahippocampal infusions of tropomyosin receptor kinase (Trk)B Fc, which prevents BDNF from binding to TrkB receptors, was found to impair LTP induction (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996; Patterson et al., 1996), E-LTP (Figurov et al., 1996; Patterson et al., 1996), and late-phase LTP (L-LTP; Kang, Welcher, Shelton, & Schuman, 1997; Patterson et al., 1996) in slice preparations. Preventing BDNF signaling also impaired hippocampus-dependent learning (Bekinschtein et al., 2007).

Recent work indicates that exogenous infusions of BDNF can induce synaptic potentiation. This was first demonstrated in the slice preparation at CA3-CA1 synapses (Kang & Schuman, 1995, 1996) and, more recently, in vivo in the dentate gyrus (DG; Messaoudi, Ying, Kanhema, Croll, & Bramham, 2002). Messaoudi and colleagues’ work suggests that BDNF-induced LTP in the DG is NMDA-R independent, while high frequency stimulation (HFS)-induced LTP requires NMDA-R activation (Messaoudi et al., 2002). However, BDNF- and HFS-induced LTP share common mechanisms as evidenced by observations that BDNF-LTP is occluded when BDNF is infused post-HFS-LTP. In addition, HFS-induced LTP induces BDNF release that is dependent on NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-R activation (Hartmann, Heumann, & Lessmann, 2001); hence, it appears that the induction of LTP by exogenous BDNF can bypass early stages of HFS-induced potentiation but that, in either case, BDNF is required for maintenance (Messaoudi et al., 2007, 2002; Santi et al., 2006). There is increasing empirical support for the role of another structure—the amygdala—in changes induced by BDNF. Indeed, temporally specific changes in BDNF gene expression were found to occur in the LA after paired stimuli that supported learning, but not after exposure to neutral or aversive stimuli alone (Rattiner, Davis, French, & Ressler, 2004).

Given the above, it is not surprising that BDNF has been shown to play an important role in the extinction of conditioned fear. Effectively, activation of the TrkB receptor by BDNF in the basolateral complex of the amygdala is necessary for the consolidation, but not...
acquisition, of fear extinction in rats (Chhatwal, Stanek-Rattiner, Davis, Ressler, & Amygdala, 2006). Deletion of BDNF in the adult hippocampus impairs extinction in mice (Heldt, Stanek, Chhatwal, & Ressler, 2007) and histone modifications were observed around the BDNF gene promoters in the mPFC following extinction of conditioned fear in mice (Bredy et al., 2007). These findings implicate the neurotrophin BDNF in the consolidation of fear extinction within the neurocircuitry that is affected in PTSD. Remarkably, Peters and colleagues (Peters, Dieppa-Perea, Melendez, & Quirk, 2010) showed that infralimbic BDNF infusions induced extinction of conditioned fear in rats even in the absence of extinction training. Taken together, these findings indicate that BDNF is both necessary and sufficient for the extinction of conditioned fear in rats.

Additional support for the role of BDNF in fear extinction retention comes from research linking a single nucleotide polymorphism (SNP) in the gene encoding BDNF (i.e., BDNF Val66Met genotype) to impaired extinction learning in mice and humans (Soliman et al., 2010). Extending this research, Felmingham and colleagues showed that PTSD patients with the BDNF Met66 allele were not as responsive to exposure therapy as were those with the Val/Val genotype (Felmingham, Dobson-Stone, Schofield, Quirk, & Bryant, 2013).

In summary, BDNF is crucial for synaptic plasticity in brain regions that are critically involved in the consolidation of extinction. Reduced BDNF release in humans is associated with impaired functioning of this extinction circuitry. Therefore, methods to enhance BDNF release may facilitate the consolidation of extinction learning and, consequently, improve exposure therapy outcomes.

**The promise of aerobic exercise for enhancing fear extinction and exposure therapy outcomes**

Basic research on fear extinction has supported the development and testing of a number of pharmacological agents, including DCS, as well as other pharmacological and somatic interventions for augmenting exposure therapy (Powers, Smits, Otto, Sanders, & Emmelkamp, 2009; Smits et al., 2013, 2014). Because patients seeking care for anxiety disorders generally prefer behavioral over pharmacological and somatic approaches (Arch, 2014; McHugh, Whitton, Peckham, Welge, & Otto, 2013; Roy-Byrne, Berliner, Russo, Zatzick, & Pitman, 2003), it is important to develop and make available behavioral interventions that can manipulate the core mechanisms involved in fear extinction/exposure therapy. Aerobic exercise emerges as a promising candidate for a number of reasons (Asmundson et al., 2013). First, patients with anxiety disorders and their providers generally already perceive exercise as a useful strategy for their recovery (Daley, 2002). Second, widely prescribed to promote health and longevity, exercise is a non-invasive intervention with low incidence of adverse events in adults with psychiatric illness (Blumenthal et al., 1999; Trivedi et al., 2011). Third, extant literature suggests that exercise significantly increases BDNF activity in regions of the brain critical to fear extinction (Cho et al., 2012; Cotman & Berchtold, 2002; Heyman et al., 2012; Stroyöhle et al., 2010). Indeed, a number of studies have shown that chronic and acute aerobic exercise increase BDNF levels in the hippocampus of rats (Chen & Russo-Neustadt, 2009; Dravid et al., 2010; Neeper, Goómez-Pinilla, Choi, & Cotman, 1996; Oliff, Berchtold, Isackson, & Cotman, 1998; Vaynman,
Fourth, an acute bout of voluntary wheel running enhances extinction retention in rats (Siette, Reichelt, & Westbrook, 2014). Siette et al. (2014) showed that wheel access just before or just after extinction training resulted in reduced freezing at test. However, wheel access long before or long after extinction (6 hours) did not enhance retention. There also appeared to be a dose–response relationship with greater running distance associated with greater fear learning/extinction. Another study showed voluntary running after extinction training increased neurogenesis in the dentate gyrus and reduced contextual fear relative to controls when tested 6 weeks later (Akers et al., 2014).

An important next step in building upon the promise of using aerobic exercise as an augmentation intervention of exposure therapy is to demonstrate that exercise, when prescribed acutely, can enhance exposure therapy outcomes in humans. In addition, keeping in mind the dissemination and utilization of this augmentation strategy in clinical practice, it is important to determine whether these putative effects can be observed with a moderate-intensity acute exercise bout (which can be prescribed to most individuals without formal medical clearance (American College for Sports Medicine, 2013)). A review of 24 studies indicates that acute exercise can yield meaningful increases in serum or plasma BDNF in healthy subjects and persons with chronic disease (psychiatric or medical; Knaepen, Goekint, Heyman, & Meeusen, 2010). These studies further indicate that a meaningful increase in peripheral BDNF levels with an acute exercise bout requires at least 15 minutes of moderate-intensity exercise (Schmolesky, Webb, & Hansen, 2013; Tang, Chu, Hui, Helmeste, & Law, 2008). Limited research with psychiatric patients confirms that 30 minutes of acute moderate- to vigorous-intensity aerobic exercise confers significant BDNF increases in adults with major depressive disorder (Gustafsson et al., 2009; Laske et al., 2010) or panic disorder (Stroëhle et al., 2010).

Building upon this extant research, we conducted a small pilot study testing whether preceding exposure therapy sessions with an acute moderate-intensity exercise bout confers increases in BDNF levels and greater reductions in symptom severity. We now provide an overview of this study and its findings.

Pilot study

Method

Design—Study participants were enrolled in a 12-session prolonged exposure therapy (PE) program and randomly assigned to either complete an acute bout of exercise prior to each session (PE+E) or no exercise prior to the session (PE-Alone). Assessments of the putative mediator (BDNF) occurred prior to the first session and immediately following the last session, and assessment of outcome (symptom severity) occurred at baseline, prior to each session, and at posttreatment.

Participants—Study participants (N = 9; 8 females, 1 male; $M_{\text{Age}} = 34, \text{SD =11.82}$) consisted of community individuals in the Dallas area. All participants met the following entry criteria: principal diagnosis of PTSD based on DSM-IV criteria; between the ages of 18 and 65 years; absence of physical conditions that could be exacerbated by exercise; body
mass index \(\text{[weight (kg)/height (m)\(^2\)]} < 35\); no history of bipolar or psychotic disorders; no diagnosis of an eating disorder or substance abuse or dependence (excluding nicotine) within the past three months; no history of organic brain syndrome, intellectual disability or other cognitive dysfunction that could interfere with the capacity to participate in CBT or to complete safety and efficacy assessments; for females, not currently pregnant and no plans to become pregnant during the course of the trial; no current involvement in a moderate-heavy intensity exercise program; no recent change in psychotropic medications (e.g., stabilized for at least 8 weeks); and, no concurrent trauma focused therapy. The study sample was 88.9% Caucasian \((n = 8)\) and 11.1% \((n = 1)\) other or mixed races, with 77.8% self identified as non-Hispanic \((n = 7)\) and 22.2% as Hispanic \((n = 2)\).

**Procedures**—Participants were recruited through a variety of local and online sources. Online advertisements contained a link to a secured eligibility prescreen survey. Individuals who appeared potentially eligible based on their survey responses were contacted via phone and given a phone screen to verify survey responses as well as information about the study. If the potential participant was still interested and appeared eligible they were invited to the site for a diagnostic screening interview. The diagnostic screen visit consisted of informed consent procedures and self-report questionnaires, followed by administration of the Structured Clinical Interview for DSM-IV-TR Diagnosis of Axis I Disorders (SCID; First, Spitzer, Gibbon, & Williams, 1996). Participants meeting all eligibility criteria were scheduled for a baseline visit one week prior to the therapy program, which consisted of an interview by an independent evaluator (IE), randomization, and a blood draw offsite (Quest Diagnostics Center). During the baseline independent evaluation, patients completed a clinician-rated assessment (PTSD Symptom Scale-Interview; PSSI) with an IE blind to study condition. Next, participants met with a trained staff member who randomized the individual (using a random number generator) and accompanied them to Quest Diagnostics, a clinical laboratory ~3 miles from the study site where 1 ml of plasma was collected via blood draw, spun, and flash frozen by Quest staff, and stored in their deep freeze until shipment. Patients then completed 12 weeks of treatment (either PE-Alone or PE+E) with an assigned protocol therapist. Immediately after the last treatment session they again met with the IE blind to condition to complete the PSSI and to Quest Diagnostics for the second and final blood draw.

**Measures**

**Brain Derived Neurotrophic Factor (BDNF):** Plasma BDNF was analyzed by RayBiotech, Inc. (Norcross, GA) using a sandwich enzyme-linked immunosorbent assay (ELISA) kit. We sampled plasma BDNF because it correlates with central BDNF levels (Angelucci, Gelfo, De Bartolo, Caltagirone, & Petrosini, 2011; Karege, Schwald, & Cisse, 2002). PTSD Symptom Scale-Interview Version (PSSI). The PSSI (Foa, Riggs, Dancu, & Rothbaum, 1993; Powers, Gillihan, Rosenfield, Jerud, & Foa, 2012) is a psychometrically sound 17-item interview that rates each of the DSM-IV symptom criteria on a 0–3 scale of frequency and severity. The PSSI yields a total score with a possible range from 0 to 51, with higher scores indicating more severe PTSD symptoms.
Exercise intervention—Participants assigned to the PE+E condition completed a 30-minute bout of moderate-intensity treadmill exercise (70% of age-predicted HR\textsubscript{max}) immediately prior to each PE session. During these exercise sessions, an exercise training management system was used similar to the method in previous studies (Smits et al., 2008, 2012; Smits, Meuret, Zvolensky, Rosenfield, & Seidel, 2009). The heart rate signal from a Polar transmitter (chest strap) was monitored and the clinician running the exercise session adjusted speed and incline of the treadmill accordingly. The training program consisted of a 5-minute warm-up at a progressively increasing speed until the target heart rate was reached. Participants then trained at that target heart rate for the time consistent with the training progression schedule. A 5-minute cool-down period followed, during which the speed was gradually reduced and participants then stretched.

Prolonged exposure therapy—All participants received PE. PE is a manualized treatment program consisting of 12 weekly treatment sessions that are approximately 90 minutes each (Foa, Hembree, & Rothbaum, 2007). PE includes the following procedures for treatment of PTSD: education about common reactions to trauma; breathing retraining (i.e., teaching the client how to breath in a calm way); prolonged and repeated imaginal exposure to the trauma memories to habituate to and process the traumatic experience; prolonged and repeated \textit{in vivo} exposure to safe situations the client is avoiding because of trauma-related fear; assignment of homework; and monitoring compliance with homework assignments. Each participant was treated by a clinical psychology doctoral student. Therapist training included a 5-day intensive workshop and 2 closely supervised cases, developed by Dr. Edna Foa and administered for this study by Dr. Mark Powers, who also provided ongoing clinical supervision.

Results

Figure 1 shows the relative increase in BDNF means and Figure 2 shows the relative declines in PTSD symptom means. More specifically, the PE pre- and post-BDNF means were 1.77 and 1.75, respectively, and the PE + E pre- and post-BDNF means were 1.38 and 3.73, respectively. The PE pre- and post-PSSI means were 37.00 and 8.25, respectively, and the PE + E pre- and post-PSSI means were 42.00 and 5.20, respectively. The dashed line in Figure 2 denotes the good end-state functioning cut-off (PSSI ≤10; Powers et al., 2012; Zandberg et al., under review). Because the sample size in this pilot trial was too small to conduct traditional significance tests, we computed between-group effect sizes (i.e., controlled Cohen’s \(d\)) of pre- to post-treatment changes in the putative mediator and outcome (see Figure 3). Consistent with prediction, PE E increased BDNF to a greater degree than PE-Alone, yielding a large between group effect size (\(d = 1.08, SE = 0.72\)). Also consistent with prediction, PE + E outperformed PE-Alone on PTSD symptom reduction, yielding a very large between-group effect size (\(d = 2.65, SE = 0.92\)).

Directions for future research

Theoretical accounts and empirical data reviewed in this article support further study of exercise as an augmentation strategy for exposure therapy. As reviewed, exercise may have the potential to enhance outcome in general and aid those individuals for whom a regular
exposure therapy regimen falls short in delivering the desired outcomes. More specifically, exercise acts as a cognitive enhancer, manipulating the core mechanisms of exposure therapy (e.g., synaptic plasticity). The development of this clinical application is in the early stages, and in this last section we offer a few suggestions for research that we believe can aid this effort.

**Mechanisms of action**

Too often treatment development has primarily focused on clinical outcomes and ignored the study of the treatment’s mechanisms of action. Without investigating the putative mechanisms, it is challenging to refine an intervention, and null findings regarding clinical outcomes are especially difficult to interpret. In previous sections, we have reviewed the literature supporting the exercise–BDNF–fear extinction relation. We would like to note here that there are a number of challenges to studying this relation. First, while exercise-induced increases in peripheral BDNF concentrations are predominately a result of BDNF release in the brain regions critical to fear extinction, there are several other sources (e.g., smooth muscle, lymphocytes, skeletal muscle, endothelium; Knaepen et al., 2010; Pareja-Galeano et al., 2015) that contribute to peripheral BDNF levels. Exercise may also increase central BDNF without resulting in a change in peripheral BDNF concentrations (Knaepen et al., 2010). Accordingly, research on the exercise–BDNF–fear extinction relation in humans should be complemented by research on this relation in animals, where it may be possible to more firmly establish BDNF release in brain areas critical to fear extinction as the mediator of the effects of exercise for enhancing fear extinction. Second, our study and others examined BDNF levels in plasma. However, as discussed by Pareja-Galeano and colleagues Pareja-Galeano et al. (2015), BDNF sampling and data analytic procedures may strongly influence the magnitude of the effect of exercise on peripheral BDNF concentrations. Specifically, they found that exercise increased BDNF concentrations in serum when samples coagulated at 4°C for 24 hrs as well as in whole blood, but not in serum coagulated at 4°C for 10 minutes or in plasma. Based on their findings and review, they provided specific recommendations for accurately determining peripheral BDNF changes induced by exercise, which include adjusting for hemoconcentration as well as specific clotting temperature and time.

In addition to further studying BDNF as a mechanism of action, it is important to consider alternative and complementary mediators. For example, exercise also impacts other systems implicated in fear extinction, including NMDA receptors (Vasuta et al., 2007), the hypothalamic–pituitary–adrenal axis (De quervain et al., 2011; Roozendaal & McGaugh, 1996; Stranahan, Lee, & Mattson, 2008), and norepinephrine (Dishman, Renner, White-Welkley, Burke, & Bunnell, 2000; Dishman et al., 2000). Future investigations should seek to assess BDNF as well as indices of these other systems.

**Target population**

The relatively high response rates of exposure therapy suggest that applying augmentation strategies in unselected samples may lead to an underestimation of their effects and utility. If the augmentation effects of exercise are mostly explained by enhanced BDNF release, one may hypothesize that those with lower BDNF levels or expression capacity benefit more
from exercise that those who do not exhibit these deficits. Initial support for this hypothesis comes from a small study by Mata and colleagues (Mata, Thompson, & Gotlib, 2010), who demonstrated that adolescent girls who are carriers of the BDNF met-allele (i.e., which is associated with lower BDNF expression) showed a stronger negative relation between exercise and depressed mood relative to girls with the val/val polymorphism. Such findings encourage further testing of this and other putative moderators of exercise augmentation, as this will enable clinicians to apply this clinical strategy more effectively. Similarly, the study we reported on only included participants with PTSD. Future trials will determine whether BDNF-mediated exercise augmentation of exposure therapy is effective in other anxiety disorders. Finally, future studies could measure physical fitness to determine whether it moderates the impact of exercise augmentation.

Treatment parameters

Another important unanswered question regarding the efficacy of exercise for mood and anxiety disorders, as well as exposure therapy augmentation, is how to best prescribe exercise. Basic research supports the application of acute bouts for enhancing BDNF release. It remains unknown, however, what the optimal intensity, duration, frequency, and timing of these bouts are for observing meaningful augmentation of exposure therapy. Here, it is interesting to note that when the aim is to enhance consolidation or retention of fear extinction, it may be important to administer the exercise bout post-session rather than pre-session, because that gives the clinician and patient the opportunity to limit the augmentation to successful sessions (see Smits et al., 2013). Likewise, it is plausible that the augmentation effects of exercise are not limited to acute bouts of aerobic activity. Studying other exercise modalities and training programs, especially in combination with patient preferences and needs, is likely to facilitate knowledge on mechanisms of action, and (thereby) aid the development of the most effective application of exercise as an augmentation strategy for exposure therapy.

Conclusions

Exercise has strong empirical support as an intervention for physical and mental health conditions. In addition to its direct effects on symptoms of anxiety and depression, exercise may be an effective aid to other established treatments for anxiety and mood disorders. In this article, we have reviewed some mechanisms by which exercise may exert these positive augmentation effects and specifically as it relates to exposure therapy. Initial data provide support and some clear direction for this research agenda.

Acknowledgments

Funding

Portions of this research were funded by grants from the National Institute on Drug Addiction: R01 DA027533 & K01 DA035930. Clinical trials registry: ClinicalTrials.gov, NCT01199107, https://clinicaltrials.gov/ct2/show/NCT01199107

Cogn Behav Ther. Author manuscript; available in PMC 2016 June 01.
References


Cogn Behav Ther. Author manuscript; available in PMC 2016 June 01.


Cogn Behav Ther. Author manuscript; available in PMC 2016 June 01.


Cogn Behav Ther. Author manuscript; available in PMC 2016 June 01.


Figure 1.
BDNF as a function of treatment condition.
Figure 2.
PTSD symptoms as a function of treatment condition.
Figure 3.
Between group effect sizes (Cohen's $d$).