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Assessing BDNF as a Mediator of the Effects of Exercise on Depression

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Abstract

Brain-derived neurotrophic factor (BDNF) is associated with neuronal growth and reduced BDNF has been implicated in depression. A recent meta-analysis documented reliable effects of exercise on BDNF levels (Szuhany et al., 2015); although, few studies included participants with mental health conditions. In this study, we examine whether increased exercise was associated with enhanced BDNF response in depressed patients, and whether this change mediated clinical benefits. A total of 29 depressed, sedentary participants were randomized to receive either behavioral activation (BA) plus an exercise or stretching prescription. Blood was collected prior to (resting BDNF levels) and following an exercise test (pre- to post-exercise BDNF change) at four points throughout the study. Participants also completed depression and exercise assessments. BDNF increased significantly across all assessment points ($p < 0.001$, $d = 0.83$). Changes in BDNF from pre- to post-exercise were at a moderate effect for the interaction of exercise and time which did not reach significance ($p = 0.13$, $d = 0.53$), with a similar moderate, non-significant effect for resting BDNF levels ($p = 0.20$, $d = 0.49$). Contrary to hypotheses, change in resting BDNF or endpoint change in BDNF was not associated with changes in depression. In an intervention that included active treatment (BA), we could not verify an independent predictive effect for changes in BDNF across the trial. Overall, this study adds to the literature showing reliable effects of acute exercise on increasing BDNF and extends this research to the infrequently studied depressed population, but does not clarify the mechanism behind exercise benefits for depression.

Clinical Trials Registry (clinicaltrials.gov): NCT02176408, “Efficacy of Adjunctive Exercise for the Behavioral Treatment of Major Depression”

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Contributors

Kristin L. Szuhany contributed to the conceptualization, methodology, investigation, formal analysis, writing, and funding acquisition of this project. Michael W. Otto contributed to the conceptualization, supervision (of patients during the study), funding acquisition, and writing of the manuscript.

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Declaration of Interest

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Keywords

brain-derived neurotrophic factor; BDNF; depression; exercise; physical activity

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Introduction

Brain-derived neurotrophic factor (BDNF) is a protein largely found in certain brain regions, such as the hippocampus, cerebral cortex, hypothalamus, and cerebellum, as well as in the peripheral nervous system. BDNF plays a role in neuronal growth and differentiation and in reducing neuro-degeneration and increasing neuroplasticity. Given its role in neuronal growth, studies have shown that decreased levels of BDNF are associated with impairments in memory consolidation, storage, and long-term memory (Cirulli et al., 2004; Roig et al., 2013).

As BDNF and exercise have similar effects on improving cognition (McMorris and Hale, 2012; Smith et al., 2010), BDNF may be the pathway by which exercise exerts its effects (Erickson et al., 2012). A recent meta-analysis aiming to explicate the first component of this pathway--the effect of exercise on BDNF—showed BDNF elevations after a single bout of exercise and after a program of regular exercise (Szuhany et al., 2015). Specifically, results indicated a moderate effect of an acute exercise on an increase in pre- to post-exercise BDNF, which was replicated in a meta-analysis of 55 studies of healthy adults (Dinoff et al., 2017). This pre- to post-exercise BDNF increase was intensified following a program of regular exercise. Resting BDNF also increased following regular exercise, but at a small effect size. Results from this study suggest reliable BDNF increases following both acute and regular exercise.

Concerning the second half of the potential causal pathway between exercise and depression, few studies have examined whether BDNF changes from exercise predict changes in depression symptoms. Few studies in the meta-analysis included participants with psychiatric conditions, and only three included depressed participants (Gustafsson et al., 2009; Laske et al., 2010; Toups et al., 2011). A recent meta-analysis only identified six studies of exercise effects on resting BDNF in patients with MDD (Dinoff et al., 2018). However, within these studies, conflicting results of the effect of BDNF change on depression exist; some suggest BDNF increases in depressed patients as depression improves (Gourgouvelis et al., 2018) and some suggest BDNF is not a factor in depression changes (Toups et al., 2011).

Yet, other research has implicated BDNF in pathways affecting depression. For example, studies have indicated that depressed patients show lower resting levels of serum and plasma BDNF than healthy controls (Bocchio-Chiavetto et al., 2010; Brunoni et al., 2008; Lee et al., 2007). Additionally, meta-analyses and reviews (Russo-Neustadt and Chen, 2005; Sen et al., 2008) have shown that antidepressant treatment significantly increases BDNF from pre- to post-treatment in depressed patients, though the relative degree of increase depends on the specific antidepressant (Zhou et al., 2017).

In the current study, we evaluate the change in BDNF after exercise in depressed outpatients and examine the link between these changes and treatment outcome. Specifically, this was a secondary analysis of possible mediating effects of BDNF in a pilot randomized controlled trial which examined the effects of exercise in combination with psychosocial treatment on depression symptoms (Szuhany and Otto, 2019). In accordance with meta-analytic results, we hypothesized that resting BDNF levels would increase following an exercise program and that the pre- to post-increase in BDNF would intensify over time. We also hypothesized that the increases in resting and pre- to post-exercise BDNF levels would be associated with the degree of improvement in depression symptoms.

Material and Methods

Participants

Participants were sedentary adults ages 18–65 with a principal diagnosis of MDD or persistent depressive disorder (PDD) with a current major depressive episode. As this was a secondary analysis, screening procedures and extended psychiatric and medical inclusion and exclusion criteria are presented in greater detail elsewhere (Szuhany and Otto, 2019). Briefly, exclusion criteria were designed for safety (e.g., low to moderate exercise risk; low suicide risk) and generalizability (e.g., no concurrent cognitive behavioral therapy, no history of psychosis or bipolar disorder). Individuals taking psychotropic medications at 8 weeks stable dose prior to entry were included. Participants provided informed consent after procedures were fully explained. All procedures were approved by the university Institutional Review Board and carried out in accordance with the latest version of the Declaration of Helsinki.

A total of 29 participants were able to provide at least 1 blood sample. Two individuals were excluded from the full sample ($n=31$) due to inability to draw blood. Of these 29 participants, 15 provided samples pre- and post-exercise across all four time points. Other participants dropped out prior to study completion ($n=10$) or were unable to provide a sample on a visit ($n=4$). All 29 participants were included in intent-to-treat analyses, with 14 randomized to the exercise condition and 15 to stretching. Overall, 59% of participants ($n=17$) reported taking psychiatric medications at baseline (13 on antidepressants, 3 on benzodiazepines, and 2 on stimulants); the other 41% were not taking any psychiatric medications.

Assessments

Participants completed a maximal exercise test using a Balke protocol consisting of 2-min stages in which speed and grade were increased over time. BDNF collection occurred immediately prior to test completion (resting serum BDNF) and immediately following test completion (changes in BDNF following acute exercise). After blood sample collection, the red top test tube was allowed to clot for 25 ± 5 minutes at room temperature before being centrifuged at 3000 RPM for 15 minutes. The resulting serum was pipetted into 5 microtubes and stored in a -80 degree freezer. Results were batch processed at the Albert Einstein School of Medicine using Quantikine ELISA assay kits for total serum BDNF from R&D Systems. All serum BDNF results are in units of ng/ml. The Quantikine ELISA assay

has specificity to assess mature BDNF with marginal reactivity to pro-BDNF (Polacchini et al., 2015).

Clinician and self-report depression ratings were made using the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) and the Beck Depression Inventory-II (BDI-II; Beck et al., 1996), respectively. Exercise was assessed via the 7-Day Physical Activity Recall (PAR; Blair et al., 1985), an interviewer-administered, timeline follow-back measure of minutes of vigorous and moderate intensity exercise and stretching. Metabolic equivalents (METs) were calculated for a combined variable of vigorous- and moderate-intensity exercise.

Assessments were completed at baseline, Week 4, Week 8, and Week 16 (1-month follow-up).

Intervention

The interventions are described in greater detail in the primary paper (Szuhany and Otto, 2019). In short, participants were randomized to either a brief behavioral activation (BA) treatment (9 sessions over 12 weeks) plus an adjunctive exercise or stretching control intervention. Stretching was designed to control for attention to bodily movement, but utilized movement at a lower intensity level hypothesized to not affect depression symptoms or BDNF levels. Exercise and stretching interventions included motivational strategies to enhance initiating and maintaining exercise/stretching regimens and planning at-home exercise/stretching with a goal of completing 150 minutes of exercise/stretching per week.

Data analysis

Analyses were conducted using mixed-effects linear regression models with likelihood-based estimation methods where follow-up assessments were entered as repeated dependent variables. For the analysis of acute changes in BDNF, treatment groups were combined to replicate meta-analytic comparisons (Szuhany et al., 2015). For subsequent models, treatment group, time, and their interaction were included as independent variables. Cross-time correlations were freely estimated using an unstructured variance-covariance matrix. Models were analyzed with both resting BDNF levels and change in BDNF levels from pre- to post-exercise as dependent variables. All analyses used SPSS Version 24.0.

Results

Patient characteristics

Baseline demographics are described in Table 1. Average resting BDNF levels at baseline were 28690 (± 6870) ng/ml and average change score from pre- to post-exercise was 5265 (± 10993) ng/ml. There was no significant difference between intervention conditions in total METs of exercise ($t(29)=0.22$, $p=0.83$, $d=0.08$) as reported in the primary paper (Szuhany and Otto, 2019), with both groups demonstrating significant increases in METs of exercise across treatment. Table 2 includes clinical, exercise, and BDNF measures by time point.

Effects on BDNF changes across an individual exercise session

In a one-sample t-test, BDNF change scores across assessment points during the study were shown to significantly increase ($t(80)=4.61$, $p<0.001$, $d=0.83$), as hypothesized. At each assessment point, BDNF levels increased significantly across an individual exercise session as evaluated by repeated measures t-test: baseline: $t(24)=2.40$, $p=0.025$, $d=0.96$; Week 4: $t(20)=2.24$, $p=0.037$, $d=1.01$; Week 8: $t(19)=2.15$, $p=0.044$, $d=1.00$; Week 16: $t(14)=2.33$, $p=0.036$, $d=1.16$. See Figure 1.

In a mixed effects model, main effects of time or condition (all $p>0.46$) and their interaction ($p=0.74$) were non-significant, consistent with the absence of differences in exercise between conditions as described in the primary paper (Szuhany and Otto, 2019). When METs of moderate and vigorous exercise were substituted for intervention condition, all effects remained non-significant (all $p>0.13$); however, the interaction between METs and time increased to a moderate effect size ($F(3, 25)=2.06$, $p=0.13$, $d=0.53$). See Figure 2.

Effects on resting BDNF levels

A similar mixed effects model was conducted on resting BDNF levels. Results indicated no significant main effects of time or condition (all $p>0.71$) or interaction ($p=0.75$). When replacing condition with METs of moderate and vigorous exercise, all results were non-significant; however, the interaction between METs and time increased to a moderate effect size ($F(3, 28)=1.64$, $p=0.20$, $d=0.49$). See Figure 3.

Effects of BDNF on depression

The change in resting BDNF across the study period (baseline to endpoint) was not associated with depression changes as assessed by the MADRS ($r=-0.19$, $p=0.49$) or the BDI-II ($r=0.25$, $p=0.34$), and reflected effect sizes in the small to medium range. Likewise, the endpoint change in BDNF across exercise was not associated with depression changes on the MADRS ($r=0.35$, $p=0.21$) or BDI-II ($r=-0.26$, $p=0.35$), but reflected effect sizes in the small to medium range.

Discussion

Recent meta-analytic review (Szuhany et al., 2015) showed reliable moderate effects for increases in pre- to post-exercise BDNF levels following both acute and programs of exercise, but poorly represented individuals with psychiatric disorders. The current study, albeit underpowered, contributes effect size estimates of pre- to post-exercise BDNF changes across an exercise program. Consistent with the meta-analysis, depressed outpatients showed significant increases in BDNF across a single exercise session at each assessment point. Though non-significant, this study found a moderate effect ($d=0.53$) for the interaction between amount of exercise and time on BDNF changes from pre- to post-exercise. This effect size is consistent with that (Hedges' $g=0.58$) found in the meta-analysis. We also found a non-significant, but moderate effect ($d=0.49$) for the interaction between amount of exercise and time on resting BDNF, an effect somewhat larger than that found in the Szuhany et al. (2015) meta-analysis (Hedges' $g=0.28$), but similar to that of the Dinoff et al. (2018) meta-analysis (SMD=0.43). Hence, though the study was underpowered to reach

significance for effects of this size, effects were generally consistent with those documented in quantitative reviews.

Previous research on the effect of acute exercise on BDNF has focused primarily on physically and mentally healthy individuals (Dinoff et al., 2017), though BDNF changes may be particularly important for depressed populations. This study found a significant change in the range of a large effect size ($d=0.83$) in BDNF at each of the four assessments from pre- to post-exercise. These results are consistent with meta-analytic results for diverse samples of participants (Hedges' $g=0.46$, Szuhany et al., 2015), as well as two previous studies assessing BDNF change across a single exercise session in depressed patients (Gustafsson et al., 2009; Laske et al., 2010). Gustafsson and colleagues (2009) noted a larger change in BDNF in males (487 pg/ml to 1627 pg/ml) than females (367 pg/ml to 642 pg/ml).

In this study, BDNF changes were not associated with changes in depression, but reflected effect sizes in the small to medium range ($r=0.25-0.35$). Though this result was contrary to original hypotheses, at least three other studies from a recent meta-analysis (Dinoff et al., 2018) have found lack of correspondence between BDNF and depression changes (Kerling et al., 2017; Salehi et al., 2016; Toups et al., 2011), with only one finding an association (Gourgouvelis et al., 2018; $R^2=0.50$). It is unclear why some studies of depressed patients show an association between changes in BDNF and depression following an exercise program while others do not. Conflicting results may be due to small sample sizes or may suggest that BDNF is not the most sophisticated biomarker for acute antidepressant effects. Future research may also consider collecting data on depression age of onset or number of depressive episodes, as evidence with plasma BDNF shows these could be important mediating factors of the association between BDNF and depression changes, particularly for certain BDNF genotypes (Colle et al., 2017).

Several factors may have limited this study's ability to produce results corresponding to previous literature. First, sample size was limited both by the pilot nature of the study and inability to obtain blood samples from some participants. Limited sample size may have interfered with the ability to find significant interactions of exercise and time on BDNF as well as BDNF associations with depression. Second, pre- and post-exercise BDNF levels were collected following a maximal exercise test. Individuals self-identify when to end this test when they feel they have reached their "maximum" capacity, thus varying length of test and possibly contributing to variable BDNF effects. Additionally, the exercise test was not administered post-intervention (Week 12); therefore, BDNF was not collected at this assessment point. Third, and perhaps most importantly, participants had two potential sources of benefit to depression symptoms: BA and exercise. Thus, the mechanism of improvement may have been diffused. Primary results indicated that BA appeared to be the stronger source of antidepressant benefit as there were no differential effects between adjunctive conditions (Szuhany and Otto, 2019).

The limitations of this study reveal methodological considerations important for future study planning. First, this includes standardizing the exercise test and recruiting a larger study sample. Given the small to moderate effect of the association between BDNF and depression

changes, a sample of at least 85 participants would provide adequate power ($\alpha=0.30$). We also recommend recruiting comparable samples of men and women to assess for moderation effects as past studies have indicated that BDNF responds differently in the sexes (Dinoff et al., 2017; Szuhany et al., 2015).

Of particular note for future research pertains to the assay for BDNF. BDNF is first synthesized as a pre-proneurotrophin (pro-BDNF) of 32KDa, which then cleaves into mature BDNF (14 KDa) or a truncated form of 28 KDa (Foltran and Diaz, 2016; Hempstead, 2015). Recent comparisons across the literature have noted discrepancies across BDNF studies, which may be due to the assays measuring BDNF (Polacchini et al., 2015). For example, the Quantikine assay used for this study has specificity to mature BDNF; whereas other assays measure both mature and pro-BDNF. Future studies should be careful to note the assay used and the type of BDNF measured.

In sum, this study provides additional data suggesting that BDNF response to acute exercise documented for healthy participants (Dinoff et al., 2017; Szuhany et al., 2015) extends to depressed outpatients. However, the effect sizes indicate that studies of approximately 85 participants may be needed to obtain significant associations between BDNF response and depression outcome when exercise is not the exclusive treatment method.

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Highlights

- BDNF increases after acute exercise in a sedentary, depressed population
- BDNF changes across acute exercise did not intensify during an exercise program
- Resting BDNF levels did not change across an exercise program
- BDNF changes were not associated with changes in depression symptoms
- Future studies may require larger sample sizes given small effect sizes

Figure 1.
Mean BDNF changes from pre- to post-exercise across all groups.

Figure 2.
Differences in pre- to post-exercise change in BDNF levels by augmentation condition (exercise or stretching) across the trial.

Figure 3. Differences in resting BDNF by augmentation condition (exercise or stretching) across the trial.

Table 1.

Baseline demographic and clinical characteristics of the randomized sample.

	BA + EX (n = 14)	BA + STR (n = 15)	P
Age (M, SD)	31.0 (13.0)	37.2 (13.9)	.23
Gender (% , n)			.18
Female	64% (9)	87% (13)	
Male	36% (5)	13% (2)	
Race (% , n)			.05
Caucasian	50% (7)	73% (11)	
African American	0% (0)	7% (1)	
Asian	21% (3)	20% (3)	
Other	29% (4)	0% (0)	
Ethnicity (% , n)			.96
Hispanic	7% (1)	7% (1)	
Non-hispanic	93% (13)	93% (14)	
Principal Diagnosis (% , n)			.90
MDD	64% (9)	67% (10)	
PDD	36% (5)	33% (5)	
Co-principal Diagnosis (% , n)			.54
GAD	14% (2)	20% (3)	
Social anxiety	14% (2)	7% (1)	

Note. p values derived from χ^2 tests for race and t-tests for all other comparisons. BA=behavioral activation, EX=exercise, STR=stretching, MDD=major depressive disorder, PDD=persistent depressive disorder, GAD= generalized anxiety disorder. .

Table 2.

Clinical, exercise, and BDNF measures at each assessment point.

	BA + EX (n = 14)				BA + STR (n = 15)			
	Baseline n=14	Week 4 n=12	Week 8 n=10	Week 16 n=8	Baseline n=15	Week 4 n=12	Week 8 n=12	Week 16 n=11
METs (M, SD)	265.1 (381.4)	690.3 (583.1)	946.2 (471.5)	739.5 (476.5)	456.0 (445.7)	492.3 (639.7)	889.5 (474.7)	578.2 (511.0)
MADRS (M, SD)	23.9 (7.6)	19.0 (8.2)	20.8 (9.1)	12.0 (7.7)	26.5 (8.2)	19.1 (9.0)	20.3 (10.3)	15.6 (9.9)
BDI-II (M, SD)	24.9 (9.7)	21.5 (10.1)	21.1 (12.5)	9.8 (9.5)	27.5 (10.2)	19.4 (10.8)	18.4 (10.2)	13.1 (10.1)
Resting BDNF (M, SD)	27289.9 (6779.1)	28222 (5436.6)	29229.7 (6880.6)	25996.9 (3807.4)	29998.3 (6924.0)	29664.4 (10946.2)	27350.6 (10479.5)	26601.1 (9237.3)
BDNF Change (M, SD)	7540.4 (12636.6)	11261.1 (13255.5)	6610.1 (13642.6)	7784.7 (15027.9)	2802.0 (8761.7)	2279.3 (12640.7)	6859.7 (14989.7)	9778.3 (15774.1)

Note. BA = behavioral activation, EX = exercise, STR = stretching, MADRS=Montgomery-Asberg Depression Rating Scale, BDI II=Beck Depression Inventory-II, METs=metabolic equivalents; METs are calculated for combined vigorous & moderate intensity activity; BDNF measured in ng/mL.