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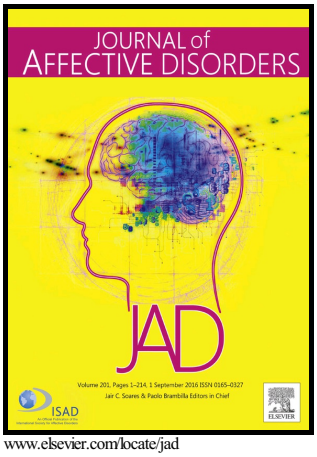

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Exercise increases serum brain-derived neurotrophic factor in patients with major depressive disorder

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Abstract

Background

Brain derived neurotrophic factor (BDNF) has been implicated in the pathogenesis of major depressive disorder (MDD). Existing data on exercise treatment in people with MDD are inconsistent concerning the effect of exercise on BDNF pointing either to increased or unaltered BDNF concentrations. However, studies in non-depressed persons demonstrated a significant effect on resting peripheral BDNF concentrations in aerobic training interventions. Given the lack of clarity mentioned above, the

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current study aimed at examining the effect of adjunctive exercise on serum BDNF levels in guideline based treated patients with MDD.

Methods

42 depressed inpatients were included, and randomized either to a 6 week structured and supervised exercise intervention plus treatment as usual (EXERCISE, n=22), or to treatment as usual (TAU, n=20). BDNF serum concentrations were assessed before and after the intervention in both study groups with established immunoassays.

Results

Serum BDNF slightly decreased in the TAU group, whilst there was an increase in BDNF levels in the exercise group. There was a significant time x group effect concerning sBDNF (p=0.030) with repeated ANOVA measures with age and BMI as covariates, suggesting an increase in BDNF concentrations in the EXERCISE group compared to TAU.

Limitations

Though there was no statistic difference in the antidepressant medication between EXERCISE and TAU potential interactions between exercise and medication on the effects of exercise in BDNF cannot be excluded. Gender was not considered as a covariate in ANOVA due to the small number of objects.

Conclusions

Exercise training given as adjunct to standard guideline based treatment appears to have additional effects on BDNF serum concentrations in people with MDD. Our results add further evidence to the beneficial effects of exercise in the treatment of MDD.

Keywords

BDNF, aerobic exercise, major depressive disorder, exercise intervention

Introduction

Depression is a leading cause of global years lived with disability (Ferrari et al., 2010) and is associated with profound economic costs (Chisholm D et al., 2016). People with depression are also at increased risk of premature mortality, largely attributed to cardiovascular and metabolic disease (Walker et al., 2015) typically engage in low levels of physical activity and have low cardiorespiratory fitness levels (Vancampfort et al., 2016). However, physical activity interventions can increase cardiorespiratory fitness levels in people with depression (Vancampfort et al., 2016) and improve symptoms of depression (Schuch FB et al., 2016c). The exact neurobiological processes by which exercise improves depressive symptoms in people with major depressive disorder have not been clearly elucidated to date (Schuch FB et al., 2016a).

One factor that has been implicated in possible accounting for the neurobiological response and a target for exercise in people with depression is brain derived neurotrophic factor (BDNF). BDNF is a protein which has a significant role in neurogenesis, neuroprotection, neuroregeneration and synaptic plasticity (Mattson et

al., 2004) and high levels of BDNF mRNA are found in the hippocampus and the cerebral cortex (Wetmore et al., 1990).

Plasma (pBDNF) and serum BDNF (sBDNF) levels have been observed to be decreased in people with MDD (Polyakova et al., 2015). Antidepressant drug treatment increases sBDNF in depressed patients either in responders or remitters (Polyakova et al., 2015).

Existing data on exercise treatment in people with MDD are inconsistent concerning the effect of exercise on BDNF pointing either to increased or unaltered BDNF concentrations (Lamego et al., 2015; Salehi et al., 2014; Schuch et al., 2014; Toups et al., 2011, Schuch et al., 2016a) However, studies in non-depressed persons demonstrated a significant effect on resting peripheral BDNF concentrations in aerobic training interventions but not in resistance training (Huang T et al., 2014).

Given the lack of clarity mentioned above, the current study aimed at examining the effect of adjunctive exercise on sBDNF levels in guideline based treated patients with MDD.

Methods and Materials

Participants

Study participants took part in a randomized pilot trial comparing the effects of adjunctive exercise on physiological and psychological parameters in depression (Kerling et al., 2015). The study was approved by the local ethics committee; after complete description of the study to the subjects, written informed consent was obtained. Forty-two inpatients with MDD treated at the Department of Psychiatry,

Social Psychiatry and Psychotherapy, Hannover Medical School were included. Diagnoses was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and confirmed with standardized clinical interviews (SCID I/II; German version).

Exercise training was given as adjunct to guideline based treatment as usual (TAU). TAU consisted of psychotherapy for each patient, plus antidepressant medication according to participated decision making. Patients were randomized either to a 6 week structured and supervised exercise intervention plus treatment as usual (EXERCISE, n=22), or to treatment as usual (TAU, n=20).

None of the patients used ß-blockers or received other cardiologic treatments. Both groups did not differ in antidepressant pharmacological treatment (see table 1). Medication did not change throughout the intervention.

Exclusion criteria were body-mass index ≥ 30, age younger than 18 years and over 60 years, acute or chronic infectious disease, current or lifetime immunological disorders, diabetes mellitus type 1 and type 2, current or lifetime cardiovascular disorders, pregnancy, schizophrenia, mental retardation, bipolar disorder, and current substance abuse or dependency.

Blood sampling

Fasting serum samples of sBDNF were collected between 0700 h and 0800 h after overnight fasting and stored at -80°C until analysis. Coffee and alcohol were not allowed for 12h, and morning medication was given after blood sampling. Analysis was performed in duplicate established immunoassays according to the manufacturer´s instruction (Quantikine HS® R&D Systems, Inc.; Minneapolis; MN;

USA). The immunoassay measures total sBDNF, i.e. free BDNF, trk-bound BDNF, pro- and mature BDNF, and is calibrated against a highly purified Sf21-expressed recombinant human BDNF produced by the manufacturer. The detection range is between 15.6 – 1.000 pg/ml. The intra assay coefficient of variation is 2.4-3.2%, the inter-assay coefficient of variation is 4.3-7.2% according to the manufacturer. All samples were stored no longer than 6 months.

Spiroergometry/EXERCISE intervention

The physician supervised training program was performed during hospitalization at the MHH Institute of Sports Medicine and consisted of three trainings sessions per week for each 45 minutes at moderate intensity. To achieve moderate intensity, participants performed a constant load test at 50% of the maximum workload achieved during the initial incremental exercise test. At this intensity, all patients trained in the aerobic-anaerobic transition zone (above the VAT and below the anaerobic lactate threshold).

The exercise training started with a 25 minute workout phase on a bicycle ergometer and training was continued at personal preference on a second endurance machine (e.g. treadmill, crosstrainer, rowing). The intervention lasted 6 weeks and all of the 22 EXERCISE patients completed the study. The patients participated in over 90% of the possible training units. Patients in the TAU group were allowed to take part in the daily activity program (walking, ball games and stretching exercises for 20 minutes).

Behavioral assessment, implementation of the spiroergometry and the exact performance of the exercise program are described under Kerling et al. (2015).

Statistical Analysis

The statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Data were tested for a normal distribution using the Kolmogorov–Smirnov test. Group effects (Exercise versus TAU) were assessed using two-tailed T-test. The chi-squared test was used to compare the rates of females and to compare antidepressant treatment strategies between remitters and non-remitters. Pearson's product-moment correlation coefficient was used to analyze correlations. Repeated measures ANOVA with age and BMI as covariates were used to compare BDNF concentrations before and after the intervention in both groups.

Values are presented as mean ± SD. All *P* values <0.05 were considered to be significant.

Results

For anthropometric and clinical data see table 1. The effects on cardiorespiratory fitness, psychological outcome, factors of the metabolic syndrome and on the amount of epicardial and subcutaneous adipose tissue were described under Kerling et al. (2015) and Kahl KG et al. (2016).

Comparison of BDNF serum concentrations

After testing for normal distribution, a repeated ANOVA with age and BMI as covariates revealed a significant effect time x group effect concerning sBDNF (F=5.05; df=1; p=0.03) (Figure 1, Table 2). Overall, sBDNF slightly decreased in the TAU group, and increased in the EXERCISE group (s. Figure 1). However, sBDNF alterations over time reached no statistical significance in both groups (sBDNF EXERCISE: T=1.52; df=21; p=0.08 versus sBDNF TAU: T=0.81; df=19; 0.42).

A correlation analysis with Δ MADRS (relative change in MADRS sum score between t0 to t1) and Δ sBDNF (relative change in sBDNF levels between t0 and t1) revealed no significant association either for the EXERCISE group, nor for the TAU group (data not shown).

Discussion

The results of this randomized controlled study add evidence to the beneficial effects of exercise in the treatment of MDD and suggest that increasing BDNF may be associated with the neurobiological mechanisms of exercise in MDD.

Szuhany et al. (2014) in a review found a moderate effect for increasing BDNF levels after single exercise units. Regular exercise improves this effect, and regular exercise units increase resting BDNF levels.

BDNF changes in exercising women were lower (Szuhany et al., 2014). Previous literature has demonstrated that exercise training enhances BDNF release from the human brain (Seifert et al., 2010) and increases concentrations of serum, plasma and platelet BDNF directly after maximum performance (Cho et al., 2012) in healthy persons. Even exercise of at least 30 minutes duration induce a temporary increase of peripheral BDNF concentrations in healthy persons as well as in patients with MDD (Ferris et al., 2007; Gustafsson et al., 2009) wherein the increase in patients with MDD is less pronounced. Physiologically sixty minutes after endurance exercise increased BDNF levels fall to baseline and even below this (Knaepen et al., 2010). Strength training in the majority of studies has no effect on peripheral BDNF levels (Huang T et al., 2014).

There is a relative paucity of studies and in particular RCTs which have considered the relationship between regular aerobic exercise and BDNF in patients with depression. Toups et al. found no differences in serum and plasma BDNF before and after a 12 week lasting exercise intervention for two groups divided into a low caloric and a high caloric expenditure group (Toups et al., 2011). An exact exercise protocol with mode or duration of the training sessions was not described. Schuch et al. (2014) found no difference in plasma BDNF levels after combined treatment with aerobic exercise in depressed patients after 3 weeks but all patients additionally received other therapies like electroconvulsive therapy (ECT). A potential factor that may have accounted for the lack of effect in this study could be due to the short study duration. Salehi et al. (2014) found increasing BDNF levels under aerobic exercise training, electroconvulsive therapy and under a combination of both in patients suffering from treatment resistant major depressive disorder. Aerobic exercise consisted of training on a treadmill three times a week (between 60 and 75% of VO_{2max}) for 30 minutes for four weeks. The highest increase of sBDNF was under electroconvulsive therapy but the highest decrease of depressive symptoms was under combination therapy. BDNF levels in this study were not associated with symptoms of depression (Salehi et al., 2014). Lamego et al. (2015) examining the effects of aerobic exercise on BDNF and cortisol alterations in depressed patients in a review could not establish an interaction between these two biomarkers and aerobic exercise. This was due to differences in the types of exercise, duration of the sessions, intensity and frequency of weekly sessions and duration of the exercise intervention (Lamego et al., 2015). Thus, our randomised study without the use of ECT sheds novel light on the potential unique influence of exercise on BDNF levels in people with MDD.

Some clinical, psychological, social and biological features such as family history of mental illness, gender and the interaction between body mass index (BMI) and BDNF may be moderators or predictors for an antidepressant effect of exercise in MDD (Schuch et al., 2016b). In patients with mild to moderate depression aerobic exercise leads to a higher decrease of depressive symptoms in participants presenting higher values of BDNF and BMI (Toups et al., 2011).

Several hypotheses have been built how exercise may influence BDNF levels. In animal models BDNF mRNA expression is induced by exercise in several brain regions mainly in the hippocampus (Cotmann et al., 2007). One hypothesis is that exercise initiates the induction of the expression of a myokine (Fndc5) which induces BDNF expression (Wrann et al., 2013). Another mechanism describes that exercise may support BDNF promotors (Koppel and Timmusk, 2013) via an endogenous molecule which is useful as a metabolite (as an energy source) as well as a regulator of BDNF transcription. This way was demonstrated for D-b-hydroxybutyrat (Sleiman et al., 2016).

Heijnen et al. (2016) conclude that aerobic exercise modulates hormone, neurotrophin and neurotransmitter levels depending on factors such as genes, age and hormonal status and hypothesize that the effect of aerobic exercise depends on the initial performance level.

The finding of decreased BDNF levels in the TAU group deserves further interpretation, since most studies found higher sBDNF levels after antidepressant treatment (Polyakova et al., 2015). However, in the study by Piccinni et al. lower sBDNF level was found after 1 year of treatment (Piccini et al., 2008).The authors argue, that lower sBDNF after antidepressant treatment might represent a trait of some depressed patients.

Limitations

Though there was no statistic difference in the antidepressant medication between EXERCISE and TAU potential interactions between exercise and medication on the effects of exercise in BDNF cannot be excluded. Gender was not considered as a covariate in ANOVA due to the small number of objects. We decided to use repeated measures ANOVA for analysis, however, general estimated equations (GEE) may also be useful.

Conclusions

Exercise training given as adjunct to standard guideline based treatment appears to have additional effects on BDNF serum concentrations in people with MDD. Our results add further evidence to the beneficial effects of exercise in the treatment of MDD.

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Fig. 1: Exercise increases BDNF concentrations in patients with depression

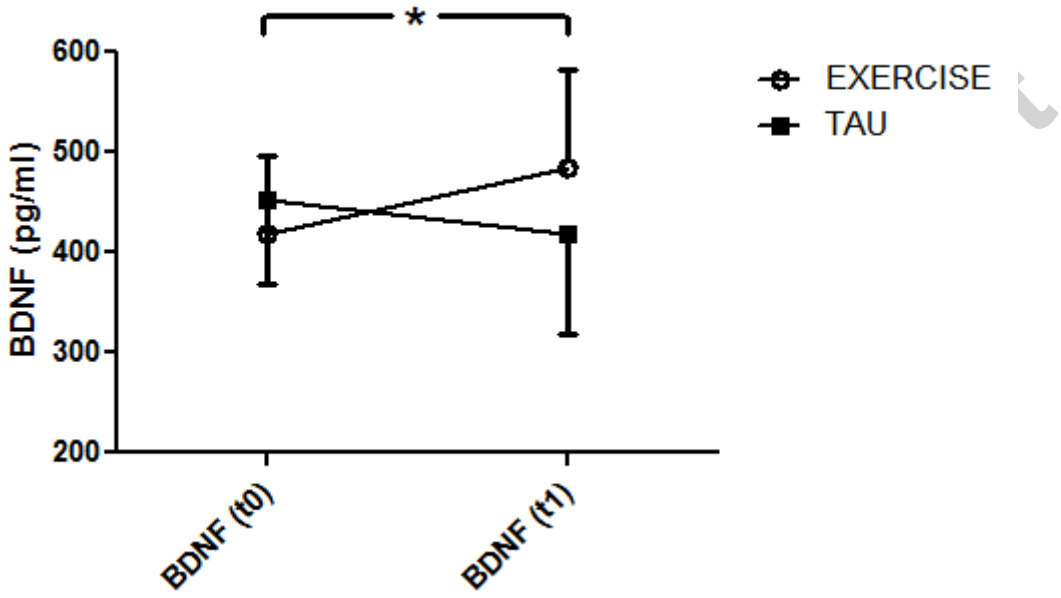

Table 1 Anthropometric data, antidepressant medication and depression scores

Measure	EXERCISE (N=22)		TAU (N=20)		
	N	%	N	%	P
Female	10	45	6	30	n.s.
	Mean	SD	Mean	SD	P
Age	44.2	8.5	40.9	11.9	n.s.
Height (m)	1.73	0.08	1.75	0.09	n.s.
Weight (kg)	81.2	20.8	82.1	14.9	n.s.
BMI	26.8	5.1	26.8	4.8	n.s.
	N	%	N	%	P
Antidepressants	17	77	15	75	n.s.

SSRI	5	23	5	25	n.s.
SSNRI	5	23	5	25	n.s.
NDRI	5	23	4	20	n.s.
Agomelatine	6	27	4	20	n.s.
	Mean	SD	Mean	SD	P
Smoking (pack-years)	5.5	7.2	5.0	8.5	n.s.
Physical activity before	3.0	1.8	2.6	1.8	n.s.
Alcoholic Drinks	4.1	6.5	0.8	1.6	0.034
BDI-2 sum score					**n.s.**
t0	29.4	10.9	28.3	11.2	n.s.
t1	13.4*	13.2	15.9*	12.5	n.s.
	Mean	SD	Mean	SD	P
MADRS sum score					**n.s.**
t0	23.5	8.7	24.5	10.3	n.s.
t1	11.8*	10.4	16.4*	9.4	n.s.

Legend: Anthropometric and clinical data. Depression scores significantly decreased in both intervention groups (marked with an asterisk).

* means a P-value < 0.05 concerning within group effects after 6 weeks treatment.

Table 2: BDNF scores

Measure	EXERCISE (N=22)		TAU (N=20)			
	Mean	SD	Mean	SD	T	P
BDNF score (pg/mL)						
t0	415.2	362.8	454.8	354.3	0.36	n.s.
t1	472.5	526.1	432.9	335.7	-0.29	0.03