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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 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.

1. Introduction

Depression is a leading cause of global years lived with disability (Ferrari et al., 2013) and is associated with profound economic costs (Chisholm 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 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 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).

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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; Schuch et al., 2014, 2016a; Toups et al., 2011) 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 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.

2. Methods and materials

2.1. 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.

2.2. 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 12 h, 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.

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.

2.3. 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 min 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 min 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 min).

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

2.4. 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.