

# Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression

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## Abstract

Major depression (MD) has been associated with decreased brain-derived neurotrophic factor (BDNF) serum levels, while antidepressant drugs were found to increase these decreased BDNF levels. We investigated if this is also caused by a single exercise session in elderly women with remitted MD. In our study 35 elderly women with a (partially) remitted depressive episode of unipolar depression according to DSM-IV criteria within the last year and 20 age-matched healthy female controls were included. Depression severity was assessed by HAMD. Serum levels of BDNF were measured by ELISA. Blood samples were taken during the rest period before beginning the exercise including spiroergometry, at the end of the exercise and after a 30-min recovery period. At baseline MD patients showed significantly decreased BDNF serum levels compared to healthy female controls. After a single 30-min exercise period, we found a significant increase of BDNF serum levels in MD patients towards values comparable with the baseline levels of the healthy controls, followed by a significant decrease after 30 min rest, while the healthy controls showed only a mild but non-significant increase. In conclusion, a single exercise session leads to a significant up-regulation and transient normalization of BDNF serum levels in elderly women with remitted MD. This mechanism may contribute to the beneficial therapeutic and relapse-preventing effects of physical activity on MD.

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## Introduction

Major depression (MD) is one of the most burdensome diseases worldwide. The current available treatment strategies in MD have a substantial non-responder rate and an important relapse risk especially during the first year (Berton & Nestler, 2006). Biomarkers may help to identify patients with good response to antidepressant treatment. Recent findings in animal

models have suggested an involvement of brain-derived neurotrophic factor (BDNF) in depression (Angelucci *et al.* 2004). BDNF is a member of the nerve growth factor family and plays an important role in neuronal survival and synaptic plasticity in the central nervous system (CNS) (Laske & Eschweiler, 2006; Van Praag *et al.* 1999). MD has been associated with decreased BDNF concentrations predominantly in the hippocampus (Shimizu *et al.* 2004) and in serum (Aydemir *et al.* 2005; Karege *et al.* 2002; Sen *et al.* 2008; Shimizu *et al.* 2003). Antidepressant drugs were found to induce an up-regulation of BDNF in adult rat hippocampus (Malberg *et al.* 2000) and in serum of depressed patients (Aydemir *et al.* 2005; Brunoni *et al.* 2008; Matriciano *et al.* 2009; Sen *et al.* 2008; Shimizu

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et al. 2003; Yoshimura et al. 2007; Zanardini et al. 2006). These studies suggest that BDNF plays a role in the pathogenesis of MD and may be associated with the therapeutic effects of different antidepressant treatment strategies. However, only few studies have addressed whether BDNF as a state or trait marker is reduced in elderly depressed subjects.

Exercise is gaining much interest as a treatment option for MD. There is growing evidence from cross-sectional and longitudinal studies that physically active people are at a reduced risk of developing depression (Goodwin, 2003; Strawbridge et al. 2002), and that exercise interventions are associated with significant benefits for patients with mild to moderate forms of depression (Babyak et al. 2000; Blumenthal et al. 1999, 2007). On the other hand, acute exercise has been demonstrated to increase BDNF levels in the hippocampus of rats (Griffin et al. 2009) and in the serum of young healthy controls and multiple sclerosis (MS) patients (Ferris et al. 2007; Gold et al. 2003; Tang et al. 2008; Zoladz et al. 2008).

The aim of the present study was to investigate the effects of acute exercise on BDNF serum concentration in both elderly women with (partially) remitted MD and age-matched healthy female controls. In order to exclude the effects of gender on BDNF serum levels, our study groups were restricted to women exclusively.

## Materials and methods

### Study population

Thirty-five elderly women (age  $\geq 50$  yr, mean  $61.1 \pm 7.2$  yr) with a depressive episode of recurrent unipolar depression according to DSM-IV criteria within the last year and 20 healthy elderly women (mean age  $58.9 \pm 6.6$  yr) without any psychiatric disease and medication free were included in the study. The severity of depressive symptoms was assessed with the Hamilton Rating Scale for Depression (HAM-D). Only MD patients with a HAM-D score of  $\leq 18$  were included in the study. The cognitive status was assessed by the Mini-Mental Status Examination (MMSE) and DemTect. The baseline level of physical activity was assessed by the habitual physical activity (HPA) score. Twenty-one out of the 35 MD patients had been treated with an antidepressant (SSRI) for at least 3 months before entry in the study.

The ethical committee of the medical faculty at the University of Tübingen approved the study and written informed consent was obtained from each participant.

## Short-term exercise

### Ergometry

A case history, physical examination and assessment were taken from the participants including echocardiography. After a physical medical examination, they performed an incremental exercise test on a motorized treadmill (Saturn; HP-Cosmos, Germany) using a modified incremental walking protocol with an initial walking speed of 3 km/h and inclination of 0% (Porszasz et al. 2003). Walking speed and inclination increased simultaneously every 3 min with linear increases in both calculated work rate and oxygen uptake. The rate of work was calculated according to the method described by Porszasz et al. (2003) and expressed in watts/kg body mass. Electrocardiogram was registered every minute. Lactate was measured every 3 min from capillary blood obtained from the hyperemized ear lobe (EBIO plus; Eppendorf, Germany). The exercise test was terminated at volitional exhaustion, muscular fatigue, dyspnoea or other complaints. The patient's perceived exertion was determined every 3 min using the Borg 15-point scale (Borg, 1970).

### Maximal oxygen consumption

Oxygen uptake was measured by spiroergometric breath-by-breath analysis (Metasoft, Version 3.9, Cortex Biophysics GmbH, Germany). Peak aerobic capacity was expressed as  $\text{VO}_2$  in ml/min.

### Individual anaerobic threshold

The time-course of lactate concentration was generated and smoothed using a computerized spline procedure (Ergonizer, Germany) and plotted *vs.* the intensity of the exercise in watts. The lactate threshold (LT) was defined at the lowest value of the lactate to performance ratio and describes the onset of lactate increase. The individual anaerobic threshold (IAT) was defined at a lactate concentration of 1.5 mmol/l above the LT during the treadmill test (Roecker et al. 1998). The IAT indicates the critical value for which a further increase in exercise intensity results in a switch from aerobic to anaerobic metabolism. IAT was calculated and presented as watts/kg and mmol/l lactate.

### Blood collection and storage

Baseline BDNF was taken between 14:00 and 15:00 hours after a 30-min rest period seated in a chair, immediately prior to the exercise test (T0). After the

exercise, the subjects rested in a supine position and blood samples were drawn directly at the end of the exercise (T1) and after a 30-min recovery period (T2). The serum tubes were immediately placed on ice and centrifuged at 2500 g for 30 min at 4 °C within 30 min of being obtained; the top third of the volumes of the resultant serum supernatants were collected and frozen at –20 °C until further analysis.

#### Measurement of BDNF serum concentration

Serum levels of BDNF were measured by ELISA (detection limit 62.5 pg/ml; R&D Systems GmbH Wiesbaden-Nordenstadt, Germany) according to the manufacturer's instructions. Every ELISA kit contained a 96-well microplate pre-coated by the manufacturer with a mouse monoclonal antibody (Ab) specific for BDNF. All concentrations of reagents of this ready-to-use ELISA are proprietary information of the manufacturer.

Recombinant human BDNF expressed in Sf21 cells, was reconstituted in 2 ml buffered protein base with preservatives designated Calibrator diluent RD6P. The result of this reconstitution was a stock solution of 4000 pg/ml, which was used to produce the standard curve in a dilution series of 4000 to 62.5 pg/ml. The serum samples required at least a 21-fold dilution into Calibrator diluent RD6P.

The assay procedure was as follows. First, 100 µl buffered protein base (assay diluent RDS1S) was added to each well, followed by pipetting 50 µl of standard or diluted sample in duplicates. Next, the plate was covered with adhesive strip and incubated for 2 h at room temperature. Then, 100 µl monoclonal mouse antibody against BDNF conjugated to horseradish peroxidase was added to each well. Again, the plate was incubated for 1 h at room temperature. After the incubation period, each well was aspirated and washed three times with 400 µl wash buffer per well. Subsequently, 200 µl of freshly prepared substrate solution composed of one part stabilized hydrogen peroxide and one part tetramethylbenzidine as chromogen was added to each well, followed by 30 min incubation at room temperature in the dark. After this time, the reaction was stopped by the addition of 50 µl of 2 N sulphuric acid to each well, which resulted in a change of colour from blue to yellow. The optical density was determined within 30 min using a microplate reader (Tecan Sunrise, Switzerland) at a wavelength of 450 nm (correction at 540 nm).

All samples and standards were measured in duplicate, and the means of the duplicates were used

for statistical analyses. The intra- and inter-assay coefficients of variation of BDNF were <10%.

#### Data analysis

The data are presented as the mean ± standard deviation (s.d.). BDNF serum levels were analysed using two-way ANOVAs with repeated measures with diagnosis (MD patients or healthy controls) as main factor × 3 time-points (T0, T1, T2). Duncan adjustment for multiple comparisons was applied if significant interactions or main effects were detected. The two-tailed *t* test for unpaired samples was used to compare quantitative parameters between the groups. Univariate ANOVA was conducted to estimate the impact of different factors on serum levels of BDNF in MD patients. Next, multiple regression analysis was performed to estimate the impact of different factors (listed in Table 2) on serum levels of BDNF at T0 and on BDNF changes from T0 to T1 in MD patients. All variables were entered initially and stepwise backward elimination was used to eliminate redundant, non-significant predictors. Correlations between two variables were calculated with Spearman's test. Significance for the results was set at  $p \leq 0.05$ . All statistical analyses were performed using the statistical analysis software package SPSS 17 (Germany).

#### Results

The baseline characteristics of the MD patients and the control group are provided in Table 1. The MD patients were significantly more obese with an increased BMI and showed less physical fitness indicated by a significant lower IAT W/kg and  $W_{\max}$ , although reported HPA was not decreased in MD patients compared to healthy controls. However, BDNF serum levels at T0 in MD patients were independent of age, HAMD, MMSE and DemTect scores, BMI, HPA,  $W_{\max}$ /kg,  $VO_{2,\max}$ , IAT lactate and IAT W/kg in univariate ANOVA (Table 2). Patients treated with an antidepressant medication (SSRI) for at least 3 months prior to entry in the study ( $n=21$ ) showed a mean BDNF serum concentration of  $23.3 \pm 5.9$  ng/ml, which was not significantly different from patients without antidepressant medication ( $n=14$ ,  $25.9 \pm 6.2$  ng/ml,  $p=0.213$ ). Multiple regression analysis identified HAMD score at T0 as the only variable significantly associated with BDNF serum concentration at T0 in MD patients (Table 3). The model explained 22% of the corrected variance in this outcome measure. BDNF changes from T0 to T1 in MD patients were best predicted by the T0 measures

**Table 1.** Baseline characteristics of major depression (MD) patients and control group

Variables (mean $\pm$ s.d.)	MD patients ( <i>n</i> =35)	Control group ( <i>n</i> =20)	<i>p</i>
Age (yr)	61.1 $\pm$ 7.2	58.9 $\pm$ 6.6	0.272
HAMD	7.5 $\pm$ 4.4	2.8 $\pm$ 2.3	<0.0001
MMSE	29.0 $\pm$ 1.4	29.3 $\pm$ 0.6	0.355
DemTect	15.4 $\pm$ 2.5	16.3 $\pm$ 2.6	0.261
Weight (kg)	71.6 $\pm$ 13.1	67.0 $\pm$ 8.9	0.171
BMI (kg/m <sup>2</sup> )	26.9 $\pm$ 5.0	24.2 $\pm$ 3.1	0.018
HPA	8.3 $\pm$ 1.0	8.2 $\pm$ 1.0	0.900
$W_{\max}$ /kg	1.2 $\pm$ 0.3	1.4 $\pm$ 0.4	0.002
$VO_{2,\max}$	1.8 $\pm$ 0.3	1.9 $\pm$ 0.3	0.379
IAT lactate	2.9 $\pm$ 0.6	2.6 $\pm$ 0.5	0.196
IAT W/kg	0.9 $\pm$ 0.2	1.2 $\pm$ 0.3	0.002

*n*, Number of subjects; s.d., standard deviation, HAMD, Hamilton Rating Scale for Depression; MMSE, Mini-Mental Status Examination; BMI, body mass index; BDNF, brain-derived neurotrophic factor; HPA, habitual physical activity;  $W_{\max}$ /kg, rate of maximal work in watts/kg body mass;  $VO_{2,\max}$ , maximal oxygen uptake in ml/min; IAT lactate, individual anaerobic threshold in mmol/l lactate; IAT W/kg, individual anaerobic threshold in watts/kg body mass.

$W_{\max}$ /kg, BDNF, HAMD scores, BMI and age. The model explained 56% of the corrected variance in this outcome measure (Table 3).

In two-way ANOVAs with repeated measures, we found a significant effect of time ( $p=0.007$ ) and time  $\times$  diagnosis ( $p=0.010$ ) and a trend for time  $\times$  BMI (0.100). In a *post-hoc* analysis of time steps, there was a significant change from T0 to T1 ( $p=0.008$ ) for time  $\times$  diagnosis (corrected for BMI), but not from T1 to T2 ( $p=0.253$ ). MD patients showed significantly decreased BDNF serum levels at T0 (24.4  $\pm$  6.1 ng/ml) and T2 (21.4  $\pm$  7.1 ng/ml), but not at T1 (28.5  $\pm$  7.3 ng/ml) compared to 20 healthy female controls (T0: 30.5  $\pm$  6.9 ng/ml,  $p=0.001$ ; T1: 31.0  $\pm$  8.1 ng/ml,  $p=0.233$ ; T2: 26.7  $\pm$  7.2 ng/ml,  $p=0.011$ ). After a single short-term exercise, we found a significant increase of BDNF serum levels in MD patients from T0 (24.4  $\pm$  6.1 ng/ml) to T1 (28.5  $\pm$  7.3 ng/ml;  $p<0.0001$ ) towards values comparable with the baseline levels of the healthy controls (30.5  $\pm$  6.9 ng/ml;  $p=0.314$ ). In contrast, healthy controls showed no significant increase of BDNF serum levels from T0 (30.5  $\pm$  6.9 ng/ml) to T1 (31.0  $\pm$  8.1 ng/ml). The amount of BDNF increase from T0 to T1 was even significantly higher in MD patients than in healthy controls ( $p=0.046$ ). After

**Table 2.** Univariate analysis of variance for brain-derived neurotrophic factor (BDNF) serum levels at T0 and possible confounders in major depression (MD) patients

Variables	<i>R</i>	<i>p</i>
Age (yr)	-0.047	0.790
HAMD	-0.121	0.490
MMSE	0.118	0.499
DemTect	0.061	0.727
Weight (kg)	0.031	0.861
BMI (kg/m <sup>2</sup> )	0.048	0.786
HPA	-0.070	0.708
$W_{\max}$ /kg	-0.100	0.614
$VO_{2,\max}$	-0.029	0.883
IAT lactate	-0.071	0.737
IAT W/kg	0.084	0.698
Intake of antidepressants (SSRI) (yes/no)	-0.185	0.288

*n*, Number of subjects, s.d., standard deviation, HAMD, Hamilton Rating Scale for Depression; MMSE, Mini-Mental Status Examination; BMI, body mass index; BDNF, brain-derived neurotrophic factor; HPA, habitual physical activity;  $W_{\max}$ /kg, rate of maximal work in watts/kg body mass;  $VO_{2,\max}$ , maximal oxygen uptake in ml/min; IAT lactate, individual anaerobic threshold in mmol/l lactate; IAT W/kg, individual anaerobic threshold in watts/kg body mass.

30 min rest, MD patients and healthy controls showed a significant decrease of BDNF serum levels with values lying significantly below baseline levels. The results are depicted in Fig. 1.

MD patients showed a trend of an inverse correlation between BDNF serum levels at baseline (T0) and the amount of serum BDNF changes from T0 to T1 ( $r=-0.325$ ,  $p=0.056$ ), but healthy controls did not ( $r=-0.337$ ,  $p=0.146$ ). In contrast,  $W_{\max}$ /kg and the amount of serum BDNF changes from T0 to T1 were not significantly correlated for MD patients ( $r=0.044$ ,  $p=0.825$ ) or healthy controls ( $r=0.080$ ,  $p=0.739$ ).

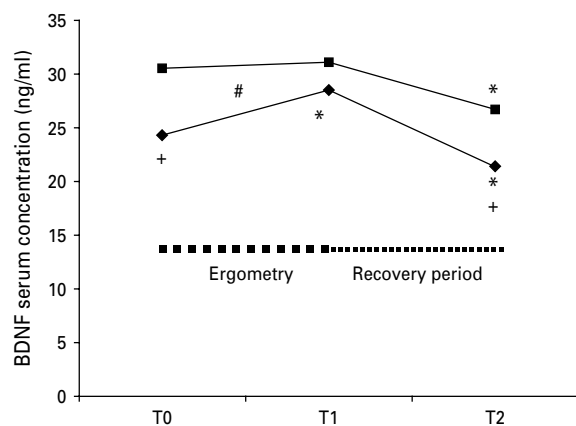
## Discussion

To the best of our knowledge, the effect of a short-term exercise on BDNF serum levels has not yet been described in MD patients. In the present study, our elderly female (partially) remitted MD patients showed significantly decreased BDNF serum levels at baseline compared to healthy controls. This finding is in line with several previous studies (Aydemir *et al.* 2005; Karege *et al.* 2002; Sen *et al.* 2008; Shimizu *et al.* 2003). After a single short-term exercise, MD patients showed a significant increase and normalization of

**Table 3.** Multiple regression analyses for brain-derived neurotrophic factor (BDNF) serum levels at T0 and significant association with HAMD at T0, respectively, BDNF changes from T0 to T1 and significant predictors in major depression (MD) patients at T0

Dependent variables: significant independent variables	Model					Coefficients		
	Variance		Analysis			Analysis		
	R <sup>2</sup>	Corr. R <sup>2</sup>	F	d.f.	p	β	t	p
BDNF at T0 HAMD at T0	0.293	0.219	3.942	21	0.037	-0.460	-2.274	0.035
BDNF changes T0–T1 BDNF at T0 W <sub>max</sub> /kg HAMD at T0 Age (yr) BMI	0.711	0.557	4.610	23	0.005	-0.525 0.827 -0.422 -0.408 0.707	-3.478 3.004 -2.762 -2.420 2.392	0.003 0.009 0.015 0.029 0.030

HAMD, Hamilton Rating Scale for Depression; BMI, body mass index; W<sub>max</sub>/kg, rate of maximal work in watts/kg body mass. The model selection was performed using a stepwise backward procedure. The initially included independent variables are listed in Table 2.



**Fig. 1.** Mean brain-derived neurotrophic factor (BDNF) serum concentration before beginning the exercise (T0), at the end of the exercise (T1) and after a 30-min recovery period (T2) in female patients with major depression (—◆—,  $n=35$ ) and in age-matched female healthy controls (—■—,  $n=20$ ). \* Significant difference to T0 in trial; + significant difference to other trial at time point; # significant difference for time  $\times$  diagnosis.

BDNF serum levels. This increase of BDNF serum levels in MD patients was significantly more pronounced than in healthy controls. However, MD patients and healthy controls showed a significant secondary decrease of BDNF serum levels after 30 min rest. In our MD patients, BDNF serum levels at T0 were best inversely associated with HAMD scores and

exercise-induced changes of BDNF serum levels from T0 to T1 were best predicted by W<sub>max</sub>/kg, BDNF at T0, HAMD scores, BMI and age.

Previous studies have examined the effect of exercise on BDNF serum or plasma levels in young (<40 years) healthy controls (Ferris *et al.* 2007; Gold *et al.* 2003; Tang *et al.* 2008; Zoladz *et al.* 2008), patients with major depression (Gustafsson *et al.* 2009), patients with panic disorder (Ströhle *et al.* 2009) and MS patients (Gold *et al.* 2003). BDNF blood levels showed a significant increase after short-term exercise in patients with MD, patients with panic disorder, MS patients and healthy controls (Gold *et al.* 2003; Gustafsson *et al.* 2009; Ströhle *et al.* 2009). This exercise-induced increase in BDNF blood levels is transient (Gold *et al.* 2003; Gustafsson *et al.* 2009; Tang *et al.* 2008) and the magnitude of BDNF increase is associated with exercise intensity (Ferris *et al.* 2007; Gustafsson *et al.* 2009). However, changes in BDNF serum levels did not correlate with changes in cognitive function scores (Ferris *et al.* 2007) and were only found after exercise above ventilatory threshold. Zoladz *et al.* (2008) have demonstrated that a 5-wk endurance cycling, but not a single maximal incremental cycling, resulted in an increase in both basal and the end-exercise BDNF plasma levels in young healthy men. In the European FINE study, severity of MD in elderly patients correlated highly with physical inactivity (Kamphuis *et al.* 2007), suggesting a link not only to decreased cortical plasticity but also to increased cardiovascular mortality in MD.

Antidepressant drugs were found to increase and in part to normalize BDNF serum levels in depressed patients (Aydemir *et al.* 2005; Brunoni *et al.* 2008; Matrisciano *et al.* 2009; Sen *et al.* 2008; Shimizu *et al.* 2003; Yoshimura *et al.* 2007; Zanardini *et al.* 2006). In the present study, we found the same effect after a single exercise session. This mechanism may contribute to the beneficial effects from physical activity on acute treatment and relapse prevention in MD (Babyak *et al.* 2000; Blumenthal *et al.* 1999, 2007). However, this exercise-induced increase of BDNF serum levels was only a transient phenomenon lasting <1 h, in accord with other studies (Gold *et al.* 2003; Gustafsson *et al.* 2009; Tang *et al.* 2008). This result may explain why there is need of a repetitive physical activity for beneficial effects from exercise in MD, as suggested by Dunn *et al.* (2005). In line with previous findings in healthy controls (Gustafsson *et al.* 2009; Ströhle *et al.* 2009), but in contrast to our MD group and previous findings in young healthy controls, we could not demonstrate a significant exercise-induced increase in our control group of healthy elderly female subjects. This result may be due to (1) the older age of the examined control group in our study compared to the other studies (Ferris *et al.* 2007; Gold *et al.* 2003; Tang *et al.* 2008; Zoladz *et al.* 2008); (2) a ceiling effect caused by the relatively high BDNF serum levels at baseline in our control group (as found by Ströhle *et al.* 2009) and (3) a higher degree of  $W_{\max}$ /kg in the control group (compared to MD patients), which represented a higher level of physical fitness in the healthy controls, as underlined by their significant higher individual anaerobic threshold in watts/kg body mass.

Under physiological conditions, BDNF is expressed primarily by neurons in the CNS. In peripheral blood, platelets have been demonstrated to be the major source of BDNF (Fujimura *et al.* 2002) and BDNF serum levels correlate with platelet activity (Laske *et al.* 2006). In addition, physical exercise has been demonstrated to increase platelet numbers and activity (Hilberg *et al.* 2008). Thus, the exercise-induced increase of BDNF serum levels could be due to platelet stimulation. Even though BDNF is also produced by skeletal muscle cells in response to contraction, muscle-derived BDNF does not appear to be released into the circulation (Matthews *et al.* 2009). As BDNF has been demonstrated to cross the blood–brain barrier (BBB) in both directions (Pan *et al.* 1998; Poduslo & Curran, 1996), BDNF serum levels may represent an important reserve pool for the brain. There is growing evidence that BDNF deficiency plays a critical role in the pathophysiology of depression (Angelucci *et al.*

2004; Hashimoto *et al.* 2004). In the brain, BDNF has been shown to induce neuroprotection, to promote the survival of neurons and to be a key mediator of functional neuronal plasticity (Laske & Eschweiler, 2006; Van Praag *et al.* 1999). In addition, the increase of BDNF serum concentrations in response to exercise may enhance learning and memory (Flöel *et al.* 2009) by increasing cortical grey-matter volume and modulating post-synaptic long-term potentiation (Kovalchuk *et al.* 2002). By these mechanisms, BDNF may be important in restoring proper brain functions and mediating antidepressant and relapse-preventing effects. Our finding of a decrease of BDNF serum levels after significant up-regulation may be due in part to a transit of BDNF from the blood through the BBB into the brain.

In conclusion, a single exercise session leads to a significant up-regulation and transient normalization of BDNF serum levels in elderly women with remitted MD. This mechanism may contribute to the beneficial effects from physical activity on acute and remitted MD. Further studies are required, especially including larger numbers of MD patients and examination of the effects of long-term exercise on BDNF serum levels, in order to elucidate the interaction between exercise and BDNF in MD.

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### Statement of Interest

None.

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