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Serum brain-derived neurotrophic factor (BDNF) at rest and after acute aerobic exercise in major depressive disorder

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ABSTRACT

Physiological mechanisms of an anti-depressive effect of physical exercise in major depressive disorder (MDD) seem to involve alterations in brain-derived neurotrophic factor (BDNF) level. However, previous studies which investigated this effect in a single bout of exercise, did not control for confounding peripheral factors that contribute to BDNF-alterations. Therefore, the underlying cause of exercise-induced BDNF-changes remains unclear. The current study aims to investigate serum BDNF (sBDNF)-changes due to a single-bout of graded aerobic exercise in a group of 30 outpatients with MDD, suggesting a more precise analysis method by taking plasma volume shift and number of platelets into account. Results show that exercise-induced increases in sBDNF remain significant ($p < .001$) when adjusting for plasma volume shift and controlling for number of platelets. The interaction of sBDNF change and number of platelets was also significant ($p = .001$) indicating larger sBDNF-increase in participants with smaller number of platelets. Thus, findings of this study suggest an involvement of peripheral as well as additional – possibly brain-derived – mechanisms explaining exercise-related BDNF release in MDD. For future studies in the field of exercise-related BDNF research, the importance of controlling for peripheral parameters is emphasized.

1. Introduction

As reported in recent meta-analyses (e.g. Cooney et al., 2013), physical exercise can serve as an effective treatment in major depressive disorder (MDD). Despite a relatively large number of studies investigating the anti-depressive effect of exercise, underlying mechanisms of this effect are only partially understood (Cotman et al., 2007; Stubbs et al., 2016). On a physiological level, the exercise-induced increase of brain-derived neurotrophic factor (BDNF) seems to be a central mechanistic component (Pereira et al., 2013). Interestingly, recent studies testing the acute effect of a single bout of aerobic exercise on BDNF levels in MDD have reported an increase of peripheral BDNF level (Gustafsson et al., 2009; Laske et al., 2010; Meyer et al., 2016). These findings led to the hypothetic model of an anti-depressive effect of long-term exercise by means of repeated exposure to acute increases in BDNF related to acute mood improvement (Brand et al., 2018; Meyer et al., 2016). While exercise-related changes in peripheral BDNF may originate partly from the brain (Sartorius et al., 2009; Seifert et al., 2010), peripheral BDNF is also released from platelets (Chacón-Fernández et al., 2016). Thus, to control for the peripheral effect of platelets, the number of platelets needs to be considered when analyzing peripheral BDNF changes (Naegelin et al., 2018; Ziegenhorn et al., 2007). Furthermore, peripheral concentration of post-exercise BDNF should to be adjusted for exercise-induced blood plasma volume shift (PVS). Due to vascular dilatation and an increase in capillary blood pressure and circulation, exhausting aerobic exercise leads to a reduction of the endothelial barrier function and thus to increased ultrafiltration of plasma from intra- to extravascular compartments (Kargotich et al., 1998). This intravascular reduction in plasma volume results in a transient increase in solute concentration and therefore to an overestimation of BDNF if

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not adjusted for PVS. Since both of these confounding factors have not been taken into account in previous studies in MDD, the acute effect of exercise on BDNF might have been over estimated.

Therefore, the aim of the current study was to propose a more precise method when studying acute aerobic exercise-related BDNF changes in MDD by a) adjusting post-exercise BDNF measures for PVS, and b) including platelet count as a covariate into the analysis. This more elaborate model may provide more reliable results on a proposed brain-derived release of the growth factor due to acute aerobic exercise. Additional references are reported in the Supplementary Material.

2. Method

2.1. Participants

Thirty MDD outpatients (mean age 39.2 ± 11.4 years, 17 females) participated in the current study. This is a sub study within a larger project on the long-term effect of physical exercise (The SPeED study: Sport/Exercise Therapy and Psychotherapy – evaluating treatment Effects in Depressive patients; (Heinzel et al., 2018)). Participants from age 18 to 65 years with a diagnosis of a mild or moderate depressive episode who passed a sport medical examination, were included. Seven patients were diagnosed with a single depressive episode and 23 patients with an episode within a recurrent depressive disorder according to the Structured Clinical Interview for DSM-IV (First et al., 1995). Participants were included if their weekly amount of physical exercise did not exceed 90 min. None of the participants took any medication that likely influences platelet function. Lists of inclusion and exclusion criteria and participants' medication are reported in the Supplementary Material. At the time of the acute exercise bout, the mean Body Mass Index (BMI) of the examined sample was 24.8 ± 5.0 kg/m^2 and participants' mean symptom severity, measured with the Beck Depression Inventory II (BDI-II, (Beck et al., 1996)), was 29.4 ± 7.0. The required number of participants to detect previously reported medium-sized effects for acute aerobic exercise on BDNF change (Meyer et al., 2016) was obtained by power analysis (G*Power 3.1.9, (Faul et al., 2007)). Thus, the thirty participants of this sub study comprise the first thirty MDD participants that were recruited within the SPeED project. The study protocol was approved by the local ethics committee of Charité Universitätsmedizin Berlin, Germany (No EA1/113/15). After detailed study description, written informed consent was obtained from all participants.

2.2. Exercise protocol

Participants had to perform a graded exercise test on a cycle ergometer (Ergoselect 100; Ergoline GmbH, Bitz, Germany), starting at 25 W with a repetitive progression of 25 W after every two minutes. Reason for test termination was being physically unable to continue, defined as point of maximum exhaustion or the occurrence of critical events. We used the WHO-exercise protocol as recommended by the German Society of Cardiology (Trappe and Löllgen, 2000) and reported in the guidelines of the American Heart Association (Fletcher et al., 2013). The test was constantly monitored by electrocardiogram (ECG), measurements of blood pressure, lactate and Borg's rating scale of perceived exertion (RPE, (Borg, 1982)) before starting the test, at the end of each level, at maximum exhaustion, as well as three and five minutes post exercise. The test was supervised by an experienced sports physician. The finally reached level, adjusted for time spent cycling within this level, determined the maximum workload in Watt (P_{max}). To get inter-individually comparable results of the exercise test, the individually P_{max} was divided by subject's body weight in kg and determined as relative maximum workload (rP_{max}, (Rost et al., 1982)).

2.3. Sample collection and storage

Resting blood samples were drawn from non-fasting subjects in supine position, via singular puncture of antebrachial veins and after a resting period of at least 20 min. Serum tubes for BDNF analysis were allowed to clot for 60 min at room temperature before centrifugation for 10 min at 1300 × *g* and 20 °Celsius. Supernatant serum was obtained into microliter tubes and stored at −30 °Celsius until final analyses. Ethylene diamine tetraacetic acid (EDTA)-tubes for haemogram were stored at room temperature until analysis within the same day. Post exercise samples were drawn within 5 min after finishing the exercise test and handled equally.

2.4. Sample analysis and calculations

Serum BDNF concentrations were measured with highly sensitive and specific flourometric two-site enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions (Promega Inc, Mannheim, Germany) but using an improved, fluorometric form which has been described in detail previously (Ziegenhorn et al., 2007). BDNF analyses were run in triplicate and results were averaged. Because of a substantially lower intra-assay vs. inter-assay variation, all corresponding pre- and post- exercise samples were measured using the identical BDNF assay. Haemogram including platelet count was produced using Sysmex XE-2100™ (Sysmex Corp. Kobe, Japan). Plasma volume shift (PVS) was calculated by the formula of van Beaumont, taking haematocrit (Hct) and hemoglobin (Hb) as underlying variables (van Beaumont et al., 1981). Individual values of pre-exercise plasma volume were set to 100%. Post-exercise BDNF level and platelet count were individually adjusted for PVS by multiplying values with the individually calculated post-exercise plasma volume/100. Methods for lactate assessments are reported in the Supplementary Material.

2.5. Statistical analysis

All data were analyzed using SPSS 24 statistical software (IBM Corporation, Armonk NY, USA). Correlation analyses were performed using Pearson's correlation coefficient. Changes from pre- to post-acute exercise were analyzed using the *t*-test for dependent samples. A repeated measure ANCOVA was performed to assess exercise induced BDNF alterations, which were already adjusted for plasma volume shift. Platelet count was used as a covariate in this ANCOVA model. Data are presented as mean (M) ± standard deviations (SD). All reported p-values are two-sided and level of significance was set to $p < .05$. Effect sizes (Cohen's d) were calculated according to (Cohen, 1992).

3. Results

3.1. Exercise induced alterations

The mean rPmax was 2.04 ± 0.49 W/kg in women and 2.16 ± 0.71 W/kg in men. Pre and post exercise values of heart rate, lactate, platelets, plasma volume, sBDNF, and RPE are reported in Table 1. Most importantly, pre-post changes in sBDNF concentrations ($T(29)_{\text{not adjusted}} = 3.88$, $p = .001$, $d = .52$) remained significant after adjusting for PVS ($T(29)_{\text{adjusted for PVS}} = 2.24$, $p = .026$, $d = .30$). PVS-adjusted post exercise sBDNF values were significantly lower than not adjusted sBDNF values ($T(29) = 8.12$, $p < .001$, $d = .20$).

3.2. Correlations

Bivariate correlations showed that PVS-adjusted pre-post changes in sBDNF were predicted by baseline platelet count ($r = -.588$, $p = .001$), indicating larger exercise-induced sBDNF-increase in participants with a smaller baseline platelet count. Correlations between PVS-adjusted pre-post changes in sBDNF and BDI ($r = -.320$, $p = .085$) and baseline sBDNF concentration ($r = -.328$, $p = .077$) indicated non-significant relationships.

3.3. ANCOVA

Results of the repeated-measures ANCOVA of PVS-adjusted sBDNF values with the within-subject factor exercise and the covariate baseline

Table 1
Effects of a graded cycle ergometer test to maximum exhaustion in patients with MDD.

Variables	pre exercise M ± SD	post exercise M ± SD	Δ% M ± SD
Heart rate (bpm)	84.3 ± 13.0	172.1 ± 11.9*	108.3 ± 32.1
Lactate (mmol/l)	1.05 ± 0.4	7.9 ± 2.3*	760.0 ± 387.2
Platelets (x10^6/ml)	266.9 ± 53.3	300.6 ± 60.7*	12.9 ± 10.2
Plasma volume (%)	100 ± 0.0	92.9 ± 3.5*	−7.1 ± 3.5
sBDNF (ng/ml)	4.7 ± 1.6	5.6 ± 1.8*	23.3 ± 32.5
$sBDNF_{adj.PVS}$ (ng/ml)	4.7 ± 1.6	5.2 ± 1.6*	14.1 ± 28.3
RPE	6 ± 0.0	19.4 ± 1.1*	223.9 ± 17.9

Note. * significant at $p < .05$; M = mean; SD = standard deviation; Δ% = mean difference post-pre in percent of pre-values; bpm = beats per minute; Platelets = platelet count x 10^6/ml; sBDNF = serum concentration of Brain-derived neurotrophic factor; $sBDNF_{adj.PVS}$ = sBDNF adjusted for plasma volume shift; RPE = rating scale of perceived exertion (range 6–20).

Table 2
Repeated-measures ANCOVA of PVS-adjusted sBDNF values (within-subject factor: exercise, covariate: baseline platelet count).

Effect	Degrees of freedom	F-value	p-value	partial η^2
Main effect of exercise	1, 28	18.70	< .001	.400
Interaction effect of exercise by platelet count	1, 28	14.81	.001	.346

Note: PVS = plasma volume shift; sBDNF = serum concentration of Brain-derived neurotrophic factor. In comparison to this ANCOVA model, an alternative ANOVA model without the consideration of baseline platelets explained lesser variance in sBDNF-concentration after an acute exercise bout ($F_{1,29}$) = 5.48, p = .026, partial η^2 = .159).

platelet count are reported in Table 2. The significant main effect indicates an acute exercise-induced increase in sBDNF when controlling for baseline platelet count and adjusting sBDNF concentration for PVS. The significant interaction effect suggests that the exercise effect is qualified by the amount of platelets, while less platelets are related to a larger BDNF-increase following a single bout of exercise.

4. Discussion

In the current study, it was shown that sBDNF increases after a single bout of graded aerobic exercise to maximum exhaustion in patients with MDD. This finding is in line with the two previous investigations that tested this effect in MDD (Laske et al., 2010; Meyer et al., 2016). While the effect size dropped from a medium to a small effect when adjusting for exercise-related PVS, it remained significant. Thus, we showed that the measured sBDNF effect does exceed mainly peripheral exercise-related adaptation mechanisms. Correlation analyses revealed that lower baseline platelet levels were associated with larger exercise-induced sBDNF increases. Our ANCOVA model showed a significant pre-post sBDNF increase also when correcting for the amount of baseline platelets. The significant interaction of time by baseline platelets indicates that an exercise-induced sBDNF-increase was larger when number of baseline platelets was lower.

Our findings are of great relevance for MDD research as they emphasize the importance to take PVS and the number of available platelets into account to disentangle peripheral from additional – possibly brain-derived – mechanisms. For the first time, it could be shown that acute exercise-induced effects on sBDNF in MDD may not be solely explained by peripheral adaptation mechanisms.

Similar to previous reports on the size of an exercise-induced blood PVS (Kargotich et al., 1998), we found a significant mean reduction in plasma volume of about 7%. Without taking this effect into account, sBDNF change would have been overestimated by the same percentage. It should be noted that the intensity and duration of an exercise bout may influence both sBDNF change and PVS, thus the values in our study may not generalize to other studies using more or less intensive exercise protocols.

Also, reported absolute values of sBDNF might not be directly compared to values reported in other studies, as the use of different ELISA-kits (Polacchini et al., 2015) as well as different pre analytic methods (Maffioletti et al., 2014) may account for some variability in absolute sBDNF values. As other factors (e.g. genetic, metabolic, and immunologic factors) may influence sBDNF values, the influence of these variables on acute exercise effects should be investigated in future studies.

While a large percentage of peripheral BDNF is stored in platelets and their activation induces a partial release of the growth factor, also an enhanced internalization of BDNF into the platelets may occur (Serra-Millàs, 2016). Our results suggest that a further increase in BDNF could have been restrained in part by enhanced BDNF uptake due to high platelet availability or altered platelet reactivity (Naegelin et al., 2018; Serra-Millàs, 2016). Increased platelet activity was previously reported in MDD and associated with MDD-related alterations in serotoninergic and adrenergic signaling (Ziegelstein et al., 2009). Additional references are reported in the Supplementary Material.

Taken together, the current results are in support of a model for a long-term exercise-induced increase in sBDNF that is partially mediated by repeated exposure to acute increased sBDNF (Meyer et al., 2016). Most importantly, the reported findings suggest an involvement of peripheral and additional – possibly brain-derived – mechanisms in exercise-related BDNF release in MDD.

Conflict of interests

The authors declared no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.12.015.

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