The impact of an aquatic exercise program on BDNF levels in Parkinson's disease patients: short-and long-term outcomes

Silvia da Silva Germanos[a]
Bernardo Vieira[b]
Ivy Reichert Vital da Silva[a]
João José da Cunha[a]
Simone Nique[b]
Vera Striebel[b]
Daniela Pochmann[a]
Viviane Rostirola Elsner[a,b,c]

[a]Programa de PósGraduação em Biociências e Reabilitação do Centro Universitário Metodista-IPA, Porto Alegre, RS-Brasil
[b]Curso de Fisioterapia do Centro Universitário Metodista-IPA, Porto Alegre, RS- Brasil
[c]Programa de PósGraduação em Ciências Biológicas: Fisiologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS-Brasil

Correspondence to: Viviane Rostirola Elsner
E-mail: elsner.viviane@gmail.com

Summary

The present study aimed to analyze the short-and long-term effects of an aquatic exercise program on plasma brain-derived neurotrophic factor (BDNF) levels in individuals with Parkinson's disease (PD). The aquatic exercise program lasted one month, and consisted of two sessions per week (1 hour per session). Blood samples were collected at four different time-points: pre-intervention (T0), immediately after the first session (T1), 48 hours after the first session (T2), and 1 month after the intervention (T3). We found a significant decrease in BDNF levels at T2 *vs* T1 ($p<0.05$). However, no changes were observed at the other time-points. Our results demonstrated that the intervention reduced plasma BDNF levels in PD individuals in a time-dependent manner: specifically, we observed acute effects, but no delayed effects.

KEY WORDS: exercise therapies, neurotrophic factors, Parkinson's disease.

Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease affecting 1~2% of the elderly population. It is characterized by motor dysfunctions such as resting tremor, rigidity, bradykinesia, gait disturbances and postural instability (Gazewood et al., 2013). Together, these symptoms contribute to an increased risk of falls in these individuals. For example, more than 60% of 34 people with PD were reported to experience a fall every year (Morris et al., 2015).

At neuronal pathway level, an important hallmark of PD is progressive degeneration of the dopaminergic neurons in the midbrain substantia nigra, which results in diminished levels of dopamine in the striatum (Michel et al., 2013). Although the mechanism underlying this dopaminergic neuron loss is poorly understood, there is evidence indicating an involvement/imbalance of brain-derived neurotrophic factor (BDNF) levels. BDNF belongs to the neurotrophin family. It has 118 amino acids, a molecular weight of ~14 kDa and a high charge (Barde et al., 1982). Widely distributed in cortical and subcortical areas (Murer et al., 2001), BDNF is known to promote neuronal protection, survival and remodeling, axonal and dendritic growth, and synaptogenesis; it acts on dopaminergic neurons (Hyman et al., 1991) by activating the high-affinity tyrosine kinase B receptor (Chao and Hempstead,1995; Arancio and Chao, 2007). Finally, it is important to note that BDNF is able to cross the blood-brain barrier in a bi-directional manner via a high-capacity saturable transport system. Furthermore, peripheral levels of BDNF seem to show a strong correlation with cerebrospinal fluid levels (Pan et al., 1998).

Dluzen et al. (2002) showed that reduced BDNF expression disrupts dopaminergic output to the striatum; this disruption has been linked to prototypic motor signs of PD observed in mice (Dluzen et al., 2002). As regards clinical evidence, reduced levels of BDNF are observed in peripheral blood (Scalzo et al., 2010) as well in nigral neurons (Mogi et al., 1999) from PD patients. In fact, Huang et al. (2019) showed that decreased alteration of BDNF levels found in patients with PD is directly related to degeneration of dopaminergic neurons. Together, these findings support the idea that BDNF contributes to PD physiopathology and progression and might be considered putative biomarker of this disease (Huang et al., 2019; Scalzo et al., 2010).

There is also robust evidence showing that anti-parkinsonian agents, including dopamine replacement therapy, exert their effect, at least in part, by upregulating BDNF (Okazawa et al., 1992). Therefore, strategies that modulate BDNF levels/content might be considered in both neuroprotective preventive and therapeutic regimens in the management of patients with PD (Huang et al., 2019; Rahmani et al., 2019; Okazawa et al., 1992).

In this sense, some lines of evidence point to exercise-induced neuroprotective effects against PD mediated by BDNF enhancement (Vaughan et al., 2014; Angelucci et al., 2016). However, it is important to note that these studies concern land-based exercise programs, while there are no data regarding the impact of aquatic exercise protocols on BDNF modulation.

This is a topic worth investigating, given that the physi-

cal properties of water and the safe conditions offered by the aquatic environment enable people with PD to move more easily while reducing their fear of falling (Plecash and Leavitt, 2014; Volpe et al., 2014). Improvements in several outcomes, such as balance and functional mobility, have been reported following aquatic therapy in this population (Volpe et al., 2014). It has also been demonstrated that PD individuals who underwent aquatic therapy showed better improvements in many outcome measures compared with a group that received traditional land-based physical therapy (Volpe et al., 2014), reinforcing the effectiveness of this exercise modality.

Finally, we recently showed that an aquatic exercise program may offer a potential strategy able to attenuate immune responses in PD individuals in a short- and long-term perspective (Pochmann et al., 2018), however, as yet there is no evidence of modulation of BDNF levels following this intervention. In view of these considerations, the current study aimed to evaluate the short- and long-term outcomes of an aquatic exercise program on BDNF levels in the peripheral blood of PD patients.

Materials and methods

Participants

Twelve patients with idiopathic PD (PD group, PDG) and 14 healthy individuals matched by age and gender (control group, CG) participated in the present study. The participants were of both genders and were aged over 51 years.

The PDG inclusion criteria were a diagnosis of idiopathic PD confirmed by a neurologist, levodopa use, and no participation in other rehabilitation treatment. Neoplastic disease, infection, cardiopulmonary, vascular or other internal medical conditions, the use of oral or local corticosteroids, and previous neurosurgical treatment were the exclusion criteria for this group.

Smoking and the use of inflammatory drugs were further exclusion criteria for both the PDG and the CG. Furthermore, all participants had to be physically inactive (this was defined as less than 1h of physical exercise in the previous 3 months). All the PD patients continued to receive their usual medication at the (disease stage-adjusted) doses normally prescribed by their usual neurologist.

Finally, all the participants gave their written consent before participating in the study, which was approved by the local ethics committee (number 1.373.911).

Experimental design

The experimental design is shown in Figure 1. First, a blood sample (15 mL) was taken from each individual's antecubital vein to evaluate pre-intervention BDNF levels. The individuals then underwent an aquatic physiotherapy program, carried out in the indoor swimming pool (depth 1.1 m, mean water temperature 32°C) of the Centro Universitário Metodista – IPA. In accordance with other similar programs (Jones et al., 2006; Bote et al., 2014), the intervention lasted 1 month and took the form of 60-minute group sessions, twice a week, in the afternoon (3:30 p.m. to 4:30 p.m.).

Specifically, the aquatic exercise program combined aerobic and resistance training, a protocol that has been shown to improve physical health and fitness.

This program followed the recommendations of the American College of Sports Medicine (ACSM, 2000) and was previously reported by Pochmann et al., (2018). Briefly, the sessions were performed as follows: a) warm-up: passive stretching of lower limbs, waist-dissociation and dual task exercises (10 minutes); b) resisted exercises, consisting of exercises to strengthen paravertebral muscles and the posterior chain of the trunk and limbs, gait exercises, balance exercises and proprioception exercises (20 minutes); c) integration exercises: this part consisted of dual-task exercises in combination with games with playful connotations to stimulate group integration (20 minutes); d) relaxation (10 minutes).

Importantly, the intervention was conducted by physiotherapists specialized in the area of neurofunctional rehabilitation and by specially trained physical therapy students; the ratio of therapists to patients was 1: 3. Also, the participants received constant verbal motivation during the training sessions and were asked to adhere to their regular diet throughout the intervention.

In order to evaluate the short- and long-term effects of the intervention on BDNF levels, we took, in the antecubital region, a total of four blood samples (15 mL) from each individual.

Blood was drawn: before the exercise program (T0), immediately after the first exercise session (T1), 48 hours after the first exercise session (T2), and 1 month after the intervention (T3).

The individuals were instructed to avoid consuming alcohol or caffeine-based beverages in the 24-hour period prior to each blood collection. All blood sampling and exercise sessions were performed during the on-phase of the medication cycle, as reported by the participant.

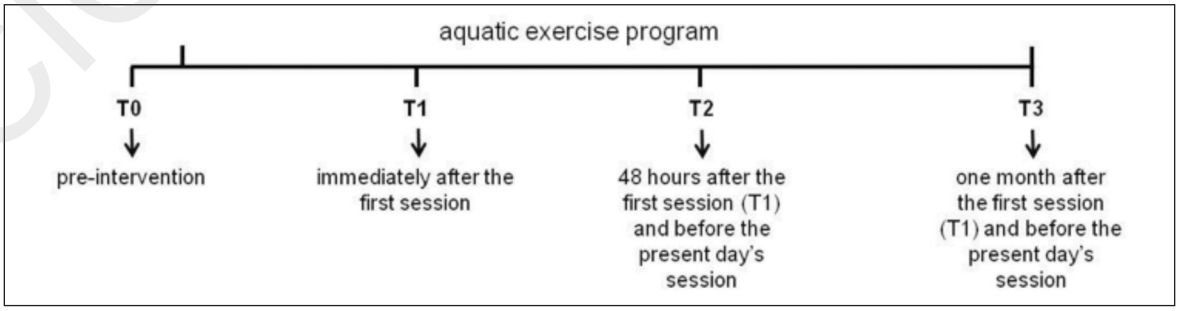

Figure 1 - Overview of the experimental design: the effect of the aquatic exercise program on BDNF levels at different time-points.

Sampling procedure
Venous blood samples were collected and stored in tubes with EDTAK3. The blood samples were diluted in a proportion of 4:3 in phosphate-buffered saline (PBS, 136 mM, NaCl, 2.7 mMKCl, 7.8 mM Na2HPO4, 1.7 mM KH2PO4; pH 7.2-7.4) and centrifuged (1500 rpm, 21° C, 20 minutes) on Ficoll-Histopaque 1077 (Sigma, MO, USA). At this time, 1.5 ml of plasma was separated and frozen at -20° C for plasma BDNF analysis.

Determination of BDNF content
BDNF levels were determined using the ELISA method, from the Sigma-Aldrich commercial kit (catalog number RAB0026), according to the manufacturer's instructions. Concisely, the plasma sample and BDNF specific standards were added to the ELISA microplate and incubated for 2.5 h at room temperature. Subsequently, the solutions were discarded and the same plate was thoroughly washed four times with wash buffer (PBS, Tween 20 0.01%). After washing, the secondary antibody was added and incubated with biotin for 1 h at room temperature with gentle agitation. The plate was thoroughly washed again with wash buffer, streptavidin solution was added, and the plate was incubated at room temperature for 45 min with gentle agitation. The solution was discarded and the plate went through the same washing process, as described above. Tetramethylbenzidine was added and the plate was incubated for 30 min at room temperature, with light deprivation and gentle agitation. The stop solution was then added to the plate. All readings were performed at 405 nm (emission) in a 96-well plate reader (ThermoPlate, São Paulo, Brazil). The plasma activities of BDNF were presented as pg/mL.

Statistical analysis
All collected data were inserted in a spreadsheet (Microsoft Excel®) and analyzed in SPSS® software version 22.0 for Windows®. Data normality was verified using the Shapiro-Wilk test, while the Kruskal-Wallis or Wilcoxon test was used to analyze the non-parametric data. All data are presented as median (interquartile range) and a significance level of $p<0.05$ was used.

Results

Twelve individuals were recruited, however, we are unable to collect blood samples from 3 patients due to technical problems, and these individuals were therefore excluded from the data analysis. During the intervention, no participants withdrew, and all 9 analyzed patients successfully completed the 1-month intervention, attending a minimum of 90% of the sessions. Table I presents the demographic characteristics of the sample, while their Unified Parkinson's Disease Rating Scale scores are shown in Table II. Figure 2 illustrates the

Table I - Characteristics of the sample.

	CG (n=14)	PDG (n=12)	p
Gender (female/male)	11 (78.6%)/3 (21.4%)	6 (50%)/6 (50%)	0.13
Age (years)	60.21±10.33	65.08 ± 6.73	0.17

Abbreviations: CG, Control Group; PDG, Parkinson's disease group.

The data are presented as mean ± standard deviation (numeric data) or relative frequency (categorical data).The comparison between groups was performed using the Student t-test for independent data or chi-square test ($p<0.05$).

Table II - Characterization of the Parkinson's disease group.

	(n=12)
Duration of levodopa use	
2-4 ears	6 (50%)
6-8 years	3 (25%)
10-17 years	3 (25%)
Hoehn&Yahr Scale	
Stage 1	2 (16.66%)
Stage 1.5	2 (16.66%)
Stage 2	2 (16.66%)
Stage 2.5	5 (41.66%)
Stage 3	1 (8.33%)
UPDRS score (mean ± SD)	15.83 ± 7.54

UPDRS: Unified Parkinson's Disease Rating Scale.

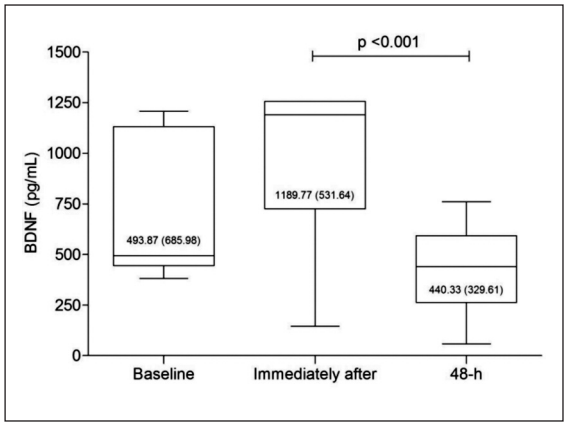

Figure 2 - The short-term effects of the aquatic exercise program on BDNF levels in PD individuals.
Data are presented as median (interquartile range). Statistical difference evaluated through Kruskal-Walis test demonstrated a significant reduction on BDNF levels at T2 compared to T1 period ($p < 0.001$).

Table III - Chronic response of the aquatic exercise program on BDNF levels in PD individuals.

	Baseline	T3	p
BDNF (pg/mL)	493.87 (685.98)	933.34 (477.47)	0.25

Data are presented as median (interquartile range). Statistical difference evaluated using the Wilcoxon test($p<0.05$). T3, one month after the intervention.

short-term effects (immediately after and 48 hours after the first session) of the aquatic exercise program. A significant reduction in BDNF levels at T2 *vs* T1 ($p<0.001$) was observed. As illustrated in Table III, the intervention had no delayed effects on BDNF levels.

Discussion

This study was performed to evaluate BDNF levels in PD at different time-points in relation to an aquatic exercise program. To the best of our knowledge, this is the first study evaluating BDNF modulation in response to a water-based intervention in PD individuals. We demonstrated that the protocol induced short-term effects, specifically it induced a reduction of BDNF levels at T2 compared withT1, but it showed no delayed effects.

It is well documented that single bouts of exercise, undertaken in various groups of subjects, healthy and pathological, can increase circulating BDNF levels (Knaepen et al., 2010; Shuch et al., 2015; da Silveira et al., 2017; Figueiredo et al., 2017). Our data show, for the first time, the acute impact of a single exercise session on BDNF levels in PD individuals. Intriguingly, however, this neurotrophin remained unchanged at long-term evaluation. Although it is impossible to define a reason for this response, it seems very likely that the intensity and exercise modality applied, as well the population studied, play an important role in the outcomes of single bouts of exercise as previously reported (Zoladz et al., 2008; Rojas et al., 2006; Alberts et al., 2001). Specifically, these data led us to hypothesize that PD patients, unlike other populations, such as bipolar, young healthy and elderly individuals, are sensitive to a single exercise exposure as a means of inducing BDNF modulation.

Our long-term data are partially in line with those obtained by Angelucci et al., (2016), who showed that an intervention including aerobic, strength and respiratory exercises (3 daily sessions) and lasting 1 month, the same period that we used, did not change circulating levels of BDNF in PD individuals. However, they found a significant increase in BDNF levels at day 7 compared with baseline. Unfortunately, we did not evaluate BDNF levels at this time-point, and thus we cannot rule out the possibility of a transient modulation in this neurotrophin in response to an aquatic exercise intervention. Future studies should focus on this time-point in order to elucidate this issue.

On the other hand, it should be noted that 8 weeks of interval training (three 1-hour sessions weekly) on a stationary cycloergometer significantly increased BDNF levels, while also alleviating parkinsonian rigidity and decreasing muscle tone (Marusiak et al., 2015). In addition, Zoladz et al., (2014) also found that a moderate-intensity interval training (three 1-hour training sessions weekly) over 8 weeks resulted in elevated peripheral BDNF levels, as well improved motor symptoms in PD individuals.

Taken together, these data might suggest that BDNF modulation in response to chronic exercise in PD individuals is strictly dependent on the protocol duration, being more sensitive to long lasting exposure.

It is important to note that in addition to the practice of physical exercise, repetitive transcranial stimulation of the primary motor cortex (M1) in both hemispheres and of the dorsolateral prefrontal cortex in the left hemisphere of PD patients has been shown to have positive therapeutic effects in these individuals, enhancing both motor and cognitive function (Yang et al., 2013). In this context, experimental and clinical studies have revealed that, in addition to activation of brain regions in terms of immediate early gene expression, the increase in BDNF levels after stimulation appears to be a relevant molecular mechanism underlying these benefits (Wang et al., 2011; Lee et al., 2013).

Considering that BDNF is capable of improving motor function and also the function of the nigrostriatal system (Shen et al., 1994), it is suggested that the increase in this neurotrophin after transcranial stimulation and physical exercise may improve aspects of PD patients' conditions through modulation of the nigrostriatal system. Other clinical studies may be performed to clarify this issue.

Another important aspect of the present study is the individuals' high attendance of the intervention. Our data regarding this adherence are in agreement with those of other studies involving structured, supervised and group-based exercise protocols in other populations such as schizophrenic individuals (Lavratti et al., 2017), which suggests that the characteristics of such protocols are strictly related to the intervention adherence. Another possible explanation for this response might be that water, due to its particular properties, offers a safer setting that reduces the risk of injury and helps to overcome the fear of falling (Palamara et al., 2017).

Some limitations of this study must be acknowledged. Firstly, since we used a pre-post intervention design, with the absence of a control group, we cannot say whether or not our treatment gives better results than sham therapy.

Furthermore, the number of subjects was relatively small, due to difficulty recruiting the sample. However, we believe that our findings will encourage future investigations in larger samples, which may also include a control group.

Such further studies might make it possible to verify other issues such as the influence of gender and age on BDNF modulation in response to an aquatic exercise protocol in PD patients.

In summary, our results suggest that 1-month water-based programs are ineffective in promoting neuroplasticity through BDNF levels in PD individuals. However, an acute effect was observed since BDNF levels were diminished at 48 hours compared with immediately after the training session. Further studies examining intensity, dose effects and long-term benefits of aquatic therapy in PD are warranted.

Acknowledgements

The Authors would like to thank the following Brazilian agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de DesenvolvimentoCientífico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support.

References

Alberts JL, Linder SM, Penko AL, et al (2011). It is not about the bike it is about the pedaling: forced exercise and Parkinson's disease. Exerc Sport Sci Rev 39: 177-186.

American College of Sports Medicine (2000). http://www.acsm.org/.

Angelucci F, Piermaria J, Gelfo F, et al (2016).The effects of motor rehabilitation training on clinical symptoms and serum BDNF levels in Parkinson's disease subjects. Can J Physiol Pharmacol 94: 455-461.

Arancio O, Chao MV (2007). Neurotrophins, synaptic plasticity and dementia. Curr Opin Neurobiol 17: 325-330.

Barde YA, Edgar D, Thoenen H (1982). Purification of a new neurotrophic factor from mammalian brain. EMBO J 1: 549-553.

Bote ME, Garcia JJ, Hinchado MD, et al (2014).An exploratory study of the effect of regular aquatic exercise on the function of neutrophils from women with fibromyalgia: role of IL-8 and noradrenaline. Brain Behav Immun 39: 107-112.

Chao MV, Hempstead BL (1995). p75 and Trk: a two-receptor system. Trends Neurosci 18: 321-326.

da Silveira FP, Basso C, Raupp W, et al (2017).BDNF levels are increased in peripheral blood of middle-aged amateur runners with no changes on histone H4 acetylation levels. J Physiol Sci 67:681-687.

Dluzen DE, Anderson LI, McDermott JL, et al (2002). Striatal dopamine output is compromised within +/- BDNF mice. Synapse 43: 112-117.

Figueiredo AI, Cunha JJ, da Silva IRV, et al (2017).Running-induced functional mobility improvement in the elderly males is driven by enhanced plasma BDNF levels and the modulation of global Histone H4 acetylation status. Middle East J Rehabil Health Stud 4: e57486.

Gazewood JD, Richards DR, Clebak K (2013). Parkinson disease: an update. Am Fam Physician 87: 267-273.

Huang Y, Huang C, Yun W (2019). Peripheral BDNF/TrkB protein expression is decreased in Parkinson's disease but not in essential tremor. J Clin Neurosci 63: 176-181.

Hyman C, Hofer M, Barde YA, et al (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350: 230-232.

Jones KD, Adams D, Winters-Stone K, et al (2006). A comprehensive review of 46 exercise treatment studies in fibromyalgia (1988-2005). Health Qual Life Outcomes 4: 67.

Knaepen K, Goekint M, Heyman EM, et al (2010). Neuroplasticity - exercise- induced response of peripheral brain-derived neurotrophic factor: a systematic review of experimental studies in human subjects. Sports Med 40: 765-801.

Lavratti C, Dorneles G, Pochmann D, Peres A, Bard A, de Lima Schipper L, Dal Lago P, Wagner LC, Elsner VR (2017). Exercise-induced modulation of histone H4 acetylation status and cytokines levels in patients with schizophrenia. Physiol Behav 168:84-90.

Lee JY, Kim SH, Ko AR, et al (2013). Therapeutic effects of repetitive transcranial magnetic stimulation in an animal model of Parkinson's disease. Brain Res1537: 290-302.

Marusiak J, Żeligowska E, Mencel J, et al (2015).Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. J Rehabil Med 47:372-375.

Michel PP, Toulorge D, Guerreiro S, et al (2013). Specific needs of dopamine neurons for stimulation in order to survive: implication for Parkinson disease. FASEB J 27: 3414-3423.

Mogi M, Togari A, Kondo T, et al (1999). Brain-derived growth factor and nerve growth factor concentrations are decreasedin the substantia nigra in Parkinson's disease. Neurosci Lett 270: 45-48.

Morris ME, Menz HB, McGinley JL, et al (2015). A randomized controlled trial to reduce falls in people with Parkinson's disease. Neurorehabil Neural Repair 29: 777-785.

Murer MG, Yan Q, Raisman-Vozari R (2001). Brain-derived neurotrophic factor in the control human brain, and in Alzheimer's disease and Parkinson's disease. ProgNeurobiol 63: 71-124.

Okazawa H, Murata M, Watanabe M, et al (1992). Dopaminergic stimulation up-regulates the in vivo expression of brain-derived neurotrophic factor (BDNF) in the striatum. FEBS Lett 313: 138-142.

Palamara G, Gotti F, Maestri R, et al. (2017). Land plus aquatic therapy versus land-based rehabilitation alone for the treatment of balance dysfunction in Parkinson disease: a randomized controlled study with 6-month follow-up. Arch Phys Med Rehabil 98: 1077-1085.

Pan W, Banks WA, Fasold MB, et al (1998). Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology 37: 1553-1561.

Plecash AR, Leavitt BR (2014).Aquatherapy for neurodegenerative disorders. J Huntington's Dis 3: 11-15.

Pochmann D, Peccin PK, da Silva IRV, et al (2018).Cytokine modulation in response to acute and chronic aquatictherapy intervention in Parkinson disease individuals: a pilot study. Neurosci Lett 674: 30-35.

Rahmani F, Saghazadeh A, Rahmani M, et al (2019). Plasma levels of brain-derived neurotrophic factor in patients with Parkinson disease: a systematic review and meta-analysis. Brain Res 1704: 127-136.

Rojas VS, Struder HK, Vera Wahrmann B, et al (2006). Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. Brain Res 1121: 59-65.

Scalzo P, Kummer A, Bretas TL, et al (2010).Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J Neurol 257: 540–545.

Schuch FB, da Silveira LE, de Zeni TC, et al (2015).Effects of a single bout of maximal aerobic exercise on

BDNF in bipolar disorder: a gender-based response. Psychiatry Res 30: 57-62.
Shen RY, Altar CA, Chiodo LA (1994). Brain-derived neurotrophic factor increases the electrical activity of pars compacta dopamine neurons in vivo. Proc Natl Acad Sci USA 91: 8920-8924.
Vaughan S, Wallis M, Polit D, et al (2014). The effects of multimodal exercise on cognitive and physical functioning and brain-derived neurotrophic factor in older women: a randomised controlled trial. Age Ageing 43: 623-629.
Volpe D, Giantin MG, Maestri R, et al (2014). Comparing the effects of hydrotherapy and land-based therapy on balance in patients with Parkinson's disease: a randomized controlled pilot study. Clin Rehabil 28: 1210-1217.
Wang HY, Crupi D, Liu J, et al (2011). Repetitive transcranial magnetic stimulation enhances BDNF-TrkBsignaling in both brain and lymphocyte. J Neurosci 31:11044-11054.
Yang YR, Tseng CY, Chiou SY, et al (2013). Combination of rTMS and treadmill training modulates corticomotor inhibition and improves walking in Parkinson disease: a randomized trial. Neurorehabil Neural Repair 27: 79-86.
Zoladz JA, Pilc A, Majerczak J, et al (2008). Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. J Physiol Pharmacol 59: 119-132.
Zoladz JA, Majerczak J, Zeligowska E, et al (2014). Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients. J Physiol Pharmacol 65: 441-448.