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Is BDNF related to spatial-temporal gait parameters in people with multiple sclerosis? An observational study

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Abstract

Background: It has been suggested that the protein Brain-derived Neurotrophic Factor (BDNF) plays a neuroprotective role in people with multiple sclerosis (pwMS). Also, BDNF seems to play a role in cognition performance. In the same line, gait in pwMS requires a higher cognitive resource, mainly during complex walking. Thus, maybe BDNF could be related to gait in pwMS.

Objective: To investigate the relationship between BDNF and gait spatial-temporal parameters during unobstructed and obstructed conditions and the Timed Up and Go (TUG) in pwMS and healthy controls (HC).

Methods: The study included 20 pwMS (11F/9M, 33.1±7.5 years, Expanded Disability Status Scale- EDSS 2.2±1.2) and 18 HC (13F/5M, 35.5±5.9 years). Both groups performed 20 gait attempts in two conditions: unobstructed walking (10 trials) and avoiding an obstacle. The obstacle was 15 cm in height and made of foam material. The BDNF serum concentration was collected with participants in fasting and completed before the clinical, gait, and mobility assessments. Clinical variables included the Symbol Digit Modality Test (SDMT), the Fatigue Severity Scale (FSS), and the International Physical Activity Questionnaire (IPAQ- short version). Associations between BDNF and spatial-temporal gait parameters, clinical variables, and TUG were determined by Pearson/Spearman correlations with Bonferroni's correction being applied ($p<0.0013$). Gait was compared by a two-way, repeated-measures ANOVA (group and condition) to characterize our cohort.

Results: Reduced BDNF was observed for pwMS (41.66±4.45 ng/ml) in comparison with HC (61.67±7.07, $p<0.001$). However, although some correlations presented a moderate correlation between BDNF with gait variables, the correlations didn't reach a significant p-value after Bonferroni's correction. Lastly, pwMS presented shorter step length and slower step velocity for both gait conditions, with more evidence for obstacle conditions. Only pwMS changed gait behavior from unobstructed walking to obstacle avoidance conditions (i.e., reduced step length and velocity and increased step duration).

Conclusion: BDNF is not related to either clinical (i.e., EDSS, SDMT, FSS, or IPAQ) or gait parameters in pwMS and HC, even in a condition involving higher cognitive demand. These results may suggest that BDNF does not play a role in these parameters' performance.

Keywords: Multiple sclerosis, BDNF, locomotion, neuroprotection, cognition.

1. Introduction

Brain-Derived Neurotrophic Factor (BDNF) is a critical protein in maintaining proper function and structure of the Central Nervous System (CNS). BDNF is widely expressed in the brain and its concentrations in the bloodstream correlate with concentrations in the CNS. Animal studies show a positive correlation between the BDNF concentrations in the bloodstream with CNS concentrations being suggested that measures of blood and plasma BDNF levels reflect brain-tissue BDNF levels (Klein et al., 2011), and has the capacity to cross the blood-brain barrier in a bi-directional way (Pan et al., 1998; Seifert et al., 2010). In multiple sclerosis (MS), the BDNF serum concentration increases after a relapse, probably to restore neuronal damage following acute inflammation (Frota et al., 2009; Sarchielli et al., 2002). Although still controversial, many studies have shown lower BDNF serum concentrations in pwMS compared to healthy individuals (Castellano and White, 2008; Frota et al., 2009; Naegelin et al., 2020).

BDNF has a vital role in the formation and maturation of synapses and spines (e.g., neurogenesis and neuroplasticity) of the CNS (Anastasia and Hempstead, 2014; Ksiazek-Winiarek et al., 2015), oligodendrocyte production (Du et al., 2003), and neuron differentiation (Anastasia and Hempstead, 2014), and is related to cognition, learning, memory (Patanella et al., 2010), and executive function (Leckie et al., 2014). Furthermore, BDNF is inversely associated with lesions in the CNS in pwMS (Comini-Frota et al., 2012) and with the Expanded disability status (EDSS) score (Mehrpour et al., 2015). Therefore, it is believed that an elevated BDNF concentration supports the CNS through fewer lesions and lessens the negative effects of MS on motor aspects.

Adequate mobility function is essential for independence and quality of life in pwMS. Gait dysfunction is one of the worst symptoms of MS, affecting at least 41% of this population, and among those suffering from gait impairments, 70% report this as one of the significant MS

symptoms (LaRocca, 2011). Shorter step length and velocity (Comber et al., 2017; Preiningerova et al., 2015; Santinelli et al., 2021) and increased time to complete the Timed up and Go (TUG) (Pau et al., 2017) are characteristics of pwMS, worsening with disease progression (Preiningerova et al., 2015; Sebastião et al., 2016). Walking complexity (e.g., parallel to cognitive demands) is related to gait disability in pwMS. Recently, our group found that in comparison to regular walking, step velocity and step length were reduced and cortical activity increased (i.e., higher power in beta and gamma frequencies in frontal and parietal areas) when pwMS were required to ambulate in a complex environment requiring greater use of cognition (i.e., with the presence of an obstacle) (Santinelli et al., 2021). It is suggested that these gait changes are related to subcortical lesions, especially in the pyramidal tract (Kalron and Givon, 2016; Santinelli et al., 2021), and to reduced cognitive resources (Chaparro et al., 2017) in pwMS.

Considering that both gait and BDNF are influenced by the number and level of CNS lesions and are cognitive-related (Leckie et al., 2014; Inbal Maidan et al., 2016; Patanella et al., 2010), it may be argued that pwMS with higher BDNF concentration would present better gait performance (e.g., faster and longer steps). Therefore, we investigated the relationship between BDNF serum concentration with spatial-temporal gait parameters during unobstructed and obstructed walking. We hypothesized that BDNF would present a positive moderate relationship with spatial-temporal gait parameters in unobstructed and moderate-to-strong relationships with obstructed conditions (e.g., higher BDNF would be linked to higher step velocity and faster TUG) in pwMS.

2. Method

2.1 Experimental design

Subjects enrolled in this study were instructed to avoid any kind of intense/vigorous physical activity for 48 hours before the assessment session and to avoid food or liquid ingestion, except for water, for 12 hours prior to assessment. All measurements were collected in the morning (7:00 am to 12:00 pm) to minimize the effects of the circadian cycle on biological samples. The subjects were informed about the experimental procedures (University Institution Review Board CAAE#99191318.0.0000.5398) and signed informed consent.

Upon arrival, 4 ml of blood were collected from all subjects, after which they were offered breakfast. Although we standardized the breakfast provided, we allowed participants to consume as much as possible. Following, reflective markers were carefully attached by a research staff member for the gait assessment. Subsequently, the subjects completed the clinical evaluation and TUG. The end of the session included a gait assessment under two conditions: normal (unobstructed) and walking with an obstacle (obstructed). The experimental design is illustrated in Figure 1.

*****Figure 1 near here*****

2.2 Participants

Twenty-two pwMS (13F/9M) and 18 (HC- 13F/5M) were recruited for this study. Common inclusion criteria included: a) age between 18 and 55 years; b) no cognitive decline (>24 points in the Mini-Mental State Exam-MMSE) (Folstein et al., 1975); and c) no orthopedic, cerebellar, cardiac, and oculomotor disabilities not corrected by glasses. For pwMS, an additional set of inclusion criteria was used, including d) clinically definitive diagnosis of relapsing-remitting MS (McDonald criteria) (McDonald et al., 2001; Thompson et al., 2018a); e) EDSS score lower than 4.5 (Kurtzke, 1983) and 4 in the Patient Determined Disease Steps (PDDS) (de David et al., 2019); f) relapse-free in the three months prior to data

collection, and g) not using fampridine. Two pwMS were not relapse-free for three months before the evaluation and were excluded from the study, leaving 20 pwMS (11F/9M).

2.3 Clinical evaluation

The disease record (time since onset and last relapse, and self-reported disease disability-PDDS) was obtained from pwMS. The level of disability (EDSS) was obtained from their neurologist. All participants completed the Symbol digit modality test (SDMT) (Smith, 1982), the Fatigue Severity Scale (FSS) (Krupp, 1989), and the International Physical Activity Questionnaire (IPAQ- short version) (Matsudo et al., 2012) with the score expressed in Metabolic Equivalent of Task units (METs).

2.4 BDNF assessment

The blood sample was based on 4 ml drawn from the arm and stored in a tube for serum separation. Then, the blood sample was centrifuged (3000 rpm, 10 minutes, 4º Celsius). The serum was later stored in an Eppendorf (0.5 ml) at -20º Celsius for 24 hours and stored at -80º Celsius until analysis. The samples were diluted 50-fold (pwMS) and 100-fold (CG) with a calibrator diluent before the assay. The Enzyme-Linked Immunosorbent Assay (ELISA) technique was used for BDNF analysis according to the manufacturer's recommendations (R&D System, Minneapolis, MN, USA). The sensitivity of the ELISA kit ranges between 1500–23.4 pg.mL^{-1} with an intra-assay coefficient of variation (CV) of 1.3%.

2.5 TUG and gait assessment

For the TUG evaluation, a single practice trial was given prior to the two attempts used for the analysis. The final score of the TUG was the average time of the two separate attempts (Sebastião et al., 2016).

As for the gait trials, the subjects walked barefoot at a self-selected speed across a walkway 8.5m long and 3.5m wide. Each subject performed 20 trials (10 attempts for each condition) in two gait conditions: unobstructed and obstructed (avoiding an obstacle). The conditions were randomized using automatic software (https://site112.com/ordenar-lista-aleatoriamente). Kinematic data were collected with ten three-dimensional infrared cameras (Vicon Motion System®, 200 frames/s. Thirty-nine reflective markers were placed on each subject in accordance with the Plug-in-Gait Full Body (Vicon®) model. Two markers were positioned at the top of the obstacle. To quantify the spatial-temporal parameters of gait, markers placed on the second metatarsal and the heel of each foot were used.

Gait raw data were filtered with a fifth-order (zero-lag) low-pass Butterworth filter (cutoff at 6 Hz). The average of the five steps performed in the middle of the walkway was considered for the unobstructed gait. Concerning the obstructed gait, the analysis was split into the approaching phase (three steps before the obstacle) and the crossing phase (leading and trailing steps). Spatial-temporal gait parameters included: step length, duration, velocity, width, and double support phase (percentage of step duration). Additional parameters were calculated, including the horizontal toe (before obstacle avoidance – T_{-1}) and heel (after obstacle avoidance – H_{+1}) and vertical toe distance (toe-clearance) to the obstacle for the leading and trailing steps. For a complete description, please see (Santinelli et al., 2021).

2.6 Statistical analysis

Data were analyzed using SPSS V.26 (IBM Corporation, Armory, N.Y). The normality of the data was checked using the Shapiro-Wilk test, and the significance level was set at $p<0.05$. All gait parameters respected data normality. An independent *t*-test compared to age, body-mass, body-mass index (BMI), height, BDNF concentration, and TUG performance between pwMS and HC. We used the Mann-Whitney *U* test to compare groups' SDMT, FSS,

MMSE, and IPAQ scores. The two-way ANOVA (group x condition), during the unobstructed x approaching phase, and one-way ANOVA, during the crossing phase in the obstructed condition, were provided to characterize our cohort. When the ANOVA showed a significant effect, the post-hoc with Bonferroni correction was performed.

Pearson's (*r*) correlation was used to examine the correlation among BDNF concentration and 1) clinical evaluations, 2) functional mobility (TUG), and 3) spatial-temporal gait parameters. The Spearman *rho* rank was employed for the EDSS, PDSS, SDMT, FSS, MMSE, and IPAQ scores. The correlation analysis was performed separately for each group. Correlation coefficients of 0-0.1, 0.1-0.39, 0.4-0.69, 0.7-0.89, and 0.9-1 were interpreted as negligible, weak, moderate, strong, and very strong, respectively (Schober and Schwarte, 2018). We further performed the partial correlations to control the relationships by confounding factors such as age, gender, and IPAQ for all subjects and EDSS score for pwMS. To mitigate the potential type I error within the correlation between BDNF and spatial-temporal gait parameters, the correction of Bonferroni was applied (0.05/38=0.0013) (Curtin and Schulz, 1998). The 95% confidence interval for the correlations is also presented.

3. Results

Groups were similar in height, body mass, BMI, age, and MMSE (Table 1). The pwMS were slower in the TUG and presented lower processing speed information and higher fatigue compared to the HC. The BDNF serum concentration was lower in pwMS than HC (Table 1 and Figure S1).

*****Table 1 near here*****

Comparisons of gait performance according to group and condition are presented in Table 2. PwMS demonstrated slower and shorter steps in both gait conditions (unobstructed,

approaching, and crossing phase) and increased step width, duration, and double support percentage in the crossing phase compared to the HC. Additionally, only the pwMS group presented slower and shorter steps during the approaching phase to the obstacle compared to the unobstructed gait.

*****Table 2 near here*****

Although some correlations presented weak-to-moderate coefficients and p-values lower than 0.05, after the Bonferroni corrections, the correlations among BDNF and clinical variables and spatial-temporal gait parameters were non-significant for both groups.

*****Table 3 near here*****
*****Table 4 near here*****

4. Discussion

Reduced BDNF serum concentration (Castellano and White, 2008; Frota et al., 2009; Islas-Hernandez et al., 2018), slower and shorter steps with greater step width (Comber et al., 2017; Santinelli et al., 2021), and slower TUG performance (Pau et al., 2017) in pwMS compared to healthy individuals are presented consistently in the literature. However, no studies have previously examined the relationship between BDNF serum concentration with gait parameters and functional mobility in pwMS. Although BDNF serum concentrations showed moderate correlations with spatial-temporal gait parameters during unobstructed and obstructed walking and functional mobility in pwMS, the correlations did not reach significance and did not support our hypothesis. Also, when controlled by confounding factors, the relationship remains non-significant. Our results contribute to the knowledge regarding the influence of BDNF on clinical and motor outcomes in pwMS.

As shown by previous studies (Islas-Hernandez et al., 2018; Kalinowska-Łyszczarz et al., 2018; Naegelin et al., 2020; Prokopova et al., 2017; Văcăraş et al., 2017), lower BDNF serum concentration is currently observed in pwMS compared to healthy people. It has been suggested that reduced BDNF concentration in pwMS is a consequence of immune cells' lower production ability (Azoulay et al., 2008) or even an inability of their muscles (Devasahayam et al., 2021) to release BDNF. In addition, no difference in BDNF concentration is observed from relapse-remitting to progressive MS phenotype or within different EDSS levels (Islas-Hernandez et al., 2018). On the other hand, previous studies have found higher BDNF concentration in pwMS experiencing relapse (Frota et al., 2009; Oraby et al., 2021). The BDNF concentration during relapses is also associated with T2 infratentorial lesions, thereby suggesting that BDNF can also be used to monitor MS activity in terms of relapse (Oraby et al., 2021). Thus, it seems likely BDNF is a promising biomarker for MS diagnosis and MS activity, but not for disease severity and progression or clinical and motor outcomes in pwMS as observed by previous studies and confirmed by our results (Damasceno et al., 2015; Islas-Hernandez et al., 2018; Oraby et al., 2021). However, this theme still needs further investigation.

Our results did not show any relationship between BDNF serum concentration with clinical or motor gait outcomes. We hypothesized that better spatial-temporal gait parameters would be related to higher BDNF serum concentration. This hypothesis was based on which both gait and BDNF have a relationship with lesion load in CNS and disease disability and are cognitive-related (Comini-Frota et al., 2012; Leckie et al., 2014; Inbal Maidan et al., 2016; Mehrpour et al., 2015; Patanella et al., 2010). The relationship observed of BDNF and lesion load in pwMS when the patient is suffering relapse (Oraby et al., 2021) or after three months (Comini-Frota et al., 2012) suggests a role of BDNF on neuroregeneration. On the other hand, when relapsing-remitting pwMS are under the remission phase of MS disease no association

between BDNF and MRI outcomes, such as total and regional brain volume and lesion load (Damasceno et al., 2015; Naegelin et al., 2020) is observed. The results linking the BDNF to EDSS have yielded conflicting results in the same line. Previously, (Mehrpour et al., 2015) observed a low-to-moderate relationship between BDNF and EDSS scores. On the other hand, this relationship in other studies was not observed (Damasceno et al., 2015; Naegelin et al., 2020), even when they analyzed the BDNF according to different BDNF isoforms (Tongiorgi et al., 2012). Thereby, although we were unable to obtain the MRI from pwMS, the lack of association between BDNF serum concentration and clinical/gait outcomes observed in our study must be due to the absence of a relationship between BDNF and EDSS/MRI outcomes, as demonstrated previously (Damasceno et al., 2015; Naegelin et al., 2020; Tongiorgi et al., 2012).

We expected that the gait parameters obtained in a higher cognitive resource condition would show some relationship with BDNF in pwMS and HC. However, we did not identify this association even with a purely cognitive measurement (i.e., SDMT). This result aligns with (Naegelin et al., 2020) findings. The BDNF is mainly expressed in the hippocampus (Neeper et al., 1996), responsible for memory and learning. Therefore, BDNF has a crucial role in cognitive performance in memory and learning tasks (Piepmeier and Etnier, 2015). Thus, our gait conditions and cognitive exams involve executive and attention (I Maidan et al., 2016; Santinelli et al., 2021) and not memory and learning aspects, which could explain the lack of correlation with the gait parameters. Maybe specific walking tasks involving memory and learning abilities can be more sensitive to find associations with BDNF concentration. We suggest future studies investigate the association of BDNF to gait learning and walking performing a memory task.

Lastly, a significant discrepancy among the studies is noticeable in BDNF concentration, different MS phenotypes, heterogeneous EDSS scores, pwMS under and not

under treatment or relapses, small sample size, and BDNF kit used and controlling of cofounding factors, which makes conclusion difficult. Therefore, we recommend future studies to standardize research in pwMS investigating BDNF serum concentration. In this way, the results of the studies can be comparable.

5. Limitations

Although our study showed interesting new findings, they should be interpreted with caution due to some limitations. As we believe this to be the first study on this specific theme, future studies should confirm our findings using a more heterogeneous sample of pwMS (e.g., progressive MS forms and a wide range of the EDSS spectrum). Furthermore, the BDNF serum concentration has a short half-life. It may be affected by several factors such as sleep quality, mood, physical fitness status, smoking, alcohol or drug use habits, and gut microbiome factors. Although we attempted to mitigate potential confounding factors by asking, for example, for the participants to arrive in a fasting state and avoid performing vigorous physical activity prior to data collection, we could not control for all the confounding factors. In addition, BDNF function and concentration are sex-dependent (Chan and Ye, 2017), and considering that our cohort did not represent at all the MS sex ratio population distribution (1M/3F ratio distribution) (Thompson et al., 2018b), we recommend that future studies recruit a more representative MS population. Finally, further investigations are required to evaluate the mature BDNF and pro-BDNF isoforms of BDNF separately. These two BDNF isoforms have distinct functions, which could change the relationship with the parameters analyzed in the present study.

6. Conclusions

In conclusion, our findings indicate no association between BDNF and clinical and gait variables in pwMS and HC. The BDNF does not have a role in gait outcomes, even in the gait condition requiring higher cognitive resources in pwMS and HC. However, we could not detect any associations because our gait task does not involve memory or learning aspects. Furthermore, we suggest future studies investigating gait involving learning and memory. Lastly, although we did not find any association in our study, we cannot disregard the importance of BDNF on neuroprotection for pwMS, as many studies have been recently showing (Diechmann et al., 2021).

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Conflict of interest

All the authors declare no conflict of interest.

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Data availability

The data used and which support the findings of the present study are available through the corresponding author upon request.

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Figure Captions

Figure 1. Experimental design of the study. People with Multiple Sclerosis (pwMS); healthy controls (HC); Mini-Mental State Exam (MMSE); Fatigue Severity Scale (FSS); International Physical Activity Questionnaire (IPAQ); Symbol digit Modality Test (SDMT).