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Association between brain atrophy and cognitive motor interference in multiple sclerosis

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ABSTRACT

Introduction: Cognitive motor interference (CMI) is performance impairment due to simultaneuous task execution and is measured using the dual task cost (DTC). No pathological feature of MS has to date been associated with CMI.

Aim: To assess the relationship between brain volumes and CMI, as measured using the DTC, in a cross-sectional study.

Methods: A group of persons with MS (pwMS) and an age- and sex-matched healthy control (HC) group underwent 3D gait analysis during using the dual task paradigm. Brain volumes were measured on T1-weighted gradient echo scans using SIENAX software. The relationships between brain volumes and the DTCs of spatial temporal parameters were evaluated using Pearson correlation. A multiple regression model was used to evaluate the ability to predict the DTC of cadence based on brain volume and grey matter (GM) volume.

Results: Forty-four patients and 16 HCs underwent MRI and gait analysis. The mean expanded disability status scale (EDSS) was 2.4 ± 1.5. Significant relationships between brain volumes and DTC were found only in the pwMS group, with higher rho scores for the DTC of mean velocity, DTC of cadence, and DTC of stride time. A statistically significant regression equation with an R^2 value of 0.684 was found using GM and Z-score on the Stroop test as predictors of the DTC of cadence ($p < 0.001$).

Conclusion: Brain atrophy, especially than in the GM, is a major determinant of DTC, although other pathological markers also contribute to CMI in patients with MS.

1. Introduction

Gait impairment is a relevant issue in multiple sclerosis (MS). In a clinical survey of 1011 patients, La Rocca et al. reported that 41% had walking difficulties (LaRocca, 2011). Although symptomatic drugs may have a positive effect on this problem (Coghe et al., 2015; Fampridine, 2017), ambulatory impairment remains the most challenging aspect of living with MS. Many factors can contribute to walking impairment (e.g., poor coordination and spasticity (Pau et al., 2015)), and cognitive problems are one of the most studied of these factors. (Bethoux, 2013) This is because, in daily life, walking is not merely a mechanical task, but requires awareness of the destination and the ability to navigate within complex environments. These neuropsychological abilities are related to planning, purposive action, and other domains pertaining to executive function (Yogev-Seligmann et al., 2008). Therefore, separate assessments of cognitive impairment and ambulation neither truly reflect everyday activity nor measure the actual gait impairment (Leone et al., 2015). As such, the gold standard for the evaluation of the abovementioned abilities in a laboratory setting is the dual task (DT) paradigm. This task comprises the simultaneous execution of a motor and a cognitive task. The neuropsychological phenomenon tested by the DT paradigm is cognitive motor interference (CMI), which is performance impairment due to simultaneous task execution. CMI may be explained by two theoretical frameworks: the capacity sharing model, and the bottleneck theory. The former model assumes that CMI arises when the combination of the two tasks requires an amount of resources that exceeds the brain's capacity. The latter postulate states that the two processes share neural pathways, which leads to delay or impairment in

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the performance of one or both tasks. CMI is measured using the dual task cost (DTC), which represents the relative ratio of a single task (ST) to DT while controlling for ST performance percentage (Baddeley et al., 1997).

The leading determinant of gait during the performance of a dual task are executive functions and the motor systems involved in ambulation. The frontal lobes are traditionally thought to be involved in executive functions, but the neural substrates of executive functions are pervasive and diffuse, and involve networks in the anterior and posterior areas (Collette et al., 2006). Gait impairments (expressed in terms of step length and double support time) have been associated with atrophy of the sensorimotor and fronto-parietal regions in the elderly. (Watson et al., 2010) It has been shown that the simultaneous execution of two tasks leads to widespread cerebral activity due to interactions between the areas involved in each task (Collette et al., 2006). Therefore, because MS is characterized by widespread brain pathology, which leads to altered connectivity, CMI is likely exacerbated in MS during the performance of tasks with heavy cognitive loads (Fleischer et al., 2017; Coghe et al., 2017). Nevertheless, a clear association between the neuropathological markers of MS and CMI has never been identified, although many MS clinical factors have been hypothesized to significantly impact. For instance, performance in the Symbol Digit Modality Test correlates with the DTC of gait speed. Expanded disability status scale (EDSS) score, fatigue, age, and education have been shown to be associated with walking speed, although these findings are controversial (Wajda and Sosnoff, 2015).

Brain volume is related to motor and cognitive performance in MS, and is considered a strong predictor for neurologic disabilities. As such, brain volume represents a kind of “summary measure” for irreversible demyelination and neuronal loss (Amato et al., 2012). Moreover, brain volume was recently shown to be associated with functional mobility performance, as measured using the instrumented Timed Up and Go (Lorefice et al., 2017). Additionally, brain volume is a standardized, objective measure sensitive to disease changes (Filippi, 2013). Based on the above, we designed a cross-sectional study to evaluate the relationships among brain volumes and CMI, as measured using the DTC.

2. Methods

A group of pwMS was enrolled. The inclusion criteria were a diagnosis of MS according to the 2010 McDonald criteria (Polman et al., 2010), ability to ambulate for 100 m with or without an assisting device, and the absence of any other condition that could affect gait. Individuals with comorbidities that could influence brain volumes, those with acute inflammation during the scan, and those in a relapsing phase during the gait assessment were excluded. An age- and sex-matched group of healthy controls (HC) served as the control group. The local ethics committee approved the study and all participants agreed to participate in the study by signing an informed consent form.

All of the patients underwent an EDSS evaluation by a neurologist expert in MS and performed the Stroop Color and Word Test (SCWT). The Stroop Test was administrated by an expert neuropsychologist in a quiet room. The SCWT results were corrected for age and sex, and the Z-score was calculated using available normative data (Amato et al., 2006).

All participants underwent a 3D gait analysis performed under DT conditions, as previously described (Coghe et al., 2017). The spatial-temporal and kinematic parameters of gait were assessed using a motion-capture system comprising 8 infrared cameras (Smart-D, BTS Bioengineering, Italy) set at a frequency of 120 Hz. The participants' anthropometric measures were collected and 22 retro-reflective passive markers were placed following the Davis protocol (Davis et al., 1991). The participants were asked to walk at a self-selected speed at least six times. We allowed suitable rest times between the trials. The raw data were processed using the dedicated software Smart Analyzer (BTS Bioengineering, Italy) to calculate gait speed and cadence, stride length, step width, stance, swing, and double support phase duration (expressed as percentage of the gait cycle).

For the DT trials, the participants walked while performing the SCWT, which was projected onto a 48″ LCD screen located perpendicularly to the gait direction (Coghe et al., 2017). The CMI was quantified using the DTC, which was calculated as percentage change in a specific gait parameter, for the two conditions, as follows:

$$DTC = 100 \cdot \frac{ST - DT}{ST}$$

where ST and DT represents respectively the value of a certain gait parameter calculated under the ST and DT conditions. For parameters such as stance and double support time, for which an increase in value denotes a worse performance, the numerator of the fraction is inverted (Baddeley et al., 1997).

Brain Magnetic Resonance Imaging (MRI) was performed in a single session using a 1.5 T Siemens Magnetom Avanto (Siemens Medical Solutions; Germany). A sagittal survey image was used to identify the anterior and posterior commissures. Three-dimensional magnetization-prepared rapid gradient-echo acquisition was used to obtain 174 contiguous sagittal 3D T1-weighted (T1W) images with slice thicknesses of 1.3 mm. Brain parenchyma volumes were measured on the T1W gradient echo scans using SIENAX software, which is a part of the FSL package. We used a previously described method to estimate the whole brain (WB) volume. We also selectively measured white matter (WM), grey matter (GM), and cortical GM volumes normalized for head size (Smith et al., 2002). Two operators screened all MR images for motion artefacts to ensure accuracy of the brain extraction and atrophy estimation (Battaglini et al., 2008).

3. Statistical analysis

Data were preliminarily screened to evaluate whether the gait parameters differed bilaterally. One-way analyses of variance revealed no significant differences between the left and right sides for any gait measure. Therefore, the mean value from the two sides was considered representative for each participant in the analysis. Differences in demographic and clinical variables of interest (i.e., brain volume [BV], age, and spatial-temporal gait parameters) between the pwMS and HCs were evaluated using Student's *t*-tests, while the sex distribution was evaluated using the chi-square test. Parametric model assumptions were verified (e.g., normality, homogeneity, and presence of outliers). The relationships between the brain volume measures and the DTCs of the gait parameters were explored using Pearson's correlation tests with a level of significance of $p = 0.05$. In order to reduce the impact of disability on gait and to focus on the CMI, the test was corrected for EDSS. Multiple regression analysis was performed to predict CMI while walking based on brain volumes and the SCWT Z-score. The DTCs of the gait parameters with higher Pearson correlation values were used as dependent variables. All analyses were performed using the IBM SPSS Statistics v.20 software (IBM; Armonk, NY, USA).

4. Results

Forty-eight pwMS (MS group, 15 men and 33 women) and 36 controls (HC group, 14 men and 22 women) were enrolled. Of these subjects, 44 pwMS and 16 HCs agreed to undergo MRI and were considered for the analysis. The mean age in the MS group was 41.1 ± 8.9 years, while the HC group has a mean age of 40.1 ± 12.6 years. All but 3 (two secondary progressive and one primary progressive) of the participants in the MS group had a relapsing-remitting course. The mean EDSS score was 2.4 ± 1.5 and the mean corrected score on the SCWT was 72.5 ± 47.9. Three patients had Z-scores < -1.5 and none had a Z-score < -2. Significant differences between the MS and HC groups were found for all of the investigated gait parameters and the MRI volumes. No differences in age or sex distribution were observed