Transcranial direct current stimulation during treadmill training in children with cerebral palsy: A randomized controlled double-blind clinical trial

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1. Background

Motor impairment is the most common abnormality in children with cerebral palsy (CP) (Rosenbaum et al., 2007). Spasticity affects approximately 80% of cases (Graham, 2000) and is characterized by a muscle tone-dependent increase in velocity and exacerbation of deep reflexes stemming from hyper-sensitivity of the stretching reflex (Scholtes, Becher, Beelen,

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& Lankhorst, 2006). Spastic diparesis is a common form of CP with a wide range of ambulatory outcomes (Bjornson et al., 2007). Diparesis is characterized by more intensive involvement of the lower limbs (Rotta, 2002). In such cases, the lower limbs often exhibit increased adduction and internal rotation of the hips as well as excessive knee flexion associated with equinovarus (Hägglund, Lauge-Pedersen, & Wagner, 2007).

Approximately 90% of children CP have altered gait secondary to muscle weakness, spasticity, abnormal joint kinematics and diminished postural reactions (Chagas, Mancini, Barbosa, & Silva, 2004; Grecco, Zanon, Sampaio, & Oliveira, 2013). These neuromotor abnormalities stem from brain damage, which leads to a reduction in the activation of the central nervous system during the execution of movements (Burton, Dixit, Litkowski, & Wingert, 2009; Shin, Lee, Hwang, You, & Im, 2012). Moreover, children with CP exhibit a global alteration in motor cortex excitability, even in the occurrence of unilateral lesions (Nevalainen et al., 2012), resulting in diminished activation of the corticospinal and somatosensory circuits (Pitcher et al., 2012).

A number of approaches have been employed to favor cortex activation, selective motor control and muscle coordination during gait in children with CP (Chagas et al., 2004; Grecco, Zanon, Sampaio, & Oliveira, 2013). The capacity to learn a new motor pattern depends on multiple behavioral and neural processes. Thus, treadmill training has been employed to improve gait performance, the results of which include improvements in gait velocity, balance and functional independence (Grecco, Tomita, et al., 2013; Grecco, Zanon, Sampaio, & Oliveira, 2013; Smania et al., 2011). The basis of this approach is the training of a specific task with multiple repetitions of the different phases of the gait cycle in a rhythmic (Mattern-Baxter, 2010).

Transcranial direct current stimulation (tDCS) is a promising resource in neurological rehabilitation. tDCS is a noninvasive technique that promotes cortex stimulation through a low-intensity (1–2 mA) direct electrical current using surface electrodes. The anode electrode facilitates and the cathode electrode inhibits cortical excitability. Thus, the tDCS can lead to increased local synaptic efficacy by acting on the dysfunctional cortex region and changing the pattern of maladaptive plasticity that arises after a cortex lesion. Given the important role of the primary motor cortex in motor control, the use of tDCS has demonstrated positive effects on motor learning and gait in both healthy subjects and stroke victims (Hummel & Cohen, 2006; Kaski, Quadir, Patel, Yousif, & Bronstein, 2012; Madhavan, Weber II, & Stinear, 2011).

Few studies have addressed the use of tDCS on children with brain lesions (Grecco et al., 2014). However, it is rational to investigate this resource in pediatric patients due to their significant cerebral plasticity. The hypothesis tested herein is that anodal tDCS applied to the motor cortex modifies cortex excitability and favors motor learning, specifically the learning of a new gait pattern practiced during treadmill training. The primary aim of the present study was to compare the effects of anodal tDCS and placebo transcranial stimulation during treadmill training on the gait pattern, cortex excitability and gross motor function in children with CP. The secondary aim was to determine whether the effects would be maintained one month after the end of the intervention.

2. Materials and methods

A prospective, analytical, double-blind, randomized, placebo-controlled clinical trial was carried out. This study received approval from the Human Research Ethics Committee of University Nove de Julho (Brazil) under process number 69803/2012 and was carried out in compliance with the ethical standards established by the Declaration of Helsinki. The study is registered with the Brazilian Registry of Clinical Trials under process number RBR-9B5DH7. All parents/guardians agreed to the participation of the children by signing a statement of informed consent. Fig. 1 displays the flow chart of the study.

2.1. Participants

Thirty-nine children were recruited from specialized outpatient clinics. The following were the inclusion criteria: diagnosis of spastic CP; classification on levels I (child can generally walk without restrictions, but tends to be limited with regard to more advanced motor skills), II (gait limitation in the outdoor environment) or III (assistance required for locomotion) of the Gross Motor Function Classification System (GMFCS) (Palisano et al., 1997); independent gait for at least 12 months; age between five and ten years; and degree of comprehension compatible with the execution of the procedures. The following were the exclusion criteria: history of surgery or neurolytic block in the previous 12 months, orthopedic deformities, epilepsy, metal implants in the skull or hearing aids.

The children were randomly allocated to an experimental group and control group. For such, block randomization was performed, with the allocation sequence stipulated in sequentially numbered, sealed, opaque envelopes. Following the initial evaluation, each participant was allocated to one of the groups by opening an envelope. This process was performed by a member of the research team who was not involved in the recruitment process or other aspects of the study.

2.2. Intervention

The intervention consisted of ten sessions of anodal tDCS applied over the primary motor cortex. The experimental group received active tDCS and the control group received placebo stimulation applied for 20 min during treadmill training. Sessions were held five times a week over two consecutive weeks. Treadmill training was performed on the Inbramed treadmill (Millenium ATL, RS, Brazil) without body weight support. Training velocity was 80% the maximum velocity reached

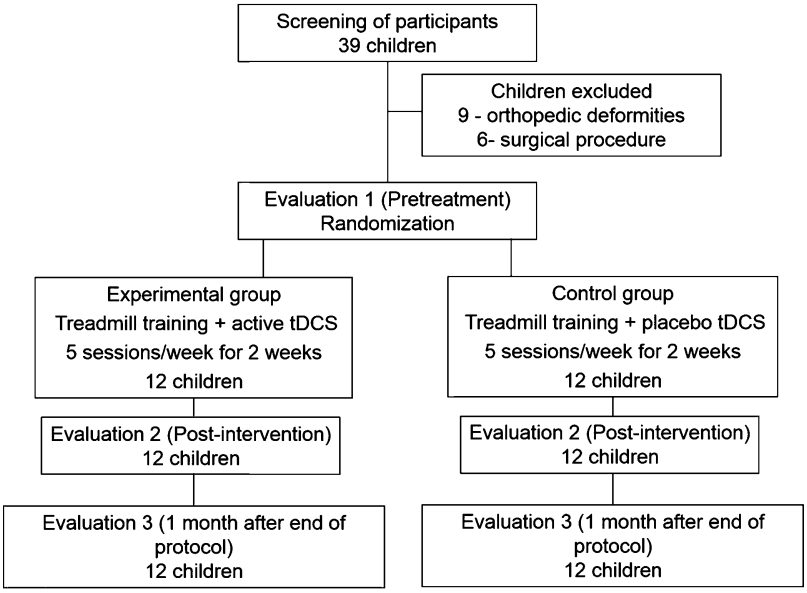

Fig. 1. Flowchart of study based on Consolidated Standards of Reporting Trials (CONSORT).

on a previous exercise test. The pace was gradually increased to the training velocity in the first 2 min of training and gradually reduced in the last 2 min (Grecco, Zanon, Sampaio, & Oliveira, 2013).

A transcranial stimulation device (Soterix Medical Inc., USA) was employed using two sponge (non-metallic) electrodes (5×5 cm) moistened with saline solution. The anodal electrode was positioned over the primary motor cortex of the dominant hemisphere following the 10–20 International Electroencephalogram System (Homan, Herman, & Purdy, 1987) and the cathode was positioned in the supra-orbital region on the contralateral side. In the experimental group, a 1 mA current was applied over the primary motor cortex for 20 min as the children performed the treadmill training. The device has a dial that allows the operator to control the intensity of the current. In the first 10 s, stimulation was gradually increased until reaching 1 mA and gradually diminished in the last 10 s of the session. In the control group, the electrodes were positioned at the same sites and the device was switched on for 30 s, giving the children the initial sensation of the 1 mA current, but no stimulation was administered during the rest of the time. This is a valid control procedure in studies involving tDCS.

2.3. Methods

The participants were evaluated one week prior to the intervention (Evaluation 1), one week after the intervention (Evaluation 2) and one month after the intervention (Evaluation 3). Each evaluation was performed over three non-consecutive days to avoid the influence of fatigue on the performance. The raters were blinded to the objectives and methods of the study. Each component of the evaluation is described below.

Gait analysis was performed using the SMART-D 140® system (BTS Engineering, Italy) with eight infrared cameras, the SMART-D INTEGRATED WORKSTATION® with 32 analog channels and a synchronized video system. After the determination of the anthropometric measures (height, weight, lower limb length, distance between the femoral condyles or diameter of the knee, distance between the malleoli or diameter of the ankle, distance between the anterior iliac spines and thickness of the pelvis), passive markers were placed at specific reference points directly on the skin for the evaluation of the kinematics of each segment of the body. The markers were placed over C7 and the sacrum as well as bilaterally over the acromion, anterosuperior iliac spine, greater trochanter, femoral epicondyle, femoral wand, tibial head, tibial wand, lateral malleolus, lateral aspect offers the foot at the fifth metatarsal head and at the heel (only for static offset measurements) (Davis, Ounpuu, Tyburski, & Gage, 1991). The Davis marker-set was chosen as the protocol of choice to acquire the movement of lower limbs and trunk based on Ferrari et al. (2008). After the child was familiarized with the process, at least six trials were performed along a 10-meter catwalk at a pace self-selected by each child. Three consistent trials of each lower limb were considered for analysis. All readings were performed by the same experienced researcher to ensure the reliability of the data collection. In the present study, only spatiotemporal and kinematic gait variables were identified and computed. The following spatiotemporal parameters were analyzed:

- velocity (m/s): mean velocity of progression;
- cadence: number of steps in a time unit (steps/min);

- stride length (m): longitudinal distance between successive points of heel contact of the same foot;
- step length (m): longitudinal distance between the point of initial contact of one foot and the point of initial contact of the contralateral foot;
- step width (m): distance between the rear end of the right and left heel centerlines along the mediolateral axis;
- stance phase: % of gait cycle that begins with initial contact and ends at toe-off of the same limb.

All kinematic gait analysis graphs were normalized as a percentage of the gait cycle, producing kinematic plots of the pelvis, hip, knee and ankle for each cycle. The Gait Profile Score (GPS) was calculated according to the procedure implemented by Baker et al. (2009). The GPS represents the root mean square (RMS) difference between particular gait trial and averaged data from people with no gait pathology and summarizes the overall deviation in kinematic gait data relative to normative data (Baker et al., 2009). This global summary measure was used because it is comprised of a number of gait variable scores (GVSs) representing an equivalent RMS difference between each normalized temporal kinematic variable and the mean data from a reference population calculated across the gait cycle (Ferreira et al., 2014). Thus, if $x_{i,t}$ is the value of gait variable i calculated at a specific point in the gait cycle t and $\bar{\boldsymbol{x}}_{i,T}^{ref}$ is the mean of the variable at the same point in the gait cycle in the reference population, then the i^{th} gait variable score is given by:

$$\boldsymbol{GVS}_i = \frac{1}{T}\sum_{t=1}^{T}\left(\boldsymbol{x}_{i,t} - \bar{\boldsymbol{x}}_{i,T}^{ref}\right)^2$$

in which T is the number of instants into which the gait cycle has been divided. The GPS is then the RMS average of the GVS variables:

$$GPS = \frac{1}{N}\sum_{i=1}^{N}\boldsymbol{GVS}_i^2$$

The overall GPS is based upon 15 clinically important kinematic variables (Pelvic Ant/Pst, Pelvic Up/Dn Obliquity, rotation of the left side, hip flexion, abduction, internal rotation, knee flexion, dorsiflexion and foot progression for the left and right sides). In the analysis, a GPS score was determined for each side based on all nine GVSs. A higher the GPS value denotes a lesser physiological gait pattern. In the literature, the GPS has been used to quantify gait alterations in different adverse health conditions in both children and adults (Baker et al., 2009; Celletti et al., 2013; Ferreira et al., 2014; Kark, Vickers, McIntosh, & Simmons, 2012; Rutz et al., 2011; Schweizer, Romkes, Coslovsky, & Brunner, 2014; Thomason et al., 2011).

The six-minute walk test quantifies functional mobility based on the distance in meters traveled in 6 min. During the test, the following physiological variables were quantified: heart rate, respiratory rate, oxygen saturation, systolic blood pressure, diastolic blood pressure as well as perceived respiratory and lower limb exertion using the Borg scale (Borg, 1982).

The Gross Motor Function Measure-88 allows a quantitative assessment of gross motor function in individuals with CP. This measure is made up of 88 items distributed among five subscales: (1) lying down and rolling; (2) sitting; (3) crawling and kneeling; (4) standing; and (5) walking, running and jumping. The items of each subscale receive a score of 0–3 points, with higher scores denoting a better performance (Russell et al., 2000).

Treadmill test: As there is no standardized test for the pediatric population with neurological disorders, a test was designed by the authors of the present study. The symptom-limited cardiopulmonary effort test was employed on a treadmill (Master I Millennium model, Inbramed, LTDA) using the ramp protocol increased 0.5 km/h each minute. The following were the criteria for interrupting the test: subjective sensation of fatigue, lower limb pain reported by the child, complex heart arrhythmia, sudden increase or drop in blood pressure, increase above maximum heart rate predicted for age of the individual, intense shortness of breath and drop in oxygenation accompanied by electrocardiographic alterations or signs and symptoms (Grecco, Tomita et al., 2013; Grecco, Zanon, Sampaio, & Oliveira, 2013).

Cortical excitability was measured through transcranial magnetic stimulation using a magnetic stimulator (MAGSTIM Bistim^2) with a figure-eight coil. Responses to stimuli applied to the motor cortex were recorded in the quadriceps muscle contralateral to the stimulated side. These measures were performed for both sides. The motor threshold was measured in each region assessed, not exceeding an intensity of 80% of the output of the machine in order to protect the child from excessive stimulation. The motor evoked potential (MEP) was evaluated using 120% intensity of the motor threshold (minimum intensity required to generate a muscle contraction) and represents the excitability of a neural network for the movement assessed in addition to all the structures involved in the execution of this movement (Kobayashi & Pascual-Leone, 2003). MEP responses were filtered and amplified using surface electromyography. The signals were transferred to a personal computer for offline analysis of the MEP amplitude. Ten individual measures of MEP were performed and the mean was used for the statistical analysis.

A comparison of treadmill training and overground walking in ambulant children with cerebral palsy: randomized controlled clinical trial.

2.4. Statistical analysis

The sample size was calculated with the aid of the STATA 11 program and based on a study carried out by "A comparison of treadmill training and overground walking in ambulant children with cerebral palsy: randomized controlled clinical trial" (Grecco, Zanon, Sampaio, & Oliveira, 2013). The six-minute walk test was considered for the calculation. This test was selected as the primary outcome based on its proven validity and reliability as a functional capacity assessment tool and was used to evaluate the functional mobility and physical fitness of the children. Considering a mean and standard deviation of 377.2 ± 93.0 m in experimental group and 268.0 ± 45.0 m in control group, a bidirectional alpha of 0.05 and an 80% test power, eight children were required for each group, to which 25% was added to compensate for possible dropouts, totaling 24 participants (12 in each group).

The data analysis involved intention-to-treat analysis. The Kolmogorov-Sirmonov test demonstrated normal data distribution. Thus, parametric tests were performed and the data were expressed as mean and standard deviation (or 95% confidence interval). To compare the effects of stimulation during motor training on gait variables, ANOVA with the Bonferroni post hoc test was performed. The dependent variable was the gait velocity and the independent fixed variables were treatment (evaluation 1, evaluation 2 and evaluation 3), group (experimental – active tDCS and control – placebo tDCS) and group-treatment interactions. Similar models were run for the other variables. The effect size was calculated from the difference between baseline (Evaluation 1) and post-treatment (Evaluation 2) as well as between baseline and follow up all outcome measures. A p-value < 0.05 indicated a statistically significant result. The data were organized and tabulated using the Statistical Package for Social Sciences (v.19.0).

3. Results

All children completed all evaluations. Table 1 displays the anthropometric and functional characteristics of the participants, demonstrating similarity between the two groups.

Table 2 displays data from the three-dimensional gait analysis (spatiotemporal and GPS with GVSs values) of the groups. As no statistically significant differences were found between the right and left lower limbs, the data from both sides were pooled for each child. The experimental group demonstrated improvements in gait velocity, cadence and GPS at Evaluations 2 and 3 ($p < 0.05$). Improvements also occurred regarding the Pelvic Tilt and Hip Ab-Adduction GVSs at Evaluations 2 and 3 as well as Knee Flex-Extension at Evaluation 2. No significant differences in gait variables were found in the control group.

Fig. 2 illustrates the results of the six-minute walk test. The experimental group demonstrated a significant increase in the distance traveled after the intervention (Evaluation 1: 223.2 ± 58.0 m; Evaluation 2: 448.2 ± 100.5 m; Evaluation 3: 409.6 ± 81.6 m) [$F_{(2.24)} = 9.966$; $p < 0.001$]. No significant difference was found in the control group (Evaluation 1: 255.4 ± 62.8 m; Evaluation 2: 367.2 ± 97.6 m; Evaluation 3: 345.4 ± 97.7 m).

Dimensions D and E of the GMFM-88 were analyzed. No statistically significant differences in dimension D were found in either the experimental group (Evaluation 1: 63.7 ± 7.0; Evaluation 2: 75.3 ± 11.6; Evaluation 3: 72.6 ± 12.4) or control group (Evaluation 1: 66.2 ± 6.2; Evaluation 2: 70.0 ± 9.2; Evaluation 3: 68.4 ± 9.8) [$F_{(2.12)} = 0.344$; $p = 0.715$]. Similar results were found regarding dimension E in both the experimental group (Evaluation 1: 54.1 ± 7.7; Evaluation 2: 59.9 ± 11.1; Evaluation 3: 60.7 ± 10.5) and control group (Evaluation 1: 60.7 ± 10.5; Evaluation 2: 61.7 ± 10.7; Evaluation 3: 60.1 ± 10.7) [$F_{(2.12)} = 0.246$; $p = 0.785$].

On the treadmill test, no statistically significant differences were found between groups or within groups at the different evaluations times regarding endurance (group experimental – Evaluation 1: 5.4 ± 1.1, Evaluation 2: 6.6 ± 1.1, Evaluation 3: 6.4 ± 0.6 min; group control – Evaluation 1: 5.0 ± 1.0, Evaluation 2: 6.2 ± 1.3, Evaluation 3: 5.9 ± 1.1 min [$F_{(1.12)} = 2.840$; $p = 0.117$]) or heart rate.

In the analysis of MEP of the quadriceps muscle, an effect was found in the experimental group [$F_{(1.51)} = 5.350$, $p = 0.022$]. Fig. 3 displays MEP findings.

Table 3 displays the different outcome measures and treatment effects.

Table 1
Anthropometric characteristics and functional classification of children studied.

	Groups	
	Experimental $n = 12$	Control $n = 12$
Gender (female/male)[a]	9/3	8/4
GMFCS (II/III)[a]	8/4	8/4
Age (years)[b]	7.8 (3.0)	8.0 (2.2)
Body mass (kg)[b]	23.4 (5.3)	24.5 (6.4)
Stature (cm)[b]	108.1 (11.5)	110.5 (9.7)
Body mass index (kg/m^2)[b]	20.1 (2.9)	21.0 (5.5)

GMFCS: gross motor functional classification system.
[a] Numbers indicate frequency (n) of children in each group.
[b] Data expressed as mean (standard deviation).

Table 2
Mean and standard deviation (SD) of spatiotemporal variables, Gait Profile Score (GPS) and Gait Variation Scores (GVS) at Evaluation 1 (baseline), Evaluation 2 (post-treatment) and Evaluation 3 (follow up) in experimental and control groups.

	Experimental group			Control group		
	Evaluation 1	Evaluation 2	Evaluation 3	Evaluation 1	Evaluation 2	Evaluation 3
Velocity (m)	0.4 (0.1)	0.9 (0.1)*,#	0.8 (0.1)*,#	0.5 (0.1)	0.6 (0.1)	0.5 (0.1)
Cadence (step\min)	94.3 (22.5)	121.6 (2.3)*,#	118.8 (7.1)*,#	103.2 (19.4)	105.8 (15.5)	102.1 (12.1)
Stride length (m)	0.71 (0.18)	0.68 (0.14)	0.81 (0.11)	0.66 (0.15)	0.65 (0.16)	0.79 (0.16)
Step length (m)	0.33 (0.05)	0.32 (0.08)	0.36 (0.04)	0.31 (0.04)	0.34 (0.05)	0.33 (0.03)
Step width (m)	0.16 (0.01)	0.17 (0.09)	0.17 (0.01)	0.16 (0.01)	0.16 (0.01)	0.15 (0.08)
Stance phase (%)	56.8 (0.01)	60.1 (2.23)	59.9 (1.4)	57.2 (0.71)	55.8 (2.01)	57.5 (0.75)
GPS (°)	11.8 (1.5)	7.5 (1.3)*,#	7.3 (1.5)*,#	11.3 (2.4)	11.1 (1.5)	11.8 (2.2)
GVS Pelvic Obliquity (°)	3.8 (1.9)	2.8 (0.8)	3.0 (0.9)	2.4 (0.9)	3.2 (1.6)	4.1 (1.6)
GVS Pelvic Tilt (°)	7.6 (5.2)	3.5 (1.7)*,#	3.9 (1.8)*,#	7.3 (5.0)	7.9 (6.5)	6.9 (4.8)
GVS Pelvic Rotation (°)	4.2 (1.1)	4.5 (1.8)	3.2 (0.2)	5.5 (1.1)	4.7 (0.9)	4.7 (1.4)
GVS Hip Ab-Adduction (°)	9.3 (8.3)	3.8 (1.5)*,#	4.8 (1.1)*,#	8.1 (4.8)	11.7 (5.7)	7.9 (4.6)
GVS Hip Flex-Extension (°)	7.3 (3.3)	8.4 (5.6)	7.4 (4.6)	9.5 (5.1)	6.9 (3.6)	6.5 (2.4)
GVS Hip Rotation (°)	19.6 (11.1)	15.1 (0.5)	18.1 (8.0)	21.6 (12.6)	20.4 (10.7)	21.6 (11.7)
GVS Knee Flex-Extension (°)	11.8 (4.4)	10.1 (3.8)#	17.2 (4.5)	14.9 (9.3)	19.6 (9.3)	16.7 (6.0)
GVS Ankle Dorsi-Plantarflex (°)	5.4 (2.8	5.8 (0.7)	6.9 (3.1)	6.8 (2.8)	6.9 (4.0)	6.4 (2.6)
GVS Foot Progression (°)	11.6 (9.4)	10.3 (4.6)	13.8 (1.9)	12.8 (7.2)	10.3 (5.0)	11.0 (3.4)

* $p < 0.05$, intragroup analysis.
\# $p < 0.05$, intergroup analysis.

4. Discussion

A large number of methods have been tested to find a rehabilitation protocol that can improve the gait pattern and overall functioning of children with spastic diparetic CP. The literature reports that treadmill training allows a global improvement in gait (Mutlu, Krosschell, & Spira, 2009; Zwicker & Mayson, 2010). In the present study, the aim of analyzing the combination of anodal tDCS administered over the primary motor cortex during treadmill training was to determine whether the change in cortex excitability would favor the effects obtained with motor training and the maintenance of these effects after the end of the training period. The findings are encouraging, as improvements occurred in gait performance and these improvements were maintained in the follow-up period one month after the end of the rehabilitation protocol.

Although the lesion in spastic diparesis secondary to CP is bilateral, anodal tDCS over the dominant primary cortex had positive global effects in this population. The use of tDCS is based on the modulatory effects that occur primarily in the target area of stimulation (the primary motor cortex, in the present study). Secondly, the effects reach underlying cortical areas due to the integration of brain structures. The authors believe that the effects found in the present study are related to the activation of dysfunctional brain areas during the practice of a specific motor activity.

Given the important role of the motor cortex in the learning process and motor control, the effects of training in a specific activity, such as treadmill training, are enhanced by anodal tDCS, allowing information to be processed more efficiently and easily due to the optimization of cortex excitability. Thus, motor responses can be triggered with greater dexterity and speed, as demonstrated by the improvements in spatiotemporal and kinematic gait variables.

The authors believe that better feedback and feedforward occurred during gait training. The synchronization of steps (repetitive training, synchronized, rhythmic gait promoted by treadmill training) with a "less dysfunctional" primary motor cortex may facilitate the learning of a better gait pattern. There is a need to test this hypothesis in further studies, but motor learning is likely, since the improvement in some parameters was maintained one month after of the end of the intervention protocol. If this hypothesis is confirmed, tDCS may offer a new possibility for pediatric neurological rehabilitation and contribute to the optimization of motor outcomes and rehabilitation time, as the present protocol lasted only ten days.

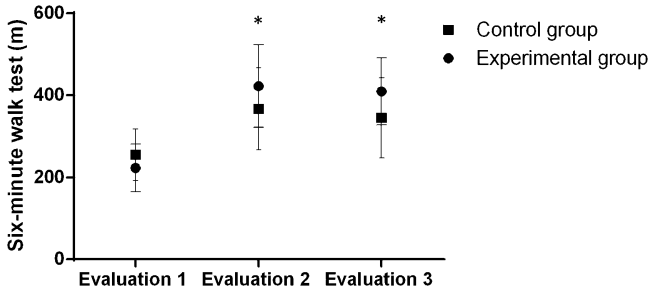

Fig. 2. Mean and standard deviation (SD) of six-minute walk test at Evaluation 1 (baseline), Evaluation 2 (post-treatment) and Evaluation 3 (follow up) in experimental and control groups. *$p < 0.05$ (experimental group vs. control group)

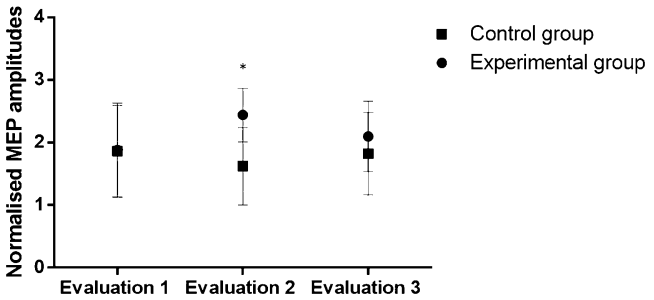

Fig. 3. Mean and standard deviation (SD) of motor evoked potential at Evaluation 1 (baseline), Evaluation 2 (post-treatment) and Evaluation 3 (follow up) in experimental and control groups. $^{*}p < 0.05$ (experimental group vs. control group).

The six-minute walk test and treadmill test were performed in the present study based on the fact that these tests are considered valid for the evaluation of mobility and cardiopulmonary fitness. Previous studies involving these tests as outcomes have demonstrated the positive effects of treadmill training on children with CP. In the present study, only the children in the experimental group (tDCS and treadmill training) demonstrated improvement after the intervention, as these children were able to walk greater mean distances at Evaluation 2 (increase of 225.0 m in comparison to Evaluation 1) and Evaluation 3 (increase of 186.4 m in comparison to Evaluation 1) than the children in the control group (Evaluation 2: 111.8 m increase in comparison to Evaluation 1; Evaluation 3: 90.9-m increase in comparison to Evaluation 1). As this was a randomized controlled double-blind study, one may infer that stimulation of the motor cortex was the determinant of these differences. Another important aspect is related to duration of the intervention. Two weeks may be considered a relatively short period for effects on gait speed. The effect obtained on the six-minute walk test was greater than that reported in a previous (increase of 149.8 m) that employed the same treadmill training parameters (Grecco, Zanon, Sampaio, & Oliveira, 2013). The study cited involved 12 training sessions conducted at a frequency of three sessions per week, whereas five sessions per week were performed in the present study.

Intervention time is extremely important in neurological rehabilitation. Patients with neurological lesions spend a long period of their lives in motor rehabilitation. Although there is no consensus in the literature that results are more easily maintained with intensive or spaced protocols, rehabilitation time has repercussions on the physical, emotional and financial aspects of patients and their families. Thus, if the tDCS results regarding the optimization of the time required to obtain motor improvements with minimal adverse effects are confirmed, this method can become an important therapeutic resource.

The experimental group exhibited significant improvements in terms of velocity of progression, cadence and global gait kinematics, as demonstrated by the GPS value. The improvement in GPS was directly related to a proximal improvement evidenced by the GVS values of Pelvic Tilt and Hip Ab-Adduction. Changes were found in two weeks (10 sessions) (Evaluation 2) and maintained one month after the end of the intervention (Evaluation 3), whereas no changes were observed in the control group. These findings suggest that anodal stimulation of the motor cortex during treadmill training provides an increase in the effect size, especially with regard to gait velocity (mean difference: 0.3 m), cadence (mean difference: 19.5steps/min) and GPS (mean difference: −3.6°).

Although anodal stimulation was conducted only on the primary motor cortex of the dominant hemisphere in children with diparesis (bilateral brain lesions), no asymmetries were identified in the kinematics of the lower limbs (before or after surgery). It is believed that tDCS has an overall modulatory effect (evidenced as motor evoked potential) promoted by the global optimization of motor function. Few studies were found that analyzed the effects of tDCS on the gait. Findings similar to those in the present study have been reported in adult stroke victims (12 sessions of gait training performed after

Table 3
Comparison of different outcome measures and treatment effects.

	Baseline–Post-treatment			Baseline–Follow up		
	Experimental	Control	Effect size	Experimental	Control	Effect size
Velocity (m)	0.3 (0.1–0.5)	0.1 (−0.1–0.2)	0.2*	0.3 (0.1–0.5)	0.07 (−0.07–0.05)	0.23*
Cadence (step\min)	22.2 (−6.5–50.0)	2.9 (−7.5–13.4)	19.3*	17.5 (−16.3–51.4)	1.2 (−12.1–14.6)	16.3*
GPS (°)	−4.3 (−6.3 to −2.2)	−0.5 (−1.6–0.5)	−4.8*	−4.4 (−6.6 to −2.3)	0.3 (−1.4–2.1)	−4.7
GVS Pelvic Tilt (°)	−2.7 (−11.0–5.5)	0.8 (−5.2–5.4)	−3.5*	−2.2 (−10.7–6.1)	−1.1 (−6.4–4.2)	−3.3
GVS Hip Ab-Adduction (°)	−0.7 (−17.0–15.0)	0.02 (−6.4–6.5)	−0.72	−1.1 (−14.2–11.9)	−1.5 (−8.1–5.0)	−0.4
GVS Knee Flex-Extension (°)	−1.5 (−8.1–5.0)	4.9 (−6.1–16.1)	−6.4*	4.9 (−2.6–12.5)	1.2 (−15.2–17.7)	3.7
6′WT (m)	199.6 (133.1–266.0)	111.8 (27.1–196.4)	87.8*	186.4 (136.7–236.0)	90.0 (5.5–174.4)	96.4*
GMFM D	11.5 (−1.6–24.7)	3.7 (−2.3–9.8)	7.8	8.8 (−3.1–20.8)	2.1 (−4.1–8.4)	6.7
GMFM E	0.8 (−1.5–3.2)	1.0 (−0.1–2.1)	−0.2	0.4 (−0.7–1.6)	−0.5 (−4.2–3.1)	−0.1
Treadmill test (min)	1.2 (−0.4–2.8)	1.1 (0.1–2.2)	0.2	0.9 (−0.3–2.1)	0.7 (−0.1–1.4)	0.2
Motor evoked potential	0.5 (−0.1–1.2)	−0.2 (−0.4–0.1)	0.3*	0.6 (−0.5–0.6)	−0.1 (−0.4–0.2)	0.5

6′WT: six-minute walk test; GMFM: gross motor function measure; GPS: Gait Profile Score; GVS: Gait Variation Scores.
* $p < 0.05$.

stimulation) (Danzl, Chelette, Lee, Lykins, & Sawaki, 2013), adults with leukoaraiosis (training conducted during stimulation) (Kaski, Dominguez, Allum, & Bronstein, 2013) and healthy adults (bi-hemispheric anodal tDCS for 15 min at rest) (Kaski et al., 2012). In these studies on adults, improvements were found in walking velocity and stride length, but no kinematic gait variables were assessed.

No statistically significant intra-group or inter-group differences were found regarding the results of the exercise test, demonstrating a lack of improvement in cardiopulmonary fitness in the children studied. The gait training protocol was based on the method proposed by Grecco, Zanon, Sampaio and Oliveira (2013), who reported an improvement in cardiopulmonary fitness following 30-min sessions of treadmill training at a frequency of three times a week for four weeks (total: 12 sessions) and at a gait velocity that allowed training at the aerobic threshold. As the present investigation involved 10 sessions over two weeks, this shorter period was insufficient to promote an improvement in cardiopulmonary fitness and the protocol employed should therefore only be considered with regard to the improvement in motor function.

Dimensions D (standing) and E (walking, running and jumping) of the GMFM-88 were included in the present study to determine the effect of the interventions on gross motor function. The authors believed that the intervention protocol would result in an overall improvement in gross motor function. However, no effects on these dimensions were found. Apparently, the effects achieved with treadmill training combined with tDCS were restricted to gait.

It should be stressed that there are no available parameters on the optimal use of tDCS for children. Moreover, no studies were found analyzing the effects of tDCS either alone or in combination with other motor therapies on children with CP, which hinders the comparison of the findings. However, the interest in the ideal dose of tDCS for children has increased in the last two years and studies have raised some important issues, such as the need to adjust the intensity (Kessler et al., 2013; Minhas, Bikson, Woods, Rosen, & Kessler, 2012). A dose of 2 mA is considered adequate to increase cortex excitability in adults, with changes in motor and cognitive aspects, but this intensity is considered excessive for children, resulting in a non-focused area of cortex stimulation (Minhas et al., 2012). Regarding the isolated administration of tDCS for the treatment of children, the intensity tested ranges from 1 to 2 mA in small samples of children, with no reports of adverse effects (Auvichayapat et al., 2013). Indeed, no adverse effects were found with the use of 1 mA in the present study. However, the evaluation of such effects was nonspecific, as only the reports of family members and the clinical observations of the therapist were considered.

The present study has limitations that should be addressed. Although the sample size was calculated using adequate parameters, the authors recognize that a sample of 24 children is too small to establish conclusive findings. Moreover, the children analyzed were classified on Levels I, II and III of the GMFCS, which denotes walking ability without (Levels I and II) and with a gait-assistance device (Level III), and the sample was made up exclusively of children with spastic diparesis. As the study demonstrates the results of anodal stimulation over the primary motor cortex of the dominant hemisphere in a small number of children with bilateral brain lesions, it is not possible to extrapolate the data to children with unilateral lesions. Future studies should involve a longer follow-up period to allow better monitoring of the maintenance of the effects as well as the analysis of possible adverse effects.

The present study offers encouraging results regarding the use of anodal tDCS over the primary motor cortex during treadmill training in children with CP. Improvements were found in gait velocity, gait pattern, functional mobility and motor evoked potential. Moreover, the effects were maintained one month after the end of the rehabilitation protocol.

Conflict of interest

The authors declare no conflicts of interest.

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