Cerebellar tDCS combined with a a task-oriented circuit training doesn't improve motor function in people with multiple sclerosis: a pilot randomized control trial.

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Cerebellar tDCS in multiple sclerosis

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Abstract

Introduction: Balance and mobility impaiments are frequent in people with multiple sclerosis, probably due to cerebellar disfunctions. Task-oriented approach promotes physical function and cerebellar transcranial direct current stimulation (ctDCS) applied during training seems to boost effects of rehabilitation through modulation of cerebellum-brain inhibition.

Aim: To test efficacy of cerebellar stimulation combined with motor training on mobility and balance in people with multiple sclerosis.

Methods: Double-blind pilot randomized clinical trial on 16 subjects, randomly assigned to receive real- or sham-ctDCS and task-oriented training daily over two weeks. Functional mobility, balance, walking performance and quality of life were tested before and after treatment and at two-weeks follow-up. Effects of cerebellar stimulation on psychological and executive functions were recorded.

Results: Walking performance, balance and quality of life improved for both groups at post-treatment assessment and improvements were maintained at 2-weeks follow up. A two-way ANOVA revealed a significant time effect for balance and walking performance. A significant interaction effect of time–treatment ($F = 3.12$, $df = 2,26$; $p < 0.05$) was found for motor aspects of quality of life assessment on group of patients who received real-ctDCS.

Conclusions: Task-oriented training improves balance and mobility in people with multiple sclerosis but ctDCS doesn't boost motor training effects.

Keywords: multiple sclerosis, mobility, balance, tDCS, task-oriented, cerebellum

Abbreviations

PwMS: people with multiple sclerosis

TOCT: task-oriented circuit training

tDCS: transcranial direct current stimulation

CBI: cerebellum-brain inhibition

ctDCS: cerebellar transcranial direct current stimulation

1. Introduction

People with multiple sclerosis (PwMS) are frequently affected by motor impairments (ambulation, balance, mobility). It has been shown how 80% of them experience a loss of ambulation function that accurses over time (Feinstein et al., 2015). Walking impairments have a high negative impact on personal activities; they are associated with loss of physical quality of life and increased risk of fall (Delgado-Mendilívar et al., 2005; Gunn et al., 2013; Pfaffenberger et al., 2006). Several studies showed the benefits of physical therapy on walking functions (Edwards & Pilutti, 2017; Khan & Amatya, 2017; Motl et al., 2017; Paltamaa et al., 2012). There is an increasing body of evidence demonstrating that the human adult brain is capable of significant adaptations providing that the quantity (duration and frequency) and quality (task-specificity) of interventions are appropriate to promote neural reorganization and motor recovery (Jang et al., 2003; Kleim & Jones, 2008).

Task-oriented circuit training (TOCT) is an example of intense task-specific intervention to promote mobility and balance. It is constituted by a set of working stations that reflect the physical activities the subject performs daily (walking, climbing stairs, maintaining balance) to promote learning and walking function (Straudi et al., 2014). In addition to the choice of functional motor tasks, the main characteristic of this rehabilitative intervention is the exercise intensity that, compared to a conventional approach, is closer to the number of repetitions needed to achieve and maintain motor learning of these movements (Lang et al., 2009; Straudi et al., 2016).

The cerebellum has a crucial role on balance and motor control, integrating primary motor cortex (M1) activity through specific pathways (Ferrucci et al., 2016; Galea et al., 2009; Grimaldi et al., 2016). The cerebellum is also activated in adaptive motor learning circuits (Celnik, 2015; Hamada et al., 2012). Furthermore, several studies demonstrated its role in cognition, emotions, and behaviour (Reeber et al., 2013; Strick et al., 2009). Cerebellum dysfunctions seem to be related to many neurological disorders as dystonia and essential tremor in Parkinson Disease and cerebellar ataxia (Ferrucci et al., 2016). Moreover, fMRI studies showed a positive correlation between gait recovery and contralesionally cerebellum activity in stroke patients (Celnik, 2015).

In PwMS, the cerebellum could be the main contributor to balance and mobility impairments (Feinstein et al., 2015). Therefore, cerebellar activity modulation might play an essential role in developing potential rehabilitation strategies for PwMS. The cerebellar activity involved in motor learning may be modulated through non-invasive brain stimulation, especially for restoring balance and gait. Transcranial direct current

stimulation (tDCS) can modulate cerebellar excitability in humans. In particular, cathodal tDCS decrease and anodal tDCS increase cerebellum-brain inhibition (CBI) (Ferrucci et al., 2016; Galea et al., 2009). Increased CBI mediated by Purkinje cells through dentato-thalamocortical pathways results in plasticity modifications of the primary motor cortex (Grimaldi et al., 2016). Furthermore, non-invasive cerebellar stimulation has been a valuable option in increasing mobility and balance in subacute stroke survivors, representing the cerebellum as an alternative target of brain stimulation for primary motor areas (Koch et al., 2018).

The loss of M1 plasticity with the progression of axonal damages in PwMS could contribute to the development of disease and the increasing of disability (Reddy et al., 2000).

Based on this background, we hypothesized that combined cerebellar tDCS (ctDCS) with TOCT could improve locomotor function and balance in PwMS and mild to moderate gait disabilities. Furthermore, due to the effects of both tDCS and physical activity on psychological status, we would test modifications of depression and anxiety (Cooney et al., 2013; Kuo et al., 2017).

Given the role of the cerebellum in executive functioning, particularly in response inhibition, we evaluated the effects of ctDCS on a Go/NoGo task (Mannarelli et al., 2020).

2. Methods

This exploratory pilot study was a double-blind, randomized clinical trial to test the efficacy of cerebellar tDCS combined with task-oriented circuit training (TOCT) on mobility and balance outcomes in PwMS. This study has been reviewed by the Ferrara University Hospital Ethics Committees and registered on clinicaltrials.gov (NCT01883843). Written informed consent was obtained before all procedures.

Inclusion criteria were as follows: (i) male and female aged >18 years, (ii) diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding three months, (iii) unassisted walking with an Expanded Disability Status Scale (EDSS) score between 4 and 5.5. Exclusion criteria were as follows: (i) impaired cognitive functioning (score less than 24 on the Mini Mental Status Examination); (ii) intracranial metal implants that can be stimulated, incorrectly positioned, or overheated by the electric current; (iii) other neurological or psychiatric disorders; (iv) severe cardiopulmonary, renal, and hepatic diseases; (v) pregnancy.

All patients matching inclusion criteria were randomized using an online program (http:// www.randomization.com/). The random list was managed by an administrator external to the research groups to prevent selection bias.

Patients enrolled were allocated in two treatment groups: the experimental group received real-ctDCS and TOCT; the control group received sham-ctDCS and TOCT. The treatment group allocation was blinded for patients, investigators, physical therapists and medical doctors involved in the study. Both groups received ten sessions (Monday-Friday) of combined treatments over two weeks; each session lasted 2 hours.

2.1. Task-Oriented Circuit Training (TOCT)

TOCT protocol is applied to a group of 3 subjects. Every subject has to exercise in six different workstations for 5 minutes in each one (3 minutes of exercises and 2 minutes of rest) supervised by a physiotherapist. During each session, the patient has to complete two laps that took about 60 minutes (6 workstations × 5 minutes × two laps), with 10 minutes of rest after each lap. During the rest periods, subjects were invited to stretch their muscles. In addition, every patient walked on the treadmill for 30 minutes, including rests if necessary. Further details on the training protocol are available elsewhere (Straudi et al., 2014).

2.2. Cerebellar Transcranial Direct Current Stimulation (ctDCS)

The direct current was delivered through a pair of sponge electrodes with a surface of 35 cm2 (7 × 5), soaked in saline solution. It was generated by a constant current stimulator with rechargeable batteries (Brainstim, EMS, Italy). The anode was placed on the right cerebellar cortex, 3cm lateral to the inion (Ugawa et al., 1995). The reference electrode was placed on the right buccinators muscle. This continuous stimulation lasted 15 minutes for the experimental group, with an intensity of 2 mA during the first TOCT lap. For the control group who received sham ctDCS, the current was delivered for only 30 seconds, and then discontinued, but the tDCS apparatus was left in place for the same time as real ctDCS (15 minutes). This procedure has been suggested as an effective blinding method in parallel clinical trials of tDCS (Brunoni et al., 2014; Gandiga et al., 2006). A tDCS side-effects questionnaire (headache, neck pain, burning, redness and/or itching at the stimulation site) was administered after each session to both groups of patients.

2.3. Procedures

Subjects were evaluated before (T0) and after treatment (T1) and at two-weeks follow-up (T2) using both functional tests (gait speed, walking endurance, mobility, balance) and self-reported questionnaires for fatigue, walking ability and health-related quality of life. The assessment and treatment were delivered by two different physical therapists to ensure the blinding of evaluators. The primary outcome was functional mobility assessed using the Timed Up and Go test (TUG) (Sebastião et al., 2016). The Figure of-Eight Walk test (F8W) was used to assess walking performance (Wong et al., 2013). Gait, balance, and fall risk were evaluated using the Dynamic Gait Index (DGI) (Forsberg et al., 2013). Impact of MS on walking ability and health-rated quality of life was assessed using the Multiple Sclerosis Walking Scale – 12 (MSWS-12) and the 36-Item Short-Form Health Survey questionnaire (SF-36) respectively (Hobart et al., 2003; Sehanovic et al., 2020).The severity and behavioral characteristics of depression and anxiety were evaluated using the self-report questionnaires Beck Depression Inventory – Second Edition (BDI-II) and State-Trait Anxiety Inventory (STAI-Y), respectively (Santangelo et al., 2016; Sica & Ghisi, 2007). Effects of ctDCS on executive functions were evaluated using the subtest "Go/Nogo" of the Test Battery for Attention (TAP), a response inhibition task (Zimmermann & Fimm, 2002). Test aims to respond to two target stimuli as accurately and as fast as possible while ignoring the three non-target stimuli (Tinnefeld et al., 2005).

2.4. Statistical analysis

Descriptive statistics (mean, standard deviation) described the sample at T0, T1, T2. Baseline characteristics and clinical tests were compared among groups to confirm the quality of randomization using the Wilcoxon rank or Pearson's Chi-Square test. A repeated-measures ANOVA analysis (within-group factor: TIME; between-group factor: TREATMENT) was conducted to detect main effects for treatment and time. Statistical analysis was performed using STATA 13.1 software. Statistical significance was set to $p < 0.05$

3. Results

Forty-three PwMS were screened for this study, and 16 were enrolled (mean age = 53.7 ± 13 years, eight males and eight females) at Ferrara University Hospital. The two groups were similar in demographic and clinical characteristics at the baseline (Table 1). Two subjects allocated to the experimental group didn't complete the

combined treatment for personal issues unrelated to the treatment received. The CONSORT flow diagram of the study is reported in Figure 1.

[INSERT TABLE 1 ABOUT HERE]

[INSERT FIGURE 1 ABOUT HERE]

No statistically differences were found between groups on functional mobility. Walking performance and balance function improved for both groups at post-treatment assessment. Improvements were maintained at 2-weeks follow up, as shown by F8WT and DGI scores (Table 2). The results of MSWS-12 and SF-36 showed improvements in both groups for all the evaluations. (Table 2).

A two-way ANOVA revealed a significant time effect for most outcome measures (F8W, DGI, MSWS-12). A significant interaction effect of time–treatment ($F = 3.12$, $df = 2,26$; $p < 0.05$) was found for Physical Component Summary of SF-36 on group of patients who received real-ctDCS (Table 3). The two groups did not differ on measures of response inhibition, neither for accuracy nor for reaction times: both of them improved at the end of treatment. The results of ctDCS Adverse Effects Questionnaires are reported in Table 4.

[INSERT TABLE 2 ABOUT HERE]

[INSERT TABLE 3 ABOUT HERE]

[INSERT TABLE 4 ABOUT HERE]

4. Discussion

Our results revealed that TOCT effectively ameliorates balance and mobility in a convenience sample of PwMS, but ctDCS doesn't boost motor training effects. A previous pilot study showed beneficial effects of TOCT on walking ability and health-related quality of life, two domains frequently affected in PwMS (Straudi et al., 2014). Anodal ctDCS seems to have no additional benefits in our sample. To our knowledge, the current study is the first to investigate the combined effect of ctDCS and motor training in PwMS. Many studies have shown enhanced cerebellum-dependent motor learning in healthy subjects using comparable ctDCS montage and stimulation parameters (Cantarero et al., 2015; Galea et al., 2011; Jayaram et al., 2012; Spampinato &

Celnik, 2017). ctDCS has been used to increase cerebellar activity and facilitate the cerebellum and the entire related network; Billeri et al. sustained that the effects of this approach would depend on the residual functional reserve of the cerebellum (Billeri & Naro, 2021). We can assume that MS-related brain damage may have reduced the impact of ctDCS on motor function. For this reason, in people with neurological disorders and variable lesions distribution, a pre-stimulation assessment could be helpful to identify patients who better respond to ctDCS and define the best patient-tailored stimulation protocol. The adoption of brain resting-state measures (ie. EEG) as biomarker of response to ctDCS could help delineate good versus poor candidates to receive this stimulation protocol. Another possible explanation of our results is that a ceiling effect on motor recovery is reached by TOCT alone, making it difficult to find further improvements due to tDCS.

The tDCS effect seems to be task-dependent, and its role on motor learning is based on the state of cortical activation at the stimulation time (Bortoletto et al., 2015). We can speculate that more challenging tasks as TOCT's activities require a greater activation of the primary motor cortex in PwMS than healthy subjects engaged in relatively standardized motor tasks like walking on a split-belt treadmill or complete finger tracking training (Jayaram et al., 2012; Summers et al., 2018). Generally, tDCS effects are polarity-dependent and anodal tDCS increases neuronal excitability (Nitsche & Paulus, 2000). However, tDCS may either facilitate or inhibit motor learning based on the state of cortical activation at the time of stimulation. In our case, ctDCS was combined with a task-oriented motor training that increases cortical excitability, hindering facilitatory effect of tDCS (Bortoletto et al., 2015).

Controversial is the identification of the exact timing of stimulation to optimize the effects of motor training. Many studies try to find the window during which brain stimulation should be applied to increase brain plasticity, without consensus between them (Giacobbe et al., 2013). Cabral et al. sustained that the overlapping effect of non-invasive brain stimulation and motor training may reduce the impact of a single treatment on the motor outcome (Cabral et al., 2015). Similar results were found by Summers et al., who recorded decreased corticospinal excitability following application of anodal ctDCS during motor training (Summers et al., 2018). Both motor training and brain stimulation seem to promote neuroplastic changes in the human cortex, but their combination may reduce the effects of the single treatment on motor outcome (Cabral et al., 2015). This possible explanation, although not directly linked to cerebellum stimulation, may justify our findings. For this reason is essential to choose a trial design that considers the appropriate temporal and spatial relationship between the combined treatments (Cabral et al., 2015; Straudi et al., 2018).

At least, the identification of the best cerebellar subregion that plays an important role in conditioning motor processes can be crucial. The anterior cerebellum is more involved in motor performance control (D'Ambrosio et al., 2017; Kern et al., 2011; Stoodley & Schmahmann, 2010). However, tDCS targeting the anterior sensorimotor cerebellum proved to be not the best ctDCS montage to modulate motor function (Rice et al., 2021). Furthermore, using this stimulation protocol, the cerebellum motor area is too far from the scalp surface to be stimulated (Grimaldi et al., 2016): this could explain our motor results outcomes. For this reason, different electrode positioning should be tried in combination with motor training.

The group treated with real-ctDCS showed improvements in psychological aspects of health-related quality of life, but the effects were evident only at post-treatment evaluation. Electrodes position in our ctDCS set up stimulates the posterior and inferior aspects of the cerebellum closest to the skull (Galea et al., 2009; Grimaldi et al., 2016). The posterior lobe plays a role in modulating cognitive performance and lesions of this cerebellum area have been observed in patients with neuropsychiatric impairments (D'Ambrosio et al., 2017; Schmahmann et al., 2007; Stoodley & Schmahmann, 2010). Our findings contrast with a recent meta-analysis that showed how motor performance was significantly more affected than cognitive performance following ctDCS in healthy subjects (Oldrati & Schutter, 2018) the presence of neurological disorders may influence the effects of stimulation on cerebellar areas (Middleton & Strick, 2001; Ramnani, 2006; Stoodley & Schmahmann, 2010).

The novelty of our study lies in the hypothesis of combining cerebellar stimulation with an intensive and task-oriented rehabilitation programme. Although preliminary studies highlighted the importance of this type of rehabilitation in PwMS (Chisari et al., 2014; Lehmann et al., 2020), the addition of ctDCS seems to have no additional effects on motor aspects. Conversely, physical health-related quality of life was superior after this non-invasive brain stimulation approach.

No major side effects were reported after either anodal or sham ctDCS, only mild side effects equally distributed among anodal and sham conditions. Only patients who received anodal ctDCS shown skin redness under site of stimulation which resolved few minutes after the end of stimulation. This in line with previous studies on tDCS in PwMS (Ayache et al., 2020; Hsu et al., 2021).

Our pilot study has several limitations. Firstly, our small sample didn't allow us to determine the efficacy of cerebellar stimulation on motor and non-motor outcomes; secondly, the level of motor impairment was probably too mild to highlight the clinical improvement in the recruited sample; finally, outcome measures we

used were not sensitive enough to discriminate walking function or balance impairment in our sample. Future directions: (i) to conduct a large RCT trial to better investigate the role of ctDCS on the motor outcome; (ii) to better explain effects of ctDCS on M1 and role of CBI on the motor function it would be necessary to add cortical function parameters (i.e. EEG, transcranial magnetic stimulation).

5. Conclusions

This pilot study assessed the preliminary effects of combining cerebellar stimulation and an intensive and task-oriented rehabilitation programme in PwMS and unassisted walking. Our main findings revealed that TOCT is effective in improving balance and mobility and that ctDCS may boost the effects of motor training on the perceived quality of life. Although positive effects on mobility and the absence of adverse effects following the combined treatment, this pilot study cannot draw definitive conclusions and further studies need to verify our results.

Authors' contributions

AB, CM, GM, GZ, NB and SS conceived the study and participated in its design. CM and LB performed the instrumented and clinical data collections. AB, GM and GZ analyzed the data. AB, SM and SS interpreted the results, and drafted and revised the manuscript. All authors approved the submitted version.

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Declaration of interest

The authors declare that they have no competing interests.

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Table 1 – Demographic and clinical characteristics of the sample

	Real-ctDCS + TOCT (n = 8)	Sham-ctDCS + TOCT (n = 8)	Total (n = 16)	p
Age (years)	55.25 (15.15)	52.13 (11.31)	53.69 (13.01)	0.67
Sex: M/F	4/4	4/4	8/8	
MS onset (years)	11.13 (6.99)	11.13 (9.95)	11.13 (8.31)	0.67
MS subtypes: RR/PP/SP	3/4/1	3/3/2	6/7/3	
EDSS	4.69 (0.53)	4.5 (0.71)	4.59 (0.61)	0.47
TUG baseline (sec)	9.92 (2.39)	8.88 (1.9)	9.39 (2.16)	0.34
F8W baseline (sec)	9.37 (2.68)	8.36 (3.06)	8.87 (2.83)	0.25
DGI baseline	16 (2.98)	16.75 (1.98)	16.38 (2.47)	0.59
MSWS-12 baseline	59.13 (16.17)	69.95 (13.61)	64.54 (15.48)	0.23
SF-36-PCS baseline	41.38 (5.34)	34.63 (8.23)	38 (7.55)	0.10
SF-36-MCS baseline	50.75 (9.19)	50.38 (11.19)	50.56 (9.89)	0.87
STAI-Y1baseline	32.17 (15.31)	29.75 (6.85)	31.2 (12.5)	0.67
STAI-Y2 baseline	33.67 (11.51)	34 (12.02)	33.8 (11.04)	0.83
BDI baseline	7 (7.48)	9.5 (8.06)	8 (7.38)	0.59
Go/Nogo correct baseline	22.88 (1.64)	21.75 (3.28)	22.31 (2.57)	0.87
Go/Nogo RTs baseline (msec)	602.79 (56.99)	581.13 (50.27)	591.96 (53.11)	0.29

ctDCS = cerebellar transcranial Direct Current Stimulation; TOCT = Task Oriented Circuit Training; n = number; SD = standard deviation; M/F = male/female; MS = multiple sclerosis; RR = relapsing-remitting; PP = primary progressive; SP = secondary progressive; EDSS = Expanded Disability Status Scale; TUG = Timed Up and Go test; F8W = Figure of-Eight Walk test; DGI = Dynamic Gait Index; MSWS-12 = Multiple Sclerosis Walking Scale – 12; SF-36 = 36-Item Short Form Health Survey questionnaire (PCS = Physical Component Summary; MCS = Mental Component Summary); STAI = State-Trait Anxiety Inventory (Y1 = trait anxiety; Y2 = state anxiety); BDI = Beck Depression Inventory; RTs = Reaction Times; p = difference between real-ctDCS + TOCT group and sham-ctDCS + TOCT group.

Table 2 - Changes in outcome measurements (mean ± SD)

	Changes at T1		Changes at T2	
	Real-ctDCS + TOCT	Sham-ctDCS + TOCT	Real-ctDCS + TOCT	Sham-ctDCS + TOCT
TUG (sec)	0.03 ± 1.13	-0.48 ± 0.48	0.28 ± 0.75	-0.54 ± 1.02
F8W (sec)	-0.20 ± 0.74	-1.09 ± 2.15	-0.82 ± 1.18	-1.23 ± 2.00
DGI	1.75 ± 2.66	2.75 ± 2.49	0.75 ± 2.38	1.62 ± 2.33
MSWS-12	-9.80 ± 7.94	-10.19 ± 5.16	-18.11 ± 10.96	-21.09 ± 15.84
SF-36-PCS	3.88 ± 4.97	2.38 ± 4.34	2.88 ± 4.36	0.25 ± 5.65
SF-36-MCS	2.13 ± 5.30	4.63 ± 10.70	-0.38 ± 3.62	4.25 ± 10.09
STAI-Y1	0.33 ± 1.57	8.50 ± 6.55	-0.96 ± 5.66	-0.08 ± 3.17
STAI-Y2	0.16 ± 0.80	1.50 ± 0.56	0.33 ± 2.46	3.67 ± 3.01
BDI	1.50 ± 0.10	-1.50 ± 0.54	1.40 ± 1.29	0.17 ± 3.09
Go/Nogo correct	0.38 ± 0.74	2.13 ± 2.99	0.50 ± 1.93	2.13 ± 3.27
Go/Nogo RTs (msec)	-32.95 ± 76.29	-8.51 ± 5.30	-33.79 ± 78.36	-54.53 ± 35.94

ctDCS = cerebellar transcranial Direct Current Stimulation; TOCT = Task Oriented Circuit Training; SD = standard deviation; TUG = Timed Up and Go test; F8W = Figure of-Eight Walk test; DGI = Dynamic Gait Index; MSWS-12 = Multiple Sclerosis Walking Scale – 12; SF-36 = 36-Item Short Form Health Survey questionnaire (PCS = Physical Component Summary; MCS = Mental Component Summary); STAI = State-Trait Anxiety Inventory (Y1 = trait anxiety; Y2 = state anxiety); BDI = Beck Depression Inventory; RTs = Reaction Times.

Table 3 – Analysis of variance for outcome variables

	Group Effect		Time Effect		Interaction (Time x Group)	
	F (1.14)	*p*	F (2.26)	*p*	F (2.26)	*p*
TUG	2.69	0.12	2.15	0.10	2.50	0.07
F8W	2.01	0.17	3.55	0.02	0.62	0.60
DGI	2.14	0.16	6.07	0.00	0.54	0.65
MSWS-12	0.68	0.42	21.07	0.00	2.11	0.11
SF-36-PCS	0.29	0.60	2.03	0.12	3.12	0.03
SF-36-MCS	0.53	0.47	2.81	0.05	0.51	0.67
STAI-Y1	0.00	0.99	2.88	0.08	1.81	0.20
STAI-Y2	0.06	0.81	0.87	0.44	2.25	0.14
BDI	0.45	0.52	0.03	0.96	0.60	0.56
Go/Nogo correct	0.00	1.00	3.87	0.03	1.68	0.20
Go/Nogo RTs	0.51	0.48	5.49	0.00	1.44	0.25

TUG = Timed Up and Go test; F8W = Figure of-Eight Walk test; DGI = Dynamic Gait Index; MSWS-12 = Multiple Sclerosis Walking Scale – 12; SF-36 = 36-Item Short Form Health Survey questionnaire (PCS = Physical Component Summary; MCS = Mental Component Summary); STAI = State-Trait Anxiety Inventory (Y1 = trait anxiety; Y2 = state anxiety); BDI = Beck Depression Inventory; RTs = Reaction Time; F = F-value; *p* = p-value.

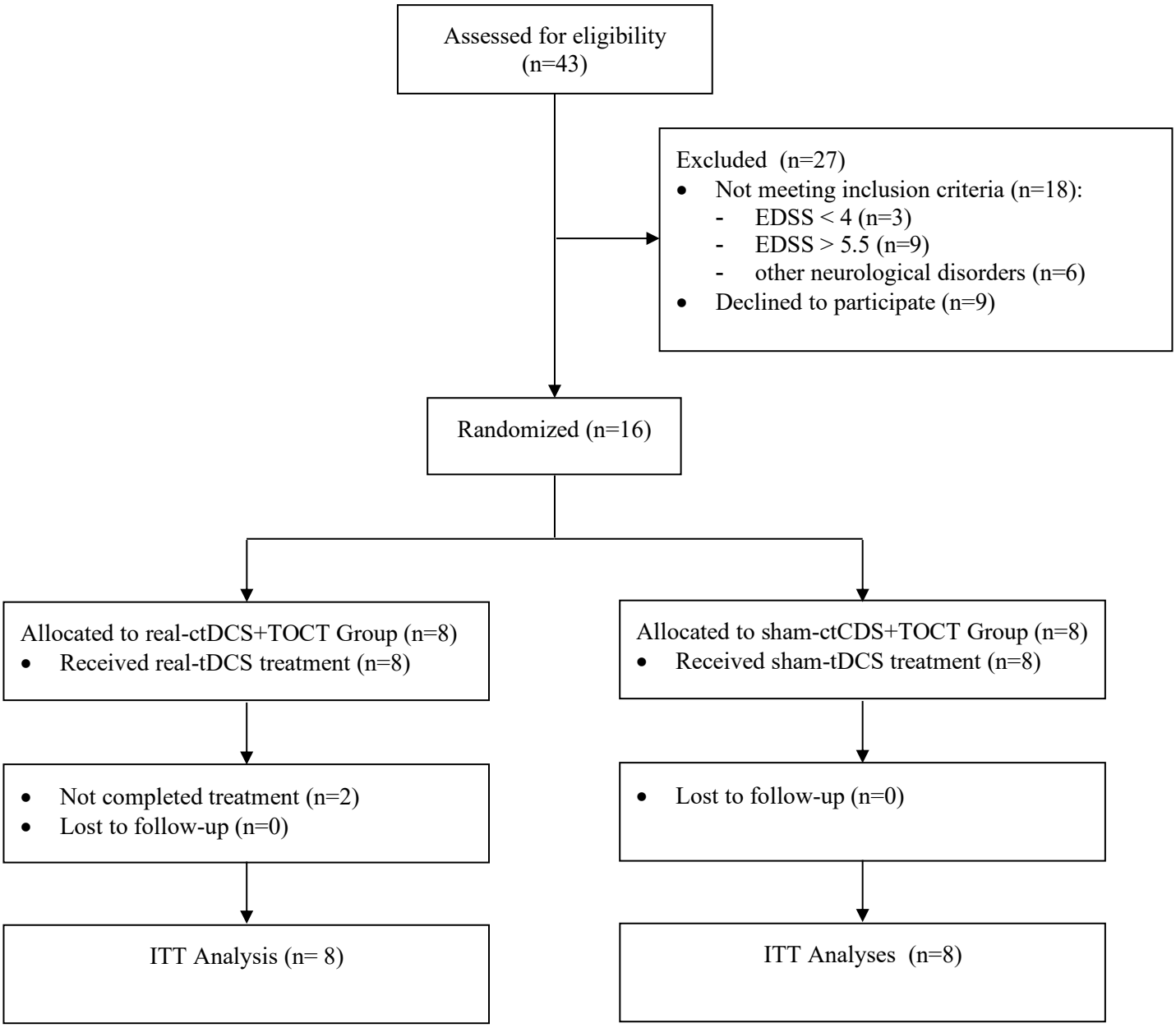
Table 4 – Frequencies of patients reported side effects after stimulation, n (%)

	Real-ctDCS (n = 8)	Sham-ctDCS (n = 8)	Total (n = 16)	p
Tingling	4 (50)	3 (37.5)	7 (43.75)	0.63
Skin redness	5 (62.5)	-	5 (31.25)	0.01
Headache	-	2 (25)	2 (12.5)	0.14
Trouble to concentrate	1 (12.5)	1 (12.5)	2 (12.5)	1.00
Sleepiness	-	1 (12.5)	1 (6.25)	0.32
Pain in the site of stimulation	1 (12.5)	-	1 (6.25)	0.32
Mood fluctuations	1 (12.5)	-	1 (6.25)	0.32

ctDCS = cerebellar transcranial Direct Current Stimulation; p = difference between real-ctDCS group and sham-ctDCS group.

Figure's caption

Figure 1 – CONSORT flow diagram


Assessed for eligibility
(n=43)
Excluded (n=27)
• Not meeting inclusion criteria (n=18):
- EDSS < 4 (n=3)
- EDSS > 5.5 (n=9)
- other neurological disorders (n=6)
• Declined to participate (n=9)
Randomized (n=16)
Allocated to real-ctDCS+TOCT Group (n=8)
• Received real-tDCS treatment (n=8)
Allocated to sham-ctCDS+TOCT Group (n=8)
• Received sham-tDCS treatment (n=8)
• Not completed treatment (n=2)
• Lost to follow-up (n=0)
• Lost to follow-up (n=0)
ITT Analysis (n= 8)
ITT Analyses (n=8)