

Transcranial direct current stimulation does not improve postural control during adapted tandem position in people with Parkinson's disease: a pilot study

Beatriz Regina Legutke^a, Lilian Teresa Bucken Gobbi^{a,b}, Diego Orcioli-Silva^{a,c}, Paulo Cezar Rocha dos Santos^{d,e}, Gabriel Antonio Gazziero Moraca^{a,b}, Rodrigo Vitória^f, Victor Spiandor Beretta^{a,b,g*}

^a São Paulo State University (Unesp), Institute of Biosciences, Posture and Gait Studies Laboratory (LEPLO), Rio Claro, Brazil.

^b Graduate Program in Movement Sciences, São Paulo State University - UNESP, Brazil

^c University of Campinas (UNICAMP), School of Applied Sciences (FCA), Laboratory of Applied Sport Physiology (LAFAP), Limeira, Brazil.

^d Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Israel

^e The Center of Advanced Technologies in Rehabilitation, Sheba Medical Center. Israel.

^f Department of Sport, Exercise and Rehabilitation, Northumbria University, Newcastle upon Tyne, United Kingdom.

^g São Paulo State University (Unesp), School of Technology and Sciences, Presidente Prudente, São Paulo, Brazil.

*Corresponding author at: São Paulo State University (Unesp), School of Technology and Sciences, Rua Roberto Simonsen, 305 CEP: 19060-900 - Presidente Prudente, São Paulo State, Brazil. Tel: +55 18 3229-5715

E-mail addresses: victor.beretta@unesp.br (V.S. Beretta)

ABSTRACT

Background: Balance impairments in people with Parkinson's disease (PD) demonstrated mainly in challenging postural tasks, such as increased body oscillation may be attributed to the deficits in the brain structures functionality involved in postural control (e.g., motor cortex, midbrain, and brainstem). Although promising results, the effect of transcranial direct current stimulation (tDCS) on postural control in people with PD is unclear, especially in objective measures such as the center of pressure (CoP) parameters. Thus, we analyzed the effects of a single session of tDCS on the CoP parameters during the adapted tandem position in people with PD. **Methods:** Nineteen people with PD participated in this crossover, randomized, and double-blind study. Anodal tDCS was applied over the primary motor cortex in two conditions of stimulation (2 mA/active and sham) on two different days for 20 minutes immediately before the postural control evaluation. Participants remained standing in an adapted tandem position for the postural control assessment for 30 seconds (three trials). CoP parameters were acquired by a force plate. **Results:** No significant differences were demonstrated between stimulation conditions (p-value range = 0.15-0.89). **Conclusions:** Our results suggested that a single session of tDCS with 2 mA does not improve the postural control of people with PD during adapted tandem.

Keywords: Movement disorders; Balance; Brain stimulation; Electrical stimulation; Neurodegenerative disease; kinetic.

1. Introduction

Postural instability is one of the most disabling motor symptoms of Parkinson's disease (PD), being prevalent in more advanced disease stages [1]. Postural control impairments in people with PD during standing tasks can be evidenced by the center of pressure (CoP) analysis, such as greater (40-175%) sway area [2,3] and amplitude of oscillation [4] compared to healthy older adults. Also, to keep postural control during challenging situations (e.g., adapted tandem position and unipedal task), people with DP have even more exacerbated postural impairments (e.g., asymmetry and greater CoP oscillation [5–7]). These postural control deficits decrease the ability to maintain balance and increase the risk of falls in people with PD [8,9], negatively impacting the quality of life in this population [10,11].

Although Levodopa improves N motor symptoms such as tremors, gait disturbances, muscular rigidity, and bradykinesia, postural control is less responsive [12,13]. Thus, potential complementary therapies have emerged to minimize postural impairments in PD. Especially, transcranial direct current stimulation (tDCS) has been explored as a possible complementary therapy for postural control and balance in PD [14–22]. tDCS is a non-invasive brain stimulation that applies low-intensity electrical over the scalp by anode and cathode electrodes, changing the cortical excitability [23,24]. In general, while anodal tDCS increases excitability, cathodal stimulation decreases cortical excitability [23]. Besides the modulation of cortical excitability, anodal tDCS promotes neurophysiological (e.g., increases dopamine release and decreases GABAergic neurotransmitters) and behavioral changes (e.g., improves gait, functional mobility, and balance performance) that are particularly relevant for PD, concerning the PD's effects on neurological and behavioral functions [15,18,25–30].

The dopaminergic decrease in the basal ganglia characteristic of PD lead to a dysfunction in the thalamocortical motor systems [25,31,32], which results, in general, in a hypoactivity of motor cortex [25,31,32]. The hypoactivity of primary motor cortex (M1) impact in the functioning of subcortical structures involved in the postural control such as the peduncle pontine nucleus and the mesencephalic locomotor region [31,33]. Additionally, this hypoactive may lead to the impaired balance evidenced in people with PD. Thus, the studies on tDCS in PD have been exploring the M1 stimulation which could also modulate the excitability of other motor cortex areas (e.g., supplementary and premotor motor area [34,35]) beyond the M1. These areas of motor cortex are also involved in postural control in static situations, mainly in more challenging and unstable positions [34], such as the tandem [35]. In addition, studies have shown that although tDCS induces changes mainly in the stimulated area, it is possible to observe changes in subcortical areas by facilitating the communication between the directed stimulated area with complementaries areas [33,36]. Besides this rationale, our previous meta-analysis indicates weak size effect regarding the specifical benefits of different stimulated area (e.g., M1, prefrontal cortex, and cerebellum) on postural control in several neurological disorders [37]. A possible suggestion is due to the low number of studies that analyzed the isolated effects of tDCS in the postural control of people with PD.

While promising, controversial results were evidenced regarding the effects of tDCS on postural control [18–20,38–40]. A previous meta-analysis has indicated that tDCS over the M1 decreased the mediolateral (ML) displacement of CoP and sway area in individuals with cerebral palsy and young adults during standing still [38]. In PD, previous studies have demonstrated controversial results of the effect of single and multiple sessions (i.e., 10 sessions) of tDCS over different brain targets (e.g., M1, prefrontal cortex, and cerebellum) on static and dynamic balance in people with PD,

where positive effects were observed in some studies [18,40] while no effect was evidenced in another study [39]. Meta-analyzed evidence indicates that tDCS does not seem to benefit balance in people with PD [19,20]. However, the results of single and multiple session of tDCS in static and dynamic balance in people with PD were evidenced by balance clinical test application (i.e., Berg Balance Scale) [18–20,38–40] with a gap in studies measuring tDCS effects on CoP parameters. A single session of tDCS enables understanding the immediate effect of a simple non-invasive brain stimulation tool on motor behavior (i.e., objective measure of postural control) in a neurological population such as PD. This study is mainly relevant for basic research and this knowledge may help in the clinical practice.

The effects of tDCS on objective measures of static and dynamic balance is unclear. Since balance involves a range of challenging postural tasks, studies examining tDCS is timely. Particularly relevant, the few existing studies in the inconsistent of nor controlled. Ricci et al. (2019) demonstrated that tDCS over the prefrontal cortex induced small changes in the area and amplitude of the body sway acceleration during tandem position. However, this study did not include a control group and/or sham condition, making it difficult to interpret the results on the effects of tDCS on postural control. The present study advances by investigating the effects of tDCS on objective measures of postural control (i.e., CoP parameters) during a challenging postural task (i.e., adapted tandem) by comparing the active stimulation with the placebo stimulation (i.e., sham) in a crossover design. Challenging postural tasks (e.g., tandem) require more involvement of brain structures (e.g., motor and prefrontal cortices) related to postural control [41–43]. Thus, PD-induced brain dysfunctions may exacerbate the postural control impairments in these tasks [44,45].

The present study aimed to analyze the effect of a single session of anodal tDCS over the M1 on the CoP parameters during a challenging postural task in people with PD. We hypothesized that a single session of tDCS over on M1 would positively alter the postural control of people with PD (i.e., decrease the CoP parameters) [6,46,47].

2. Methods

2.1 Participants

A priori analysis indicated that 19 participants would be necessary to detect the difference between Active and Sham condition, with a paired Student's t test ($\alpha < 0,05$) and a $(1-\beta)$ of 0.80. The analysis was performed considering a moderate Standardized Response Mean (SRM) as effect size (0.6). Thus, 19 community-dwelling people with PD (diagnoses based on criteria determined by the UK Brain Bank - [48]) with a score below three on the modified Hoehn & Yahr scale [49] participated in this crossover, randomized, double-blind, and sham-controlled study. The exclusion criteria were: (i) the presence of any musculoskeletal or uncorrected visual impairments that affected balance; (ii) presence of uncontrolled disease that could affect peripheral sensory functions; (iii) risk of receiving tDCS (e.g., neural implants, pacemakers, history of seizures, and epilepsy); (iv) indicative of dementia signs (score < 20 on the Mini-Mental State Examination – MMSE) [50]; and (v) non-participation in both days of stimulation/assessment.

2.2 Experimental design

The study was conducted at the Posture and Gait Studies Laboratory at São Paulo State University, Rio Claro, Brazil. This study was approved by the research ethics

committee of the same university (CAAE: 87653818.2.0000.5465) and all participants provided written informed consent to participate in this study.

All assessments were performed in the "ON" state of the PD medication (between 45 and 60 minutes after medication intake). For the sample characterization, a clinical (degree of PD motor impairment) and cognition assessment was performed using the Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III (motor) [51] and the MMSE [50], respectively. Levodopa equivalent daily dose (LEDD) was calculated [52]. After the clinical and cognitive assessments, people with PD participated in the experimental protocol on two different days (day 1 and day 2) with an interval of at least two weeks between them (median = 14 days; 1st and 3rd quartiles = 14 and 28 days, respectively).

Experimental procedures were similar on all days and included: anodal tDCS protocol (with 2 mA or sham intensity) and assessment of postural control. The order of tDCS conditions was counterbalanced between subjects randomly by a team member who did not give any instruction during the postural control assessment and did not participate in the data analysis. Thus, the researchers that evaluated the postural control and analyzed the data were blinded regarding the tDCS condition. Also, the participants were blinded to the conditions of tDCS applied each day. A structured questionnaire regarding the sides effect of tDCS was performed before the assessment of postural control each day [16,53–55]. At the end of day 2, participants were asked about the perception of which stimulation condition they received each day [16] in order to minimize the possible influence of the response on day 1 in the motivation and blinding efficacy in of the postural control assessment on the second day.

2.3 tDCS protocol

The electrical stimulation was applied using the Microestim GENIUS device (NKL Electronics Products, Brusque/SC, Brazil) by two conductive-rubber electrodes placed in two saline-soaked sponges (7x5 cm) while participants remained seated on a chair. Active stimulation condition consisted of applying the anodal current with 2 mA for 20 minutes with a 30-seconds ramp-up at the beginning and 30-seconds ramp-down at the end of the stimulation period (Figure 1). For the sham condition, the stimulation remained active only for 10 seconds between the ramp-up/ramp-down periods (Figure 1) [16]. The simulation characteristics were chosen based on previous evidence suggesting a superior effect of 2 mA intensity and 20 minutes duration of tDCS on postural control [16] and cortical excitability [56–58], respectively.

Anodal electrode was positioned over M1 (C3 or C4 position according to the international 10-20 electroencephalography system) of the cerebral hemisphere more affected by PD [59] and the cathodic electrode was positioned over the contralateral supraorbital region. The cerebral hemisphere most affected by PD was determined by the MDS-UPDRS items [6,16].

2.4 Assessment of postural control

Postural control evaluation was performed only after tDCS protocol. The participant remained in an adapted tandem position with a distance between the feet of approximately five cm on a force plate (Figure 1) [6]. The adapted tandem position was chosen since it is more challenging than the bipodal position. However, the adaptation of the tandem position was needed since some people with PD could not maintain the balance for all 30 seconds. Thus, the adaptation was important so that the participants could perform the task. The participant was instructed to quietly stand looking at a fixed target at eye level two meter in front of them. Also, the participant selected the lower limb

that was positioned in the front during the familiarization (i.e., left, or right). The same foot positioning was maintained on all trials of the postural evaluation determined by the Scotch tape. Three trials of 30 seconds each were performed on both days. Besides, a rest of 30 seconds between trials was performed to avoid prolonged periods in the same static position.

2.5 Data analysis

A force plate (AccuGait, Advanced Mechanical Technologies, Boston, MA) with a sampling frequency of 200 Hz was used to acquire the CoP data. CoP analysis was performed in a Matlab™ environment (Mathworks, Inc., Natick, Massachusetts, USA), considering only the last 20 seconds of each trial. The initial 10 seconds were excluded due to the period of task adaptation [6]. CoP data were filtered through a 4th order digital low-pass Butterworth filter with a cut-off frequency of 5 Hz [60]. The following parameters were analyzed in the ML direction: amplitude (i.e., the difference between the minimum and maximum displacement), the mean velocity (i.e., the total displacement over time), and the RMS of the displacement (i.e., indicative of variability of the CoP displacement). In addition, the total displacement and the sway area were analyzed considering both anteroposterior and ML directions [6,7,60,61].

2.6 Statistical analysis

Statistical analyses were performed in SPSS 21.0 software (SPSS, Inc., Armonk, New York, USA) and the significance level was maintained at $p < 0.05$. Normality and homogeneity were verified by Shapiro-Wilk and Levene tests, respectively. The Fisher's test was performed considering the number of correct answers for the stimulation

condition in each session to assess the blinding efficacy. Descriptive measures were also considered for the blinding efficacy analysis. Paired Student's t test and Wilcoxon test were performed to analyze the effect of tDCS conditions on postural control (active vs. sham). The effect size of the comparison between the tDCS condition was determined calculating the Cohen's d. Also, as male and female characteristics could impact differently the response to the tDCS [62,63], we have performed additional analysis of the tDCS effect on postural control for male and female separately (details in the supplementary material). In addition, the Standardized Response Mean (SRM) was calculated as effect size considering the mean difference between the conditions ($\Delta = \text{active} - \text{sham}$) divided by the standard deviation of the difference (i.e., Δ) between the conditions. SRM was interpreted as <0.2 = trivial, >0.2 and <0.5 = small, >0.5 and <0.8 = moderate, and >0.8 = large responsiveness [64].

3. Results

Table 1 presents the demographics, clinical and cognitive characteristics of the sample.

3.1 CoP parameters

No significant statistical differences were demonstrated between the tDCS conditions (active x sham) for the CoP parameters during the adapted tandem position (Table 2). These results indicated that anodal tDCS did not change the postural control. The responsiveness to tDCS was considered as trivial to small (Table 2). The additional analysis of the effect of tDCS on postural control regarding the sex (i.e., male and female) demonstrating that tDCS did not modulates the postural control regardless the sex (Table S1 and Table S2).

3.2 Adverse effects of tDCS

The most reported adverse effects of tDCS were tingling and itching. Tingling sensation was reported by ~58% and 63% of participants in active and sham conditions, respectively. Itching sensation was reported by ~21% in both conditions. It should be noted that the tingling intensity was considered mild according to the score of the structured questionnaire, suggesting that tDCS was safe (mild sensations/discomfort). Furthermore, participants reported burning sensation and sleepiness in active condition, ~10.5% and ~5% respectively. Also, the evaluator noted skin redness and skin irritation in participants in the sham condition, ~10.5% and ~5% respectively.

3.3 Stimulation condition perception

Based on a descriptive analysis, it is possible to observe that 53% of people with PD were not able to perceive differences between the stimulation conditions (Figure 2a). When analyzing the total number of sessions performed (38 sessions), the stimulation conditions were correctly identified in 42% of the sessions (Figure 2b). These results suggest that more than half of the sample did not correctly identify the stimulation condition (maintaining the blinding characteristic of the tDCS protocol). In addition to the descriptive measures, the Fisher's test showed no significant difference in the number of correct identification between the conditions of stimulation, which indicate the blinding efficacy ($X^2_{(1)} = 0.432$; $p = 0.743$).

4. Discussion

The present study aimed to analyze the effect of a single session of anodal tDCS over the M1 on the CoP parameters during an adapted tandem position in people with PD. Unexpectedly, our results demonstrated that a single session of anodal tDCS did not

improve postural control in people with PD. An important limitation of the present study is the lack of assessment of postural control before the stimulation (i.e., baseline performance of the postural control). The evaluation of the postural control before the stimulation would allow to minimize possible motor fluctuations, which can influence the postural control of people with PD [65,66]. Thus, although relevant, the results from our pilot study should be considered with caution.

Despite the limitation highlighted above, a possible explanation for the lack of the effects of tDCS may be the heterogeneity of the participants in responding to the tDCS, meaning that while part of the participants may have increased some of CoP parameters (e.g., increased CoP amplitude), another part of them may have decreased or did not respond to tDCS. This may be particularly supported by the relatively high standard deviations for all the CoP outcomes (Table 2). This high heterogeneity in tDCS response to CoP behavior may be due to the variability in the flexibility of the central nervous system to control the balance, which is diminished in people with PD [67–69]. Although there is an overall idea that people with PD have difficulty in adapting postural control according to the characteristics of the task (i.e., velocity and amplitude of external perturbation) due to the deficits in recruiting brain resources to maintain the balance [12,70,71], the multiple possibilities, brain networks, degree of freedom, anatomic particularities among the participants may explain individuals differences in responding to tDCS. Thus, a single session of tDCS may have led people with PD to adopt different strategies (e.g., increasing or decreasing CoP oscillation) to maintain balance [72,73]. Furthermore, while widely accepted a decrease in CoP oscillation after active tDCS as an indication of improved postural control [74], there is still no consensus whether such a decrease indeed represents improvements in maintaining balance [72,73]. A great sway area and CoP displacement may suggest the need to explore the space to maintain the

balance that could indicate a success in the postural control, signaling flexibility of the central nervous system in controlling postural control [72,73]. However, whether the CoP oscillation is excessive and very close to the limits of stability, this behavior becomes problematic, making it difficult to maintain balance and increasing the risk of falls, mainly in conditions in which the neuromuscular control is impaired, such as PD [75,76].

In addition to the different strategies for postural control, stimulation and task characteristics may have influenced the results. While systematical data suggest that a single session of tDCS applied to the motor cortex areas effectively improves overall motor functions in people with PD [77,78], its effects on objective measures of postural control during static balance in PD was not yet analyzed [37]. We observed an absence of tDCS effects over the M1 on objective measures of postural control, such as the CoP parameters, while previous studies suggesting positive effects of single and multiples sessions of tDCS on field test (i.e., TUG and Berg) of balance and when tDCS was applied over prefrontal cortex [18,37,40,47]. The slightly superior positive effect of tDCS applied to prefrontal cortex on balance was demonstrated in a recent meta-analysis [37]. In agreement, Ricci and colleagues (2019) indicated that the positive effects of multiple sessions of tDCS over prefrontal cortex appear to be higher on field tests rather than on objective measures of postural control such as the postural sway area (SRM = 0.79 vs. -0.43, respectively). Presumably, objective measures of postural control require fine motor control adjustments being less sensible to tDCS effects. On the other hand, field balance assessments reflect a current state, let's say of dynamic balance, since it is more global and, therefore, being more sensible to tDCS effects. Although unexpected, our results corroborate recent systematic reviews and meta-analyses that showed that tDCS did not improve the balance of individuals with neurological disorders, such as people with PD [19,20] and stroke participants [79]. This observation reiterates that, perhaps, fine postural

control vs. field global balance adjustment is lesser sensible to or change to additional therapy.

Another possible explanation for the lack of balance improve (i.e., decrease of CoP parameters) is due to a single session of tDCS alone may have a limited effect on postural control in people with PD [80]. There is evidence suggesting additional benefits when tDCS is combined with interventions (cognitive and/or motor) on balance in people with PD [15]. Kaski et al. (2014) showed significant results for balance recovery when combining the application of anodal tDCS in M1 with physical training [80]. It should be noted that this study showed that a single session of tDCS did not alter the balance recovery of people with PD and that positive effects on balance were observed only when tDCS was combined with physical training [80]. A possible explanation for the superior effects of the combination of tDCS with other interventions is the possibility of stimulation to increase cortical excitability and favor/facilitate the positive neurophysiological changes generated by physical exercises [80].

4.1 Limitations and future directions

This study has some limitations. Firstly, we did not evaluate the postural control before the tDCS application. The baseline assessment of the postural control before each condition of tDCS would allow us to better understand the effects of tDCS on CoP parameters. A better understanding would be possible due to the minimization of possible motor fluctuations that occur in people with PD [65,66], which can influence the CoP parameters (i.e., postural control). Although the experimental procedures were performed at the same time on different days, motor fluctuations may occur due to the specific PD medication [65,66]. Thus, future studies should assess postural control in people with PD before and after the tDCS conditions to avoid the baseline postural behavioral state

affecting with the responsiveness of tDCS. Also, although we performed the a priori analysis of sample size power, the number of participants in our study may influenced the results of the study and should be considered as a study limitation. In addition, the adaptation of the task (tandem position) may have made it difficult to detect the effects of tDCS, reducing the challenging aspect of the task and the complexity of the postural control system to maintain balance in this position. However, the adaptation of the original tandem position was needed for participants of our sample to be able to remain on task for 30 seconds [6,7,46]. Another limitation was that the assessment of postural control was performed immediately after the end of the tDCS intervention, which may have interfered with the time required for the cortical activity modulation and the consolidation of these changes (e.g., five to 60 minutes after stimulation) [56,58].

Although important mainly for basic research, a single session of tDCS provided lower applicability for the clinical practice. A single session of tDCS enables understanding the immediate effect of a simple brain stimulation tool on motor behavior in a neurological population. However, for a better applicability in clinical practice, studies have been demonstrating that the combination of tDCS with another intervention and/or performing multiple sessions of tDCS may reflect in a superior improvement for people with PD [15,37,77,78]. For instance, empirical data reported that when tDCS combined with other intervention or multiple sessions of tDCS resulted improvements in balance gait and cognition [40,80,81]. Therefore, future studies should investigate the efficacy of multiple sessions of tDCS in objective measures combined or not with additional intervention in postural control in people with PD.

5. Conclusion

A single session of tDCS over M1 did not improve the postural control, analyzed by the CoP behavior, in people with PD during adapted tandem position.

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Declarations of interest

None.

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Table 1. Demographic, clinical, and cognitive data of the participants. Parametric variables are presented as mean and standard deviation values. Non-parametric variables are presented as median and quartiles (25-75).

Variables	Mean $\pm$ std., Median (1st-3rd quartiles) or frequency
Sex (male/female)	12/7
Age (years)	68.95 $\pm$ 6.96
Body mass (kg)	71.84 $\pm$ 11.45
Body height (cm)	163.37 $\pm$ 10.31
MDS-UPDRS III (0-132)	33.0 (30.0-41.5)
MMSE (0-30)	28.0 (26.0-28.0)
PD duration (years)	3.0 (3.0-7.0)
LEDD (mg/day)	557.11 $\pm$ 265.58
Hohen & Yahr (1.5/2/2.5)	1/13/5

MDS-UPDRS III = Movement Disorders Society – Unified Parkinson’s disease Rating Scale motor part; MMSE = Mini Mental State Examination; PD = Parkinson’s disease; LEDD = Levodopa Equivalent Daily Dose; std = standard deviation.

Table 2. Comparison of CoP variables between active and sham conditions. Variables with normal distribution are presented as mean and standard deviation values. The variable with non-normal distribution is presented as median and quartiles (25-75).

CoP variables	Conditions		t/Z	Cohen's <i>d</i>	<i>p</i>	SRM
	Active	Sham				
<i>ML direction</i>						
Amplitude (cm)	2.03 ± 0.70	1.99 ± 0.51	0.25	0.06	0.81	0.06
RMS (cm)	0.44 ± 0.15	0.44 ± 0.11	0.13	0.03	0.89	0.15
Mean velocity (cm/s)	0.78 (0.59-1.04)	0.79 (0.66-0.93)	-0.604	0.16	0.55	0.03
<i>Both directions</i>						
Displacement (cm)	194.80 ± 59.29	187.20 ± 39.64	0.69	0.16	0.50	0.16
Area of sway (cm²)	2.47 ± 1.68	2.03 ± 0.90	1.5	0.34	0.15	0.34

CoP = center of pressure; ML = mediolateral; SRM = standardized response mean; RMS = root mean square.

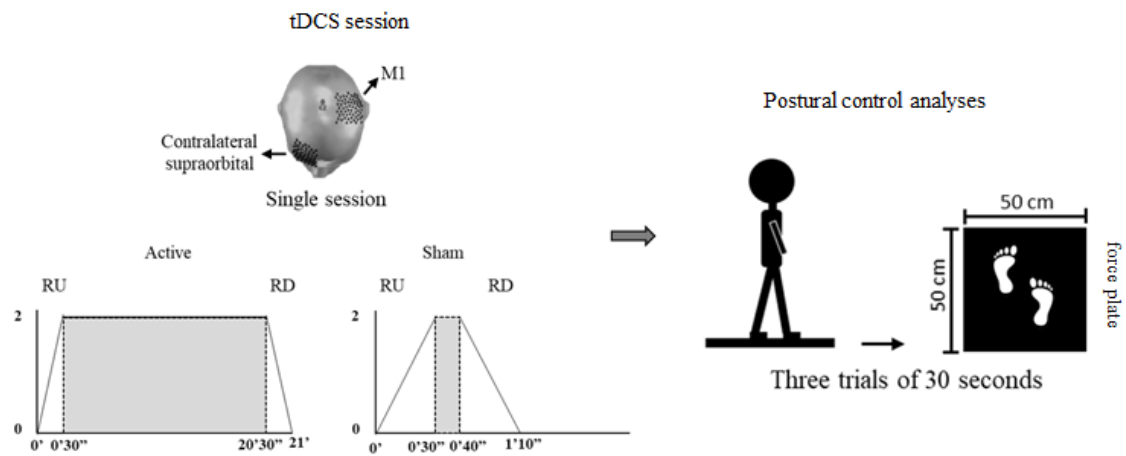


Figure 1. Experimental procedures including tDCS protocol and the postural assessment.

The gray area in the tDCS protocol represents the period of active stimulation. RU = ramp-up (30 seconds); RD = ramp-down (30 seconds).

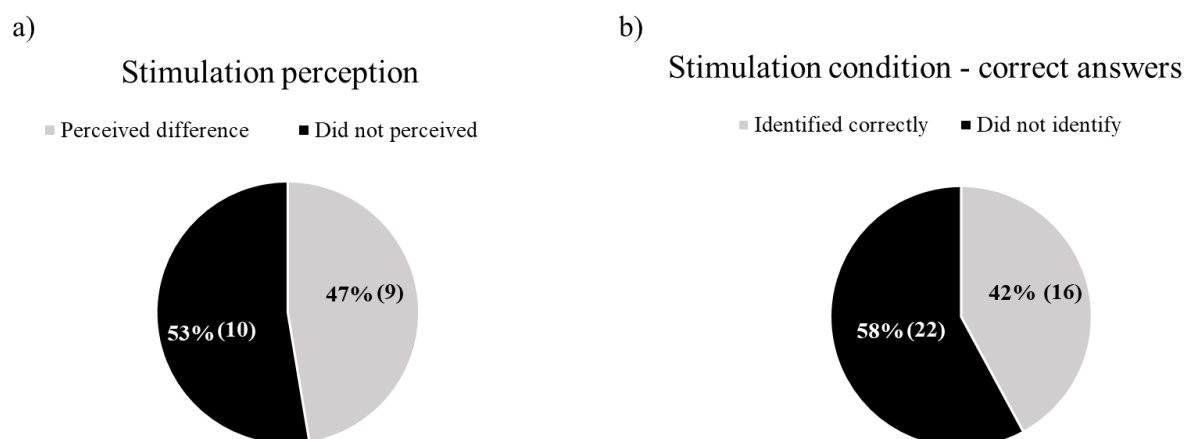


Figure 2. Values in percentage of patients who perceived differences in the stimulation conditions (a) and the number of correct answers for the stimulation condition in each session (b).