Title: Combined Balance Training and tDCS Intervention for the Recovery of Postural Control Following Chronic Stroke: A Study Protocol for A Multi-Centre, Double Blind, Randomized Control Trial

Running Title: Brain Stimulation with Balance Training on Functional Balance and COP Analysis Outcomes in Stroke

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Abstract

Background

Stroke is one of the most debilitating diseases among the adults around the world which leads to persistent rehabilitation needs even at chronic stage. Achievement of good postural control is a critical requirement for daily activities which enhances quality of life in patients with stroke. There is increasing evidence that transcranial direct current stimulation (tDCS) may be considered as a promising adjunct technique to improve motor recovery after stroke. Evidence of augmented neuroplasticity after tDCS suggests that a paired rehabilitation followed by consecutive use of tDCS may optimize recovery outcomes. Although a few RCTs have been conducted on upper limbs rehabilitation in chronic stroke using tDCS, however no study focused on balance training in chronic stroke patients. This randomized, sham-controlled, double-blinded clinical study aims to address brain stimulation targeting postural control using tDCS in chronic stroke.

Methods

The study participants will be chronic ischemic stroke individuals with postural control impairments who meet no exclusion criteria. Active or sham anodal tDCS will delivered to lesioned leg motor cortex combined with balance training. Experimental group receive active anodal tDCS stimulation (2mA) for 20 min, daily for 5 days paired with balance training. Linear and nonlinear approaches will be used to analyse postural sway changes pre and post-intervention. Postural sway fluctuation, Functional balance assessment using Berg balance scale, Timed Up-and-Go Test will be compared in active and sham groups.

Conclusions

This trial could have significant implications for balance rehabilitation after stroke in the ambulatory setting. If found to be effective, this novel approach may improve rehabilitation protocol in this population.

Keywords:

tDCS, Chronic stroke, Motor cortex, Postural control, Complexity, Multiscale entropy

Introduction

Stroke is the main cause of long-term disability in adults which affects the independence, social participation and quality of life in survivors. The incidence of stroke in low-to-middle income countries is increasing and these countries are most affected (Strong et al., 2007). Based on the results of a study in 2010, the annual incidence of first ever stroke is 139 per ten thousand among the Iranian population which is significantly higher than in most western countries and also occurs at lower age ranges. The majority of individuals with stroke have postural deficits, moderate to severe walking disability and reduced gait speeds (Azarpazhooh et al., 2010).

The balance impairment is considered a challenging issue for health care providers due to its high prevalence of falling as well as its physical and financial burden to society. An increased postural sway and asymmetrical weight distribution with centre of pressure(COP) shift towards the unaffected side, increased spontaneous postural sway, is characteristic of postural impairment in hemiplegic stroke patients (Roerdink et al., 2006, Geurts et al., 2005). Individuals with stroke also have sensory deficits, abnormal sensory reweighting, and muscle weakness. Rehabilitation methods which improve balance and balance-recovery reactions are crucial for reducing the cost of long term care of stroke patients and to prevent such a load on the healthcare system (Harris et al., 2005). It was demonstrated that balance training improves walking through effects on weight-bearing after stroke (de Haart et al., 2004, Yavuzer et al., 2006).

Previous studies proved limited effectiveness of sensory stimulation by transcutaneous electrical nerve stimulation, functional electrical stimulation, electromyography feedback or body weight supported treadmill training on balance and related ADL in patients with stroke (Verheyden et al., 2013, Brewer et al., 2012). But no particular physiotherapy approach was more successful than any other in the recovery of postural control and lower limb function (Geurts et al., 2005). Evidence revealed that and postural control is extremely influenced by cerebral cortex and cognitive mechanism. Moreover, cerebral cortex plays a significant role in control of locomotion (Jacobs and Horak, 2007). Conventional physiotherapy protocols for neurological disease have a limited potential for neural repair rehabilitation and techniques which promote neuroplastic changes claim to have significant functional achievement in patient's recovery (Dimyan and Cohen, 2011).

Transcranial direct current stimulation

Post-stroke patients exhibited changes in motor cortical excitability and disrupted inter-hemispheric inhibition from the unaffected to the affected motor cortex. This is based on the theory that following a focal lesion output from the lesioned hemisphere declines and the balance of interhemispheric communication interrupts (Di Pino et al., 2014). Transcranial direct current stimulation (tDCS) gained a lot of attention as a promising neurorehabilitation tool in recent years (Nair et al., 2011). tDCS elicits regional neuroplasticity by induction of weak intracerebral ionic current between a positively charged anode and negatively charged cathode (Stagg and Nitsche, 2011). Different mechanisms such as calcium-dependent synaptic plasticity of glutamatergic neurons and also impact on glutamatergic plasticity due to reducing gamma-aminobutyric acid (GABA) neurotransmission could explain the therapeutic effect of tDCS (Nitsche et al., 2003). Accordingly, tDCS is considered a safe, portable, and inexpensive modality to alter cortical excitability (Bikson et al., 2016). Trials with tDCS applications have established motor skill learning enhancement and improves new motor skill learning enhance execution and skills in chronic stroke patients (Reis et al., 2009, Kaminski et al., 2016). Previous studies suggest that daily tDCS stimulation is required to occur significant cortical plasticity (Alonzo et al., 2012). Galea and Celnik observed anodal tDCS (a-tDCS) enhances retention of motor memories (Galea and Celnik, 2009). Moreover, the effectiveness of tDCS in stroke patients have been reported in recent systematic reviews (Marquez et al., 2015, Bastani and Jaberzadeh, 2012). A more recent meta-analysis of tDCS interventions in stroke rehabilitation concluded that a-tDCS over the lesioned hemisphere can enhances motor cortex excitability and improve upper limb function with rehabilitation interventions (Butler et al., 2013). Many studies have focused on the effects of tDCS on upper limb rehabilitation. A few tDCS interventions on lower limbs function are mostly investigated in healthy individuals. Jeffry and his colleagues showed that the excitability of corticospinal tract projections to the tibialis anterior muscle increased after a-tDCS (Jeffery et al., 2007). Others have emphasized the utility of anodal tDCS in increasing maximum leg pinch force in healthy volunteers and also knee extension force in individuals with hemiparetic stroke (Tanaka et al., 2009, Tanaka et al., 2011). Beck and his colleagues work demonstrated that leg motor area is mainly involved in postural tasks and quiet standing (Beck et al., 2007, Tokuno et al., 2009). There is evidence which supports the utility of effectiveness of tDCS applied to the leg area of primary motor cortex in improvement of balance performance in subacute stroke (Kaski et al., 2013).

Remarkably, Studies that combined tDCS with motor recovery protocols have yielded promising results. A very recent study points toward the ability of a-tDCS over M1 leg area to enhance dynamic balance learning in healthy young adults, suggesting that tDCS over M1 is capable of modulating adaptive motor control processes in young adults (Kaminski et al., 2016).

The evaluation of postural stability is necessary for planning effective balance rehabilitation. Postural stability is provided by multiple physiological systems interacting with one another throughout multiple scales of time series. This highly complex process provides the postural control system the ability to adapt to the various stressors of everyday life (Lipsitz, 2002). At this point, determining of the impaired balance with of conventional measures of the COP (COP surface area, COP velocity) to quantify postural control may yield an incomplete picture of postural control and have some limitations for proper identification of integrity of the postural control system. Loss of complexity hypothesis" was first expressed Lipsitz and Goldberger. This theory suggests that systems displaying a reduction in the number of dynamic interactions involved in the regulation of physiological outputs cause failure in physiological function, related to aging and disease (Lipsitz, 2002). It is established that individuals with stroke demonstrated overall more regular sway during quiet standing than controls. Reduced physiologic complexity of postural sway has been linked to deterministic pattern and to deficit in adaptability to intrinsic and external perturbations. They showed that sway regularity decreased in the course of rehabilitation (Roerdink et al., 2006).

Multiscale entropy (MSE) is one method used to evaluate the complexity of postural sway, as revealed by COP time series recorded with a force plate (Costa et al., 2005). Recently, the use of MSE for examining (COP) dynamics has received a significant amount of attention, particularly in older adults (Duarte and Sternad, 2008, Manor et al., 2010, Zhou et al., 2015). The effects of tDCS on postural sway complexity in chronic stroke, however, are currently unknown. Given that, there is a critical need to explore therapeutic effects of tDCS paired with balance training targeting postural control in chronic stroke patients, we hypothesized that a-tDCS is capable of enhancing leg motor area in its excitability and seems to be a promising approach in balance recovery in chronic stroke. Moreover, we suppose that tDCS would alter the postural sway dynamics as computed by (MSE). To our knowledge, no study has analysed the effects of a-tDCS with balance rehabilitation in chronic stroke patients. This is the first study to identify tDCSs objective outcomes as well as investigate the impact of intervention on variability of postural stability in chronic stroke.

Methods

Study design

The study protocol follows the Consolidated Standards of Reporting Trials (CONSORT) Statement on randomized trials. In this randomized, sham-controlled, double blind study, participants will be assigned randomly to two groups: a-tDCS plus balance training with Biodex balance system or sham tDCS plus Biodex balance training. All outcome measures will be measured in 5 time points: pre-test, post-test after 5 sessions of intervention, and after 1 week and 1 month's post intervention as follow ups.

Objectives and hypotheses

The objectives of this study is to examine the efficacy of a-tDCS combined with Biodex balance training on postural control in chronic stroke patients using laboratory and clinical assessments. To analyse the postural behaviour of standing stroke patients after intervention, the changes in amount and temporal structure of variability due to ischemic stroke by evaluating COP time series in chronic stroke patients will be determined. It is hypothesized that subjects who undergo the anodal tDCS targeting primary leg motor cortex plus balance training program will exhibit significant differences in the temporal structure and amount of variability in COP time series and Berg balance scale, Timed Up-and-Go(TUG) as compared with control group.

Participants

Chronic ischemic stroke patients with postural control impairments will be recruited from multicentre University hospitals within the healthcare system and through outpatient care programs. The inclusion criteria will be: age ≥18 years; first-ever unilateral ischemic stroke; chronic phase of recovery (>6 months); ability to walk 6- meter supported or unsupported; ability to stand at least unsupported for 40-seconds with eyes closed; only ischemic stroke confirmed by CT or MRI. The exclusion criteria are: use of any neuro- or psycho-active medications that alters balance; any other neurological conditions or sensory disorders affecting postural control; such as brain tumor, or substance abuse; orthopedic diseases; ongoing/recent (within 3 months) balance rehabilitation. Patients with impaired ability to follow simple verbal instructions were also excluded from the study.

Ethics, consent, study organization and registration

The study is being conducted in agreement with the principles of the Declaration of Helsinki, and the Regulating Norms and Directives for Research Involving Human Subjects. The study protocol has been approved by the local and independent Ethics Committee of University. The study is also registered as a clinical trial on IRCT2016121715840N1.

During the consent process, the investigator explains the benefits and risks of participation in the study and provides an informed consent form approved by University Ethics committee. Only patients who provide written informed consent by signing the consent document are enrolled in the study. Safety will be assessed daily throughout the study by monitoring of adverse events during the active phase and at all follow-up time points and are routinely reviewed by the principal investigator.

Randomization and Blinding

Allocations are concealed in an opaque envelope and keep in a locked drawer. Using a sequence of computer generated random numbers the number “1” or “2” will be allocated to each group. They are opened by a research coordinator not involved in data collection or analysis. Participants and investigators (both trainers and assessors) are blinded to the group assignment.

In all sessions both, participants and investigators are blinded to the intervention type. The experimenter who applies the intervention (Active tDCS or Sham) is different from the investigator determining the outcome measures. The DC current is initially increasing in a ramp-like fashion over several seconds until reaching 2 mA which makes successful blinding of subjects possible. In sham condition, DC current will turn off slowly over a few seconds, out of the field of view of the patients. Double blinding is intended to minimize bias that could occur from participants’ perceptions of therapy or observer bias.

Sample size

Static balance, Berg balance scale and TUG test will serve as primary outcome measures, with all other assessments and time points serving as secondary outcome measures. Sample size and power calculations for the main study will be based on repeated-measures ANOVA with pre- to post intervention change in z-score of the primary outcome from the initial pilot study. For each sample size calculation, power will be set at 80% and a two-sided test at the alpha level of 5%. On the basis of data from a previous study, the pilot study involved 12 participants (Sohn et al., 2013).

(α = 0.05, β = 20%)

$$n = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2 \left({\delta_1}^2 + {\delta_2}^2\right)}{(\mu_1\text{-}\mu_2)^2}$$

Intervention group

tDCS set up

We use a battery-driven electrical stimulator (Activa DoseЦ_ Iontophoresis System-USA) connected to a (3*4) 12 cm^2 saline-soaked anode electrode and 35 cm^2 saline-soaked reference electrodes placed on the contralateral supraorbital region for more focal current density (Bastani and Jaberzadeh, 2013).

a-tDCS is delivered to the leg area (CZ) at a dose of 2 mA for 20 minutes for 5 sessions consecutive days to elicit excitability of the leg motor area (Jeffery et al., 2007). Participants will be exposed to participants to daily balance training combined with active/sham tDCS. For all participants, the current is ramped up slowly at the onset of intervention to minimize abrupt tingling and maintain blinding.

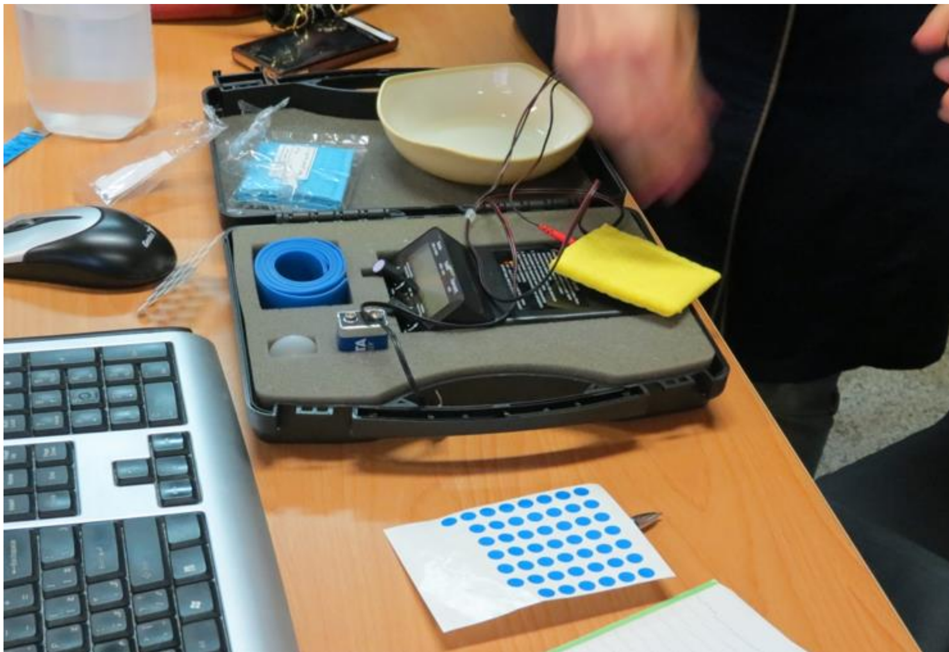

Fig1. tDCS (Activa DoseII_ Iontophoresis System-USA)

Balance training

Once participants are randomly assigned to relevant groups, Biodex balance training will be delivered under supervision of the study principal investigator. The Biodex balance system uses a circular platform that is free to move in the anterior–posterior and medial - lateral axes simultaneously. The stability of the platform can be varied by adjusting the level of resistance given by the springs under the platform. The platform stability ranges from 1–8, with 1 representing the greatest instability. The lower the resistance level the less stable the platform. It provides visual feedback, on a screen at eye level, regarding the location of the participant's COP. For example, if the participant weight shifts to the right, the cursor moves to the right. During the task, the participant attempts to maintain the cursor in a single position (static) or shift the cursor around the screen (dynamic) depending on the goal of the activity, mobility improving dynamic balance. The protocol of Biodex balance training discussed here would be from the pilot study. All patients receive balance training for 5 days which also includes Biodex dynamic functional exercises, involves a graded, feedback-driven approach combined with tDCS intervention. a-tDCS combined with Biodex balance training providing rich sensory stimuli with a modified excitability threshold of the leg M1 to enhance local synaptic efficacy and potentiate motor learning.

Fig2. Biodex balance training

Control group

Participants in the control group receive the Biodex balance training matched to the intervention group treatments with sham tDCS. During sham stimulation, the current ramped up for 30 seconds, ramped back down for 30 seconds, and then remained off for the duration of the stimulation.

Outcome measures

This study will compare two outcome measures: First, functional dynamic balance improvements according to Berg scale, TUG test, postural sway fluctuations according to linear and nonlinear analysis of force plate data. Functional scales as well as advanced laboratory systems are employed for assessing posture control. On the other hand, the complex behaviour of standing postural control has been studied using different mathematical linear and nonlinear methods. In this study we use both functional and advanced laboratory system. Berg balance scale is also used to get further information on functional posture deficits in participants. Furthermore, the analysis of COP dynamics and postural sway assessment could add information about the patient's postural control.

Functional balance assessment

The Berg Balance Scale will be used for the assessment of functional balance. In this study we will use validated translated version of Berg Balance scale. It is a valid instrument used for evaluation of the effectiveness of interventions and for quantitative reports of function in research and clinical practice. This is a simple 14-item measure that addresses the performance of functional balance. Each item has a five-option ordinal scale ranging from 0 to 4 points, with a maximal overall score of 56. Scoring is based on both objective and subjective measures of the participant's abilities to complete tasks such as transfers, standing with feet together and turning 360 degrees. The points are based on the time in which a position is maintained, the distance an upper limb is able to reach in front of the body and the time needed to complete the task (Salavati et al., 2012, Berg et al., 1995). TUG Test is widely used in the assessment of functional mobility and dynamic balance and measures the time (in seconds) necessary to stand up from a chair with arm rests, walk three meters, turn around, walk back to the chair and sit down again.

COP analysis methods

Measures of amount of variability included the range of COP displacement, which assessed the distance moved by the centre of mass towards the outside of the base of support. Centre of pressure (COP) data would be obtained using strain gauge Bertec 4060-10 force platform and Bertec AM-6504 amplifier (Bertec Corp., Columbus, OH). Postural sway will be measured for 40s while participants stood on a force platform acquisition frequency: 500 Hz. The patients will be instructed to stand on the platform, barefoot, with feet shoulder-width apart and their arms relaxed at their sides, gazed fixed on a point in front of them. Foot position was marked to ensure consistency between trials. One trial was acquired with eyes open and one with closed eyes and between each trial participants were allowed to rest and sit down for 2 min. Postural measurements were obtained by the same rater in two sessions 48 h apart. The outputs of the force platform allowed us to compute the COP time series in the A/P direction COP (AP) and the M/L direction COP (ML). The first 10 s interval will be discarded in order to avoid the transition phase in reaching the postural steady state. The antero-posterior and medio-lateral coordinates of the COP trajectory undergo a post-acquisition filtering using a low-pass filter with a cut-off frequency based on our pilot study. Analysed COP variables will include: ellipse area involving 95% of data (COP area), mean velocity (COP velocity), and amplitude displacement in both directions for anteroposterior and mediolateral directions, respectively, will be computed by the difference between maximal and minimum values obtained for each direction. We would also analyse the temporal structure of variability included entropy analysis, which measures the self-similarity of the time series. Entropy analysis is a nonlinear measure, and it quantifies the predictability of a time series. It measures the probability that the distance between certain data point patterns will remain similar upon the next increment in time. Entropy-based methods have potential as a valuable measure of detecting undetectable, subtle physiological changes after stroke. Several authors reported entropy has potential to assess specific postural behaviours induced by age, health conditions, and cognitive conditions (Busa et al., 2016, Chen and Jiang, 2014, Kang et al., 2009). In this study temporal structure will be measured using nonlinear mathematical techniques and the amount of variability with using linear mathematical techniques. With linear and nonlinear analysis we are able to estimate which variable or variables change under different stance conditions represent the clinical quantification of balance after intervention.

Complexity analysis of postural control

We estimate the degree of COP complexity, as defined by the presence of fluctuations existing over multiple timescales, using MSE (Costa et al., 2005). Prior to MSE analysis, signals decomposition and reconstruction (EMD). was used to remove low-frequency trends and high-frequency noise in the raw time series, which was well-established previously (Gow et al., 2015). MSE uses sample entropy to quantify the degree of irregularity of a time series by employing "coarse-graining" technique. Sample entropy (SE) reflects the negative natural logarithm of the conditional probability that a time-series repeating itself within a tolerance r for m points (pattern length), will also repeat itself for m+1 points without self-matches. Thus, both the tolerance level r and pattern length m need to be set in SE algorithm for the MSE calculation. The coarse-grained time-series for time scale n is the sequence of mean COP values provided by dividing the original time-series into non overlapping windows with n data points, and then computing the mean value for each window.

In this study MSE will be computed for scale factors 1–20 to ensure sufficient samples (Richman and Moorman, 2000).

Here, we use m =2 and r =15% of the standard deviation of the original signal.

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, \quad 1 \leqslant j \leqslant N/\tau.$$

After plotting the sample entropy of each coarse-grained time series as a function of time scale, the COP complexity index was calculated (CI). CI was identified as the area under the MSE resulting curve.

$$C_I = \sum_{i=1}^{N} S_E(i)$$

It provides us an index for measuring the degree of the postural sway complexity. A larger area reflects higher greater complexity which means a more irregular and information rich pattern while a lower CI value specifies poor adaptability. Then we compare between traditional COP analysis and the complexity index (CI) (Costa et al., 2005, Duarte and Sternad, 2008, Jiang et al., 2013).

Adverse effects

tDCS is considered as a safe non-invasive brain stimulation approach with with a rare chance of adverse effects related to the procedure. At every tDCS sessions, all of the reported side effects related to tDCS, such as tingling, headache, itching, fatigue, pain and problems concentrating, will be documented by the researcher who is applying the tDCS intervention.

Statistical data analyses

Patient characteristics will be described using means, standard deviations, medians, and interquartile ranges (dependent on whether data is normally distributed or not) and percentages. Group comparisons at baseline will be performed with Student's t tests, Mann–Whitney U tests and $\chi 2$ tests where appropriate. Primary efficacy analysis will be performed on an intention-to-treat basis. The effect of the two interventions (a-tDCS vs. sham) on the outcome measures will be determined using two-way, repeated-measures analysis of variance (ANOVA) with two factors: 1) group (tDCS active versus sham group), and 2) time (pre- versus post-training, follow ups). Paired samples T tests with 95% level of confidence will be used to evaluate statistical differences between AP and ML variables in each group. An alpha level of $P < 0.05$ will be set to determine significance. Sensitivity analyses will employ simulation and will test a range of scenarios assuming plausible arm-specific differences in outcomes for individuals who were lost to follow-up. Statistical analyses will be performed using SPSS version 22.0 (SPSS Inc., Chicago, IL) software.

Discussion

We have described the protocol of our ongoing clinical trial study in chronic stroke, where we test efficacy and safety of balance rehabilitation combined with transcranial stimulation targeting the leg motor area in the affected hemisphere. Few exploratory studies have investigated the potential clinical efficacy of tDCS on balance and gait but not chronic stroke patients and follow up (Kaminski et al., 2016, Sohn et al., 2013, Inukai et al., 2016)(Kaminski, E.,2016, Sohn, M.K.,2013, Inukai Y, 2016, Nomura T,2018). In our ongoing clinical trial, the effectiveness of tDCS cortical stimulation combined with Biodex balance training on patient's postural steadiness on chronic stroke with follow up would be tested. Because of the gap in balance rehabilitation in chronic stroke survivors, this proposed study is the first study which aimed to provide knowledge of potential effects of tDCS intervention on postural control, including laboratory measurements and clinical tests. We enhance current focality using a novel approach in balance rehabilitation by employing a-tDCS in chronic stroke with different electrode size that differs from the classical ones. COP fluctuation analysis provides information regarding the neuromuscular control of posture and therefore will reveal the intrinsic mechanisms responsible for maintaining balance, if there are problems with the intrinsic control of posture these will become apparent in the COP time series. In this study both of functional and laboratory balance assessments will be used. In summary**,** nonlinear measures along with linear measures to evaluate different aspects of the temporal structure and amount of variability in COP time series will offer a better paradigm to examine effectiveness of interventions (Zhou et al., 2015, Fino et al., 2016). Usage of functional balance training which promote rich multiple sensory stimuli will promote motor learning as motor learning depends on a change in the excitability of the cerebral cortex, a-tDCS stimulation seems to be a way to modulate cortex activity, enhancing functional gains achieved with balance training. It has been suggested that balance rehabilitation intervention might exploit a crucial stage in which the postural control and weight shifting is primed to be repaired, and this benefit walking late after stroke (Yavuzer et al., 2006, Dimyan and Cohen, 2011). There are several limitations to our proposed study. Since no neuroimaging analysis are included, it would not be possible to estimate whether specific brain structures are contributed to the intervention and also potential tDCS effects on neuronal networks. The result of this intervention can only be generalized to individuals with ischemicand chronic stroke. In our study hemorrhagic patients and patients with cerebellar lesions are not recruited, so effects of a-tDCS might be different in patients who also have defects in cerebellar regions or haemorrhagic stroke.

Finally, the results would have strong contribution in rehabilitation setting which may even offer a new method to apply during long-term outpatient rehabilitation, and may eventually prime to reduce health-care costs and improve mobility and quality of life in these patients.

There is no conflict of interest in this study to declare**.**

Fig3. Flow chart of study based on Consolidated Standards of Reporting Trials (CONSORT)

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Figure Legends:

Figure 1: Image obtained from tDCS device showing electrodes.

Figure 2: Image obtained from Biodex balance training on patient with chronic stroke.

Figure 3: The CONSORT 2010 Diagram for attrition of subjects in the study.