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**Original Article**

# A single session of anodal transcranial direct current stimulation applied over the affected primary motor cortex does not alter gait parameters in chronic stroke survivors.

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**Running title: Effect of tDCS on gait in chronic stroke people**

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**ABSTRACT**

**Objectives.** The excitability of some neural circuits involved in walking and affected in individuals with chronic stroke can be modulated during and/or immediately after anodal transcranial direct current stimulation (a-tDCS). This study was designed to investigate the effects of a-tDCS during and immediately after application on leg muscle activity during gait, and on spatiotemporal and kinematic gait parameters in patients with chronic stroke.

**Methods.** This study was randomized, sham-controlled and double-blinded with a cross-over design and included 24 individuals with chronic stroke. Each participant underwent one 30-minute session each of effective a-tDCS at 2 mA and sham tDCS. In both sessions, the anode was placed over the leg motor cortex of the affected hemisphere and the cathode over the contralateral orbit. Six gait trials were performed before, during and immediately after each effective/sham tDCS session. Electromyographic activity of leg muscles, as well as spatiotemporal (e.g. gait speed) and kinematic (e.g. peak knee flexion and ankle dorsiflexion in the swing phase of gait) gait parameters were recorded. Genotyping for the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism was undertaken since this gene may influence motor skill learning and the effects of tDCS.

**Results.** No significant effects of a-tDCS on gait parameters were found either for the total group or for the Val66Met (n=10) and Val66Val (n=14) subgroups.

**Conclusion.** A single session of a-tDCS delivered to the leg motor cortex did not immediately improve gait parameters in individuals with chronic stroke, regardless of their BDNF genotype.

**KEYWORDS:** EMG; lower limb muscles; spasticity; tDCS; walking

## INTRODUCTION

Stroke refers to a vascular event within the brain caused either by a lack of blood or bleeding into the brain. The ensuing lesions frequently disrupt the normal function of motor and sensory pathways, significantly altering the motor control of gait [14, 29, 59]. Typical gait alterations include loss of peak knee flexion during the swing phase of gait (stiff-knee gait) accompanied by reduction in peak ankle dorsiflexion during both stance and swing. Hyperextension of the knee (genu recurvatum) may also occur in stance (see Balaban et al. [4] for review). These changes are mainly due to inappropriate muscle activity resulting from spasticity (hyperexcitability of the monosynaptic stretch reflex), muscle weakness, muscle co-contraction and/or reduced cortical neural drive [27, 29, 47, 59] and result in reduced functional mobility, autonomy and quality of life [9, 13, 28, 54]. Improving the neural control of gait in patients with chronic stroke is therefore of considerable clinical importance. A novel approach that has shown potential for restoration of the neural control of gait in patients with chronic stroke is transcranial direct current stimulation (tDCS).

tDCS is a non-invasive brain neuromodulation technique that is delivered via electrodes placed externally on the cranium. During application, increased spontaneous motor neurone activity is observed close to the anode while reduced neuronal activity is observed close to the cathode [44, 46]. In healthy subjects, anodal tDCS over the leg area of the motor cortex has been found to increase corticospinal excitability of the tibialis anterior muscle (TA), while cathodal tDCS has no effect on corticospinal excitability [24]. Lattari et al. [34] reported that muscle power of healthy subjects was enhanced after anodal tDCS but was not modified after cathodal tDCS. In patients with stroke, the anodal tDCS has been shown to increase maximal force production of the knee extensor muscles, likely mediated by enhanced cortical neural drive [56, 58]. Anodal tDCS may therefore improve motor control in patients with chronic stroke by increasing the excitability of the cortical structures involved in the control of gait.

In healthy subjects, anodal tDCS has been shown to modulate the excitability of some spinal cord circuits involved in walking, such as recurrent homonymous inhibition, reciprocal inhibition and lumbar propriospinal responses [31, 50–52]. Given that these latter two circuits are associated with co-contraction, spasticity and/or gait disorders in patients with stroke [5, 16, 39], it was hypothesized that tDCS stimulation would improve gait in patients with stroke. To date, few studies have investigated the effects of a single session of tDCS on gait in patients with chronic stroke. Tahtis et al. [57] found that performance on the Timed-Up-and-Go test was improved in patients with subacute stroke after 20-min of bilateral tDCS with the anode over the ipsilesional leg motor cortex and the cathode over the contralesional leg motor cortex (stimulation intensity: 2 mA). However, the Timed-Up-and-Go test does not only evaluate gait ability since it involves standing up, walking 3 meters, turning, walking back and sitting down. Furthermore, the patients included in that study were in the subacute stage of stroke, a time when neuroplasticity and motor recovery processes are more active [53]. Recently, Van Asseldonk and Boonstra [2] evaluated the effects a single application of anodal uni-or dual-hemispheric tDCS (duration: 10 minutes; stimulation intensity: 2 mA) on spatiotemporal and kinetic gait variables in 10 healthy participants and 10 participants with chronic stroke. In healthy participants, the results showed slight post-effects for some gait variables, such as an increase in force production during the push-off phase, 15 and 45 minutes after tDCS application. In contrast, no effects were observed in the patients with stroke. Surprisingly, the effect(s) of tDCS on gait during and just after stimulation have never been investigated while tDCS-related effects on corticospinal and/or spinal excitability have been shown to be strongest at these times [46, 51].

Some studies into non-invasive brain stimulation techniques have suggested that the patient's response may have a genetic factor. The brain-derived neurotrophic factor (BDNF) Val66Met genotype polymorphism, which inhibits production of BDNF, has been linked with altered

brain responsiveness to brain stimulation [1, 12]. This association has, to date, rarely been considered in tDCS studies yet facilitation of corticospinal excitability after anodal tDCS and of corticospinal inhibition after cathodal tDCS have been shown to be greater in individuals with the BDNF Val66Met polymorphism compared to those without [1]. Its presence has also been associated with reduced cortical plasticity and motor-learning capacity [11, 35, 43]. It can be therefore hypothesized that changes in gait pattern during and after tDCS would be different in participants with stroke who had this BDNF Val66Met polymorphism compared with those who did not.

The aim of this randomized sham-controlled study was to investigate the acute effects of anodal tDCS during and immediately after application in patients with chronic stroke on the patterns of muscle activity during gait, and on spatiotemporal and kinematic parameters of gait. Based on research in healthy participants indicating that anodal tDCS would reduce the excitability of the stretch reflex pathway [51], we predicted that there would be a reduction in rectus femoris (RF) activity during swing and triceps surae activity during the stance phase of gait. The clinical aim of this research would be to increase function for stroke patients by reducing stiff-knee gait and knee hyperextension during stance phase of gait and increasing ankle dorsiflexion in both stance and swing. We also included a BDNF genotype assessment to investigate the influence of BDNF genotype on the effects of tDCS on each gait parameters.

## METHODS

### Participants

Twenty-four patients with chronic stroke were included in this study. Their anthropometric and clinical characteristics are presented in table 1. Inclusion criteria were: male or female aged 18 years or older, hemiparesis following unilateral hemispheric cerebral lesions of

vascular origin more than 6 months previously, able to walk for 10 minutes non-stop without gait aids and able to provide informed consent. Exclusion criteria were: presence of cardiac pacemaker, aphasia or cognitive difficulties that could interfere with comprehension of instructions, neuro-orthopedic surgery to the lower limbs less than 6 months previously, concomitant progressive disease, one or more epileptic seizures within the year prior to the date of inclusion, an intracerebral metal clip, non-affiliation to the social security regime or being under guardianship. None of the participants were taking drugs that have been shown to have an impact on the effects of tDCS [40]. All subjects were volunteers and were informed of the aims of the study as well as the nature, potential risks and possible discomfort associated with the method before they gave written consent for participation. This study was performed in accordance with the ethical codes of the World Medical Association and was approved by the French National Drugs and Health Administration and by the National Ethics Committee section Ile de France IV (reference number: P120135/AOM12126, 2013-A00952-43/ClinicalTrials.gov: NCT02134158).

**Experimental design**

This study used a randomized, sham-controlled and double-blind crossover experimental method. During each experimental session, neither the participant nor the operator was aware of whether the tDCS electrodes generated a current ('effective') or not ('sham'). Each participant participated in two sessions, one week apart: i) one session with effective anodal tDCS and ii) the other with sham tDCS. The order of sessions was randomized in order to ensure that equal numbers (12) of participants began with each type of session (effective anodal tDCS or sham tDCS). Prior to the first session, the spasticity of the quadriceps and triceps surae muscles was evaluated using the modified Ashworth scale [6]. At the beginning of each session, baseline muscle activity of leg muscles was recorded with the participant

lying in a prone position. During the session, six gait trials were recorded with the participants walking at their preferred speed along a 10 m gait corridor: i) before receiving the effective or sham tDCS, ii) 3 minutes after the beginning of the effective or sham tDCS (during tDCS); and finally iii) immediately after the end of the tDCS treatment (Fig.1).

## Interventions

*Effective tDCS*

Anodal tDCS was administered using a constant current electrical stimulator (Eldith DC-stimulator, Ilmenau, Germany). Rectangular electrodes (35 cm²; 7x5 cm) covered by a saline-soaked sponge were used for the anode and cathode. The anode was placed over the leg area of the motor cortex on the affected side with the medial border of electrode placed laterally to Cz on the international electroencephalogram 10–20 system [30] (Fig. 2A). The cathode was placed above the contralateral orbit. The stimulation intensity was set at 2 mA for 30 minutes. This intensity was reached progressively over a period of 8 seconds at the beginning of tDCS and was reduced to 0 mA over the last 8 seconds. A current density of 0.06 mA·cm−2 (2 mA / 35 cm²) was used in order to remain below the threshold that can lead to tissue damage [45].

*Sham tDCS*

The electrodes were placed in the same position as for anodal tDCS and the same stimulation procedure as for the effective anodal tDCS was respected (Fig. 2A). However, a current was only delivered for 120 seconds at the beginning of the application to reproduce the sensation of an increase in current intensity. This stimulation duration was chosen because it is below the 180 seconds that Nitsche and Paulus [46] showed to be required to induce anodal tDCS post-effects. This sham tDCS administration has been shown to be indistinguishable from effective tDCS [18]. To ensure that the session was blinded, an independent physician set-up

the tDCS equipment in either anodal or placebo mode; this person was uninvolved in data recording, collecting or processing.

**Gait assessment**

The 3D gait analysis was conducted using a 3D optoelectronic system (Motion Analysis Corporation, Santa Rosa, CA, USA, sampling frequency 100 Hz) with eight optoelectronic cameras. Thirty markers were placed on the patient's body according to the Helen Hayes model commonly used by the biomechanical community for gait analysis [26].

**Electromyographic assessment**

EMG activity of the RF, gastrocnemius medialis (GM), soleus (SOL), and TA muscles of the paretic side were recorded during the gait trials. After cleaning the skin of the electrode placement sites with alcohol swabs, surface EMG electrodes (model MA-311; Motion Lab Systems, Baton Rouge, LA, USA) were placed over the target muscles according to SENIAM recommendations [20] (Fig. 2B,C). The EMG sensors were composed of two circular dry button electrodes with double-differential preamplifiers. The two active electrodes measured 12 mm in diameter and the inter-electrode distance was 17 mm. All EMG signals were sampled at 1000 Hz.

**Blood sample**

Five milliliters of blood were collected from each participant in an EDTA tube using a standard method. A commercial kit (Illustra blood genomicPrep Mini Spin Kit, GE Healthcare) was used for the DNA preparation.

**Data analysis**

Data from gait assessment (i.e. kinematic and spatiotemporal parameters and EMG activity) were analyzed using a customized Matlab routine (version 9 R2016a, MathWorks Inc., Natick, MA, USA). Data from one representative subject are presented in Fig. 3.

*Kinematic and spatiotemporal gait parameters*

The marker trajectories were first filtered using a fourth-order zero-lag Butterworth low-pass-filter, with a 6-Hz cut-off frequency [62]. Gait velocity was computed from the toe marker for the paretic limb. Step length was calculated for the paretic leg. Maximal knee flexion angle during the swing phase and maximal knee extension angle during the stance phase were calculated to determine the effects of tDCS on stiff knee gait and genu recurvatum, respectively. Peak dorsiflexion in the stance and swing phases and plantar flexion in swing were also evaluated since motion of the ankle during gait has a strong impact on function [7].

*EMG transformation and normalization*

Before processing, the EMG signals were band-pass filtered between 5 and 500 Hz. The raw EMG signals from each muscle were time-normalized to 1000 points, corresponding to a gait cycle from 0 to 100% with 0.1% increments. The linear envelope of the EMG signals was calculated after full wave rectification and filtering at 10 Hz with a fourth-order low-pass Butterworth filter. For each muscle and experimental session, the amplitude of the linear envelope was normalized with respect to the maximum value recorded in all the gait trials [19, 63].

*EMG signals during gait*

A cut-off value of the mean +3 standard deviations of the EMG signals recorded at rest was used for detection of the onset and offset of muscle activity during gait. This method has been

validated for this purpose and was used to minimize muscle activity detection errors [21, 25]. The total duration of muscle activity during the stance and swing phases of gait were also calculated. The area under the curve (AUC) of each EMG signal was calculated only when muscle activity was detected [48] to estimate the level of muscle activity during each phase of gait cycle.

*BDNF genotyping*

The BDNF Val66Met SNP rs6265 gene (c.196G>A) was detected using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method with forward (5′-AAA GAA GCA AAC ATC CGA GGA CAA G -3′) and reverse fluorescent (5′-6-Fam-ATT CCT CCA GCA GAA AGA GAA GAG G -3′) primers and further digestion of the PCR product with NlaIII enzyme (Cat. No. R0125S, New England Biolabs). The amplified 271 bp fragments carried a mandatory NlaIII site as an internal control. Fragments were separated by capillary electrophoresis using a genetic analyzer machine (ABI 3500, Applied Biosystems). The two alleles, G (Val66) and A (Met66), were identified by fluorescent bands of 216 bp and 139 bp (respectively) and results from patients who were GA heterozygous contained both.

**Statistical analysis**

Statistical tests were performed in Statistica v10.0 (Statsoft, Tulsa, OK, USA). Distributions consistently passed the Kolmogorov-Smirnov normality test, and thus means ± SD are reported for all data. The level of significance was set at $P<0.05$. To verify the effect of tDCS on kinematic, spatiotemporal and EMG parameters in the two BDNF genotype subgroups, separate analyses of variance (ANOVAs) were performed with group (×2: Val66Val *vs*. Val66Met) as the between-participants factor. The within-participant factors were time (×3:

pre vs. during vs. post) and stimulation (×2: effective vs. sham). Post-hoc analyses were performed using Tukey HSD comparisons.

Although session-order (effective vs. sham tDCS) was randomized, to be certain there was no order effect, we carried out separate t-tests to compare baseline gait parameters at the start of each session, regardless of the stimulation condition (effective vs. sham tDCS).

## RESULTS

There was no effect of session-order on any of the gait parameters (all P values > 0.31).

### Kinematic and spatiotemporal parameters of gait

The kinematic and spatiotemporal parameters are reported in Table 2. There was no main effect of the factor "stimulation" (effective vs. sham tDCS) on any kinematic or spatiotemporal parameter (All *P* values >0.28). There was a main effect of the factor "time" on gait velocity ($F_{(2,42)}$ = 9.0 ; $P$<0.001), step length ($F_{(2,42)}$ = 10.8; $P$<0.001), peak knee flexion angle in swing ($F_{(2,42)}$ = 4.8; $P$<0.05) and peak dorsiflexion angle in stance ($F_{(2,42)}$ = 7.6; $P$<0.01). The post-hoc tests revealed that gait velocity, step length and maximal knee extension angle were significantly lower during both effective and sham tDCS than afterwards ($P$<0.05). Peak dorsiflexion angle in the stance phase was significantly lower during both effective and sham tDCS than either before or after ($P$<0.01). The lack of interaction between the factors "stimulation" and "time" (all *P* values >0.18) showed that the effect of "time" could not be attributed to the effective anodal tDCS.

### Muscle activity during gait

The EMG parameters (intensity and duration of EMG activity) during the swing and stance phases of gait are reported in Table 3.

There was no main effect of the factor "stimulation" (effective vs. sham tDCS) for any muscle during gait (All *P* value >0.27). There was a main effect of the factor "time" for the RF AUC ($F_{(2,42)}$ = 14.7; P<0.001) and duration of activity ($F_{(2,42)}$ = 7.2 ; *P*<0.01) in stance, duration of TA activity in stance ($F_{(2,42)}$ = 3.5; *P*=0.04), duration of RF activity ($F_{(2,42)}$ = 6.3; *P*<0.01) and the SOL AUC in swing ($F_{(2,42)}$ = 3.9; *P*<0.05). The post hoc tests revealed that i) the RF AUC during stance was significantly greater after both effective and sham tDCS than during or before (P<0.01), ii) the duration of RF activity during stance was significantly greater during and after both effective and sham tDCS than before (*P*<0.01), iii) the duration of RF activity during swing was significantly longer during both effective and sham tDCS than before (*P*<0.01), iv) the duration of TA activity was significantly greater during both effective and sham tDCS than before (*P*<0.05), and v) the SOL AUC was significantly greater after both effective and sham tDCS than during (*P*<0.05). The lack of interaction between the factors "stimulation" and "time" (All *P* value >0.10) showed that the effect of "time" could not be attributed to the effective anodal tDCS.

**BDNF genotype**

The BDNF genotypes are presented in Table 1. Fourteen of the 24 participants were GG homozygous (Val/Val), 10 were GA heterozygous (Val/Met) and none were AA homozygous (Met/Met). There were no significant statistical interactions between changes in gait parameters and the factor "BDNF genotype", indicating that the effects of tDCS on gait parameters were not influenced by BDNF genotype. For clarity, therefore, all results are presented regardless of BDNF genotype in tables 2, 3 and 4.

**DISCUSSION**

To our knowledge, this is the first randomized, double-blinded, sham-controlled cross-over study to investigate the effect of a single session of anodal tDCS on the pattern of muscle activity during gait in individuals with chronic stroke. We expected to find a reduction in leg muscle hyperactivities (particularly the RF and triceps surae) during gait since anodal tDCS has been shown to increase the excitability of cortical motor neurons and decrease the excitability of some spinal circuits involved in spasticity [33, 46, 51, 52]. The results clearly showed, however, that neither the patterns of muscle activity on the paretic side nor the kinematic or spatiotemporal parameters of gait were modified either during or immediately after 30 minutes of anodal tDCS in the participants with chronic stroke, regardless of their BDNF genotype. We therefore reject our hypothesis that a single session of anodal tDCS would improve the gait pattern of patients with chronic stroke.

**Participant's gait characteristics**

The gait characteristics of the participants included were typical of those with chronic stroke. The values of gait velocity (~82 $cm.s^{-1}$) and step length (~52 cm) were consistent with reports in previous investigations in similar populations and were reduced compared to healthy adults [7, 22, 55]. Peak knee flexion in the swing phase was reduced (~41° *vs.* ~60° in healthy individuals) showing that stroke patients had a stiff-knee gait that was probably due, at least in part, to RF hyperactivity [8, 10, 27]. They also had a loss of ankle dorsiflexion, especially in the swing phase of gait (~-2° vs ~5° in healthy individuals [7]), probably due to hyperactivity of the triceps surae muscle and/or weakness of dorsiflexor muscles. Finally, peak knee extension was increased in stance (Table 2), demonstrating genu recurvatum. The ratings on the modified Ashworth scale (see Table 1) and the high EMG activity of RF, SOL and GM during gait demonstrated the presence of spasticity. The results clearly showed changes in some gait characteristics during the experimental sessions, regardless of the type

of stimulation (anodal or sham). The mechanisms that may explain these changes were not assessed in this study and are therefore not known. Nevertheless, we assume that these changes may be due to warm-up and/or learning effects.

**Effect of a single session of anodal tDCS on gait**

Van Asseldonk and Boonstra [2] reported increased force production during the push off phase of gait 15 minutes and 45 minutes after the application of anodal or bi-hemispheric tDCS in healthy subjects, but not in patients with chronic stroke. The present study was original in that it evaluated gait during the application of anodal tDCS, based on the fact that the neural effects during anodal tDCS may differ from the post-effects (see Roche et al [49]). Taken together, the results of the present study and those of Van Asseldonk and Boonstra [2] suggest that a single session of anodal tDCS does not modify gait parameters in patients with stroke either during its application, or immediately after as well as 15 and 45 minutes later. The results also clearly showed that there was no effect of BDNF genotype on changes in muscle activity patterns, kinematic or spatiotemporal parameters of gait. The potential reasons for the lack of an acute effect of anodal tDCS on gait parameters are discussed below.

**Does a single session of anodal tDCS affect corticospinal tract function in patients with chronic stroke?**

One possible explanation for the lack of an acute effect of anodal tDCS on gait parameters is that tDCS would have only a limited impact on neural function in patients with chronic stroke. In healthy individuals, tDCS applied to the cortical leg motor area has been shown to modulate corticospinal excitability of the lower limb muscles [24]. As previously demonstrated, this modulation however is highly variable [37, 61, 66]. For instance, it has been shown in a sample of 53 healthy participants that nearly half showed minor or no

response in their upper limb following anodal tDCS [61]. Furthermore, inhibition of cortical excitability after anodal tDCS occurred in 25% of the participants. While the distribution (facilitation *vs.* inhibition *vs.* no effect) of the effects of anodal tDCS on corticospinal excitability has, to our knowledge, not been investigated in a large sample of patients with chronic stroke, some studies have reported modulations in corticospinal excitability after a single session of anodal tDCS in these patients. For instance, Jayaram and Stinear [23] found an increase in motor excitability of the medial hamstring and TA muscles during gait after 10 minutes of anodal tDCS (2 mA) in 9 patients with chronic stroke. Madhavan et al. [38] found an increase in corticospinal excitability of the TA muscle during a voluntary submaximal contraction (10% of the strength produced during a maximal dorsiflexion contraction) following 15 minutes of anodal tDCS (0.5 mA) also in patients with chronic stroke. While it is likely that the anodal tDCS altered corticospinal excitability of some muscles in the present study, the results suggested that this did not affect muscle activity patterns during gait.

**Does a single session of anodal tDCS affect neural circuits in patients with chronic stroke?**

In order for anodal tDCS to have altered patterns of muscle activity during gait, the excitability of some spinal cord networks would have had to have been modified by the anodal tDCS since gait is primarily controlled by neural circuits located within the spinal cord (i.e. central pattern generators) [41, 65]. In healthy subjects, a single session of anodal tDCS has been shown to modulate the excitability of some spinal cord circuits that are involved in gait, [31, 50–52]. However, its effect on the excitability of the spinal cord circuits involved in both gait and spasticity in patients with stroke [3, 15, 32], such as pre-synaptic inhibition, reciprocal inhibition, homosynaptic depression and lumbar propriospinal system have not yet been studied in patients with chronic stroke. The results of the current study suggest that these

circuits were not acutely affected by a single session of anodal tDCS, or at least not sufficiently to alter leg muscle activity patterns. Marque et al. [39] showed that the excitability of the lumbar propriospinal system is greater in patients with stroke than in healthy individuals. Since Roche et al. [52] showed that anodal tDCS decreases the excitability of this spinal pathway in healthy individuals, it could have been expected that anodal tDCS might normalize the excitability of the lumbar propriospinal system in patients with stroke. However, the lack of a change in RF EMG activity during and following anodal tDCS in the present study suggested that this was not the case. This observation could explain the lack of an alteration in peak knee flexion during swing. In the same manner, patients with chronic stroke commonly present a decreased reciprocal Ia inhibition [3]. Roche et al. [51] found a decrease in reciprocal Ia inhibition between TA and SOL during anodal tDCS in healthy subjects. Since EMG activity of the TA and the SOL was not modified by anodal tDCS in the present study, this suggests that a single session of anodal tDCS did not have a sufficient impact on reciprocal Ia inhibition to modify gait in these patients with chronic stroke. It may also contribute to the explanation of why no tDCS-related changes were found in dorsiflexion and plantar flexion during either the swing or stance phases.

**Was the tDCS stimulation set-up optimal?**

Although one cause for the lack of effect of anodal tDCS on gait parameters could have been a sub-optimal stimulation set-up, we believe that the set-up modalities used were appropriate: the stimulation intensity was set at 2 mA, which is both similar to most published tDCS studies and in line with the safety criteria for the use of tDCS in humans [2, 23, 24, 36, 45, 50–52]. The size of the stimulating electrodes (35 $cm^2$) was chosen to ensure a focal effect and was also similar to most previous tDCS studies [2, 24, 36, 45, 50–52]. The duration of stimulation (30 minutes) was longer than in many previous studies which generally used 10 to

20 minutes of stimulation [2, 23, 24, 36, 38, 45]. In agreement with two previous reports in healthy participants [42, 60], this long duration of anodal tDCS could have cancelled or even reversed the expected after-effects of anodal tDCS on corticospinal excitability (i.e. an increase in corticospinal excitability) in our sample of patients with chronic stroke. However, it is not known to date if a long duration of stimulation has a different effect from a short duration of stimulation on corticospinal excitability in patients with chronic stroke.

Another explanation for the lack of effect of a single session of anodal tDCS could relate to the placement of the electrodes. The anodal electrode was placed over the presumed area of the leg motor cortex [30] for each participant but transcranial magnetic stimulation was not used to determine electrode position [64]. Although that method of leg motor cortex location is precise and used in research [64], its use in clinical practice is limited because it is complex, costly and time-consuming. Since the object of this study was to determine the potential therapeutic use of a single session of anodal tDCS, we chose conditions that reflected clinical practice. Furthermore, in view of the size of the electrode used (35cm²), it seems unlikely that the hot-spot of the leg motor cortex was not covered by some part of the electrode. Finally, Roche et al. [51] found that anodal tDCS placed on the hand motor cortex induced the same effect on reciprocal Ia inhibition in the lower limb as that when it was placed on the leg motor cortex. It is therefore unlikely that the lack of effect of a single session of anodal tDCS on gait was related to the size or the placement of the electrodes.

Finally, to ensure that participants could not differentiate effective from sham tDCS, we chose a duration of sham stimulation (120 s) that was longer than in most tDCS studies [17]. However, we strongly believe that the sham stimulation did not induce any changes in the neural activity of the lower limb motor cortex. Nitsche and Paulus [46] found that using a current intensity of 1 mA, changes in corticospinal excitability of the abductor digiti minimi muscle only occurred from 180 s of anodal tDCS. A higher current intensity was used in the

present study (2 mA), which could have reduced the duration needed to obtain changes in cortical excitability [46]. However, it has been shown that anodal tDCS of the hand motor cortex at 1 mA and anodal tDCS of the leg motor cortex at 2 mA produce analogous neural effects [24]. It appears that in order for the current to penetrate deeply enough to affect the leg area, an intensity of 2 mA is required [24]. It is therefore unlikely that the sham tDCS protocol used in the present study (120 s of anodal tDCS at 2 mA) induced any post-effects. Nonetheless, further studies should be conducted to identify the minimum duration required to induce changes in the corticospinal excitability of the leg muscles after anodal tDCS at 2 mA.

## CONCLUSION

Although a single session of anodal tDCS has been shown previously to modify the excitability of neurons in the leg motor area, in the present study it was not found to alter muscle activity patterns during gait in patients with chronic stroke, regardless of their BDNF genotype (Val66Met vs. Val66Val). There is currently no evidence for the use of a single session of anodal tDCS on the leg motor cortex of patients with chronic stroke to alter leg muscle activities during gait and improve the gait pattern. Nevertheless, because the current study only focused on the acute effects of anodal tDCS on gait parameters in individuals with chronic stroke, any potential chronic effects of tDCS (i.e. effects following repeated sessions of anodal tDCS) cannot be ruled out.

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## CONFLICT OF INTEREST STATEMENT

The Authors declare that there is no conflict of interest.

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## FIGURE CAPTIONS

**Figure 1** Timeline of the experimental procedure. tDCS: transcranial direct current stimulation; EMG: electromyography.

**Figure 2** Schematic view of the electrode placements for the transcranial direct current stimulation (A) and the position of the EMG electrodes (B & C). In *A*, the right brain hemisphere is the lesioned hemisphere and the left leg the paretic limb. *B* represents the placement of EMG electrodes. SOL: soleus; GM: gastrocnemius medialis; RF: rectus femoris; TA: tibialis anterior.

**Figure 3** Kinematic and electromyographic signals recorded during gait in the paretic leg of one representative participant during the application of effective anodal transcranial direct current stimulation. The vertical dashed line indicates toe-off. SOL: soleus; GM: gastrocnemius medialis; RF: rectus femoris; TA: tibialis anterior.

**Table 1** Anthropometric and clinical characteristics of the participants

| Participants | Age (years) | Sex | Mass (kg) | Height (cm) | BDNF genotype | Paretic limb | Time SS (years) | Stroke type | Stroke location | Medication | MAS score quadriceps | MAS score triceps surae |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 60 | M | 73 | 174 | Val66Val | L | 6 | ISCH | D&S | AH, AA | 1 | 1+ |
| **2** | 49 | M | 57 | 170 | Val66Met | L | 16 | HEMO | DEEP | AH, CH | 2 | 3 |
| **3** | 72 | M | 80 | 174 | Val66Val | R | 10 | HEMO | D&S | AH, CH | 2 | 3 |
| **4** | 62 | M | 72 | 175 | Val66Met | L | 10 | HEMO | D&S | AH, CH | 1+ | 1 |
| **5** | 50 | M | 50 | 160 | Val66Met | R | 10 | ISCH | DEEP | AH, AA | 2 | 0 |
| **6** | 55 | M | 106 | 176 | Val66Met | R | 10 | ISCH | D&S | AH, CH | 1 | 2 |
| **7** | 56 | M | 70 | 177 | Val66Val | R | 12 | ISCH | DEEP | AH, AA | 1+ | 1 |
| **8** | 57 | M | 72 | 174 | Val66Val | L | 10 | HEMO | DEEP | AH, CH | 1 | 1 |
| **9** | 35 | F | 57 | 163 | Val66Val | L | 33 | ISCH | D&S | AH, AA | 1+ | 3 |
| **10** | 62 | M | 70 | 170 | Val66Met | R | 8 | ISCH | DEEP | AH, AA | 1+ | 2 |
| **11** | 80 | F | 65 | 164 | Val66Met | L | 7 | ISCH | DEEP | AH, AA | 0 | 1 |
| **12** | 68 | M | 84 | 180 | Val66Val | R | 15 | ISCH | DEEP | AH, AA | 3 | 2 |
| **13** | 27 | M | 73 | 184 | Val66Val | R | 11 | HEMO | D&S | AH, CH | 0 | 3 |
| **14** | 65 | M | 66 | 178 | Val66Met | R | 6 | ISCH | D&S | AH, AA | 1+ | 1+ |
| **15** | 61 | M | 82 | 179 | Val66Met | L | 1 | ISCH | DEEP | AH, AA | 0 | 1+ |
| **16** | 57 | M | 62 | 163 | Val66Met | L | 10 | ISCH | D&S | AH, AA | 3 | 3 |
| **17** | 38 | M | 72 | 170 | Val66Val | L | 12 | HEMO | DEEP | AH, CH | 1+ | 2 |
| **18** | 39 | F | 55 | 160 | Val66Val | R | 7 | HEMO | DEEP | AH, CH | 2 | 2 |
| **19** | 76 | F | 62 | 158 | Val66Val | R | 8 | ISCH | SUP | AH, AA | 1+ | 0 |
| **20** | 70 | F | 58 | 152 | Val66Val | L | 11 | ISCH | DEEP | AH, AA | 0 | 1 |
| **21** | 55 | M | 84 | 172 | Val66Val | L | 1 | ISCH | D&S | AH, AA | 0 | 1+ |
| **22** | 68 | M | 102 | 175 | Val66Val | L | 2 | ISCH | DEEP | AH, AA | 1 | 1 |
| **23** | 51 | M | 100 | 173 | Val66Val | L | 25 | ISCH | DEEP | AH, AA | 1+ | 2 |
| **24** | 66 | M | 105 | 193 | Val66Met | R | 2 | ISCH | DEEP | AH, AA | 1 | 1+ |
| **Mean (SD)** | **57 (13)** | **5 F<br>19 M** | **74 (16)** | **171 (9)** | **14 Val66Val<br>10 Val66Met** | **11 R<br>13 L** | **10 (7)** | **17 ISCH<br>7 HEMO** | **14 DEEP<br>1 SUP<br>9 D&S** | | **1.3 (0.8)** | **1.7 (0.8)** |

M: male; F: female; R: right; L: left; BDNF: brain-derived neurotrophic factor; Time SS: time since stroke; ISCH: ischemic; HEMO: hemorrhagic; COMP: complete; D&S: deep and superficial; SUP: superficial; AA: Antiplatelet Agents; AH: Antihypertensive therapy; CH: cholesterol-lowering therapy; MAS: modified Ashworth scale.

**Table 2** Mean (SD) values of kinematic and spatiotemporal gait parameters in the paretic limb of the patients with chronic stroke before (pre), during and immediately after (post) anodal tDCS, and significance levels of the ANOVAs.

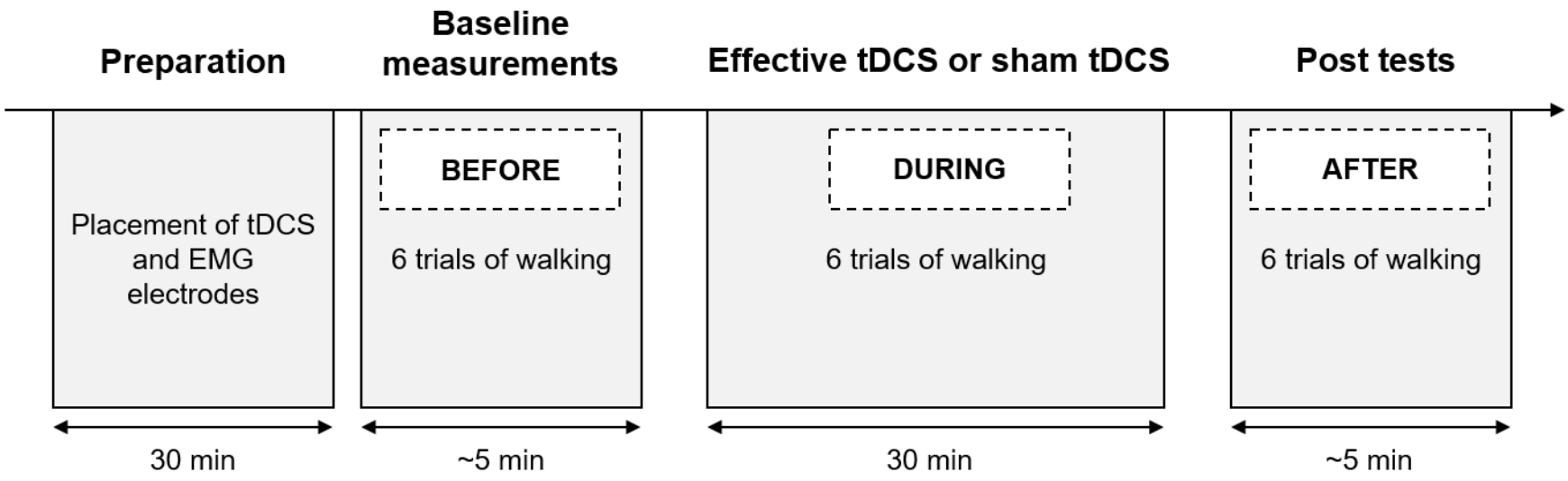
| | **Anodal tDCS** | | | **Sham tDCS** | | | **ANOVA (*p*-value)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Pre** | **During** | **Post** | **Pre** | **During** | **Post** | **S** | **T** | **S x T** |
| **Gait speed, cm.s$^{-1}$** | 81.9 (24.9) | 81.6 (21.9) | 87.2 (26.5) | 82.8 (23.5) | 80.8 (20.9) | 87.0 (26.1) | 0.73 | **<0.001** | 0.66 |
| **Step length, cm** | 52.5 (9.4) | 51.6 (8.5) | 54.5 (9.8) | 53.6 (9.1) | 52.0 (8.0) | 54.0 (9.2) | 0.95 | **<0.001** | 0.18 |
| **Swing phase** | | | | | | | | | |
| Peak knee flexion angle, ° | 42.0 (13.0) | 41.4 (12.8) | 42.6 (13.5) | 41.1 (13.1) | 39.8 (14.7) | 40.8 (13.8) | 0.28 | 0.18 | 0.54 |
| Peak dorsiflexion angle, ° | -1.7 (5.8) | -1.2 (5.4) | -1.9 (5.6) | -1.3 (7.80) | -1.7 (5.6) | -1.6 (5.9) | 0.69 | 0.66 | 0.11 |
| Peak plantar flexion angle, ° | 11.8 (7.3) | 10.9 (6.9) | 12.0 (7.1) | 12.1 (7.0) | 10.7 (5.8) | 11.7 (6.2) | 0.87 | **0.01** | 0.41 |
| ***Stance phase*** | | | | | | | | | |
| Peak knee extension angle, ° | -1.0 (9.0) | -0.2 (9.6) | -1.2 (9.3) | -2.2 (8.2) | -1.7 (8.5) | -2.8 (8.5) | 0.27 | **0.01** | 0.73 |
| Peak dorsiflexion angle, ° | 10.9 (5.7) | 11.0 (5.7) | 10.7 (5.7) | 10.5 (4.9) | 10.6 (4.9) | 10.3 (5.0) | 0.35 | 0.18 | 0.98 |

tDCS: transcranial direct current stimulation. S: factor “Stimulation”; T: factor “Time”; S x T: interaction between the factors “Stimulation” and “Time”.

**Table 3** Mean (SD) intensity and duration of EMG activity during gait in the paretic limb of the patients with chronic stroke before (pre), during and immediately after (post) anodal tDCS, and significance levels of the ANOVAs.

| | Anodal tDCS | | | Sham tDCS | | | ANOVA (*p*-value) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Pre** | **During** | **Post** | **Pre** | **During** | **Post** | **S** | **T** | **S x T** |
| **AUC (a.u.)** | | | | | | | | | |
| Stance phase | | | | | | | | | |
| *RF* | 27.7 (22.0) | 36.0 (23.3) | 41.7 (27.0) | 29.5 (24.5) | 32.9 (22.7) | 42.8 (28.7) | 0.90 | **<0.001** | 0.52 |
| *SOL* | 67.9 (57.3) | 74.4 (59.5) | 71.8 (50.1) | 62.2 (57.2) | 66.0 (47.8) | 76.9 (57.6) | 0.77 | 0.11 | 0.31 |
| *GM* | 50.7 (45.1) | 53.2 (41.0) | 54.2 (40.5) | 55.6 (51.3) | 52.9 (41.4) | 58.9 (46.4) | 0.60 | 0.47 | 0.81 |
| *TA* | 36.7 (35.0) | 40.4 (25.9) | 36.7 (29.0) | 37.0 (36.5) | 43.5 (34.3) | 39.2 (33.6) | 0.63 | 0.37 | 0.87 |
| Swing phase | | | | | | | | | |
| *RF* | 9.2 (11.3) | 10.2 (11.2) | 10.7 (10.4) | 10.1 (14.3) | 9.9 (10.0) | 10.1 (9.5) | 0.94 | 0.13 | 0.10 |
| *SOL* | 13.9 (20.9) | 15.6 (20.9) | 16.1 (18.5) | 13.2 (14.7) | 15.6 (16.3) | 16.4 (17.8) | 0.79 | **0.03** | 0.82 |
| *GM* | 15.4 (26.3) | 16.8 (26.2) | 16.16 (22.7) | 14.2 (19.1) | 14.9 (18.6) | 14.0 (18.8) | 0.56 | 0.63 | 0.97 |
| *TA* | 31.7 (41.6) | 32.6 (37.3) | 30.4 (38.3) | 24.4 (29.6) | 26.3 (29.0) | 25.9 (30.5) | 0.26 | 0.68 | 0.80 |
| **Duration (%)** | | | | | | | | | |
| Stance phase | | | | | | | | | |
| *RF* | 57.2 (30.8) | 61.5 (28.4) | 63.3 (25.4) | 56.0 (31.9) | 61.6 (29.4) | 63.1 (29.0) | 0.89 | **<0.01** | 0.93 |
| *SOL* | 83.2 (10.8) | 84.1 (10.2) | 82.8 (18.9) | 79.7 (19.2) | 80.0 (18.9) | 83.0 (16.8) | 0.33 | 0.48 | 0.25 |
| *GM* | 70.9 (20.8) | 71.3 (17.7) | 72.2 (18.1) | 71.9 (17.0) | 71.8 (18.2) | 76.5 (14.3) | 0.69 | 0.06 | 0.30 |
| *TA* | 58.0 (24.5) | 63.9 (22.4) | 58.3 (21.7) | 57.1 (26.9) | 64.2 (22.9) | 65.8 (21.9) | 0.61 | **0.04** | 0.16 |
| Swing phase | | | | | | | | | |
| *RF* | 33.8 (26.4) | 41.4 (25.8) | 39.0 (21.8) | 37.3 (28.8) | 42.2 (27.2) | 39.9 (27.0) | 0.78 | **<0.01** | 0.71 |
| *SOL* | 38.1 (27.9) | 40.8 (28.4) | 42.9 (26.8) | 38.7 (28.6) | 40.8 (29.1) | 42.2 (28.4) | 0.89 | 0.06 | 0.90 |
| *GM* | 34.4 (24.2) | 34.7 (23.0) | 34.7 (21.9) | 39.1 (23.7) | 40.3 (23.5) | 37.9 (23.1) | 0.28 | 0.73 | 0.60 |
| *TA* | 73.7 (27.3) | 77.6 (22.6) | 76.3 (25.3) | 72.5 (22.7) | 77.1 (21.4) | 75.4 (22.0) | 0.70 | 0.38 | 0.87 |

tDCS: transcranial direct current stimulation; AUC: area under the curve; RF: rectus femoris; SOL: soleus; GM: gastrocnemius medialis; TA: tibialis anterior. S: factor "Stimulation"; T: factor "Time"; S x T: interaction between the factors "Stimulation" and "Time".


Preparation
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Post tests
Placement of tDCS and EMG electrodes
BEFORE
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DURING
6 trials of walking
AFTER
6 trials of walking
30 min
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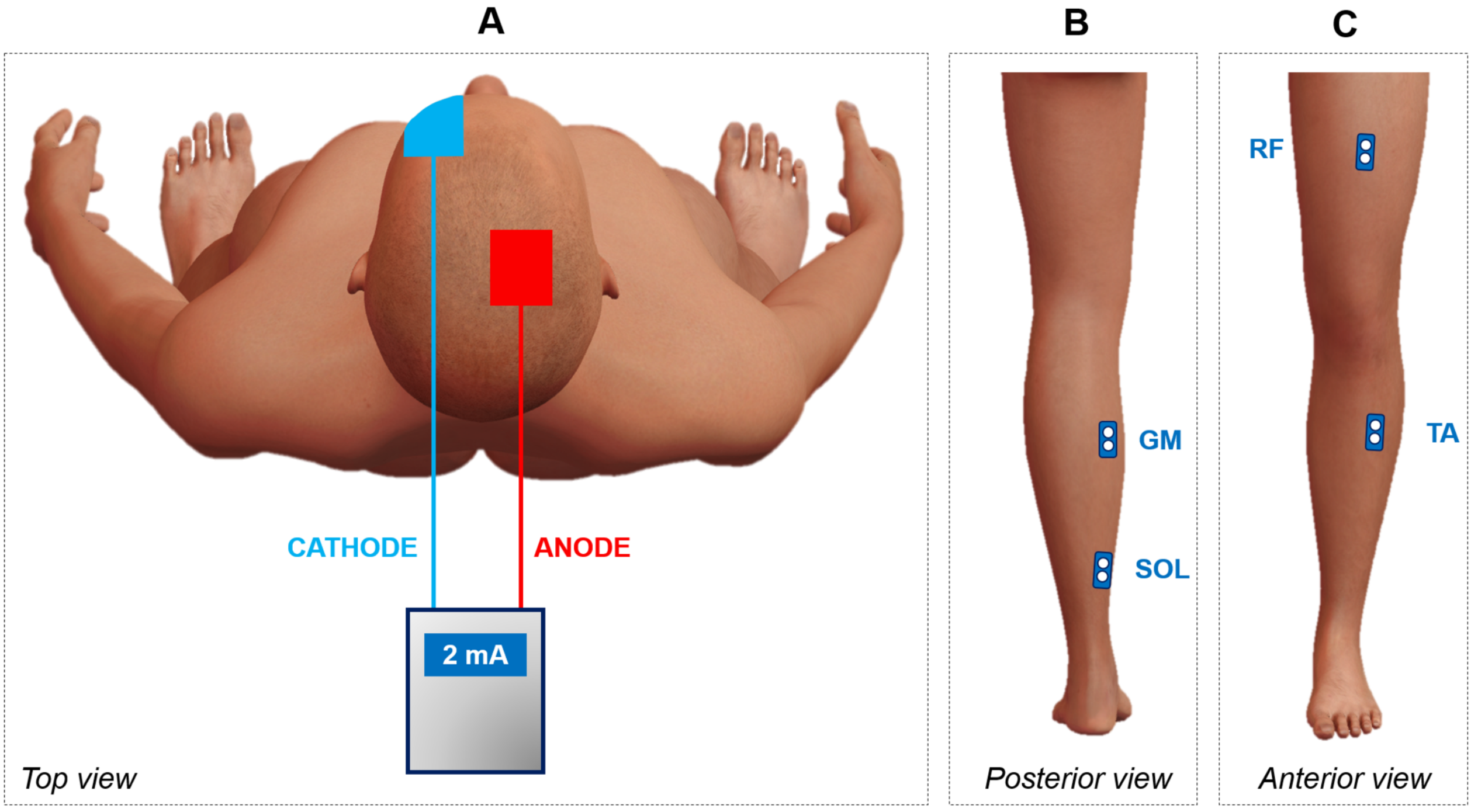
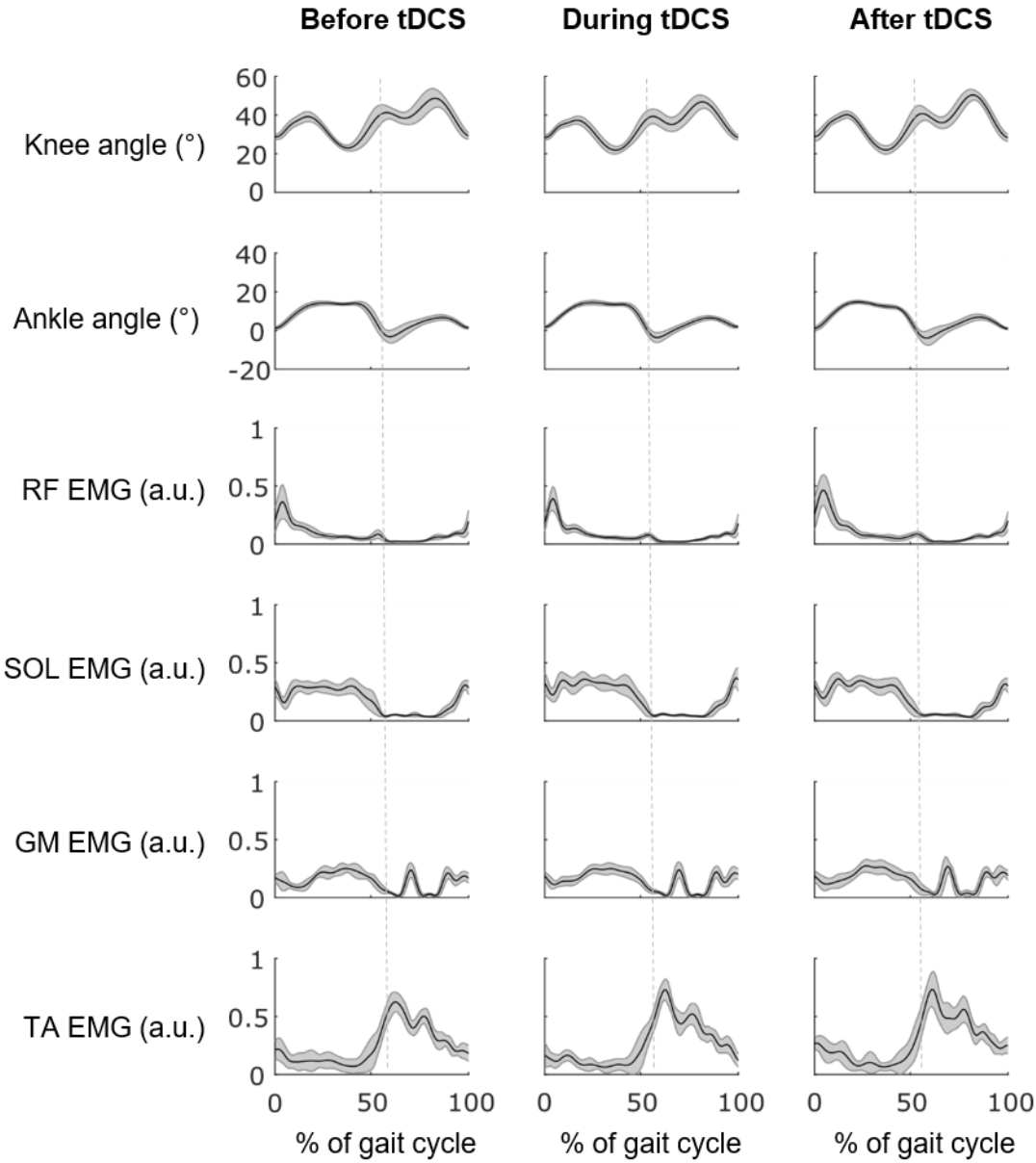
30 min
~5 min


A
B
C
CATHODE
ANODE
2 mA
Top view
GM
SOL
Posterior view
RF
TA
Anterior view


Before tDCS
During tDCS
After tDCS
Knee angle (°)
Ankle angle (°)
RF EMG (a.u.)
SOL EMG (a.u.)
GM EMG (a.u.)
TA EMG (a.u.)
60
40
20
0
40
20
0
-20
1
0.5
0
0
50
100
% of gait cycle