Original Article

Determining the safety, feasibility, and effects of anodal transcranial direct current stimulation on corticospinal excitability and quadriceps performance after anterior cruciate ligament reconstruction: a randomized crossover design

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Background: Alterations in corticospinal excitability (CSE) to the quadriceps persist after anterior cruciate ligament reconstruction (ACLR). Centrally targeted interventions, such as transcranial direct current stimulation (tDCS), may be necessary to increase CSE and quadriceps muscle strength. The purpose of this study was to determine (I) the feasibility and safety of a single session of tDCS and (II) the effects of a single session of tDCS on CSE and quadriceps muscle performance in participants after ACLR.

Methods: This was a randomized crossover design of a single session of active *vs.* sham tDCS, including 20 participants (nine male) 4–6 months post-ACLR. Surgical limb quadriceps performance [peak torque normalized to body mass, rate of torque development from onset to 100 ms (RTD100), and RTD from 100 to 200 ms (RTD200)] and CSE [active motor threshold (AMT) and slope of a stimulus-response curve (SLOPE)] were measured using an isokinetic dynamometer and transcranial magnetic stimulation (TMS), respectively. Anodal tDCS (a-tDCS) was delivered over the primary motor cortex while the participant rode a stationary bike for 20 minutes. Adverse events were collected after each tDCS session. Repeated measures 2×2 analyses of variance (ANOVAs) were used to test the effect of condition and time on CSE and quadriceps performance.

Results: There were no adverse events reported and no participant drop out. There was no significant condition by time interactions for CSE ($P \geq 0.17$) or quadriceps performance ($P \geq 0.53$). There was a significant main effect of time for RTD200 ($P=0.02$) with decreased RTD200 post-intervention regardless of condition.

Conclusions: TDCS is safe and feasible for participants recovering from ACLR. There were no acute effects of a single session of a-tDCS on CSE and quadriceps performance measures. Multiple sessions of tDCS and/or tDCS during other tasks (e.g., during isolated quadriceps exercises) may lead to improved CSE and quadriceps performance.

Trial Registration: ClinicalTrials.gov ID: NCT04504344.

Keywords: Anterior cruciate ligament reconstruction (ACLR); transcranial direct current stimulation (tDCS); corticospinal excitability (CSE)

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Introduction

Quadriceps muscle dysfunction persists for years after anterior cruciate ligament reconstruction (ACLR), despite the advances in surgery and the development of post-operative rehabilitation protocols (1). This indicates that traditional methods of strengthening do not fully restore quadriceps muscle function, even after months of rehabilitation. Emerging evidence indicates that altered corticospinal excitability (CSE) is present early after ACLR and does not change during rehabilitation (2-5). Additionally, alterations in CSE to the quadriceps are present years after ACLR (6-11). Thus, altered CSE may serve as a mechanism by which quadriceps muscle dysfunction persists after ACLR. Interventions known to modulate CSE and increase muscle strength, such as transcranial direct current stimulation (tDCS) (12,13), have the potential to address alterations in CSE that traditional methods of strengthening may not address.

Only one study to our knowledge has investigated the effect of tDCS on quadriceps muscle performance. Rush *et al.* found no effects of one session of active tDCS compared to sham tDCS in 10 participants after ACLR (mean, 39 months) (14). An obvious limitation of this study was the small sample size, long mean time from ACLR, and no evaluation of CSE. A recent meta-analysis examining the acute effects of tDCS on muscle strength found a small effect of increased strength in healthy participants. Additionally, a separate meta-analysis indicates that tDCS is effective in increasing CSE in healthy participants. The two aforementioned meta-analyses taken together indicate that tDCS has the potential to improve quadriceps muscle strength and performance via increasing CSE in patients after ACLR. Therefore, the purposes of this study were to determine (I) the feasibility and safety of a single session of tDCS and (II) the effects of a single session of active *vs.* sham tDCS during stationary bike riding on quadriceps muscle performance and CSE in individuals 4 to 6 months after ACLR. We hypothesized that the intervention would be feasible and safe. Additionally, we hypothesized that quadriceps muscle performance and CSE would increase more following active tDCS than sham tDCS. TDCS was paired with stationary bike riding for the following three reasons: (I) tDCS is more effective when paired with a task that involves activation of the muscle of interest; (II) stationary bike riding is safe to perform early after ACLR (i.e., minimizes stress to the graft); and (III) stationary bike riding is commonly performed during post-operative rehabilitation. We present this article in accordance with the CONSORT reporting checklist (available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-15/rc).

Highlight box

Key findings

- Anodal transcranial direct current stimulation (a-tDCS) is a safe and feasible intervention for individuals after anterior cruciate ligament reconstruction (ACLR).

What is known and what is new?

- Prior evidence indicates that tDCS increases corticospinal excitability and improves muscle performance in healthy control participants. This study provides evidence that a single session of tDCS is feasible and safe for patients recovering from ACLR. To our knowledge, only one other published study has examined the effects of tDCS in individuals after ACLR.

What is the implication and what should change now?

- Future work will determine the effectiveness of multiple sessions of tDCS in patients recovering from ACLR. Additionally, future studies will examine tDCS administered during different tasks (e.g., isolated quadriceps exercises rather than stationary bike riding).

Methods

Design

A randomized cross-over design examining the effectiveness of a single session of tDCS to increase CSE and quadriceps muscle performance was used. Using an online random number generator, participants were randomly assigned to first receive either active anodal tDCS (a-tDCS) or sham tDCS. All participants were blinded to the intervention (i.e., active *vs.* sham a-tDCS). The primary author conducted all testing sessions and was blinded to the treatment condition. Research assistants determined group assignments. Participants received the second condition 7 to 10 days after the first session to minimize carry over effects (15). Both sessions were performed at the same time of day to control for diurnal variation and participants were asked to refrain from exercising 1 day prior to testing. Quadriceps muscle performance and CSE were measured pre- and post-a-tDCS at each session.

Subjects

Twenty participants within 4–6 months from primary ACLR were recruited from the community. The CONSORT

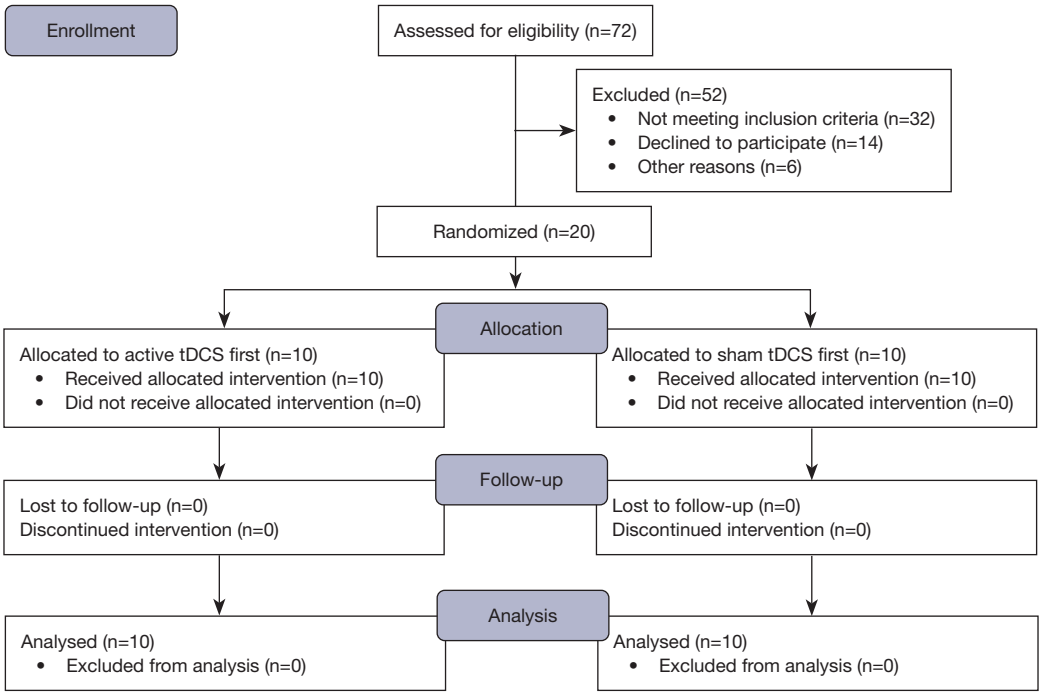

Figure 1 CONSORT 2010 flow diagram. tDCS, transcranial direct current stimulation.

flow diagram describes our recruitment process in more detail (*Figure 1*). Participants were between the ages of 18 and 42. Exclusion criteria included: (I) multiple ligament reconstruction; (II) osteo-chondral procedures; (III) any previous lower extremity surgery; and (IV) previous ACL injury. Metal or implants in the head or neck, history of neurological disease, seizures, severe migraines, and concussion within the last 6 months are transcranial magnetic stimulation (TMS)-specific exclusion criteria. All participants achieved a "quiet knee" prior to testing (i.e., demonstrated full knee range of motion, minimal/no effusion, and were walking without a visible gait deviation). All participants completed our consent form, and this study was approved by Arcadia University's Institutional Review Board (IRB) (No. 2123524-2). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All testing procedures were administered at the primary author's institution between November 2020 and November 2022.

Quadriceps strength and rate of torque development (RTD) testing

Participants were seated on an isokinetic dynamometer (HUMAC NORM, CSMi, Stoughton, MA, USA) with hips flexed to 90° and the knee flexed to 60°. Three submaximal isometric contractions were performed to warm up, followed by three maximal voluntary isometric contractions (MVICs). Participants were instructed to kick out into the shank pad of the dynamometer as hard and as fast as they can for five seconds. Maximal verbal encouragement and visual feedback of the time-torque curve were provided to ensure maximal effort during each MVIC. Peak isometric torque was normalized to body weight. RTD was defined as the RTD from onset to 100 ms (RTD_{100}) and RTD from 100 to 200 ms (RTD_{200}) as described in previous studies (16,17). The average slope of three MVICs were used for analysis.

CSE testing via TMS

Electromyography (EMG) data was collected using an MA-300 system (Motion Lab Systems, Baton Rouge, LA, USA) sampled at 5000 Hz. Surface EMG electrodes (bar shaped double differential preamplifiers) were placed over the muscle bellies of the vastus medialis bilaterally per Seniam placement recommendations (18). Skin preparation (shaved if hair present, isopropyl alcohol to clean/abrade the skin) preceded electrode placement. Wraps were used to stabilize

the electrodes and improve electrode to skin contact. All data were acquired through Signal Software (Cambridge Electronic Design Limited, Cambridge, UK).

Excitability of the corticospinal tract using TMS (Magstim bistim, Magstim®, West Wales, UK), was examined with the participant seated on the isokinetic dynamometer and actively contracting their quadriceps muscle to 5% of their maximal isometric contraction. First, the vertex of the skull was identified by measuring the distance from the inion to the nasion and the distance from the tragus of each ear. The point where the two lines intersect is the vertex of the skull. This location was used as a starting point to locate the hot spot which is defined as the location of the coil where TMS elicits the greatest EMG response to the vastus medialis. Once the hot spot was identified, it was be marked with a washable ink, and all subsequent TMS measurements were elicited from this location.

Single pulse TMS was used to quantify two measures of CSE. First, the active motor threshold (AMT) was determined for each participant. The AMT is defined as the lowest magnetic stimulator output needed to elicit a response of at least 100 µV in at least 5 of 10 consecutive trials while the participant maintained a quadriceps torque at 5% of their MVIC via visual feedback from the isokinetic dynamometer. Second, stimulus-response (SR) curves were generated for each task. The stimulator intensity level for the SR curves was based on the individuals AMT. Pulses were elicited from 90–140% of the AMT. Each participant received six pulses in 10% increments from 90–140%. The average peak-to-peak amplitude of each motor evoked potential (MEP) elicited at a given percentage of AMT were plotted as a SR curve. Using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), a linear function was applied to the data and the slope of the SR curve (SLOPE) served as the second measure of CSE.

a-tDCS

a-tDCS (Soterix 1×1, Soterix Medical Inc., New York, NY, USA) was delivered over the primary motor cortex contralateral to the surgical limb (i.e., hot spot for the vastus medialis muscle representation found during TMS testing). A pair of carbon electrodes placed in saline-soaked sponges (surface area: 5×7 cm^2) were secured to the scalp using straps (Soterix EASYstrap, Soterix Medical Inc.). The anode was centered over the hotspot while the cathode will be placed on the opposite supraorbital area. a-tDCS was administered while the participant rode a stationary bike for 20 minutes. The bike seat was adjusted for each participant so that maximal knee flexion range of motion was 90°. Participants were also instructed to maintain a neutral ankle angle. Stationary bike riding was chosen as this task is commonly performed early after ACLR with minimal stress to the healing graft and requires quadriceps activity. The first 5 minutes served as a warmup with the patient maintaining a rate of perceived exertion (RPE) of light or 1 out of 10. Over the next 10 minutes, the resistance was increased to maintain a RPE of moderate or 3/10. The last 5 minutes served as a cool down at the same intensity/resistance as the warmup. Active a-tDCS was applied at an intensity of 2 mA with a 30-second ramp-up and 30-second ramp-down for the entire duration of bike riding, while the sham a-tDCS was be applied for the first 30 seconds and last 30 seconds of bike riding.

Feasibility and safety

To assess safety we used the tDCS Adverse Events Questionnaire (19,20) following the active and sham tDCS sessions. All participants were asked "Do you experience any of the following symptoms or side effects (headache, neck pain, scalp pain, tingling, burning, itching sensation, skin redness, sleepiness, trouble concentrating, acute mood changes, vision changes, discomfort during the session, other symptoms)?" If they experienced any of these symptoms, then the participants were asked to rate the symptom as mild, moderate, or severe. They were also asked, "Is this symptom related to tDCS?" with the following potential responses (no, remote, possible, probable, definite). Feasibility was determined by assessing the number of participants that completed both the active and sham tDCS sessions.

Statistical analysis

For purpose 1, descriptive statistics were used to describe safety and feasibility. For purpose 2, repeated measures analyses of variance (2×2) were used to test the effect of condition (active a-tDCS *vs.* sham a-tDCS) and time (pre-*vs.* post-intervention) on CSE (AMT and SLOPE) and quadriceps performance (peak isometric torque and RTD) for the surgical limb using SPSS v24 (IBM Corp., Armonk, NY, USA).

G*Power (version 3.1.9.2, Universität Kiel, Kiel, Germany) was used to compute the required sample size of 20 participants. Previous studies examining CSE,

Table 1 Demographics (n=20)

Measures	Values
Age (years)	23.9±6.3
Body mass index (kg/m^2)	24.3±3.3
Months from ACLR to first testing session	5.4±1.1
Graft type	
BPTB	14 [70]
HS	2 [10]
Quad	1 [5]
Allograft	3 [15]
Activity level	
Level I	13 [65]
Level II	7 [35]

Values are presented as mean ± SD or n [%]. ACLR, anterior cruciate ligament reconstruction; BPTB, bone-patellar tendon-bone autograft; HS, hamstring autograft; Quad, quadriceps tendon autograft; SD, standard deviation.

Table 2 Adverse events and severity of symptoms

Symptoms	Number of participants	Severity
Headache	2	All mild
Neck pain	0	–
Scalp pain	1	All mild
Tingling	1	All mild
Itching	1	All mild
Burning sensation	0	–
Skin redness	1	All mild
Sleepiness	7	All mild
Trouble concentrating	0	–
Acute mood changes	0	–
Other	0	–

specifically motor threshold, reported medium to large effect sizes (d=0.53–1.39) when examining differences between individuals after ACLR and control participants (2-4). In an a priori power analysis, we used a medium-large effect size of 0.7 (d), a power of 0.80, α=0.05, and a correlation among repeated measures of 0.5 to ensure we will have an adequate sample size.

Table 3 CSE results

Measures	Mean ± SD	P value	
		Interaction	ME time
AMT (% MSO)		0.17	0.94
Pre-active tDCS	44.8±10.9		
Post-active tDCS	45.3±11.7		
Pre-sham tDCS	44.6±12.3		
Post-sham tDCS	44.0±11.9		
SLOPE (mV·MSO^{-1})		0.64	0.42
Pre-active tDCS	0.052±0.036		
Post-active tDCS	0.047±0.040		
Pre-sham tDCS	0.057±0.053		
Post-sham tDCS	0.056±0.054		

CSE, corticospinal excitability; SD, standard deviation; ME, main effect; AMT, active motor threshold; MSO, maximal stimulator output; tDCS, transcranial direct current stimulation; SLOPE, slope of the stimulus-response curve.

Results

Demographics

Twenty subjects with ACLR (11 female, 9 male) completed both testing sessions. *Table 1* lists the means and standard deviations for age, BMI, time from surgery to testing, and graft type distribution.

Feasibility and safety

Table 2 lists the number of participants who experienced each adverse event and the severity of each symptom. Sleepiness was the most commonly reported symptom (35%), followed by headache (10%), scalp pain (5%), tingling (5%), itching (5%), and skin redness (5%). All reported symptoms were rated as mild and completely resolved within hours after the treatment session. In terms of feasibility, all participants completed both tDCS sessions and both testing sessions (i.e., 100% retention).

CSE and quadriceps performance

There was no significant condition by time interactions for AMT (P=0.17) or SLOPE (P=0.64) (*Table 3*) and no significant main effects of time for AMT (P=0.94) or

Table 4 Quadriceps performance results

Measures	Mean ± SD	P value	
		Interaction	ME time
Peak torque (Nm/kg)		0.69	0.08
Pre-active tDCS	1.92±0.80		
Post-active tDCS	1.83±0.84		
Pre-sham tDCS	1.97±0.99		
Post-sham tDCS	1.92±0.99		
RTD_{100} (Nm/s)		0.65	0.72
Pre-active tDCS	387±244		
Post-active tDCS	369±199		
Pre-sham tDCS	365±187		
Post-sham tDCS	367±209		
RTD_{200} (Nm/s)		0.53	0.02*
Pre-active tDCS	227±125		
Post-active tDCS	198±128		
Pre-sham tDCS	224±124		
Post-sham tDCS	176±104		

*, P value <0.05. SD, standard deviation; ME, main effect; tDCS, transcranial direct current stimulation; RTD_{100}, rate of torque development from onset to 100 ms; RTD_{200}, rate of torque development from 100 to 200 ms.

SLOPE (P=0.42). There was no significant condition by time interactions for all quadriceps performance measures (P≥0.53) (*Table 4*). There was a significant main effect of time for RTD_{200} (P=0.02). Regardless of the condition, RTD_{200} decreased from pre- to post-intervention.

Discussion

The aim of this study was to examine safety, feasibility, and the short-term effects of a-tDCS on CSE to the vastus medialis and quadriceps muscle performance measures. In support of our hypotheses, a-tDCS was safe and feasible for individuals 4–6 months from ACLR. Contrary to our hypotheses there were no significant condition by time interactions for CSE or quadriceps muscle performance. This indicates that one session of active a-tDCS applied during stationary bike riding did not significantly change CSE or quadriceps muscle performance. There was a main effect of time for RTD_{200} with RTD_{200} decreased at the post-intervention time point regardless of whether the intervention included active or sham tDCS. Our results suggest that an application of a-tDCS to stationary bike riding does not have an acute effect on CSE or quadriceps muscle performance.

The lack of changes in quadriceps strength and CSE from this study may be due to a single session of tDCS being insufficient to produce measurable effects. Additionally, our null findings may in part be due to the task selected during a-tDCS application. We chose stationary bike riding because stationary bike riding is commonly performed early after ACLR, involves high activation of the quadriceps muscle group, and causes minimal stress on the healing graft. However, stationary bike riding involves activation of multiple lower extremity muscle groups. It is possible that interference from the activation of multiple muscle groups during our chosen task led to the lack of changes in quadriceps strength and CSE. Finally, fatigue from 20 minutes of stationary bike riding could have masked the effects of tDCS in this study. Future research should investigate the effect of multiple sessions of tDCS during various tasks (i.e., isolated quadriceps exercises and multijoint exercises such as stationary bike riding and/or closed kinetic chain exercises).

To our knowledge, only one other study has investigated the acute effects of a-tDCS on quadriceps muscle performance in patients after ACLR. Rush *et al.* examined the effects of active *vs.* sham tDCS in 10 patients at a mean of 39 months from ACLR. Like our current study's findings, there were no significant differences in quadriceps muscle performance after one session of active a-tDCS compared to sham tDCS. Interestingly the authors found a decrease in quadriceps isometric strength and quadriceps activation regardless of tDCS condition which is similar to our current study's finding of a decreased in RTD_{200}. A key methodological difference between our study and the study conducted by Rush *et al.* is the task used during tDCS application. We selected stationary bike riding as a common activity performed during ACLR rehabilitation and a quadriceps dominant task; however, neither walking nor bike riding are isolated quadriceps activities and the null findings from a single session in both our study and the previous may in part be due to the task selection. This study administered the tDCS during 20 minutes of treadmill walking. It is possible that the task in both studies (i.e., 20 minutes of walking and 20 minutes of biking riding) led to acute decreases in muscle performance regardless of the tDCS condition.

A recent systematic review and meta-analyses

investigated the effects of a single dose of tDCS to improve muscle strength in healthy men and women (12). The analysis found a small effect size for maximal voluntary isometric strength between one session of active tDCS and one session of sham tDCS. Three individual studies from the analysis indicate that one session of a-tDCS can lead to increases in shoulder internal and external rotation, knee extension, and lower extremity pinch strength (21-23). All three studies provided a similar protocol to the current study's protocol (i.e., a-tDCS to M_1 at 2 mA *vs.* sham) with one difference. All three studies from the systematic review administered a-tDCS at rest compared to the current study which administered tDCS during stationary bike riding. While active muscle contraction paired with tDCS leads to better improvements in muscle performance, the current study's use of a stationary bike may have led to muscle fatigue and thus no significant changes in muscle performance. The fact that RTD_{200} decreased regardless of the condition (active *vs.* sham) supports the premise that fatigue may have affected our results; however, no other deficits in quadriceps muscle performance were found.

Another study, not included in the aforementioned systematic review examined changes in quadriceps muscle strength (i.e., peak torque) in response to a-tDCS administered during rest and during a low-level quadriceps matching task (24). Both groups (rest *vs.* matching task) underwent an active tDCS session and a sham tDCS session. Participants in the matching task tDCS group demonstrated increased quadriceps peak torque and relative MVIC compared to the rest group after sham subtraction. The matching task consisted of low-level quadriceps contractions (5% of MVIC) that lasted for 5 seconds with a 20-second rest time. Overall, the participants completed 24 contractions during the application of tDCS. The task in the aforementioned study differed from our current study's task of stationary bike riding. The overall amount of quadriceps muscle activation was likely greater during 20 minutes of bike riding. Additionally, stationary bike riding involves activation of additional muscles (knee flexors and ankle plantarflexors). Activation of multiple muscle groups may have led to interference effects. Additional studies are needed to determine the optimal task, muscle contraction type, and dosage of muscle activation needed to promote the effects of tDCS on quadriceps muscle performance.

Another recent systematic review and meta-analysis examined the effects of a-tDCS on CSE in healthy participants (13). A total of 73 studies included in the meta-analysis examined the effects of a-tDCS on excitability to muscles in the upper extremity (e.g., abductor digiti minimi, first dorsal interosseous). Results from this analysis indicate that a-tDCS is effective in increasing CSE, specifically MEP amplitudes. Additionally, the increases in CSE were also found in the muscle ipsilateral to the stimulation. This review did not include any studies that examined the effects of a-tDCS on CSE of lower extremity muscles. Therefore, it is difficult to compare our findings to the results of this analysis as CSE to lower extremity muscles may be affected differently by a-tDCS. It is also important to note that the meta-analysis included studies with varying number of tDCS sessions and the primary measure of CSE was MEP amplitude. Our study only examined the effects of a single session of tDCS and used two different measures of CSE (AMT and SLOPE). More research is needed to determine the effects of tDCS on multiple measures of CSE to lower extremity muscles.

This study is not without limitations. First, we did not control for graft type. The majority (70%) of our cohort underwent ACLR with a bone-patellar tendon-bone (BPTB) autograft. While quadriceps impairments are present regardless of graft type, greater quadriceps impairments are present after BPTB autografts (25). Second, we did not examine EMG during the intervention. Doing so would have allowed us to determine if and how active *vs.* sham tDCS altered quadriceps activity during the bike riding activity. Future studies should include EMG analysis during the administration of tDCS to better elucidate the mechanisms underlying tDCS and determine if neuromuscular fatigue was produced by the task. Finally, all participants were recruited between 4 and 6 months after ACLR. It is possible that one session of tDCS administered earlier after ACLR would show different results.

Conclusions

In conclusion, a-tDCS is safe and feasibility for individuals recovering from ACLR. Additionally, there were no changes in quadriceps muscle performance or CSE after one session of active tDCS compared to sham tDCS. Future research should determine the effectiveness of multiple session of tDCS after ACLR. In addition, evidence suggests that tDCS is task/activity dependent. Therefore, future studies should also examine the effectiveness of different quadriceps tasks paired with tDCS including isolated quadriceps exercises (i.e., open kinetic chain knee extension).

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-15/rc

Trial Protocol: Available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-15/tp

Data Sharing Statement: Available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-15/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aoj.amegroups.com/article/view/10.21037/aoj-24-15/coif). S.H. is a consultant with Arthrex, Inc. and uses their devices during ACLR surgery. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Arcadia University's Institutional Review Board (IRB) (No. 2123524-2) and all participants provided consent to participate.

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