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Anodal transcranial direct current stimulation (tDCS) modulates quadriceps motor cortex inhibition and facilitation during rehabilitation following anterior cruciate ligament (ACL) reconstruction: a triple-blind, randomised controlled proof of concept trial

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ABSTRACT

Objectives Following anterior cruciate ligament reconstruction (ACLR), maladaptive changes occur in the motor cortex representation of the quadriceps, evidenced by increases in intracortical inhibition and facilitation. The primary objective of this proof-of-concept study was to determine if anodal transcranial direct current stimulation (tDCS) can alter quadriceps intracortical inhibition and facilitation in an early-ACLR population after 6 weeks of application during exercise.

Methods We performed a randomised, triple-blind controlled trial for proof of concept comparing anodal-tDCS to sham-tDCS following ACLR. Anodal-tDCS or sham-tDCS was delivered to the primary motor cortex for 20 min, three times per week, for 6 weeks from week 2 post ACLR. Transcranial magnetic stimulation quantified quadriceps short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI) and short-interval intracortical facilitation (SICF). Significance at $p<0.05$.

Results Participants were randomised to anodal (n=11) or sham (n=10) tDCS. Participants were predominantly male (n=13) and had a mean (SD) age of 24.4 (4.7) years. For SICI, there was a group-by-time effect for anodal-tDCS (β=0.519, 95% CI 0.057 to 0.981, p=0.028) and an effect for time (β=−1.421, 95% CI −1.919 to −0.923, p<0.001). For LICI, there was no group-by-time (β=−0.217, 95% CI −0.916 to 0.482, p=0.543) or time effect (β=0.039, 95% CI −0.815 to −0.893, p=0.928). For SICF, there was a group-by-time effect for anodal-tDCS (β=−0.764, 95%CI −1.407 to −0.120, p=0.020) but not time (β=0.504, 95% CI −0.627 to 1.635, p=0.383).

Conclusion This study provided proof of the efficacy of anodal-tDCS post ACLR in reducing maladaptive quadriceps inhibition and facilitation. We demonstrated anodal-tDCS improved facilitation and inhibition post ACLR, which are drivers of arthrogenic muscle inhibition.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immediately following anterior cruciate ligament reconstruction (ACLR), maladaptive changes occur in the primary motor cortex representation of the quadriceps, evidenced by increases in intracortical inhibition and facilitation.

WHAT THIS STUDY ADDS

⇒ This study provides proof of concept for the efficacy of anodal-transcranial direct current stimulation (tDCS) post ACLR. Our data shows that anodal-tDCS improved quadriceps facilitation and inhibition post ACLR.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Anodal-tDCS may be a useful adjunct to existing exercise rehabilitative practices, effectively improving primary motor cortex dysfunction, which may improve quadriceps and hamstring muscle function long term.

INTRODUCTION

Anterior cruciate ligament (ACL) injuries are a substantial problem, being the knee injury with the highest time-loss burden in athletic populations.[1] ACL reconstruction (ACLR) is a common intervention for people with ACL injury, with over 75% of ACL injuries progressing to surgery.[2] Thus, it is unsurprising that ACL injuries predispose athletes to knee osteoarthritis (OA) and are associated with a growing economic burden.[3]

Following ACLR, exercise-based rehabilitation is the best practice intervention to optimise function and return to sport.[4] However, even with exercise rehabilitation,

people with ACLR struggle to regain quadriceps strength and voluntary activation.[5] Deficits in quadriceps strength play a significant role in the ongoing dysfunction following ACLR and OA progression.[6 7] In people with ACLR, a recent meta-analysis assessing voluntary activation deficits demonstrated a large effect size (standardised mean difference=−0.84) for reduced quadriceps voluntary activation in ACLR populations versus controls.[5] This effect is almost identical to that reported in a meta-analysis of people with knee OA.[8]

These deficits in muscle activation are likely a result of arthrogenic muscle inhibition, or AMI, which has been shown to lead to poorer athlete outcomes.[9] Specifically, if an athlete cannot sufficiently contract and activate a muscle, it is harder to provide that muscle with sufficient loading to result in physiological adaptation.[10] One of the major drivers of AMI is dysfunction of the primary motor cortex.[11] Available evidence suggests that changes in cortical excitability are likely to persist and drive continued weakness following ACLR.[12]

Changes in corticospinal tract (primary motor cortex (M1) and the main efferent pathway to the muscle) function are assumed to be a contributor to reduced voluntary activation following ACLR.[12] As an example, more primary motor cortex inhibition is associated with larger deficits in voluntary quadriceps activation in people who have completed ACLR rehabilitation.[13] Increased inhibition of the primary motor cortex, associated with decreased quadriceps strength, has also been demonstrated in the early stages following ACLR.[14] Further, in people with experimentally induced muscle pain, immediate increases in intracortical facilitation occur, followed by increases in intracortical inhibition.[15] Even in people with persistent lower-limb joint pain, higher levels of facilitation are associated with higher pain levels.[16] Following ACLR, there are significant increases in inhibition and facilitation as early as 2 weeks post surgically.[17] Thus, following joint injury, increases in intracortical facilitation and inhibition are maladaptive changes. If altered primary motor cortex function following ACLR underpins reduced quadriceps activation, interventions to reduce primary motor cortex inhibition could improve functional outcomes. Interventions directly targeting primary motor cortex function are not typically used in traditional rehabilitation programmes.[18]

One intervention that has been shown to alter primary motor cortex excitability is non-invasive brain stimulation.[19] Transcranial direct current stimulation (tDCS) is one type of non-invasive brain stimulation. Depending on stimulation parameters in healthy populations, tDCS can bidirectionally alter primary motor cortex excitability (eg, increase or decrease excitability).[20] Anodal-tDCS has been shown to increase primary motor cortex excitability[21] and improve strength and motor control in various populations.[22 23] tDCS has also improved patient-reported outcomes in clinical populations, such as knee OA.[24]

Objective

The primary objective of this proof-of-concept study was to determine if anodal-tDCS can alter quadriceps intracortical inhibition and facilitation in an ACLR population after 6 weeks of application during exercise (from week 2 post ACLR). Our secondary objectives included the evaluation of whether anodal-tDCS can alter quadriceps maximal voluntary isometric contraction (MVIC) and hamstring intracortical inhibition and intracortical facilitation in an ACLR population after 6 weeks of application during exercise (from week 2 post ACLR).

METHODS

Study design

We performed a triple-blind, randomised, controlled proof of concept trial between October 2022 and February 2024 to determine the effect of anodal-tDCS on primary motor cortex excitability (assessed by transcranial magnetic stimulation, TMS).

Study protocol

Our protocol was registered prospectively on the Australian New Zealand Clinical Trials Registry (Registration Identification: ACTRN12622000183785). Our study was reported in accordance with the Consolidated Standards of Reporting Trials 2010 checklist.

Participants

We included people between 18–60 years of age with an acute ACL rupture requiring surgical reconstruction. We included participants who have suffered a non-contact, primary ACL rupture during type one (very strenuous activities like jumping or pivoting as in basketball or soccer) or two (strenuous activities like heavy physical work, skiing or tennis) physical activity, using the International Knee Documentation Committee (IKDC) classification system. We only included participants who had received an ipsilateral hamstring tendon ACL graft. Our exclusion criteria are presented in online supplemental appendix A.

Recruitment

Participants were recruited directly via the surgical lists of an orthopaedic surgeon who specialises in knee surgery (PDA) before being screened by a sports physiotherapist (MCM) and sports medicine doctor (CS) to ensure they were medically appropriate for inclusion.

Group allocation and blinding

Following their ACLR, a single study investigator randomly assigned participants with a 1:1 ratio to either (1) anodal-tDCS plus exercise or (2) sham-tDCS plus exercise. Randomisation was performed using a random number-generating software. The randomisation investigator had no role in the participants' assessment or intervention. Thus, all personnel performing assessment and intervention delivery were blinded. Statistical analysis was performed with groups labelled A and B without

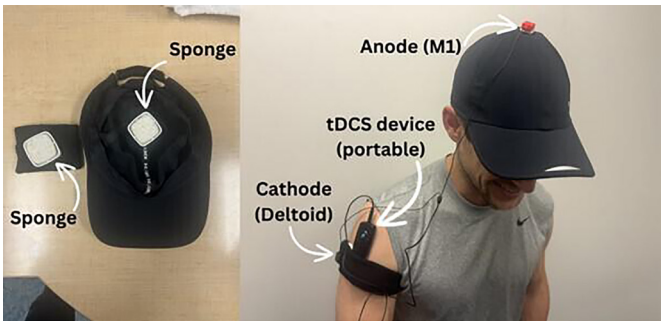

Figure 1 Example of Focus V3 device incorporation in a cap to enable use while performing exercise. tDCS, transcranial direct current stimulation.

awareness of which group corresponded to the anodal or sham intervention; thus, the analysis was also blinded.

Assessment procedures

Maximal voluntary isometric contraction

A VALD Performance Force Frame, a validated isometric dynamometer for MVIC testing, was used to quantify the quadriceps MVIC. Participants could visually monitor their force output in real-time via the VALD force frame app, displayed on an Apple iPad. Participants were placed in a seat with the knee set at a 45° angle, measured by a preset goniometer (online supplemental appendix B). This angle was selected as opposed to a 90° angle, which may have been difficult for some participants to achieve post surgery. Participants were instructed on performing an isometric knee extension and given time to familiarise themselves with the technique. Three maximum effort attempts were performed, with a 30-s rest in between efforts, and the maximal value was recorded as the MVIC. Additional attempts were allowed if the participants' values continued to increase with each attempt.

Transcranial magnetic stimulation

We recorded muscle activity via surface electrodes. We recorded muscle activity of the vastus medialis (active electrode placed 80% of the distance from the anterior superior iliac spine to the anterior portion of the medial collateral ligament) and semitendinosus (active electrode placed 50% of the distance from the ipsilateral ischial tuberosity to the medial collateral ligament). The recording electrodes were grounded to an electrode placed over the lateral epicondyle of the humerus and patella. Electromyography (EMG) signals were amplified and filtered (×1000; 16–1000 Hz; CED 1902 amplifier, Cambridge Electronic Design, Cambridge, UK) with a sampling rate of 5000 Hz. We digitised and stored analogue signals using a computer interface (CED 1401 Micro 3 and Signal Software, Cambridge Electronic Design).

Single-pulse and paired-pulse TMS was delivered via a double cone coil (11 cm outside diameter, Magstim) with a standard magnetic stimulator (Bistim2, Magstim, Whitland, UK) to elicit motor evoked potentials (MEPs) of the vastus medialis (hereafter referred to as quadriceps) and semitendinosus (hereafter referred to as hamstrings) muscles. TMS was delivered with the coil placed tangentially to the scalp with the handle positioned backwards and rotated away from the midline by~45° to induce a posterior–anterior current in M1 contralateral to the affected limb (n=17 right knee). The optimal stimulation site (ie, hotspot) was defined as the site that elicited the largest and most consistent MEPs in the quadriceps while performing an isolated quadriceps contraction at 5% of MVIC. To find the optimal site for eliciting MEPs (while the quadriceps was at rest), numerous scalp sites were stimulated starting near Cz of the International 10–20 System and moving the coil in the anterior–posterior and lateral-medial plane in ~0.5 cm steps. The optimal site was marked with ink on a tightly fitted cap to ensure reliable coil placement throughout the experimental session.

The following outcomes were assessed using TMS: 1 mV intensity (1 mV); active motor threshold (AMT); short-interval intracortical inhibition (SICI); long-interval intracortical inhibition (LICI); short-interval intracortical facilitation (SICF). The TMS intensity to elicit an MEP in quadriceps of ~1 mV (peak-to-peak amplitude) and AMT were obtained during an isometric quadriceps contraction of 5% MVIC (±20% of the 5%MVIC). During testing, the force output and acceptable range were displayed in real time on a handheld display (Apple iPad) via the VALD application. Given the acute postoperative period we were testing, we opted to use a 5% MVIC hold instead of 10% MVIC to ensure all participants could tolerate this post-operatively. The TMS pulse intensity (as a percentage of the maximal stimulator output, %MSO) that generated a 1 mV response in the quadriceps was determined. TMS intensity was increased until five consecutive pulses between 0.75 and 1.25 mV were elicited during a 5% quadriceps MVIC. The AMT was determined as the minimum intensity (%MSO) to generate an MEP greater than or equal to 0.2 mV in three out of five consecutive trials during a 5% quadriceps MVIC. This value was used to calculate the conditioning stimulus intensity for SICI and the test stimulus for SICF testing.

Primary outcomes

Inhibition (SICI and LICI)

Single-pulse and paired-pulse TMS was delivered to measure SICI and LICI. For SICI and LICI, single-pulse, test-stimulus trials were delivered at the 1 mV intensity. For SICI, paired-pulse trials were delivered with a conditioning stimulus set at 80% of the AMT followed by a test stimulus set at the 1 mV intensity, with an interstimulus interval (ISI) of 3 ms. For LICI, paired pulse trials were delivered with the conditioning stimulus and the test stimulus set at the 1 mV intensity, with an ISI of 100 ms. Single-pulse and paired-pulse trials were delivered in

Table 1 Baseline participant characteristics

	Anodal (n=11)		Sham (n=10)	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Demographics				
Age (years)	24 (5)	24(12)	25 (5)	25 (17)
Height (cm)	173 (8)	171 (27)	181 (12)	181 (36)
Weight (kg)	77 (15)	75 (59)	86 (18)	89 (50)
Pain and function				
KOOS (symptoms)	51 (10)	50 (32)	53 (13)	50 (36)
KOOS (pain)	70 (9)	71 (28)	75 (17)	80 (47)
IKDC	52 (9)	54 (28)	56 (11)	58 (32)
Pre-TMS EMG				
Quadriceps	0.01 (0.00)	0.01 (0.01)	0.02 (0.01)	0.01 (0.03)
Hamstrings	0.01 (0.00)	0.01 (0.01)	0.02 (0.02)	0.01 (0.06)
MVIC				
Quadriceps	144 (66)	136 (175)	154 (91)	129 (266)
Intensities				
1 mV Intensity (%MSO)	67 (9)	67 (32)	61 (10)	62 (27)
Active motor threshold (%MSO)	56 (8)	56 (23)	48 (10)	48 (28)
Corticospinal excitability				
Single-pulse MEP amplitude: quadriceps	1.20 (0.47)	1.21 (1.32)	1.49 (0.45)	1.38 (1.35)
Single-pulse MEP amplitude: hamstring	0.70 (0.41)	0.58 (1.40)	0.95 (0.97)	0.59 (3.14)
Inhibition				
SICI: quadriceps (ratio to MEP)	0.40 (0.14)	0.40 (0.43)	0.51 (0.20)	0.54 (0.57)
SICI: hamstrings (ratio to MEP)	0.60 (0.32)	0.56 (1.20)	0.68 (0.21)	0.65 (0.71)
LICI: quadriceps (ratio to MEP)	1.23 (1.21)	0.69 (4.03)	0.47 (0.30)	0.42 (0.92)
LICI: hamstrings (ratio to MEP)	2.02 (1.42)	1.70 (4.63)	0.89 (0.41)	0.85 (1.17)
Facilitation				
SICF at peak 1: quadriceps (ratio to MEP)	2.30 (1.54)	1.85 (5.44)	1.76 (0.66)	1.64 (2.19)
SICF at peak 1: hamstrings (ratio to MEP)	2.07 (1.16)	1.54 (3.22)	1.57 (0.49)	1.38 (1.27)
SICF at peak 2: quadriceps (ratio to MEP)	1.89 (1.22)	1.53 (4.42)	1.55 (0.49)	1.47 (1.59)
SICF at peak 2: hamstrings (ratio to MEP)	1.59 (0.66)	1.31 (2.21]	1.33 (0.26)	1.32 (0.91)
SICF at peak 3: quadriceps (ratio to MEP)	1.63 (0.86)	1.35 (3.10)	1.36 (0.36)	1.23 (1.03)
SICF at peak 3: hamstrings (ratio to MEP)	1.47 (0.74)	1.22 (2.58)	1.21 (0.28)	1.13 (0.82)

EMG, electromyography; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; LICI, long-interval intracortical inhibition; MEP, motor evoked potential; %MSO, percentage of maximal stimulator output; MVIC, maximal voluntary isometric contraction; n, number; Peak 1, interstimulus interval of 1.5 ms; Peak 2, interstimulus interval of 3 ms; Peak 3, interstimulus interval of 4.5 ms; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.

blocks of 15 trials: five single-pulse trials, five paired-pulse SICI trials and five paired-pulse LICI trials (order pseudorandomised). There were four blocks in total, resulting in 20 trials for each stimulus condition. Studies have shown that a minimum of 20 trials is needed to reliably produce a mean for MEP amplitude.[25] All trials were delivered during 5% MVIC.

Facilitation (SICF)

Single-pulse and paired-pulse TMS were delivered to measure SICF.[26] Single-pulse, test-stimulus trials were delivered at the 1 mV intensity. Paired-pulse trials were delivered with a test stimulus set at the 1 mV intensity and a conditioning stimulus set with an intensity of 90% AMT. Three ISIs were used to measure the first three SICF peaks: 1.5 ms, 3 ms and 4.5 ms.[27 28] Single-pulse and paired-pulse trials were delivered in blocks of 16 trials: four single-pulse trials and four paired-pulse trials at each of the three ISIs (1.5 ms, 3 ms and 4.5 ms); the order of trial was pseudorandomised. There were five blocks in total, resulting in 20 trials

for each condition. All trials were delivered during 5% MVIC. SICF had been included as three separate categories based on the respective peaks, but these data were highly correlated (Pearsons r range for correlations between datasets ranging from r=0.981 to 0.991). Thus, these data were collapsed into a single variable (SICF).

Additional variables

Demographic data

Age, sex, weight, height, ethnicity, dominant hand and dominant foot were self-reported.

Knee related function

The IKDC[29] score was used to capture knee-related function.

Medication usage

Participants were required to list all medications, which were then categorised as being for pain (yes/no).

Pain locations

Participants recorded areas of musculoskeletal aches, pains and injuries (neck, shoulders, upper back, elbows, wrist/hands, lower back, hips/thighs, knees, ankles/feet, none) in the previous 12 months using the Nordic Musculoskeletal Questionnaire.[30 31]

Intervention

Transcranial direct current stimulation

During the initial TMS session, the assessor (CS) had the participant fit a regular running cap on their head before marking the anodal location and cutting a hole in the location of the M1 (via the same location method as TMS). The assessor assisted participants in photographing themselves in the cap using their smartphone devices following the initial fitting to ensure accurate placement during sessions. This ensured that the location of the Focus V3 tDCS device anode was positioned at the site that best corresponds to the quadriceps representation in M1. This procedure also meant the assessor never contacted the tDCS devices to ensure blinding.

Participants brought their individualised caps to their initial physiotherapy consultation, where their treating physiotherapist set up the tDCS device by inserting the sponge holder into the hole in the running cap (figure 1). The devices were preprogrammed by a research team member to ensure physiotherapists and participants were unaware of group allocation. Participants were given preallocated numbers of tDCS devices corresponding to a real anodal-tDCS or sham-tDCS setting. To use the tDCS device, participants had to press the 'go' button until they felt the stimulation. The bottom half of the tDCS device screen was covered, so only the amount of stimulation ramping was displayed.

The cathode was secured on the upper arm (contralateral to the injured knee) via a fabric sweatband with a hole that again allowed the cathode to connect to the underlying 35 mm × 35 mm sponge. Saline solution was used to wet sponges and allow conduction. All participants (both anodal-tDCS and sham-tDCS) were shown how to check sufficient sponge contact and confirmed that they received a sensation of tingling under the anode when the device was used and were advised this would fade. Thus, procedures for both anodal-tDCS and sham-tDCS were identical, except for the amplitude of the stimulation.

Anodal-tDCS

A 2-mA anodal current was delivered to the primary motor cortex (M1) of the ACLR side via a Focus V3 tDCS device for 20 min (including a ramp up and down in stimulation), per prior research in knee OA.[32] Anodal-tDCS was applied three times weekly during exercise rehabilitation, which was viewed as feasible by our consumer engagement and more than what was performed in a pilot anodal-tDCS trial in knee OA.[24]

Sham-tDCS

The sham procedure was identical to the anodal-tDCS procedure, with an identical amplitude and stimulation duration displayed. However, the device ramped to true stimulation for 30 s before ramping down to no stimulation, but the screen falsely reported a 2-mA current was being delivered.

Exercise

Participants in both the anodal-tDCS and sham-tDCS groups received 6 weeks of physiotherapist-supervised exercise rehabilitation (from week 2 post ACLR). A training manual was developed to assist the clinicians in the standardised delivery of the exercises, templates were created within Physitrack and participants had access to the complete programme on their smartphones using the PhysiApp. Exercise rehabilitation was based on the standard postoperative protocol of the orthopaedic surgeon and informed by the research team. The exercise intervention varied in duration, based on the week of recovery, but was always greater than 20 min duration, yet shorter than 60 min duration per day. The programme was adapted to the individual participant as able based on the judgement of the physiotherapist, however at a minimum, all programmes comprised:

1. A single joint exercise for each of the following muscle groups: abdominals; hip extensors; hip flexors, hip abductors; hip adductors; knee flexors; knee extensors; and ankle plantar flexors.
2. A multijoint squat pattern (eg, squat) and bend pattern (eg, deadlift) movement.
3. One balance-based exercise (eg, star excursion balance).

The exercise intervention was to be completed daily. However, only three sessions per week were required to be completed on-site (rehabilitation gymnasium at SportsMed Subiaco). During that time, the tDCS intervention would be delivered for the first 20 min of the exercise session.

Table 2 Within-group changes following 6 weeks of anodal-tDCS or sham-tDCS (from week 2 post ACLR)

	Anodal (n=11)	Sham (n=10)
	Mean (SD)	Mean (SD)
Pre-TMS EMG		
Quadriceps	0.003 (0.005)	−0.001 (0.007)
Pre-TMS EMG: hamstrings	0.001 (0.005)	0.001 (0.005)
MVIC		
Quadriceps	50.00 (43.08)	60.67 (67.38)
Intensities		
1 mV Intensity (%MSO)	−1.18 (5.46)	−0.78 (6.94)
Active motor threshold (%MSO)	−1.64 (6.61)	2.00 (5.85)
Corticospinal excitability		
Single-pulse MEP amplitude: quadriceps	0.03 (0.47)	−0.26 (0.59)
Single-pulse MEP amplitude: hamstring	0.07 (0.43)	−0.01 (0.39)
Inhibition		
SICI: quadriceps (ratio to MEP)	0.21 (0.23)	−0.07 (0.33)
SICI: hamstrings (ratio to MEP)	0.20 (0.30)	0.08 (0.45)
LICI: quadriceps (ratio to MEP)	−0.23 (0.97)	0.03 (0.56)
LICI: hamstrings (ratio to MEP)	−0.55 (1.38)	0.02 (0.50)
Facilitation		
SICF at peak 1: quadriceps (ratio to MEP)	−0.48 (0.66)	0.57 (1.24)
SICF at peak 1: hamstrings (ratio to MEP)	−0.52 (0.79)	0.09 (0.57)
SICF at peak 2: quadriceps (ratio to MEP)	−0.32 (0.51)	0.25 (0.80)
SICF at peak 2: hamstrings (ratio to MEP)	−0.23 (0.34)	0.05 (0.29)
SICF at peak 3: quadriceps (ratio to MEP)	−0.28 (0.44)	0.25 (0.63)
SICF at peak 3: hamstrings (ratio to MEP)	−0.26 (0.46)	0.04 (0.32)

LICI, long-interval intracortical inhibition; MEP, motor evoked potential; %MSO, percentage of maximal stimulator output; MVIC, maximal voluntary isometric contraction; n, number; Peak 1, interstimulus interval of 1.5 ms; Peak 2, interstimulus interval of 3 ms; Peak 3, interstimulus interval of 4.5 ms; SICF, short-interval intracortical facilitation; SICI, short-interval intracortical inhibition.

Sample size estimation

Power calculations were performed in G.Power (V.3.1.9.7) to determine the sample size needed for a between-group design using an α=0.05, β=0.80. No work has been done in this area for ACLR previously, so given the equipment cost and additional workload for application and use, we felt that anything other than a large effect size (>0.6) would not be clinically meaningful. Therefore, for independent t-tests evaluating differences in group changes, it was determined that a sample size of 10 per group would be required for this proof-of-concept study.

Table 3 The effect of group and time on quadriceps short-interval intracortical inhibition

Variable	Beta-estimate	95% CI	P value
Group (anodal-tDCS)	−0.379	−0.801 to 0.044	0.079
Time	−1.421	−1.919 to −0.923	<0.001*
Group (anodal-tDCS)* time	0.519	0.057 to 0.981	0.028*
Quadriceps pre-TMS EMG	−14.604	−32.116 to 2.907	0.102
Quadriceps pre-TMS EMG* time	24.322	3.847 to 44.797	0.020*

*Significant at p<0.05.
EMG, electromyography; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

Table 4 The effect of group and time on quadriceps long-interval intracortical inhibition

Variable	Beta-estimate	95% CI	P value
Group (anodal-tDCS)	0.740	0.040 to 1.440	0.038*
Time	0.039	−0.815 to −0.893	0.928
Group (anodal-tDCS)* time	−0.217	−0.916 to 0.482	0.543
Quadriceps pre-TMS EMG	−3.839	−25.570 to 17.892	0.729
Quadriceps pre-TMS EMG* time	−1.553	−36.709 to 33.603	0.931

*Significant at p<0.05.
EMG, electromyography; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

Statistical analysis

All data are presented descriptively, as appropriate, in text or tables, and a detailed description of our data processing is presented in online supplemental appendix C. The data distribution was examined visually (via graphs) and then statistically with the One-Sample Kolmogorov-Smirnov Test (online supplemental appendix D). The effect of group and time on primary outcomes for (quadriceps SICI, LICI and SICF) were evaluated via separate generalised estimating equations (GEE). The effect of group and time on secondary outcomes (quadriceps MVIC, hamstring SICI, LICI and SICF) were also evaluated via separate GEE. To ensure consistency of EMG across sessions and validity of our experimental controls, the pre-TMS EMG for the entire sample was included within statistical modelling and adjusted for interaction with time. We opted to use GEE as it is appropriate for non-normally distributed longitudinal data and allows for the specification of both time-varying and individual difference variables. Significance was accepted when p<0.05. All data analysis was performed in IBM SPSS Statistics (V.29.0).

RESULTS

Participant recruitment

We screened 40 participants for eligibility, recruiting 24 participants, of which three dropped out before receiving the intervention (online supplemental appendix E). Thus, 21 participants (38% female) were included in this study and received the intervention. All included participants completed >80% of prescribed tDCS/exercise rehabilitation sessions.

Participant characteristics

Participants had a mean (SD) age of 24.4 (4.7) years, height of 176.6 (10.2) cm and weight of 81.1 (16.8) kg. All participants were Australian residents, and complete demographic data by group were provided (online supplemental appendix F). Baseline group characteristics are provided in table 1, and within-group change for all variables is provided in table 2.

Primary outcomes

Quadriceps SICI

The complete analysis for quadriceps SICI is presented in table 3, and individual participant data in online supplemental appendix G. There was a significant group-by-time effect for anodal-tDCS (β=0.519, p=0.028) and a significant effect for time (β=−1.421, p<0.001).

Quadriceps LICI

The complete analysis for quadriceps LICI is presented in table 4. There was no significant group-by-time effect (β=−0.217, p=0.543) or effect for time (β=0.039, p=0.928).

Quadriceps SICF

The complete analysis for quadriceps SICF is presented in table 5, and individual participant data are in online supplemental appendix H. There was a significant group-by-time effect for anodal-tDCS (β=−0.764, p=0.020) but not time (β=0.504, p=0.383).

Table 5 The effect of group and time on quadriceps short-interval intracortical facilitation

Variable	Beta-estimate	95% CI	P value
Group (anodal-tDCS)	0.464	−0.344 to 1.272	0.260
Time	0.504	−0.627 to 1.635	0.383
Group (anodal-tDCS)* time	−0.764	−1.407 to −0.120	0.020*
Quadriceps pre-TMS EMG	14.318	−16.524 to 45.178	0.363
Quadriceps pre-TMS EMG* time	−7.436	−55.472 to 40.600	0.762

*Significant at p<0.05.
EMG, electromyography; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

Secondary outcomes

Quadriceps MVIC

There was no significant group-by-time effect for anodal-tDCS (β=−10.667, 95% CI −59.166 to 37.953, p=0.667) or group effect (β=−9.911, 95% CI −78.145 to 58.323, p=0.776). However, there was a significant effect for time (β=60.667, 95% CI 19.166 to 102.167, p=0.004).

Hamstring SICI

There was no significant group-by-time effect for anodal-tDCS (β=0.077, 95% CI −0.295 to 0.449, p=0.685) or group effect (β=0.100, 95% CI −0.211 to 0.410, p=0.529). However, there was a significant effect for time (β=0.374, 95% CI 0.007 to 0.741, p=0.046).

Hamstring LICI

There was no significant group-by-time effect for anodal-tDCS (β=−0.582, 95% CI −1.409 to 0.246, p=0.168) or effect for time (β=0.146, 95% CI −0.557 to 0.849, p=0.684). However, there was a significant effect for group (β=1.070, 95% CI 0.205 to 1.935, p=0.015).

Hamstring SICF

There was a significant group-by-time effect for anodal-tDCS (β=−0.413, 95% CI −0.791 to −0.035, p=0.032). However, there was no effect for group (β=0.418, 95% CI −0.087 to 0.923, p=0.105) or time (β=0.012, 95% CI −0.425 to 0.450, p=0.956).

DISCUSSION

Our study has provided proof of concept for 6 weeks of anodal-tDCS as an adjunct to exercise rehabilitation for modulating intracortical motor drive in the immediate postoperative ACLR period (from week 2 post ACLR) for quadriceps (inhibition and facilitation) and hamstring (only facilitation). This research suggests that anodal-tDCS, as an adjunct to exercise rehabilitation in the acute postoperative period, can modulate primary motor cortex function by reducing quadriceps intracortical inhibition and facilitation. As primary motor cortex function provides a substantial driver to motor control, our research may be able to change existing ACLR rehabilitation.

Our previous research has shown that measurements such as AMT remain stable in the acute postoperative ACLR stages, whereas intracortical inhibition and facilitation increase.[17] Specifically, quadriceps primary motor cortex SICI and ICF (but not LICI)[14 33] have been shown to change within weeks of an ACLR.[34] Further, changes in intracortical inhibition (SICI)/facilitation (ICF) have been linked to the ability to generate maximal muscle force.[13 14 33 35] Thus, we have hypothesised that these impairments to normal primary motor cortex function following ACLR contribute to suboptimal rehabilitation outcomes.[10] Given that overall cortical excitability is a balance of inhibition and facilitation,[16] it may be the case that increases in facilitation occur to counteract increases in inhibition (or vice versa) and preserve a stable level of cortical excitability.[36] Therefore, as we know, increases in inhibition and facilitation are maladaptive in the post-ACLR phase. Reducing inhibition and/or facilitation might reflect improved primary motor cortex control.

We observed that anodal-tDCS significantly reduced quadriceps, but not hamstring, SICI. Pharmacological evidence suggests that SICI is mediated by gamma-aminobutyric acid (GABA-A) receptor activity,[37] The reduction of inhibition we observed in the quadriceps suggests that anodal-tDCS reduces GABA-A receptor activity. We may have been underpowered to detect this effect given the larger variability in hamstring responses, which is likely due to both TMS and tDCS location being optimised for quadriceps and not hamstring responses. Alternatively, this could be a specific adaptation due to all participants receiving ipsilateral hamstring tendon grafts. Future research should examine SICI with TMS parameters optimised for the hamstring to determine the specificity of primary motor cortex inhibition changes following ACLR and anodal-tDCS intervention.

We did not detect meaningful or significant between-group differences in LICI for the quadriceps or the hamstring. This is consistent with our previous research showing that LICI is unchanged in the acute postoperative ACLR period.[17] Given that LICI is unaffected by ACLR, it is not entirely unexpected that anodal-tDCS did not modulate LICI in this population. Pharmacological studies provide strong evidence that LICI is mediated by GABA-B receptor activity.[38] Taken together with the SICI findings, the current results suggest that anodal-tDCS in the postoperative period influences GABA-A-mediated inhibition but not GABA-B-mediated inhibition in the motor cortex.

Finally, we observed a significant effect of tDCS in modulating both quadriceps and hamstring facilitation when we pooled the data from the different SICF peaks to reduce the number of statistical comparisons due to being near identical (Pearsons r>0.98 for all peaks). Research suggests that SICF reflects activity within indirect-wave circuitry in M1,[27 28] and that early (SICF peak 1) and later peaks (SICF peak 2 and SICF peak 3) have different functional roles,[39] and different sensitivity to long-term potentiation-like and long-term depression-like neuroplasticity.[39] It would be interesting for future, larger research studies to investigate the functional effect of changes in SICF at peak 1, peak 2 and peak 3 following anodal-tDCS.

Several studies in ACLR populations have demonstrated widespread cortical involvement for simple motor tasks (eg, increased activation of visual areas).[34] This cortical dysfunction likely results in the poor performance of complex motor tasks that involve reactivity or an over-reliance on visual input.[34 40] It is suggested that this excessive activation of areas outside of the normal regions (eg, more frontal and occipital involvement) of the brain responsible for motor function is a result of excessive intracortical facilitation.[41 42] Thus, our research shows that anodal-tDCS reduces both intracortical

inhibition and facilitation, suggests anodal-tDCS may present an adjunct to existing practice for people with poor performance of complex motor tasks that involve reactivity. However, further research reflecting the long-term effects of anodal-tDCS is needed before being recommended for clinical practice.

In addition to needing more data, the implementation barriers to tDCS must be considered. Our qualitative exploration of the use of tDCS in clinical practice reported athletes and people with injury would use tDCS to improve injury recovery or performance enhancement.[43] However, factors such as fear of brain stimulation, poor usability and device discomfort would reduce the likelihood of tDCS use and must be considered before implementing this practice.[43]

While this study provides proof of concept for anodal-tDCS improving intracortical function following ACLR, evaluating the long-term neurophysiological and clinical outcomes (and performing larger studies that demonstrate repeatability) is important. Specifically, future studies must determine the ability (if any) of anodal-tDCS to optimise functional outcomes and ameliorate risk factors of subsequent rupture before it can be recommended in clinical practice.

Limitations

Our sample comprised predominantly left ACLRs in male participants. We suspect some selection bias due to the burden of having tDCS delivered on site, as the right ACLRs cannot drive in the early postoperative phase. While we performed sample size calculations to detect between-group differences of >0.6, the large variance in both groups was larger than anticipated, which means we may have been underpowered to detect the significance of some between-group differences that appeared meaningful. However, given our relatively small sample, we are likely more at risk of type I error. Finally, all participants had their ACLR performed privately, which means that they all had private health insurance, resulting in a selection bias towards higher socioeconomic participants. Future studies should also explore other quadriceps and hamstring muscle groups and different muscles considered important in post-ACLR function (eg, gluteal muscles).

CONCLUSION

This study provided proof of concept for the efficacy of anodal-tDCS post ACLR in improving intracortical inhibition and facilitation. Our data showed that anodal-tDCS significantly modulates quadriceps facilitation and inhibition post ACLR, a known driver of AMI. However, no differences between groups were observed in MVIC, and the relationship of primary motor cortex changes to MVIC post ACLR requires further investigation. Nevertheless, anodal-tDCS appears effective at improving primary motor cortex dysfunction following ACLR. Thus, anodal-tDCS represents a low-cost, simple-to-apply intervention, which could be performed as an adjunct to current exercise rehabilitation that may address maladaptive changes to the primary motor cortex postoperatively.

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