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RESEARCH ARTICLE

Quadriceps muscle function following anterior cruciate ligament reconstruction: systemic differences in neural and morphological characteristics

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Abstract

Quadriceps muscle dysfunction is common following anterior cruciate ligament reconstruction (ACLR). Data considering the diversity of neural changes, in-concert with morphological adaptations of the quadriceps muscle, are lacking. We investigated bilateral differences in neural and morphological characteristics of the quadriceps muscle in ACLR participants ($n = 11$, month post-surgery: 69.4 ± 22.4) compared to controls matched by sex, age, height, weight, limb dominance, and activity level. Spinal reflex excitability was assessed using Hoffmann reflexes (H:M); corticospinal excitability was quantified via active motor thresholds (AMT) and motor-evoked potentials (MEP) using transcranial magnetic stimulation. Cortical activation was assessed using a knee flexion/extension task with functional magnetic resonance imaging (fMRI). Muscle volume was quantified using structural MRI. Muscle strength and patient-reported outcomes were also collected. 2×2 RM ANOVAs were used to evaluate group differences. Smaller quadriceps muscle volume (total volume, rectus femoris, vastus medialis, and intermedius) and lower strength were detected compared to contralateral and control limbs. Individuals with ACLR reported higher levels of pain and fear and lower levels of knee function compared to controls. No differences were observed for H:M. ACLR individuals demonstrated higher AMT bilaterally and smaller MEPs in the injured limb, compared to the controls. ACLR participants demonstrated greater activation in frontal lobe areas responsible for motor and pain processing compared to controls, which were associated with self-reported pain. Our results suggest that individuals with ACLR demonstrate systemic neural differences compared to controls, which are observed concurrently with smaller quadriceps muscle volume, quadriceps muscle weakness, and self-reported dysfunction.

Keywords Functional magnetic resonance imaging · Transcranial magnetic stimulation · Muscle atrophy · Cortical activation · Quadriceps weakness

Introduction

Anterior cruciate ligament (ACL) rupture, and subsequent reconstruction (ACLR), is one of the most common musculoskeletal injuries, with an estimated 250,000 ACL ruptures occurring each year in the United States (Griffin et al. 2006). The societal and economic impact of ACL injuries is substantial, as the yearly cost of ACLR and rehabilitation amounts to $3 billion in the United States alone (Griffin et al. 2006; Neuman et al. 2008). Staggeringly, the economic burden of ACL injury escalates to nearly $8 billion per year when lifetime burdens such as work status, disability, and osteoarthritis development are taken into consideration (Mather et al. 2013). Unfortunately, despite intensive therapy and large financial investments, individuals often leave

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formalized rehabilitation with suboptimal physical function. In fact, recent data suggest that only 54–63% of individuals will return to pre-injury activity levels (Ardern et al. 2011; Flanigan et al. 2013), approximately 23% of patients will sustain a second ACL rupture (Paterno et al. 2012; Wiggins et al. 2016), and that ACLR itself is not protective to the lifetime burden of developing knee osteoarthritis (Hoxie et al. 2008).

Quadriceps muscle strength is a modifiable factor that is often targeted during the recovery from ACLR. Quadriceps strength has demonstrated strong positive associations with greater self-reported knee function (Pietrosimone et al. 2013, 2016) and physical performance (Lohmander et al. 2004), and lower risk of re-injury (Paterno et al. 2010) and osteoarthritis development (Tourville et al. 2014). Though quadriceps strengthening is often a central tenant of current rehabilitation programs, strength deficits often continue to exceed 20% at the conclusion of rehabilitation compared to pre-operative levels, and can persist for upwards of 15 year post-surgery (Ingersoll et al. 2008; Lohmander et al. 2004; Palmieri-Smith et al. 2008). As a result of the suboptimal outcomes associated with the current standard of care, more research is needed to better understand the multifaceted origins of quadriceps strength deficits.

Several investigations have separately identified impairments in neural (Kapreli et al. 2009; Lepley et al. 2015b; Pietrosimone et al. 2015) and morphological (Gumucio et al. 2018; Lindstrom et al. 2013; Noehren et al. 2016; Strandberg et al. 2013; Williams et al. 2005b) characteristics of the quadriceps muscle after ACL injury. To date, only a few investigations have examined measures of both muscle activation (central activation ratio) and morphological characteristics (muscle volume) of the quadriceps in the same cohort of ACL participants (Krishnan and Williams 2011; Kuenze et al. 2016; Norte et al. 2018b; Thomas et al. 2016; Williams et al. 2005a). However, these investigations only used gross measures of muscle activation, and the inclusion of more sensitive measures capable of identifying the underlying origins of neural alterations is notably missing. Recent data have indicated that neural changes following joint injury are more complex than simple measures of gross muscle activation (Needle et al. 2017; Pietrosimone et al. 2012), as changes in the activation of cortical areas in the brain (Grooms et al. 2015; Kapreli et al. 2009), and excitability of descending corticospinal (Heroux and Tremblay 2006; Lepley et al. 2014, 2015b; Pietrosimone et al. 2015) and spinal reflex pathways (Hoffman and Koceja 2000; Lepley et al. 2015b; Pietrosimone et al. 2015; Rosenthal et al. 2009) have all been observed following ACL injury with the potential of influencing quadriceps strength (Lepley et al. 2014).

Although neural excitability of the quadriceps muscle is an important consideration to muscle function, morphological factors of the muscle, such as muscle volume, can also influence clinical measures of strength following ACLR. Several studies have shown that the quadriceps muscle in the injured limb of ACLR participants is smaller compared to their contralateral and control limbs (Konishi et al. 2007; Norte et al. 2018b; Thomas et al. 2016). Unfortunately, a comprehensive assessment that considers the diversity of neural function, in-concert with muscle volume of the quadriceps muscle does not exist in the same cohort of ACL participants. The concurrent assessment of neural and morphological quadriceps function would allow for a systemic view of the impact that ACLR has on multiple components of muscle function and deepen our understanding of the origins of the well-documented decreases in muscle and knee function that follows ACLR.

Therefore, the primary aim of this study was to comprehensively investigate differences in neural (spinal reflex excitability, corticospinal excitability, cortical activation) and morphological (muscle volume) characteristics of the quadriceps muscle in individuals with ACLR compared to individuals without history of major lower extremity musculoskeletal injury. We hypothesized that ACLR participants would demonstrate lower levels of corticospinal excitability, and different brain activation patterns and smaller quadriceps muscle volume of the ACLR injured limb compared to controls.

Methods

A cross-sectional case–control study design was used to evaluate bilateral differences in quadriceps neural and morphological characteristics between participants with a history of ACLR and matched controls. Based on the previous work investigating differences in neuromuscular dysfunction following ACLR (Lepley et al. 2015b), an *a priori* power analysis using means and standard deviations from active motor thresholds and muscle strength of the ACLR injured limb and controls, estimated that we would need 10 participants in each group (total $n = 20$) to find a significant difference between limbs (ACLR and contralateral) and groups (ACLR and control) with an alpha level of 0.05 and $1 - \beta$ of 0.80.

Participants between the ages of 16–35 with a history of primary, unilateral ACLR were recruited from the Department of Orthopaedic Surgery and University population, and were matched by sex, age, height, weight, limb dominance, and activity level to control participants with no history of major lower extremity injury. The limb designated as the injured limb in control participants was assigned according to limb dominance (i.e., if an ACLR participant injured their dominant limb, the dominant limb of their matched control counterpart would be designated as their injured

limb). In addition, all participants reported no history of previous orthopedic surgery or ligamentous knee injury, or any lower extremity musculoskeletal injury in the last six months. Further exclusion criteria included history of a concussion or head injury in the past 6 months, previous loss of consciousness associated with a concussion, history of a stroke, cranial neurosurgery, migraines, cancer in the brain, a diagnosed psychiatric or neurological disorder, currently taking medications that alter neural activity, or imbedded intracranial metallic clips. All participants provided written, informed consent, and all procedures were approved by the University's Institutional Review Board.

Testing was completed during a single session with outcomes collected in a standardized order to prevent the influence of magnetic or electrical stimulation techniques on brain activation. Thus, the order of testing was as follows: brain activation, quadriceps muscle volume, spinal reflex excitability, corticospinal excitability, muscle strength, and patient-reported outcomes. During each outcome, the testing order for limbs (injured, contralateral) was randomized.

Brain activation

Brain functional magnetic resonance imaging (fMRI) was collected using a 3-Tesla Siemens Prisma scanner with a 20-channel phase array receiver only head coil. A 3-dimensional high-resolution T1-weighted image (TR: 2530 ms, TE: 1.80 ms, field of view: 256 × 256 mm; matrix: 256 × 256; anterior-to-posterior phase encoding; slice thickness 1 mm, 176 slices) was collected for image registration. Functional imaging was completed with: a 2.0 mm^3 voxel size, a 2 mm slice thickness for 55 slices, field of view 200 mm, anterior-to-posterior phase encoding, interleaved slice timing; TR: 3000 ms, TE: 30 ms. During functional collection, each participant performed unilateral knee extension–flexion movement (ACLR injured limb and Control injured matched limb) paced by an auditory metronome at 1.2 Hz for 30 s, followed by 30 s of rest, and repeated for a total of four cycles (Grooms et al. 2015, 2017; Kapreli et al. 2009). The fMRI data underwent standard neuroimaging pre-processing (Woolrich et al. 2001b) using the software package FSL 5.1.0 (FMRIB, Oxford UK) (Smith et al. 2004). Image analysis began with standard pre-statistic processing applied to individual data, including: non-brain removal, spatial smoothing using a Gaussian kernel of full width at 5 mm standard motion correction and realignment parameters (3 rotations and 3 translations) as covariates to limit confounding effects of head movement (Jenkinson et al. 2002; Smith 2002). High-pass temporal filtering at 90 Hz and time-series statistical analyses was carried out using a linear model with local autocorrelation correction (Woolrich et al. 2001a). Functional images were co-registered with the respective high-resolution T1 image and standard MNI 152, 2 mm space using linear image registration. This registration process allowed data from each patient to be spatially aligned on a standardized brain template for comparison (Figs. 1a, 2).

Quadriceps muscle volume

Participants were positioned supine/feet first in the same 3-Tesla Siemens Prisma MRI scanner to measure quadriceps muscle volume in each limb simultaneously using the Body 18 coil. A T1-weighted turbo spin echo with fat saturation protocol was used with a repetition time (TR) of 616 ms, echo time (TE) of 9.7 ms, voxel size of 1.0 × 1.0 × 10.0 mm, and a slice thickness of 10 mm obtained every 1.5 mm (gap between slices) with a 216 × 384 matrix and a field of view that was customized based on the size of each participant. Computing imaging software (OsiriX medical imaging software, OsiriX version 9.0, Atlanta, GA, USA) and a tracking tablet (Intuos Art Track Pad tablet; Wacom Graphics; Kazo, Saitama, Japan) were used to objectively assess cross-sectional area by individually tracing the outline of each head of the quadriceps muscle in every axial image in which the muscle appeared. Muscle volume (cm^3) of the rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL), and vastus intermedius (VI) were quantified separately by summation

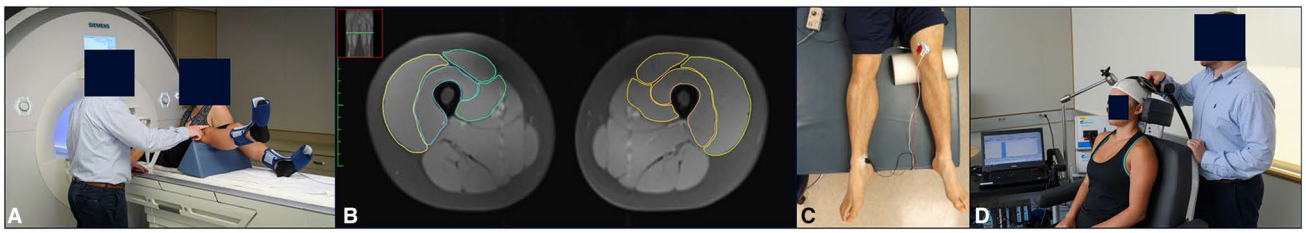

Fig. 1 Setup and testing images for **a** fMRI movement task to quantify brain activation, **b** representative 2D structural MRI slice and cross-sectional area of the quadriceps muscle. Muscle volume (cm^3) of the rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL), and vastus intermedius (VI) were quantified separately by summation of the cross-sectional area of the muscle in each slice that the muscle was visualized. **c** Electrical stimulation during Hoffmann reflex testing, and **d** transcranial magnetic stimulation to assess active motor threshold and motor-evoked potentials

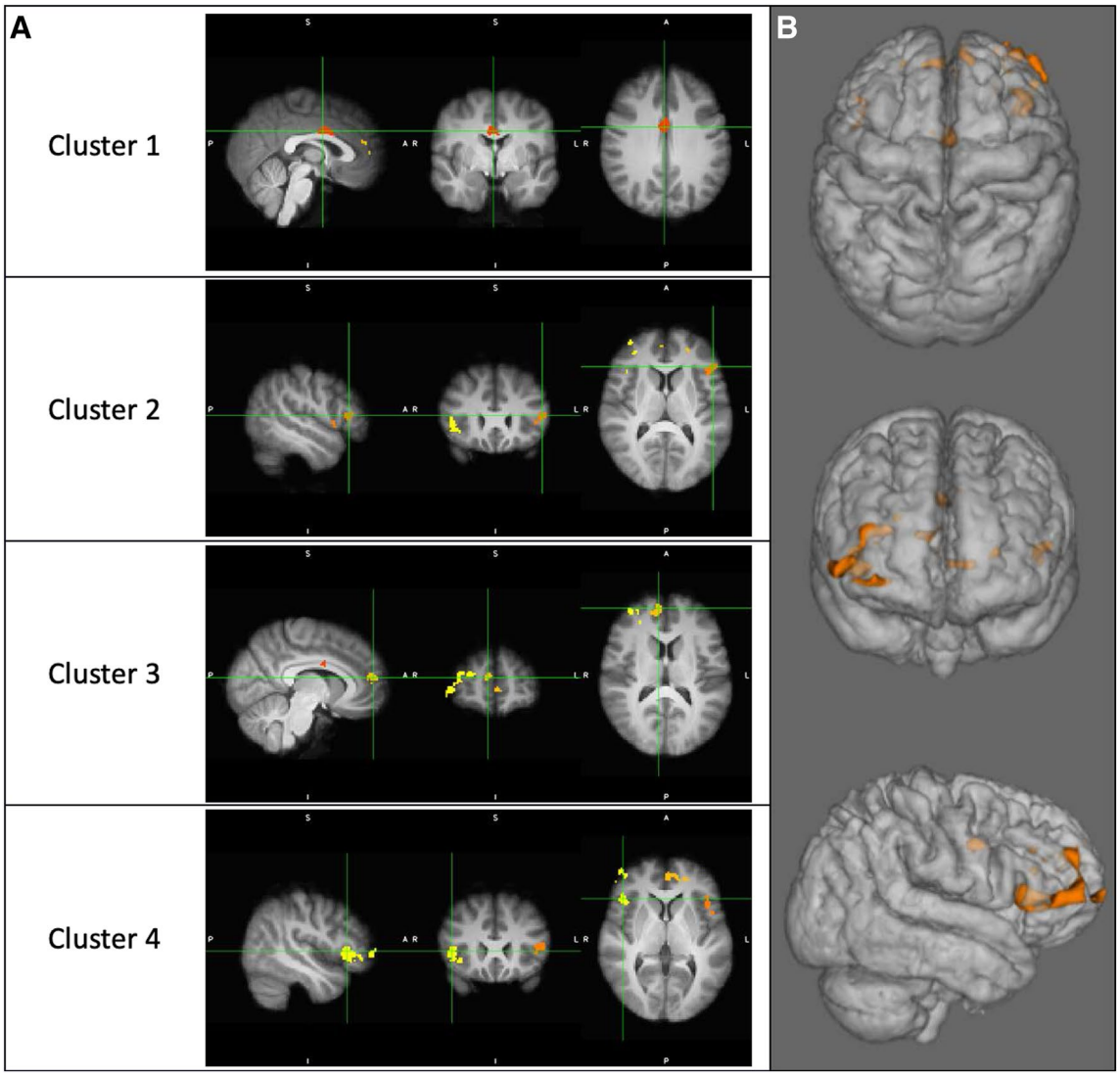

Fig. 2 Brain regions with significantly increased BOLD signal (neural activity) in the ACL group relative to controls for knee motor control. **a** Each cluster of activity from Table 3 color distinguished and cross-hairs indicating peak voxel of activity in each respective cluster. **b** 3D reconstruction of the ensemble data from Table 3 and in **a**

of the cross-sectional area of the muscle in each slice, multiplied by the distance between slices, as previously reported (Maden-Wilkinson et al. 2013; Morse et al. 2007). RF, VM, VL, and VI muscle volumes were added together for a representative total quadriceps (TQ) volume outcome (Fig. 1b).

Spinal reflex excitability

Hoffmann reflexes were used to assess spinal reflex excitability. Two 10 mm, pre-gelled Ag–AgCl (EL503, BIOPAC Systems Inc., Goleta, CA, USA) disc-shaped surface electromyographic (EMG) electrodes, with an inter-electrode difference of 1.75 cm, were positioned over the distal belly of the vastus medialis muscle belly after standard EMG preparation (Palmieri and Ingersoll 2005). The ground electrode was placed over the ipsilateral medial malleolus. During testing, participants were positioned supine with their arms comfortably at their side, their knee supported by a half bolster, and their head in a neutral position. A 2 mm shielded disc stimulating electrode (EL252RT, BIOPAC Systems Inc) was placed superficially over the femoral nerve and secured with hypoallergenic tape, while a round self-adhesive dispersive electrode was positioned over the hamstring muscle. A BIOPAC stimulator module (STM100C, BIOPAC Systems, Inc) and a 200 V maximum stimulus adaptor (STMISOC, BIOPAC Systems Inc) were used to deliver a 1 ms square wave stimulus to the femoral nerve, and EMG signals were band-pass filtered from 10 to 50 Hz and collected at 1024 HZ with a common-mode-rejection ratio of 110 dB (Hopkins et al. 2001a). Stimulation intensity was increased

incrementally by 0.2 volts until a maximum Hoffmann reflex was elicited, and then, three maximal Hoffmann reflexes were collected at that voltage. The stimulus was increased further until a maximal muscle response was elicited, in which an increase in the stimulus intensity resulted in no further increase in the peak-to-peak amplitude of the muscle response. Three maximal muscle responses were collected at that intensity. The average of the three Hoffmann reflexes was normalized to the average of the three maximal muscle responses for analysis (H:M ratio; Fig. 1c). Testing was conducted on both limbs.

Corticospinal excitability

Transcranial magnetic stimulation (TMS) was used to determine active motor threshold (AMT) and amplitude of motor-evoked potentials (MEP) elicited at 120% of AMT, in both limbs. The same EMG electrode placement procedures used during spinal reflex excitability testing were used during corticospinal excitability testing. Participants were seated in a testing chair (MagVenture Treatment Chair, 9016B008 MagVenture Inc., Atlanta, GA) with their knees and hips at 90 ° of flexion. A Lycra swim cap, with a 0.5 cm grid, was placed on the participant's head to allow for identification of the motor cortex location (Lepley et al. 2015b; Norte et al. 2010). A double cone angled TMS coil (D-B80, MagVenture Inc., Atlanta, GA) was positioned over the intersected grid lines and moved in increments of 0.5 cm in anterior-to-posterior and medial-to-lateral directions until the optimal stimulating point was detected, which was defined as the location producing the greatest MEP amplitude in the vastus medialis (Livingston and Ingersoll 2008). The TMS coil was secured over that spot using a flexible mount (Super Flex Arm, MagVenture Inc.). Once the optimal stimulating point was located, AMT was identified by detecting the lowest TMS intensity required to evoke a measurable (> 100 μV) MEP in five out of 10 trials (Lepley et al. 2015b; Pietrosimone et al. 2015). Once AMT was established, five MEPs were elicited at 120% of AMT. The five peak-to-peak MEP amplitude values were averaged and normalized to the average of three maximal muscle responses elicited during spinal excitability testing (Lepley et al. 2015b). During all corticospinal excitability testing, participants were instructed to generate an isometric knee extension contraction of 10% of their maximal muscle force production, which was objectively assessed and monitored by the investigator via a belt-stabilized handheld dynamometer which was secured to the testing chair (micro FET; Hoggann Scientific LLC, West Jordan UT) (Lepley et al. 2015b) (Fig. 1d). Prior to testing, participants performed three trials at their maximal effort on the handheld dynamometer to establish the 10% force production value.

Quadriceps muscle strength

Quadriceps strength was assessed bilaterally using maximal voluntary isometric contractions (MVIC). Participants were secured into an isokinetic dynamometer using both shoulder and lap straps (Biodex Medical Systems 4, Shirley, New York, USA) with their hips and testing knee secured at 90° of flexion (Lepley et al. 2015b). During testing, participants were instructed to cross their arms over their chest. The participants performed a standardized series of three submaximal warm up trials, followed by three MVIC trials with verbal and visual feedback to encourage maximal effort. The maximal torque produced during the three testing trials was averaged and normalized to body mass (Nm/kg) for analysis (Lepley et al. 2015b).

Patient-reported outcomes

Patient self-reported function was evaluated using three reliable and validated clinical scales: the International Knee Documentation Committee (IKDC) (Higgins et al. 2007) Self-reported Questionnaire represents overall knee function; the five subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS) which provide objective values for levels of pain, disease-specific symptoms, activities of daily living, sport and recreation function, and knee-related quality of life (Salavati et al. 2011); and the Tampa Scale of Kinesiophobia (TSK) was used to assess fear of movement (Chmielewski et al. 2008).

Statistical analysis

Demographic variables between groups were compared using independent *t* tests. Separate 2 × 2 (group × limb) repeated measures analyses of variance (RM ANOVA) were used to evaluate differences between groups (ACLR and controls) and limbs (injured, contralateral) for each outcome variable. The designation of the "injured limb" for controls is explained at the beginning of the "Methods" section. Bonferroni post-hoc pairwise comparisons and *t* tests were used when appropriate. Alpha level was set a-prior at $p \leq 0.05$ and all statistics were performed using SPSS software version 25.0 (IBM, Armonk, NY, USA) was used for statistical analyses, with a priori levels of significance set at $p \leq 0.05$. In addition, a multivariate analysis of variance (MANOVA) was performed using each of the dependent variables, which provided the same results as the RM ANOVA, and thus is not presented.

fMRI data were submitted to a separate analysis (Worsley 2001). Participant level fMRI analyses (knee movement relative to rest) were thresholded non-parametrically using clusters determined by $Z > 3.1$ and a cluster corrected significance threshold of $p \leq 0.05$, higher level group

level analyses were thresholded $z > 3.1$ and $p \leq 0.01$ using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 (Beckmann et al. 2003; Woolrich 2008; Woolrich et al. 2004). The fMRI analysis allowed us to compare brain activation during movement of the ACLR-injured limb compared to the injured matched limb of the control. To determine the relationship between brain activation and patient-reported outcomes, spearman rho correlations were conducted in the ACLR group between KOOS pain, KOOS symptoms, TSK, and the ensemble mean brain activation of clusters observed to be statistically different in ACLR participants.

Table 1 Demographic information by group

	ACLR	Control	*p* value
n (female/male)	11 (6/5)	11 (6/5)	–
Age (years)	22.6 ± 1.8	23.2 ± 1.6	0.41
Height (cm)	167.4 ± 7.9	168.5 ± 10.3	0.77
Mass (kg)	66.2 ± 12.2	66.2 ± 12.7	1.00
Tegner activity level	7.9 ± 1.3	8.7 ± 1.7	0.23
Time from surgery (months)	69.4 ± 22.4	n/a	–
IKDC	85.7 ± 9.8[a]	100.0 ± 0.0	< 0.001
KOOS pain	90.6 ± 6.9[a]	100.0 ± 0.0	< 0.001
KOOS symptoms	83.4 ± 13.7[a]	100.0 ± 0.0	0.001
KOOS ADL	98.1 ± 3.2	100.0 ± 0.0	0.06
KOOS sport	88.6 ± 7.4[a]	99.5 ± 1.5	< 0.001
KOOS QOL	83.5 ± 14.8[a]	100.0 ± 0.0	0.001
TSK	31.1 ± 6.1[a]	20.9 ± 4.0	< 0.001
MVIC (Nm/kg) injured leg	2.95 ± 0.56[a]	3.52 ± 0.61	0.03
MVIC (Nm/kg) contralateral leg	3.27 ± 0.70	3.23 ± 0.71	0.75

ACLR anterior cruciate ligament reconstruction, *IKDC* International Knee Documentation Committee subjective questionnaire, *KOOS* Knee Osteoarthritis Outcome Score, *ADL* activities of daily living, *QOL* quality of life, *TSK* Tampa Scale of Kinesiophobia, *MVIC* maximal voluntary isometric contraction

[a]Denotes significant difference from the Control group

Results

A total of 22 participants (11 ACLR, 11 Control) volunteered for the study, and participant demographics can be found in Table 1. Nine participants were reconstructed using a patellar tendon autograft, while 2 were reconstructed using a semitendinosus/gracilis autograft. Two of the ACLR participants reported having medial meniscectomy during reconstruction.

No significant group differences were observed in demographic variables of age, height, mass, and activity level. ACLR participants reported significantly lower scores on all patient-reported outcomes compared to controls, indicating a greater level of disability, except for KOOS ADL. The ACLR participants also exhibited isometric quadriceps weakness in their injured limb compared to controls.

Means and standard deviations for all main outcome variables are reported in Table 2. No significant differences were observed for spinal reflex excitability. A significant group main effect was detected for AMT ($F_{1,20} = 14.12$, $p = 0.001$), indicating that AMT was significantly higher in the ACLR group regardless of limb compared to the control group, demonstrating a reduced ability to excite descending corticospinal neurons originating at the motor cortex. A significant group by limb interaction effect was detected for MEP ($F_{1,20} = 9.04$,

Table 2 Means ± standard deviations for major outcome variables

	ACLR		Control	
	Injured	Contralateral	Injured	Contralateral
H:M (%)	0.310 ± 0.172	0.256 ± 0.155	0.304 ± 0.204	0.288 ± 0.177
AMT (%T)	49.8 ± 9.6[†]	45.1 ± 9.4[†]	37.6 ± 5.3	37.8 ± 5.2
MEP (%)	0.0134 ± 0.0077*	0.0374 ± 0.0513	0.0225 ± 0.0121	0.0439 ± 0.037
RF muscle volume (cm^3)	143.2 ± 67.2*	151.5 ± 72.2	153.7 ± 61.5	149.0 ± 62.5
VM muscle volume (cm^3)	313.1 ± 151.8*	329.2 ± 151.4	340.7 ± 116.3	330.8 ± 105.1
VL muscle volume (cm^3)	433.5 ± 158.0	443.0 ± 140.3	424.1 ± 137.5	418.8 ± 128.2
VI muscle volume (cm^3)	351.0 ± 118.9*	359.3 ± 113.7	404.0 ± 150.1	393.5 ± 138.5
Total quadriceps muscle volume (cm^3)	1241.0 ± 463.6*	1283.3 ± 450.9	1322.6 ± 444.5	1292.3 ± 419.6

ACLR anterior cruciate ligament reconstruction, *H:M* Hoffmann reflex normalized to maximal muscle response, *AMT* active motor threshold, *MEP* motor-evoked potentials normalized to maximal muscle response, *RF* rectus femoris, *VM* vastus medialis, *VL* vastus lateralis, *VI* vastus intermedius

*Significantly different from ACLR contralateral and control limbs

[†]Significant group main effect. Regardless of limb, both limbs of ACLR group significantly different than controls (post-hoc pairwise comparisons)

$p = 0.007$), with uncorrected post-hoc analyses consistent with the idea that the injured limb of the ACLR group demonstrated smaller MEPs compared to the ACLR contralateral limb ($p = 0.02$) and both of the control group limbs ($p < 0.05$), which indicates that when activated, a smaller percentage of corticospinal signals reach the quadriceps muscle.

Significant group by limb interaction effects were discovered for muscle volumes of the RF ($F_{1,20} = 4.83$, $p = 0.04$), VM ($F_{1,20} = 7.32$, $p = 0.01$), VI ($F_{1,20} = 4.26$, $p = 0.05$), and TQ ($F_{1,20} = 11.82$, $p = 0.003$), with uncorrected post-hoc analyses consistent with the idea that muscle volumes were lower in the ACLR-injured limb compared to the contralateral and control limbs ($p < 0.05$), indicating systemic quadriceps muscle atrophy of the injured limb (Table 2).

fMRI analysis revealed that relative to the matched injured limb in the controls, the ACLR group demonstrated greater activation in four statistical clusters during the extension/flexion motor task of their injured limb encompassing anatomical regions: the frontal gyri, inferior frontal pole, paracingulate gyrus, and anterior cingulate gyrus (Table 3; Fig. 2). KOOS pain ($r = -0.66$, $p = 0.03$) and KOOS symptoms ($r = -0.81$, $p = 0.004$) was significantly correlated with increased frontal lobe brain activation, indicating that increased patient level of perceived pain and knee symptoms was related to increased activation of frontal lobe areas. TSK was not significantly associated with brain activation ($r = 0.58$, $p = 0.07$).

Discussion

Restoring quadriceps strength remains a critical component of therapeutic rehabilitation programs following ACLR, as quadriceps weakness is independently associated with many short- and long-term outcomes in these individuals. Unfortunately, quadriceps weakness has proven difficult to rectify, as it appears to result from multifaceted changes in neural and morphological characteristics of the muscle. This investigation aimed to improve our understanding of the persistent muscle weakness that is common following ACLR by simultaneously examining discrete differences in measures of neural activity and muscle morphology of the quadriceps. The results indicate that compared to controls, individuals with ACLR demonstrate differences in neural function in the presence of lower muscle strength, highlighted by a lesser ability to generate descending action potentials from the motor cortex (higher AMT), lower overall motor output (lower MEP), and greater activation in frontal areas of the brain responsible for motor planning and attention. Individuals with ACLR also exhibited smaller quadriceps muscle volume of their injured limb. Importantly, these systemic neural and morphological differences are observed concurrently with quadriceps muscle weakness and self-reported dysfunction, at an average of 6 years removed from surgery.

Other investigations have independently examined neural characteristics of the quadriceps muscle and have observed similar results to the current study. Several studies have discovered higher motor thresholds in ACLR participants in a range from 6 months to 4 years following reconstruction, with greater deficits observed the further the patient cohort

Table 3 fMRI contrast comparing brain activation between ACLR and matched controls

Cluster index	Brain region	Voxel (#)	*p* value	*z* max	MNI coordinate of peak voxel			*Z* center of gravity		
					x	*y*	*z*	*X*	*Y*	*Z*
1	BILATERAL Anterior cingulate gyrus	135	0.00487	5.18	2	−2	30	1.32	0.68	30.4
2	LEFT Inferior frontal gyrus (Pars triangularis & Pars opercularis)	149	0.00266	5.39	−50	26	10	−46.8	19.7	5.75
3	BILATERAL Paracingulate gyrus	232	0.000102	5.04	8	52	14	−2.34	47.1	8.15
4	RIGHT Frontal gyri, Frontal Operculum, Frontal pole	742	3.23e−11	5.81	46	24	4	41.4	40.5	3.49

Voxel #: indicates number of activated voxels in this cluster. The clusters are identified statically using Gaussian random field theory to identify the number of contiguous voxels whose voxelwise stats are above threshold

MNI Montreal Neurologic Institute provides a standardized reference atlas for region location and identification. *x, y, z* indicates 3D location of voxel with highest activity level in the cluster

Z center of gravity: considers the location of the other voxels in the cluster and computes a spatial center

z max: *Z*-score of the voxel with highest activity, z-score is level of activity relative to rest

was from injury (Heroux and Tremblay 2006; Lepley et al. 2015b; Norte et al. 2018a; Pietrosimone et al. 2015). Interestingly, these neural differences have also been discovered in other patients with musculoskeletal injuries of a chronic nature, including those with chronic ankle instability (Harkey et al. 2015; Pietrosimone and Gribble 2012), patellar tendinopathy (Rio et al. 2015), and knee osteoarthritis (Kittelson et al. 2014). Taken together, these results indicate that corticospinal deficits are present in chronic states of injury compared to controls and are progressive in nature. Longitudinal data are needed to substantiate this finding.

We believe that our data demonstrate systemic reorganization in the excitability of the motor cortex following ACLR. Specifically, we observed higher AMT bilaterally, physiologically indicating that neurons originating in the motor cortex responsible for voluntary quadriceps muscle contraction have higher cell membrane excitability compared to controls, making it more difficult for the individual to activate those neurons to fully control the muscle (Groppa et al. 2012). Concurrently, lower MEP values were also discovered, signifying that once an action potential is produced at the motor cortex, less of that signal will actually reach the muscle in ACLR participants (Luc-Harkey et al. 2017). Current theories suggest that this negative adaptation at the corticospinal level is in response to somatosensory and mechanical deficits arising from the injured joint (Needle et al. 2017), and is thought to be protective in nature by limiting unnecessary movement of an injured or painful joint (Hopkins and Ingersoll 2000). While the bilateral difference in AMT is interesting, this finding has been previously demonstrated in ACLR patients at a time when they were returned to sport activity by their orthopedic surgeon (Lepley et al. 2015b). Bilateral differences in corticospinal excitability may help to explain the strength deficits that are often detected on the contralateral limb in ACLR patients (Hiemstra et al. 2007; Mirkov et al. 2017); however, further investigation is needed to understand the significance of these bilateral differences. Although neural and morphological differences have separately been documented before, the current study demonstrates impairments in corticospinal excitability and muscle volume in the same cohort of ACLR participants compared to controls while also displaying quadriceps muscle weakness. Although these data help to improve our understanding of muscle weakness following ACLR, further research is needed to determine how clinicians can better develop a more targeted rehabilitation approach to intervene in these underlying corticospinal factors of muscle function.

The ACLR participants in the current study demonstrated smaller muscle volumes of the RF, VM, VI, and total quadriceps compared to their contralateral limbs, and both control limbs. This finding strengthens previous research, which has shown varying levels of quadriceps atrophy in the injured limb, anywhere from 5 to 28% smaller compared contralaterally or to controls (Konishi et al. 2007; Norte et al. 2018a; Thomas et al. 2016; Williams et al. 2005a). It is important to note that the majority of the literature focuses on patients within 1-year from surgery, demonstrating that muscle atrophy is still present at a time when physician clearance is typically granted, and therapeutic rehabilitation has finished. Less information is available regarding muscle function in later stages of injury; however, our study shows smaller quadriceps muscles of the injured limb (4–7% smaller compared contralaterally, 7–14% smaller compared to controls) even at an average of 6 years removed from surgery. This indicates that muscle atrophy is a chronic problem that is not restored through normal rehabilitation, persists through medical clearance and return to play, and may have long-lasting implications for these patients. In particular, recent research has suggested that persistence deficits in muscle size and strength can influence the development of post-traumatic joint osteoarthritis that affects nearly 50% of ACLR patients within 10–15 years (Silva et al. 2018; Tourville et al. 2014). Due to the case–control study design of the current investigation, we are unfortunately unable to determine how muscle volume changes over time in ACLR participants, or how changes in neural excitability influence changes in muscle volume. However, we believe that the findings of the current study support further investigations using longitudinal study designs to better understand changes in these parameters over time.

Our fMRI data indicate that during the knee extension/flexion task, ACLR participants had more brain activation (i.e., more blood flow) in several areas of the frontal lobe. These specific areas of the brain are known to play a role in motor planning (Molnar-Szakacs et al. 2005), directing attention (Hoffstaedter et al. 2014), inhibiting motor control (Rae et al. 2015), and engaging motor sequences (Lohse et al. 2014) and complex motor coordination (Wenderoth et al. 2005). Our results corroborate the work by Baumeister et al. (2008, 2011) who also discovered increased frontal lobe and anterior cingulate gyrus activity (as measured via electroencephalography) in ACLR participants compared to controls during force reproduction and joint reposition tasks. These authors hypothesized that the increase in frontal lobe activity was due to higher neurocognitive attention/processing that is required by individuals with ACLR during motor tasks. Increased activation of the anterior cingulate gyrus, paracingulate gyrus and inferior frontal gyrus have all previously been related to error response during motor tasks, especially when that task involves switching between movements or stimuli (Heun et al. 2000; Ruby et al. 2002; Woodward et al. 2006). The role of the frontal cortex in error correction is, in part, driven by its inhibitory effects via subcortical motor pathways which may in turn affect downstream motor activity within and from the cortex. Increased

activation in these frontal and attention areas could also represent degraded neural efficiency or generally increased neural processing during the task (Rae et al. 2015), and may manifest as increased reaction time and\or impaired motor coordination during sport (Del Percio et al. 2009; Dunst et al. 2014). It is possible that during simple tasks (like the extension/flexion task employed in this study), individuals with ACLR engage more neural resources that are typically reserved for more complex coordination and motor planning, thus leaving less potential neural resources for increasing task complexity, which may have implications on safety during sport and dynamic activities.

Increased cortical activation of the areas discovered in our ACLR participants have also been associated with higher levels of fear and the expression of fear and pain-related avoidance behaviors and negative emotion (Gao et al. 2004). Given that the ACLR participants in the current study all reported some level of pain (as denoted via KOOS pain and symptom scores; Table 1) and fear of movement (as denoted via TSK scores; Table 1), we chose to further explore this relationship by performing correlation analyses between KOOS pain, KOOS symptoms, TSK, and the ensemble mean brain activation of the four frontal lobe clusters observed to be statistically different in individuals with ACLR (as visually depicted in Fig. 2b). Interestingly, KOOS pain and KOOS symptoms were significantly correlated with increased frontal lobe brain activation, indicating that increased patient level of perceived pain and knee symptoms was related to increased activation of frontal lobe areas. Both fear and pain can have negative influences on muscle function, and although we cannot make direct inferences based on the current data, it is possible that increased levels of reported pain are associated with increased activation of these cortical areas, which in turn results in decreased excitability (i.e., inhibition) of the motor cortex to limit unnecessary movement of the injured/painful joint. This theory would also help to explain the smaller quadriceps muscle volume and clinical deficits in muscle strength observed in these participants, although further exploration is warranted.

Only two other investigations (Grooms et al. 2017; Kapreli et al. 2009) have examined fMRI brain activation in individuals following ACL injury. Both studies found lower activation in the ipsilateral motor areas in these participants compared to controls. This finding was not corroborated by our work. Kapreli et al. (2009) examined individuals who remained ACL deficient and were 26.2 months from injury, while Grooms et al. (2017) investigated ACLR participants on average 38.1 months from surgery. Noticeably different from these other two studies is that the current investigation used ACLR participants much further from injury, on average 69.4 month post-surgery. It is possible that lower activation of ipsilateral motor areas is present during this stage of injury (i.e., 26–38 months) and is a mechanism for triggering reductions in motor cortex excitability over time. This theory would also support the hypothesis stated above suggesting that neural changes at the cortical level are progressive. Larger scale, longitudinal study designs are warranted to thoroughly explore this relationship and the dynamic of neural and morphological changes as individuals progress following ACLR.

Limitations

Among the limitations to this investigation are the fact that M responses were elicited while the participants were supine, and used to normalize corticospinal measures that were elicited while seated. Although muscle length is different between these positions, potentially providing a different M response, this method is widely used in the literature and was conducted in the same manner for every participant in the current study, which we strongly believe limits the impact of this positional difference. Another limitation is that the authors are unable to conclude whether the neural and morphological differences in quadriceps function were present prior to the injury occurring, or as a result of the injury itself. Although prospective data regarding the influence of neural excitability on primary ACL injury risk are lacking, the authors believe that these neural differences occur as a response to injury based on published data following joint injury models (Hopkins et al. 2000, 2001b; Lepley et al. 2015a; Palmieri et al. 2004a, b; Palmieri-Smith et al. 2007; Rice et al. 2014), and longitudinal changes in neural excitability over time in ACLR patients, which does not occur in control participants (Lepley et al. 2015b).

Conclusions

This investigation examined differences in discrete measures of quadriceps neural activity and muscle morphology in individuals with a history of ACLR compared to controls. ACLR participants in this study demonstrated differences in neural excitability and quadriceps muscle morphology compared to controls. Specifically, a lesser ability to generate descending action potentials from the motor cortex, lower motor output, and higher activation to frontal lobe areas of the brain responsible for motor processing was found in the ACLR group compared to controls. Importantly, these systemic neural differences are observed concurrently with smaller quadriceps muscle volume of the injured limb, quadriceps muscle weakness, and self-reported dysfunction, at an average of 6 years removed from surgery.

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