



Original research

Does brain functional connectivity contribute to musculoskeletal injury? A preliminary prospective analysis of a neural biomarker of ACL injury risk



Jed A. Diekfuss^{a,*}, Dustin R. Grooms^b, Weihong Yuan^c, Jonathan Dudley^c,
Kim D. Barber Foss^a, Staci Thomas^a, Jonathan D. Ellis^{a,d}, Daniel K. Schneider^{a,d},
James Leach^e, Scott Bonnette^a, Gregory D. Myer^{a,f,g,h}

^a The SPORT Center, Division of Sports Medicine, Cincinnati Children's Hospital Medical Center, USA

^b Ohio Musculoskeletal & Neurological Institute and Division of Athletic Training, School of Applied Health Sciences and Wellness, College of Health Sciences and Professions, Ohio University, USA

^c Pediatric Neuroimaging Research Consortium, Cincinnati Children's Hospital Medical Center, USA

^d University of Cincinnati College of Medicine, USA

^e Division of Radiology, Cincinnati Children's Hospital Medical Center, USA

^f Departments of Pediatrics and Orthopaedic Surgery, University of Cincinnati, USA

^g The Micheli Center for Sports Injury Prevention, USA

^h Department of Orthopaedics, University of Pennsylvania, USA

ARTICLE INFO

Article history:

Received 12 January 2018

Received in revised form 25 June 2018

Accepted 4 July 2018

Available online 10 July 2018

Keywords:

Resting-state fMRI

Knee

Musculoskeletal injury

Central nervous system

ABSTRACT

Objectives: We aimed to present a unique prospective neurological dataset for participants who experienced an ACL injury.

Design: Prospective longitudinal case-control.

Methods: High school female soccer athletes were evaluated using functional magnetic resonance imaging to capture resting-state brain connectivity prior to their competitive season. Two of these athletes later experienced an ACL injury (ACLI). We matched these ACLI participants with eight teammates who did not go on to sustain an ACL injury (uninjured controls, Con) based on age, grade, sex, height, and weight to examine differences in preseason connectivity. Knee-motor regions of interest (ROIs) were created based on previously published data from which five specific areas were selected as seeds for analysis. Independent-samples *t*-tests with a false discovery rate correction for multiple comparisons determined differences in connectivity between the ACLI and Con.

Results: There was significantly greater connectivity between the left primary sensory cortex (a brain region responsible for proprioception) and the right posterior lobe of the cerebellum (a brain region responsible for balance and coordination) for the Con relative to ACLI, $t(8) = 4.53$, $p = 0.03$ (false discovery rate corrected).

Conclusions: These preliminary data indicate that those who do not later sustain an ACL injury exhibit a stronger functional connection between a cortical sensory-motor region and a cerebellar region responsible for balance and coordination. These findings may help to guide development of brain-driven biofeedback training that optimizes and promotes adaptive neuroplasticity to reduce motor coordination errors and injury risk.

© 2018 Sports Medicine Australia. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Peripheral musculoskeletal injuries, such as anterior cruciate ligament (ACL) trauma, are associated with alterations in the central nervous system (CNS).^{1,2} When the ligament is ruptured,

mechanoreceptors are lost^{3,4} and afferent pathways are disrupted, causing motor compensations and CNS remodeling.^{3,5} The most common mechanism of ACL injury is non-contact which can be attributed to motor coordination errors that result in excessive knee valgus position and load that can subsequently overload the tissue properties of the ACL.⁶ The motor coordination errors that result in high injury risk knee positioning are in part due to the nervous system failing to ensure a safe knee position while navigating through the athletic field and interacting with other players.⁷

* Corresponding author.

E-mail address: Jed.Diekfuss@cchmc.org (J.A. Diekfuss).

Thus, it is possible that the aberrant neurologic patterns detected after injury,^{2,8,9} are actually present, in part, prior to the injury and contribute to the initial injury mechanism.

CNS function has been prospectively examined with respect to ACL injury using neurocognitive testing¹⁰ and measures of muscle strength and activation.¹¹ Intercollegiate athletes who experienced non-contact ACL injuries exhibited significantly poorer test scores on all four subtests of the Immediate Post-Concussion Assessment and Cognitive Testing (ImpACT), including reaction time, processing speed, visual memory, and verbal memory compared to matched controls,¹⁰ indicating a potential neurocognitive predisposition to ACL injury. Additionally, decreased quadriceps activation was reported in a single subject hours prior to an ACL injury,¹¹ indicating that components of the CNS are potentially disrupted prior to the injury incident. However, neurocognitive testing provides only an indirect measure of potential neural deficits, and quadriceps activation, as measured using the central activation ratio,¹¹ does not allow inference as to what aspect of the nervous system is driving the potential muscle inhibition. While these studies have provided the foundation for prospectively examining CNS factors contributing to ACL injury, there is a paucity of data examining more direct measures of CNS function prior to injury. Prospectively quantifying CNS differences prior to an ACL injury event could provide novel insights into the design of interventions that leverage neuroplasticity to facilitate motor control changes and injury reduction.

One method to assess predisposing differences in brain processing is by assessing differences in resting-state functional magnetic resonance imaging (fMRI) connectivity (functional connectivity). Defined as temporal correlations of spontaneous low frequency fluctuations of the blood oxygen dependent level (BOLD) signal between different brain regions at rest,¹² functional connectivity can differentiate between groups with various pathologies,¹³ and coordination expertise or capability.¹³ Thus functional connectivity could provide additional insight into CNS differences that predispose an individual to an ACL injury. The purpose of this study was to present a unique dataset originally captured for a concussion intervention, but which also provided prospective neurological data for participants who experienced an ACL injury. We hypothesized that those who experienced an ACL injury would have different brain connectivity characteristics than those who did not experience a traumatic knee injury. Specifically, we evaluated prospective differences in resting state functional connectivity in cases that went on to ACL injury relative to matched teammates that did not go on to ACL injury during their competitive season.

2. Methods

Seventy-two female participants were enrolled in a prospective longitudinal neuroimaging study from two local high schools. Fifteen participants were excluded due to metal orthodontics, leaving a total of 57 athletes who completed a preseason imaging testing session. From this cohort, two athletes experienced non-contact complete ACL tears during their competitive soccer season (ACLI: $n=2$, 16.0 ± 0 years, 169.0 ± 2.8 cm, 60.1 ± 8.3 kg) and were matched with eight athletes who did not sustain an ACL injury (controls, Con) based on age, team, year in school, sex, height, and weight (Con, $n=8$, 15.9 ± 0.8 years, 164.0 ± 4.9 cm, 58.3 ± 7.6 kg). Individual demographic data is presented in Table 1. Magnetic resonance imaging (MRI) scans were completed prior to the soccer season for all participants. One ACLI participant injured her ACL two weeks after the testing session and the second ACLI participant injured her ACL approximately 3.5 months after the testing session. No other musculoskeletal injuries or concussions were reported prior to the ACL injury. The institutional review board approved the project and informed consent was obtained prior to commencing the study.

MRI was conducted on a Phillips 3T Ingenia scanner (Philips Medical Systems, Best, the Netherlands) with a 32-channel, phase array head coil. First, a MPRAGE sequence was used to acquire high resolution 3D T1-weighted images (sagittal): TR=8.1 ms, TE=3.7 ms; field of view=256 × 256 mm; matrix=256 × 256; in-plane resolution=1 × 1 mm; slice thickness=1 mm; number of slices=180. Next, resting state fMRI data were acquired with the following parameters: TR=650 ms; TE=30 ms; flip angle=53°; field of view=200 × 200 mm; acquisition matrix=68 × 66; SENSE factor=1.5; reconstructed in-plane resolution=2.5 × 2.5; slice thickness=3.5 mm; number of slices=40; multi band factor=4. Participants were asked to look at a crosshair reflected on a projector and remain still. A total of 500 frames of data were collected with the total time of the resting-state fMRI session at approximately 5.5 min.

Spatial and temporal preprocessing of fMRI data were carried out using the CONN toolbox (version 17.F, <http://www.nitrc.org/projects/conn>).¹⁴ Spatial preprocessing steps utilized routines from the Statistical Parametric Mapping (SPM) 12 package (Wellcome Institute of Cognitive Neurology, London) and included: realignment & unwarping, normalization to Montreal Neurological Institute (MNI) template space (resampled to 2 mm isotropic), and smoothing (8 mm full-width half-max kernel). Temporal preprocessing steps were completed in CONN and included: scrubbing

Table 1
Individual demographic information.

Participant	Age (years)	Height (cm)	Weight (kg)	Hormonal birth control	Experience (years)	Grade	^a Injury side
Injured							
1	16	167	73.8	No	9	11th	Left
2	16	171	60.8	No	10	11th	Right
Control							
3	15	168	68.7	–	–	10th	N/A
4	16	158	64.0	–	–	11th	N/A
5	15	165	66.8	–	–	10th	N/A
6	16	168	59.9	–	–	10th	N/A
7	15	169	54.7	No	12	11th	N/A
8	17	157	50.5	No	3	12th	N/A
9	16	160	51.6	No	10	11th	N/A
10	17	167	50.2	No	14	12th	N/A

– indicates participant did not report this data.

^a Both injuries were non-contact and resulted in complete ruptures of the ACL.

Table 2
Knee-motor-related regions of interest.

Regions of interest	MNI coordinate of peak voxel		
	X	Y	Z
Left primary sensory cortex ^a	-12	-36	72
Left primary motor cortex ^a	-4	-16	72
Left supplementary motor area ^a	-4	0	54
Left primary sensorimotor cortex	-16	-40	64
Left supplementary motor area	-2	-24	66
Left cingulate motor area	-12	-6	44
Left premotor cortex	-24	-26	64
Left secondary sensory cortex	-40	-28	20
Left Basal Ganglia, External Segment of Globus Pallidus	-32	-16	8
Left Thalamus	-18	-22	10
Left Cerebellum (Vermis)	-2	-48	-8
Left Cerebellum (Anterior Lobe)	-14	-38	-18
Left Cerebellum (Posterior lobe)	-22	-60	-40
Right lingual gyrus ^a	20	-66	-4
Right primary sensorimotor cortex	12	-38	64
Right supplementary motor area	0	-24	68
Right cingulate motor area	10	-6	42
Right premotor area	12	-22	72
Right secondary sensory cortex	30	-26	20
Right basal ganglia, external segment of globus pallidus	28	-10	16
Right Thalamus	20	-18	-2
Right VIIb Cerebellum ^a	34	-54	-46
Right Cerebellum (Vermis)	4	-50	-16
Right Cerebellum (Anterior Lobe)	14	-40	-22
Right Cerebellum (Posterior Lobe)	20	-50	-50

Regions of interest selected from knee-motor flexion-extension data from Karepli et al.¹⁷

^a Indicates the regions selected from Grooms et al.¹⁶ using the same paradigm, but with a participant who ruptured their ACL days later.

of motion-outlier frames (>2 mm or ± 3 standard deviation in global signal), regression of the top five principle components of the BOLD signal from cerebrospinal fluid and white matter compartments (aCompCor),¹⁵ as well as zero- and first-order derivatives of realignment parameters and band-pass filtering to a window of 0.008 Hz–0.09 Hz. Functional connectivity measures were computed as the Fisher transformed Pearson correlation coefficients between the average residual BOLD time series of pairs of regions of interest (ROIs).¹²

To determine neurological differences in brain connectivity related to knee motor control, we created regions of interest based on previously published knee-related fMRI data.^{16,17} These previous reports have localized the brain regions for knee flexion and extension. Briefly, patients were asked to flex and extend their knee in conjunction with an auditory metronome (1.2 Hz) using a block design paradigm. Results indicated that the active regions for knee movement were unique from the regions associated with finger, ankle, and toe movement.¹⁷ Three-dimensional spheres (10 mm diameter) centered at the MNI coordinates corresponding to each region active during knee movement¹⁷ were created and used as ROIs in the current investigation. These regions included the left and right primary sensorimotor cortex, supplementary motor area, cingulate motor area, premotor cortex, secondary sensory cortex, basal ganglia (external segment of globus pallidus) and left and right sections of the cerebellum (anterior lobe, posterior lobe, vermis).

In addition, we included ROIs from a recent case study between a participant who had a history of ACL injury and shortly after brain imaging, experienced a second ACL rupture in the previously unaffected limb relative to a matched control.¹⁶ In the present study, we used the unique areas of activation from this previously unaffected limb relative to the matched control as seeds (also 10 mm spheres centered at the reported MNI coordinates) for subsequent ROI analyses due to their association with ACL injury. The unique regions were the left primary sensory cortex, right VIIb cerebellum, right lingual gyrus, left primary motor cortex and left supplementary motor area. In summary, our analyses investigated 25 ROIs in which 5 of these regions (taken from Grooms et al.¹⁶) were used as seeds due to their more direct prospective association with an ACL injury event (see Table 2 for MNI coordinates).

We conducted ROI analyses to test our hypothesis that differences in knee-motor-related connectivity would be present between groups (ACLI and Con) prior to the injury occurrence. Specifically, independent-samples *t*-tests were used to determine differences in connectivity between the ACLI and Con using the five pre-selected ACL-related ROIs as seeds. Results are reported when significant at a level of $p < 0.05$ with multiple comparison error corrected using the false discovery rate (FDR) approach.¹⁸ Due to the small and uneven sample sizes, we conducted secondary Mann-Whitney *U* tests for any significant findings to account for potential non-normality in the data.

3. Results

Results revealed significantly greater connectivity between the left primary sensory cortex and the right posterior lobe of the cerebellum for the Con relative to ACLI, $t(8) = 4.83$, $p = 0.03$ (FDR corrected for multiple comparisons). Our secondary Mann-Whitney *U* test further confirmed significant group differences (Con median connectivity = 0.39; ACLI median connectivity = -0.14), $U = 0.0$, $p = 0.04$. See Fig. 1 for a graphical display of the significant ROIs and individual subject connectivity data between these two regions.

4. Discussion

The purpose of this study was to provide prospective neurological data for participants who experienced an ACL injury. We evaluated altered brain connectivity that may have predisposed athletes to ACL injury. We hypothesized differences in CNS function, as measured by functional connectivity, between those who go on to experience an ACL rupture relative to matched controls. Results supported our hypothesis and revealed that those who go on to experience an ACL injury exhibit a functional connectivity difference relative to controls. Specifically, those that go on to ACL injury have decreased functional connectivity between the left primary sensory cortex (S1) and right posterior lobe of the cerebellum (Lobule XIIb) prior to their injury. The contribution of this study is the assessment of CNS function prior to an ACL injury, whereas the vast majority of previous literature has only assessed nervous system function after an ACL injury.^{8,9,19–21} While Grindstaff et al.¹¹ did report quadriceps muscle activation deficits and Swanik et al.¹⁰ reported decreased neurocognitive function prior to an ACL injury, our data supplements these findings by assessing CNS function directly at the cerebral level.

Planning, executing, and controlling movement requires complex neural processing dependent on the integration of sensory input from the body and external environment.²² The S1 plays a critical role in processing sensory signals to guide subsequent motor actions, and the cerebellum is highly involved in postural stability.²³ Considering that poor biomechanical coordination is prospectively linked to ACL injury,⁶ our finding of depressed

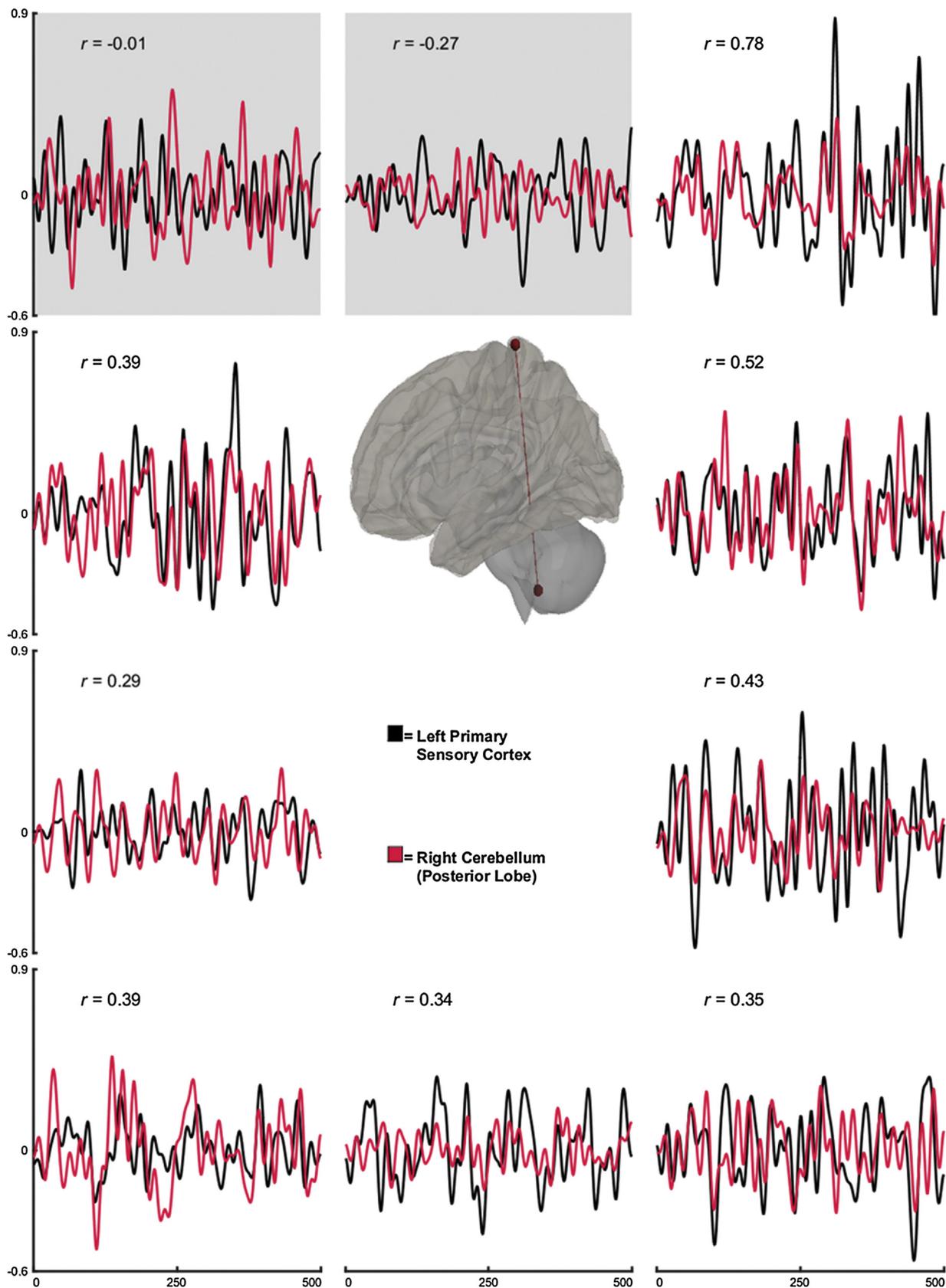


Fig. 1. Each panel corresponds to individual subject connectivity data between the left primary sensory cortex and right posterior lobe of the cerebellum. There was significantly greater connectivity for the eight control participants relative to two participants who later experienced an ACL rupture (shaded gray), $t(8) = 4.57$, $p = 0.04$, $U = 0.0$, $p = 0.04$. R values are Fisher transformed Pearson correlation coefficients between the average residual BOLD time series of pairs of regions of interest. The y -axis is the BOLD signal and the x -axis is volumes.

connectivity between the S1 and cerebellum for those who later experienced an ACL rupture indicates a possible neural motor dysfunction underlying ACL injury risk. In addition to supporting previous literature indicating supraspinal processing contributions to ACL injury risk,¹⁰ our data also support previous research that has identified sensory-cerebellar connectivity as vital for motor control.²⁴ To successfully navigate throughout the environment, an individual must coordinate their movements despite changing temporal and spatial demands (e.g., a soccer player predicting when and where to jump to head a moving soccer ball). Evidence from a perceptual judgement task revealed that tasks requiring spatial and temporal dimensions increased brain activity and connectivity within sensory and cerebellar regions, while cerebellar activity was absent for tasks requiring only a spatial dimension.²⁵ Considering compromised knee positions occur under spatially and temporally demanding situations,⁷ and our findings of prospective reduced sensory-cerebellar connectivity prior to the injury incident, we provide preliminary evidence of a neural biomarker that may predispose an athlete to an ACL injury. However, the small sample size for our injured population requires cautious interpretation and requires further investigation.

In line with our prospective alterations in S1 connectivity, increased somatosensory activity using EEG was observed post-ACL injury to engage in knee position control.^{8,9} Additional results revealed increased frontal Theta power in the ACL patients relative to matched controls suggesting increased attentional activity from the anterior cingulate cortex. In other words, those with an ACL reconstruction required higher focused attention to achieve the same force control behavioral results.⁸ Similar increased theta power results were revealed when comparing ACL injured and reconstructed limbs to healthy limbs during a joint position task.⁹ Collectively these data further indicate sensory CNS disruption prior to, and following ACL injury.

Previous literature has reported a variety of potential risk factors for ACL injury in young females including excessive knee valgus position and load,⁶ reduced neurocognitive function,¹⁰ increased joint laxity,²⁶ small femoral notch widths,²⁷ and altered neuromuscular properties.^{11,28} As such, all of these factors have warranted discussion as to potential interventions to target the relevant processes. The present findings are the first to report differences in functional connectivity to identify ACL injury risk by measuring correlated spontaneous low frequency fluctuations of the BOLD signal between different brain regions at rest. While utilizing fMRI to assess injury risk can be costly and time consuming, these data provide mechanistic understanding of the potential neural control of motor coordination factors contributing to ACL injury and adds a potential intervention target to ACL prevention programs.

Albeit we had an *n* of 2 for our ACL injured sample, continued work investigating functional connectivity could aid in novel neural, mechanistic, targeted interventions. A variety of techniques derived from motor behavior literature (e.g., autonomy support, enhanced expectancies, focus of attention) could be utilized to promote neural plasticity for enhanced motor control.²⁹ For example, directing an individual towards the effects of his or her movement instead of on movement execution (i.e., an internal focus), has been theorized to activate dopaminergic pathways by strengthening synaptogenetic processes for memory consolidation via co-activation of various brain regions.²⁹ Further, evidence from an ACL injury prevention program revealed that a 10-week landing skill training program reduced corticomotor excitability in the gluteus maximus relative to strength training, indicating potentially increased use of sub-cortical or cerebellar areas to regulate movement.³⁰ These results indicate that ACL injury prevention programs could potentially be merged with various motor behavior principles to promote adaptive neuroplasticity to decrease motor coordination errors that lead to injury.

Several limitations must be considered associated with the current results indicating that altered functional connectivity underlies ACL injury risk. First, the sample size for our ACLI group is small. However, the prospective data are rare and offer a novel contribution to the literature. The current results align with previous neurologic work investigating ACL post-injury^{2,3,16} and provide a foundation for future investigations that aim to prospectively examine ACL injury risk. We also attempted to control for our uneven sample sizes and any non-normality in the data by completing a secondary Mann Whitney *U* test on significant results. Second, this data does not necessarily suggest a direct causal relationship between S1 and cerebellar Lobule XIIB connectivity with ACL injury incidence. This data is intended to purely document the differences in connectivity prospectively and allow for future investigations to isolate these regions in further analyses. Lastly, the length of time from the resting-state scan prior to the ACL injury varied for our two ACLI participants (two weeks versus 3.5 months). Future research should aim to: (a) evaluate larger samples of prospective ACL patients; (b) include time between testing sessions, as well as other ACL injury risk factors not collected as part of this study including mental health challenges, current medications and menstrual cycle as covariates to account for any potential confounding effects; (c) investigate changes in connectivity within the S1 and cerebellar lobule XIIB following ACL prevention programs; (d) consider integrating motor behavioral principles into ACL recovery and prevention to explore their relative influence on brain function; and (e) future investigations with larger sample sizes could investigate whether our non-significant connectivity comparisons could provide any further insight on the cerebral CNS contributions to ACL injury.

5. Conclusion

This study provides a potential neural biomarker for clinicians and researchers developing ACL injury prevention methods. Novel clinical tests to assay sensory-cerebellar connectivity could be developed to potentially help identify athletes who may be at higher risk for knee injury and benefit from novel, neural-driven, mechanistic interventions. Decreased sensory-cerebellar connectivity could possibly be increased by merging motor behavior principles with current neuromuscular training programs. However, our sample size was small, thus novel interventions should be implemented with caution, and likely only done in an adjunct manner supplementing current standard of care.

Practical implications

- Decreased sensory-cerebellar connectivity may predispose an athlete to an ACL injury.
- Altered S1 and cerebellar Lobule XIIB connectivity could be a target for neural-driven interventions.
- Motor learning principles could facilitate adaptive neuroplasticity and restore connectivity.²⁹

Funding

The authors would like to acknowledge funding support from the National Institutes of Health/NIAMS Grant U01AR067997 and Cincinnati Children's Hospital Research Innovation and Pilot Fund (IA# 31-41165-587000).

Acknowledgements

The authors would like to thank the following from Seton High School: Ron Quinn, Lisa Larosa, Holly Laiveling, and the entire soccer

coaching staff as well as the Seton administration and athletic director Wendy Smith; from Madeira High School soccer head coach Dan Brady, athletic director Joe Kimling, and principal David Kennedy for their support and assistance to conduct this study. Thank you to the soccer parents and players for participating and support the efforts to complete the project. We appreciate their patience with the testing scheduling and follow-up testing. Their enthusiastic support made this study possible. Special acknowledgement goes to the Athletic Trainers at Seton High School, Cindy Busse and Madeira High School, Glenna Knapp. Without their time, commitment, and passion for the health and well-being of their student athletes, this study would not have been possible. The authors would also like to thank Lacey Haas, Brynne Williams, Matt Lanier, and Kaley Bridgewater in the Imaging Research Center as their support made this study possible.

References

- Courtney C, Rine RM, Kroll P. Central somatosensory changes and altered muscle synergies in subjects with anterior cruciate ligament deficiency. *Gait Posture* 2005; 22(1):69–74.
- Grooms DR, Page SJ, Nichols-Larsen DS et al. Neuroplasticity associated with anterior cruciate ligament reconstruction. *J Orthop Sports Phys Ther* 2017; 47(3):180–189.
- Kapreli E, Athanasopoulos S. The anterior cruciate ligament deficiency as a model of brain plasticity. *Med Hypotheses* 2006; 67(3):645–650.
- Valeriani M, Restuccia D, Lazzaro VD et al. Central nervous system modifications in patients with lesion of the anterior cruciate ligament of the knee. *Brain* 1996; 119(5):1751–1762.
- Melnyk M, Faist M, Gothner M et al. Changes in stretch reflex excitability are related to “giving way” symptoms in patients with anterior cruciate ligament rupture. *J Neurophysiol* 2007; 97(1):474–480.
- Hewett TE, Myer GD, Ford KR et al. Biomechanical measures of neuromuscular control and valgus loading of the knee predict anterior cruciate ligament injury risk in female athletes. *Am J Sports Med* 2005; 33(4):492–501.
- Krosshaug T, Nakamae A, Boden BP et al. Mechanisms of anterior cruciate ligament injury in basketball: video analysis of 39 cases. *Am J Sports Med* 2007; 35(3):359–367.
- Baumeister J, Reinecke K, Schubert M et al. Altered electrocortical brain activity after ACL reconstruction during force control. *J Orthop Res* 2011; 29(9):1383–1389.
- Baumeister J, Reinecke K, Weiss M. Changed cortical activity after anterior cruciate ligament reconstruction in a joint position paradigm: an EEG study. *Scand J Med Sci Sports* 2008; 18(4):473–484.
- Swanik CB, Covassin T, Stearne DJ et al. The relationship between neurocognitive function and noncontact anterior cruciate ligament injuries. *Am J Sports Med* 2007; 35(6):943–948.
- Grindstaff TL, Jackson KR, Garrison JC et al. Decreased quadriceps activation measured hours prior to a noncontact anterior cruciate ligament tear. *J Orthop Sports Phys Ther* 2008; 38(8):502–507.
- Biswal B, Zerrin Yetkin F, Haughton VM et al. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 1995; 34(4):537–541.
- McLeod KR, Langevin LM, Goodyear BG et al. Functional connectivity of neural motor networks is disrupted in children with developmental coordination disorder and attention-deficit/hyperactivity disorder. *NeuroImage: Clin* 2014; 4:566–575.
- Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect* 2012; 2(3):125–141.
- Behzadi Y, Restom K, Liu J et al. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage* 2007; 37(1):90–101.
- Grooms DR, Page SJ, Onate JA. Brain activation for knee movement measured days before second anterior cruciate ligament injury: neuroimaging in musculoskeletal medicine. *J Athl Train* 2015; 50(10):1005–1010.
- Kapreli E, Athanasopoulos S, Paphathanasiou M et al. Lower limb sensorimotor network: issues of somatotopy and overlap. *Cortex* 2007; 43(2):219–232.
- Chumbley J, Worsley K, Flandin G et al. Topological FDR for neuroimaging. *Neuroimage* 2010; 49(4):3057–3064.
- Konishi Y. ACL repair might induce further abnormality of gamma loop in the intact side of the quadriceps femoris. *Int J Sports Med* 2011; 32(04):292–296.
- Konishi Y, Konishi H, Fukubayashi T. Gamma loop dysfunction in quadriceps on the contralateral side in patients with ruptured ACL. *Med Sci Sports Exerc* 2003; 35(6):897–900.
- Madhavan S, Shields RK. Neuromuscular responses in individuals with anterior cruciate ligament repair. *Clin Neurophysiol* 2011; 122(5):997–1004.
- Wolpert D, Pearson K, Ghez C. The organization and planning of movement. *Principles of Neural Sci* 2013; 5:743–767.
- Morton SM, Bastian AJ. Cerebellar control of balance and locomotion. *Neuroscientist* 2004; 10(3):247–259.
- Manto M, Bower JM, Conforto AB et al. Consensus paper: roles of the cerebellum in motor control—the diversity of ideas on cerebellar involvement in movement. *Cerebellum* 2012; 11(2):457–487.
- O'Reilly JX, Mesulam MM, Nobre AC. The cerebellum predicts the timing of perceptual events. *J Neurosci* 2008; 28(9):2252–2260.
- Söderman K, Alfredson H, Pietilä T et al. Risk factors for leg injuries in female soccer players: a prospective investigation during one out-door season. *Knee Surg Sports Traumatol Arthrosc* 2001; 9(5):313–321.
- Emerson R. Basketball knee injuries and the anterior cruciate ligament. *Clin Sports Med* 1993; 12(2):317–328.
- Solomonow M, Baratta R, Zhou B et al. The synergistic action of the anterior cruciate ligament and thigh muscles in maintaining joint stability. *Am J Sports Med* 1987; 15(3):207–213.
- Wulf G, Lewthwaite R. Optimizing performance through intrinsic motivation and attention for learning: the OPTIMAL theory of motor learning. *Psychon Bull Rev* 2016;(2).
- Powers CM, Fisher B. Mechanisms underlying ACL injury-prevention training: the brain-behavior relationship. *J Athl Train* 2010; 45(5):513–515.