THE FUTURE OF ACL PREVENTION AND REHABILITATION

INTEGRATING TECHNOLOGY TO OPTIMIZE PERSONALIZED MEDICINE

EPIDEMIOLOGY OF ACL INJURY AND SECONDARY INJURY
A recent meta-analysis revealed that one in 29 females and one in 50 male athletes rupture their ACL when monitored over the years of their athletic participation. Despite widespread interest in research and application of injury prevention programs for athletic populations, the incidence of ACL injuries continues to rise. This is at odds with a large volume of evidence supporting that implementing ACL injury reduction training programs, especially neuromuscular and strength-based training, reduces the risk of sustaining an ACL injury. Unfortunately, up to 50% of injured athletes do not return to their prior level of sport. As a result of several factors that contribute to re-injury, those who do return to sport are 30 to 40 times more likely to suffer a second ACL injury on the same or contralateral knee. Specifically, within two years of an ACL reconstruction (ACL-R), up to 30% of athletes experience a second ACL tear. It has also been observed that as many as 55% of the recurrent ACL injuries are noncontact events, which supports the suggestion that sensorimotor deficits are present following ACL reconstruction and rehabilitation. Cumulatively, current evidence points toward shortcomings in current approaches to ACL injury prevention, rehabilitation, and risk assessment methods. These must be addressed to reduce the negative effects of ACL injuries such as pain, depression, lost athletic identity, fear of re-injury, and ultimately prevent initial ACL injuries on a wider scale.

CURRENT STRATEGIES FOR INJURY PREVENTION

Current injury prevention programs, while effective at curtailing risk factors in laboratory settings, have not reduced widespread ACL injury rates.

The shortcomings of current programs may arise from several common problems, including athlete noncompliance, the type of training program, and the resources needed to institute in practice. Further details are provided below.

a. Participant noncompliance
Participant noncompliance is a unique issue to consider in developing a successful injury prevention program because it is a source of variability typically not directly related to or measured relative to the empirical motivation for the designed intervention (e.g., what risk factors are targeted, what methods are used to reduce these factors, and when the program is implemented). High compliance and adherence are difficult to achieve at a cost-effective and widespread scale, and noncompliance is integrally intertwined with the success of a program to reduce ACL injury rates. For example, a participant with low compliance...
to ACL prevention training is at 4.9 times greater risk of an ACL injury compared to a participant with high compliance\textsuperscript{20}. Although it is difficult to determine exact reasons for noncompliance, participant motivation seems to play a key role. Steffen et al. (2008) reported that low motivation of participants likely caused their study’s high noncompliance, while incentives (such as free, personalized athletic training from an expert), though not as cost effective, do appear to increase compliance\textsuperscript{24}.

b. Types of training programs
Although several studies have demonstrated that training interventions can reduce rates of ACL injury and that specific biomechanical variables associated with ACL injury risk can be successfully targeted for improvement, there is considerable variation among the training design of these interventions\textsuperscript{7,25}. The most salient differences are among the content, length, frequency, and total duration (for reviews see\textsuperscript{21-23,26}). Most successful programs included more than one type (e.g., modality, exercise type, etc.) of training content\textsuperscript{7,25}. Whereas, utilizing a single intervention modality, such as balance training or strength training alone does not appear to be successful\textsuperscript{27,28}. Furthermore, programs of heightened intensity in terms of the length, frequency, and total duration have reported increased benefits which is an important consideration given the previously discussed issues related to compliance. There is currently insufficient evidence to provide specific prescription parameters; however, a meta-analysis determined that 70\% of ACL injury risk could be alleviated with 30 minutes or more of training per week throughout a sports season\textsuperscript{29}.

c. Resources for instituting injury prevention programs
One of the most challenging practical difficulties to overcome in decreasing ACL injury rates is the amount of resources required to implement a prevention program. Monetary costs are reported to range from approximately $190-480.00* per athlete per season\textsuperscript{26}. In addition, there are also personnel resources required. Although it appears that the source of training (who or what provides it) is less important than how an athlete receives and processes information relating to the proper execution of preventative training exercises\textsuperscript{26,30-32}, ensuring that the feedback received during training is correct usually requires the presence of a trained professional such as an athletic trainer or physical therapist. A trained professional increases the required resources, financial and otherwise required for implementing an effective ACL prevention program.

Figure 1: Displayed is a 3D rendering of our experimental configuration for obtaining fMRI data during lower extremity body movements. In this particular force production task, participants are asked to perform combined ankle, knee, and hip flexion and extension movements while interacting with a biofeedback stimulus driven from real-time biomechanical data. As seen in the left panels, real-time position is indicated by the horizontal center black line; the green bar indicates the target position for the patient. Real-time force is indicated by the size of the red ball and the patient is to keep the red ball within the black circle (the target force). Participants are first asked to ‘match’ their movements with the real-time biofeedback stimulus and are then asked to repeat these movements without the real-time biofeedback to assess movement error (kinematic and kinetic ‘mismatches’). The amount of movement error is then associated with brain activity to identify disrupted neural processes.

MOTOR LEARNING

balance tests, and agility measures. However, even with guidelines to assess RTS readiness in the ACL-R population, re-injury rates in the adolescent athletic population remain as high as 30% when returning to sport. This indicates a potential shortcoming of the RTS assessment in that either the criteria or components of those assessments need further evaluation. One possible area to consider as an indicator for readiness to RTS is motor control. While the ACL provides structural stability to the knee joint, a rupture of the ACL likely creates more dysfunction in the knee joint than just stability since the ligament itself contains mechanoreceptors which play an important role in neuromuscular control of the knee. The initial disruption of the ligament mechanoreceptors propagates deficits in motor control, proprioception, postural control, and strength that are difficult to restore and assess at RTS. These sensorimotor disruptions lead to deficits in motor control, such as dynamic knee valgus during sport-specific tasks which has been associated with cognitive deficits, specifically in a visual memory task. This relationship suggests that not only are physical assessments of motor control important, cognitive assessments of motor control should also be incorporated into the rehabilitation and subsequent assessment to RTS after ACL-R to possibly reduce the chance of an ipsilateral re-injury or a new injury to the contralateral side.

ADDRESSING OPPORTUNITIES TO IMPROVE ACL INJURY RISK AND OUTCOMES

Current strategies for ACL injury prevention and rehabilitation exhibit shortcomings that represent opportunities to improve ACL injury outcomes through the advancement of screening methods and neuromuscular training to reduce injury risk.

a. Brain mechanisms underlying ACL injury risk

Recently, our lab has published work on resting-state functional brain connectivity (using functional magnetic resonance imaging [fMRI]) related to ACL injuries in female and male athletes. In our first investigation, prospective longitudinal data indicated that female soccer players who went on to experience a non-contact ACL injury exhibited disruptions in connectivity between the primary somatosensory cortex and cerebellum (regions vital to maintain a safe knee position during sport). We also found that male football players exhibited similar prospective functional brain connectivity disruptions throughout similar regions important for sensorimotor control that were associated with their future ACL injury. Collectively, our data in both sexes revealed potential neural biomarkers that may predispose an athlete to a traumatic ACL tear and indicate that dysfunctional neural processes are a potential key contributor to injury-risk neuromuscular control.

In addition to the functional connectivity results described above, we have also found differences in the electrocortical behavior of athletes who went on to injure their ACL and those who did not. Prospectively injured athletes exhibited lower spectral power, a basic indicator of brain activity in cortical behavior associated with sensorimotor function, attentional demand, and task complexity. Interestingly, while the fMRI results indicated less adaptive activity in sensorimotor regions, the decreased electrocortical activity associated with attentional demand and task complexity may reflect possible attempts at neurological compensation. These findings highlight the need for additional prospective studies that investigate CNS function and its relationship to biomechanical performance in order to identify potential biomarkers for musculoskeletal injuries (i.e., ACL). It may then be possible to target known biomarkers related to ACL injury risk through innovative biofeedback designed to promote neuroplasticity and the discovery of optimal neuromuscular control strategies. However, one limitation precluding our capability for discovering a neural biomarker of musculoskeletal injury has been the technical challenges for capturing lower extremity movement during active brain scanning (our previous prospective studies have primarily been at rest).

b. Motion analysis and fMRI integration

One of the challenges for using fMRI to better understand musculoskeletal injury is that participants must keep their bodies as stationary as possible, especially the head, as motion produces artifact within the fMRI data. This is especially limiting for investigating brain activity associated with whole-body behaviors that is common during sport participation (e.g., running or kicking a soccer ball). Further, collecting data using fMRI requires that all equipment be free of metal, specifically ferrous metals that can result in additional artifact and/or result in injury to the researcher or participant (objects can become ‘magnetic projectiles’). To overcome these limitations, we have developed custom ‘MRI-safe’ apparatuses.

Figure 2: Shown above is an example of a VR scenario our lab has recently developed to investigate dynamic cutting. Participants’ actual body movements are recorded by a motion capture system and translated to a virtual environment. In the above example it is an athletic gym where waypoints (indicators that direct participants to goal locations) are randomly placed to encourage participants to make sudden directional changes in response to the environment.
and associated paradigms to safely simulate lower extremity movement\textsuperscript{44,46}. However, precisely quantifying lower extremity movement (e.g., knee flexion angles, force control) during our neuroimaging paradigms has been further challenging as standard technology to precisely measure movement is typically not MRI-safe (e.g., 3D motion analysis cameras).

Recent technological advancements are solving some of these experimental constraints. For example, MRI-safe motion capture equipment and force transducers are now available, and this makes it possible to capture precise kinematic and kinetic data during neuroimaging. Motion capture systems such as Metria (Metria Innovation, Inc.; WI, USA) are capable of tracking the position of a participant’s body safely during fMRI\textsuperscript{47-49}. When combined with MRI-safe force transducers\textsuperscript{50,51}, such as those produced by JR3 (JR3 Inc.; CA, USA), it is now possible to investigate brain activity during more realistic sport-like behavior. An illustration of our current method for obtaining fMRI data during a lower-extremity movement is displayed in Figure 1.

c. VR testing to identify deficits

Traditionally, laboratory-based biomechanical assessment of sport-relevant tasks, such as landing, jumping, and cutting, have been used to assess neuromotor deficits that are purported to increase athletes’ risk of sustaining musculoskeletal injury during sport\textsuperscript{52-54}. These screening assessments typically involve athletes performing a battery of tests in a standard, systematic manner (i.e., according to a prescribed set of instructions and in a specific order) and are subsequently used as proxies for assessing how these athletes are likely to perform in real-world sport environments. Assessing biomechanical deficits in this manner is beneficial in that it controls for confounding factors and unwanted variability in task performance, which can make isolation of various neuromuscular or physiological mechanisms that result in elevated injury risk difficult. Importantly, accurate insight into injury risk mechanisms is needed to deliver effective, targeted interventions to decrease injury risk.

This may partially explain why interventions based on traditional biomechanical assessments are often ineffective at widespread reduction of injury rates\textsuperscript{55}. Although on-field, sport-specific assessments would provide a solution to this issue, several factors make this impractical. For example, variable environmental conditions, such as poor lighting, uncontrollable weather (in the case of outdoor sports), or non-optimal vantage points from which to capture data make high-fidelity recording of real-world sport performance difficult. Moreover, as sport competition is inherently unpredictable, capturing desired events (e.g., risky landings, fast accelerations or change-of-direction cutting) is more challenging and time-consuming than laboratory-based assessments, and recreating the same experimental conditions (absent interrupting or otherwise modifying gameplay) in which these desired events occur for every athlete is virtually impossible.

Virtual reality (VR) based assessments offer an alternative solution with the potential to present athletes with closer to true-to-life sport-specific scenarios, while maintaining the control of a laboratory setting\textsuperscript{56,57}. While there are useful non-sport specific VR assessments that can be used to investigate biomechanics in general (see Figure 2), VR assessments that utilize a wireless head mounted display (HMD) and custom-designed sports simulations (see Figure 3) allow for untethered, ambulatory movement and the presentation of visual

Figure 3: A sport specific VR scenario for soccer. In this particular scenario, the athlete’s task is to head the soccer ball from a corner kick towards the goal. The participant is free to interact and move untethered within the virtual environment due to the wireless head mounted display and motion capture system. This creates a feeling of greater immersiveness, which encourages more sport like behavior and effort. The projector screen is not normally present during an athlete’s participation, but is included in the current figure to demonstrate the participant’s view during the VR scenario.
and auditory information that mimics what athletes experience on the field to a greater degree than is possible in standard laboratory assessments. As such, investigators are able to simulate dynamic, real-world sport performance while simultaneously preserving the experimental conditions by which athletes respond to and exhibit motor responses in these scenarios, thereby enhancing their reproducibility and generalizability to injury risk during actual sport performance.

**d. aNMT Training**

To the best of our knowledge, traditional training methods have not previously been quantified to induce successful transfer of injury-risk-reducing-movement-patterns to the VR sport-specific setting. We contend this is due to the inability of standard training to induce the required neuroplasticity for widespread injury risk reduction movement pattern adaptation, retention, and transfer. Our lab has recently demonstrated that enhanced sensory integration neural activity that supports motor cortex efficiency is vital for injury-risk reducing movement patterns to transfer from the intervention to VR simulated sport. To target the neuroplasticity that enables injury-risk reduction in this regard, novel interventions are needed.

One such breakthrough is the use of augmented reality (AR), which like VR, can provide additional opportunities to design and develop new methods for screening and reducing ACL injury risk. Our lab has recently developed an augmented neuromuscular training system that is designed to display objective information about multiple kinematic and kinetic variables related to ACL injury risk to participants in real time. The information is displayed as follows:

**Figure 4:** The figure is displaying an example of a participant interacting with our aNMT system. The motion capture cameras (the red circles), force platform (grey square with green light the participant is standing on), and a custom written program are used generate the stimulus (big blue polygon). It should be noted that the stimulus is displayed to the participant via a Microsoft HoloLens (Microsoft Corp.; WA, USA) and the above example is only a demonstration of what the participant is seeing—the stimulus is only visible with the HoloLens on.

**Figure 5:** Top row demonstrates how contemporary neuromuscular training fails to induce the neuroplasticity required for transfer, even if immediate improvements in mechanics are achieved. Bottom row displays potential new therapies that can induce the neuroplasticity to ensure injury risk reduction transfer to sport. Blue indicates decreased brain activity; orange indicates increased brain activity. Standard neuromuscular training increases reliance on the motor cortex for knee control and fails to support the sensory integration required for injury risk reduction transfer. Augmented neuromuscular training decreases reliance on the motor cortex for knee control and supports sensory integration to ensure injury risk reduction transfer. Specifically, aNMT (bottom left panel) has been shown to increase functional connectivity between sensory areas of the brain and the thalamus (bottom middle brain panel).
displayed interactively to participants and their real-time biomechanical performance controls the display of information in the form of a simplified geometric shape viewed on a screen (see Figure 4). Participants perform specific exercises such as a body-weight squat using the shape as a guide to achieve correct movement form to enhance learning of injury-resistant movement patterns. While performing the exercise, the exact shape of the interactive biofeedback object is determined by the values of biomechanical variables related to ACL injury risk whereas the “goal” shape is a perfect rectangle. Participants are instructed simply to “move so as to create a perfect rectangle,” using the interactive shape as a guide but not requiring any additional instruction or supervision beyond basic exercise definition. aNMT was designed to elicit external perceptual control and engage implicit motor learning strategies that can result in faster learning and improved transfer24,48 while also permitting holistic learning of complex movements involving optimization of multiple, interdependent neuromotor and biomechanical variables. These factors are hypothesized to enhance the efficacy of aNMT relative to standard neuromuscular training by targeting the neural mechanisms supporting injury-risk reducing movement pattern adaptation and transfer to sport (see Figure 5).

Although aNMT requires technological resources, ultimately it is much less resource-intensive than current ACL injury risk reduction protocols. This is because it removes the need for one-on-one instruction from a trained professional. aNMT also has the advantages of being objective and highly precise, allowing detection and ultimately correction of sensorimotor deficits that even a trained professional may not be able to detect. It is also personalized to the individual athlete and allows customization of motor and feedback parameters. Our preliminary studies have provided evidence for the effectiveness of very brief and limited aNMT interventions (e.g., a minimal intervention of 4 sets of 10 body-weight squats) for enhancing motor performance34 and transferring those improvements to an unrelated drop-vertical jump task that has been shown to be predictive of ACL injury46,64. In addition to biomechanical changes, aNMT has also been shown to increase the functional connectivity between sensory areas of the brain and the thalamus (responsible for relaying sensory and motor signals; see Figure 5). The results of a more extensive intervention (6 weeks of twice-weekly aNMT training with a progression of exercises including squats, pistol squats, overhead squats, and jump squats) are forthcoming (ClinicalTrials.gov identifiers: NCT04068701 and NCT02933008).

CONCLUSION
We have described some shortcomings of current strategies for ACL injury prevention and rehabilitation that may be associated with the continued increase in ACL injury (and re-injury) rates, along with opportunities for advancing the current standard of care. Technological resources including advanced neuroimaging methods, virtual reality for injury risk screening and RTS assessment, and interactive AR-based neuromuscular training methods offer new approaches and tools for researchers and clinicians to address this important biomedical problem. The cost and availability of many of these technologies will continue to decrease, providing greater availability, scientific rigor, and ultimately, utility for cost-effective and data-driven assessments. The future is now and the tools exist to finally stem the tide of ACL injury, with the methods laid out here as an initial roadmap to promoting a healthy and active lifestyle across the lifespan for these athletes.

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Available at www.aspetar.com/journal

Scott Bonnette Ph.D.*
Postdoctoral Research Fellow

Manish Anand Ph.D.*
Postdoctoral Research Fellow

Kim D. Barber Foss MS, ATC, LAT*
Senior Research Assistant

Christopher A. DiCesare PhD*
Clinical Research Coordinator IV

Jed A. Diekfuss Ph.D.*
Postdoctoral Research Fellow

Dustin R. Grooms Ph.D.**
Associate Professor

Adam W. Kiefer Ph.D.***
Assistant Professor

Katie Kitchen B.Sc.*
Clinical Research Coordinator III

Danielle Reddington M.Sc.*
Clinical Research Coordinator II

Christopher Riehm Ph.D. Candidate*, Ph.D. Candidate

Michael A. Riley Ph.D.+ Professor

Andrew Schille M.Sc.*
Clinical Research Coordinator II

Jessica Shafer* Research Assistant

Staci Thomas M.Sc.*
Clinical Research Coordinator IV

Gregory D. Myer Ph.D.*, **, +++
Director of Research*

Director of SPORT Center and The Human Performance Laboratory

Professor++

* The SPORT Center, Division of Sports Medicine, Cincinnati Children’s Hospital Medical Center, Cincinnati, USA
** Ohio Musculoskeletal & Neurological Institute and Division of Athletic Training, School of Applied Health Sciences and Wellness, College of Health Sciences and Professions, Ohio University, Athens, USA
*** Department of Exercise and Sport Science, University of North Carolina at Chapel Hill, USA
++ Center for Cognition, Action & Perception, Department of Psychology, University of Cincinnati, Cincinnati, USA
+++ The Micheli Center for Sports Injury Prevention, Waltham, USA

Contact: scott.bonnette@cchmc.org