Baseline Predictors of Health-Related Quality of Life After Anterior Cruciate Ligament Reconstruction
A Longitudinal Analysis of a Multicenter Cohort at Two and Six Years

Warren R. Dunn, MD, MPH, Brian R. Wolf, MD, MS, Frank E. Harrell Jr., PhD, Emily K. Reinke, PhD, Laura J. Huston, MS, MOON Knee Group*, and Kurt P. Spindler, MD

Background: Limited information exists regarding predictors of general quality of life following anterior cruciate ligament (ACL) reconstruction with up to six-year follow-up. We hypothesized that certain variables evaluated at the time of ACL reconstruction will predict the general quality of life as measured by the Short Form-36 (SF-36).

Methods: All unilateral ACL reconstructions from 2002 to 2004 in patients currently enrolled in a prospective multi-center cohort were evaluated. Patients preoperatively completed the SF-36 validated outcome instrument. Surgeons documented intra-articular pathological conditions and treatment, as well as the ACL reconstruction surgical technique. At baseline and at a minimum of two and six years postoperatively, patients completed the SF-36. Longitudinal analysis was performed for the two-year and six-year end points.

Results: Of the initial 1512 subjects, at least one follow-up questionnaire was obtained from 1411 subjects (93%). The cohort was 44% female, and the median patient age at enrollment was twenty-three years. The mean scores were 41.9 points for the Physical Component Summary (PCS) and 51.7 points for the Mental Component Summary (MCS) at baseline, 53.6 points for the PCS and 52.0 points for the MCS at two years, and 54.0 points for the PCS and 52.4 points for the MCS at six years. Significant predictors of a higher PCS score were a higher baseline PCS score, younger age, lower baseline body mass index, having >50% of the lateral meniscus excised, or having no treatment done on a lateral meniscal tear. In contrast, significant predictors of a lower PCS score were a shorter follow-up time since surgery, revision ACL reconstruction, smoking at baseline, fewer years of education, and chondromalacia of the lateral tibial plateau. The mean utility gained at six years after ACL reconstruction was 5.3 quality-adjusted life years (QALYs).

Conclusions: Large improvements in the PCS (with an effect size of 1.2) were noted at two years and were maintained at six years after ACL reconstruction. Lower education and smoking were significant predictors of lower PCS and MCS scores. ACL reconstruction resulted in a relatively high gain of QALYs.

Level of Evidence: Prognostic Level I. See Instructions for Authors for a complete description of levels of evidence.

*Samuel K. Nwosu, MS, Christopher C. Kaeding, MD, Richard D. Parker, MD, Rick W. Wright, MD, Jack T. Andrish, MD, Eric C. McCarty, MD, Annunziato Amendola, MD, Robert G. Marx, MD, MSC, Michelle L. Wolcott, MD, Zhounwen Liu, MS, and JoAnn M. Alvarez, MS, are MOON (Multicenter Orthopaedic Outcomes Network) Knee Group members.

Disclosure: One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. In addition, one or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, one or more of the authors has a patent or patents, planned, pending, or issued, that is broadly relevant to the work. Finally, one or more of the authors has had another relationship, or has engaged in another activity, that could be perceived to influence or have the potential to influence what is written in this work. The complete Disclosures of Potential Conflicts of Interest submitted by authors are always provided with the online version of the article.

Disclaimer: The contents of this article are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.

J Bone Joint Surg Am. 2015;97:551-7  •  http://dx.doi.org/10.2106/JBJS.N.00248
There is sparse literature regarding the prognosis and predictors of anterior cruciate ligament (ACL) reconstruction outcomes at six years as measured by validated patient-based outcome instruments and assessed by multivariable analysis. Knowing prognostic information would be valuable in physician counseling of patients considering ACL reconstruction.

Large sample sizes with adequate follow-up are necessary for such analysis. A previously published randomized controlled trial had an enrollment of 225 patients, which limits risk factor analysis. A previous cohort study utilizing multivariable analysis was limited by 69% follow-up and the lack of baseline measurements of the outcomes, which are important to adjust for, as they are often the strongest predictor of follow-up scores.

The Short Form-36 (SF-36) is a widely used measure of general quality of life. It allows for comparison across different disease categories; therefore, normative-based scoring converts the scores such that they have direct interpretation related to the general United States population, with a mean score (and standard deviation) of 50 ± 10 points. Hence, a 1-point change in a score is one-tenth of a standard deviation or an effect size of 0.10. The Short Form-6 dimension (SF-6D), a preference-based utility measure, can be calculated from the SF-36, allowing the calculation of quality-adjusted life years (QALYs). Previous studies utilizing the SF-36 in athletic populations have compared domain scores, ranging from 0 to 100 points, to normative values, which do not as easily lend themselves to interpretation, but have not reported normative-based scores. The eight subscales of the SF-36 can be collapsed into two components, the Physical Component Summary (PCS) score and the Mental Component Summary (MCS) score. The use of the PCS and MCS has been advocated for large studies, particularly when there is a focus on the general effect on health.

The aim of the current study was to determine the prognosis and predictors of health-related quality of life as measured by the SF-36 at two and six years after surgery as well as the utility gained following ACL reconstruction as measured by the SF-6D. These results should aid evidence-based decision-making as related to a patient’s prognosis following ACL reconstruction, should provide a high level of evidence for surgeon decision-making, and should have the potential to identify future modifiable risk factors that could be altered to improve outcomes of ACL reconstruction. Furthermore, the improvements in health-related quality of life and utility according to the SF-6D should provide justification for expenditures related to patients with ACL injuries.

Materials and Methods

Study Population

The Multicenter Orthopaedic Outcomes Network (MOON) Knee Group began on January 1, 2002, as a consortium of six sites with eight surgeons with the aim of prospectively enrolling and following subjects undergoing ACL reconstruction. Vanderbilt University served as the data-coordinating center for the study and was responsible for entering baseline data and for collecting follow-up data on all subjects. Institutional review board approval was obtained from all participating centers. All subjects who had undergone ACL reconstruction at participating sites in 2002 through 2004 (from January 1, 2002, to December 31, 2004) were invited to enroll in the study (Fig. 1).

Data Sources

Following documentation of written informed consent, participants completed a thirteen-page questionnaire that has been described previously. Regarding the thirteen-page questionnaire, the SF-36 was used as a measure of general health. The SF-6D can be calculated from the SF-36, allowing the calculation of QALYs. This questionnaire was completed before the day of surgery in the vast majority of cases; otherwise, it was completed within two weeks following the surgery date. If it was completed following surgery, subjects were instructed to complete it from the preoperative perspective.

Surgeons completed a forty-nine-page questionnaire that has been described previously. Meniscal injuries were classified by size, location, and type of tear (partial or complete), and treatment was recorded as not treated, repaired, or the extent of resection. All patients were given standardized evidence-based guidelines for ACL reconstruction rehabilitation.

Study End Points

The eight SF-36 domain scores and the two component summary scores were measured longitudinally at follow-ups of at least two and six years. The PCS and MCS were the primary end points used for multivariable modeling. Subjects could contribute either two-year or six-year end points or both. Lastly, the utility gained at six years using the SF-6D was calculated.

Statistical Analysis

Multivariable analysis is necessary to see not only how different factors influence outcome but also what the relative strength of the association is. In evaluating the ACL-injured knee, associated meniscal tears and articular cartilage injury cannot be randomized. Therefore, a prospective cohort is the preferred design. Further, because these injuries are often induced at the same time as the ACL injury, a natural experiment has occurred given that a proportion of the ACL injuries will have concomitant intra-articular damage and others will not. In cohort studies, where variables cannot be randomly and equally distributed, multivariable analysis is the only way to account for uneven distributions of factors and potential confounders. Risk factors likely to be relevant to ACL reconstruction outcomes include age, sex, mechanism of injury, body mass index, concomitant medial and lateral meniscal tears and treatment, articular cartilage injuries and treatment, ACL reconstruction technique, and graft choice.

Flow diagram of subject enrollment. PCL = posterior cruciate ligament, LCL = lateral cruciate ligament, and MCL = medial cruciate ligament.
Multivariable analysis was used to determine which baseline variables measured at the time of the index ACL surgery were significant predictors of health-related quality of life at two and six years after surgery. Longitudinal analysis was performed with use of proportional-odds ordinal logistic regression to fit a single model for the two-year and six-year end points. We used the Huber-White cluster sandwich estimator to adjust the variance-covariance matrices to correct for correlated responses from two observations on the same patient.

The proportional-odds model makes fewer distributional assumptions than ordinary regression. The subscales of the SF-36 as well as the component summary scores were the dependent variables, and one model was fit for each. The independent covariates in the models included the baseline measure of the outcome, patient age, sex, race, education level, smoking status, BMI, activity level as assessed with use of the Marx activity rating scale, the patient-reported primary sport and competition level, the surgeon’s years of experience, the year of surgery, the follow-up time since surgery, whether the patient had a previous ACL reconstruction on the contralateral knee, whether the surgery was a revision, graft type, degree of damage to the cartilage, meniscal pathological condition and treatment, and whether the hoop stress fibers of either meniscus were disrupted. Missing data were imputed and continuous covariates (e.g., age) were modeled with use of splines to permit nonlinear relationships (see Appendix).

Nomograms were constructed to display the relationships between predictor variables and the outcomes, based on the fitted models. A nomogram can be used to estimate the mean response for individual patients and to show the relationship among the different predictor variables and how this affects the response.

Statistical analysis was performed with free open-source R statistical software and the rms package.

**Source of Funding**

This project was partially funded by grants from the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (5K23 AR052392 and 5R01 AR053684). This project was partially supported by the Clinical & Translational Science Awards (award number UL1TR000445) from the National Center for Advancing Translational Sciences. The project was also supported by the Vanderbilt Sports Medicine Research Fund, which received unrestricted educational gifts from Smith & Nephew Endoscopy and DonJoy Orthopaedics. Funds were used to pay for salaries, core biostatistical support, subject remuneration, and study supplies.

**Results**

**Study Population**

From January 1, 2002, to December 31, 2004, 1512 subjects met the inclusion criteria of having a unilateral ACL reconstruction and are included in our analyses; see the flow diagram for exclusion criteria (Fig. 1). Of the initial 1512 subjects, at least one repeat questionnaire was obtained from 1411 subjects (93%). Two-year follow-up was obtained for 1308 subjects (87%), and six-year follow-up was obtained for 1308 subjects (87%).

![Normative-based scoring of the SF-36 profile.](image_url)
1307 subjects (86%). The median age of the cohort was twenty-three years (interquartile range [IQR], seventeen to thirty-five years), and the cohort was 44% female.

**Study End Points**

The mean subscale scores as well as the PCS and MCS scores at baseline and two and six years are presented in Figure 2. The mean scores were 41.9 points for the PCS and 51.7 points for the MCS at baseline, 53.6 points for the PCS and 52.0 points for the MCS at two years, and 54.0 points for the PCS and 52.4 points for the MCS at six years. The mean utility gained at six years was 5.3 QALYs.

Multivariable analysis was used to determine which baseline variables measured at the time of index ACL surgery were significant predictors of health-related quality of life at two and six years after surgery. We summarized the results of the ten models by including two plots, one for the physical domain models and the PCS (Fig. 3) and one for the mental domain models and the MCS (Fig. 4). The plots show the independent variables on the vertical axis, and the relative portion of the variation in the outcome accounted for by the given variable on the horizontal axis. This importance is measured by Wald chi-square statistics minus the degrees of freedom. The subscale measured at the time of surgery tended to be the most important variable in predicting the corresponding subscale measured at subsequent times. The different domain scores showed consistency in the ranking of the importance of the independent variables. Hence, results are presented for the two summary scores and not for all subscale scores.

**PCS**

The following variables were significant predictors of higher scores: a higher baseline PCS (IQR odds ratio [the change in log odds from the twenty-fifth to the seventy-fifth percentile for continuous predictors], 1.57 [95% confidence interval [95% CI], 1.26 to 1.96]; p < 0.0001); younger age (IQR odds ratio, 2.04 [95% CI, 1.28 to 3.23]; p = 0.002); lower baseline BMI (IQR odds ratio, 1.35 [95% CI, 1.18 to 1.53]; p < 0.0001); lateral meniscal treatment (p = 0.009), specifically, having >50% of the lateral meniscus excised (IQR odds ratio, 2.45 [95% CI, 1.49 to 4.01]); or having no treatment done for a lateral meniscal tear (IQR odds ratio, 1.27 [95% CI, 1.01 to 1.59]).

The following variables were significant predictors of lower scores: shorter follow-up time since surgery (IQR odds ratio, 0.64 [95% CI, 0.50 to 0.82]; p < 0.0001), revision ACL reconstruction (IQR odds ratio, 0.51 [95% CI, 0.39 to 0.68]; p < 0.0001), fewer years of education (IQR odds ratio, 0.70 [95% CI, 0.59 to 0.84]; p = 0.0001), current smoker (IQR odds ratio, 0.52 [95% CI, 0.37 to 0.73]; p = 0.0004), and chondromalacia of the lateral tibial plateau (IQR odds ratio, 0.53 [95% CI, 0.31 to 0.92]; p = 0.03).

A nomogram, which can be used to estimate the mean response for individual patients and to show the relationship...
among the different predictor variables and how this affects the predicted PCS score, is shown in the Appendix.

MCS
The significant predictors of a higher MCS were a higher baseline MCS (IQR odds ratio, 1.99 [95% CI, 1.58 to 2.52]; p < 0.0001) and a higher baseline Marx activity rating scale score (IQR odds ratio, 1.46 [95% CI, 1.13 to 1.88]; p = 0.01). The following variables were significant predictors of a lower MCS: fewer years of education (IQR odds ratio, 0.76 [95% CI, 0.64 to 0.92]; p = 0.003) and smoking status (p < 0.0001), specifically, being a previous smoker (IQR odds ratio, 0.72 [95% CI, 0.52 to 0.99]) or current smoker (IQR odds ratio, 0.50 [95% CI, 0.36 to 0.69]). A nomogram of the MCS model is shown in the Appendix.

Discussion
This study produced several interesting findings that merit further discussion. First, this study showed that the SF-36 is responsive to ACL reconstruction. Next, although no significant changes were observed in the MCS in this relatively young and healthy cohort, large improvements were noted in the PCS at two years and were maintained at six years (effect size of 1.2 at two and six years), demonstrating the durability of the improvement after ACL reconstruction. Specific factors were identified as significant predictors of PCS scores and MCS scores. Our data demonstrated gained QALYs after ACL reconstruction and this gain was clinically important. Lastly, our data exposed some perplexing relationships between concomitant meniscal surgery and SF-36 outcomes after ACL reconstruction.

Our study demonstrated that ACL reconstruction resulted in large improvements in the PCS, with a mean improvement of 12 points at both the two-year and six-year follow-ups. It was encouraging to see maintenance of improved physical scores up to six years after surgery, which demonstrates intermediate-term durability. Baseline activity level as measured with use of the Marx scale was a significant predictor of MCS scores but not PCS scores in the current study. To our knowledge, comparative literature has been limited. Eitzen et al. found lower bodily pain subscores at two years in subjects with concomitant ACL reconstruction and meniscal injuries requiring treatment, but subjects who had meniscal injuries requiring repair were excluded from that study. Månsson et al. examined baseline predictors of health-related quality of life using the SF-36 at three to six years following ACL reconstruction and found that the pre-injury activity level was a predictor of two of the SF-36 subscales. Specifically, a higher baseline Tegner activity level was associated with higher general health scores and lower role emotional scores, whereas we did not find activity level to predict outcome. This discrepancy may be due to the different activity scales (Marx compared with Tegner) used in the two studies.

In contrast to the physical score changes after ACL reconstruction, the MCS and the general health subscale were
both well above the population norm of 50 points at baseline and did not change dramatically over time (Fig. 2). The subjects also reported baseline mental health and vitality subscale scores above the population norm of 50 points (Fig. 2). This reflects the relatively young and healthy patient cohort studied. Consistent with our data, Busija et al. found the SF-36 to be a useful metric for measuring group changes over time for several orthopaedic procedures, including ACL reconstruction, and noted that there had been very little change in the general health subscale over the two-year follow-up period. However, others have noted that the baseline subscale scores, excluding general health, have been below population norms prior to ACL reconstruction. Although subjects in the current study had baseline general health, vitality, and mental health subscale scores above the population norm of 50 points, the other five subscale scores were below the norm prior to surgery.

The QALY findings are intriguing and novel for ACL reconstruction. One QALY represents one year of perfect health. Six months of perfect health, or one year of health that is considered to be half as good as perfect health, corresponds to 0.5 QALY.

The mean utility gained at six years in the current study was 5.3 QALYs. To our knowledge, five authors have previously reported on QALYs gained following ACL reconstruction, and these have ranged from 0.78 to 5.1. QALYs have been reported following other surgical procedures as well. Vitale et al. found that the mean QALYs gained at one year following rotator cuff repair were 0.81 using the Health Utility Index and 3.43 using the European Quality-of-Life measure. Rasmussen et al. found that the mean QALYs gained at one year were 1.3 for primary total hip arthroplasty, 0.2 for revision total hip arthroplasty, and 0.6 for primary total knee arthroplasty. Al-Ruzzeh et al. found that the mean QALYs gained at six months following coronary artery bypass surgery was 0.3. Thus, the gain in QALYs after ACL reconstruction exceeds other procedures renowned for improving quality of life. It appears that health-care expenditures on ACL reconstruction are clearly justified by these findings.

The outcomes relative to meniscal treatment in the setting of ACL reconstruction are perplexing. However, in the current cohort of more than 1400 ACL reconstruction cases, meniscal treatment is not easily dismissed. Our data demonstrated that having >50% of the lateral meniscus excised was associated with higher outcome scores. This may be the most difficult finding to explain. With an ACL tear, the knee pivots and the anterolateral aspect of the distal part of the femur contacts the posterior aspect of the lateral tibial plateau. In some cases, this can be quite traumatic and can result in subclinical impaction fractures noted as bone bruising on magnetic resonance imaging. Lateral meniscal tears are commonly seen at the time of acute ACL injury, and this is thought to be due to the meniscus being trapped or crushed during these pivoting events. In the MOON cohort, lateral meniscal tears were not found in 49% of ACL reconstruction cases. One could theorize that the meniscus is not normal (despite the absence of a tear), or is covertly damaged, in those cases in which resection did not occur, resulting in lower outcomes. The relationship between meniscectomy and meniscal repair after ACL reconstruction is compelling enough that it warrants further investigation. Our data would suggest that current meniscal tear treatments and algorithms need to be closely examined and to be investigated further. We do not advocate resection of a normal-appearing meniscus. These intermediate-term data also cannot speak to possible long-term outcomes relative to meniscus-preserving compared with meniscus-removing surgery in the setting of ACL reconstruction. Leaving some lateral meniscal tears untreated was associated with improved PCS scores, consistent with previous studies.

This study had several limitations. The SF-36 is a general health measure and may not be as responsive to ACL reconstruction as joint and condition-specific measures. These knee and disease-specific data were collected but were beyond the scope of the current study, in which impact on general health was the focus. It is possible that other potential influential variables were not included in our analysis efforts despite our attempt to use an exhaustive list of potential variables. To our knowledge, there has been limited information in the orthopaedic literature regarding QALYs, and thus the relative importance of the QALYs gained after ACL reconstruction is difficult to relate in the context of other procedures. Lastly, the findings related to meniscal treatment are perplexing. It is possible that these findings do not reflect reality. However, intensive scrutiny and the use of a very large cohort size suggest that there is merit to further investigating the role of meniscal treatment on outcome in the setting of ACL reconstruction.

In summary, ACL reconstruction results in a large improvement in the SF-36 PCS at two years and is durable to a minimum of six years. The QALYs gained after ACL reconstruction are substantial relative to other successful operations where this has been explored, suggesting that ACL reconstruction utilization is appropriate. Lastly, interesting relationships appear to exist between the treatment of meniscal pathological conditions during concomitant ACL reconstruction and the ultimate outcome assessed using SF-36 measures, which may be explained by patient characteristic confounders.

Appendix

Text providing the details of the statistical methods, figures showing nomograms for the SF-36 PCS and MCS score models, and tables showing the baseline and follow-up cohort descriptive statistics and the modeled data descriptive statistics are available with the online version of this article as a data supplement at jbjs.org.

Warren R. Dunn, MD, MPH
University of Wisconsin Medical Center,
References


Neuroplasticity Associated With Anterior Cruciate Ligament Reconstruction

Individuals who experience a primary anterior cruciate ligament (ACL) injury are at substantially increased risk of experiencing a second ACL injury, despite surgical reconstruction and rehabilitation. Athletes who attempt to return to activity are at an exceptionally high risk of reinjury (30 to 40 times greater relative to those without injury history). The mechanisms for the heightened injury risk may extend beyond the physiological and biomechanical changes of the reconstructed knee joint and may involve a systematic neurological response to the injury. Neuroplasticity following ACL injury is likely due to a combination of altered sensory feedback from the injury, as well as behavioral motor control compensations. The lost ligament mechanoreceptors and associated physiologic cascade of inflammation and joint effusion may alter input to the central nervous system (CNS). Simultaneously, experience-dependent factors, including behavioral changes due to injury-associated pain, instability, compensatory movement patterns, and physical rehabilitation, also can cause unique and interacting neuroplastic changes, along with the afferent disruption.

The altered afferent input into the CNS due to the lost mechanoreceptors of the native ACL decreases innervation to the primary sensory cortex. This may lead to absent somatosensory-evoked potentials in those with ACL injury and anterior cruciate ligament reconstruction (ACLR). The efferent output also is altered, with disrupted gamma-motor neuron feedback loops, delayed long latency reflexes, and altered spinal and cortical excitability. Depressed cortical excitability after ACLR increases the stimulus required at the motor cortex to generate quadriceps contractions. The increased need for input to the motor cortex may contribute to the increased frontal and parietal cortex activation for knee joint position and force control after ACLR. As the frontal and parietal brain regions have a high degree of connectivity to the motor cortex and provide sensory and cognitive contri-
butions for motor planning, increased activation of these regions may be able to provide a compensatory mechanism to increase stimulus to the motor cortex.5,6,28,43,91 This combined disrupted input and limitation of the efferent signal contributes to arthrogenic muscle inhibition and motor control changes, leading to sensory-motor nervous system compensations.5,14,37,72,73

Previous investigators have hypothesized that following ACL injury, the CNS may increase reliance on alternative sensory sources, such as visual-feedback and spatial awareness.1,17,20,25,59 One previous investigation used neuroimaging to quantify brain activation differences between persons with ACL deficiency who did not return to previous levels of physical activity and a healthy control group.20 Those with ACL deficiency had increased activation in the posterior inferior temporal gyrus (visual processing), presupplementary motor area (motor planning), and secondary somatosensory area (pain and sensory processing).25 While this initial work supports the conceptual framework of neuroplastic changes after ACL injury and the possibility of altered sensory-visual-motor brain activation, it is unknown how these changes may present after reconstruction, rehabilitation, and return to activity. As biomechanical deficits remain years after completion of rehabilitation and return to activity,72,73 understanding how the brain is generating knee motion may help us to understand why motor deficits persist.

The purpose of this study was to compare brain activation during knee flexion/extension between persons who have undergone ACLR and a matched control group. Based on previous literature, it was hypothesized that those with ACLR would have brain activation differences related to motor planning (premotor and motor cortex) and sensory function (cross-modal sensory-visual regions and secondary somatosensory area) relative to the matched controls.

**METHODS**

**Participants**

Subjects were recruited from the local University and orthopaedic clinics. Prospective participants were directed to an online survey to determine whether they met the following inclusion criteria: magnetic resonance imaging [MRI] compliance, minimum score of 5 on the Tegner scale, and participating in running and cutting/change-of-direction activity on the Marx scale at least once a week. Subjects also were screened to include only left-side ACLRs. This was done to allow aggregation of the brain activation data without concern for unique unilateral brain changes that might have been missed if the cohort had mixed left and right ACLRs. Individuals with a history of other lower extremity injuries were excluded. In addition, control participants had no history of lower extremity injury.

All ACLR participants were 6 months to 5 years postsurgery, cleared for full return to activity by their physician, and engaged in regular physical activity. Participants in the control group were matched to those in the ACLR group by age, sex, height, mass, leg and arm dominance, education level, and physical activity history and current level, including specific sport participation by level and years of participation.

Individuals with ACLR (n = 131) were screened, and 15 fit the inclusion criteria and agreed to participate in the study. Potential control participants (n = 371) were screened, and 15 fit the inclusion criteria and provided a viable match to a participant with ACLR. The MRI restrictions (limited metal implants, no metal dental work) and the strict matching criteria greatly reduced participant inclusion. Participant demographics are described in **TABLE 1**. Participants with ACLR engaged in a standardized rehabilitation program, with 13 of the 15 coming from the same local physical therapy network. All participants with ACLR reported engaging in extensive unilateral strengthening and range-of-motion exercises, progressing to agility and plyometric training before return to activity. All participants completed the International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC) to assess subjective knee function, as well as a short rehabilitation survey.

This study was approved by The Ohio State University Institutional Review Board, and informed consent was obtained prior to study enrollment. An a priori power analysis was completed using our preliminary data (fmripower.org), allowing for estimation of power with the same scanning parameters and experimental protocol as the current investigation. Using the sensorimotor cortex as a primary region of interest, we had 80% power with a .05 type I error rate and 13 participants per group.

**Data Collection**

Functional magnetic resonance imaging (fMRI) data were collected on a 3.0-T MAGNETOM (Siemens AG, Munich, Germany) scanner using a 12-channel array, receiver-only head coil. The MRI session consisted of 90 whole-brain, gradient-echo, echo-planar scans, acquired every 3.0 seconds with an anterior/posterior phase encoding direction (slice thickness, 2.5 mm; 55 transversal slices). This equated to 10 whole-brain data sets per knee movement block, or 40 whole-brain activation maps for knee movement, contrasted with 50 whole-brain maps for rest. After the fMRI scanning, an anatomical 3-D, high-resolution, T1-weighted image (repetition time, 2000 milliseconds; echo time, 4.58 milliseconds; field of view, 256-mm matrix; slice thickness, 1 mm; 176 slices) was completed for registering the activation data and for brain region identification and normalization to compare the ACLR and matched participants.

Each participant was positioned supine in the scanner, with the legs placed on a custom cushion that limited knee flexion to 45°. Each participant then performed cyclic, non–weight-bearing knee extension/flexion from 45° of flex-
Participant Demographics, IKDC Instrument, and Head Motion Parameters During the fMRI Task

<table>
<thead>
<tr>
<th>Sex</th>
<th>ACLR</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7</td>
<td>7</td>
<td>...</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>217 ± 2.7</td>
<td>23.2 ± 3.5</td>
<td>.13</td>
</tr>
<tr>
<td>Height, m</td>
<td>17 ± 0.1</td>
<td>17 ± 0.1</td>
<td>.49</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>70.4 ± 15.8</td>
<td>69.7 ± 14.3</td>
<td>.92</td>
</tr>
<tr>
<td>Tegner activity level scale</td>
<td>72 ± 1.3</td>
<td>6.8 ± 1.5</td>
<td>.27</td>
</tr>
<tr>
<td>Marx activity rating scale</td>
<td>12.5 ± 3.9</td>
<td>11.2 ± 2.9</td>
<td>.31</td>
</tr>
</tbody>
</table>

Abbreviations: ACLR, anterior cruciate ligament reconstruction; fMRI, functional magnetic resonance imaging; IKDC, International Knee Documentation Committee Subjective Knee Evaluation Form.

*Values are mean ± SD unless otherwise indicated.

†Reported from t tests comparing group means.

**FIGURE 1.** Experimental setup. The stimuli for the flexion/extension movements were cued with a visual prompt and paced with a metronome.

Rest 30 seconds Move Stop

Rest 30 seconds Move 30 seconds Rest 30 seconds

Knee flexion/extension is a critical component of daily physical function, and fMRI is limited by any accessory head motion; therefore, completing a more dynamic weight-bearing lower extremity task is exceedingly difficult and has high risk to generate excessive activation artifact. Head movement artifact was limited with padding and straps to at most 1 mm absolute and 0.30 mm relative displacement across all participants. There was no between-group difference in head motion (P+.05). An ankle-toe splint was used to restrict ankle and toe movement, and the participant was monitored for accessory motions. The thigh, pelvis, and torso were secured to the table with straps, and the head was surrounded by molded padding and sandbags to limit head translation. Practice of the movement was completed in a full-mock scanner session prior to completing the actual fMRI session to ensure the participant could complete the movement smoothly with minimal head motion.

**Data Analysis**

The fMRI technique used in this study quantified the blood oxygen level-dependent signal via the hemodynamic response (blood flow) to various stimuli or tasks. Functional MRI collection and analysis has been validated against actual neural recordings. The reliability of fMRI quantification of the neural activation associated with knee movement has been determined to be high. The fMRI image analyses and statistical analyses were performed using the Oxford Centre for Functional MRI of the Brain Software Library. Image analysis began with standard prestatistic processing applied to individual data, which included nonbrain removal, spatial smoothing at 6 mm, and standard motion correction and realignment parameters (3 rotations and 3 translations) as covariates to limit confounding effects of head movement. High-pass temporal filtering at 90 Hz and time-series statistical analyses were carried out using a linear model with local autocorrelation correction. Functional images were coregistered with the respective high-resolution T1 image and the standard Montreal Neurological Institute template 152 using linear image registration. This registration process allowed data from each participant to be spatially aligned on a standardized brain template for comparison.

To our knowledge, the present study is the first to perform a whole-brain analy-
sis to examine knee motor control after ACLR. The only previous study to use neuroimaging in a similar population examined low-functioning, ACL-deficient patients.\textsuperscript{11} It is likely that the brain activation pattern differences in the present sample might not exactly match those of the previous work, considering the highly selective matching, higher physical activity level, and the reconstruction status of our sample and differences in analysis method (Oxford Centre for Functional MRI of the Brain Software Library versus Statistical Parametric Mapping by the Wellcome Trust Centre for Neuroimaging) and scanning parameters (3-T Siemens scanner versus 1.5-T Philips scanner).

The subject-level analysis of knee movement relative to rest was completed using a $z$ score greater than 4.6 and a (corrected) cluster significance threshold of $P = .001$. The cluster correction for multiple comparisons uses a variant of the Gaussian random field theory to decrease type I error in statistical parametric mapping of imaging data by evaluating the activation not only at each voxel, but also at the surrounding voxel cluster (as it is unlikely that the voxel tested and surrounding voxels are active above the threshold due to chance).\textsuperscript{71}

The paired contrast between the participants with ACLR and matched controls was performed with group $z$ statistic images set at a threshold of $z$ scores of greater than 3.5 and a corrected cluster significance level of $P = .01$. The higher threshold and lower $P$ value for both the participant- and group-level analyses were selected to mitigate interparticipant variability, decrease probability of motion artifact in the data, as well as further decrease the probability of type I error and multiple-comparison error beyond traditional measures.\textsuperscript{71}

**RESULTS**

The ACLR group had a significantly lower IKDC score (88 ± 8.1) compared to the control group (98 ± 2.1; $P < .001$). The brain area activation is reported as contralateral (indicating activation on the opposite side of motion, or the right side, as the movement was always completed with the left knee) or ipsilateral (being the same side of motion, or the left side). The results are presented as $z$ score (activation level relative to the contrast of ACLR versus control participants) and percent signal change for each group from baseline to knee movement in

---

**FIGURE 2.** Cross-sections of each area that demonstrated higher or lower activation in the ACLR cohort relative to controls. Blue indicates lower activation in the ACLR cohort and orange indicates higher activation. The center 3-D rendering is a top-down view (top), posterior view (middle), and side view (bottom) of a partially transparent 3-D rendering of the brain activations on a standard brain template. The regions are labeled contralateral if the peak voxel of the cluster is in the hemisphere contralateral to the left leg movement (right hemisphere), and ipsilateral if the peak voxel of the cluster is in the hemisphere ipsilateral to the left leg movement (left hemisphere). Abbreviation: ACLR, anterior cruciate ligament reconstruction.
The ACLR group demonstrated increased activation of the contralateral primary motor cortex, ipsilateral lingual gyrus, and secondary somatosensory cortex, and diminished activation of the ipsilateral motor cortex and vermis of the cerebellum area, compared to the matched control group (FIGURE 2, TABLE 2).

**DISCUSSION**

The purpose of this study was to quantify the brain activation changes associated with ACLR during a knee flexion/extension task. Utilizing neuroimaging, the results of this investigation suggest that after ACLR, specific brain regions responsible for sensory, motor, and sensory-visual-spatial processing may have altered activation. The primary motor cortex exhibited greater activation during involved-limb knee extension/flexion in the ACLR group, which may be due to the increased need for cortical drive to engage the quadriceps after injury and reconstruction. The increased primary motor cortex activation corroborates previous research indicating that motor cortex excitability is diminished after ACLR. The finding of depressed motor cortex excitability suggests that greater motor cortex activation is required to achieve motor drive and/or that motor cortex input from the rest of the brain in the form of structural or functional connectivity must increase to achieve motor drive. Following ACL injury and subsequent reconstruction, which disrupts sensory input, and the development of altered motor control strategies to compensate for the associated biomechanical insufficiencies (strength, range of motion), the processing demands on the motor cortex may increase to maintain even simple motor control integrity. Of note, we utilized the peak voxel of an activation cluster to determine the brain region; therefore, the motor cortex cluster may include the supplementary motor area anteriorly and the primary sensory cortex posteriorly at the edges of the activation threshold. However, these appeared to not be distinct activation increases relative to the primary motor area and may implicate increased premotor as well as motor cortex activation in the ACLR group.

We also observed that the secondary somatosensory area was activated to a greater degree in the ACLR participants, similar to the findings of Kapreli et al in ACL-deficient individuals. This area is responsible for somatosensory processing, with the anterior region integrating sensory stimuli and the posterior region addressing painful stimuli. Our participants were beyond the acute stage of injury and did not report any discomfort during the fMRI, but did have a significantly decreased IKDC score, indicating a level of subjective knee dysfunction. The increased activation in the secondary somatosensory area may represent a functional cortical sensory processing reorganization secondary to the knee trauma and/or treatment increasing nociceptive-related processing during any related involved-knee movement. Interestingly, the secondary sensory area activation was on the ipsilateral side of movement, which may indicate a bilateral neuroplastic effect of the injury to induce adaptations in sensory processing.

The contralateral side of the brain controls the ipsilateral leg, but the secondary somatosensory area functions bilaterally, with little lateralization in activation due to unilateral stimuli. Thus, the increased ipsilateral secondary somatosensory activation after injury, reconstruction, and rehabilitation may represent functional reorganization of sensory processing in both hemispheres. Adapted sensory processing also has been demonstrated with increased parietal lobe activation to reproduce joint positions in those with ACLR. The disruption to sensory processing after ACLR is

**TABLE 2**

<table>
<thead>
<tr>
<th>Measure/Group</th>
<th>Contralateral Motor Cortex</th>
<th>Ipsilateral Motor Cortex</th>
<th>Ipsilateral Lingual Gyrus</th>
<th>Secondary Somatosensory</th>
<th>Cerebellum (Vermis)</th>
<th>Ipsilateral Motor Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean region signal change, %</td>
<td>2.18</td>
<td>0.67</td>
<td>0.71</td>
<td>-0.26</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>ACLR</td>
<td>1.59</td>
<td>0.28</td>
<td>0.29</td>
<td>0.10</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.35</td>
<td>1.88</td>
<td>1.57</td>
<td>-0.07</td>
<td>1.93</td>
<td></td>
</tr>
<tr>
<td>Peak signal change, %</td>
<td>3.02</td>
<td>1.11</td>
<td>0.83</td>
<td>0.38</td>
<td>2.54</td>
<td></td>
</tr>
<tr>
<td>ACLR</td>
<td>0.70</td>
<td>0.39</td>
<td>0.22</td>
<td>0.11</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.55</td>
<td>0.29</td>
<td>0.20</td>
<td>0.13</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Mean z value</td>
<td>5.15</td>
<td>4.58</td>
<td>5.60</td>
<td>5.77</td>
<td>5.18</td>
<td></td>
</tr>
<tr>
<td>MNI coordinates (peak voxel)</td>
<td>x</td>
<td>8</td>
<td>4</td>
<td>-68</td>
<td>2</td>
<td>-2</td>
</tr>
<tr>
<td>y</td>
<td>-30</td>
<td>-72</td>
<td>-20</td>
<td>-62</td>
<td>-34</td>
<td></td>
</tr>
<tr>
<td>z</td>
<td>76</td>
<td>-10</td>
<td>22</td>
<td>-42</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACLR, anterior cruciate ligament reconstruction; MNI, Montreal Neurological Institute.

*All voxels are cluster corrected (P<.01).
bilaterally, whereby the ipsilateral motor cortex activates to inhibit contralateral or bimanual contraction during unilateral movement (as completed in this study). A recent study indicated that only 45 minutes of balance training can change the structural morphology and functional activity of the motor cortex, thus the months of focused rehabilitation likely contributed to the activation differences. Thus, it is possible that the ipsilateral motor areas became more efficient and required less neural activation to execute unilateral movement due to the therapy targeting the involved knee. Alternately, cortical motor control may become less bilateral due to inhibition and compensations after injury to increase reliance on the contralateral knee. While unilateral rehabilitation is advised to address the significant asymmetries in strength and function after ACLR, the bilateral neurological effects are well documented, ranging from gamma-motor neuron dysfunction to cortical excitability. The depressed ipsilateral motor cortex activation as observed in our study adds to the contralateral adaptations after this unilateral trauma. Additionally, the decreased cerebellum activation may be a consequence of increased contralateral motor cortex activation increasing cortical descending control after injury. These decreases in brain activation may influence the depressed postural control and altered neuromuscular control of the contralateral limb after unilateral ACLR. This finding provides further evidence that the “healthy” knee may not serve as a sufficient comparison to gauge functional status, as brain activation changes that influence bilateral lower extremity function may have occurred.

When compared to the only other neuroimaging study after ACL injury, the present study found fewer regions that had increased activation in the control participants relative to those with ACLR. Specifically, only the ipsilateral motor cortex and cerebellum were found to activate more in the controls. However, Kapreli et al noted that several regions, including the cerebellum, basal ganglia, cingulate motor area, parietal cortex, thalamus, and both sensorimotor cortices, had increased activation in their control group relative to their ACL-deficient group. This is likely due to the similarity in our ACLR cohort and matched controls. Kapreli et al enrolled ACL-deficient, less active, and poorer functioning individuals and matched them with healthy controls, which could have resulted in a greater difference in brain activation compared to the more active ACLR cohort. In an attempt to further isolate the effects of ACL injury and reconstruction, we matched participants by sex, limb dominance, activity level, motor skill specialization, mass, height, sport participation (by sport, level, and years of participation), education level, and age, and completed a paired analysis with a decreased alpha value. Kapreli et al only matched on sex, limb dominance, activity level, and motor skill specialization.

Clinical Implications
As traditional rehabilitation encourages a focus of attention on the knee with increased visual and cognitive knee position control during movement training, it is likely that the brain activation differences are in part due to the rehabilitation process. Previous reports of altered neuromuscular control following ACL injury, as that reported in the present study, suggest that there are acute injury effects as well as chronic long-term neuroplastic changes associated with rehabilitation and motor adaptations. To influence the sensory-visual-related brain activation, clinicians may consider incorporating varied visual conditions via blindfold, external targets, stroboscopic glasses, or dual tasking during rehabilitation. Forcing the focus of attention to the external environment with instruction or feedback, as opposed to the typical internal feedback of focusing on knee position or the quadriceps, in rehabilitation may increase conscious attention, sensory-visual spatial navigation, processing of congruent visual and sensorimotor feedback, and connectivity of the lingual gyrus. Activation of the lower extremity tends to engage through rehabilitation. Motor control of the lower extremity becomes altered with increased activation of higher-level sensory integration areas.

The ACLR group also exhibited increased activation of the lingual gyrus, a brain region involved in the cross-modal processing of congruent visual and sensory feedback, for limb positioning, sensory-visual spatial navigation, attention, memory, and movement perception. Recent data suggest that the higher-order visual cortex may have a motor-oriented organization due to the connections with the sensorimotor cortex that use feedback from visual regions to control motor output. Activation and connectivity of the lingual gyrus region also have been shown to adapt with altered sensory input and motor demands. Therefore, the increased lingual gyrus activation after ACLR may be due to the adapted sensory feedback of the lost ACL mechanoreceptors and the continued motor demands (all individuals were returned to activity). In addition to the altered afferent input influencing sensory-visual brain activation, the targeted rehabilitation to increase quadriceps activation immediately after surgery may increase conscious awareness of the injured joint, creating a visual-motor link during recovery. Thus, the participants with higher lingual gyrus activation may be engaging in a visually biased strategy to engage knee movement.

The decreased ipsilateral motor cortex activation during knee motion may be the result of the extensive unilateral rehabilitation that is provided after surgical reconstruction. Upon enrolling in the study, participants completed a short survey regarding their rehabilitation, and all indicated extensive unilateral exercises throughout rehabilitation. Motor control of the lower extremity tends to engage further supported by the absent or depressed somatosensory-evoked potentials after injury that are not restored with reconstruction. It is possible that, due to the pain and loss input to the primary sensory cortex associated with the injury, sensory processing for movement becomes altered with increased activation of higher-level sensory integration areas.
patient function. Alternatively, a direct approach to reducing visual feedback (blindfold, stroboscopic glasses, virtual reality) during rehabilitation may be beneficial to encourage increased utilization of proprioceptive sensory input, as opposed to increasing the reliance on a visual-spatial neural strategy. To influence motor cortex activation, clinicians may consider motor-learning approaches, such as various forms of augmented feedback, to facilitate advancement in expertise during movement training. Previous investigators have reported that using biofeedback and skill training can directly influence motor cortex excitability and activation.

**Limitations**

It is possible that the brain activation differences observed in the current study were not due to the injury but were prospective in nature and present in those who went on to experience ACL injury. It is unlikely that this would account for all of the activation differences observed, as activation of the inferior temporal region or lingual gyrus has only been documented in ACL-injured individuals during a knee motor task and not reported in the study of healthy individuals engaging in the same task. The relative activation of this area indicates that the injury or rehabilitation process could have induced at least some of the neurological differences, and it is unlikely that they are entirely predisposing phenomena.

Neuroimaging is prone to variability and spurious findings. To limit potential error, we included additional controls in the analysis to decrease this variability and utilized conservative corrections and thresholding. Additionally, each participant’s activation pattern was contrasted with that of a control participant matched on many of the factors that generate this variability, including age, sex, height, mass, activity level history, current activity level, education level, hand and leg dominance, and previous and current sport participation. While our sample size was relatively small, we completed an a priori power analysis to ensure sufficient participants based on previous neuroimaging reports and the noise associated with our scanner, specifically via pilot data analysis. Also, while fMRI is a powerful modality for assessing brain function, it is unable to quantify the neural activation of complex, multi-joint, or dynamic lower extremity tasks due to any task-correlated head motion generating excessive data artifact. The simple motor task utilized in our study required extensive measures to mitigate head movement, including participant task practice, a mock scanner session, head foam, bracing, strapping, and other restraints to ensure head stabilization during movement.

**Future Directions**

A longitudinal design with control for the rehabilitation and surgical intervention will allow determination of within-participant neuroplasticity due to injury, surgery, and rehabilitation. The next steps in quantifying musculoskeletal injury–induced neuroplasticity will require more advanced motor control tasks, such as force or position matching and multi-joint movements, to improve the clinical applicability of these results. The integration of transcranial magnetic stimulation and/or electroencephalography with fMRI also presents an opportunity to quantify brain function with superior spatial and temporal resolution to further capture aspects of motor control that may be playing a role in the ACL injury risk profile. As more investigators begin to explore the neurological changes associated with motor control after musculoskeletal injury, novel rehabilitation approaches that maximize both nervous system and musculoskeletal system adaptations will be developed.

**CONCLUSION**

The current study found brain activation differences between individuals with a history of ACLR and matched healthy controls during a knee flexion/extension task. After ACL injury, reconstruction, rehabilitation, and return to activity, knee motion requires increased activation of motor, visual, and secondary sensory areas in the brain. These brain activation differences indicate a possible neuroplastic effect of musculoskeletal trauma that is not normalized after treatment or return to activity. Clinicians may consider embracing the principles of neuroplasticity in musculoskeletal rehabilitation, including motor-learning and visual-motor compensations, to address the brain activation differences after injury.

**KEY POINTS**

**FINDINGS:** Anterior cruciate ligament injury, surgery, and rehabilitation may cause specific brain activation changes related to sensory-visual-motor control.

**IMPLICATIONS:** Following ACLR and return to activity, an altered sensory-visual knee neural control strategy remains that may have the capability to be targeted with novel rehabilitation strategies.

**CAUTION:** The current study design is unable to determine when the neuroplastic changes occurred after injury or whether any of the brain activation differences were present prior to injury.

**ACKNOWLEDGMENTS:** We thank The Ohio State University Center for Cognitive and Behavioral Brain Imaging for its technical expertise.

**REFERENCES**


66. Seidl RD, Noll DC. Neuroanatomical correlates


PUBLISH Your Manuscript in a Journal With International Reach

Jospt offers authors of accepted papers an international audience. The Journal is currently distributed to the members of APTAs Orthopaedic and Sports Physical Therapy Sections and 33 orthopaedics, manual therapy, and sports groups in 26 countries who provide online access either as a member benefit or at a discount. As a result, the Journal is now distributed monthly to more than 30,000 individuals around the world who specialize in musculoskeletal and sports-related rehabilitation, health, and wellness. In addition, Jospt reaches students and faculty, physical therapists and physicians at more than 1,500 institutions in 56 countries. Please review our information for and Instructions to Authors at www.jospt.org in the Info Center for Authors and submit your manuscript for peer review at http://mc.manuscriptcentral.com/jospt.