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Neuroplasticity in Corticolimbic Brain Regions in Patients After Anterior Cruciate Ligament Reconstruction

Shelby Baez, PhD, ATC*; Anders Andersen, PhD†; Richard Andreatta, PhD†; Marc Cormier, PhD, CMPC, LPCA†; Phillip A. Gribble, PhD, ATC†; Johanna Marie Hoch, PhD, ATC†

*Department of Kinesiology, Michigan State University, East Lansing; †University of Kentucky, Lexington

Context: Fear has been cited as the primary barrier to return to sport (RTS) by athletes after anterior cruciate ligament reconstruction (ACLR). Understanding the neural factors that contribute to fear after ACLR may help us to identify interventions for this population.

Objective: To characterize the underlying neural substrate of injury-related fear in patients after ACLR versus healthy matched control individuals during a picture imagination task (PIT) consisting of sport-specific images and images of activities of daily living (ADL).

Design: Case-control study.

Setting: Research laboratory.

Patients or Other Participants: A total of 24 right-hand–dominant participants (12 with left-sided ACLR and 12 control individuals) were enrolled. Participants underwent full-brain functional magnetic resonance imaging.

Main Outcome Measure(s): Functional data were acquired using blood oxygen level–dependent (BOLD) echoplanar imaging. Independent *t* tests were conducted to identify between-groups differences in BOLD signal changes during all images of the PIT. Paired *t* tests were computed to examine differences in BOLD signal change between sport-specific and ADL images in the ACLR group.

Results: Increased activation in the inferior parietal lobule and the mediodorsal thalamus was observed during PIT in the ACLR group. An inability to suppress the default mode network in the ACLR group was noted. The ACLR group exhibited increased activation in the cerebellum and inferior occipital regions during the sport-specific images versus the ADL images, but no other regions of interest demonstrated differences.

Conclusion: After ACLR, patients may be more predisposed to fear, anxiety, and pain during sport-specific activities and ADLs. Psychosocial interventions may be warranted after ACLR to reduce injury-related fear and mitigate potentially maladaptive neuroplasticity.

Key Words: neuroscience, fear, knee, sport injury

Key Points

- After anterior cruciate ligament reconstruction, individuals displayed activation differences in the corticolimbic brain region during a picture imagination task when compared with a healthy matched control group.
- These activation differences may reflect injury-related fear associated with sport-specific tasks and activities of daily living.

Injury to the anterior cruciate ligament (ACL) involves serious athletic trauma that often requires surgical reconstruction (ACLR) to repair and augment knee stability.[1] The principal goal of this surgical procedure is to allow patients to return to their previous level of sports participation and physical activity.[1] However, 1 out of 3 patients will not return to the previous level of sport participation, with injury-related fear often cited as the primary reason for this failure.[2] Unfortunately, injury-related fear has not only been cited as a barrier to return to sport (RTS) but also as being associated with an increased risk for secondary injury.[3] Previous researchers[3] suggested that patients with increased injury-related fear at RTS were 13 times more likely to sustain a second ACL injury within 24 months of RTS clearance. Despite the negative effects of injury-related fear, further explorations of the underlying mechanisms associated with injury-related fear in this population have yet to be conducted.

In addition to increased injury-related fear after ACLR, patients also experience neuroplasticity in select sensorimotor brain regions consequent to their injury.[4] *Neuroplasticity* is the ability of the brain to dynamically reorganize synaptic connections and functional networks in response to all forms of salient experiences, including injury.[5] Neuroplasticity has been theorized to occur after ligamentous injury as a result of disrupted sensory feedback from the site of the injury to the brain.[5] Earlier investigators[4] demonstrated that after ACLR, patients exhibited increased activation in the contralateral motor cortex, lingual gyrus, and ipsilateral secondary somatosensory area during a knee extension-flexion task when compared with healthy control participants. We found it interesting that the secondary somatosensory area is a

cortical region activated during painful stimuli and increased activation in this region was observed, although the participants were an average of 38 months post-ACLR.[4] Furthermore, the participants did not report discomfort while completing the knee extension-flexion task during functional magnetic resonance imaging (fMRI) scans.[4] Lepley et al[6] demonstrated similar brain-activation patterns in participants approximately 6 years post-ACLR and showed that activation in these regions was associated with increased reports of pain on the Knee Injury and Osteoarthritis Outcome Score. The combined results of Grooms et al[4] and Lepley et al[6] suggest that psychological factors, coincident with peripheral neural adaptations, may have influenced the observed changes in brain-activation patterns. Thus, injury-dependent neuroplastic events in brain regions related to processing emotions (ie, corticolimbic system areas) may have occurred.[4]

Other populations with musculoskeletal conditions have displayed similar patterns of injury-dependent neuroplasticity in corticolimbic brain regions. Among patients with medial patellofemoral ligament deficiency, increased activation in the corticolimbic regions was observed during a patellar-mobilization task when compared with healthy matched control individuals.[7] Patients with chronic musculoskeletal pain also exhibited increased activation in the corticolimbic regions of the brain.[8] To examine corticolimbic activation, Taylor et al[8] used a blocked picture imagination task (PIT) paradigm in which patients were instructed to view pictures of activities of daily living (ADL) and imagine themselves completing those tasks. This PIT paradigm may be a useful means of examining injury-dependent neuroplasticity in the corticolimbic brain regions among patients with different musculoskeletal conditions, including ACLR.

Characterization of the underlying neural substrate of injury-related fear in patients after ACLR is critically needed. Understanding injury-related fear may allow us to develop more appropriate and targeted intervention strategies to mitigate this concern after ACLR. Appropriate interventions for addressing injury-related fear may enable patients to return to sport or ADL more successfully. As such, the primary purpose of our study was to identify brain-activation patterns underlying the neural substrate of injury-related fear during a visually based PIT in individuals with ACLR and healthy, age-matched controls. We hypothesized that those with ACLR would exhibit more blood oxygen level–dependent (BOLD) percentage signal changes in the corticolimbic brain regions than healthy matched control participants. The secondary purpose of our study was to examine the differences in BOLD signal changes in the corticolimbic brain regions while viewing sport-specific versus ADL images among individuals with ACLR. We hypothesized that the corticolimbic brain regions would display increased activation while the participants viewed sport-specific versus ADL images.

METHODS

Design

A case-control study design was used to examine mean BOLD percentage signal changes in the corticolimbic regions among a cohort of individuals after ACLR compared with a healthy matched control group. The dependent variable was mean BOLD percentage signal change, and the independent variable was group identification (ACLR versus healthy control). For the secondary purpose, the dependent variable was mean BOLD percentage signal change and the independent variable was picture category (sport-specific versus ADL).

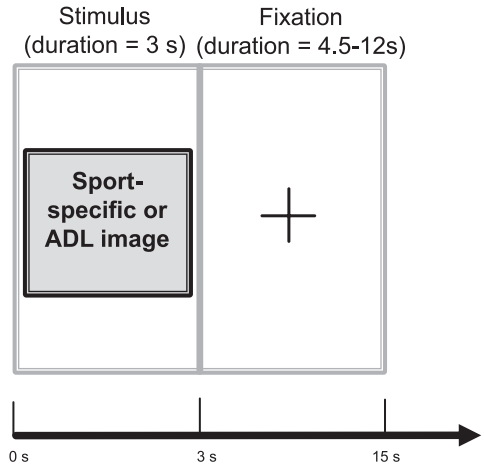

Figure 1. Functional magnetic resonance imaging trial timing.

Participants

Twelve female participants with ACLR and 12 healthy matched control individuals were recruited for this study. We selected women for this study due to internal validity concerns given that sex differences in emotional regulation have been observed.[9] Those in the ACLR group were 18 to 35 years old, had injured their knees playing or training for sport (recreational or organized), had a history of unilateral left-sided ACLR, were right-hand dominant, were a minimum of 1 year postsurgery, were cleared for full return to activity by a physician, and last, demonstrated compliance with magnetic resonance imaging (MRI) instructions. Healthy matched control individuals were right-hand dominant and matched for age (±20% of age in years), height (±20%), mass (±20%), and physical activity history of participating in the same sport. Only those with left-sided ACLRs were included to ensure that the unique unilateral brain changes associated with the ACLR limb were not missed due to mixing the cohort.[4] In addition, participants enrolled in this study must have recorded a minimum score of 5 on the Tegner Physical Activity Assessment[10] for activity levels before the index ACL injury. *Compliance with MRI* referred to having no metal or other devices in the body or conditions that might have put them at risk for having metal in the body. The University of Kentucky Institutional Review Board approved the study, and all participants reviewed and signed an approved informed consent form before data collection began.

Procedures

The ACLR and healthy matched control groups completed a demographic questionnaire to assess anthropometric measures and injury history. After completion of the demographic questionnaire, they underwent a functional MRI (fMRI) scan. During the scan, participants were presented with 40 sport-specific pictures (eg, jumping,

running, hopping) and 20 ADL pictures (eg, sitting, reading, grocery shopping). The presentation of the pictures followed a modified version of the protocol (Figure 1) originally implemented by Taylor et al.[8] Images selected for the task were chosen from the International Affective Picture System (IAPS)[11] and the Photographic Series of Sports Activities for ACLR (PHOSA-ACLR).[12]

The IAPS[11] consists of a set of images of normative emotional stimuli for investigations into personality traits associated with reactivity and emotional states. We chose 28 sport-specific images and 20 ADL images from the IAPS catalog. Sport-specific images were selected if the description included a sport activity (ie, weightlifting, boxing, running). The ADL images (ie, sitting, lying, reading) exhibited low arousal ratings. The PHOSA-ACLR is a subjective scale intended to grade perceptions of fear of harm by having the patient examine pictures of individuals engaging in sport-specific tasks that may be salient to a patient after ACLR (eg, image of a person jumping). All 12 images in the PHOSA-ACLR were used in the protocol to depict knee-specific functional tasks (eg, lunging, pivoting, sliding). Images from the PHOSA-ACLR and the IAPS were combined and randomly distributed during the fMRI scan.

Picture Imagination Task

Once situated in the MRI machine, participants first focused on a visual fixation cross to allow the participant's hemodynamic response to stabilize to baseline level (Figure 1). The stimulus presentation followed a slow event-related design with image category (ie, sport-specific versus ADL) in random order and was distributed across 2 fMRI runs, lasting approximately 5 minutes per run. The duration of the fixation cross occurred in random fixed order across the photographs: that is, the order of the sport-specific and ADL images was randomized, but each participant saw the images in the same order; Figure 1). Based on the previously established protocol of Taylor et al,[8] participants were given standardized instructions to carefully imagine themselves physically and mentally completing the tasks demonstrated in the picture while the image was displayed. For example, if shown an image of a person running, the participant would then physically and mentally imagine herself running. No contextual information about the images were provided to the participants during the PIT. Each image was presented once for 3 seconds and, regardless of category, was followed by a fixation cross presented for a randomized duration of 4.5 to 12 seconds. This was to allow activation to return to baseline measures.

At the end of the fMRI protocol, all participants completed the Fear-Avoidance Beliefs Questionnaire (FABQ),[13] which measures fear-avoidance beliefs, and the Tampa Scale of Kinesiophobia-11 (TSK-11),[14] which measures fear of movement. The PHOSA-ACLR[12] was also completed to allow participants to subjectively grade their perceptions of the photos shown while in the MRI device. The FABQ,[13] TSK-11,[14] and PHOSA-ACLR[12] perceptions were collected as additional demographic information to characterize the levels and constructs of injury-related fear in the ACLR and control groups. These surveys were administered after all fMRI testing was completed in order to avoid interference with the fMRI results.

Statistical Analysis

We calculated descriptive statistics for participant demographics, including patient-reported outcome scores. Mann-Whitney *U* tests were conducted to examine between-groups differences in baseline demographics and injury-related fear as measured by the patient-reported outcomes.

Image Acquisition, Processing, and Analysis

Because this was an exploratory study, we obtained whole-brain functional scans to ensure that no unique activation patterns in this population were missed. Whole-brain functional images were collected via a 3T PRISMA MRI scanner (Siemens Medical Solutions USA) using a 64-channel array, receive-only head coil at the Magnetic Resonance Imaging and Spectroscopy Center at the University of Kentucky. Functional data were acquired with BOLD echoplanar imaging (EPI) using a gradient echo simultaneous multi-slice (acceleration factor of 2) EPI pulse sequence with repetition time = 1500 milliseconds and echo time = 32 milliseconds. Increases in BOLD signal indicate increased activation, and decreases indicate decreased activation. The acquisition matrix was 64×64, with a field of view of 224 mm and a slice thickness of 3.5 mm (n = 42 axial slices). Acquisition of the data was synchronized with the presentation of the images. A double-echo gradient recalled echo image dataset with the resolution matched to the EPI was acquired for correction of the geometric distortion. Anatomical data consisted of volumetric T_1-weighted magnetized prepared rapid acquisition gradient echo images with repetition time = 2530 milliseconds, echo time = 2.3 milliseconds with 1100 milliseconds inversion time, parallel imaging implementation acceleration = 2, and generalized autocalibrating partial parallel reconstruction. The resultant voxel resolution was $1 \times 1 \times 1$ mm^3.

Functional data were processed using Analysis of Functional NeuroImages (http://afni.nimh.nih.gov/) and FMRIB Software Library (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) research software. Images were corrected for motion, slice timing, and geometric distortion and were spatially smoothed. Image data were then analyzed using multiple regression procedures. We used the general linear model to estimate the mean activation response for all images during the PIT, regardless of picture category, measured as the percentage of fractional signal change. Regressors consisted of sport-specific and ADL images, as well as the motion parameter estimates as additional nuisance variables. Based on previously established fMRI methods for second-level group analyses, voxelwise maps of the percentage fractional signal change activation responses for each participant were transformed to a common stereotaxic Talairach coordinate space.[15] The Talairach coordinate space then allowed us to identify region-of-interest (ROI) measurements, which were obtained using the automated anatomical labeling atlas template.[15] Qualitative post hoc ROI analyses were performed to further characterize the brain responses observed on the whole-brain functional scan during the PIT. On completion of the qualitative post hoc ROI analyses, we used independent *t* tests to quantitatively

Table 1. Participants' Demographics and Patient-Reported Outcome Measure Scores

Characteristic	Group, Median (Interquartile Range)			Mann-Whitney Test *P* Value
	ACLR (n = 12)	Control (n = 12)	Total (n = 24)	
Age, y	21.5 (6.8)	23.0 (1.8)	22.5 (3.8)	.27
Height, cm	168.9 (16.5)	166.4 (14.6)	167.6 (14.6)	.98
Weight, kg	68.5 (22.8)	66.9 (19.3)	68.0 (17.9)	.32
Time from index ACLR, y	5.5 (4.2)			
Fear-Avoidance Beliefs Questionnaire score				
Physical Activity	7.5 (12)	0.0 (5)	4.0 (10)	.01
Sport	13.0 (17)	0.0 (6)	4.0 (17)	.01
Total	19.5 (30)	0.0 (11)	8.00 (26)	.01
Tampa Scale of Kinesiophobia-11	20.0 (6)	14.0 (7)	17.50 (8)	.01
Photographic Series of Sports Activities After Anterior Cruciate Ligament Reconstruction	1.9 (2)	0.2 (1.5)	1.1 (2.2)	.04

Abbreviation: ACLR, anterior cruciate ligament reconstruction.

compare brain activation in these ROIs during the PIT in the ACLR group with that in the control group.

Secondary Analysis

Paired *t* tests were conducted to examine differences in mean BOLD percentage signal change based on image category (ie, sport specific versus ADL) in the ACLR group. Our selection of brain regions for the secondary analysis was based on the results of the primary aim of the study. Only areas that demonstrated significant differences between the ACLR and healthy control groups were included in this secondary analysis. Quantitative analyses for the primary and secondary analyses were conducted via SPSS (version 22; IBM Corp).

RESULTS

Twenty-four participants (12 individuals with ACLR and 12 healthy matched control individuals) were scanned. Participants' demographic information is presented in Table 1. The data were not normally distributed, so nonparametric tests were used to analyze demographic information. Differences were noted between the ACLR and control groups on the FABQ, TSK-11, and PHOSA-ACLR (Table 1). Those with ACLR exhibited increased

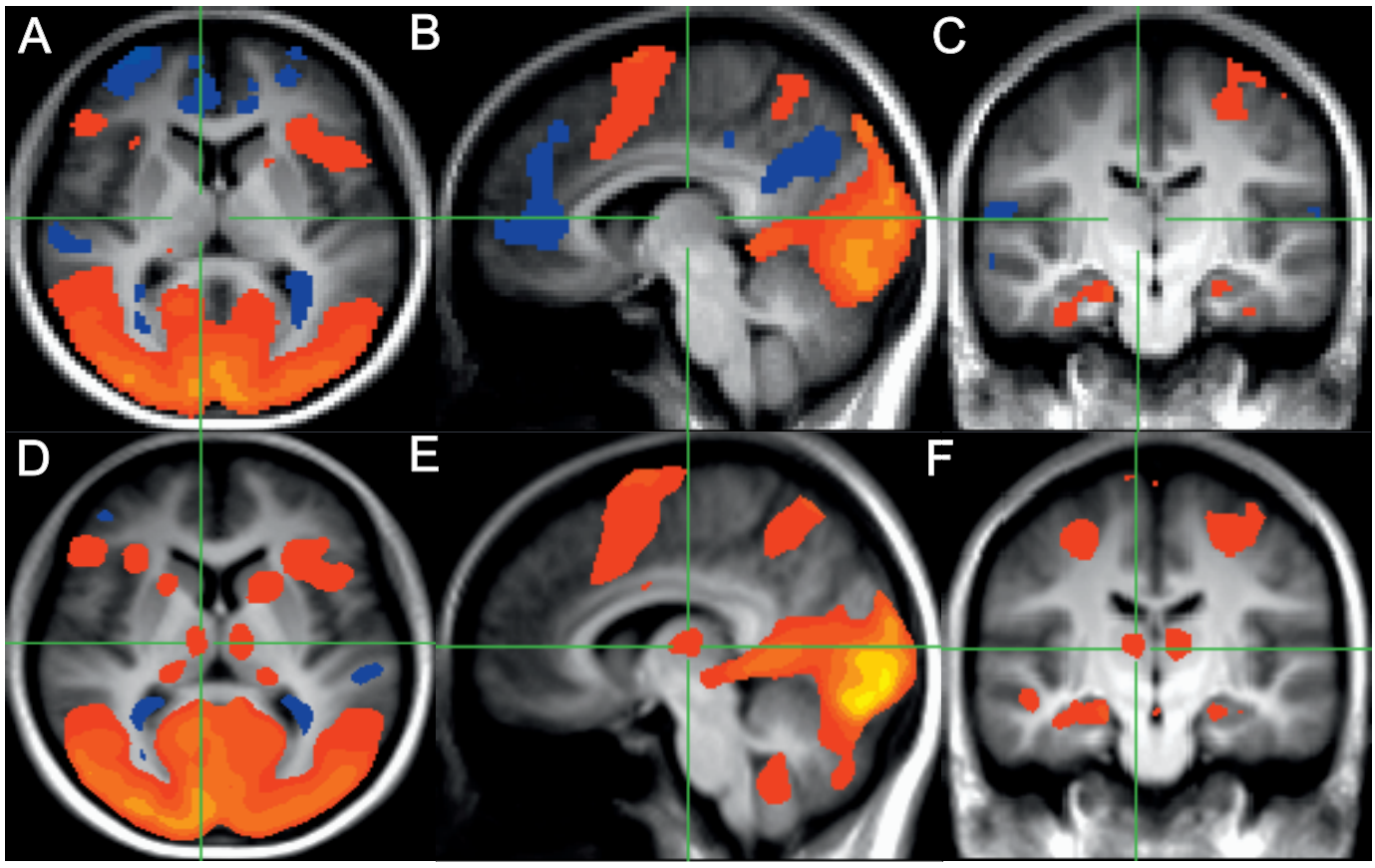

Figure 2. Thalamus activation during the picture imagination task.

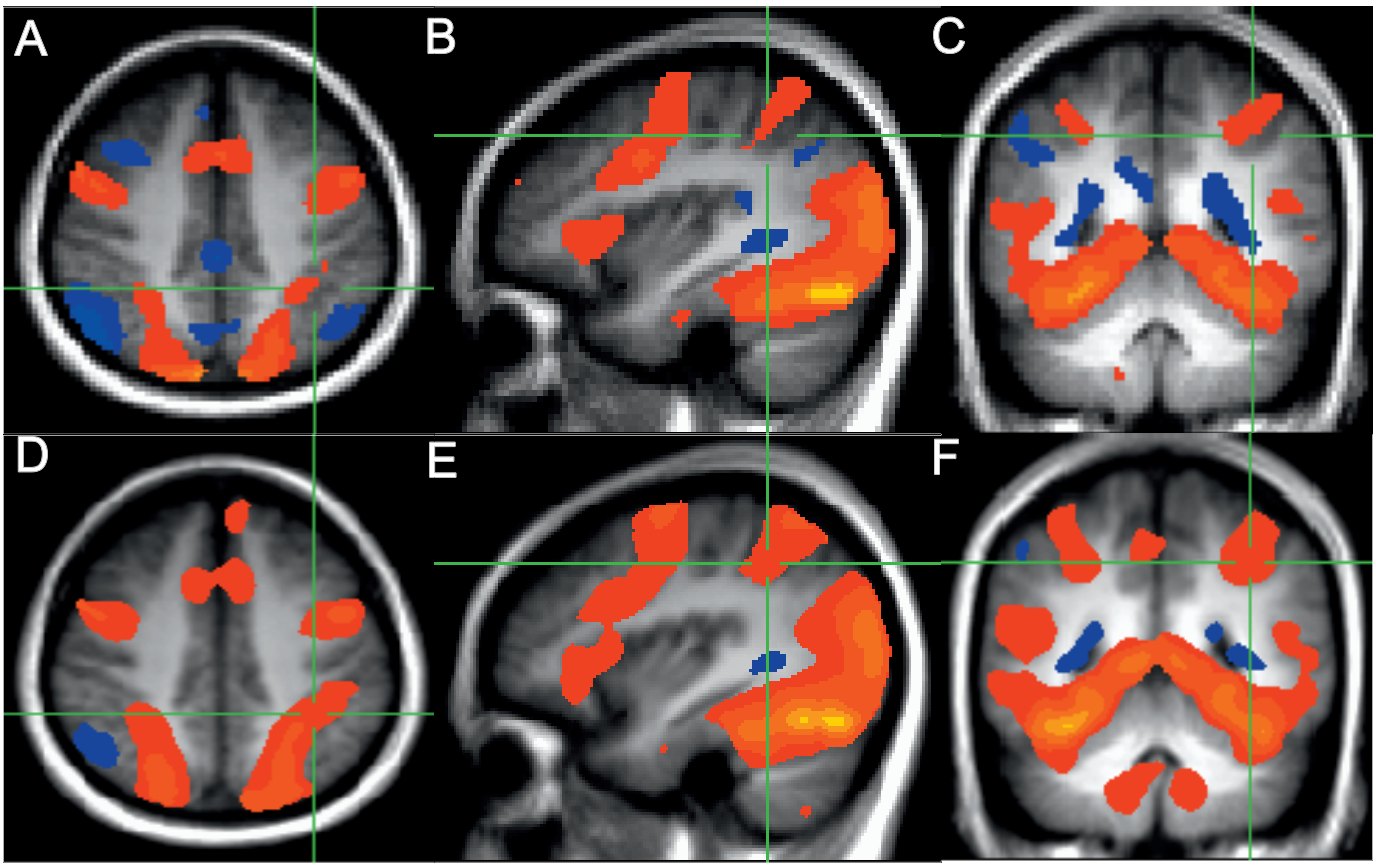

Figure 3. Inferior parietal lobule activation during the picture imagination task.

levels of self-reported injury-related fear when compared with the control group.

Imaging Outcomes

The primary aim of our study was to examine differences in corticolimbic brain activation among individuals with ACLR and healthy matched control participants. Differences in BOLD responses occurred between groups during the PIT (Figures 2 and 3). The analyses demonstrated that participants with ACLR exhibited increased activation in the corticolimbic brain regions, including the mediodorsal thalamus (MDT; Figure 2), inferior parietal lobule (IPL; Figure 3), and cerebellar lobule IX, irrespective of picture category when compared with the control group. The ACLR group displayed an inability to suppress the default mode network (DMN; eg, posterior cingulate, precuneus, and ventromedial prefrontal cortex) irrespective of picture category when compared with the control group (Table 2). Activation differences during the PIT are presented in Table 2.

Sport-Specific Versus ADL Images in the ACLR Group

Using the findings associated with our primary purpose, we examined differences in mean BOLD percentage signal changes in 22 brain regions (Table 3). Differences were observed between sport-specific and ADL images in the inferior occipital region and cerebellum IX region. Increased activation was present in these regions when participants visualized sport-specific images compared with ADL images. No differences occurred between sport-specific and ADL images for any other regions in the ACLR group. Activation patterns were similar in the MDT, IPL, and DMN, regardless of picture category.

DISCUSSION

The primary purpose of our investigation was to examine differences in corticolimbic brain region activation among individuals with ACLR compared with healthy, age-matched control participants. Our hypothesis that individuals with ACLR would exhibit increased activation in corticolimbic brain regions was supported. Increased activation in the MDL, IPL, and cerebellar lobe IX were observed in the ACLR group compared with the control group. We also noted that compared with the control group, the ACLR group was unable to suppress the DMN, a finding that has been correlated with depression, anxiety, and chronic pain in other populations.[8,16,17] Our secondary purpose was to examine the differences in activation patterns associated with image category (ie, sport specific versus ADL) in individuals with ACLR. Our hypothesis that increased activation in corticolimbic brain regions would be associated with sport-specific images was partially supported. Increased activation in the inferior occipital region and the cerebellar region was observed; however, no differences were found for any other regions of interest.

To our knowledge, besides Lepley et al,[6] we are the only researchers to examine the brain-activation patterns under-

Table 2. Group Differences for the Picture Imagination Task

Region	Side	Group Fractional % Signal Change, Mean ± SD		*t* Value	*P* Value[a]
		ACLR	Control		
Frontal superior	R	0.03 ± 0.06	−0.04 ± 0.08	2.52	.019
Frontal superior medial	L	0.09 ± 0.11	−0.02 ± 0.11	2.21	.038
Frontal superior medial	R	−0.03 ± 0.12	−0.12 ± 0.14	2.14	.043
Frontal orbital medial	L	0.09 ± 0.12	−0.07 ± 0.19	2.50	.020
Cingulum anterior	R	−0.01 ± 0.07	−0.08 ± 0.09	2.10	.047
Cingulum mid	L	0.05 ± 0.06	−0.02 ± 0.01	2.14	.043
Cingulum posterior	L	0.09 ± 0.18	0.06 ± 0.15	3.79	.001
Cingulum posterior	R	0.06 ± 0.15	−0.12 ± 0.07	3.84	.001
Hippocampus	R	0.13 ± 0.05	0.07 ± 0.07	2.43	.023
Occipital inferior	L	0.70 ± 0.21	0.52 ± 0.15	2.44	.023
Angular gyrus	L	0.05 ± 0.12	−0.06 ± 0.11	2.24	.035
Angular gyrus	R	−0.01 ± 0.13	−0.14 ± 0.08	2.88	.009
Caudate	L	0.06 ± 0.07	−0.02 ± 0.09	2.45	.022
Thalamus	L	0.12 ± 0.09	0.008 ± 0.07	3.36	.003
Thalamus	R	0.10 ± 0.08	0.008 ± 0.07	3.06	.006
Cerebellum crus 2	L	0.06 ± 0.08	−0.02 ± 0.06	2.90	.008
Cerebellum crus 2	R	0.06 ± 0.06	0.007 ± 0.05	2.08	.049
Cerebellum IX	L	0.15 ± 0.08	0.05 ± 0.04	3.85	.001
Cerebellum IX	R	0.17 ± 0.09	0.06 ± 0.06	3.14	.005
Cerebellum X	L	0.24 ± 0.12	0.13 ± 0.09	2.44	.023
Vermis I	NA	0.05 ± 0.09	−0.03 ± 0.10	2.08	.049
Vermis IX	NA	0.16 ± 0.05	0.06 ± 0.07	4.29	.000

Abbreviations: ACLR, anterior cruciate ligament reconstruction; L, left; NA, not applicable; R, right.

[a] Region-of-interest analysis using the automated anatomical labeling atlas: uncorrected *P* values are presented.

lying the neural substrates of injury-related fear in patients after ACLR. These results indicated that injury-related fear after ACLR was not merely subjectively occurring as a response to injury but may induce neuroplastic adaptations in corticolimbic brain regions, changes that can be objectively measured and quantified. Whereas our results supported the concept that sport-specific activities may induce a fear response, we also suggest that injury-related fear may be induced as a result of ADL in individuals with ACLR. This contradicts the assumptions that only more demanding functional tasks would be considered fear inducing in this high-functioning, physically active population.

Inferior Parietal Lobule and Mediodorsal Thalamus Activation

When compared with the healthy group, the ACLR group exhibited increased activation in the IPL, MDT, and cerebellar lobule IX. The IPL is located at the junction of the auditory, visual, and somatosensory cortices and is involved in the perception of emotions in facial stimuli and body images.[18] Traditionally, the IPL processes body and facial images that display fearful behaviors, such as screaming or crying.[18] For example, Engelen et al[18] used an image of a male actor jumping backward with his hands forward as a response to something fearful. We thought it was interesting that none of the images in our study showed athletes being "afraid" during the demonstrated activity. All photographed individuals were either simply performing their sport or engaging in simple ADL. However, the ACLR group appeared to interpret these images more emotionally than did the healthy group. Thus, contemplation of sport participation and ADL may have engendered an emotional response, likely fear or anxiety, in these individuals.

In addition to the IPL, increased activation in the MDT in the ACLR group was consistent with the important role of the MDT in the acquisition, consolidation, or retrieval of Pavlovian contextual fear conditioning.[19] Activation of the thalamus is typically associated with somatosensory inputs, but the MDT serves as an associative hub to and from the limbic and hypothalamic brain regions. This connectivity allows the MDT to influence autonomic processing, such as increasing heart rate, which is also related to sympathetic autonomic arousal (ie, fight or flight). Furthermore, the MDT has been associated with the mediation of emotional responses specifically related to pain-evoking stimuli.[20] Our ACLR group's viewing of the PIT images may have trigged an emotional response due to episodic memories associated with the ACL injury and the subsequent immediate limitations in ADL after surgery. Sport participation can lead to painful experiences, such as sustaining an ACL injury; therefore, the ACLR individuals may have experienced a sympathetic autonomic response as a result of these memories. When compared with the control group, the ACLR group did demonstrate increased activation in the angular gyrus, an area of the brain associated with the recall of episodic memories (Table 2). Angular gyrus activation further supports the hypothesis of increased episodic memory retrieval in the ACLR group during the PIT.

Fear-avoidance beliefs, a type of injury-related emotional state that refers to fear of pain or reinjury and was correlated with learned avoidance behaviors,[13] was increased in the ACLR participants when compared with the control participants. Increased fear-avoidance beliefs, as measured by the FABQ, may subjectively represent the objective feedback loop between the MDT and prefrontal cortex. Activation of the MDT may be part of the functional

Table 3. Differences Between the Sport-Specific and Activities of Daily Living Images

Region	Side	Images Fractional % Signal Change, Mean ± SD		*t* Value	*P* Value[a]
		Sport-Specific	Activities of Daily Living		
Frontal superior	R	0.05 ± 0.09	0.02 ± 0.06	1.35	.21
Frontal superior medial	L	0.09 ± 0.13	0.08 ± 0.13	0.21	.84
Frontal superior medial	R	0.03 ± 0.10	0.02 ± 0.08	0.28	.78
Frontal orbital medial	L	0.10 ± 0.20	0.08 ± 0.11	2.50	.73
Cingulum anterior	R	−0.01 ± 0.09	−0.02 ± 0.07	0.75	.47
Cingulum mid	L	0.08 ± 0.08	0.02 ± 0.07	1.83	.09
Cingulum posterior	L	0.13 ± 0.20	0.07 ± 0.18	1.57	.15
Cingulum posterior	R	0.06 ± 0.15	0.07 ± 0.17	−0.08	.94
Hippocampus	R	0.12 ± 0.06	0.14 ± 0.07	−0.74	.48
Occipital inferior	L	0.74 ± 0.20	0.66 ± 0.23	2.44	.04[b]
Angular gyrus	L	0.06 ± 0.16	0.05 ± 0.11	0.26	.80
Angular gyrus	R	0.01 ± 0.15	−0.03 ± 0.12	2.14	.06
Caudate	L	0.08 ± 0.09	0.04 ± 0.07	1.33	.21
Thalamus	L	0.13 ± 0.11	0.11 ± 0.10	0.48	.64
Thalamus	R	0.11 ± 0.09	0.10 ± 0.09	0.48	.64
Cerebellum crus 2	L	0.08 ± 0.10	0.04 ± 0.08	1.60	.14
Cerebellum crus 2	R	0.06 ± 0.07	0.05 ± 0.07	0.31	.76
Cerebellum IX	L	0.21 ± 0.09	0.10 ± 0.90	3.99	.02[b]
Cerebellum IX	R	0.21 ± 0.10	0.12 ± 0.11	3.22	.01[b]
Cerebellum X	L	0.27 ± 0.14	0.21 ± 0.16	1.20	.26
Vermis I	NA	0.07 ± 0.13	0.03 ± 0.15	0.54	.60
Vermis IX	NA	0.19 ± 0.07	0.14 ± 0.08	1.37	.20

Abbreviations: L, left; NA, not applicable; R, right.

[a] Region-of-interest analysis using the automated anatomical labeling atlas: uncorrected *P* values are presented.

[b] Indicates a difference.

system that leads to the rumination of painful memories in the prefrontal cortex, creating a feedback loop that results in pain memories being consistently processed in a person's consciousness during sport participation. Such a feedback loop may negatively change the cognitive appraisal of sport participation among patients after ACLR, thereby changing their subjective views and ultimately leading to increased fear-avoidance beliefs. This connection between the MDT and prefrontal cortex may also explain why the ACLR group exhibited an inability to suppress the DMN.

Default Mode Network

The DMN is a cortical network that shows greater activity during resting-state conditions while actively performing a goal-directed task (eg, the PIT).[17] The functional network hubs associated with the DMN include the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex, and angular gyrus.[17,21] The PCC is activated during all tasks related to the self, others, past memories, and thoughts about the future. The precuneus is activated during the processing of attentional and spatial information.[21] Previous researchers determined that an inability to suppress the DMN was linked with psychopathological conditions, including depression,[22] anxiety,[23] and the development and maintenance of chronic pain.[8,16] Echoing the results demonstrated by Taylor et al[8] in patients with chronic musculoskeletal pain, our ACLR group also was unable to suppress the DMN compared with the healthy control group. Specifically, the ACLR group displayed an inability to suppress the PCC, precuneus, and ventromedial prefrontal cortex. An inability to suppress the DMN when attending to a task suggests that after ACLR, patients may be predisposed to processing fear, anxiety, or perceived pain. Taylor et al[8] proposed that the inability to suppress the DMN may also occur because the brain is constantly processing pain. However, we hypothesize that rather than processing pain, the ACLR group may instead constantly remain in the act of processing the memory of the painful event. We asked participants before, during, and after scanning about their comfort and pain levels. None reported discomfort or pain while in the scanner. Very similar to the results of Grooms et al,[4] our participants were approximately 5.5 years from index ACLR, and none complained of pain while in the scanner. Grooms et al[4] noted increased activation of the ipsilateral secondary somatosensory area during the knee extension-flexion task performed while in the scanner and attributed this to a reorganization of functional cortical sensory processing as a result of knee trauma. However, given our results, we suggest that the ipsilateral secondary somatosensory area may have been activated during the knee flexion-extension task because the DMN may have been continuously processing pain memories in these patients.

Cerebellar Activation

We observed increased activation in the cerebellum of the ACLR group when compared with the control group. Activation in the cerebellar lobule IX was consistent with the findings of Grooms et al,[4] indicating that after ACLR, patients relied more on their vision to complete functional tasks. Cerebellar lobule IX is an area considered essential for the visual guidance of movement.[24] These outcomes add to the growing body of literature that suggests patients after ACLR compensate for changes in the sensorimotor system by relying on vision to complete functional tasks.[4] Increased activation in the cerebellar region and the inferior occipital region also occurred during the imagining of sport-specific tasks versus ADL. This further supports the

overreliance on the visual system noted during the completion of functional tasks in patients after ACLR. However, activation in the cerebellum may not only result from increased visual reliance.

In the past, cerebellar activity was described only in the context of motor function, but recent researchers[25] have begun to explore the involvement of the cerebellum in Pavlovian fear conditioning. It has been shown that the cerebellum, specifically the vermis, is associated with high arousal and negative emotional regulation.[25] The cerebellum has direct connections with limbic regions, including the amygdala and the hippocampus.[25] Recognition of potential fear-eliciting stimuli and activation of the cerebello-hypothalamic brain regions may be a result of the sympathetic autonomic response (fight or flight). During the PIT, the ACLR group may have undergone a sympathetic autonomic response that was also incorporated in cerebellar networks.

As proposed by Andersen and Williams[26] in the stress and injury model, maladaptive stress responses can increase the risk of sustaining an athletic injury.[26] The stress and injury model proposes that an athlete's cognitive appraisal of an athletic situation can lead to physiological and attentional changes.[26] However, multiple factors, including previous injury, can influence this stress response.[26] An athlete who experiences increased levels of stress and is unable to overcome the physical and psychological demands of the situation is at an increased risk of injury.[26] The results of our research align with the model, given that the brain areas associated with the physiological and attentional responses to stress appeared to display increased activation in our ACLR group. Earlier investigators[3] demonstrated that after ACLR, patients who exhibited increased injury-related fear were 13 times more likely to sustain a second ACL injury within 24 months of RTS. We hypothesize that the stress response, as a result of increased activation in the corticolimbic brain regions, may be partially related to this increased risk of reinjury associated with increased levels of injury-related fear in patients with ACLR.

Psychologically Informed Clinical Practice

Our findings highlight the possible significance of integrating psychologically informed clinical practice techniques while treating patients after ACLR. First, it is important for rehabilitation specialists to integrate patient-reported outcomes that measure injury-related fear into the management of individuals after ACLR. As demonstrated by our participant demographics, the ACLR group had increases in fear-avoidance beliefs as measured by the FABQ, fear of movement as measured by the TSK-11, and fear of harm as measured by the PHOSA-ACLR when compared with the control group. Using these outcome measures may allow rehabilitation specialists to identify tasks that lead to increased injury-related fear in patients after ACLR, such as hopping. Increased injury-related fear can occur when functional tasks are introduced toward the end of rehabilitation and, if not addressed, the fear may remain elevated after RTS.[27] Such outcome measures can help rehabilitation specialists to objectively measure these constructs and monitor changes.

Psychologically informed clinical practice also emphasizes the integration of cognitive behavioral therapies and psychoeducational techniques in conjunction with traditional musculoskeletal rehabilitation.[28] Rehabilitation specialists can effectively implement cognitive behavioral therapies and psychoeducational techniques to decrease injury-related fear.[29] Specifically, in vivo exposure therapy has been successfully used by rehabilitation specialists to decrease injury-related fear in patients with chronic low back pain.[29] *In vivo exposure* is a psychological technique that gradually exposes patients to functional tasks they fear.[30] Rather than using pain or soreness as a guide for progression, rehabilitation specialists use fear as their guide through different levels of exercises with the goal of decreasing the patient's fear response to that specific exercise.[30] This technique may not only decrease injury-related fear in patients after ACLR, but it may induce long-term adaptive neuroplasticity in the corticolimbic regions.

Limitations

We identified the following limitations of this study. First, the activation patterns observed in the ACLR group may have been present before the ACL injury. We are unable to definitively state that the ACL injury led to these changes in activation, although the lack of similar activity in the control population does suggest that activation patterns in the ACLR group were likely related to ACL injury or repair. Second, fMRI is an indirect measure of neural activity, and we could not distinguish connectivity between brain regions. Thus, we can only speculate about the connectivity between the corticolimbic regions in the brain based on the activation patterns. Third, whereas the questionnaires used to examine injury-related fear have been previously used after ACLR, not all have been validated for an ACLR population. Last, we did not quantify pain levels in these patients. It is possible that pain may have led to the activation patterns observed in the ACLR group. However, no participant complained of pain before, during, or after the fMRI scan. Future researchers should consider including a direct pain measure (eg, visual analog scale) before, during, and after the scan to objectively measure pain throughout testing.

CONCLUSIONS

Brain-activation differences were present in the corticolimbic brain regions of individuals with ACLR when compared with healthy matched control individuals during the PIT. In addition, these activation patterns may be a result of fear associated with sport-specific tasks and ADL. Future investigators should explore the effectiveness and appropriate dosage of and the most efficient time point for implementing psychological interventions to decrease injury-related fear and mitigate brain-activation differences in patients after ACLR.

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Address correspondence to Shelby Baez, PhD, ATC, Department of Kinesiology, Michigan State University, 308 W Circle Drive, 27P, East Lansing, MI 48824. Address email to baezshel@msu.edu.