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*short report*

# Brain Activation for Knee Movement Measured Days Before Second Anterior Cruciate Ligament Injury: Neuroimaging in Musculoskeletal Medicine

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***Background:*** Anterior cruciate ligament (ACL) injury has multifactorial causes encompassing mechanical, hormonal, exposure, and anatomical factors. Alterations in the central nervous system also play a role, but their influence after injury, recovery, and recurrent injury remain unknown. Modern neuroimaging techniques can be used to elucidate the underlying functional and structural alterations of the brain that predicate the neuromuscular control adaptations associated with ACL injury. This knowledge will further our understanding of the neural adaptations after ACL injury and rehabilitation and in relation to injury risk. In this paper, we describe the measurement of brain activation during knee extension-flexion after ACL injury and reconstruction and 26 days before a contralateral ACL injury.

***Methods:*** Brain functional magnetic resonance imaging data for an ACL-injured participant and a matched control participant were collected and contrasted.

***Results:*** Relative to the matched control participant, the ACL-injured participant exhibited increased activation of motor-planning, sensory-processing, and visual-motor control areas. A similar activation pattern was present for the contralateral knee that sustained a subsequent injury.

***Conclusions:*** Bilateral neuroplasticity after ACL injury may contribute to the risk of second injury, or aspects of neurophysiology may be predisposing factors to primary injury.

***Clinical Implications:*** Sensory-visual-motor function and motor-learning adaptations may provide targets for rehabilitation.

***Key Words:*** neuroplasticity, functional magnetic resonance imaging, motor control

**Key Points**

- After anterior cruciate ligament reconstruction, rehabilitation, and return to play, neurologic differences in knee motor control may persist.
- Anterior cruciate ligament injury and recovery may induce specific changes in brain processing regarding sensory-visual-motor integration.

Individuals who experience a primary anterior cruciate ligament (ACL) injury and return to sport may have up to a 25% chance of experiencing a second ACL injury to either knee, despite surgical reconstruction and rehabilitation.[1,2] The contralateral knee may be at greater risk of injury than the involved knee,[2] suggesting possible postinjury bilateral neurologic alterations or the presence of bilateral factors that contributed to the initial injury.[3] Researchers have reported that these postinjury neurologic differences include disrupted central nervous system afferent function,[4,5] altered efferent output,[3,6] and changes in brain activity for motor control.[7,8]

Few investigators have prospectively studied the neurologic changes that occur in the brain after ACL injury, reconstruction, and rehabilitation and before subsequent injury. Therefore, the purpose of this paper was to describe the brain activation for knee motor control measured after initial ACL reconstruction (ACLR) and 3 weeks before a contralateral ACL injury. We hypothesized that the ACLR participant would have greater motor-planning and sensory-area activation than a healthy matched control participant. This postinjury neuroplasticity or predisposing neurologic function may help to explain the underlying mechanisms contributing to prolonged deficits in neuromuscular control after ACL injury.[9]

## METHODS

### Participants

A 25-year-old man (height = 1.83 m, mass = 73.4 kg, Tegner scale = 9) who had a bachelor's degree, was right-hand and right-leg dominant, and had been and was currently active in football sustained a left noncontact ACL injury during a semiprofessional football game while changing direction to avoid a tackler. Four months later, arthroscopic reconstruction was completed using an ipsilateral bone–patellar tendon–bone graft; no concurrent

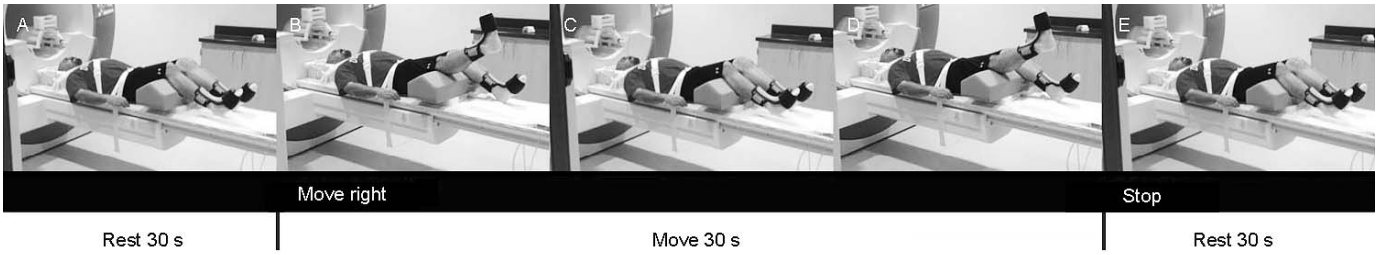


**Figure 1. A–E, Experimental setup. The stimulus was cued with an auditory metronome and a 2-second visual prompt.**

damage was reported. After return to sport and 10 months after surgery, this man completed a study to examine the brain alterations after ACLR with functional magnetic resonance imaging (fMRI). This participant was matched with a healthy control participant (age = 26 years, height = 1.80 m, mass = 83.9 kg, Tegner scale = 9, bachelor's degree education level, right-hand and right-leg dominant, currently active and with a history of activity in football). Both participants provided written informed consent, and the study was approved by the Institutional Review Board of The Ohio State University. Twenty-six days after completing the study, the injured participant experienced a contralateral ACL injury via similar noncontact mechanisms.

### Data Collection

In this context, fMRI data indirectly measured neural activation via blood-flow changes or blood oxygen level-dependent signal. These data are collected very rapidly, in this case taking 55 images or slices in the axial plane of the brain every 3 seconds. We collected the fMRI data (Appendix) while each participant performed 4 sets of 30-second unilateral knee extension-flexion movements triggered by an auditory metronome at 1.2 Hz (Figure 1). With a 3-second collection rate, 10 full-brain activation maps were generated during each 30-second session, resulting in 40 full-brain maps for movement and 50 full-brain maps for rest for each lower extremity.

### Data Analysis

We performed fMRI analyses using the software package FSL (The Oxford Centre for Functional MRI of the Brain, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom).[10] First, we standardized image preprocessing to remove noise and signal drift and to align and rectify the data for each participant (Appendix). Second, we used statistical parametric mapping to determine brain activation for each participant. All data are presented as a contrast; thus, the brain activation for knee movement is the brain activation remaining after subtracting the baseline, or rest, condition. This process involved fitting the hemodynamic, or blood-flow, response to the experimental design using a general linear model; given the onset time of movement versus rest, the model attempts to fit the activation data to this paradigm. Therefore, when the knee-movement activation map was created for each participant, the 2 maps were contrasted with each other to determine areas of higher or lower relative activation. The very high sensitivity and volume of data collected for just 1 participant allows the possibility of finding differences even for the same tasks if the participant has a distinguishing characteristic, which in this case was previous severe trauma to the moving joint. However, the analysis completed in this case cannot be generalized to reflect the entire population; the analysis method and low sample size prevent broad conclusions from being drawn and the findings apply to only this case.

The brain-area activation is reported as either contralateral, occurring on the opposite side of motion, or ipsilateral, occurring on the same side of motion; *ACL-POST-R* indicates the knee that underwent ACLR, and *ACL-PRE-I* indicates the knee that was healthy at testing but sustained an ACL injury shortly after testing. The results are presented as a Z score (activation level relative to baseline condition and the matched control activation) of the peak voxel of that activation cluster (region).

## RESULTS

The ACL-POST-R knee demonstrated greater activation of the contralateral lingual gyrus, cerebellum, and premotor area and the ipsilateral secondary somatosensory cortex and less activation of the ipsilateral cerebellum than the matched healthy control knee (Figure 2).

The ACL-PRE-I knee demonstrated greater activation of the ipsilateral cerebellum, ipsilateral lingual gyrus, and contralateral primary sensory cortex and less activation of the contralateral supplemental motor area and primary motor areas than the matched healthy control knee (Table).

## DISCUSSION

To our knowledge, we are the first to quantify brain activation for knee movement before an ACL injury. Primary ACL injury causes a cascade of altered neuromuscular control[3,5,6] that influences the bilateral risk of second injury.[1,2] These neurologic alterations may be prospective indicators of injury risk, or this severe unilateral injury may cause bilateral neuroplastic effects, as the differences in brain activation were not limited to the involved lower extremity.

### Cerebral Activation Differences for the ACL-POST-R Knee

Similar to a recent report[8] of the same movement task in a cohort of ACL-deficient individuals, the ACL-POST-R knee had increased activation of a visual-spatial area (lingual gyrus), premotor areas, and the secondary somato-

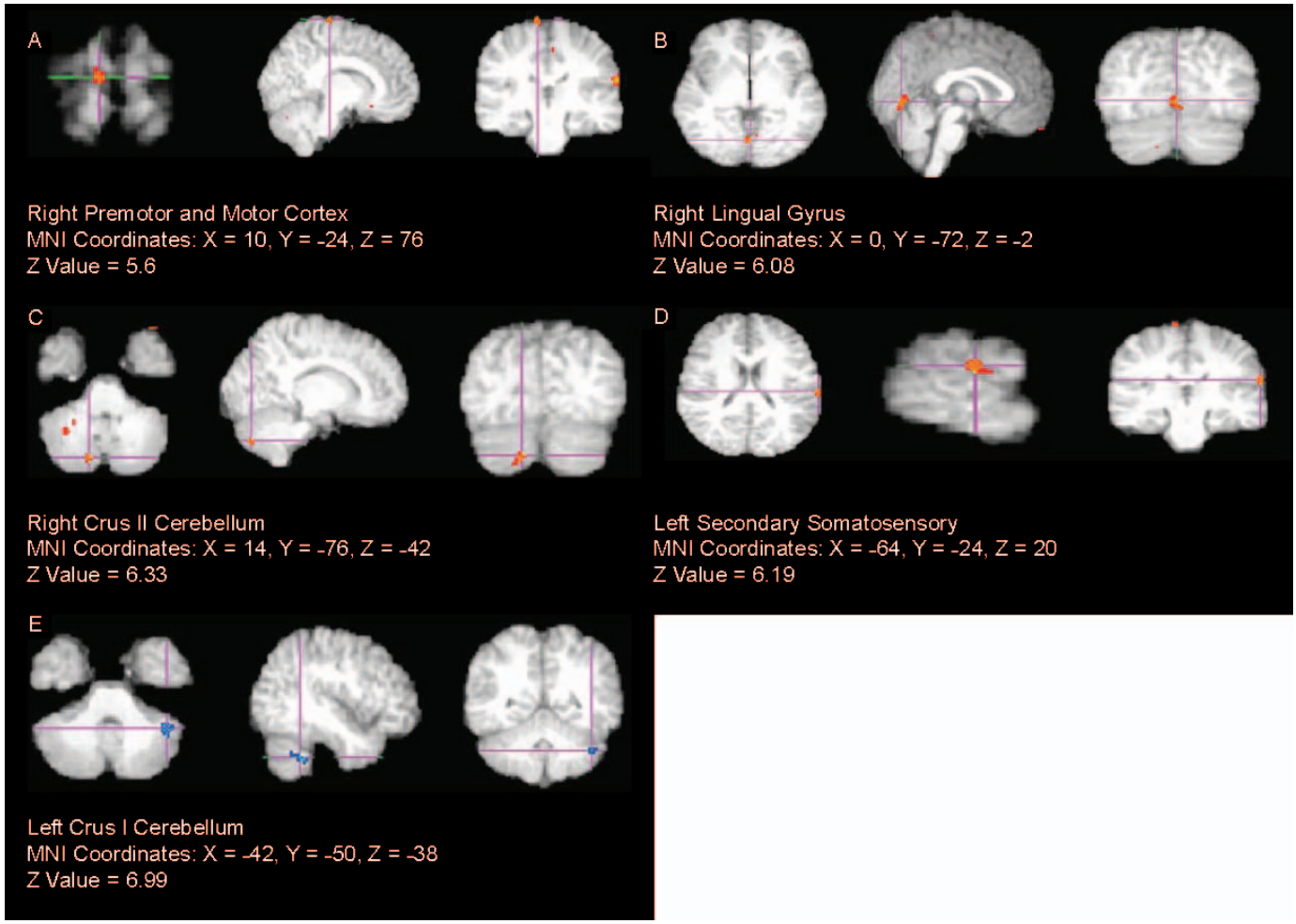


**Figure 2. Regions with greater activation in movement of the anterior cruciate ligament-reconstructed knee. A, Right premotor and motor cortex. B, Right lingual gyrus. C, Right crus II cerebellum. D, Left secondary somatosensory. E, Region with lower activation in movement for the anterior cruciate ligament-reconstructed knee: Left crus I cerebellum. All values reported are cluster corrected for multiple comparisons at $P < .01$. Abbreviation: MNI, Montreal Neurological Institute and Hospital. Color image available in online version.**

sensory cortex. The role of the lingual gyrus in motor control is unclear, but it may be related to visual processing and specifically to encoding images and memory related to motion.[11] Increased visual-motor–related activation may occur in response to the disrupted afferent input from the ACL injury and ACLR process, inducing cortical reorganization to maintain motor function by reweighting sensory versus visual input.[5,7]

In addition to the lingual gyrus, the premotor area had greater activation, which may be due to the increased need to engage higher-level cortical processing to plan movement.[12] The secondary somatosensory area was also more activated during the ACL-POST-R knee motion, similar to what Kapreli et al[8] reported in ACL-deficient individuals. This area is responsible for sensory processing, including advanced afferent integration and pain.[13] The ACLR

**Table. Regions With Higher or Lower Activation in ACL-PRE-I Movement[a]**

| Area | Montreal Neurological Institute and Hospital Coordinates | | | Peak Z Value |
|---|---|---|---|---|
| | X | Y | Z | |
| Higher activation in anterior cruciate ligament than control for right (ACL-PRE-I) knee | | | | |
| Left primary sensory cortex | −12 | −36 | 72 | 4.89 |
| Right VIIb cerebellum | 34 | −54 | −46 | 5.13 |
| Right lingual gyrus | 20 | −66 | −4 | 4.50 |
| Higher activation in control than anterior cruciate ligament for right (ACL-PRE-I) knee | | | | |
| Left primary motor cortex | −4 | −16 | 72 | 7.72 |
| Left supplementary motor | −4 | 0 | 54 | 6.30 |

Abbreviation: ACL-PRE-I, knee that was healthy at the time of testing but sustained an anterior cruciate ligament injury shortly after testing.

[a] All values reported are cluster corrected for multiple comparisons at $P < .01$.

participant did not report pain during or after scanning, which may provide further evidence of longer-term functional sensory cortical reorganization.

### Cerebral Activation Differences for the ACL-PRE-I Knee

The ACL-PRE-I knee had greater lingual gyrus activation than the healthy control knee. This observation was similar to the ACL-POST-R result, which may indicate a bilateral motor-control strategy that incorporates visualization to assist in movement. The ACL-PRE-I knee also demonstrated increased sensory cortex activation but decreased motor cortex and supplementary motor activation, which differed from the ACL-POST-R knee. This decreased activation of the motor-action and planning areas during ACL-PRE-I knee motion may have been due to the extensive unilateral therapy targeting the injured knee. The contralateral side of the brain controls the ipsilateral lower extremity, but injury, reconstruction, or rehabilitation may have caused functional reorganization of motor areas to assist in moving the ipsilateral injured side and decreased activation when moving the contralateral side.[14] Alternately, compensations after injury to increase reliance on the ACL-PRE-I knee may have made cortical motor control more efficient, thereby reducing the activation required.[15]

### Cerebellum

Both ACL-POST-R and ACL-PRE-I knee movement had increased right (ACL-PRE-I side) cerebellar activation specifically in the crus region, which contains the corticospinal and corticobulbar tracts that convey motor information to and from the brain and body to maintain balance and coordination.[16] The ipsilateral side typically is active during extremity movement,[16] and this was true for our ACLR participant. However, relative to the control participant, the ACLR participant engaged in greater right cerebellar activation, regardless of which knee was moving, and decreased ipsilateral activation during ACL-POST-R movement. This altered cerebellum activation, combined with the increased primary motor cortex activation, may indicate a relative shift from a subcortical to a cortical motor-control strategy.

Taken together, these altered brain-activation patterns may indicate a functional cortical and subcortical reorganization to produce knee extension-flexion in the ACL-injured individual. Another possibility is that this brain-activation pattern was prospective and contributed to injury risk, as some of the key differences were also present during movement of the ACL-PRE-I knee, specifically in the lingual gyrus and cerebellum.

### Limitations

The 4-month gap between injury and reconstruction may have induced neuromuscular compensations that are unique to this participant. However, researchers studying altered neuromuscular control typically have reported neuromuscular changes after longer periods of ACL deficiency,[17] and the ACLR participant did not attempt a "coper" strategy (ie, return to participation without reconstruction). Concussion history is a concern, especially in American football athletes. We screened for concussion with self-report questionnaires, and neither participant gave a history of concussion. However, limitations in concussion self-reporting are well known,[14] and it is possible that the nature of their sport history resulted in some of the neurologic differences in movement. We attempted to control for this possibility by matching participants by sport. In addition, due to the case-study design, these data possibly reflect individual differences and may not represent the ACLR population. We accounted for this possibility to some degree by using conservative statistical corrections (Appendix) and matching participants on many factors that generate intersubject variability. Lastly, we can only speculate as to whether these neural control differences were present before the initial injury; were induced by the injury-recovery process; or perhaps most likely, involved some combination of the two.

### Clinical Implications

Whereas limited to 1 participant, these novel findings present unique insights into rehabilitation strategies that may address neuroplasticity after injury. Our results specifically identified the brain regions responsible for motor preparation, and integration of sensory-visual-motor function may be the key neuroplastic target for postinjury therapy. Future investigation into the neuroplastic effects of musculoskeletal trauma or the prospective nature of neurophysiology on injury risk may allow additional sensorimotor factors to be targeted in interventions to optimize neuromuscular control and decrease primary or secondary injury risk.

The increased cortical activation for movement of the ACL-POST-R knee was consistent with an increase in internal focus of control, likely due to the increased conscious awareness of the injured joint and subsequent internal focus of training.[18] Such an internal focus of attention may be beneficial during early rehabilitation, when explicit focus is needed to restore muscle function. Nevertheless, later in rehabilitation, moving away from internally focused feedback may improve transfer to the athletic field when conscious attention is being paid to the environment and not to knee position. Advancing rehabilitative feedback to an external focus may facilitate this transfer of motor control to subcortical regions and free cortical resources for programming more complex motor actions.[19]

The increased lingual gyrus, secondary somatosensory area, and premotor activation seemed to indicate adapted sensory-motor processing, possibly with increased dependence on visual feedback to engage in knee movement. Observations from biomechanical studies also support the possibility that visual feedback is a key compensatory mechanism after ACL injury, as blindfolded conditions had a greater effect on balance and movement performance in ACL-injured individuals than in healthy control individuals.[20] Neuromuscular training that incorporates visual or neurocognitive processing, such as ball tracking or engaging other players, task complexity (reaction and decision making), anticipatory aspects, and cognitive load (dual task), can address the possible sensory reweighting of visual feedback for motor control.[21–23]

## CONCLUSIONS

We presented the brain-activation pattern for knee motor control before a second ACL injury. Future research is needed to quantify musculoskeletal-injury–induced neuroplasticity, using more advanced motor-control tasks, such as force or position matching or multijoint movements, to improve the clinical applicability of these results. The integration of transcranial magnetic stimulation 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 play a role in the ACL injury-risk profile.


## ACKNOWLEDGMENTS

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## Appendix. Data Collection and Analysis for Functional Magnetic Resonance Imaging

### Data Collection

The functional magnetic resonance imaging (fMRI) data were collected on a 3.0-T magnetic resonance imaging scanner (MAGNETOM Trio; Siemens Medical Solutions USA, Inc, Malvern, PA) using a 12-channel–array receive-only head coil. The session included 9 functional time series, consisting of 90 whole-brain gradient-echo echoplaner scans acquired every 3.0 seconds with anterior-posterior phase-encoding direction, 2.5-mm slice thickness, and 55 transversal slices. This equated to 10 full-brain datasets per knee movement, so 40 full-brain activation maps for knee movement (4 sessions) contrasted with 50 full-brain maps for rest (5 sessions). After the functional runs, an anatomical 3-dimensional high-resolution T1-weighted image with a 2000-millisecond repetition time, 4.58-millisecond echo time, 256-mm matrix field of view, 1-mm slice thickness, and 176 slices was completed for registering the activation data, brain region identification, and normalization to compare the participant with anterior cruciate ligament (ACL) injury and the matched control participant.

The ACL-injured participant was positioned supine in the scanner with the lower extremities on a custom cushion that limited knee flexion to 45°. Movement artifact was limited with padding and straps to 0.35-mm absolute and 0.13-mm relative displacement during the entire run. An ankle-toe splint was used to restrict ankle or toe movement, and the participant was monitored for accessory motions. A mock scanner session was completed before the actual scanning session to ensure the participant was familiar with the movement.

### Data Analysis

The fMRI technique measures the hemodynamic blood oxygen level-dependent response in each voxel (cubic millimeter) under the indirect assumption that blood flow increases with neural activity.[24,25] The response during a stimulus is contrasted with a rest condition to determine regions active during the task using a general linear model. Magnetic resonance imaging can detect this change in blood flow due to the precise magnetic field alignment of protons at a predefined Larmor frequency and the subsequent flip angle of the field that disrupts phase coherence. This magnetic field causes the release of a small amount of energy that varies by tissue; given that the transport of oxygen requires hemoglobin and is less magnetic, blood flow in more vascularized tissue creates a different signal than in less vascularized tissue.[26] This key difference in the magnetic properties of the tissue and relative blood flow allows image analyses to be performed to determine the relative blood oxygen level-dependent response during a task. This began with standard prestatistical processing applied to individual data, including nonbrain removal (or skull stripping), spatial smoothing using a full-width Gaussian kernel at 8 mm, standard motion correction, and realignment metrics (3 rotations and 3 translations) as covariates to limit the confounding effects of head movement.[27] We carried out high-pass temporal filtering at 120 Hz and time-series statistical analyses using a linear model with local autocorrelation correction.[28] Functional images were coregistered with the respective high-resolution T1 image and standard Montreal Neurological Institute and Hospital 152 template (a database of 152 healthy normal individual brains that were averaged together to create 1 standard brain template) 2-mm space using linear image registration.[27,29] This registration process allowed the data from the 2 participants to be spatially aligned on a standardized brain template for comparison. First-level analysis of functional knee movement relative to rest was carried out with $Z > 3.5$ and a corrected cluster threshold of $P = .001$. The cluster correction uses a variant of Gaussian random field theory to decrease type I error in statistical parametric mapping of imaging data by not only evaluating the activation at each voxel but also at the surrounding voxel cluster, as it is further unlikely that the tested voxel and surrounding voxels are active above threshold due to chance.[26,30] The contrast between the ACL-reconstructed participant and matched control participant then was conducted with fixed-effects analysis and group Z-statistic images set at a $Z > 3.5$ threshold and a corrected cluster level of $P = .01$. This high threshold and lower $P$ value were selected to mitigate the high intersubject variability of reporting neuroimaging data of a single case and to decrease the probability of type I error.[26]

### Suggested Resources

Several free resources that provide greater detail on the science and methods behind neuroimaging are available from the National Institutes of Health, several of the fMRI analysis software development teams, and fellow scientists. We suggest the following:

(1) http://culhamlab.ssc.uwo.ca/fmri4newbies/. Jody Culham, PhD, at the Brain and Mind Institute at the University of Western Ontario maintains this Web site.
(2) http://www.brainmapping.org/NITP/. The National Institutes of Health sponsors an fMRI training program at the University of California, Los Angeles; the presentation videos and slides are freely available.
(3) http://fsl.fmrib.ox.ac.uk/fslcourse/. The FSL software for the fMRI analysis training course, presentation materials, and slides are freely available.

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