

Retinal and Balance Changes Based on Concussion History: A Study of Division 1 Football Players

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Abstract

Background: The long term effects of a sports concussion or mild traumatic brain injury (mTBI) is poorly understood. The term chronic traumatic encephalopathy (CTE) is associated with protein deposition observed post mortem; thus the diagnosis of CTE in living subjects is impracticable using protein deposition as a diagnostic criterion. To date, there is no validated, objective method to observe and document pathologic changes post mTBI. The brain, optic-nerve, retina axes is closely linked; it is believed that some aspects of mTBI may be reflected in the retinal nerve fiber layer (RNFL) and that optical coherence tomography (OCT) could be a means to observe and document these changes. In this paper we show an association between a history of concussion and RNFL changes in college athletes.

Methods: Each member of the University of Cincinnati football team was surveyed for a history of diagnosed concussion during pre-season camp. All players participating in camp were consented and were subjected to both a retinal exam using the Optovue iVue OCT retinal imaging system and a balance challenge by performing a visual motor task (Dynavision D2) on a BOSU Pro Balance Trainer (BOSU ball) and on a firm surface. Eye-hand coordination, balance and RNFL thickness measurements for the athletes with a history of concussion were compared to those the athletes with no history of concussion.

Results: A total of 34 athletes reported having at least one previously diagnosed concussion that occurred up to 10 years prior to data collection; 73 reported no history of diagnosed concussion. Data analysis of the OCT retinal images demonstrated significant thickening of the RNFL in those athletes with a remote history of concussion when compared to athletes with no history of concussion, 106.8 μm vs 103.7 μm ($p = 0.009$), respectively. With the BOSU ball challenge there was no change in performance with or without a balance challenge 4.57 vs 4.63 hits per minute ($p=0.93$) for those with history of concussion versus no history. The performance task on the Dynavision D2 is an eye hand coordination task and a balance task, so eye hand coordination was not impacted by the RNFL changes.

Discussion: In this paper we report significant sustained chronic RNFL thickness changes occurring in athletes with a remote history of concussion when compared to similar athletes without a reported history of concussion. However, there were no statistically significant sustained changes in eye hand coordination or balance challenge performance tasks. We suggest that RNFL changes may be an indicator of a structural brain injury following a post-concussive event and may be caused by subclinical increases in intracranial pressure or other neurovisual-related pathologies.

Keywords: Concussion; Mild traumatic brain injury; mTBI; Football; Balance; Vision; Eye; Retina; Optical coherence tomography; Vestibular

Abbreviations:

BESS: Balance Error Scoring System; BOSU ball: BOSU Pro Balance Trainer; CSF: cerebral spinal fluid; CTE: Chronic Traumatic Encephalopathy; GCC: Ganglion Cell complex; ICP: Intracranial

pressure; IRB: institutional review board; mTBI: Mild Traumatic Brain Injury; OCT: Optical Coherence Tomography; NATA: National Athletic Trainers Association; RNFL: Retinal Nerve Fiber Layer; SOT: Sensory Organization Test

Introduction

Sports-related concussion, a form of mild traumatic brain injury (mTBI) has been estimated to affect 300,000 young American adults

annually [1]. Despite this significant prevalence, and that sports medical professionals have dealt with concussion or mTBI for years, there are few standardized methodologies for diagnosing or managing those athletes. Often, evaluation methods require the athlete to self-report symptoms, as many of the signs of a concussion are highly variable from patient to patient [2]. Findings using imaging methods such as x-ray, CT and MRI are not well-understood for concussion injuries despite intensive research effort [3,4]. Neuro psychological testing, while popular, has been of uncertain utility when making return to play decisions [5,6].

As 85% of concussion symptoms appear to resolve in less than three weeks [7] many athletes are cleared for return to activity quickly, but documenting their status has remained problematic. To address this problem, many organized sports have adopted baseline testing, with the goal being that the athlete should return to baseline should a concussion occur. However, athletes are aware of this strategy and there are concerns regarding players manipulating the tests. This concern of reliable baselines and objective return to play parameters exemplifies the need for improved testing methods that are objective.

Of recent intensive research effort and national media scrutiny [8-10] are the long-term sequelae that may be associated with concussions. The term chronic traumatic encephalopathy (CTE) was coined to address the chronic pathology reported in athletes or patients who have experienced multiple concussions [11,12]. Currently, CTE can only be conclusively diagnosed on post-mortem by the presence of protein tangles, which have been associated with pathology in athletes who were exposed to multiple concussive events in life. To date there is no reliable and objective method that demonstrates neurologic changes in live subjects who have a history of a concussion.

Spectral domain optical coherence tomography (SD-OCT) was first developed at the Massachusetts Institute of Technology and published in 1991 [13-25]. OCT emits near-infrared light through the pupil into the back of the eye to create a three dimensional image of the retina with micrometer resolution that visualizes each individual cell layer. The ophthalmology community and eye care professional have utilized this imaging modality quite extensively to describe a number of pathologic ocular conditions such as macular degeneration and diabetic macular edema, however, it has not been used previously for the evaluation of traumatic brain injury patients [26,27].

In this study we have identified a group of Division 1 college football players and dichotomized them into "history of diagnosed concussion" versus "no history of concussion". These athletes were subjected to two different examinations; optical coherence tomography (OCT) and a balance challenge. We sought to compare observable retinal nerve clinicopathology and hand-eye coordination in athletes reporting a history of concussion, to those reporting no history.

Methods

Student athlete recruitment

Subjects for the study were recruited from a pool of Division I college football players. Inclusion criteria: (i) healthy college-aged males, ranging in age from 18 to 23 years; (ii) official membership on the pre-season football camp roster; (iii) attendance at the pre-season football training camp. Athletes were excluded if they had a present injury or illness that prevented safe participation in data collection.

Athletes with a history of orthopedic injury were not excluded. The criteria for a subject to safely participate in the study were agreed upon by the team physician and the head athletic trainer and subjects were cleared for participation through this process. The protocol and informed consent for this project were reviewed and approved by the Institutional Review Board (IRB) of the University of Cincinnati prior to commencement of study enrollment.

Concussion history

Each athlete was administered a survey questionnaire. The survey tool is found in Figure 1. Subjects who reported having a prior concussion diagnosed by a health care professional were counted in the concussion group.

Name: _____
Date of exam: ____/____/____

Concussion History Survey

1. Have you had a concussion in the past? Yes No
If no, skip to question # 7
If yes, have you had more than one? Yes No

2. Who diagnosed your concussion(S)? _____

3. How old were you when you had your first concussion? _____
If more than one, When was your last concussion? _____

4. Have you ever been admitted to the hospital for a concussion? Yes No

5. How many days of play have you missed due to a concussion? _____

6. Have you ever had any trauma to one or both of your eyes? Yes No
If yes - please detail in space below

Figure 1: The survey tool used to determine a history of concussion. Of note is that the survey is focusing on diagnosed concussions as determined by a health care provider of the athlete's. The eye health question is standard for performing the iVue exam.

iVue

The athletes were administered an OCT exam, using Optovue's iVue (Fremont CA, USA). The exam took less than 10 minutes, and required no sedation or dilation of the eyes. We performed four exams on each eye per manufacturer's instructions. These were to collect the cell layer thicknesses (in microns) of the retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC).

Dynavision

Reaction time and performance data were collected from the participant's use of the Dynavision™ D2 Visuomotor Training Device (D2) (Dynavision International, LLC, West Chester, OH). Two D2 protocols were utilized for testing, the A-star (A*) test and the Reaction Test. The D2 computer program collects and stores reaction time and total score data with each run on the system. With each test, the participant presses buttons on the light board as they become illuminated. The A* is one minute long test in which buttons at any location on the light board are illuminated in a random pattern. The program measures the total number of illuminated button hits as well

as reaction time from illumination of a button to depression of that button. The Reaction Test assessed the subjects' reaction time of the right hand and left hand separately. The data captured in this test includes reaction time from release of the originally depressed button to the depression of the newly illuminated button. A recently published study found the D2 system to be a reliable assessment of reaction in active young adults [13].

Depending on the participant's participation year and arrival time at the University, subjects could have had several years of data. However, all of the testing presented on the D2 system was completed during the 2013 pre-season football camp. During these testing sessions, the participants performed the same D2 tests described above with the addition of a challenge of their balance. A BOSU Pro Balance Trainer ("BOSU ball") (BOSU, Ashland, OH) was utilized to achieve an unstable surface. With the semi-spherical surface to the ground, the participants stood on the flat surface of the BOSU ball within arm's reach of the D2 system. The height of the light board was adjusted to mimic the environment used for baseline testing. After demonstrating proficiency on a firm surface, participants completed one trial of each, A* and Reaction Tests while standing on the BOSU ball.

Four separate D2 systems were utilized in data collection for the current study with data stored on each system's laptop computer.

A* Test: Data from the D2 system was gathered for both the stable ground testing and the unstable surface, BOSU ball, testing for the 96 male athletes who completed the study. Data for A* are reported as hits per minute. Those with a concussion history were compared to those without a history of concussion. Then, the athletes with concussion history were again compared to those without a history of concussion using the data from the D2 system while the participant was standing on the BOSU ball.

Reaction test: The D2 Reaction Test is able determine overall visuomotor reaction time by recording visual (time from illumination of a new button to release of the already depressed button) and motor (time from release of the depressed button to depression of the newly illuminated button) reaction time. Comparisons were made between the non-concussion group and those with a history of concussion.

Statistical Analysis

Data were analyzed using SAS[®], version 9.3 (SAS Institute, Cary, NC). Data were examined for deviation from normality and for outlying values. Unpaired t-tests were used to compare the group with history of concussion to those without history, for the D2 systems variables; hits per minute and reaction time for the closest, best, BOSU ball and difference between closest and BOSU ball. The iVue data were analyzed using a generalized linear model due to the repeated measures design, to include information from both eyes. The dependent variables of interest were RNFL and GCC. Due to the method of analysis, means and associated standard errors are reported. P-values of <0.05 were considered statistically significant.

Results

A total of 107 pre-season athletes were consented and found to be eligible to participate in the research study. Based on the concussion survey we identified 34 players with a documented history of concussion and 73 without a history of concussion.

Balance challenge

In 96 athletes, we analyzed Dynavision D2 (with and without the BOSU ball) data, for both the concussion and non-concussion group in the following ways: absolute performance on the D2 on stable surface, absolute performance on the D2 on a BOSU ball and the change in performance from the stable surface to on BOSU ball. Tables 1 and 2 summarize the results for these comparisons. The group with history of concussion scored slightly higher in each condition; however, none of the differences were statistically significant (Table 1).

Condition	Closest A*	Fastest A*	BOSU A*	Delta**
No Concussion (n=68)	87.22 (1.14)	92.26 (1.11)	82.59 (1.11)	4.63 (0.97)
Concussion (n=28)	91.00 (1.94)	97.07 (2.65)	86.43 (1.75)	4.57 (1.68)
p-value (t-test)	0.12	0.20	0.16	0.93
Data presented as mean (standard error)				
** Delta is the change in performance as measured by closest A* on a hard surface minus BOSU Run in hits per minute.				

Table 1: A* Hits per minute with and without balance challenge.

In addition the difference between the two groups in the non-balance and balance state was not statistically significantly different; 4.57 (SEM 1.68) versus 4.63 (SEM 0.97), p=0.93, for the history of concussion groups and no history group respectively. Reaction times are reported in Table 2 with similar results to the hits per minute. No significant differences are seen in absolute performance or change in performance with the balance challenge. The difference in reaction times between BOSU ball and hard surface are -0.032 s (SEM 0.013) and -0.026 s (SEM 0.008), p=0.79, for the history of concussion groups and no concussion history group respectively.

OCT and iVue data

Three dimensional retinal images were obtained for 107 athletes attending at least one session of the University of Cincinnati football team pre-season camp in the month of August 2013 using the iVue OCT retinal imaging system. From the questionnaire, we identified 34 (32%) players with a history of at least one concussion ranging in time from 6 months to 10 years prior to the date of retinal imaging.

Condition	RTT Closest	RTT Fastest	RTT BOSU	Delta *
No Concussion (n=66)	0.346 (0.005)	0.333 (0.004)	0.372 (0.007)	-0.026 (0.008)
Concussion (n=27)	0.347 (0.007)	0.334 (0.007)	0.380 (0.016)	-0.034 (0.013)
p-value (t-test)	0.88	0.88	0.72	0.79
Data presented as mean (standard error)				
* Delta is the change in performance as measured by closest reaction test run on a hard surface minus BOSU Run in seconds.				

Table 2: Reaction test time (RTT) on hard surface and with balance challenge.

An analysis was performed comparing the thicknesses of the RNFL and the GCC for those football players with a history of concussion (n=34) (at least 6 months prior to imaging) versus those with no history of concussion (n=73). Both the RNFL and GCC bell curves showed a shift toward the right, which indicates thickening, in the group of football players with a history of concussion (Figure 2).

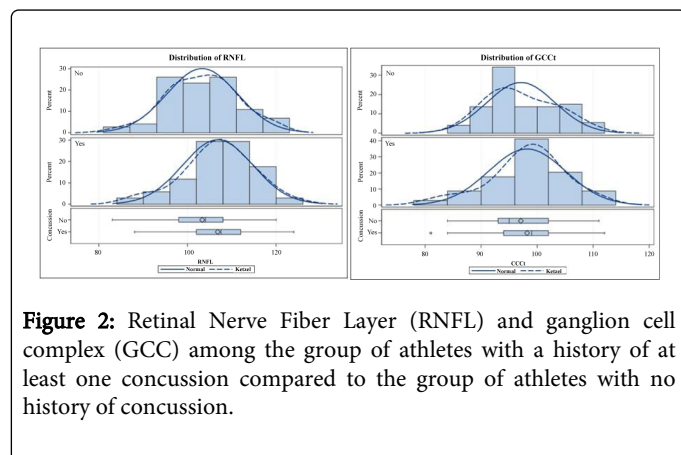


Figure 2: Retinal Nerve Fiber Layer (RNFL) and ganglion cell complex (GCC) among the group of athletes with a history of at least one concussion compared to the group of athletes with no history of concussion.

When comparing the actual average values among the two groups, the group with a history of concussion had a statistically significant thickening of the RNFL (106.8 μm SEM=0.96 vs 103.7 μm SEM=0.65 $P<0.01$, respectively) and a thickening of the GCC that was not statistically significant but showed a trend towards thickening (98.1 μm SEM=0.78 vs 96.7 μm SEM=0.54 $P=0.15$) (Table 2). Therefore, this data would suggest that there may be chronic effects of concussion (at least 6 months from time of injury) that can be seen as sustained changes in the RNFL when imaged with the iVue OCT retinal imaging system.

Pre-season OCT images and a concussion history questionnaire were obtained for all members of the University of Cincinnati football team. There were 34 athletes with a history of at least one concussion with a time from last concussion to the date of acquiring the OCT images of at least six months. The average number of concussions per athlete among this cohort of 34 individuals was 1.5 (range 1 to 5). These data were compared to the 73 athletes who reported no history of concussion. Statistical comparison of the averages of the RNFL and GCC between the group of athletes with a history of at least one concussion and the group with no history of concussion revealed a highly statistically significant thickening of the RNFL ($p<0.01$) in those athletes with a history of concussion. There also was a slight thickening of the GCC in those athletes with a history of concussion but this did not reach statistical significance ($p=0.15$). (Figure 2 and Table 2) Explanations for the apparent thickening of the RNFL among those athletes with a remote (greater than 6 months) history of concussion can be hypothesized. Previous descriptions of RNFL thickening in physiologic states of elevated ICP have described a possible extravasation of axoplasmic fluid from the axons within the RNFL due to the pressure gradient established in the optic nerve sheath near the optic disk [28]. The description of transient RNFL thickening in the acutely symptomatic concussion patient described earlier may be secondary to elevations of ICP and a similar extravasation of axoplasmic fluid could occur. This extravasated material may induce a gliotic scarring immune response that may lead to thickening of the RNFL after a history of one or more concussions. Therefore, thickening of the RNFL may be a useful measure to

objectively assess an individual's accumulative degree of concussive injuries over time.

Power calculation

The unequal group sizes of 34 (history of concussion) and 73 (no history of Concussion), give 80% power for a 2-sided test to detect an effect size of 0.59 or greater. Where the effect size is defined as the expected difference between the means divided by the standard deviation. This is between a medium, 0.5, and large, 0.8 effect size. Similarly, using the sample sizes of 28 and 68 respectively available for the Dynavision D2 analyses detection of an effect size of 0.64 or more is possible.

We identified 34 players with a documented history of concussion and 73 without a history of concussion. For the Dynavision D2 analysis there were a total of 96 athletes; 28 and 68, in the history of concussion and no history groups respectively. In the 96 athletes, we analyzed Dynavision D2 (with and without the BOSU ball) data, for both the concussion (n=28) and non-concussion (n=68) group in the following ways: absolute performance on the D2 on stable surface, absolute performance on the D2 on a BOSU ball and the change in performance from the stable surface to on BOSU ball (Figure 3).

Discussion

In this study we report that Division 1 college football players who have been cleared to play have good balance and performance characteristics that are not different when the players with a history of a diagnosed concussion are compared to those with no history of concussion. This is consistent with the typical parameters used to clear an athlete for play; unsurprisingly, athletes are very good at performing physically demanding tasks.

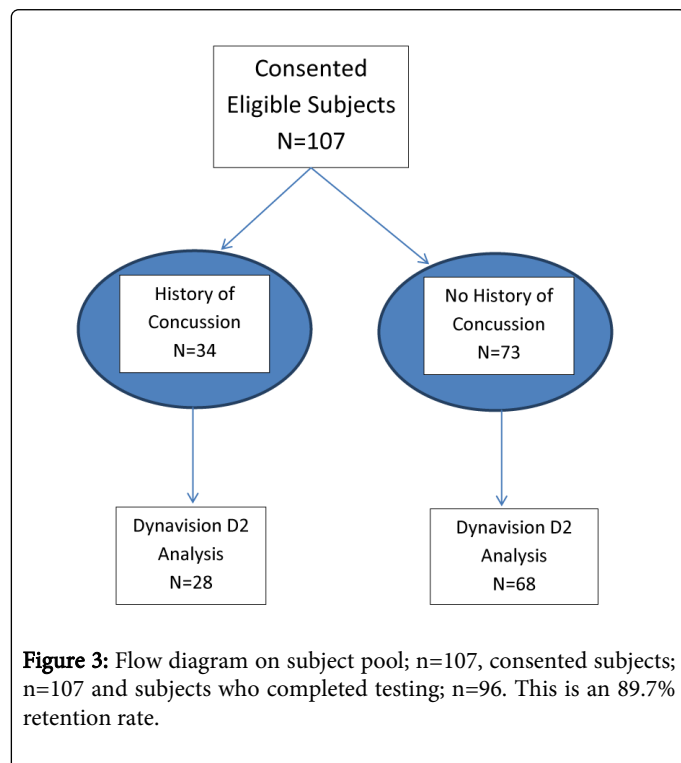
According to the National Athletic Trainers Association (NATA) and the National Collegiate Athletic Association, current best practice for concussion management includes an evaluation of symptoms, neuropsychological testing and a balance assessment [14,15]. The NATA recommends the use of the Balance Error Scoring System (BESS) [15]. The BESS, because of its simplicity, has stood out as the most clinically applicable assessment of balance related to concussive injuries. The BESS was developed to be an inexpensive and portable assessment to provide objective measures of an individual's postural stability [16].

During BESS testing the tester records the number of errors during leg balance, tandem balance and narrow stance postures. Recent American Academy of Neurology guidelines support the BESS test as a valid tool for assessment of balance following concussion, citing 91% specificity (34-64% sensitivity) [17]. The BESS test should be used post-concussion for the assessment of postural stability and motor control when baseline scores of the BESS are available for that individual.

Other, more sophisticated systems have been used to objectively balance as well. However, since these other systems are much more expensive, they are less available and also more difficult to use. The most widely used of these tools is the Sensory Organization Test (SOT), generally performed on the NeuroCom Smart Balance Master. This test uses a sophisticated computer system and motorized platform which records alterations in the participants' postural sway. The SOT is a reliable tool [18] and it has been found to be sensitive in measuring post-concussive balance deficits [19]. Although these

measures may provide more sensitive results, the testing may be cost prohibitive or inaccessible.

Rehabilitation of balance and return of normal function following concussion follows a step-wise process and the duration of rehabilitation is dependent upon severity of symptoms and patient response to the rehabilitative process. Generally, a period of relative rest is recommended following an acute concussive episode. This rest period is variable in length; it is generally accepted that the patient should continue relative rest until they are no longer experiencing concussion symptoms while at rest [20].



Sound postural control is reliant upon the proper functioning and integration of the visual, vestibular and somatosensory systems. One must consider each of these systems as well as other factors (extremity injury, sensation) when rehabilitating balance deficits following a concussion [21]. Balance and gait exercises should begin in a quite environment with eyes open. Balance exercises might include single or tandem balance on flat ground progressing to foam or a rocker board. Exercises can also be progressed to be performed with eyes closed or with head movements. Eventually, exercises should be progressed to include balance activities with upper or lower extremity movements and sport specific drills (i.e. soccer player performing single leg balance on foam while volleying a soccer ball).

In contrast to the consistency in balance and performance characteristics between players with or without a history of a diagnosed concussion, we saw differences in OCT results between the two groups. The cells of the retina have direct communication to the brain via axons traveling through the optic nerve. For a long time, practitioners have recognized that changes in brain pressure are transmitted to the optic nerve through a continuous column of cerebral spinal fluid (CSF) located in the optic nerve sheath [22]. These changes can be visualized in the back of the eye as swelling of the optic nerve head (papilledema). Traumatic brain injury causes diffuse injury

to the brain and in severe cases causes severe elevations of intracranial pressure (ICP). Concussion falls under the classification of mild traumatic brain injury and has clinically also been associated with subjective complaints of visual changes, such as photophobia, blurred vision and double vision, that have been found to occur in 50 to 80 percent of patients following the concussive injury [23,24]. Current medical understanding is unable to anatomically explain the pathophysiologic mechanism of these vision changes and multiple imaging modalities have failed to accurately describe changes that occur in the visual pathway among concussion patients.

Previous literature has reported utilization of OCT to define cellular changes occurring in patients with elevated intracranial pressure, as within the population of patients with idiopathic intracranial hypertension, also known as pseudotumor cerebri [27-29]. They have described thickening of the RNFL that occurs in physiologic states of elevated ICP and hypothesize that this is a result of a pressure gradient that is established between the elevated pressure of the CSF found in the optic nerve sheath that stops at the level of the lamina cribrosa and the normal intra-ocular pressure of the eye. This pressure gradient causes swelling of the axons located in the RNFL, therefore, resulting in the apparent thickening of this layer on OCT imaging [28].

Previous data collected among concussion patients at the University of Cincinnati has described a similar OCT imaging change of the RNFL in an acutely symptomatic concussion patient as that described previously in patients with idiopathic intracranial hypertension. We had one patient with an acute concussion who had baseline OCT and acute OCT, data not shown. In this one patient there was thickening seen of the RNFL. This thickening was present at 5 days post injury and resolved 5 months post injury. Future studies on acute subjects' RNFL changes acutely are warranted.

The finding that the population of players with a history of diagnosed concussion had OCT changes is novel and unexpected. It appears to suggest a long term pathologic difference in the concussion group that is distinct from the non-concussion group. While a cause and effect relationship is impossible to establish at this time there are pathophysiologic reasons as to why the RNFL may be thickening in the concussion group.

In the brain the ICP is conducted along the optic nerve up to the optic disc. Historically substantial increases in ICP have been found to cause papilledema; a blistering around the optic nerve head. It is possible that patients who have had a concussion that resulted in subclinical increases in ICP there might have been sufficient pressure at the optic disc and RNFL to produce scarification. Scarring in the absence of injury is common in medicine; "stretch marks" look like scars but result from tension on the skin. Something similar may be happening in the retinas of the concussion patient.

The utility of OCT to monitor and or manage concussion patients could be substantial. Having baseline OCT measures on athletes could be used to document the health and or history of athletes. Post injury the OCT measures could be used to confirm or manage return to play decisions. Should changes persist, players could have participation restricted with increased monitoring, or may be categorized as at-risk. At-risk individuals might be given more scrutiny should they return to play, or experience an impact likely to cause concussion.

Interpretation with caution is needed. In sports science and conditioning there are numerous exercises that may transiently increase ICP. For example many strength exercises cause large rises in ICP and intrathoracic pressure. It remains to be determined if high-

weight weight-training could lead to similar thickening of the RNFL. Following athletes over the course of an extended competitive sports career and monitoring for other causes of RNFL changes is called for.

Conclusion

We conclude that OCT is a novel and valuable tool to assess concussion history in athletes. It may reflect chronic changes associated with concussions. The observation that apparent chronic changes remained as observed with OCT was not associated with deficiencies in the BOSU ball challenge is consistent with traditional methods for making return to play decisions, symptoms have resolved. However, the OCT may be more sensitive to the subclinical changes that remain post-concussion. More work correlating chronic changes post-concussion are needed to determine a cause and effect relationship.

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