

Time Course of Clinical and Electrophysiological Recovery After Sport-Related Concussion

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Background and Purpose: Recent neuroimaging studies suggest that abnormalities in brain function after concussion exist beyond the point of observed clinical recovery. This study investigated the relationship between an index of brain dysfunction (traumatic brain injury [TBI] Index), concussion severity, and outcome. **Methods:** EEG was collected from forehead locations in 65 male athletes with concussion within 24 hours of concussion, with follow-up at 8 and 45 days postinjury. Neurocognitive and symptom assessments were also performed and used to classify subjects in mild or moderate concussion categories. Time to return to play was recorded. **Results:** The TBI Index was higher in the moderate than mild concussion group at injury, day 8, and day 45. The moderate group had increased symptoms and decreased cognitive performance only at the time of injury. At the time of injury, only the TBI Index was significantly associated with the length of time to return to play. **Conclusions:** Recovery of brain function after sport-related concussion may extend well beyond the time course of clinical recovery and be related to clinical severity. An index of brain dysfunction may be an objective indicator of injury, recovery, and readiness to return to play. The relatively small sample indicates the need for further study on the time course of physiological recovery. **Key words:** electroencephalography, mTBI, neuroimaging, sports concussion, TBI Index

AN estimated 1.6 million to 2.3 million individuals are affected by mild traumatic brain injury (mTBI), or concussion, each year in the United States.¹ Research findings indicate that the vast majority of individuals with concussion follow a course of recovery in behavioral and cognitive signs and symptoms within approx-

imately 1 week of injury.^{2–4} Functional neuroimaging studies have reported, however, that neuronal function may be abnormal for a period of several weeks postinjury despite normal structural findings on conventional computed tomographic (CT) scan and magnetic resonance imaging (MRI) studies.^{2,5}

In recent studies, we investigated whether an index of brain dysfunction based on brain electrical activity (TBI Index) was more sensitive to the time course of recovery from sport-related concussion than measures of clinical signs and symptoms, postural stability, and cognitive functioning at the time of injury and at 8 days and 45 days postinjury.⁶ The TBI Index derived from these methods discriminated injured subjects from normal controls and reflected significant persistence of brain dysfunction beyond the point of clinical recovery in injured subjects. In addition, these studies also clearly demonstrated the feasibility of using measures of brain electrical activity in the acute injury setting.

In terms of severity of concussion, many attempts have been made to develop grading scales of the severity of concussive injury and to correlate these grades with recovery and outcome. Most grading scales (Cantu, the American Academy of Neurology, Colorado) are based primarily on the presence and duration of acute injury characteristics (loss of consciousness [LOC], posttraumatic amnesia, and altered mental status), whereas some

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others are symptom based.^{7,8} Attempts to empirically demonstrate the relationship of severity, as defined by these grading scales, to clinical outcome, however, have not been successful. In this study, we used information related to LOC and amnesia, in combination with reported symptoms, considering the severity and number of symptoms to characterize the severity of sport concussion injury, with the goal of using this information to predict outcome.

The purpose of this study was to examine the relationship between concussion symptom severity and the presence and persistence of neurophysiological patterns of abnormal brain function in individuals with concussion at the time of injury, for 45 days after concussion, and as related to time to return to play. The potential clinical utility of the use of brain electrical activity in the evaluation of sport concussion was aided by the use of a limited montage, only frontal forehead regions of the scalp, which allows for rapid, easily acquired brain electrical activity to be collected at the point of care. The use of a limited montage was supported by the scientific literature, which demonstrates the maximum structural and functional vulnerability of the frontal regions of the brain to mTBI.⁹⁻¹³

METHODS

Subjects

Male football players from 8 high schools and 2 colleges in the greater Milwaukee, Wisconsin, area were enrolled in the study prior to the 2008, 2009, and 2010 football seasons. Over the 3 seasons, 873 player seasons (ie, each sport season of injury exposure; individual athletes may have participated for more than 1 season) were under investigation, of which the subset who sustained a concussive injury during play were considered candidates for this study. This study was approved by the institutional review board for protection of human research subjects at the host institutions of the principal investigators. Written informed consent was obtained from all participants (or parent/guardian of minors), and each subject voluntarily elected to participate in the study.

Design and procedures

Injured subjects were identified for this study by professional staff members (eg, certified athletic trainers) located on the sideline during an athletic contest or practice. For inclusion as an injured subject in this study, *concussion* was defined as an injury resulting from a blow to the head or to the body, causing head deceleration leading to an alteration in mental status and 1 or more of the following symptoms prescribed by the American Academy of Neurology Guideline for Management of Sports Concussion: headache,

nausea, vomiting, dizziness/balance problems, fatigue, trouble in sleeping, drowsiness, sensitivity to light or noise, blurred vision, difficulty remembering, or difficulty concentrating.^{14,15} Loss of consciousness, post-traumatic amnesia (eg, inability to recall exiting the field, aspects of the examination), and retrograde amnesia (eg, inability to recall aspects of the play or events prior to injury, score of the game) and other acute injury characteristics were also documented immediately after each injury.

The clinical “sideline” evaluations and electrophysiological evaluations were conducted within 24 hours of injury (regardless of injury severity), in a controlled testing setting (eg, locker room, classroom), and at 8 days and 45 days postinjury. Team personnel contacted the local investigators and briefed them on details of injury characteristics and the early course of recovery. The local investigators then arranged for the follow-up protocol of the player with concussion. Additional testing, performed on the day of injury and on postinjury days 8 and 45, included a computerized neuropsychological testing battery and electrophysiological testing. All examiners were trained to perform these evaluations, and quality control guidelines were followed rigorously.

Clinical measures

*Concussion Symptom Inventory*¹⁶

The Concussion Symptom Inventory (CSI) is a brief screening measure assessing the presence and severity of 12 common postconcussion symptoms. Higher scores on the CSI indicate more severe symptoms reported.

Standardized Assessment of Concussion^{3,17}

The Standardized Assessment of Concussion (SAC) is a brief cognitive screening tool that has been used extensively to assess the cognitive effects of concussion. It includes brief subtests of orientation, immediate memory, concentration, and delayed recall. Lower scores on the SAC indicate poorer cognitive performance.

Balance Error Scoring System^{3,18,19}

The Balance Error Scoring System (BESS) is a brief clinical measure of postural stability. It assesses balance during 6 separate trials, including 3 stances (single leg, double leg, and tandem) on 2 surfaces (firm and foam). Higher scores on BESS indicate poorer performance.

*Automated Neuropsychological Assessment Metrics*²⁰⁻²²

Automated Neuropsychological Assessment Metrics (ANAM) is a computerized neuropsychological test battery that includes measures of cognitive processing speed, reaction time, and visual memory. Measures of accuracy and speed are recorded, which combine to form

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a composite throughput score. For each subtest, a lower throughput score indicates poorer performance. These variables have been shown to be sensitive to the effects of concussion at the time of injury. It has a test–retest reliability coefficient of 0.87 when throughput scores are used to assess cognitive functioning.²³

Total days lost to play

Total days lost to play is a measure of the amount of time in days before each player was allowed to return to play, as reported by the athletic trainer. Return-to-play decisions were made by clinicians on the basis of their conventional methods, independent of study-related data. The TBI Index was not available to the athletic trainer.

Classification of clinical severity of concussive injury

All athletes with concussion were divided into having mild or moderate concussive injury, empirically based on the acute characteristics, signs, and symptoms of their head injury (eg, unconsciousness [LOC], amnesia, disorientation, alteration of mental status). Subjects were considered moderate if they reported LOC or amnesia and 2 or more of the following symptoms or signs (at the severity level indicated): difficulty remembering (ratings of 4–6 on CSI), impaired delayed recall (scores of 0–3 on SAC), disturbance in concentration (scores of 0–3 on SAC), “feeling slowed down” (ratings of 4–6 on CSI), feeling like “in a fog” (ratings of 4–6 on CSI), disturbance in orientation (scores of 0–3 on SAC or on neurological examination), or altered mental status. Subjects were considered to be mild if they did not report LOC or amnesia or had LOC or amnesia but did not report 2 or more symptoms at the level indicated. The symptoms used in dividing patients in this way took into consideration the overlap between several of the existing guidelines for severity of sports concussion (eg, Cantu et al⁷ and Erlanger et al⁸). It is also noted that symptoms included those whose distributions of scores on the SAC or ratings on the CSI were most bimodal (contained a peak of high scores and peak of low scores) when the entire population was taken into consideration.

Electrophysiological evaluation

Injured subjects underwent 10 minutes of eyes-closed, resting electroencephalographic (EEG) recording acquired on a hand-held device. The EEG recordings were made from frontal electrode sites of the International 10/20 system by using self-adhesive electrodes pasted on the forehead and referenced to linked ears. The frontal electrode sites included FP1, FP2, AFz (located just anterior to Fz on the forehead, below the hairline), F7, and F8. All electrode impedances were less

than 10 k Ω . Amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points). Electrode placement in all cases was completed in less than 5 minutes. The EEG data were subjected to artifact rejection to remove any biologic and nonbiologic contamination, such as that from eye movement or muscle movement. Previous experience has demonstrated that sufficient artifact-free data (60–120 seconds) can be obtained from this 10-minute recording.

Quantitative analysis of brain electrical activity

The artifact-free EEG data were then submitted for quantitative analyses off-line to calculate an independently developed quantitative EEG discriminant function, which was derived to maximally separate a normal control population ($n = 255$) from patients who had suffered a TBI/concussion ($n = 358$) in an emergency department population with high sensitivity and specificity.²⁴ This binary discriminant classification algorithm was constructed by using iterative methods and cross-validation (leave-one-out and 10-fold,²⁵) based on features extracted from all patients in the algorithm development database. The algorithm consists of a weighted combination of selected linear and nonlinear features of brain electrical activity, which mathematically describe the profile of TBI, as distinguished from normal brain activity. The result is expressed as a discriminant score or index (TBI Index) ranging from 0 to 100. This index was calculated for each subject in the study and relates to the probability that the patient belongs to the group of patients with disturbances to brain function. It is important to point out that patient age was taken into account prior to calculation of the TBI Index because all EEG features were age regressed prior to inclusion in discriminant analyses.²⁶

Statistical analyses

One-way analyses of variance with 2 between levels corrected for unequal N were calculated, comparing the players with mild and moderate concussion symptoms. Separate analyses were conducted for the CSI, SAC, and BESS total scores and the subtests of the ANAM and the TBI Index of brain function at the time of injury and at days 8 and 45 after injury. On the basis of our prior research, we hypothesized that differences in the clinical measures would be small at the time of injury between those with mild and those with moderate concussions and that these differences would resolve beyond the first week after injury. In contrast, we hypothesized that the TBI Index of brain function would be elevated at injury and persist at 8 days and 45 days postinjury.

In order to assess the degree to which information at injury is related to the length of time to return to

play symptom-free, analyses of variance described earlier were repeated, comparing players who were reported to return to play in less than 14 days with those whose return to play was 14 days or longer. This cut point was chosen as believed to be a clinically significant time point that was used in other studies of return to play. We hypothesized that the TBI Index at the time of injury would be greater for those players whose return to play was delayed beyond 14 days.

RESULTS

Subjects

A total of 65 athletes (mean age = 17.9 years, with a range of 15.1–23.2) sustained a concussion and were studied at the time of injury and at various time points postinjury. The players with concussion were placed into 2 categories based on the severity of the concussion symptoms displayed at the time of injury. Using the method described earlier, a total of 51 players (17.9 years; range, 15.1–23.2) were placed in the mild concussion group, and a total of 14 players (17.8 years; range, 15.1–22.6) were placed in the moderate concussion group. There was no significant difference between the 2 severity groups for history of prior concussions. Seventy-three percent of the athletes were reported to return to play in less than 14 days (mean = 5.46 days; SE = 1.30), and 27% did not return to play until more than 14 days (mean = 20.38 days; SE = 9.2).

Clinical measures

The mean values and standard errors for each of the clinical measures at the time of injury and at 8 days and 45 days postinjury are shown in Table 1. At the time of injury, players with moderate concussions showed more severe symptoms on the CSI ($F = 14.8$; $P = .0003$) and poorer cognitive performance on SAC ($F = 9.1$; $P = .0038$) than those with mild concussions. There were no significant differences between the 2 groups on the CSI or the SAC on repeat assessment at 8 days or 45 days after injury. There were no significant differences between the 2 groups on the BESS total scores at injury or at 8 days or 45 days postinjury. At the time of injury, those with moderate concussions showed poorer performance than those with mild concussion on the following ANAM subtests: delayed code substitution ($F = 14.7$; $P = .0003$), code substitution learning ($F = 7.4$; $P = .0087$), match to sample ($F = 4.5$; $P = .0383$), simple response time ($F = 5.9$; $P = .0177$), and simple reaction time repeated ($F = 5.9$; $P = .0179$). There were no significant differences between the 2 groups on any of the ANAM subtests 8 days or 45 days postconcussion. Players with moderate concussions took longer before returning to play than did those with mild concussions (13.8 days vs 9.6 days; $F = 4.35$; $P = .0420$).

Traumatic Brain Injury Index

The mean values and standard errors for the TBI Index at the time of injury and at 8 days and 45 days postinjury

TABLE 1 Means and standard errors (se) for all measures for the mild and moderate concussion groups at the time of injury, 8 days postinjury, and 45 days postinjury^a

	At injury		8 days postinjury		45 days postinjury	
	Mild	Moderate	Mild	Moderate	Mild	Moderate
SAC total	26.3 (0.3)	23.8 (1.1) ^b	28.0 (0.3)	27.8 (0.6)	28.2 (0.3)	28.2 (0.5)
CSI total	17.1 (1.6)	31.5 (3.8) ^b	2.8 (0.8)	2.9 (0.9)	1.1 (0.4)	0.92 (0.6)
BESS total	15.4 (1.2)	17.4 (4.1)	12.4 (0.9)	11.6 (2.6)	10.8 (0.8)	9.7 (1.7)
ANAM: CDD	51.5 (1.9)	34.4 (5.8) ^c	53.7 (1.8)	46.0 (3.6)	52.1 (2.1)	51.0 (3.3)
ANAM: CDS	55.1 (1.7)	45.2 (3.3) ^b	60.2 (1.6)	54.4 (2.5)	60.8 (1.5)	56.0 (3.1)
ANAM: M2S	36.8 (1.9)	28.0 (3.6) ^d	38.7 (1.6)	35.7 (2.9)	38.3 (2.0)	34.9 (4.0)
ANAM: Math	20.5 (1.0)	17.6 (1.8)	22.7 (1.0)	19.3 (1.7)	24.8 (1.1)	20.5 (2.0)
ANAM: SRT	176.8 (5.3)	148.4 (11.0) ^d	199.3 (4.0)	190.5 (9.4)	196.6 (3.2)	186.7 (8.1)
ANAM: SR2	174.7 (6.0)	143.3 (10.7) ^d	194.5 (4.0)	188.9 (8.8)	187.0 (3.3)	182.7 (7.7)
TBI Index	7.7 (2.6)	31.3 (12.0) ^b	14.3 (3.9)	40.2 (15.8) ^d	6.2 (1.6)	26.9 (12.4) ^c
Return to play	9.7 (0.9)	13.8 (2.2) ^d	NA	NA	NA	NA

Abbreviations: ANAM, Automated Neuropsychological Assessment Metrics; BESS, Balance Error Scoring System; CDD, delayed code substitution; CDS, code substitution learning; CSI, Concussion Symptom Inventory; M2S, match to sample; NA, not applicable; SAC, Standardized Assessment of Concussion; SRT, simple response time; SR2, simple reaction time repeated; TBI, traumatic brain injury.

^aReturn to play is measured only once and shown in the table at the time of injury.

^bSignificances of the difference between mild and moderate groups are shown with $P < .01$.

^cSignificances of the difference between mild and moderate groups are shown with $P < .005$.

^dSignificances of the difference between mild and moderate groups are shown with $P < .05$.

are shown in Table 1. The TBI Index was greater in the players with moderate concussion than in those with mild concussion at the time of injury ($F = 9.09$; $P = .0038$), remained so 8 days postinjury ($F = 5.61$; $P = .0218$), and continued to be elevated 45 days postinjury ($F = 10.2$; $P = .0025$). It can be seen in Figure 1 that the differences in the TBI Index between the groups was present at all time points and the moderate group never fell below the threshold for moderate classification by index value, suggesting the persistence of the brain dysfunction out to at least 45 days in the moderate group. It is of interest to note that a TBI Index lower than 27 is considered to indicate mild concussion and a TBI Index of 27 or greater is considered to be moderate. Sensitivity of the TBI Index to moderate concussion at the time of injury was 55% (confidence interval = 28.0%–78.7%) and specificity was 94% (confidence interval = 84.0%–98.0%).

Return-to-play outcome

The mean values, standard errors, and analysis of variance results for all measures at the time of injury for those who returned to play in less than 14 days and those who returned to play in 14 days or more are shown in Table 2. There were no significant differences for any of the clinical measures at the time of injury. However, there was a significant difference ($P = .0161$) between the TBI Index at the time of injury for the group that returned to play in less than 14 days (mean TBI Index = 5.46) and those who returned to play in 14 days or more (mean TBI Index = 20.37). Thus, the only acute injury measure demonstrating a significant relationship to eventual return-to-play outcome was the one that

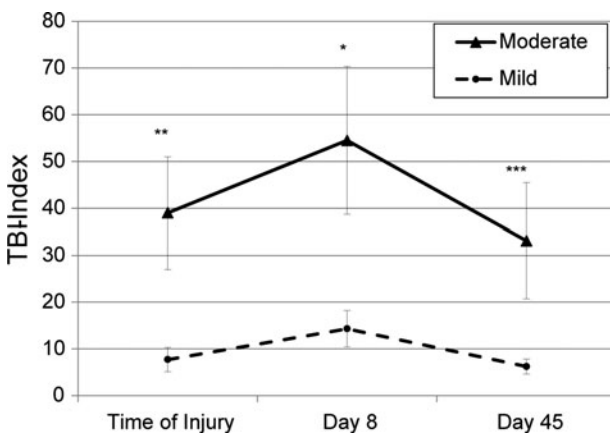


Figure 1. Mean and standard errors (se) of the traumatic brain injury (TBI) Index at the time of injury, day 8, and day 45 for the mild concussive group (dotted line) and the moderate concussive group (solid line). It is noted that a TBI Index lower than 27 is considered to indicate mild concussion and that 27 and greater is considered to be moderate. Significances of the difference between mild and moderate groups at each time point are marked with * $P < .05$, ** $P < .01$, and *** $P < .005$.

TABLE 2 Means and standard errors (se) for all measures for the group that returns to play in less than 14 days and those who return to play in 14 days or more^a

	<14 days	≥14 days	F	P
SAC total	26.1	24.5	3.14	.0830
CSI total	16.8	22.4	1.69	.1999
BESS total	16.0	18.2	0.43	.5145
ANAM: CDD	48.0	51.1	0.42	.5219
ANAM: CDS	53.2	56.7	0.84	.3631
ANAM: M2S	35.4	34.4	0.06	.8134
ANAM: Math	18.9	20.6	0.64	.4287
ANAM: SRT	177.6	168.5	0.54	.4672
ANAM: SR2	176.6	162.8	1.09	.3013
TBI Index	5.46	20.37	6.22	.0161 ^b

Abbreviations: ANAM, Automated Neuropsychological Assessment Metrics; BESS, Balance Error Scoring System; CDD, delayed code substitution; CDS, code substitution learning; CSI, Concussion Symptom Inventory; M2S, match to sample; SAC, Standardized Assessment of Concussion; SRT, simple response time; SR2, simple reaction time repeated; TBI, traumatic brain injury.

^aThe F and P values are given for statistical comparisons between the 2 groups.

^b $P < .05$.

quantified severity of brain dysfunction (TBI Index) at the time of injury.

Figure 2 shows the percentage of athletes with concussion who returned to play in less than 14 days (hatched bars) and those who returned to play in 14 days or more (solid black bars), for those with mild injury and those with moderate injury, as reflected in the TBI Index. It can be seen that approximately 80% of those with scores on the TBI Index indicating mild concussive injury returned to play within 14 days, whereas 80% of those with TBI Index scores indicating moderate concussive injury returned to play in 14 days or more. While suggestive, caution should be used in interpreting the data from the moderate group as the number of subjects was small.

DISCUSSION

In our previous publications, it was demonstrated that an EEG-based discriminant index (TBI Index) of brain dysfunction could be used to differentiate football players with concussion from matched controls at the time of injury and that these differences persisted for at least 8 days after injury. This occurred even though the concussion and control groups could not be distinguished from each other on measures of clinical recovery in symptoms, cognitive functioning, and postural stability after 5 days. Findings from the current study show that this TBI Index is also sensitive to the severity of

concussion symptoms at the time of injury. Of more importance is the finding that this index of brain dysfunction remains significantly more elevated in those players with moderate concussions than in those with mild concussions at 8 days and 45 days after injury.

These findings are in agreement with those reported in other studies using functional neuroimaging techniques that suggest that brain function remains compromised in individuals with concussion beyond the period of clinical recovery when behavioral and cognitive symptoms are alleviated. For example, Jantzen et al,²⁷ using functional MRI (fMRI), found increased blood/O₂ activation in parietal and lateral frontal brain regions in individuals with concussion compared with controls using a finger sequence task 1 week postinjury. Also, Chen et al,^{5,28} using fMRI, found atypical activation patterns during task performance in individuals with concussion more than 1 month after injury, with the degree of decreased activation related to postconcussion symptoms of depression. This decreased activation was localized to dorsal-lateral prefrontal, medial frontal, and temporal cortical regions. Gosselin et al²⁹ reported event-related electrical potential and fMRI abnormalities that were present 6 months postconcussion and were localized to dorsal-lateral prefrontal regions as well as in subcortical structures. The fMRI activation during a working memory task was reported to be related to concussion symptom severity as well.³⁰ Vagnozzi et al³¹ used proton magnetic resonance and found evidence of disturbed metabolic function in athletes with concussion, which persisted for up to 22 days postinjury. Abnormal neurochemical changes were also seen 1 to 6 days after concus-

sion by using proton magnetic resonance spectroscopy with decreased glutamate seen in primary motor cortex and decreased N-acetylaspartate in prefrontal and primary motor cortex.³² Event-related potential indices of attention and cognitive decision processes were reported to be disturbed in individuals with concussion at 1 year³³ and up to 3 years³⁴ postconcussive injury. Interestingly, these functional neuroimaging findings also suggest the vulnerability of the prefrontal and frontal cortical regions of the brain to concussive injury, lending support to the use of the frontal locations of the limited montage used to collect the brain electrical activity in this study.

Although the pathophysiology of TBI is still unclear, several recent studies using diffusion tensor imaging (DTI) and positron emission tomographic scans have reported evidence of diffuse axonal injury in TBI in acute injury, which might result in edema and inflammatory responses, resulting in persistence of the sequelae of mTBI.^{35,36} Cubon et al³⁷ used DTI and found evidence of disturbed white matter integrity after concussion that was related to concussion severity in a small clinical sample. Sponheim et al³⁸ reported a significant relationship between DTI evidence of axonal injury and EEG phase synchrony between frontal regions in soldiers with blast-related concussions. The phase synchrony measure found to be significant in their study included 4 of the 5 frontal regions used to compute the TBI Index in the current study. These neuroimaging studies suggest that diffuse axonal injury, and possibly related neuroinflammation, may in part contribute to abnormalities in the TBI Index. Collectively, the findings from this and other studies underscore the need for further research on the time course of physiological recovery after concussion.

With regard to the severity of concussive injury, previous attempts to demonstrate outcome relationships to such categorizations have largely been unsuccessful or inconsistent, regardless of whether based on presence and duration of LOC or amnesia, severity of symptoms, or history of concussions.^{8,39} In one of the few studies in which this has been demonstrated, it was found that the presence and severity of certain key symptoms may indicate more severe injury or prolonged recovery.⁴⁰ In the current study, results suggested that there may be a significant relationship between severity of concussion and outcome, based mainly on the presence and intensity of symptoms reflecting “disorientation” (eg, “feeling like in a fog” or orientation, as measured on the SAC) and “memory/cognitive impairment” (eg, delayed recall on SAC or difficulty remembering), and presence or absence of LOC or amnesia. Evidence presented in this study also supports the difference between mild and moderate concussions at the time of injury, day 8, and day 45 by using an electrophysiologically based index of brain dysfunction. Furthermore, the TBI Index derived from brain electrical activity at the time of injury

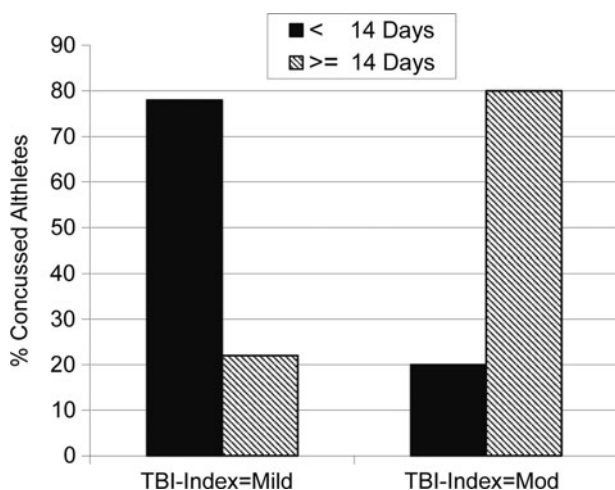


Figure 2. Histogram of percentage of athletes with concussion, who returned to play in less than 14 days (hatched bars) and those who returned to play in 14 days or more (solid black bars), shown for the group who had a traumatic brain injury (TBI) Index indicating mild concussive injury (left 2 bars) and those where the TBI Index indicated moderate concussive injury (right 2 bars).

was the measure most significantly related to the time to return to play symptom-free, suggesting that such a measure is reflecting additional information not immediately forthcoming from a symptom profile alone.

The measures of brain electrical activity made in this study employed an easy-to-use, forehead-recording device and suggested the feasibility of performing such evaluations in the sports arena. Furthermore, results demonstrate that the assessment of abnormality of brain function at the time of injury is related to the length of time until “return to play” after concussive injury. Such measures could be the basis for a clinically useful sideline tool to assess the severity of concussive injury at the point of injury as an aide in “return to play” decisions.

The major limitations of this study involve the relatively small number of individuals with concussion who were studied. This becomes especially relevant when these individuals are divided into those with concussions of mild and moderate severity (51 and 14, respectively). Clearly, larger sample sizes are necessary to further validate the suggested clinical utility of such measures on the playing field.

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