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Daniel Hanley
The Johns Hopkins Medical Institutions

Leslie S. Prichep
New York University School of Medicine

Neeraj Badjatia
R. Adams Cowley Shock Trauma Center

Jeffrey Bazarian
University of Rochester Medical Center

Richard Chiacchierini
R.P. Chiacchierini Consulting, LLC

See next page for additional authors

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A Brain Electrical Activity Electroencephalographic-Based Biomarker of Functional Impairment in Traumatic Brain Injury: A Multi-Site Validation Trial

Daniel Hanley,[1] Leslie S. Prichep,[2,3] Neeraj Badjatia,[4] Jeffrey Bazarian,[5] Richard Chiacchierini,[6] Kenneth C. Curley,[7,8] John Garrett,[9] Elizabeth Jones,[10] Rosanne Naunheim,[11] Brian O'Neil,[12] John O'Neill,[13] David W. Wright,[14] and J. Stephen Huff[15]

Abstract

The potential clinical utility of a novel quantitative electroencephalographic (EEG)-based Brain Function Index (BFI) as a measure of the presence and severity of functional brain injury was studied as part of an independent prospective validation trial. The BFI was derived using quantitative EEG (QEEG) features associated with functional brain impairment reflecting current consensus on the physiology of concussive injury. Seven hundred and twenty adult patients (18–85 years of age) evaluated within 72 h of sustaining a closed head injury were enrolled at 11 U.S. emergency departments (EDs). Glasgow Coma Scale (GCS) score was 15 in 97%. Standard clinical evaluations were conducted and 5 to 10 min of EEG acquired from frontal locations. Clinical utility of the BFI was assessed for raw scores and percentile values. A multinomial logistic regression analysis demonstrated that the odds ratios (computed against controls) of the mild and moderate functionally impaired groups were significantly different from the odds ratio of the computed tomography (CT) postive (CT+, structural injury visible on CT) group ($p = 0.0009$ and $p = 0.0026$, respectively). However, no significant differences were observed between the odds ratios of the mild and moderately functionally impaired groups. Analysis of variance (ANOVA) demonstrated significant differences in BFI among normal (16.8%), mild TBI (mTBI)/concussed with mild or moderate functional impairment, (61.3%), and CT+ (21.9%) patients ($p < 0.0001$). Regression slopes of the odds ratios for likelihood of group membership suggest a relationship between the BFI and severity of impairment. Findings support the BFI as a quantitative marker of brain function impairment, which scaled with severity of functional impairment in mTBI patients. When integrated into the clinical assessment, the BFI has the potential to aid in early diagnosis and thereby potential to impact the sequelae of TBI by providing an objective marker that is available at the point of care, hand-held, non-invasive, and rapid to obtain.

Keywords: brain electrical activity; concussion; ED triage; EEG; functional impairment; mTBI; TBI

[1]Brain Injury Outcomes-The Johns Hopkins Medical Institutions, Baltimore, Maryland.
[2]Department of Psychiatry, New York University School of Medicine, New York, New York.
[3]BrainScope Co., Inc., Bethesda, Maryland.
[4]R. Adams Cowley Shock Trauma Center, Baltimore, Maryland.
[5]University of Rochester Medical Center, Rochester, New York.
[6]R.P. Chiacchierini Consulting, LLC, Gaithersburg, Maryland.
[7]Iatrikos Research and Development Strategies, LLC, Tampa, Florida.
[8]Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, Maryland.
[9]Baylor University Medical Center, Dallas, Texas.
[10]University of Texas Memorial Hermann Hospital, Houston, Texas.
[11]Washington University Barnes Jewish Medical Center, St. Louis, Missouri.
[12]Detroit Receiving Hospital, Detroit, Michigan.
[13]Allegheny General Hospital, Department of Emergency Medicine, Pittsburgh, Pennsylvania.
[14]Emory University School of Medicine & Grady Memorial Hospital, Atlanta, Geogia.
[15]University of Virginia Health System, Charlottesville, Virginia.

Introduction

Traumatic brain injury (TBI) visits to the emergency department (ED) have been reported to have increased by 29% between 2006 and 2010[1], whereas overall ED visits only increased 3.6%. This surge likely reflects heightened public awareness of the potential long-term consequences of TBI and concussion.[2] Of the estimated 4.8 million people evaluated annually in the United States for TBI,[3] approximately 90% are found to be ''mild'' (mTBI/concussion)[4] by current clinical criteria. Thus the ability to objectively and effectively identify those with mTBI/concussion is of major public health interest.

There is currently no ''gold standard'' for the diagnosis of concussion. More than 20 different published guidelines exist for grading concussion severity and determining return to activity. Head impact sensors can provide a warning system of hits, but readings have not been demonstrated to correlate with or predict concussion.[5] Although advanced neuroimaging has greatly contributed to a better understanding of the pathophysiology of concussion, limited accessibility, relatively long exam times, and diagnostic imaging expertise limit the clinical utility of such technologies. Clinical symptom checklists and neurocognitive tests are used commonly, but the disadvantages include lack of clinical validation, poor test-retest reliability, and frequent under-reporting and or exaggeration of symptoms.[6]

TBI is a complex and heterogeneous disorder, resulting in a spectrum of associated injury severity. Brain injuries visible on computed tomography (CT) represent the more severe end of this pathology spectrum. Advanced functional neuroimaging can detect brain injuries not visible on CT and have led to a better understanding of injury mechanisms and sequelae of concussive injury. Changes in ''functional connectivity'' between regions of the brain have been demonstrated in diffusion tensor imaging (DTI) studies providing evidence of the disruption of white matter tract integrity in concussive injury [7–12] In addition, changes in magnetic resonance spectroscopy (MRS) demonstrate evidence of changes in brain metabolism as a consequence of concussive injury.[13]

The physical injuries visible in DTI and MRS images impact the generation, transmission, and processing of neural signals within and across regions of the brain that can be measured directly by encephalography (EEG). This has been observed in studies that demonstrate a high correlation between DTI/MRS measures and changes in brain electrical activity, suggesting the utility of such measures as markers of functional brain injury. In a study comparing DTI and EEG in blast-concussed soldiers, Sponheim and colleagues[14] reported a significant correlation between changes in mean fractional anisotropy (FA) of four major white matter tracts related to frontal interhemispheric communication and changes in phase synchrony of the EEG between frontal and frontotemporal regions. Another measure of brain electrical activity reported to reflect brain injury in mTBI/concussion is based on the ''complexity'' or entropy of the EEG signal, which drops in concussive injury.[15] Changes in the frequency spectra of the EEG, power relationships, and coherence between regions have also been demonstrated in the presence of concussion.[16–19]

The temporal resolution of brain electrical activity presents an analytic advantage over other functional neuroimaging methods including availability at the point of care, ease of use with limited training, and non-invasive application. This article describes the development and validation of a novel quantitative EEG-based Brain Function Index (BFI) to aid in the assessment of mTBI following a head injury. The BFI is derived from those QEEG features associated with functional brain impairment reflecting current consensus on the physiology of concussive injury.[11–16] The study demonstrates potential clinical utility of the BFI in supporting the evaluation of functional brain injury and the relationship between the BFI and severity of functional impairment in an independent prospective validation population.

Methods

Study design and population

The B-Ahead III Validation Trial[a] consisted of a prospective convenience sample of adult patients presenting to 11 participating U.S. ED sites.[b] Patients between the ages of 18 and 85 years who presented to an ED within 72 h of sustaining a closed head injury, and who had a Glasgow Coma Scale (GCS) score between 12 and 15 (at the time of the Ahead 300 evaluation) were candidates for study inclusion.

Patients were excluded if they had scalp lacerations, skull abnormalities, or any other clinical condition that precluded placement of the electrodes on the forehead in the prescribed locations. Patients were also excluded if intoxicated to the point where they could not participate in the study or give informed consent. Patients with advanced dementias, Parkinson's disease, known chronic drug or alcohol dependence, known seizure disorder or other central nervous system disorder were also excluded. Other exclusion criteria included history of transient ischemic attack (TIA) or stroke in the past year, currently receiving dialysis or in end-stage renal disease, active fever greater than 100°F or 37.7°C, in critical condition or requiring advanced airway management, and currently receiving procedural sedation medications. Patients exhibiting drug/alcohol intoxication but otherwise satisfying the above criteria were not excluded. Signed informed written consent, or in a few cases consent by proxy, was obtained. Assessment of the capacity of the subject to give informed consent was performed using the Conley criteria.[20]

Clinical assessments

The evaluation of the study subjects was performed using standard practice clinical procedures of each ED site. In all cases the determination to receive a CT scan was made by the site ED physician, according to local standard of care. To address the potential differences between neuro-radiological reads of the CT scans across sites, independent blinded adjudication was performed by the contract research organization (CRO; Brain Injury Outcomes [BIOS] Division, Johns Hopkins University). The adjudication followed a rigorous and quantitative procedure involving sequential evaluation by imaging specialists and physician specialist readers with image-based initial independent determination of CT+ or CT–, requiring unanimity for final determinations.[21] Evaluation of clinical signs and symptoms included the Standardized Assessment of Concussion scale (SAC)[22,23] and the Concussion Symptom Inventory (CSI),[24] acquired by trained ED personnel.

A categorical classification of functional severity (mild/moderate) was computed for CT negative subjects based on the report of focal neurological signs, loss of consciousness (LOC), post-

[a]NCT02367300; https://clinicaltrials.gov/ct2/show/NCT02367300?term=BrainScope&rank=5; accessed June 17, 2016.

[b]The 11 ED sites included: Washington University Barnes Jewish Medical Center, St. Louis, MO; Detroit Receiving Hospital, Detroit, MI; University of Virginia Health System, Charlottesville, VA; R. Adams Cowley Shock Trauma Center, Baltimore, MD; Baylor University Medical Center, Dallas, TX; Emory University/Grady Memorial Hospital, Atlanta, GA; Wayne State University Sinai-Grace Hospital Detroit, MI; University of Rochester Medical Center, Rochester, NY; Allegheny General Hospital, Pittsburgh, PA; University of Texas Memorial Hermann Hospital, Houston, TX; and Hartford Hospital, Hartford, CT.

traumatic or retrograde amnesia, and the presence and severity of scores for cognitive function/memory, orientation, headache and presence of focal neurological signs, and high-risk criteria (e.g., persistent vomiting, post-traumatic seizure, GCS score <15) gathered using the above scales.[17] Those with focal neurological signs, or LOC or amnesia and two or more symptoms of moderate to severe severity (e.g., 4–6 on the Likert scale) were considered moderate. Those who did not meet criteria for moderate, did not have focal neurological signs but had altered mental status (AMS) and at least one concussion symptom or report of LOC or amnesia, were considered mild. This scoring was performed in a blind retrospective manner performed by the independent CRO (BIOS) and was used for the characterization of severity of functional impairment only.

EEG data acquisition

Subjects underwent 5 to 10 min of eyes-closed resting EEG in the ED. The EEG was recorded using a disposable self-adhesive headset that positioned electrodes on the standard frontal locations (FP1, FP2, AFz, F7, and F8) of the expanded International 10/20 system referenced to linked ears. Electrode impedances were required to be below 10 kΩ for data collection. The EEG data were subjected to a series of artifact detection algorithms that identified and removed any biological and non-biological contamination, such as that from eye movement or muscle movement,[25] producing a ''clean'' artifact-free record of 1 to 2 min required for all further analyses.

Computation of quantitative features of brain electrical activity EEG (QEEG) for algorithm development

The artifact-free EEG data were subjected to quantitative offline analyses to derive an extensive set of univariate and multivariate features (both linear and non-linear) using advanced signal processing methods. The univariate feature sets included a broad range of measures from conventional features derived from power spectrum estimates in the conventional EEG frequency bands to non-traditional features based on chaos theory, information theory, and functional connectivity in the spatiotemporal EEG signal. The univariate features are age-regressed (where an appropriate age relationship in the normal population is present) and normalized to standard *z*-scores. The multivariate features are derived from the univariate feature *z*-scores and the formulations are designed to describe changes in brain dynamics across brain regions and across the EEG frequency bands. See the article by Prichep and associates [25] for a more complete description of the feature extraction methodology.

Ahead 300 structural injury classification

The likelihood that a patient was CT positive (CT+) was predicted by the application of the EEG-based structural injury classification algorithm (Ahead 300 device FDA 510(k) clearance, K161068) described in detail elsewhere.[21] This algorithm was independently developed using a least absolute shrinkage and selection operator (LASSO) methodology,[26] which uses a regularized logistic regression model. The classifier consists of a weighted combination of selected linear and non-linear QEEG features, enhanced with selected clinical features. The features that are inputs to the algorithm were selected to optimally reflect traumatic structural brain injury. The Ahead 300 classification also produced a ternary classification output implementing a second threshold (T2) which, together with the binary threshold (T1), defined an equivocal zone (EZ) as a third classification category. This classifier was demonstrated to obtain extremely high accuracy for predicting the likelihood of being CT+, with high negative predictive value (NPV) and sensitivity to any traumatic bleeding and to hematomas. Specificity was significantly higher than standard CT decision rules (for details see Hanley and colleagues[21] and Prichep and associates[27]).

Analysis

EEG data analysis

Development of the EEG Brain Function Index (BFI). Two databases were used for development of the BFI, the algorithm development database ($n = 2407$) and the healthy volunteer normative database ($n = 384$). The two databases and the subjects they represent were mutually independent as well as completely independent from the one used for the validation trial. A brief description of both databases is provided below. Informed consent was obtained from each subject (each site obtained Institutional Review Board approval to conduct the study at its site).

The *algorithm development database* was constructed through multiple studies across several years of development, under consistent protocols. Study sites included 20 EDs and 11 colleges and high schools across the United States. Subjects were a convenience sample ($n = 2407$; 36% female, 64% male). Of these subjects 29.1% were controls and 70.9% were TBI patients (29.3% mTBI/concussed with mild functional impairment, 25.6% mTBI/concussed with moderate functional impairment, and 16.0% CT+). It is noted that ''controls'' contained both head-injured normal controls (patients who sustained a closed head injury but for whom the report of symptoms/severity indicated normal function) as well as ED controls with no head injury; TBI patients included males and females between the ages of 15 and 92, who suffered a closed head injury and had a GCS score of 8 or higher. The mean GCS score of the cohort was 14.9 (median, 15; standard deviation [SD], 0.4; range, 9–15). The mean age of the cohort was 39.5 years (median, 36.2; SD, 17.6; range, 15.1–91.7). The inclusion/exclusion criteria for enrollment were consistent with those described in the ''Patient Population'' section for the validation trial.

The healthy volunteer *normative database* consisted of a total of 384 healthy volunteer subjects (59.6% female; 40.4% male) between the age of 18 and 85 years, GCS score of 15, and not under duress. These subjects were recruited from the community surrounding three clinical sites using a single predefined protocol and assessed for presence and severity of symptoms using the same clinical assessment tools as used in the current validation population. The mean age of the cohort was 46.0 years (median, 46.7; SD, 16.4; range, 18.0–80.8). The inclusion/exclusion criteria for this group included those described in the ''Patient Population'' section for the validation trial with the additional exclusions for subjects with injury above the clavicle, neck or head injury within the past year, a primary complaint of generalized weakness, a primary complaint of headache or migraine, a history of brain surgery, TBI, or a history of motor vehicle accident (MVA) requiring an ED visit within the past year.

With regard to drugs or alcohol, fatigue, pain, and other factors that may be present in head injury cases, the method used in this investigation was to include them in all subject groups (controls and TBI patients), except as defined by exclusion criteria. By doing this, they are eliminated as differentiating factors between groups, and features sensitive to these factors are not selected by the classifier, whereas features independent of such factors that differentiate between groups are candidates for selection.

The BFI was designed to be an aggregate representation of brain abnormality that reflects functional impairment in concussive injury. Based on concussion literature (reviewed above, see Introduction), a subset of features was identified that have been reported to be reflective of the pathophysiology of concussion. These features include measures of connectivity between regions of the brain (including coherence, phase synchrony, power ratios) measures of ''complexity'' of the EEG signal (including fractal and scale-free dimension), and

features that relate to changes in the frequency spectra (including changes in alpha power activity). The formulations were tested on the algorithm development database in a five-fold cross validation framework to prevent over-fitting to the data.

BFI computation. The EEG BFI is computed as a linear combination of the selected subset of the QEEG feature *z*-scores. The linear combination includes additional weight assigned to values that are outside the age-expected normal range for that feature (to increase the relative contribution of the features with abnormal values to the index). The general formulation of the index (Y) for any EEG recording session may be expressed as follows:

$$Y = w_N \sum_{i=1}^{N_N} x_i + w_A \sum_{i=1}^{N_A} x_i$$

where, w_N is the weight associated with a feature value that is in the normal range for that feature, N_N is the number of features for the given EEG recording session that are in the normal range, x_i is the value of the ith feature, w_A is the weight associated with a feature value that is outside the normal range, and N_A is the number of features for the given EEG recording session that are outside the normal range. The normal range of values for any given feature was computed as the range for a theoretical normally distributed feature ($\mu = 0$, $\sigma = 1$) within which 80% of the values lie. This normality requirement translates to an *absolute* feature *z*-score value <1.2816 ($p < 0.10$). This range was computed on the large independent population of healthy volunteer subjects contained in the normative database. In summary, the computation yields a multivariate combination of those QEEG features (linear and non-linear) that were most related to the physiology of concussion (based on current consensus), weighted for each patient by their individual pattern of significant deviations (relative to normal) for this feature set.

To aid in interpretability, the BFI is expressed as a percentile relative to the distribution for this measure in the normal (healthy volunteer) population. In addition to the continuous raw score, three percentile categories are reported, including: (1) those greater than or equal to the 10th percentile (within the normal range), (2) those less than the 10th percentile (1.2816 SDs from the mean of the normal distribution) but greater than or equal to the 2.5th percentile, and (3) those less than the 2.5th percentile (approximately 2 SDs from the mean of the normal population).

Analysis of trial data. All EEG data processing was completed off-line to maintain data acquisition blind to the clinical presentation and to blind the classification results at the clinical site. It is important to note that because the BFI was finalized a priori, only those specific features used in the BFI computation are extracted from the independent validation population as part of the BFI calculations. It is also noted that the validation of the BFI was a secondary end-point of this prospective validation trial. Primary end-points findings were reported elsewhere.[21]

Statistical analysis

To statistically demonstrate the scaling of the BFI with increasing severity of impairment, a multinomial logistic regression[28] was computed for the BFI raw scores and the percentile-based categories (i.e., at or above the 10th percentile, between the 10th percentile and the 2.5th percentile, and below the 2.5th percentile) with a target alpha of 0.05.

In addition, to assist in illustrating group separation tested in the multinomial logistic regression analysis, a post hoc Kruskal-Wallis analysis of variance (ANOVA) was performed to determine if the mean BFI scores were different for groups of subjects classified by degree of functional impairment. This non-parametric test was selected because the assumption of normality for the parametric ANOVA was not met. Further post hoc analysis using the sensitivity index (d') is reported to quantify the separation between the groups.[29] Other exploratory analyses were also run to illustrate the scaling of the BFI with degree of impairment, using histograms (along with fitted normal distributions), and trends in the probability ratio of group membership.

Results

Characteristics of the validation study population

Seven hundred and twenty (720) closed head-injured subjects were enrolled in this study. For seven of these subjects, the categorical classification of functional severity could not be computed due to incomplete symptom information and they were therefore, dropped from further analysis. The remaining 713 subjects (60.9% male; 39.1% female) had a mean age of 43.6 years (SD, 18.7; median, 42.3; range 18–85.6) and a mean GCS score of 14.96 (SD, 0.23; median, 15; range, 12–15). In addition to the CT+ group ($n = 156$), the computation of the categorical classification resulted in two CT negative sub-populations: head-injured normal (patients who sustained a closed head injury but for whom the report of symptoms/severity indicated normal function, $n = 120$) and mTBI/concussed (mild functional impairment, $n = 267$ or moderate functional impairment, $n = 170$; total $n = 437$).

Multinomial logistic regression analysis

According to the method of Hosmer and Lemeshow,[28] in this study the odds ratios of the various groups computed against the head-injured normal group (reference group) were compared by testing the difference in the slopes of the multi-nomial logistic regression of the raw BFI scores, $\beta 1$ (mild with reference), $\beta 2$ (moderate with reference), and $\beta 3$ (severe [CT+] with reference). Alpha inflation was controlled by the Hochberg method.[30] The results of this multinomial logistic regression analysis appears in Table 1.

As can be seen in Table 1, the BFI score demonstrated statistically significant differences between odds ratios (computed against the head-injured normal group) of the mild functionally impaired group (CT–, with mild clinical symptomatology) and the CT+ structural TBI (visible on CT) group, $p = 0.0009$. It also demonstrated significant differences in the odds ratios between the moderate functionally impaired group (CT– with moderate clinical symptomatology) compared with that of the CT+ structural TBI group, $p = 0.0026$. A similar analysis with the percentile-based BFI categories (at or above the 10th percentile, between the 10th percentile and the 2.5th percentile, and below the 2.5th percentile) also demonstrated statistically significant differences between the odds ratios (computed against the head-injured normal group) for the same two comparisons ($p = 0.0017$ for mild CT– vs. CT+ TBI to reference and $p = 0.0011$ for moderate CT– vs. CT+ TBI). This result indicates that the order of the BFI (raw score and percentile categories) is correlated with the severity of the functional impairment. No significant differences in the odds ratios between mild functionally impaired group compared with that of the moderately functionally impaired group to the reference group ($p = 0.5120$). It is noted that the *p*-values

Table 1. Slope Comparisons from the Multinomial Regression of EEG Brain Function Index Scores

Comparison	*Difference*	*Variance*	*Z-statistic*	*P-value*
β_1 vs. β_3	–0.00192	$3.78\text{x}10^{-7}$	–3.1212	0.0009
β_1 vs. β_2	0.00002	$4.44\text{x}10^{-7}$	0.0300	0.5120
β_2 vs. β_3	–0.00194	$4.80\text{x}10^{-7}$	–2.8007	0.0026

β1 refers to the odds ratio comparing mild with reference, β2 refers to odds ratio comparing moderate with reference, and β3 refers to odds ratios comparing severe (CT+) with reference group.

CT, computed tomography; EEG, electroencephalographic.

noted correspond to differences in the long odds, which implies differences in the odds ratios.

Post hoc analysis

The supporting post hoc non-parametric Kruskal Wallis ANOVA demonstrated that the group means of the three groups (normal, mTBI/CT–, and CT+) were significantly different. The null hypothesis of equal group means was rejected ($p = 0.001$) showing a statistically significant relationship between BFI score and functional impairment severity. The means and standard errors for the three groups are shown in Table 2.

The sensitivity index (d') value for the separation of CT+ group from the head-injured normal group was computed to be 0.62, indicating a large degree of separation between the two groups. The d' for the separation between the mTBI/concussed and CT+ groups was computed to be 0.35, which indicates a moderate level of separation between the groups and supports the ability of the BFI to distinguish between the two groups. Within the mTBI/concussed group, the d' for the separation between mild and moderately functionally impaired groups was less than 0.1,which indicates a lack of separation between the two groups.

Relationship of BFI score and severity of impairment

Figure 1 illustrates the distributions of the BFI scores for the three groups using shifts in a normal distribution fitted to the group-wise BFI histograms. The fitted curves show that the group-wise BFI distributions shift to the right (increase in BFI) in response to increasing severity of brain injury.

Figure 2 illustrates the probability ratio analysis of group membership with increasing BFI severity, where the *x* axis shows the BFI score (binned to the nearest hundredths place) and the *y* axis shows the group membership odds ratios. The trend lines were obtained using a second order polynomial regression. The differences in the slopes of the trend lines for the three groups provide additional support that when the BFI score is greater than 450, a clear relationship can be seen with TBI severity. That is, as the BFI score increases (i.e., brain function becomes more abnormal), the probability of being normal decreases and the probability of being mTBI/concussed or CT+ increases. It is further noted that the rate of the increase for the mTBI/concussed group is lesser than that for the CT+ group.

Table 2. Group Means, Medians, and Standard Error for the Three Patient Groups (Normal, mTBI/CT-, and CT+)

		BFI score			*BFI percentile*		
Group	*N*	*Mean*	*Median*	*Std. Error*	*Mean*	*Median*	*Std. Error*
Normal	120	222.5	187.5	1.0	36.2	31	0.2
mTBI/CT-	437	247.1	213.1	0.3	32.3	24	0.1
CT+	156	299.4	247.0	1.2	27.1	16	0.2

BFI, Brain Function Index; CT, computed tomography; mTBI, mild traumatic brain injury.

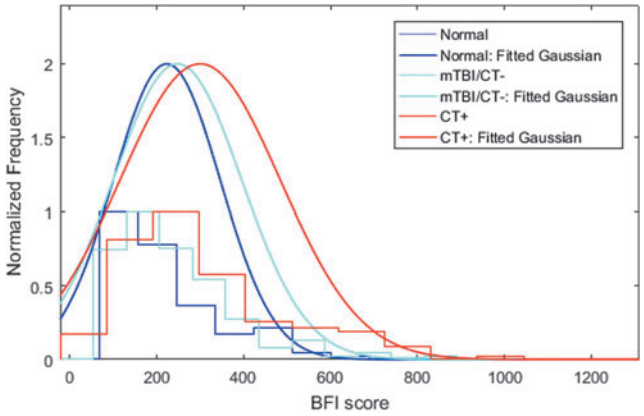

FIG. 1. Normal distributions fitted to Brain Function Index (BFI) score to illustrate the BFI increase in response to increasing severity of brain injury. Frequencies are normalized such that each histogram has a peak value of 1, and each fitted distribution has a peak value of 2. CT, computed tomography; mTBI, mild traumatic brain injury.

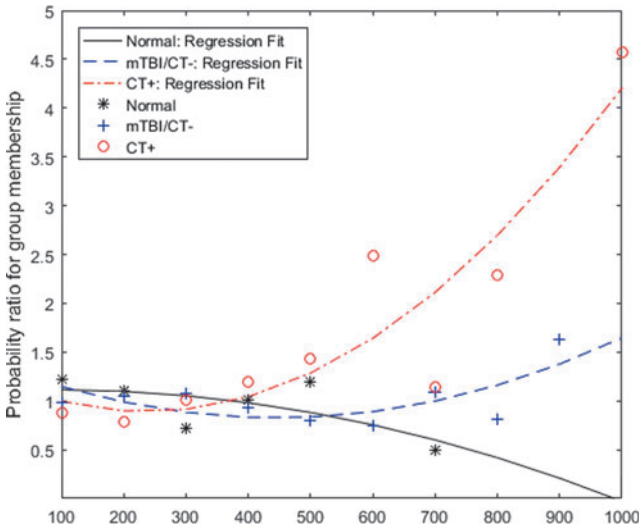

FIG. 2. Trends (regression using second order polynomial fit) in the probability ratios of group membership for the three subject groups (normal, mild traumatic brain injury [mTBI]/computed tomography [CT]–, and CT+). The Brain Function Index (BFI) scores were binned to the nearest hundreds place (e.g., any score between 350.00 and 449.99 was placed in a bin with the center at 400). The probability ratio was computed for any bin *i* as the ratio of the conditional probability of membership in group *j* given bin *i* to the prior probability of membership in group *j*.

Discussion

TBI injuries visible on CT scan represent only a portion of the full spectrum of TBIs. Although advanced neuroimaging tools have demonstrated clear abnormalities in mTBI/concussion, such technologies are not readily available in the ED where the CT scan remains the standard of care for assessing head injury. The importance of early identification of mTBI/concussion is a significant concern, as untreated concussions can contribute to morbidity with potentially debilitating and lingering post-concussive symptoms (including cognitive impairment, development of depression and anxiety, and somatization disorder).[31,32] Additionally, in athletes there is a higher incidence of repeat concussion following a first concussion and an increase chance for worse injury if an athlete is allowed to return to play prior to symptom resolution.[33,34] This head-injured normal validation study demonstrated as a secondary end-point, the potential clinical utility of the EEG BFI in providing important quantitative information about the status of brain function in mTBI relative to an uninjured normal population at the initial point of triage in the emergency setting.

The BFI is derived from advanced signal processing measures reflective of the physiological changes reported in functional neuroimaging studies of concussion. For example, changes in connectivity reported in TBI using DTI are consistent with phase synchrony abnormalities reported using QEEG.[14] Increasing evidence supports the use of EEG as a surrogate for conventional neuroimaging, both reflecting the impact of head injury of neuronal function in the presence of TBI and concussion. EEG has several advantages, which include the superior temporal resolution of EEG recordings as well as the ease of use and availability at the point of care.

In the absence of a ''gold standard'' for concussion, the BFI reports results as a percentile relative to a normal healthy volunteer population, creating a de facto standard aiding in the interpretability of the results. Further, because the use of percentiles is routine in the reporting of neurocognitive test results, the BFI percentile can be easily incorporated into a panel of assessment results that can aid the clinician in reaching the clinical diagnosis of concussion. This validation study demonstrates an inverse relationship between the severity of symptoms reported (evaluated taking into consideration both the number and severity of symptoms) and the percentile of the BFI. That is, as the severity increases, the percentile decreases, indicating increased likelihood of abnormal brain function. It is of interest to note that a post hoc analysis demonstrated that subjects who were classified as equivocal by the Ahead 300 classifier and had a higher BFI were more likely to be mTBI than normal.

It was also observed that the sensitivity index (d') value for the separation of CT+ patients from the head-injured normal controls was 0.62, implying a large separation. Although this is to be expected, a CT+ finding (any injury visible on CT in patients with GCS score = 13–15) does not necessarily mean that the patient is concussed. In addition, the sensitivity index for the separation between mTBI/concussed and CT+ patients was 0.35, which supports the ability of the BFI to distinguish between these two groups. Incidentally, the sensitivity index for the separation between mild and moderately functionally impaired patients is less than 0.1, indicating a lack of separation. It is important to note that currently, concussion diagnosis is a clinical determination relying on subjective report of signs and symptoms and there is no consensus on the predictive nature of these measures. The Ahead 300 device is cleared by the U.S. Food and Drug Administration (FDA) as an adjunctive tool and is not expected to be used in isolation, but rather as part of a clinical evaluation for the presence of concussion. As such, this quantitative, objective, multivariate measure can add information to the evaluation not otherwise available. In addition, the derivation of the measure adds specificity because the features included are those most related to the pathophysiology of concussion, especially ''connectivity.''

Limitations

This study was limited to an adult population. Further studies are underway to expand into the pediatric population where the objective assessment of mTBI and concussion is greatly needed. Additionally, clinical sites did not include urgent care or concussion facilities where such capabilities could be clinically important. The analyses in this validation study were conducted off-line. Future studies need to explore the implementation of the device into normal patient triage to allow evaluation of the impact of physicians using such data in real-time acute evaluation individual mTBI/concussed patients. The lack of significant separation between the patients with mild and moderate functional impairments suggests the need for further study and perhaps a multi-modal approach to improve this separation.

Conclusion

In this independent validation study, an index based on measures of brain electrical activity reflective of the physiology of concussion was demonstrated to provide a quantitative index of brain function impairment in mTBI. The BFI was further demonstrated to scale with severity of functional impairment in mTBI patients. These results suggest that the BFI directly addresses the need for an objective, readily available, assessment of brain function following head injury, aiding in rapid initial diagnosis and having the potential in the future to provide a quantitative marker for progression or resolution of mTBI/concussion.

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Author Disclosure Statement

Drs. Badjatia, Bazarian, Garrett, Huff, Jones, Naunheim, O'Neil, O'Neill, and Wright were principal investigators at participating clinical sites, and whose institutions received research contracts for data acquisition. Dr. Hanley led the Brain Injury Outcomes (BIOS) Division of Johns Hopkins, the independent CRO for the trial. Dr. Prichep is the Chief Scientific Officer of BrainScope Co., and a Professor at NYU School of Medicine. Dr. Prichep holds potential financial interest through patented technology licensed by BrainScope Co. from the NYU School of Medicine. Dr. Curley is a

consultant to BrainScope Co., who at the time the study was conducted was the Neurotrauma Research Portfolio Manager for the Combat Casualty Care Research Program and Defense Health Program at the U.S. Army Medical Research and Materiel Command. Dr. Chiacchierini served as the independent consulting biostatistician to BrainScope Co. for this study.

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Address correspondence to:
Leslie S. Prichep, PhD
Department of Psychiatry
NYU School of Medicine
1115 Broadway, Room 1082
New York, NY 10010

E-mail: leslie.prichep@nyumc.org