Quantitative EEG Biomarkers for Mild Traumatic Brain Injury

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Purpose: The development of objective biomarkers for mild traumatic brain injury (mTBI) in the chronic period is an important clinical and research goal. Head trauma is known to affect the mechanisms that support the electrophysiological processing of information within and between brain regions, so methods like quantitative EEG may provide viable indices of brain dysfunction associated with even mTBI.

Methods: Resting-state, eyes-closed EEG data were obtained from 71 individuals with military-related mTBI and 82 normal comparison subjects without traumatic brain injury. All mTBI subjects were in the chronic period of injury (>5 months since the time of injury). Quantitative metrics included absolute and relative power in delta, theta, alpha, beta, high beta, and gamma bands, plus a measure of interhemispheric coherence in each band. Data were analyzed using univariate and multivariate methods, the latter coupled to machine learning strategies.

Results: Analyses revealed significant ($P < 0.05$) group level differences in global relative theta power (increased for mTBI patients), global relative alpha power (decreased for mTBI patients), and global beta-band interhemispheric coherence (decreased for mTBI patients). Single variables were limited in their ability to predict group membership (e.g., mTBI vs. control) for individual subjects, each with a predictive accuracy that was below 60%. In contrast, the combination of a multivariate approach with machine learning methods yielded a composite metric that provided an overall predictive accuracy of 75% for correct classification of individual subjects as coming from control versus mTBI groups.

Conclusions: This study indicates that quantitative EEG methods may be useful in the identification, classification, and tracking of individual subjects with mTBI.

Key Words: mTBI, EEG, Absolute power, Relative power, Interhemispheric coherence.

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The incidence of head trauma is approximately 370 per 100,000, with more than 2.5 million people sustaining a head injury each year in the United States alone.[1] Mild traumatic brain injury (mTBI) is of special concern in both civilian and military populations, accounting for almost 80% of all traumatic brain injuries (TBIs). Immediately after mild head trauma, many victims complain of headache, cognitive problems, irritability, and mood disruption, but in most cases, these symptoms subside within a few weeks. However, even when there is no loss of consciousness, 10% to 30% of individuals who suffer minor head trauma still report postconcussive problems several years after the incident.[2–6]

Because routine clinical structural imaging by computed tomography or MRI generally fails to reveal any persistent abnormalities in the victims of mild head trauma,[7,8] the neurobiological basis for persistent postconcussive symptoms in this population is often uncertain,[9,10] with some even questioning the existence of persistent brain damage for these patients.[11] However, advanced imaging and electrophysiological studies using methods like quantitative MRI,[12,13] diffusion tensor imaging,[14,15] functional MRI,[16,17] magnetic resonance spectroscopy,[18,19] single photon computed emission tomography,[20–22] positron emission tomography,[23,24] EEG,[25–27] and magnetoencephalography (MEG),[28–31] all provide group-level evidence of significant neurobiological differences between patients with persistent postconcussive symptoms and normal comparison subjects.

The initial physical forces of trauma can directly cause axonal injury and cell death. They may also set into motion a secondary injury cascade that causes additional damage over the minutes, hours, days, and even months postinjury. Given this, the best diagnostic tests, key biomarkers, and treatment strategies during acute, subacute, and chronic postinjury periods may differ. Animal and human studies indicate that both the primary and the secondary injuries caused by head trauma often affect the mechanisms that support the generation, transmission, and processing of electrophysiological signals within and between

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brain regions.[32–34] Noninvasive electrophysiological methods like EEG and MEG thereby hold high promise for the evaluation of mTBI. Available data suggest that MEG has high individual subject sensitivity to mTBI,[28,30] but the high cost, sophistication, and sparse availability of MEG equipment limits the use of MEG as a general strategy for routine clinical evaluation of mTBI patients. In contrast, EEG technology is inexpensive, easy to use, and portable. However, the sensitivity of routine clinical EEG to mTBI is generally reported to be relatively low. When TBI is moderate or severe, clinical EEG may show epileptiform activity, focal slowing, or generalized slowing, especially during the acute period, but such abnormalities are rare following mTBI, with most studies finding only 10% to 20% of symptomatic participants to show EEG slowing during the chronic period, at least for civilian populations.[35,36]

However, we recently reported clinical EEG abnormalities (focal and/or generalized slowing) for 28 of 71 individuals with chronic postconcussive symptoms following military-related mTBI (~40%).[37] The data were obtained preintervention from participants in the DoD-sponsored BIMA clinical trial—*Brain Injury Mechanisms of Action of Hyperbaric Oxygen for Persistent Post-concussive Symptoms After mTBI*.[38] Admittedly, when present, the observed slowing was typically quite mild, but in each case, it was identified independently by at least two of three reviewing EEG clinicians. Also, when EEG data from control, neurotypical comparison participants were blindly evaluated by the same clinicians using identical procedures and criteria, only 7% showed abnormalities. These control datasets were drawn from a companion study to BIMA–NORMAL: *Development of Normative Datasets for Assessments Planed for Use in Patients with Mild Traumatic Brain Injury*; $N = 82$.

To better understand the potential utility of EEG in the evaluation of military-related mTBI, we subsequently performed a series of additional quantitative EEG (qEEG) evaluations on these BIMA and NORMAL datasets. Quantitative EEG methods have several potential advantages over more typical clinical evaluation. First, methods are completely objective, with computer-generated results. Data undergo a series of mathematical analyses with derived parameters evaluated statistically with respect to a normative database. Quantitative methods also allow for exploration of the statistical relationships between signals at each electrode, with metrics like coherence indexing functional connectivity between brain regions. Finally, quantitative methods are more readily amenable to multivariate analyses and the development of discriminant functions that have the potential to classify each participant's clinical status.

METHODS

Participants

The main study population consisted of 71 active duty or veteran military personnel who had participated in the BIMA study. Participants were evaluated using the Ohio State Traumatic Brain Injury Identification Method. Entry criteria included a history of at least one mTBI caused by a nonpenetrating trauma or blast exposure, with persistent cognitive, somatic, and/or psychiatric symptoms. Mild traumatic brain injury was defined by a period of altered consciousness of no more than 30 minutes. Participants were eligible for study even with a history of multiple mild traumatic events. In all cases, it was required that the most recent event occurred while on active duty. The time of injury was required to be more than 3 months, but less than 5 years prior to testing (the actual data range for the presented data was 5–60 months). Participants were excluded if they had any premorbid axis-I Diagnostic and Statistical Manual diagnoses, premorbid neurological dysfunction, premorbid learning or developmental abnormalities, or evidence of memory loss for more than 24 hours surrounding the incident event. Current post-traumatic stress disorder (PTSD), depression, and/or anxiety were not exclusionary.

This report focuses on qEEG data collected at the BIMA baseline visit, prior to any intervention with hyperbaric oxygen. Data were also obtained from 82 control participants enrolled in NORMAL, a companion study to BIMA. Each participant self-reported that he/she was neurotypical and without history of head trauma, neurological, psychiatric, or cognitive compromise. All participants in NORMAL reported that they were not taking any prescription medications.

Participants in both the BIMA and the NORMAL studies completed a wide range of evaluations, including questionnaires (medical history, PTSD symptoms, etc.); structural and functional brain imaging (structural MRI, diffusion tensor imaging, functional MRI, computed tomography angiography); and cognitive, sensory, and motor assessments. Primary results of these evaluations are being reported elsewhere, although some data on correlation of qEEG findings with observations from some of these tests are briefly reported herein.

EEG Data Collection

EEG was collected using a Cadwell Easy III digital EEG recording system (Cadwell, Kennewick, WA). Electrodes were applied individually according to the International 10/20 System of Placement, with supplementary electrodes at T1 and T2. All electrode impedances were maintained below 5,000Ω. EEG data were collected in an A1 referential montage with a bandwidth of 1 to 70 Hz and a digitization rate of 300 Hz. electro-cardiogram and electro-oculargram data were also collected. The night before study, participants were instructed to go to sleep at their normal time and to wake the next morning as usual. On the day of evaluation, participants were asked to refrain from consuming coffee or tobacco for at least 30 minutes prior to evaluation.

Each EEG recording session was approximately 30 minutes long. Data were collected during several activities, including periods of (1) resting with eyes closed, (2) resting with eyes open, (3) reading, (4) performing math problems, (5) hyperventalization, and (6) watching photic stimulation. All analyses reported herein focus exclusively on the 5 to 7 minutes of resting-state, eyes closed data that were obtained from each subject.

EEG Data Analysis

Data were analyzed using the NeuroGuide software suite (Applied Neuroscience Inc, Largo, FL). An automated algorithm was used to identify data segments without evidence of drowsiness, and free of eye blink, eye movement, and cardiac

artifacts. Additional visual inspection was applied to ensure that data segments contaminated by artifacts were not processed. Acceptable data segments were concatenated and then subdivided into 2-second-long epochs. A Fast Fourier transform autospectral and cross-spectral analysis was then performed using a 75% sliding window method.

Data from the BIMA mTBI group and the NORMAL control group were compared against each other using a series of one-way analysis of variance models. Analyses focused on absolute and relative power in six spectral bands—delta (1.0–3.5 Hz), theta (4.0–7.5 Hz), alpha (8–12 Hz), beta (12.5–25 Hz), high beta (25.5–30 Hz), and gamma (30–50 Hz), at each electrode—and measures of functional connectivity as indexed by interelectrode coherence, amplitude asymmetry, and phase lag.[26,39,40] Absolute power data were log-transformed prior to analyses to provide a Gaussian distribution.

A known limitation of this initial analysis plan was involvement of a high number of multiple comparisons ($n >$ 1,000). So, to avoid spurious results, an additional Benjamini–Hochberg correction (with a false discovery rate of 25%) was applied to make sure that any individual observations identified as significant were not likely due to chance. In addition, we performed a separate, more directed analysis with a reduced number of global metrics ($n = 18$). Specifically, we evaluated global absolute and regional power (as calculated in each frequency band by averaging across all electrodes), and a global measure of interhemispheric coherence, derived by averaging coherence values across homotopic interhemispheric derivations (i.e., Fp1-Fp2, F7-F8, F3-F4, T3-T4, C3-C4, T5-T6, P3-P4, O1-O2). A Benjamini–Hochberg correction was still applied in all statistical evaluations.

In addition to this univariate approach, machine learning strategies were used to develop a multimodal classifier intended to provide for better prediction of group membership (BIMA vs. NORMAL) at the individual participant level. Briefly, from each participant, spectral data (absolute power and relative power at each electrode [referenced to A1]), coherence measures, amplitude asymmetry, and phase lag measures, along with global spectral measures and interhemispheric coherence were provide for evaluation, with a forward–backward elimination procedure from a logistic regression used for feature selection. Several different machine learning strategies were evaluated. Employed strategies included logistic regression, multilayer perceptron, support vector machine, random forest, naive Bayes, nearest neighbor, and decision tree approaches.[41] Receiver operating characteristics were derived using a 5-fold cross-validation strategy.

RESULTS

The mean age for the 71 BIMA participants was 33 years (range: 21–53 years). Thirty-five of these participants showed evidence of comorbid post-traumatic stress disorder (PTSD) based on a structured clinical interview. Most BIMA participants were taking prescription medications—narcotics (14%), antidepressants (55%), anti-epileptics (11%), anti-migraine (42%), or stimulants (4%). NORMAL participants were on average older than BIMA participants, with a mean age of 39 years (range: 18–65 years). None were taking psychoactive prescription medications.

Reasonably good quality EEG data were acquired from all subjects. The total number of clean, artifact-free, 2-second-long, eyes-closed epochs varied from 46 to 183 across subjects. There were no significant differences in the average number of clean epochs for NORMAL versus BIMA participants (with or without PTSD), $P = 0.27$.

We have previously reported that 28 of 71 BIMA mTBI participants showed evidence of either focal or more commonly, generalized slowing.[37] When evaluated with respect to the 600+ subject NeuroGuide normative database (Applied Neuroscience), quantitative analyses revealed significantly increased ($P <$ 0.025) absolute, or more commonly relative, delta or theta power for at least one electrode location in 20 of these cases. Eight BIMA participants with mild generalized slowing on clinical evaluation were within normal limits on the qEEG evaluation. There were five BIMA participants who showed significant slowing on qEEG, but for whom the clinical EEG was interpreted to be within normal limits. Clinical slowing was seen for only 7% of participants in the NORMAL study, whereas qEEG analyses indicated slowing for 11% of these participants. Figure 1 illustrates the relationship between clinical EEG and qEEG findings for BIMA and NORMAL study participants.

However, following the Benjamini–Hochberg (false discovery rate = 25%) correction for multiple comparisons, none of

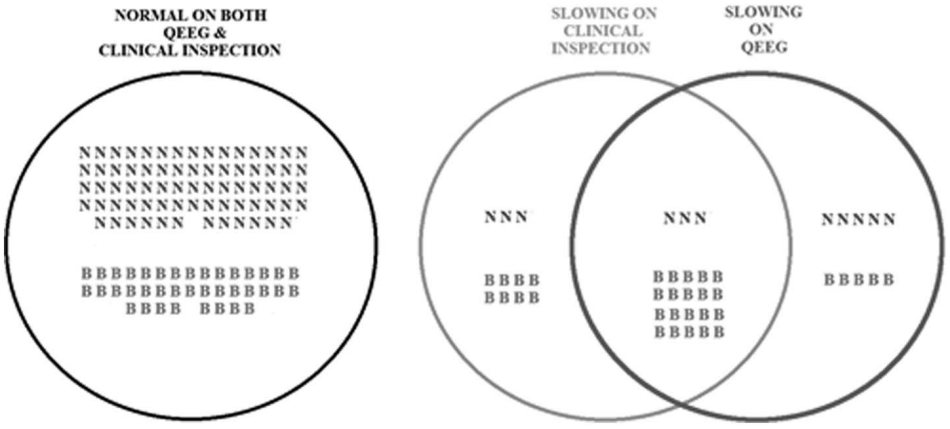

FIG. 1. The EEG of individual NORMAL (N) and BIMA (B) participants was evaluated for slowing by both visual clinical inspection and qEEG. Data were classified as being within normal limits or showing slowing in the delta and/or theta range. qEEG, quantitative EEG.

the individual electrode-by-electrode spectral comparisons between BIMA and NORMAL participants showed no significant differences, although there was a trend for electrodes F3, F7, Fp1, Fpz, and F4 to show increased relative theta power in the BIMA group (each individual electrode at $0.1 > P > 0.05$). Evaluation of the global spectral measures which integrate information across electrodes, proved somewhat more fruitful. On the one hand, as described in Table 1, analyses of absolute global spectral power in delta, theta, alpha, beta, high beta, and gamma frequency bands still failed to reveal any significant differences between BIMA and NORMAL participants. However, mTBI participants as a group showed significantly increased relative theta activity ($P = 0.01$) and significantly decreased relative alpha activity ($P = 0.043$) when compared with the NORMAL control group. These observations remained significant even after correction for multiple comparisons. The BIMA participants also showed significantly reduced global interhemispheric coherence in the beta band when compared to NORMAL control participants ($P = 0.048$).

TABLE 1. Quantitative EEG for mTBI (BIMA, $n = 71$) Versus Controls (NORMAL, $n = 82$)

	NORMAL	BIMA	F(1,152)	*P*
Absolute power				
Delta	8.7	9.8	2.98	0.086
Theta	8.3	10.0	0.52	0.471
Alpha	24.4	20.5	1.03	0.312
Beta	8.0	7.8	0.46	0.501
High beta	1.0	1.6	2.39	0.125
Gamma	5.5	5.3	0.03	0.868
	NORMAL	**BIMA**	**F(1,152)**	***P***
Relative power				
Delta	0.16	0.18	2.71	0.102
Theta	**0.14**	**0.18**	**6.84**	**0.010†**
Alpha	*0.44*	*0.38*	*4.16*	*0.043**
Beta	0.14	0.14	0.65	0.454
High beta	0.02	0.03	1.67	0.198
Gamma	0.10	0.09	0.33	0.567
	NORMAL	**BIMA**	**F(1,152)**	***P***
Interhemispheric coherence				
Delta	0.62	0.63	0.66	0.417
Theta	0.53	0.51	1.23	0.269
Alpha	0.56	0.51	1.41	0.236
Beta	*0.50*	*0.44*	*3.98*	*0.048**
High beta	0.47	0.42	3.71	0.055
Gamma	0.46	0.45	0.51	0.482

Top panel—Average absolute power values in various frequency bands for NORMAL and BIMA participants. Power values are in $\mu V^2/Hz$. F-test statistics and *P*-values are also provided. Note that statistical tests were performed on log-transformed power values to provide a Gaussian distribution. Middle panel—Average relative power values in various frequency bands for NORMAL and BIMA participants. Values show what proportion of the total power is accounted for by the frequency band in question. Lower panel—Average interhemispheric coherence values in various frequency bands for NORMAL and BIMA participants. The three individual significant observations each survive Benjamini–Hochberg correction for multiple comparisons with a false discovery rate of 0.25.

Bold values indicate that BIMA is significantly lower than NORMAL.

Italic values indicate that BIMA is significantly higher than NORMAL.

*$P < 0.05$.

†$P < 0.01$.

mTBI, mild traumatic brain injury.

Although there were clear univariate group differences between the BIMA and NORMAL participants when evaluating global spectral measures, it is important to note that the accuracy of the single measures (i.e., relative theta, relative alpha, and beta-band interhemispheric coherence) for distinguishing BIMA mTBI versus NORMAL control participants at the individual subject level was below 60% for each measure. For example, Fig. 2A, shows the 95% confidence interval for mean relative theta power for NORMAL and BIMA participants. The group difference is significant, at $P = 0.01$. However, as shown in Fig. 2B, there is extensive overlap in the relative theta values for individual NORMAL and BIMA participants. Based on evaluation of the receiver operating characteristics of the relative theta power dataset, the most accurate overall classification of individual participants as having mTBI or not was achieved at a relative theta threshold of 0.20, with participants having values exceeding this predicted to have had a mTBI and come from the BIMA group. Unfortunately, even this optimized strategy provides an accuracy of only 58% in the classification of individual participants.

As described in Table 2, additional analyses were performed to determine if qEEG measures were correlated to other clinical variables. After taking into account group (BIMA vs. NORMAL) membership, and correcting for multiple comparisons, no significant relationships were seen between qEEG measures and scores on the Neurobehavioral Symptom Inventory, the Automated Neuropsychological Assessment Metric, or the number of white matter lesions seen on MRI. Across all subjects, and within the BIMA and NORMAL groups in isolation, a statistically significant, albeit weak, linear correlation was seen between global interhemispheric coherence in the beta band and diffusion tensor imaging–based measures of fractional anisotropy (FA) for the corpus callosum [$F(1,152) = 5.45$ for the whole group, $P = 0.021$, $R = 0.318$, $R^2 = 0.101$]. Lower coherence was associated with lower FA, as illustrated in Fig. 3A. Note that this was a planned comparison using global interhemispheric coherence measures in each frequency band. The beta band result survives Benjamini–Hochberg correction for the six planned multiple tests.

Within the BIMA group, there were no significant relationships between and qEEG measures and time since injury, although there was a trend for global relative theta power to be slightly higher in BIMA mTBI subjects evaluated closer to their time since injury. No qEEG measure from individual electrodes showed a correlation with PTSD status. However, a significant relationship was seen between global absolute high beta activity and a diagnosis of current PTSD (based on a structured clinical interview), with higher values for the PTSD group [$F(1,70) = 4.81$; $P = 0.032$]. Note that this was a planned comparison based on prior studies, so there were not multiple comparisons. Figure 3B shows relevant values for all study groups.

As expected, a multivariate approach coupled with machine learning provided improved discrimination between BIMA and NORMAL participants at the individual level. A logistic regression strategy proved most effective, yielding a composite metric that showed a difference between NORMAL and BIMA participants

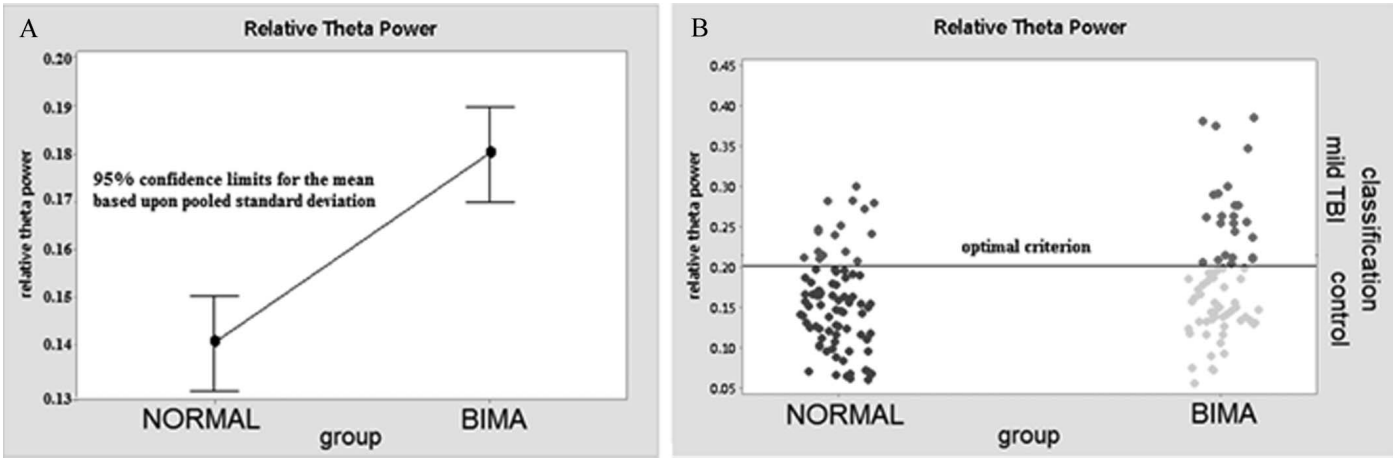

FIG. 2. **A**, Mean and 95% confidence interval for the mean for relative theta activity averaged across all electrodes. The NORMAL versus BIMA difference is highly significant at $P < 0.01$, F(1,152) = 6.84. **B**, Average relative theta power for individual NORMAL and BIMA participants. Each point represents an individual participant. Best overall accuracy in classification of participants as being from mTBI versus control groups is achieved with a relative theta power value of >0.20. Unfortunately, this best classification is only 58% accurate. Red indicates hits—BIMA participants classified as having an mTBI. Blue indicates correct rejections—NORMAL participants classified as a control without mTBI. Green indicates a miss—a BIMA participant incorrectly classified as a control. Purple indicates false positives—NORMAL participants classified as having mTBI. mTBI, mild traumatic brain injury; TBI, traumatic brain injury.

with $P < 0.00001$, and accuracy for the classification of individual participants at 75% (Fig. 4). The composite metric was based on five variables—global relative alpha power, global relative theta power, global high beta absolute power, interhemispheric coherence in the beta band, and global phase shift magnitude in beta. The other machine learning algorithms generally locked onto to similar features (relative alpha and theta power and beta interhemispheric coherence were each present in all but two models), but they yielded less accurate classifiers: multilayer perceptron—71%; support vector machine—67%; random forest—62%; naive Bayes—59%; nearest neighbor—59%; and decision tree—55%.

DISCUSSION

Quantitative analyses of resting-state EEG measures hold promise as a biomarker of chronic neurobiological disruption caused by mTBI. Consistent with clinical observations on the present data sets[37] and the published work of others,[42] several participants with postconcussive symptoms show a clear slowing of background activity with an increase in global relative theta power and a decrease in global relative alpha power. In addition, there was a TBI-related reduction in global interhemispheric coherence, with beta coherence values correlating with callosal

TABLE 2. Relationships Between qEEG Variables and Other Measures

Measure	Observation
Neurobehavioral symptom inventory—total score	There were no significant relationships ($P > 0.1$) between any qEEG variables and Neurobehavioral Symptom Inventory scores after taking group membership into account and correcting for multiple comparisons.
ANAM	There were no significant relationships ($P > 0.1$) between any qEEG variables and ANAM scores after taking group membership into account and correcting for multiple comparisons.
No. of white matter lesions on MRI (FLAIR/T2 sequences)	There were no significant relationships ($P > 0.1$) between any qEEG variables and lesion counts after taking group membership into account and correcting for multiple comparisons.
Callosal FA	Global interhemispheric beta-band coherence showed a statistically significant, albeit weak correlation with callosal FA [F(1,152) = 5.45 for the whole group, $P = 0.021$, R = 0.318, $R^2 = 0.101$]. This was true for the overall dataset, and the BIMA and NORMAL subgroups, with similar relationships seen in each subgroup.
Time since injury	Within the BIMA group, there were no significant relationships ($P > 0.1$) between any EEG measures and time since injury, although there was a trend for increased global relative theta to be more prominent in subjects evaluated closer to the injury time point [F(1,70) = 3.18, $P = 0.077$, $R^2 = 3.8\%$].
PTSD	There was significantly increased global absolute high beta power in BIMA participants with PTSD relative to BIMA subjects without PTSD [F(1,70) = 4.81, $P = 0.032$].

ANAM, Automated Neuropsychological Assessment Metric; FA, fractional anisotropy; FLAIR, Fluid Attenuation Inversion Recovery; PTSD, post-traumatic stress disorder; qEEG, quantitative EEG.

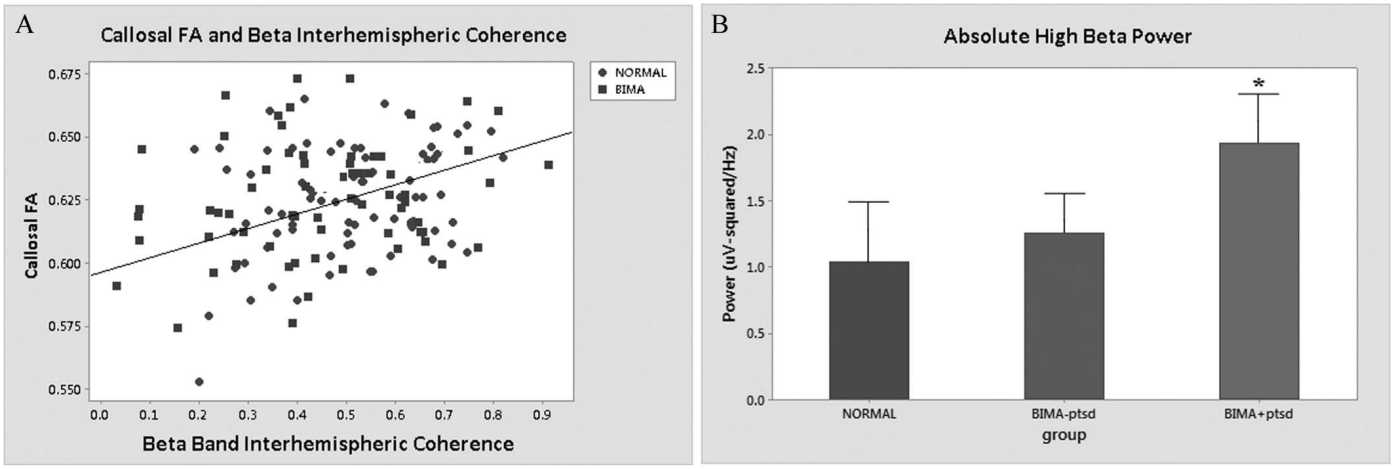

FIG. 3. **A**, Values for beta band interhemispheric coherence are significantly correlated with callosal fractional anisotropy for the entire study population [$F(1,152) = 5.45$, $P = 0.021$, $R = 0.318$, $R^2 = 0.101$]. Differences were not seen between subjects from the BIMA versus NORMAL study groups. **B**, Absolute high beta power for NORMAL, BIMA-PTSD, and BIMA + PTSD subjects. Absolute high beta power was significantly higher for BIMA subjects with versus without PTSD [$F(1,70) = 4.61$, $P = 0.035$]. FA, fractional anisotropy; PTSD, post-traumatic stress disorder. * indicates that observation for the tbi+ptsd group is significantly different from the observation in the other two groups at $P < 0.05$.

FA values for both BIMA and NORMAL groups. This association between beta-band coherence and measures of callosal integrity has been seen in several different clinical populations (e.g., multiple sclerosis, Alzheimer disease[43,44]).

However, although there were several global EEG variables that showed statistically significant differences across BIMA and NORMAL groups, none were particularly useful at the individual subject level. Unfortunately, this has been a common theme in the search for biomarkers of mTBI, especially during the chronic period. Group level differences are significant, but there is extensive overlap in control and mTBI distributions, often making it impossible to tell, based on a single variable, if a particular patient has persistent brain damage. Nevertheless, the observation that single measures (like the current qEEG measure, diffusion tensor imaging measures, or volumetric measures) are often poor predictors of mTBI at the individual subject level does not mean that such measures are useless. Consider, for example, the relative theta values in Fig. 2B. If an individual patient had a value of 0.15, it would be difficult, on the basis of this measure alone, to determine if the patient had a persistent mTBI. However, if the value were 0.33, it would be more likely than not that the patient was from a mTBI group, and this could be stated with some degree of confidence, as no control subjects demonstrate a value this high. This is not to suggest that EEG data alone are sufficient to make a diagnosis of mTBI, but EEG data can be supportive of a diagnosis based on an individual patient's integrated medical history that includes clinical, neurobehavioral, cognitive, imaging, and physiological profiles.

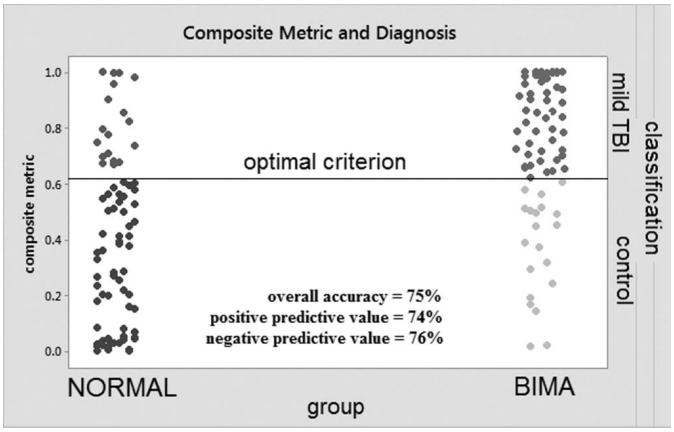

FIG. 4. Multivariate classification of individual participants. Each point represents an individual participant. Best accuracy was achieved when the classifier composite metric was 0.62. Briefly, the composite metric is an indicator of whether a participant is predicted to have an mTBI. The optimal criterion maximizes overall accuracy of classification, in this case, 75%. Red indicates hits—BIMA participants classified as having an mTBI. Blue indicates correct rejections—NORMAL participants classified as controls without mTBI. Green indicates a miss—a BIMA participant classified as a control. Purple indicates false positives—NORMAL participants classified as having mTBI. mTBI, mild traumatic brain injury, TBI, traumatic brain injury.

The lack of statistical differences between BIMA and NORMAL subjects in spectral measures at individual electrodes most likely reflects the heterogeneous nature of head trauma, with different brain regions implicated in different subjects. For example, some mTBI subject showed increased relative theta over the left frontal lobe, whereas others showed such a theta increase only over the right parietal lobe. Nevertheless, by examining a spatially global measure across all electrodes, it became clear that BIMA subjects showed more relative theta power overall than NORMAL subjects.

Using a multivariate approach combined with machine learning strategies, the predictive accuracy of qEEG for distinguishing subjects with versus without a mTBI history was improved from less than 60% (for univariate measures) to

75%. Positive and negative predictive values for the composite metric were also approximately 75%. This level of predictive power is approaching what might be clinically useful in routine practice with individual patients, although a value of above 85% is desirable. To address this, analyses are underway to determine if a multimodality approach—that is, adding information from other tests (e.g., MRI, eye-tracking) to the qEEG composite metric—might further improve predictive accuracy.

Recently, there has been significant effort by the Department of Defense and industry to use qEEG in the acute period to identify the presence of TBI and the need for radiographic evaluation with computed tomography.[27] Data from those efforts clearly demonstrate disruption of frontal qEEG profiles in patients with TBI and computed tomography positive evaluations. The current observations that a qEEG composite metric can be of utility in identifying patients with persistent mTBI in the chronic phase of injury extends these observations and has implications for rehabilitation clinical trials.

It is also noteworthy that qEEG revealed differences between mTBI participants with versus without comorbid post-traumatic stress disorder (PTSD), in the form of increased high beta activity. Increased beta activity has been reported in other qEEG and MEG studies of PTSD.[45–47] Also, in a completely independent study, members of our team have reported increased high beta activity in PTSD that was seen to normalize following clinically effective cognitive–behavioral treatment (Lewine et al. A pilot study of quantitative EEG markers of post-traumatic stress disorder: Baseline observations and the impact of the reconsolidation of traumatic memories treatment protocol, submitted to *Biological Psychiatry*, 2018).

When considering the initial clinical reads of the EEG data,[37] there were paradoxical negative correlations between EEG abnormalities and MRI and clinical findings. These unexpected relationships were not seen for qEEG metrics—a result more consistent with *a priori* expectations.

A primary goal of the overall BIMA study was to evaluate the potential impact of treatment with hyperbaric oxygen on clinical and neurobiological variables. These treatment data are undergoing analyses, with key results to be reported elsewhere. However, with respect to treatment-related changes in qEEG variables, findings were minimal. There were a handful of scattered changes in qEEG variables from baseline to posttreatment sessions, but no qEEG findings were found to be significant following correction for multiple comparisons.

The present study has two key limitations. First, essentially all of the mTBI participants, but none of the control participants, were taking some form of psychoactive medications. Acutely, some of these medications are known to alter the EEG. However, secondary analyses of the current data, with the type of medication entered as a covariable, did not provide evidence of consistent medication effects that could account for the ability of qEEG to distinguish mTBI and control groups. Medication differences also failed to account for high beta activity differences between mTBI subjects with versus without PTSD. A second limitation is the lack of an independent test sample. Five-fold cross-validation methods were additionally used to evaluate the classifier, with a resultant accuracy of 78%, but it is not uncommon for these methods to slightly overestimate classification accuracy when a new independent sample is evaluated. Nevertheless, it seems likely that the present classifier will be able to perform in the 70% to 75% correct range.

In considering these data, it is important to note that all of our subjects were evaluated at 5+ months since injury—time points that are already beyond the acute and subacute phases. Traumatic brain injury is a dynamic process, and qEEG profiles at time points closer to the injury may be quite different from what was observed here during the chronic period.

Overall, the current data are encouraging that qEEG can play a substantive role in the evaluation and tracking of persistent brain dysfunction induced by head trauma. Future efforts will focus on further identification of specific clinical correlates of altered EEG and the evaluation of additional independent patient samples to cross-validate multivariate classifiers.

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