



Traumatic brain injury detection using electrophysiological methods

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Measuring neuronal activity with electrophysiological methods may be useful in detecting neurological dysfunctions, such as mild traumatic brain injury (mTBI). This approach may be particularly valuable for rapid detection in at-risk populations including military service members and athletes. Electrophysiological methods, such as quantitative electroencephalography (qEEG) and recording event-related potentials (ERPs) may be promising; however, the field is nascent and significant controversy exists on the efficacy and accuracy of the approaches as diagnostic tools. For example, the specific measures derived from an electroencephalogram (EEG) that are most suitable as markers of dysfunction have not been clearly established. A study was conducted to summarize and evaluate the statistical rigor of evidence on the overall utility of qEEG as an mTBI detection tool. The analysis evaluated qEEG measures/parameters that may be most suitable as fieldable diagnostic tools, identified other types of EEG measures and analysis methods of promise, recommended specific measures and analysis methods for further development as mTBI detection tools, identified research gaps in the field, and recommended future research and development thrust areas. The qEEG study group formed the following conclusions: (1) Individual qEEG measures provide limited diagnostic utility for mTBI. However, many measures can be important features of qEEG discriminant functions, which do show significant promise as mTBI detection tools. (2) ERPs offer utility in mTBI detection. In fact, evidence indicates that ERPs can identify abnormalities in cases where EEGs alone are non-disclosing. (3) The standard mathematical procedures used in the characterization of mTBI EEGs should be expanded to incorporate newer methods of analysis including non-linear dynamical analysis, complexity measures, analysis of causal interactions, graph theory, and information dynamics. (4) Reports of high specificity in qEEG evaluations of TBI must be interpreted with care. High specificities have been reported in carefully constructed clinical studies in which healthy controls were compared against a carefully selected TBI population. The published literature indicates, however, that similar abnormalities in qEEG measures are observed in other neuropsychiatric disorders. While it may be possible to distinguish a clinical patient from a healthy control participant with this technology, these measures are unlikely to discriminate between, for example, major depressive disorder, bipolar disorder, or TBI. The specificities observed in these clinical studies may well be lost in real world clinical practice. (5) The absence of specificity does not preclude clinical utility. The possibility of use as a longitudinal measure of treatment response remains. However, efficacy as a longitudinal clinical measure does require acceptable test–retest reliability. To date, very few test–retest reliability studies have been published with qEEG data obtained from TBI patients or from healthy controls. This is a particular concern because high variability is a known characteristic of the injured central nervous system.

Keywords: event-related potentials, EEG, traumatic brain injury, qEEG, non-linear dynamical analysis

INTRODUCTION

Mild TBI is caused by initial physical trauma that shears or compresses brain tissue. The initial trauma can lead to a cascade of delayed neurodegenerative events that may include diffuse axonal injury, activation of excitotoxic inflammatory cascades, and transneuronal degeneration. While initial damage in mild traumatic brain injury (mTBI) may be minimal or occult, the chronic neurodegenerative effects can persist for weeks or months post-injury and lead to significant cognitive, sensory, and psychiatric dysfunctions (DeKosky et al., 2010). Over 75% of the 266,000 brain injuries reported during U.S. military operations from 2000 to 2012 were classified as mTBI, thus underscoring mTBI as a major health issue in the U.S. military (Hoge et al., 2008). It is anticipated that rapid and accurate mTBI detection would improve prognoses and minimize impacts to military operations; however, a technological gap exists, especially in field-based settings. To address this critical need, the Department of Defense is actively seeking new technologies capable of rapid, accurate, non-invasive, and field-capable detection of mTBI (Rigg and Mooney, 2011).

One promising avenue is measurement of brain electrical activity with quantitative electroencephalography (qEEG), in which detection of altered patterning may indicate concussion. Since qEEG is a nascent technology for mTBI detection, and significant controversy exists in the field, a comprehensive evaluation of technology/measure efficacy as a detection tool is warranted. Critically surveying the state-of-the-science also provides an opportunity to establish recommendations on specific qEEG measures or signal processing technologies of promise, thus driving advanced development decision-making.

BACKGROUND ON qEEG

The electroencephalogram (EEG) records the electrical potential difference between brain electrical activities recorded between two electrodes (a single EEG channel). Multiple scalp electrodes (generally >20) are connected in various patterns called montages, resulting in a series of channels of EEG activity. Often the scalp electrodes are compared to one or more neutral reference electrodes. Detection of a scalp electrical potential requires the synchronous activity of millions of neurons over at least 10 cm² of cortex. The EEG detects the synchronous occurrence of dendritic synaptic potentials (excitatory and inhibitory post-synaptic potentials) principally on the apical dendrites of cortical pyramidal neurons. Therefore, the EEG records the average membrane potential of these apical dendrites, which tends to oscillate. The physiological basis of these oscillations is a manifestation of both intrinsic properties of neurons (ionic conductances) and, importantly, network interactions (connectivity). Intrinsic resonant properties permit and promote frequency range-specific oscillations based on network activity [see Berridge and Rapp (1979)]. Different frequency oscillations are governed principally by cortico-cortical connections and thalamocortical connections to varying degrees depending on the specific oscillation. EEG oscillations exist in a broad range of frequencies from well below one Hertz to several hundred Hertz. The physiology is best understood for several “classic” frequency bands including delta (0.5–4 Hz), theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma (30–100 Hz). These frequency ranges are not arbitrarily divided [see

Penttonen and Buzsáki (2003)], but represent different oscillatory phenomena with unique underlying physiological mechanisms, cortical topographies, and functions, of which many are still being delineated. Different combinations of frequency bands in different quantities comprise different states of the brain (e.g., attentive wakefulness, drowsiness, various stages of sleep).

The “clinical” evaluation of the EEG typically involves a visual inspection of brain electrical activity across a range of brain states and the assessment of the topography and “quantity” of state-appropriate oscillatory activity, as well as examination for the presence of pathological potentials. For the detection of epileptiform activity, the human eye actually outperforms computerized waveform analysis despite decades of attempts to automate EEG interpretation (Harner, 2010). However, when it comes to the assessment of the topography and quantity of oscillatory activity, and what constitutes a normal or abnormal distribution of such activity, visual inspection fails considerably. Very poor inter-rater reliability is common for visual inspections of oscillatory activity, even in determining what constitutes normal vs. abnormal. Additionally, visual inspection can shed no light whatsoever on the nature of interregional interactions, both locally and globally, which constitute the basis for cognition and consciousness (Tononi et al., 1994). This requires the use of computerized algorithmic methodologies called qEEG, which we will use as a broad encompassing term for all such analyses. For example, to obtain a quantitative assessment of the amount of oscillatory activity at any and all frequencies in a particular brain region, qEEG frequency analysis transforms the original EEG data over a period of time into a representation of its frequency content, generating a continuous EEG “power spectrum.” Ultimately, however, using methodologies that require averaging of data over relatively long periods of time will be insensitive to the rich dynamics of the cortex, which operates on a multitude of timescales down to the order of milliseconds (see below).

EEG IN mTBI

Pathologically, mTBI is a complex process, resulting in neuronal dysfunction that may be manifested in EEG changes apparent even to visual inspection for a duration ranging from hours to up to a few weeks post-injury. Beyond the acute and subacute stages, the structural pathology of mTBI is characterized by diffuse axonal injury involving the white matter as well as simplification of the dendritic architecture of neurons in cortical gray matter, with a relative absence of neural loss, leading to varying and often subtle degrees of cortical atrophy or thinning (Bigler and Maxwell, 2011). Such effects below a certain threshold of severity will not manifest on standard magnetic resonance imaging (MRI) at any stage. Newer MRI methods, such as diffusion tensor imaging, may be capable of detecting these more subtle structural disturbances, but these imaging techniques are not common in practice and are still in early stages of use.

Electroencephalogram, however, may be sensitive to detecting the physiological effects of these processes. The simplified dendritic system of neurons may result in a decrease in power of fast frequencies. Even subtle relative deafferentation from the thalamus or ascending neuromodulator systems (i.e., cholinergic, noradrenergic, dopaminergic) due to axonal injury will increase

the power of slow frequencies, due to an alteration of firing properties of thalamic and cortical neurons (resulting in a net increase in theta frequency activity), and due to the release of intrinsically generated network oscillatory activity normally suppressed by cholinergic afferents (from the basal forebrain) and glutamatergic afferents (from the thalamus). Additionally, and importantly, axonal injury will reduce the effectiveness of synchronization of distributed cell assemblies located throughout the cerebral cortex, which are essential for cognition. The physiological basis of the EEG, as described above, makes qEEG methodologies potentially well-suited to detect these physiological alterations in the “free-running” EEG oscillatory activity. Additionally, these pathological changes can alter the timing and amplitude of slower non-oscillatory electrical potentials, which are caused by the phase resetting of these oscillatory rhythms during the performance of cognitive tasks, the so-called event-related potentials (ERPs). Thus, the assessment of ERPs is another potentially valuable tool in the qEEG repertoire for the study of altered cortical physiology in the setting of mTBI.

What is the function of EEG oscillations, and how can a quantitative analysis of EEG activity provide insight into impaired brain function in TBI? For several decades from 1960s to 1990s, the prevailing view was that EEG activity/oscillations were epiphenomenal and unrelated to moment-to-moment cerebral cortical function, but simply reflected the general state of the brain (e.g., awake and alert, drowsy, asleep). The tide has turned dramatically and it is now understood that moment-to-moment brain function is directly linked to EEG oscillations. Cognitive processes are a function of the rapid formation and subsequent dissolution of distributed cell communication assemblies on the order of several hundred milliseconds in duration (Breakspear et al., 2004), and these assemblies form transiently based on a functional (as opposed to structural) connectivity patterns established by the synchronization patterns of EEG oscillations. This synchronization allows effective communication among the members of the transient assembly (Fries, 2005). True synchronization of neuronal activities only occurs within a few millimeters. A better term may be “polychronization” (Izhikevich, 2006), as most functionally connected neurons are not truly synchronized, but that term will suffice for our purposes. Fast frequencies (especially gamma) are involved in the synchronization of relatively local cell assemblies in the processing of specific cortical representations and slower frequencies synchronize highly distributed cell assemblies that span many centimeters of cortex and may involve both hemispheres. Theta and delta frequency activity also support the synchronization of faster frequencies among multiple localized assemblies via the phenomenon of “cross-frequency coupling” (Canolty and Knight, 2010). Computerized signal analysis of EEG data has evolved significantly to address the complex interregional interactions of brain connectivity, including the causal relationships among interacting regions of brain during a cognitive act and how these relationships may be deranged. For example, in brain injury one could demonstrate altered causal relationships in which control of action is more reactive or stimulus-based, such that cortical sensory networks predominantly influence frontal-executive networks instead of vice versa. A so-called “small-world” connectivity analysis can determine whether or not the cerebral cortices

in a population of patients is performing with a functional connectivity pattern that optimizes the ratio of local to long-range functional connectivity. This ratio has shown to be altered in TBI (Cao and Slobounov, 2010; Tsirka et al., 2011). Overall, recent developments in the analysis of EEG activity to characterize brain function hold tremendous promise for our ability to understand the physiology of cognitive processes and their pathophysiological derangement in neurological disorders such as traumatic brain injury.

The effects of TBI can be significant and long-lasting. Fazel et al. (2014) compared mortality rates 6 months or more after injury against a control population. They found that TBI is associated with substantially elevated risks of premature mortality, particularly from suicide, injuries, and assaults. Similarly, TBI is a significant risk factor for neuropsychiatric disorders (Rapp et al., 2013a). These results argue against the view that TBI, even mTBI, typically resolves without lasting consequences. In addition, these results establish the need to identify individuals at-risk of delayed onset neuropsychiatric disorders following brain injury. Quantitative measures of altered brain electrical behavior may provide quantitative prodromes of neuropsychiatric disorders. This possibility is encouraged by noting that changes in brain electrical behavior following TBI can be persistent. Slobounov et al. (2012) found that 85% of the mTBI patients who presented significant EEG alterations in the immediate post-injury period still presented altered EEGs up to 12 months post-injury. Segalowitz et al. (2001) found that ERPs were altered in mTBI patients in a patient group that was on average 6.4 years post-injury. De Beaumont et al. (2009) examined healthy former athletes in late adulthood (mean age 61 years) who had sustained their last sports related concussion in early adulthood (mean age at time of last injury 26 years). These participants were compared against healthy former athletes who did not have a history of concussion (average age 69 years). Participants with a history of concussion had significantly different ERPs. These results must be considered with care; however, as they represent a problem that is common to studies in this area: in almost all cases, pre-injury data are not available. It is possible, for example, that central nervous system (CNS) abnormalities in the athletes in the de Beaumont study were present prior to injury and were themselves a factor leading to injury. Nonetheless, these results and other studies summarized in this report suggest that measurement of brain electrical behavior may be a valuable complement to other assessment procedures.

COMPARATIVE UTILITY OF qEEG FOR mTBI DETECTION

Aside from the direct connection between qEEG and the physiological responses described above, EEG supplements conventional medical approaches to imaging the structure and function of the brain. EEG as a neuroimaging modality holds several advantages over more conventional medical approaches. Computed tomography (CT) and MRI are current the “gold standards” for imaging assessment of neurophysiological trauma. These techniques provide excellent spatial resolution for easily identifying lesions; however, significant limitations of CT and MRI reduce the practical utility for mTBI detection. For instance, both approaches require very large and expensive equipment, special facilities for their use, and dedicated technicians for operation. CT uses small

doses of radiation, which may carry potential risks for long-term side effects if patients are scanned often. MRI uses an extremely strong magnetic field (>1 T), necessitating careful operating procedures. Perhaps most limiting for MRI is the contraindication of medical devices, implants, and any foreign ferrous metal objects in the patient's body. Since service members may have metal fragments lodged in their bodies from the same injury event, this limitation is particularly difficult to reconcile for military use. In contrast to CT and MRI, equipment used for EEG is substantially more portable, less expensive, requires no special facilities, and, in most cases, can be applied by personnel with very minimal training. All of these characteristics contribute to a substantially higher level of fieldability and a broader operational effectiveness beyond dedicated medical centers. The fieldability of qEEG also facilitates neuroscience research outside of laboratory environments, for which more accurate "real world" data can be captured and compared to findings in the laboratory, thus driving advancements in neurotechnology applications (McDowell et al., 2013).

The data derived from EEG are also fundamentally distinct as compared to CT and MRI data. In particular, while CT and MRI have excellent spatial resolution, the resulting images (which take several minutes to acquire) are temporally static, and thus provide no direct measurement of functional, ongoing brain activity. Even the best current methods of "functional MRI" are limited to multiple seconds for the acquisition of whole-brain images. In contrast, EEG is extremely high-resolution in the time domain (EEG can be sub-millisecond) and, as described above, is a direct measurement of neuronal activity. This allows a great number of analyses (as described above and in the following sections), which capitalize on direct responses to stimuli, cognitive responses, inter-relatedness of continuous signals, and the oscillation of both discrete and cross-regional networks of brain areas.

LITERATURE INDEX OF qEEG STUDIES RELEVANT TO mTBI LITERATURE SEARCH METHODOLOGY

A literature search was conducted in peer-reviewed primary sources from PubMed and the "gray" literature (i.e., documents not peer-reviewed) from the defense technical information center (DTIC) technical report database. Keyword searches were chosen to identify studies that specifically measured qEEG in head injured groups. See Supplementary Material for keyword search terms and record returns. Studies using established statistical approaches to demonstrate differential qEEG between injured and control groups were considered particularly important. Statistical methods of high value included effect size statistics such as Cohen's d , odds ratio, and area under receiver operating characteristic curve. In addition, studies exploring test-retest reliability were flagged. To efficiently filter the large number of initial hits and maintain a pertinent collection for TWG review, the following study characteristics resulted in *exclusion* from the primary qEEG literature index:

1. Studies that used severe TBI or comatose patients,
2. Studies exploring pharmacologic or biologic agent efficacy,
3. Rehabilitation or therapeutic studies (those not diagnostic in nature),
4. Studies using animal models of neurological injury, and

5. Studies exploring the use of qEEG in dysfunctions besides head injury (e.g., neurodegenerative diseases, psychological dysfunctions).

The primary qEEG literature index was further down selected to focus on studies that provide statistical evidence for *qEEG measures* as detection tools for mTBI. Therefore, the following study characteristics resulted in removal from the qEEG-refined literature index:

1. Retrospective studies (i.e., symptom catalogs)
2. Studies without direct statistical comparisons.

LITERATURE SEARCH RESULTS

Using the methodology described above, the primary qEEG literature index consisted of 40 studies (Supplementary Material). Twenty-five of these studies were further down selected as providing direct statistical evidence related to qEEG measure discriminatory ability. The refined literature index was subsequently used by the TWG to evaluate major qEEG measure types, power spectra, connectivity measures, and the use of discriminant functions. Each analysis of the measure types and the use of discriminant functions includes a general description of the approach, the potential utility for detection of mTBI, an evaluation of the statistical evidence to discriminate between injured and non-injured persons, research gaps and future directions to improve upon the evidentiary data, and conclusions on the overall prospects for use as an mTBI detection method. Section "Advanced Signal Processing Technologies" extends the scope of the original literature search to introduce important approaches with high perceived value (based on the opinion of this TWG) as mTBI diagnostic tools, but with low evidentiary support to date.

MEASURES REPRESENTED IN THE DOWN SELECTED qEEG LITERATURE INDEX

Examination of the down selected literature index revealed two main types of qEEG analysis investigated for mTBI detection efficacy: spectral analysis (see **Table 1**) and functional connectivity analysis. Each type of analysis is introduced below, followed by critical evaluation of the literature-based evidence and recommendations for future research.

SPECTRAL ANALYSIS

Definition (spectral analysis)

Spectral analysis is a common form of EEG interpretation in which the distribution of signal is evaluated over various EEG frequencies. Spectral analysis is usually limited to a narrow frequency band from 0.1 to 100 Hz, which is further subdivided into several sub-bands (e.g., delta, theta, alpha, beta, and gamma bands). The boundaries of the sub-bands can differ slightly among various researchers, resulting in potential variation of results across studies. A typical sub-band range, used by Prichep et al. (2012a,b), is as follows: delta (1.5–2.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), alpha1 (7.5–10.0 Hz), alpha2 (10.0–12.5 Hz), beta1 (12.5–25.0 Hz), beta2 (25.0–35.0 Hz), gamma (35.0–50.0 Hz). The spectral power for each band is obtained either by (1) calculating the power spectrum of the total signal recorded at an electrode site

Table 1 | Studies using spectral analysis.

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
Chen et al. (2006a) “Electroencephalogram and evoked potential parameters examined in Chinese mild head injury patients for forensic medicine” <i>Notes:</i> this study supports qEEG as a more sensitive method for detecting mTBI compared to evoked potential recording (auditory and flash). This conclusion is somewhat contradictory to other studies in the field	60	30	Eyes closed, resting, wakeful	Glasgow coma scores (13–15)	Frequency band average power Frequency band power ratios Frequency band power ratios and average power	Unpaired <i>t</i> -test 1. $\alpha 1$ ($p < 0.001$) 2. θ , $\alpha 2$, $\beta 1$, $\beta 2$ (all $p > 0.05$) (NS) Unpaired <i>t</i> -test 1. $\theta/\alpha 1$ and $\theta/\alpha 2$ (both $p < 0.05$) 2. $\alpha 1/\alpha 2$ ($p < 0.01$) Paired <i>t</i> -test Initial vs. 3 month retest ($p > 0.05$ for all comparisons) (NS)
Coutin-Churchman et al. (2003) “Quantitative spectral analysis of EEG in psychiatry revisited: drawing signs out of numbers in a clinical setting” <i>Notes:</i> qEEG was reported to bin normal subjects and psychiatric patients with good specificity and sensitivity. However, this study does not find any clear association between particular qEEG measures and specific disorders. In addition, the patient group mostly consisted of individuals with mood and psychological disorders, not cognitive impairments due to injury	4 (Post-traumatic headache 336 With other neurological disorders)	67	Eyes closed, resting, wakeful	Post-traumatic headache diagnosis	Power spectra (all bands), converted to Z-score (all disorders combined) Absolute power and power asymmetry (all disorders combined) Beta activity increase (all disorders combined) Slow band decrease (all disorders combined)	Z-score abnormality defined as Z-score > 3 or < -3 1. Sensitivity (0.838) 2. Specificity (0.9104) 3. Positive predictive value (0.979) 4. Negative predictive value (0.526) Various tests Overall correspondence between qEEG abnormality pattern and clinical diagnosis ($\chi^2 = 315.8$, Cramer's $V = 0.305$, Contingency coefficient = 0.694; $p = 0.00001$) Pearson's correlation Medication use in all patients (Pearson $\chi^2 = 7.865$, $df = 1$, $p = 0.005$) Pearson's correlation Medication use in all patients ($\chi^2 = 2.963$, $df = 1$, $p = 0.085$) (NS)
Gosselin et al. (2009) “Sleep following sport-related concussions” <i>Notes:</i> while this report did not find differences in sleep architecture (frequency activities) between concussed and control athletes, concussed athletes showed significant increased delta and reduced alpha activities in the waking qEEG analysis. This study also demonstrates effective combinatorial technology use (fMRI and ERP)	10	11	Eyes closed, resting, wakeful Eyes closed, asleep Frontal region (Fz, F3, F4), central region (CZ, C3, C4), parietal region (Pz, P3, P4), occipital region (O1 and O2), temporal region (T7, T8, P7, P8)	Glasgow coma scores (13–15)	Relative spectral power (all frequencies) (eyes closed asleep) Relative delta power (eyes closed, wakefulness) Relative alpha power (eyes closed, wakefulness) Slow to fast frequencies ratio (eyes closed, wakefulness)	Two-way ANOVA (no significance for any region) Two-way ANOVA ($F_{1, 14} = 12.7$, $p < 0.01$) (all regions) Two-way ANOVA ($F_{1, 14} = 8.8$, $p < 0.05$) (all regions) Two-way ANOVA ($F_{1, 14} = 11.5$, $p < 0.01$) (all regions)
Haglund and Persson (1990) “Does Swedish amateur boxing lead to chronic brain damage? A retrospective clinical neurophysiological study” <i>Notes:</i> study reports no differences in qEEG measures between patient groups, but the effort was exploratory and used grand averages for each frequency band. Importantly, inter-rater reliability was reported to be sufficient	47 22 High-match boxers 25 Low-match boxers	50 25 Soccer players 25 Track and field players	Eyes closed, resting, wakeful	High number of boxing matches (> 25)	Average power spectrum (grand averages from each frequency)	Chi square (no significant differences between all groups)

(Continued)

Table 1 | Continued

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
Korn et al. (2005) "Focal cortical dysfunction and blood-brain barrier disruption in patients with post-concussion syndrome" <i>Notes:</i> the main purpose of this study was to correlate abnormal EEG, brain imaging, and blood-brain barrier disruptions, especially as related to localization. Arciniegas' (2011) review provides critical perspective on this study (classification of some experimental group subjects as having mTBI, but CT scans suggest a more severe form of TBI)	17	17	N/A	Glasgow coma scale >12, post-concussion syndrome (PCS) diagnosis 1 month to 7 years post-injury	Delta frequency power Alpha frequency power	Student's <i>t</i> -test Increased delta ($p < 0.01$) Student's <i>t</i> -test Lower alpha 1 ($p < 0.05$) Lower alpha 2 ($p < 0.05$)
Montgomery et al. (1991) "The psychobiology of minor head injury" <i>Notes:</i> the theta band was the only abnormal frequency in the qEEG analysis. However, no normative sampling or pre-injury measures, or control group measures were used. The comparison was only between immediate post-injury (approximately 24 h) and 6 weeks later. So, reduction in theta power may be considered persistent	26	None	Eyes closed, resting, wakeful	Head injury requiring overnight hospital stay; post-traumatic amnesia >12 h	Mean theta power (comparison between day 0 and 6 weeks) Mean alpha power (comparison between day 0 and 6 weeks) Mean delta power (comparison between day 0 and 6 weeks)	Two-tailed paired <i>t</i> -tests 1. Right temporal, T4–T6 ($p < 0.025$) 2. Right parietal, P4–O2 ($p < 0.01$) 3. Left temporal, T3–T5 ($p < 0.01$) 4. Left parietal, P3–O1 ($p < 0.01$) Two-tailed paired <i>t</i> -tests No significance at any region Two-tailed paired <i>t</i> -tests No significance at any region
Slobounov et al. (2012) "Residual brain dysfunction observed 1 year post-mild traumatic brain injury: combined EEG and balance study" <i>Notes:</i> this study suggests qEEG and balance analysis as good prognostic tools; efficacy as a diagnostic tool was not explored	49	None (used baseline testing from mTBI group pre-injury)	Eyes closed, resting, wakeful Eyes open, resting, wakeful Eyes closed, standing, wakeful Eyes open, standing, wakeful	Grade 1 mTBI (Cantu Dad Driven Revised Concussion Grading Guideline, 2006)	Alpha power suppression (from resting to standing posture) increase	<i>t</i> -Test (baseline vs. day 7 post-injury) 1. Occipital region of interest: $F = 11.77 (1,48), p < 0.01$ 2. Parietal region of interest: $F = 8.2 (1,48), p = 0.038$
Tebano et al. (1988) "EEG spectral analysis after minor head injury in man" <i>Notes:</i> this report suggests differences in power band frequencies occur between healthy and patients with mTBI. This is an early study and may be considered exploratory	9 (No loss of consciousness) 9 (Reported loss of consciousness)	9	Eyes closed, resting, wakeful (baseline recording) Eyes open, resting, wakeful (recording)	Reported loss of consciousness after injury	Alpha I band power (higher in injured group) Alpha II band power (reduced in injured group) Mean frequency of total alpha band power (reduced in injured group) Frequency band total power (if significant, reduced in injured group)	Mann–Whitney test $U = 28, p < 0.01$ Mann–Whitney test $U = 47, p < 0.05$ Mann–Whitney test $U = 46, p < 0.05$ Mann–Whitney test 1. Alpha (alpha I and II), (NS) 2. Delta, $U = 45, p < 0.05$ 3. Beta II, $U = 41, p < 0.025$
Thatcher et al. (2001) "Estimation of the EEG power spectrum using MRI T ₂ relaxation time in traumatic brain injury" <i>Notes:</i> Nuwer et al. (2005) criticizes this study due to lack of age-matching and broad spread of TBI severity	18 (Mild-severe TBI)	11	Eyes closed, resting, wakeful	Chronic TBI diagnosis	Correlation between relative EEG frequency power and T2 relaxation time (MRI scan) (decreased alpha and beta; increased delta and theta with MRI T2 abnormalities)	ANOVA 1. Delta ($t = 8.876, p < 0.0001$) 2. Theta ($t = 8.529, p < 0.0001$) 3. Alpha ($t = -9.276, p < 0.0001$) 4. Beta ($t = 2.421, p < 0.016$)

(Continued)

Table 1 | Continued

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
Thatcher et al. (1991) "Comprehensive Predictions of Outcome in Closed Head-Injured Patients" <i>Notes:</i> a gradient of prognostic strength of diagnostic measures was EEG phase > EEG coherence > GCS-T > CT scan > EEG relative power	162	None	N/A	Closed head injury and admittance to Neurotrauma hospital center	EEG relative power	Prediction accuracy (extreme outcome scores) (1 year) 67.1%
Thornton (2003) "The electrophysiological effects of a brain injury on auditory memory functioning. The QEEG correlates of impaired memory" <i>Notes:</i> twenty-seven patients of the mTBI group were on various medications. Age was statistically different between groups (mTBI group was slightly older)	85	56	Eyes closed, resting, wakeful, during auditory memory task Eyes open, resting, wakeful, during auditory memory task	Loss of consciousness <20 min	Power band frequency measures for alpha, beta, theta, and delta (includes absolute/relative magnitude, peak amplitude, peak frequency, and symmetry)	<i>t</i> -Test 1. Increased beta1 relative power ($p < 0.05$)
Tomkins et al. (2011) "Blood-brain barrier breakdown following traumatic brain injury: a possible role in posttraumatic epilepsy" <i>Notes:</i> study focuses mostly on blood-brain barrier localization with qEEG abnormalities	37 (19 With post-traumatic epilepsy, PTE)	13	Eyes closed, wakeful	Glasgow coma scale > 13	Delta power (increase) Alpha power (decrease) Theta power (increase)	Mann-Whitney <i>U</i> test Injured vs. controls ($p = 0.002$) (equivalent among PTE and non-PTE mTBI patients) Mann-Whitney <i>U</i> test Injured vs. controls ($p = 0.005$) (only seen in PTE group, $p = 0.01$) Mann-Whitney <i>U</i> test PTE group of mTBI patients vs. controls ($p = 0.04$)
von Bierbrauer et al. (1992) "Computer assisted vs. visual EEG-analysis in patients with minor head injury (a follow-up examination)" <i>Notes:</i> this study also provides evidence for qEEG as a relevant technology for patient diagnosis and analysis as compared to standard EEG. Original article is in German; analysis adapted from review article (Nuwer et al., 2005)	31	None	N/A	N/A	Median posterior alpha frequency (increase over time) Theta/alpha ratio (decrease over time)	<i>t</i> -Test 1. 24 h vs. 1 week (NS) 2. 24 h vs. 3 weeks ($p < 0.01$) 3. 24 h vs. 2 months ($p < 0.01$) <i>t</i> -Test 1. 24 h vs. 1 week (NS) 2. 24 h vs. 3 weeks ($p < 0.05$) 3. 24 h vs. 2 months ($p < 0.01$)
Watson (1995) "The post-concussional state: neurophysiological aspects" <i>Notes:</i> study suggests combined use of qEEG power spectral analysis and brainstem audio evoked potential (BAEP) I-V latency analysis could provide utility to diagnose mTBI symptoms (both organic and psychological)	25	None	Eyes closed, resting, wakeful	Men; aged 14–30; uncomplicated head injury with post-traumatic amnesia <12 h	Alpha/theta ratio (at day 0, day 10, and 6 weeks post-injury)	Paired two-tailed <i>t</i> -test (day 0 vs. day 10 post-injury) 1. Right temporal (T4–T6), $p < 0.006$ 2. Right parieto-occipital (P4–O2), $p < 0.02$ (day 10 vs. 6 weeks) – not significant for any region
Williams et al. (2008) "Polysomnographic and quantitative EEG analysis of subjects with long-term insomnia complaints associated with mild traumatic brain injury" <i>Notes:</i> this study shows limited ability of qEEG power spectra analysis to differentiate among mTBI patients suffering from sleep disorders and control groups	9	9	Eyes closed, resting, asleep	Glasgow coma scale 13–15; loss of consciousness <20 min; hospitalization <48 h; reported sleep dysfunction	Beta 2 power (decrease in injured patients) Variability in power (greater variability in mTBI patients)	Two-tailed <i>t</i> -tests with Welch's corrections (Wilcoxon rank sum test also used if outliers were apparent) 1. Beta 2 ($F(1, 16) = 8.9, p = 0.008$) Two-tailed <i>t</i> -tests with Welch's corrections (Wilcoxon rank sum test also used if outliers were apparent) 1. Sigma ($F_{1,16} = 10.5, p = 0.005$) 2. Theta ($F_{1,16} = 6.8, p = 0.019$) 3. Delta ($F_{1,16} = 9.2, p = 0.008$)

and then summing the contributions of the frequencies included in the band, or (2) subjecting the total signal to an appropriate passband filter and then calculating the power spectrum of the filtered signal. The resulting band power is typically averaged over electrode sites and reported either as “absolute power” or as “relative power,” which is the ratio of the band power to the total power over all bands. Other common parameters of spectral analysis include median frequency and spectral edge frequency (Dressler et al., 2004).

Utility for mTBI detection (spectral analysis)

A key feature of spectral analysis that allows for strong utility as an mTBI detection tool is that spectral data can be obtained from as few as two electrodes. Therefore, fielded devices do not require the costs or burden of large montages of electrodes. This feature reduces equipment burden, administration time, and cost. Simplified devices also allow for faster training and simplified analysis.

Evidence of efficacy (spectral analysis)

Of the 25 studies comprising the down selected qEEG literature index, 15 studies used spectral analysis as a measure to compare injured and control groups. Most of the studies report statistically significant alteration in at least one frequency band in mTBI patients compared to control groups. To visualize the overall trends in results, **Table 2** summarizes the reported changes to spectral power (either absolute or relative power) across frequency sub-bands from relevant studies. The table also displays the recording montage and statistical significance from each finding. Measurements were made under eyes closed, no task, but awake conditions, with few exceptions [e.g., Tebano et al., 1988 – eyes open; Gosselin et al. (2009) – asleep condition; Thornton (2003) – EEG recorded during memory task]. While results are somewhat varied, generalizations can be inferred. For instance, mTBI injury is often associated with a decrease in alpha power and an increase in delta, beta, and theta bands. We note this evidence is not based entirely on well-designed studies with large sample groups and strong statistical significance. As an example, Thornton (2003) reported increased beta activity in the injured group, but used 27 mTBI patients that were on some type of medication. Furthermore, the age difference between injured and control groups was statistically significant. These inconsistencies could potentially skew EEG recordings. Korn et al. (2005), which reported decreased alpha and increased delta power in the injured group, has been criticized due to the potential misclassification of moderate-severe TBI patients as mTBI patients (Arciniegas, 2011). The absence of a uniformly applied criterion for defining mild TBI is a significant complicating factor. Tebano et al. (1988), inconsistent with several other studies, reported results based on very small sample sizes and recorded brain activity with a single bipolar derivation (O1–T5) using an eyes open paradigm. Other inconsistencies in the findings may be attributed to the various montages and derivations used during data acquisition sessions (see **Table 2** for details). Overall, differential spectral power in injured patients is strongly suggested in the literature, but specific findings need to be confirmed based on robust studies that use similar recording conditions.

Several additional studies from the literature index investigated spectral measures, but did not compare results to a control group. For example, Montgomery et al. (1991), Slobounov et al. (2012), von Bierbrauer et al. (1992), and Watson (1995) reported spectral changes in injured patients over time (theta reduction, alpha power reduction plus theta/alpha ratio changes, and alpha/theta ratio changes, respectively). Contradicting these studies, Chen et al. (2006a) reported all spectral power measures returned to normal levels after a three month retest (alpha1, theta/alpha1 ratio, theta/alpha2 ratio, and alpha1/alpha2 ratio). These results suggest spectral analyses may have utility for longitudinal evaluations, but confirmatory experiments must be matched with respect to time post-injury and recording condition.

Additionally, some studies reported no spectral differences between injured and control groups when a broad frequency window was used (Haglund and Persson, 1990; Coutin-Churchman et al., 2003; Gosselin et al., 2009). Such findings suggest power spectral analysis using sub-bands is preferred to observe significant differences in mTBI patients. We note that the patient group in the Coutin-Churchman et al. (2003) study included individuals with a wide range of psychiatric disorders (only 4/340 patients were classified with “post-traumatic headache”) and patients were not controlled for medication usage. Therefore, the study should only be considered a demonstration of the ability of spectral analysis to uncover dysfunction across many neurological conditions. Finally, Williams et al. (2008) reported higher variability in power in mTBI patients compared to normal participants (sigma, $p = 0.005$; theta, $p = 0.019$; delta, $p = 0.008$), but only limited ability of power spectral analysis to differentiate among injured and normal. Refer to **Table 2** for a full listing of the 15 studies reporting use of spectral analysis.

Research gaps and future directions (spectral analysis)

The variability of qEEG recording conditions across studies severely impedes the formulation of strong conclusions on spectral analysis utility or effectiveness. While studies strongly suggest spectral analysis may be used as an mTBI detection tool, efforts should be made to corroborate previous findings using high-quality studies with controlled recording conditions and injured group selection criteria. In addition, the use of smaller electrode montages should be emphasized if field-based qEEG recording devices are expected to be preferred for U.S. military operations.

Spectral power averaged over all electrode sites is a global measure. It provides no information about the energy generated at individual sites or about the connectivities of different sites. This more detailed information is provided, in part, by functional connectivity measures, such as coherence and phase difference (see below), and by inter- and intra-hemispheric power asymmetries. Research should be devoted to identify the most promising spectral measures, but with the overall goal to use spectral measures in combination with other measures.

Summary of analysis (spectral analysis)

There are some examples in the literature suggesting that spectral analysis can be used to detect mTBI. Studies generally report altered alpha, delta, beta, and theta power as potential indicators of mTBI. However, while trends of specific spectral power

Table 2 | Summary of changes in spectral power associated with mTBI^a.

Frequency range	Decrease in spectral power	Increase in spectral power	Unchanged spectral power
Delta (1.5–3.5 Hz)	Tebano et al. (1988) ($p < 0.01$; O1–T5, relative power)	Korn et al. (2005) ($p < 0.01$; 128 channels, relative power); Gosselin et al. (2009) ($p < 0.01$, asleep, relative power); Tomkins et al. (2011) ($p = 0.002$, 23 channels)	
Theta (3.5–7.5 Hz)		Tomkins et al. (2011) ($p = 0.04$, 23 channels); Montgomery et al. (1991) ($p < 0.025$, T4–T6; $p < 0.01$, P4–O2; $p < 0.01$, T3–T5; $p < 0.01$, P3–O1) ^b	Tebano et al. (1988) (O1–T5, relative power); Chen et al. (2006a) (16 channels, specific locations unknown)
Alpha1 (7.5–10 Hz)	Korn et al. (2005) ($p < 0.05$; 128 channels, relative power)	Tebano et al. (1988) ($p < 0.01$; O1–T5); Chen et al. (2006a) ($p < 0.01$; 16 channels, specific locations unknown)	
Alpha2 (10.0–12.5 Hz)	Korn et al. (2005) ($p < 0.05$; 128 channels, relative power); Tebano et al. (1988) ($p < 0.05$; O1–T5, relative power)		Chen et al. (2006a) (16 channels, specific locations unknown)
Alpha (7.5–12.5 Hz)	Gosselin et al. (2009) ($p < 0.05$, asleep, relative power); Tomkins et al. (2011) ($p = 0.005$, only in post-traumatic epilepsy mTBI subgroup)		Tebano et al. (1988) (O1–T5, relative power)
Beta (12.5–25 Hz)			Tebano et al. (1988) (O1–T5, relative power)
Beta1 (13–32 Hz)		Thornton (2003) ($p < 0.02$, auditory memory task)	Chen et al. (2006a) (16 channels, specific locations unknown)
Beta2 (25–35 Hz)	Tebano et al. (1988) ($p < 0.025$; O1–T5, relative power); Williams et al. (2008) ($p = 0.008$, 10/20 config, asleep)	Thornton (2003) ($p < 0.05$, auditory memory task)	Chen et al. (2006a) (16 channels, specific locations unknown)
Gamma (35–50 Hz)			
Theta/alpha		Watson (1995) ($p < 0.006$, T4–T6; $p < 0.02$, P4–O2, P3–O1) ^c	
Theta/alpha1	Chen et al. (2006a) ($p < 0.05$; 16 channels, specific locations unknown)		
Theta/alpha2		Chen et al. (2006a) ($p < 0.05$; 16 channels, specific locations unknown)	
Alpha1/alpha2		Chen et al. (2006a) ($p < 0.01$; 16 channels, specific locations unknown)	

^aEEGs were measured in 19 channels during eyes closed, awake recording sessions, unless otherwise noted. Reported changes are in absolute power relative to normal controls, unless otherwise noted.

^bMontgomery et al. (1991) noted a decrease in theta power of the same subject from day 0 to 6 weeks post-concussion suggesting that theta power may have increased as a result of the concussion and was trending back to normal 6 weeks later as the patient recovered.

^cWatson (1995) found that for channel pairs T4–T6, P4–O2, P3–O1, the theta/alpha ratio had decreased from day 0 to day 10 post-injury for the same subjects suggesting that the ratio may have increased as a result of the concussion and was trending back to normal 10 days later as the patient recovered.

alterations are apparent (decreased alpha and increased delta, beta, and theta in injured groups), the literature contains a high degree of contradictory results. This uncertainty is most likely due to poor study design and a lack of recording condition consistency.

Therefore, additional studies with carefully controlled conditions must be conducted to identify the best spectral measures for mTBI detection. We anticipate spectral analysis would not be a sufficient detection tool in isolation, and, in fact, multiple studies suggest

improved accuracy only when combined with other qEEG measures (Thatcher et al., 1989, 1991; Trudeau et al., 1998; Thornton, 1999, 2003; McCrea et al., 2010; Barr et al., 2012; Prichep et al., 2012a,b). Additionally, there is some evidence that depression is also marked by a decrease in alpha power and an increase in beta power similar to those seen in mTBI patients (Thornton, 2003). This finding raises the possibility of confounding test results in patient populations that may be prone to depression or PTSD. In summary, spectral analysis in and of itself does not appear to be a viable tool for mTBI detection.

FUNCTIONAL CONNECTIVITY MEASURES

Definition (functional connectivity)

Analysis of functional connectivity quantifies the relationships between EEG signals recorded simultaneously at different sites. EEG connectivity measures fall into three groups: time domain measures, frequency-domain measures, and measures calculated from the geometry of embedded data.

Time domain measures quantify the correlation between EEG time series. They can be used to assess the connectivity of discrete feedback loops and the stereotyped propagation of signals across neural networks (Koenig et al., 2005). There are four commonly used time domain measures of functional connectivity to assess the correlation between pairs of observations: (1) Pearson product moment correlation, (2) Spearman rank order correlation, (3) Kendall rank order correlation, and (4) mutual information. Additional time domain measures of note include a normalization of mutual information [recently constructed by Reshef et al. (2011)] and EEG microstate topography, in which the occurrence of spontaneous short-lasting brain states is assessed (Koenig et al., 2005).

Frequency-domain measures quantify the correlation between spectra rather than between the original time series, or quantify the relationship between the phases of two signals. Variations on these themes that have been applied to EEG signals include coherence (Nunez et al., 1997, 1999), phase synchronization (Aviyente et al., 2011), phase locking index (Hurtado et al., 2004; Sazonov et al., 2009; Stam et al., 2009), phase locking value (Lachaux et al., 1999), imaginary coherency (Nolte et al., 2004; Stam et al., 2007), synchronization index (Gross et al., 2004), and phase lag index (Stam et al., 2007, 2009).

Measures of embedded data are more recent additions to the assessment of functional connectivity. Consider a scalar voltage time series measures at a scalp electrode, (v_1, v_2, \dots, v_N) . This time series is used to construct points in m -dimensional space, $Z_i = (v_i, v_{i+1}, \dots, v_{i+(m-1)})$. While there are more complicated versions of the embedding process, in each version the original time series in this example becomes a directed trajectory in m -dimensional space, as motivated by the Takens embedding theorem (Takens, 1981). This powerful result demonstrates that, to an approximation, an intimate relationship exists between the geometry of the embedded set and the dynamical structure of the system that generated the observed time series. Now suppose two time series are measured simultaneously and used to generate two separate m -dimensional trajectories. Functional connectivity between the two original time series may be assessed by constructing measures relating the two trajectories. Examples include synchronization likelihood (Stam and van Dijk, 2002; Wendling et al., 2009) and

cross recurrence diagrams (Romano et al., 2004; Richardson et al., 2008).

Distinction must also be made between connectivity measures and measures of causal relationships. Functional connectivity measures are computed from voltage signals recorded at different electrodes to determine if there is a relationship between two signals. These measures are adirectional. In contrast, causality measures specifically assess the direction of information movement. Measuring causality for mTBI detection is examined in Section "Analysis of Causal Relationships" of this report.

Utility for mTBI detection (functional connectivity)

Alterations in the functional connectivity of multichannel EEG have been reported in a range of neuropsychiatric disorders, including TBI (Table 3). This suggests reasonable utility of using functional connectivity measures for mTBI detection. It should

Table 3 | Pathological conditions associated with altered functional connectivity (adapted from Bonita et al., 2014).

Disorder/dysfunction	Relevant publications	
Alzheimer's disease	Georgopoulos et al. (2007)	Rosenbaum et al. (2008)
	Güntekin et al. (2008)	Stam et al. (2006, 2007, 2009)
	Locatelli et al. (1998)	Zhou et al. (2008)
Epileptic seizures	Ponten et al. (2007)	
Intra-arterial amobarbital injection	Douw et al. (2010)	
Autism spectrum disorder	Belmonte et al. (2004)	Murias et al. (2007)
	Just et al. (2004)	Rippon et al. (2007)
	Kana et al. (2007)	Vidal et al. (2006)
Brain tumors	Bartolomei et al. (2006)	
	Bosma et al. (2008)	
Multiple sclerosis	Georgopoulos et al. (2007)	
	Lenne et al. (2012)	
Preterm birth	Mullen et al. (2011)	
PTSD	Lanius et al. (2004)	
	Shaw (2002)	
Schizophrenia	Breakspear et al. (2004)	Lynall et al. (2010)
	Georgopoulos et al. (2007)	Michelyannis et al. (2006)
	Lawrie et al. (2002)	Symond et al. (2005)
Stroke	Grefkes and Fink (2012)	
Traumatic brain injury	Cao and Slobounov (2010)	Kumar et al. (2009a,b)
	Castellanos et al. (2010, 2011a,b)	Nakamura et al. (2009)
	Ham and Sharp (2012)	Sponheim et al. (2011)
	Kasahara et al. (2010)	Tsirka et al. (2011)

be noted, however, that multichannel EEG usually requires more complex electrode montages and advanced computational capacity for data analysis. These features may be contrary to simple, lightweight devices capable of field-based use and easy operation. Additionally, the signal analysis and neuroinformatics challenges of these investigations should not be underestimated (Irimia et al., 2009, 2012; Goh et al., 2014).

Evidence of efficacy (functional connectivity)

The various functional connectivity measures described above offers specific advantages and disadvantages as detection tools of neurological dysfunction. For example, Bonita et al. (2014) recently compared the four classical measures of time domain connectivity (Pearson product moment correlation, Spearman rank order correlation, Kendall rank order correlation, and mutual information) with multichannel EEGs obtained in two behavioral states (eyes open, no task and eyes closed, no task) from healthy control participants. It was found that mutual information distinguished between behavioral states with less data and was more robust to noise. This result was not unanticipated since mutual information is a non-linear measure that captures relationships not detected by the other three time domain measures. In addition, time domain measures have been most commonly applied to event-related data, since common reference points in time are often required for calculations (Koenig et al., 2005). EEG microstate topography analysis, however, does not require external time reference points and may be used with spontaneous qEEG recording to assess individuals with varied cognitive states or dysfunctions (Koenig et al., 1999; Lehmann et al., 2005; Müller et al., 2005). Frequency-domain measures are not robust to naïve application. For example, Schiff (2005) showed coherence calculations can produce misleading results and Guevara et al. (2005) reported synchronization values can be sensitive to the common reference signal used in EEG recordings. Insofar as we know, a comparative study of frequency-domain measures, analogous to the Bonita et al. (2014) time domain measure study, has not been conducted. Similarly, essential comparative studies have not been reported for measures of embedded data.

Specific evidence related to mTBI detection is relatively sparse: only three studies from the refined literature index investigated the efficacy of functional connectivity measures (see Table 4). Sponheim et al. (2011) reported reduced synchrony between specific frontal electrode positions for delta, beta, and gamma frequency bands. The results were statistically significant with a strong criterion (limited to $p < 0.05$ for all comparisons; Cohen's $d = 0.92\text{--}1.20$), but we note the study used small sample group sizes (nine injured and eight normal) and follow-up studies with larger groups could improve significance. Interestingly, the use of neurocognitive assessment tools (battery of multiple tests) failed to properly classify individuals as injured or uninjured, suggesting that this new method may uncover dysfunctions below the thresholds of current mTBI detection methods. Thatcher et al. (1991) reported EEG phase was reasonably accurate in predicting outcome scores of patients 1 year post-injury (90.2% accuracy). This study also ranked the prognostic strength of EEG phase and EEG coherence above CT scan and spectral relative power. The Thatcher et al. (1991) study was longitudinal and no control group

was used to assess diagnostic capacity of the functional connectivity measures. Finally, Thornton (2003) used an audio memory task paradigm and reported that phase and coherence were lowered for beta1 and beta2 spectral bands ($p < 0.05$ for each test). This study involved reasonable sample groups (85 injured, 56 controls), but has been challenged since 27 patients from the mTBI group were on medications and there was a statistically significant difference in age between the groups. Nevertheless, this study suggests functional connectivity should be further investigated as a diagnostic approach for mTBI. Details on the three studies investigating functional connectivity in mTBI are presented in Table 4.

Research gaps and future directions (functional connectivity)

Since a limited number of studies have specifically investigated detection efficacy of mTBI, future research should be directed to corroborate previous findings. Concerns of study quality are abundant; therefore, future studies should ensure robust study design and limited reliance on medicated patient groups. The signal processing methods for coherence should also be investigated, since studies have reported misleading results depending on the analysis method.

Summary of analysis (functional connectivity)

In the context of mTBI, functional connectivity has not been investigated to the same extent as spectral analysis. The small number of available studies report that coherence may be a useable measure for accurate mTBI detection. However, the studies are fundamentally weak in their experimental design and need to be corroborated. Furthermore, the strongest positive results were reported for a longitudinal study. Similar to spectral analysis, coherence may be best suited as a contributing measure of a discriminant function for mTBI detection.

DISCRIMINANT FUNCTIONS

While not specific to qEEG, discriminant functions were identified during the literature search as a common methodology for mTBI detection. Discriminant functions in this context comprise more than one qEEG measure and so deserve consideration here. Similar to the evaluation of spectral analysis and functional connectivity, discriminant functions are defined below, followed by an analysis of the evidentiary support for use as an mTBI detection tool.

Definition (discriminant functions)

The term “discriminant functions” refers to an entire class of analysis approaches in which a specific model is used to classify a set of data as belonging to a specific group (or not). Broadly defined, this involves the use of a specific rule (or set of rules), which define members of a class, and applying the rule to a set of data where membership is unknown in order to classify where the target member belongs. This is most commonly a discrete decision, but can even be used to estimate the location within a categorized continuum. Within the domain of TBI, discriminant functions may be used to classify a patient based on level of severity (e.g., severe TBI vs. mTBI) or the presence of injury (e.g., TBI vs. no injury) through the combination of various metrics (such as spectral or functional connectivity features) within a single discriminant model.

Table 4 | mTBI studies using connectivity measures.

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
Sponheim et al. (2011) "Evidence of disrupted functional connectivity in the brain after combat-related blast injury" <i>Notes:</i> this study uses a new method for calculating phase synchrony in qEEG recordings, and identifies several statistically significant synchrony disruptions in mTBI patients. Neurocognitive assessment tools (battery of multiple tests) were unable to distinguish between groups	9	8	Eyes closed, resting, wakeful	American Congress of Rehabilitation Medicine Special Interest Group on Mild Traumatic Brain Injury and the concussion grading system by the American Academy of Neurology	EEG synchrony between F7 and Fp2 (reduced) EEG synchrony between F7 and F4 (reduced) EEG synchrony between F8 and Fp1 (reduced)	Wilcoxon ranksum test and Cohen's <i>d</i> 1. Delta frequency: $p < 0.05$, $d = 1.19$ 2. Theta: $p < 0.05$, $d = 1.07$ 3. Beta-1: $p < 0.05$, $d = 1.06$ 4. Beta-2: $p < 0.05$, $d = 1.20$ Wilcoxon ranksum test and Cohen's <i>d</i> 1. Delta: $p < 0.05$, $d = 1.00$ Wilcoxon ranksum test and Cohen's <i>d</i> 1. Gamma: $p < 0.05$, $d = 0.92$
Thatcher et al. (1991) "Comprehensive Predictions of Outcome in Closed Head-Injured Patients" <i>Notes:</i> a gradient of prognostic strength of diagnostic measures was EEG phase > EEG coherence > GCS-T > CT scan > EEG relative power	162	None	N/A	Closed head injury and admittance to Neurotrauma hospital center	EEG phase	Prediction accuracy (extreme outcome scores) (1 year) 90.2% Correlation (intermediate scores) $R = 0.664$
Thornton (2003) "The electrophysiological effects of a brain injury on auditory memory functioning. The QEEG correlates of impaired memory" <i>Notes:</i> twenty-seven patients of the mTBI group were on various medications. Age was statistically different between groups (mTBI group was slightly older)	85	56	Eyes closed, resting, wakeful, during auditory memory task Eyes open, resting, wakeful, during auditory memory task	Loss of consciousness <20 min	Connectivity measures (includes phase and coherence)	<i>t</i> -Test 1. Lowered beta 1 phase and coherence ($p < 0.05$) 2. Lowered beta 2 phase and coherence ($p < 0.05$)

Evidence of efficacy (discriminant functions)

Nine studies were identified that investigate the utility of discriminant function analysis of qEEG data for the detection of mTBI (Table 5). Four studies investigate the efficacy of the same discriminant function currently under development by BrainScope, Inc. (McCrea et al., 2010; Naunheim et al., 2010a,b; Naunheim and Casner, 2010; Barr et al., 2012; O'Neil et al., 2012; Prichep et al., 2012a,b). McCrea et al. (2010) introduces the BrainScope method and device in which seven qEEG features comprise the discriminant function. The group does not provide complete details in this paper, but report the discriminant function consists of measures of asymmetry, coherence, and spectral power in the beta frequency range. Of note, the device only acquires data from three frontal electrode sites, and thus discrimination cannot be based on large network interactions. Twenty-eight concussed athletes were compared to age-matched controls and the data indicated statically significant differences between injured and control groups immediately after injury and 8 days post-injury, but not at day 45 post-injury. While specifics of the discriminant function are missing, the study is sound and provides evidence that the BrainScope discriminant function is efficacious as a detection tool immediately after injury.

The Barr et al. (2012) study is similar to the McCrea study, but recorded qEEG from a larger cohort of mTBI patients and healthy controls and used a five electrode montage. Similar results were reported as well; statistically significant discriminant function indices were observed on the day of injury and at day 8 post-injury, but not at day 45 post-injury. A larger difference (yielding higher significance criterion) was observed compared to the McCrea et al. (2010) study, implying that the discriminant function was altered compared to the McCrea version. However, no details were provided about the specific measures that comprise the function; thus this possibility cannot be confirmed.

O'Neil et al. (2012) also report on the utility of the BrainScope discriminant function, but do not use a control group. The study compares the classification outcome of the discriminant function (called the TBI-index) to classification by medical examination and CT scan. The sensitivity of the discriminant function was good (94.7%), but specificity and positive predictive value were poor (approximately 50%). Problems with the study design are not evident, but the results suggest improvement of the BrainScope discriminant function is required to attain reasonable specificity and avoidance of false negatives.

Table 5 | mTBI studies using discriminant functions.

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
<p>Barr et al. (2012)</p> <p>“Measuring brain electrical activity to track recovery from sport-related concussion”</p> <p>Notes: this study provides further evidence for the BrainScope discriminant function as a potential mTBI diagnostic tool and may suggest utility after acute phases of injury. Commercial funds (BrainScope) were used to complete this study</p>	59	31	Eyes closed, resting, wakeful	Concussion (diagnosed at hospital admittance)	<p>BrainScope index (proprietary discriminant function index)</p> <p>Course of recovery (day of injury to day 8–45)</p> <p>Course of recovery, control group</p>	<p>t-Test, corrected for unequal n's (TBI vs. control)</p> <p>1. Day of injury ($t = 3.75, p = 0.0004$)</p> <p>2. Day 8 ($t = 2.76, p = 0.008$)</p> <p>3. Day 45 ($t = 1.49, p = 0.15$) (NS)</p> <p>One-way ANOVA (TBI group)</p> <p>1. Day of injury compared to day 8 and day 45 ($F = 3.2; p = 0.046$)</p> <p>One-way ANOVA (control group)</p> <p>1. Day of injury compared to day 8 and day 45 ($F = 0.5; p = 0.67$) (NS)</p>
<p>Leon-Carrion et al. (2008)</p> <p>“A QEEG index of level of functional dependence for people sustaining acquired brain injury: the Seville independence index (SINDI)”</p> <p>Notes: investigates validity and reliability of a qEEG discriminant function for evaluating patient functional dependence. This function is less likely to be accurate for various levels of mTBI severity</p>	40 (TBI)	40 (TBI patients, FIM + FAM score binning) Group 1: complete dependence Group 2: modified dependence Group 3: independence	Eyes closed, resting, wakeful	CT or MRI scan	<p>Mean SINDI score</p> <p>Correlation between new discriminant and FIM + FAM scores</p> <p>Correlation between predicted scores from multiple regression and FIM + FAM scores</p> <p>Leave-one-out method (discriminant function validation)</p> <p>External validation (33 patient group)</p>	<p>One-way ANOVA</p> <p>Group 1 vs. Group 2 vs. Group 3 ($F = 48.9, p < 0.0001$)</p> <p>Pearson coefficient</p> <p>$R = 0.81 (p < 0.001)$</p> <p>Pearson coefficient</p> <p>$R = 0.85 (p < 0.0001)$</p> <p>Classification accuracy (96.65%)</p> <p>Classification accuracy (75%)</p>
<p>McCrea et al. (2010)</p> <p>“Acute effects and recovery after sport-related concussion: a neurocognitive and quantitative brain electrical activity study”</p> <p>Notes: this study used the BrainScope device, currently under commercial development. The BrainScope TBI index discriminant is based on 7 qEEG variables identified as good measures for comparison and differentiation (by ANOVA) and converted to standard z-scores</p>	28	28	Eyes closed, resting, wakeful Frontal electrode site data acquisition only (FP1, FP2, AFz)	Concussion diagnosis (using American Academy of Neurology Guideline for Management of Sports Concussion)	Multivariate discriminant (BrainScope TBI index) combining various measures across frequency bands (main variables included measures of asymmetry, coherence, high beta power, and low beta power)	<p>MANOVA</p> <p>Comparison between injured and control groups</p> <p>1. Baseline: $F = 1.65, p = 0.164$ (NS)</p> <p>2. At injury: $F = 4.4, p = 0.002$</p> <p>3. Day 8: $F = 2.53, p = 0.04$</p> <p>4. Day 45: $F = 0.6, p = 0.74$ (NS)</p>
<p>O'Neil et al. (2012)</p> <p>“Quantitative brain electrical activity in the initial screening of mild traumatic brain injuries”</p> <p>Notes: this study describes the BrainScope Index (a qEEG discriminant function) as an effective screening tool for emergency room patients with suspected TBI. Note that BrainScope funded this study and authors are BrainScope employees or consultants</p>	119	None	Eyes closed, resting, wakeful	American congress of rehabilitation criteria	<p>TBI-Index</p> <p>TBI-Index plus New Orleans Criteria (NOC)</p> <p>Correlation between TBI-Index and NOC</p>	<p>Sensitivity = 94.7</p> <p>Specificity = 49.4</p> <p>Positive predictive value = 47.4</p> <p>Negative predictive value = 95.3</p> <p>Positive likelihood value = 1.92</p> <p>Negative likelihood value = 0.10</p> <p>Odds ratio = 18.5</p> <p>Sensitivity = 97.0</p> <p>Specificity = 50.6</p> <p>Positive predictive value = 48.05</p> <p>Negative predictive value = 97.62</p> <p>Positive likelihood value = 1.97</p> <p>Negative likelihood value = 0.06</p> <p>Odds ratio = 36.1</p> <p>Pearson correlation</p> <p>$R = 0.33, p < 0.0001$</p>

(Continued)

Table 5 | Continued

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
<p>Prichep et al. (2012a) “Classification of traumatic brain injury severity using informed data reduction in a series of binary classifier algorithms”</p> <p>Notes: this method provides evidence for algorithms that can be used in portable devices to effectively score suspected mTBI patients based on qEEG recording analysis. The sensitivities and specificities were reported to be better than neurocognitive assessment tools, such as the MACE. A wide-scale multicenter trial is underway</p>	633	None	Eyes closed, resting, wakeful	<p>Glasgow coma scale >8</p> <p>Category 1: no evidence of acute injury and no visible CT scan abnormality)</p> <p>Category 2: no visible CT scan abnormality; neurocognitive assessment</p> <p>Category 3: presence of acute injury (visible CT scan abnormality)</p>	<p>Custom algorithm 1 (captures wide range of measures)</p> <p>Custom algorithm 2 (captures wide range of measures)</p>	<p>Classification of Category 3 from Categories 1 and 2</p> <p>Sensitivity = 96.3%</p> <p>Specificity = 77.5%</p> <p>Positive predictive value = 47.1%</p> <p>Negative predictive value = 99.0%</p> <p>AUC = 0.911</p> <p>Cohen's <i>d</i> = 1.94</p> <p>Classification of Category 1 from Categories 2 and 3</p> <p>Sensitivity = 80.5%</p> <p>Specificity = 73.9%</p> <p>Positive predictive value = 85.4%</p> <p>Negative predictive value = 66.5%</p> <p>AUC = 0.797</p> <p>Cohen's <i>d</i> = 1.29</p>
<p>Thatcher et al. (2001) “An EEG Severity Index of Traumatic Brain Injury”</p> <p>Notes: Nuwer et al. (2005) criticizes this paper indicating that factors such as drowsiness and medication are well known to effect EEG results, contrary to the results of this study</p>	108 (40 mTBI, 25 moderate TBI, 2 severe TBI) 503 (cross- validation)	None	Eyes closed, resting, wakeful	mTBI subgroup: Glasgow coma score 13–15; posttraumatic amnesia <1 h; loss of consciousness <20 min	EEG severity index (discriminant function)	<p>Classification accuracy</p> <p>mTBI accuracy = 95.08%</p> <p>Pearson correlation</p> <p>1. EEG index and neuropsychological performance (various tests) ($p < 0.05$)</p> <p><i>t</i>-Test</p> <p>1. Mild vs. moderate ($p < 0.0001$)</p> <p>2. Mild vs. severe ($p < 0.000001$)</p> <p>3. Moderate vs. severe ($p < 0.00001$)</p>
<p>Thatcher et al. (1989) “EEG discriminant analysis of mild head trauma”</p> <p>Notes: this study showed that EEG discriminant functions can be accurately (> 90%) be used to classify normal subjects vs. those with mild TBI. Nuwer contends that results from use of this discriminant function have not been published since 1989 and the TBI patients were on a variety of medications that could skew the results</p>	608	108	N/A	Glasgow coma score 13–15; loss of consciousness <20 min	<p>Thatcher discriminant function (comprises 20 measures) accuracy</p> <p>Thatcher discriminant score change (for injured patients) over 2 weeks</p> <p>Thatcher discriminant score change (for injured patients) vs. number of days from injury to EEG test</p>	<p>1. 204 mTBI subjects vs. 83 controls (94.8% accuracy)</p> <p>2. 130 mTBI subjects vs. 21 controls (95.4% accuracy for mTBI, 90.5% for normals)</p> <p>3. Test-retest classification accuracy using 93 patients ranged from 77.8 to 92.3%</p> <p>4. Off-site test with 70 new patients (92.8% accuracy for TBI patients and 100% for normals)</p> <p>Pearson correlation</p> <p>$R^2 = 29.9\%$, $p < 0.68$ (NS)</p> <p>Pearson correlation</p> <p>$R^2 = 48.3\%$, $p < 0.38$ (NS)</p>
<p>Thornton (1999) “Exploratory investigation into mild brain injury and discriminant analysis with high frequency bands (32–64 Hz)”</p> <p>Notes: introduces a discriminant function for mTBI based on high frequency frontal coherence (2945 variables). Author acknowledged the study as exploratory and preliminary. Combination of both Thatcher and new discriminant functions resulted in perfect accuracy</p>	32	52	Eyes closed, resting, wakeful	Hit head on part of car during car accident; loss of consciousness <2 min or none	<p>Thatcher discriminant (over 1 year post-injury)</p> <p>New high-frequency (up to 64 Hz) discriminant</p> <p>New high-frequency discriminant plus Thatcher discriminant</p> <p>FP1 position variables</p> <p>Relative power</p> <p>Coherence theta</p> <p>Coherence beta 2</p> <p>Phase beta2</p>	<p>Accuracy (79% for injured group)</p> <p>Accuracy (89% for injured group across all time periods; 100% for injured group within 1 year of injury)</p> <p>False hit rate (normal sample = 52%)</p> <p>Accuracy = 100%</p> <p>Levene's test for homogeneity of variances</p> <p>$p < 0.05$ for all variables</p>

(Continued)

Table 5 | Continued

General study information (spectral analysis)	Study design				Results	
	mTBI group (n)	Control group (n)	qEEG recording condition	Criteria for TBI patient	Measures	Statistical test/ comparison/significance
Trudeau et al. (1998) “Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion” <i>Notes:</i> this study provides data that suggests the Thatcher discriminant function can be used to differentiate previous blast-induced mTBI among veterans suffering from PTSD from those PTSD patients who did not suffer a blast mTBI. While the discriminant function was not able to accurately bin TBI vs. non-TBI, the sample size was small and the range in age and post-injury timeframe was quite large	27 (blast history)	16 (no-blast history)	Eyes closed, wakeful	PTSD patient with blast history (note: control group also PTSD patients)	Thatcher discriminant score	t-Test Blast group vs. no-blast group ($t = 5.4$, $df = 41$, $p < 0.0001$) t-Test Regrouping of TBI history vs. no-TBI history ($t = 0.32$, $df = 41$, $p = 0.75$) (NS) ANOVA ADHD, other mTBI history, TBI history, or psychoactive substance abuse (no significance)

Prichep et al. (2012a) provides data from a large mTBI group of 633 patients. Although the study design was similar to O’Neil et al. (2012), the project was substantially improved by including comparison to other approaches and improving the complexity of the analysis. For example, Prichep et al. compared the BrainScope discriminant function to a more relevant group of common TBI assessment tools (e.g., military acute concussion evaluation) and inclusion of an “artifact detection module” to minimize EEG noise and artifacts. The discriminant function itself was significantly more complex and includes variables such as spectral analysis measures, information theory-based measures, scale-free brain activity measures, fractal dimension measures, functional connectivity measures, and various multivariate measures. Two algorithms were devised to separate various levels of severity of TBI and specificity was improved compared to O’Neil et al. (2012). Specifically, the new discriminant function was able to differentiate between mTBI and moderate/severe TBI patients with a sensitivity of 80.5% and a specificity of 73.9%. Positive predictive value was also improved compared to the O’Neil data (85.4%), but negative predictive value was poorer (66.5%). These results indicated the newer BrainScope discriminant function was able to detect mTBI, differentiate it from more severe forms, and decrease incidence of false negative classification. Overall, this paper provides excellent evidence that a well-designed discriminant function may be a serviceable mTBI detection tool.

Leon-Carrion et al. (2008) described another discriminant function not associated with BrainScope. However, this discriminant function, the Seville independence index (SINDI), was built to classify patients according to the level of functional dependence, such as complete dependence, modified dependence, and independence. These classifications are less meaningful for initial detection of injury, but rather are used to predict the level of care required during the rehabilitation phase. The discriminant function comprised nine qEEG variables including four coherence variables, three phase lag variables, one absolute amplitude

variable, and one absolute asymmetry variable at specific frequency bands. Accuracy was 100% for classification between complete dependence ($n = 15$) and independence ($n = 14$), which may correlate with severe TBI and mTBI, respectively. In addition, the SINDI scores correlated well ($p < 0.0001$) with established tests of functional dependence (Functional Independence Measure + Functional Assessment Measure). Overall, this paper reports the qEEG-based discriminant function may be used to predict the level of functional dependence in injured patients, but does not investigate the diagnostic potential of SINDI.

The remaining papers in the literature index present results based on a collection of discriminant functions from the same group. The original discriminant function comprised 20 measures of coherence, phase, amplitude asymmetry, and relative power at various frequency bands (Thatcher et al., 1989). The function was reported to be >90% accurate in discriminating mTBI patients (Glasgow coma score 13–15; loss of consciousness <20 min) from healthy controls in a large dataset (total of 608 mTBI patients and 108 controls). It also reported good test–retest accuracy using 93 patients (77.8–92.3%). The paper, however, has received strong criticism since the TBI patients were on a variety of medications (Nuwer et al., 2005). The same group published another report on another discriminant function that used 16 measures of EEG coherence, phase, and amplitude asymmetry (Thatcher et al., 2001). Notably, none of the measures used in the 2001 study were the same as those in the 1989 study. This discriminant function was able to classify mTBI from moderate TBI with high probability of success (t -test, $p < 0.0001$). Overall classification accuracy of mTBI patients from controls was also high (95%). This study was criticized since it was assumed that medications did not alter EEG, even though such an effect is widely accepted in the field (Nuwer et al., 2005). Nuwer’s argument does not, however, question the overall study design or methodology [unlike the criticism leveled against Thatcher et al. (1989)]. The Thatcher et al. (1999) discriminant function was also tested in concert with another

discriminant function and the authors found the discriminant to maintain reasonable classification accuracy (79%) over 1 year post-injury. Supplementation with a new high-frequency discriminant function improved accuracy to 100% in a sample group of 32 mTBI injured patients and 52 controls. Use of the high-frequency discriminant function alone was reported to provide not only high accuracy (89%) but also a high false hit rate (52%). These studies also suggest high potential value of using a discriminant function as a mTBI detection tool.

Research gaps and future directions (discriminant functions)

The primary challenge in the use of discriminant functions with qEEG is in deciding the most appropriate functions to use, which is directly tied to which features are most relevant. The problems here are threefold. First, there are an extremely large number, potentially hundreds, of possible analytic approaches and data features, which could be used as the basis for classification. These range from time-based measures, such as ERPs, to frequency-domain analytics, to more complex time-frequency hybrid features such as cross-channel phase relationships described above. Second, the function or class of functions used for discrimination must be relatively specific to the state being detected, so as to include both a high successful “hit” rate, and decrease as much as possible the occurrence of false-identifications. That is, in the example of mTBI, the functions must be precise enough to discriminate not only the occurrence of mTBI from no trauma but also the occurrence of trauma from other states such as extreme exhaustion, sleepiness, or cognitive fatigue, which may share similar response features. Finally, in most cases discrimination requires either some level of *ad hoc* adjustment or comparison against a known baseline in order to perform accurately for multiple individuals, due to the high variability between individuals, and between situations. Access to a state considered to be “ground truth” is required. While this is generally not a problem in research, gaming, or repeated-access medical applications in which the conditions of detection system can be predicted and controlled, access to the patient will most likely occur only after trauma has occurred.

Summary of analysis (discriminant functions)

qEEG-based discriminant functions represent a promising solution for detecting mTBI, since the use of multiple measures in the evaluation process improves specificity and sensitivity. Studies with large sample sizes have reported strong discriminatory abilities of discriminant functions (Thatcher et al., 2001; Prichep et al., 2012a). Criticism of earlier studies has been warranted due to the known effects of medication on the EEG, but improved study design of more recent studies (i.e., Prichep et al., 2012a) suggests discriminant functions may be considered highly valuable mTBI detection tools.

ADDITIONAL MEASURES NOT REPRESENTED IN THE DOWN SELECTED qEEG LITERATURE

Additional EEG-related technologies not represented in the original literature search are also relevant to mTBI detection and deserve consideration here. Many of these technologies are based on newer mathematical analysis techniques not previously investigated with respect to mTBI. Relevant technologies include assessment using ERPs, information dynamics, symbolic dynamics,

analysis of causal relationships, and graph theory. Each technology is introduced below and includes a summary of the available evidence for mTBI detection utility based on additional literature reviews.

EVENT-RELATED POTENTIALS

Event-related potentials are stereotyped responses to a discrete sensory, cognitive, or motor event. An ERP is distinguished from an evoked potential (EP) by having a longer latency and in being altered by the cognitive significance of the stimulus to the subject. EPs may be referred to as “exogenous” because they are strongly dependent on the physical properties of the stimulus being used to elicit the response (e.g., auditory vs. visual stimulation). Conversely, ERPs may be described as “endogenous” in nature because, although they are also related to some external event, they are heavily influenced by higher level cognitive processes and are less dependent on the stimulus modality or physical characteristics of the stimulus. Can ERPs reliably diagnose mTBI? Gaetz and Bernstein (2001) reviewed the use of ERPs in the assessment of traumatic brain injury. Specifically, they considered alterations in the amplitudes and latencies of well characterized components of ERPs, for example, the P3, as indicators of injury. They concluded:

Visual P3 latency seems to be the most sensitive electrophysiologic procedure covered in this review. All studies using this technique to assess mTBI have found differences in P3 latency compared with normal controls. In addition, the P3 word technique may be very useful for the simultaneous assessment of PTSD, malingering, and brain injury. This procedure seems to be sensitive to injury while resistant to false positives when a 2.5 SD normal limit is used.

and,

An electrophysiologic assessment battery may be the most effective method to detect differences in MTBI subjects who experience cognitive dysfunction.

In addition, Lew et al. (2006) also suggested that “longer latency ERP components hold promise in predicting recovery of higher cognitive functions.” Since deficits in emotional processing may be an element in the clinical presentation of TBI, ERP investigations using emotionally valenced stimuli (Catani, 2003; Lew et al., 2005b; Solbakk et al., 2005) may be particularly informative with this patient population.

There are, however, two notable caveats that are unique to the collection of ERPs. First, because responses are analyzed in respect to the occurrence of a specific event, there is a necessity for a more complex data acquisition system than in the passive collection of qEEG data (Spencer, 2005). Specifically, a secondary device, system, or method must be available to provide the stimulus used to drive the ERP (examples include a PC and monitor, audio amplifier, LED driver, or vibrotactile stimulator). The stimulation device must be very tightly coordinated with the EEG data acquisition system (on a sub-millisecond time scale), so that accurate time-locking of the ERP to the original event(s) can be achieved. While this level of integration is not technically challenging, it adds bulk, complexity, and additional use effort on behalf of the device operator and requires special EEG acquisition hardware,

which is designed for integration with other devices. It should be noted, however, that ERPs may be used in clinical settings with fairly minimalistic equipment.

A second caveat of ERPs that stems from the reliance upon a stimulation paradigm is the intimate, but somewhat limiting, specificity between the stimulus used and the type of brain activity, which will occur in response to that event. By definition, the response elicited by an ERP is related to a specific event, and (in a good paradigm) will include response *only* to that event, because of the extreme complexity and high specificity of various sensory regions of the brain. For example, at least in a normal healthy brain, auditory-evoked-potentials will not activate the occipital cortex (which is primarily dedicated to vision), while visual-evoked-potentials tend to be isolated to this very region. As a result, the type of paradigm used to elicit ERPs is critical to their understanding and analysis, and leaves opportunity for abnormalities in other, non-stimulated brain regions to be overlooked. In the case of mTBI, which can manifest in a wide variety of manners and stem from many possible neurophysiological dysfunctions, it is a substantial challenge to identify a single paradigm, which might be sufficient to cover all, or even the majority of potential cases.

Besides the studies referenced above, a large number of other published reports have obtained ERPs from TBI patients (Table 6). However, the collective experience does not yet provide a definitive answer as to whether ERP is an accurate diagnostic tool (Rapp and Curley, 2012). To date, the examination of ERPs obtained from TBI patients has been limited to reports of differences in amplitude and latencies of identified components of the ERP.

ADVANCED SIGNAL PROCESSING TECHNOLOGIES

This section provides evidence that the clinical utility of qEEG may be advanced significantly by expanding the set of measures that are computed from EEG signals. The mathematical field of dynamical systems theory has expanded dramatically during the past 30 years. Research activity is continuing and, indeed, accelerating. To date, the application of these new methods has been mostly confined to the analysis of physical and financial systems. These methods have not yet received systematic application in EEG. Four areas are particularly promising: information dynamics, symbolic dynamics, measures of causal relationships, and measures of network dynamics derived from graph theory.

Information dynamics

A digitized EEG signal is a sequence of voltage measurements. As classically defined, the Shannon entropy (Shannon, 1948) of this signal is insensitive to the sequential order of the voltage measurements. That is, if the voltage measurements are randomly shuffled, the same value of Shannon entropy will be obtained. Kolmogorov (1958, 1959) and Sinai (1959) extended the concept of entropy by constructing a generalization of the original concept that quantifies the sequential structure of a signal. Kolmogorov–Sinai (K–S) entropy has been described as the rate at which a system generates information (Eckmann and Ruelle, 1985), which may also be considered the central function of the CNS. K–S entropy and related measures provide the mathematical foundation of information dynamics (Deco and Schürmann, 2001). While K–S entropy is a

Table 6 | Index of ERP studies of traumatic brain injury.

Arciniegas and Topkoff (2004)	Gaetz and Weinberg (2000)	Olbrich et al. (1986)
Arciniegas et al. (2005)	Gaetz and Bernstein (2001)	Onofrj et al. (1991)
Baguley et al. (1997)	Geisler et al. (1999)	Papanicolaou et al. (1984)
Bennouna et al. (2007)	Giaquinto (2004)	Perlstein et al. (2006)
Broglio et al. (2009)	Gosselin et al. (2006)	Polo et al. (2002)
Campbell et al. (1986)	Gosselin et al. (2011)	Pontifex et al. (2009)
Campbell et al. (1990)	Gosselin et al. (2012)	Potter and Barrett (1999)
Campbell and DeLugt (1995)	Heinze et al. (1992)	Potter et al. (2001)
Catani (2003)	Kaipio et al. (1999)	Potter et al. (2002)
Chen et al. (2006a)	Kaipio et al. (2001)	Pratap-Chand et al. (1988)
Clark et al. (1992)	Kane et al. (1996)	Rappaport et al. (1990)
Cremona-Meteyard and Geffen (1994)	Keren et al. (1998)	Reinvang (1999)
Curry (1980)	Lachapelle et al. (2008)	Reinvang et al. (2000)
Curry et al. (1986)	Lavoie et al. (2004)	Reuter and Linke (1989)
Deacon-Elliott and Campbell (1987)	Lew (2001)	Rizzo et al. (1978)
Deacon-Elliott et al. (1987)	Lew (2005)	Rugg et al. (1988)
Deacon et al. (1991)	Lew et al. (1999)	Rugg et al. (1993)
Deacon et al. (1991)	Lew et al. (2002)	Sangal and Sangal (1996)
De Beaumont et al. (2007a)	Lew et al. (2003)	Segalowitz et al. (1992)
De Beaumont et al. (2007b)	Lew et al. (2004)	Segalowitz et al. (1997)
De Beaumont et al. (2009)	Lew et al. (2005a)	Segalowitz et al. (2001)
di Russo and Spinelli (2010)	Lew et al. (2005b)	Solbakk et al. (1999)
Drake and John (1987)	Lew et al. (2008)	Solbakk et al. (2000)
Duncan et al. (2003)	Lew et al. (2006)	Solbakk et al. (2002)
Duncan et al. (2005)	Lew et al. (2007a,b)	Solbakk et al. (2005)
Dupuis et al. (2000)	Mazzini (2004)	Spikman et al. (2004)
Dywan and Segalowitz (1996)	Mazzini et al. (1999)	Unsal and Segalowitz (1995)
Elting et al. (2008)	Mazzini et al. (2001)	Viggiano (1996)
Folmer et al. (2011)	Münste and Heinze (1994)	von Bierbrauer and Weissenborn (1998)
Ford and Khalil (1996a)	Olbrich et al. (1986)	Wang et al. (2004)
Ford and Khalil (1996b)	Onofrj et al. (1991)	Werner and Vanderzant (1991)
Gaetz et al. (2000)	Papanicolaou et al. (1984)	
	Perlstein et al. (2006)	

limiting process requiring, by definition, an infinite amount of data, it is possible to construct approximations computed with finite data sets. The most commonly utilized approximations are approximate entropy (Pincus, 1991) and sample entropy (Richman and Moorman, 2000). Approximate entropy and sample entropy have been used to quantify EEG records (Bruhn et al., 2000; Abásolo et al., 2005; Sabeti et al., 2009; Yuan et al., 2011; Yun et al., 2012), heart interbeat interval sequences (Pincus and Goldberger, 1994; Ho et al., 1997), and human postural sway data (Ramdani et al., 2009). Insofar as we know, they have not been used in the analysis of EEGs obtained from TBI patients.

A variant of sample entropy is multiscale entropy (Costa et al., 2002). The original time series is used to construct a sequence of coarse-grained time series. The Scale 2 time series is obtained by averaging every two values. The Scale 3 time series is obtained by averaging every three values, and so on. The sample entropy is calculated for each time series to produce entropy as a function of temporal scale. The procedure was originally applied to the analysis of heart interbeat interval sequences and was found to discriminate between healthy controls and patients presenting congestive heart failure, atrial fibrillation or advanced age (Costa et al., 2002, 2005). The same method has been used in the analysis of EEG signals to discriminate between control participants and those with autism spectrum disorder (Bosl et al., 2011; Catarino et al., 2011), Alzheimer's disease (Park et al., 2007; Mizuno et al., 2010), schizophrenia (Takahashi et al., 2010), and Parkinson's disease (Chung et al., 2013) patients. Insofar as we know, multiscale entropy has not been used to analyze EEG records obtained from TBI patients. The approach was, however, used to analyze intracranial pressure records obtained from TBI patients where it was found that multiscale entropy correlates with outcome.

There are technical issues associated with estimation of multiscale entropy that require attention. Nikulin and Brismar (2004) argued (in our view, correctly) that the scaling length in the embedding space used to calculate sample entropy should be adjusted with the temporal scale of the time series. In their calculations with simulated data, the temporal scale dependence of entropy was lost when this modification was introduced. Costa et al. (2004) replied and argued that in the case of the heart interbeat interval data analyzed in their paper, scale dependence is preserved. Wu et al. (2013) noted that the coarse graining procedure used in Costa et al. (2002), and in other papers using the method, reduces the length of the data set with each increase in temporal scale length. Substituting a moving average retains much of the multiscale characteristics of the original implementation of multiscale entropy without introducing the loss of reliability that results from attempting entropy calculations with small data sets. Systematic validation calculations are required to confirm this assertion.

Symbolic dynamics

As will be seen, the terms entropy and complexity lose specificity, rather than gain it, as a function of time. Complexity measures derived from symbolic dynamics share the important property of sequence sensitivity with K-S entropy and its variants. As the term complexity is used here, there is a fundamental difference between symbolic dynamic measures and K-S entropy. Approximate entropy and sample entropy are computed directly from

the voltage values. In the case of symbolic dynamic measures, the original sequence of voltages is converted to a symbol sequence. Complexity is a measure of the orderliness or lack of orderliness of this symbol sequence. The procedure for converting voltages to a symbol sequence can be simple. For example, the symbol "A" is entered into the sequence if the value of the voltage is greater than the median or the symbol "B" is entered if the voltage value is less than the median (note that the use of the median, rather than the mean, is statistically important). More elaborate procedures for generating a symbol sequence from a voltage are possible. A complicating clarification must be introduced, while the immediate emphasis here is on measures computed from symbol sequences, some of these measures, such as mutual information, can be recast in versions that utilize continuous variables such as voltages. Sequence sensitive measures of symbol sequences include topological entropy (Crutchfield and Packard, 1983), metric entropy [also in Crutchfield and Packard (1983)], forbidden word entropy (D'Alessandro and Politi, 1990), context free grammar complexity (Jiménez-Montanó, 1984), Lempel-Ziv complexity (Lempel and Ziv, 1976), mutual information (Gallager, 1968; Cellucci et al., 2006), n -th order entropy (Ebeling, 1997), and conditional entropy (Steuer et al., 2001).

Xu et al. (1994) found that the forbidden word complexity of EEG data is sensitive to the participant's behavioral state (e.g., eyes open vs. eyes closed recording conditions), mental load, and sleep stage. Watanabe et al. (2003) found that EEG Lempel-Ziv complexity changes in response to work load and eyes open vs. eyes closed recording conditions. Symbol sequence complexity measures have also been used in the analysis of clinical EEG records including assessment of schizophrenia and depression (Li et al., 2008; Sabeti et al., 2009), diagnosis of Alzheimer's disease (Abásolo et al., 2006), anesthetic depth (Fan et al., 2011), and seizure detection (Hu et al., 2006). Our limited literature review on symbolic dynamics did not locate papers using these methods in the analysis of EEG data obtained from TBI patients.

Analysis of causal relationships

The measures of functional connectivity described in Section "Functional Connectivity Measures" are used to establish the degree of association between two simultaneously recorded signals. However, these measures are insensitive to the direction of information movement. Measures of causal relationship extend the analysis of functional connectivity by addressing directionality. The operationalization of causality that was used to construct mathematical measures of directionality was published by Wiener in 1956 (Wiener, 1956). Stated simply, if measuring Signal A improves the prediction of Signal B, then the process generating Signal A is, to some degree, a causal driver of the process generating Signal B. This relationship is not necessarily unidirectional, as measuring Signal B may also improve the prediction of Signal A. The relative magnitude of these relationships can be used to define net information flow.

Mathematical methods of assessing the direction of information movement fall into four groups: linear regression methods (Granger, 1969; Sims, 1972; Kaminski et al., 2011), information theory methods (Kaneko, 1986; Vastano and Swinney, 1988; Schreiber, 2000), frequency-domain methods (Baccalá and

Sameshima, 2001; Nolte et al., 2008), and methods constructed with embedded data (Rulkov et al., 1995; Le Van Quyen et al., 1998, 1999; Arnhold et al., 1999).

There is a prior literature describing the application of these methods to scalp EEG signals (Inouye et al., 1983, 1993; Mars and Lopes da Silva, 1983; Mars et al., 1985; Hesse et al., 2003; Chen et al., 2006b). It would seem plausible to speculate that TBI alters network relationships, and that post-injury alterations of information flow direction would provide a sensitive assessment of CNS damage. Unfortunately, this optimistic anticipation has not been realized. To this end, several problems must be addressed. The first set of difficulties is specific to EEG analysis. Haufe et al. (2011) showed that because of volume conduction, all EEG channels drive each other. Their simulations indicate that Granger causality used with the usual statistical tests can lead to spurious relationships. The same authors subsequently constructed procedures that can, to a degree, address these difficulties (Haufe et al., 2013). The second set of difficulties exists independently of the special problems associated with EEG. Namely, mathematical analysis shows that spurious identifications of causality can occur (He and Maekawa, 2001; Breitung and Swanson, 2002; Albo et al., 2004).

An additional complication should be considered: causal relationships are not static. Consider two processes, Process A and Process B. Suppose that Process A is a strong causal driver of Process B from time t_0 to time t_1 . Now suppose this relationship reverses and Process B is a strong driver of process A from time t_1 to time t_2 . If the analysis is conducted over time t_0 to time t_2 , evidence of any causal relationship may be lost. Therefore, the identification of transitions between domains of dynamical behavior is a first step in causal analysis. The identification of transitions between different dynamical regimes is not, however, as straightforward as one might suppose, and this characteristic difficulty is particularly true of EEG data. While noise contamination can be a main cause, the problem can be more subtle. For example, transitions in CNS activity form a temporal hierarchy (Kiebel et al., 2008; Perdikis et al., 2011a,b; Papo, 2013), and a transition that is dynamically significant on a time scale of 1 s may not be significant on a time scale of 1 min (Rapp et al., 2013b). Causal relationships will show similar time-scale dependence. Therefore, as is often the case, the translation of an elegant mathematical concept to practical application in EEG can be more difficult than initially anticipated.

Graph theory

Viewed mathematically, a network is a collection of nodes and edges (lines). When applied to EEG, the nodes are electrodes and the edges are the connections between them. There are three possible characterizations of edges. In the simplest case, the edge is either present or absent. This is implemented by selecting a connectivity measure from the previously described measures and selecting a threshold. A connection between two electrodes is deemed to be present if the connectivity measure's value exceeds the threshold and absent if the value is less than the threshold. A second possible characterization of an edge is a weighted edge where the strength of the connection between two electrodes is determined by the value of the selected connectivity measure. The third characterization of an edge is the directed edge where, in

Table 7 | Studies reporting altered network geometries in neuropsychiatric disorders.

Disorder/dysfunction	Relevant publications
Alzheimer's disease	Stam et al. (2007)
CNS tumor	Bartolomei et al. (2006)
Depression	Leistedt et al. (2009), Park et al. (2014)
Epilepsy	Bernhardt et al. (2011), Ponten et al. (2007), van Dellen et al. (2009)
Schizophrenia	Li et al. (2008), Rubinov et al. (2009)
Traumatic brain injury	Cao and Slobounov (2010), Castellanos et al. (2011a), Castellanos et al. (2011b), Nakamura et al. (2009), Tsirka et al. (2011), Zourdakos et al. (2011), Irimia et al. (2013a), Irimia et al. (2013b), Goh et al. (2014)

addition to a weighting, the direction of information transfer is determined using a causality measure.

Once the geometry of the network has been determined, it is possible to use the methods of graph theory to provide a concise, quantitative description. The most commonly employed metrics are the clustering coefficient and the path length (Watts and Strogatz, 1998). The validity of these measures in characterizing the CNS is suggested by Smit et al. (2008). The investigators examined EEG records from 574 monozygotic or dizygotic twins and found that 46–89% of individual differences in the clustering coefficient and 37–62% of individual differences in path length are heritable. Alterations of network geometries as determined by EEG, magnetoencephalography (MEG), or MRI have been found in clinical populations, including TBI patients (Table 7).

Once again, however, initial enthusiasm must be tempered by analyses showing spurious identifications of network properties. Bialonski et al. (2011) examined binary networks (an edge is either present or absent) constructed by a simple threshold criterion. These results suggest that “small world” topologies in networks constructed from empirical data “may be partly or solely due to finite length and frequency content of time series.” They suggest that random networks constructed from surrogate data may provide important comparisons for results obtained from multichannel EEG [surrogate data calculations are an important statistical procedure for validating the results obtained with experimental data, Theiler et al. (1992), Prichard and Theiler (1994)]. It should be noted, however, that inappropriately constructed surrogates can result in the false-positive rejection of the surrogate null hypothesis, that is, the procedure can indicate the presence of deterministic non-linear structure in a signal constructed from linearly filtered random numbers (Rapp et al., 2001). Bli-nowska and Kaminski (2013) found that networks constructed from adirectional measures (correlation, coherence, mutual information, synchronization likelihood, transfer entropy) can result in spurious correlations. Indeed, they report that spurious correlations can outnumber true correlations. Giving all connections an equal weight (a binary network) exacerbates this problem. They recommend directional, causally dependent measures

(directed transfer function, partial directed coherence), but as noted above volume conduction in the CNS introduces significant problems when directional measures are applied to EEG signals.

DISCUSSION

CONTROVERSY WITHIN THE qEEG FIELD

The earlier literature describing the application of qEEG technologies in the assessment of TBI has been marked by strident disagreement. In 1989, Thatcher et al. published a study based on EEG records obtained from 608 patients with mTBI and 108 healthy control participants. In this study, qEEG-derived measures discriminated between the two groups with a sensitivity of 96.6% and specificity of 89.1% (as outlined presently, the reports of specificity require reconsideration). Subsequently, the same group constructed a qEEG-based Severity Index of TBI and obtained a sensitivity of 95.5% and specificity of 97% (Thatcher et al., 2001).

In 1997, in part in response to the Thatcher et al. (1989) report, a highly critical review of clinical qEEG was published (Nuwer, 1997). Nuwer concluded “on the basis of current clinical literature, opinions of most experts, and proposed rationales for their use, qEEG remains investigational for clinical use in post-concussion syndrome, mild or moderate head injury, learning disability, attention disorders, schizophrenia, depression, alcoholism, and drug abuse. . .” Nuwer continued, “Because of the very substantial risk of erroneous interpretations, it is unacceptable for EEG brain mapping or other qEEG techniques to be used clinically by those who are not physicians highly skilled in clinical EEG interpretation.”

Vigorous responses to the 1997 Nuwer paper were published by Thatcher et al. (1999), and by Hoffman et al. (1999). The Nuwer paper has been an element in court actions, for example, County Court at Law No. 1, Travis County Texas, Cause No. 227,520. As summarized by Thatcher et al. (2003), the judge in the Travis County case admitted qEEG evidence in a TBI case and denied admission of the 1997 Nuwer paper (see also *Zawski v. Giggs*). In 2005, Nuwer et al. returned to the subject and focused specifically on the application of qEEG in the assessment of TBI. Nuwer et al. concluded that “overall the disadvantages of qEEG panels and diagnostic discriminants presently outweigh the advantages of these studies in the diagnosis of MTBI.” In spite of this assessment, qEEG as a potential TBI detection tool has still received a great deal of attention since Nuwer’s 2005 paper. This more recent research argues against an unreservedly negative assessment of qEEG utility. Indeed, while the evidence supporting the sole use of qEEG (as defined by the TWG) for the assessment of mTBI is weak it would be unwarranted to conclude that EEG is not a valued metric in the search for the proper assessment protocol for mTBI. Upon expansion of the definition of “qEEG” to include other EEG-based datasets (e.g., ERPs and EPs), EEG will most likely be a necessary component of any assessment protocol for mTBI. In addition, evidence suggests that the value of qEEG in the assessment of mTBI will increase as the methods used in the analysis of these signals become more sophisticated.

Evidence supporting the value of more elegant analysis procedures for EEG in the assessment of mTBI comes in part from McCrea et al. (2010), Prichep et al. (2012a,b), and Tsirka et al. (2011). Prichep et al. (2012a,b) and McCrea et al. (2010) used

a modest EEG montage to collect short epochs of EEG that were subjected to rigorous artifact detection algorithms: traditional and non-traditional univariate and multivariate analysis procedures that feed into an informed data reduction protocol. This protocol controls for replicability, over-fitting, and cross-validation of metrics. In addition, we see the value of integration of various demographic, neurocognitive, and self-report datasets along with the physiological datasets to achieve increased sensitivity and specificity for assessment of mTBI. Tsirka et al. (2011) adds positive assessment value to this approach by using small world network metrics, which utilize mean power analysis, and synchronization likelihood parameters to assess suboptimal network organization in EEGs obtained from mTBI victims.

SPECIFICITY OF EEG BASED mTBI DETECTION

Published reports suggest that dynamical measures calculated from EEGs are altered following TBI, that is, the sensitivity of these measures to TBI is supported. Reports of high specificity must, however, be interpreted with care. While high specificities have been obtained in carefully constructed clinical studies, which compare TBI patients against healthy control participants, dynamical measures calculated from EEG records thus far are not specific to TBI. This lack of specificity is indicated by the results summarized in **Table 8**. Altered EEG synchronization is observed following traumatic brain injury, but it is also observed in most neuropsychiatric disorders. Therefore, while it may be possible to discriminate between TBI patients and healthy individuals using these measures alone, it will probably not be possible to discriminate between TBI and depression, schizophrenia, or several other clinical conditions.

Importantly, the absence of specificity does not preclude clinical utility of qEEG as an evaluation tool. Non-specific measures are particularly important in longitudinal assessment. The classical example is body temperature. Fever is non-specific, but body temperature is nonetheless a central clinical measure. Nevertheless, an important technical point on reliability must be emphasized here. Temperature would not be an effective longitudinal measure if it varied randomly between 85° and 105°. Stated differently, meaningful longitudinal application requires acceptable test–retest reliability. To date, very few test–retest reliability studies of dynamical measures calculated from EEGs have been published. Thus, systematic test–retest determinations in healthy participants are essential next steps in the construction of a clinically useful qEEG technology.

RELIABILITY OF qEEG MEASURES

The reliability of quantitative EEG measures is crucial to their clinical utility. This has been recognized at least since the pioneering work of Kennard and Schwartzman (1957). Nonetheless, test–retest reliabilities are not typically reported and this deficiency is a significant factor limiting the widespread application of qEEG. EEG reliabilities depend on the electrode site(s), the kind of electrode technology used, the frequency band, sampling frequency, the resolution of the digitizer, the duration of the recording epoch, the behavioral task implemented during the recording, the qEEG measure computed, the procedure used to compute it, and the retest interval. Additionally, there has been

Table 8 | Studies reporting altered synchronization of EEGs in various neuropsychiatric disorders.

Disorder/dysfunction	Relevant publications
AD/HD	Barry et al. (2002, 2003, 2005)
Alcohol abuse	Georgopoulos et al. (2007), Kamarajan et al. (2005)
Alexithymia	Matsumoto et al. (2006), Symond et al. (2005)
Autism	Grice et al. (2001), Just et al. (2004), Orekhova et al. (2007), Rippon et al. (2007), Welsh et al. (2005), Wickelgren (2005)
Bipolar disorders	O'Donnell et al. (2004)
Dementia	Adamis et al. (2005), Adler et al. (2003), Brunovsky et al. (2003), Georgopoulos et al. (2007), Koenig et al. (2005), Leuchter et al. (1987), Prichep et al. (2006), Stam et al. (2003)
Depression	Armitage et al. (1999), Lee et al. (2007), Linkenkaer-Hansen et al. (2005), Llinás et al. (1999), Park et al. (2007)
Hallucinations	Baldeweg et al. (1998)
HIV dementia	Fletcher et al. (1997)
Migraine	Angelini et al. (2004)
Multiple sclerosis	Georgopoulos et al. (2007)
Neuropsychiatric disorders: general reviews	Herrmann and Demiralp (2005), Llinás et al. (1999), Schnitzler and Gross (2005), Stam et al. (2003), Stam (2005), Uhlhaas and Singer (2006)
Parkinson's disease	Akbari and Gharibzadeh (2009), Levy et al. (2000), Raz et al. (2000), Stoffers et al. (2007)
Post-traumatic stress disorder	Kolassa and Elbert (2007)
Schizophrenia and other psychotic disorders	Basar-Eroglu et al. (2009), Bob (2007), Bob et al. (2008), Breakspear et al. (2004), Brenner et al. (2003), Bressler (2003), Cho et al. (2006), Ferrarelli et al. (2012), Ford and Mathalon (2005), Ford et al. (2007, 2008), Georgopoulos et al. (2007), Green et al. (1999), Hirano et al. (2008), Koukkou et al. (1995), Kwon et al. (1999), Lee et al. (2003a,b), Lewis et al. (1999, 2005), Light et al. (2006), Pinault (2008), Ramos-Loyo et al. (2009), Rockstroh et al. (2007), Roopun et al. (2008), Siegel et al. (2006), Spencer et al. (2003), Spencer et al. (2004, 2008a,b), Spencer and McCarley (2006), Symond et al. (2005), Tononi and Edelman (2000), Uhlhaas and Singer (2006), Uhlhaas et al. (2008), van der Stelt and Belger (2007), Vierling-Claassen et al. (2008), Whittington (2008), Williams et al. (2008), Winterer et al. (2000)
Traumatic brain injury	Dockree et al. (2004), Hoffman et al. (1995), Kumar et al. (2009a,b), Roche et al. (2004), Slewa-Younan et al. (2002), Thatcher et al. (1999, 2001), Thatcher (2000, 2006)

no agreement in the literature concerning the choice of statistical measure used to quantify EEG reliability. Measures that have been used in EEG studies include Cornbach alpha (Burgess and Gruzelier, 1993; Lund et al., 1995), rank correlation (Gasser et al., 1985; Van Albada et al., 2007), intraclass correlation coefficient (Fein et al., 1983; Tomarken et al., 1992; Gudmussen et al., 2007; Ambrosius et al., 2008; Gram et al., 2014), Pearson correlation coefficient (Fein et al., 1984; Salinsky et al., 1991; Tomarken et al., 1992; Kondacs and Szabo, 1999), Fisher's r (Pollock et al., 1991), two-way analysis of variance (Sloan and Fenton, 1993), coefficient of variation (Maltez et al., 2004; Fingelkurts et al., 2006), and the coefficient of determination (Fingelkurts et al., 2006). This diversity of statistical analysis has made it impossible to obtain a clear understanding of the reliability of many qEEG measures.

We recommend using the intraclass correlation coefficient to report test–retest reliability. Several considerations have motivated this recommendation including the intraclass correlation coefficient's immediate relationship to the standard error of measurement and the minimal detectable difference. These variables in turn help inform the identification of the minimal clinically important difference, where it is explicitly recognized that clinical significance is determined only in part by statistical significance (Jaeschke et al., 1989; Crosby et al., 2003).

Important conditions should be met when using the intraclass correlation coefficient in reliability studies. This is not a single measure but a class of measures. Shrout and Fleiss (1979) constructed six intraclass correlation measures and McGraw and Wong (1996) constructed ten. The choice of intraclass correlation coefficient is crucial to the analysis. Depending on the formula used, large differences in the numerical value of the coefficient can be obtained with the same data. Guidelines for the choice of appropriate statistical model for a given study, and hence the choice of the appropriate intraclass correlation coefficient, are given in Müller and Büttner (1994) who included a decision tree to summarize the selection process. As noted by Krebs (1986), it is therefore essential to identify the form of coefficient when reporting results. A specification of the coefficient's confidence interval is also a critical element in the data report (Stratford, 1989). Identification of the confidence interval is important because the interval must be considered when interpreting the coefficient. For example, Morrow and Jackson (1993) have shown that a high value of the coefficient, which suggests that the measure is reliable, can have a large confidence interval, which argues against this interpretation. Donner and Wells (1986) provide a comparison of procedures for constructing confidence intervals for the coefficient. We suggest the Wald method that was used by Zou (2012) to construct an

algorithm for estimating the sample size required in studies that use the intraclass correlation coefficient as the statistical measure of reliability.

Two additional issues should be considered in reliability studies. First, reliability is population dependent. A measure that presents adequate reliability in one population may fail to do so in a different population. Examples are found in a study of EEG reliability (Lund et al., 1995) comparing healthy controls and schizophrenics and in a study by Fein et al. (1983) that compared EEG reliabilities obtained with healthy controls and dyslexic participants. Population-dependent determination of reliability is particularly important in the investigation of traumatic brain injury because it has long been recognized that high variability is a characteristic of an injured CNS (Head, 1926; Bleiberg et al., 1997). Second, distributions presented by EEG measures can be markedly non-normal (Gasser et al., 1982). Non-normal distributions can reduce test–retest reliability (Dunlap et al., 1994). Van Albada and Robinson (2007) have shown that a transformation to a near normal distribution can improve EEG test–retest reliability.

CONCLUSION AND RECOMMENDATIONS

ELECTROPHYSIOLOGICAL ASSESSMENT AND mTBI DETECTION

Based on our critical evaluations of qEEG as an mTBI assessment tool, the following general conclusions are made:

1. qEEG provides, at best, an imperfect assessment of mTBI. The published literature does indicate, however, that it can be an important complement to other assessment procedures.
2. TBI is not a discrete clinical entity. Different injury events can initiate very different pathophysiological processes. It follows that, just as there is not a single test for cancer, there is not a single test for TBI.
3. Reports of high specificity of qEEG evaluations of TBI must be interpreted with care. High specificities have been reported in carefully constructed clinical studies in which healthy control participants were compared against a carefully selected TBI population. The published literature indicates, however, that similar abnormalities in qEEG measures are observed in other neuropsychiatric disorders. While it may be possible to distinguish a clinical patient from a healthy control with this technology, these measures are unlikely to discriminate between, for example, major depressive disorder, bipolar disorder, or TBI. The specificities observed in these clinical studies may well be lost in real world clinical practice.
4. The absence of specificity does not preclude clinical utility. Efficacy as a longitudinal clinical measure does, however, require acceptable test–retest reliability. To date, very few test–retest reliability studies have been published with qEEG data obtained from TBI patients. This is a particular concern because high variability is a known characteristic of the injured CNS.
5. Specific measures and analysis methods were qualitatively assessed based on the degree of testing in mTBI patients, the usefulness for mTBI detection as a unique entity, and the usefulness as a component in a discriminant function for mTBI detection. **Table 9** provides a summary of our findings. For example, spectral analysis has been tested extensively in mTBI

Table 9 | Summary of TWG conclusions on electrophysiological measures for mTBI detection (0 < 1 < 2 < 3 < 4).

Measure/ analysis method	History of testing in mTBI patients	Usefulness for mTBI detection as a unique entity	Usefulness for mTBI detection as part of a discriminant function
Spectral analysis	4	0	2
Connectivity measures	3	1	3
ERPs	4	2	4
Information dynamics	0	Unknown ^a	Unknown ^a
Symbolic dynamics	2	3	Unknown ^a
Analysis of casual relationships	2	2	Unknown ^a
Graph theory	1	3	Unknown ^a

^aUnknown, but high perceived potential.

patients, but its usefulness as a mTBI detection tool (in isolation) is low. The usefulness of spectral analysis as a component in a discriminant function, however, is more promising. Note that some methods require additional investigation before qualitative scores of usefulness can be assigned, but the TWG considers the methods to hold considerable promise.

RECOMMENDATIONS FOR RESEARCH AND CONTINUED ADVANCED DEVELOPMENT

The qEEG TWG recommends the following actions to best advance qEEG and other electrophysiological assessment methods as mTBI detection tools:

1. Reliability in a healthy population is a necessary, but not sufficient, property of a useful clinical measure. Systematic test–retest reliability studies of qEEG measures should be conducted as the first step in the rigorous development of a clinical qEEG technology. Reliability must be established for each candidate measure.
2. We define the clinical validity of a measure as its ability to discriminate between a clinical population and healthy controls and, ideally, its ability to discriminate between different clinical populations. For any given measure, systematic validity studies are required once reliability has been established as outlined in the first recommendation. In the first instance, these studies should compare results obtained with well characterized TBI patients and healthy controls. If the results of these studies are positive, they can be expanded to include other psychiatric populations.
3. Evidence indicates that ERPs can identify abnormalities in cases where EEGs alone are non-disclosing. It should be noted that the same signal amplifiers are used for EEGs and ERPs. Thus, there is no technical barrier to incorporating ERP measurements in an EEG evaluation, as long as careful considerations are made to ensure precise time-locking between stimulus and recording instrumentation. Reliability and validity evaluations must also be performed with ERP-derived measures.

4. The mathematical methods used in signal analysis in other application areas have expanded enormously during the past 30 years. Important growth areas include non-linear dynamical analysis, complexity measures, analysis of causal interactions, graph theory, and information dynamics. These methods have received limited application in the analysis of EEG records obtained from TBI patients. It seems possible that, as was the case in other research domains, the systematic application of these methods in the analysis of mTBI will be similarly useful. The standard mathematical procedures used in the characterization of mTBI EEG abnormalities should be expanded to incorporate these methods of analysis.
5. Reliability and validity study data should, following de-identification, be made available on a publically accessible website for download and reanalysis by other investigators. As this is standard practice in genomics research and astronomy, it should also be standard practice in neuropsychiatry. This recommendation is motivated in part by the rapid advances being made in signal analysis. Public access to well documented EEG records will make it possible for investigators throughout the world to test the reliability and validity of new mathematical measures as they are developed.
6. As argued in the second conclusion, the diversity of underlying neuropathology in the TBI population precludes the development of a single test for TBI. As a potential solution, an integrated neuropsychiatric assessment platform can be developed that will permit simultaneous acquisition of EEG records including ERPs, heart rate variability data, and eye tracking records during a neuropsychological assessment. This system should include an onboard signal analysis capability and be capable of incorporating additional data types including genomic, epigenetic, proteomic/biomarker, and imaging data. The result would be a comprehensive, statistically valid characterization of the CNS.

ACKNOWLEDGMENTS

The opinions and assertions contained herein are the private opinions of the authors and are not to be construed as official or reflecting the views of the United States Navy, Department of Defense nor the US Government. This research effort was supported by the Combat Casualty Care Research Program (CCCRP) of the U.S. Army Medical Research & Materiel Command (USAMRMC). Paul E. Rapp and David O. Keyser would like to acknowledge support from the Traumatic Injury Research Program of the Uniformed Services University of the Health Sciences, from the Defense Medical Research and Development Program and from the United States Marine Corps Systems Command. Drs. John D. Hughes and Rene Hernandez are military service members. This work was prepared as part of their official duties. Title 17 U.S.C. §105 provides that “Copyright protection under this title is not available for any work of the United States Government.” Title 17 U.S.C. §101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person’s official duties.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at <http://www.frontiersin.org/Journal/10.3389/fnhum.2015.00011/abstract>

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 04 August 2014; accepted: 07 January 2015; published online: 04 February 2015.

Citation: Rapp PE, Keyser DO, Albano A, Hernandez R, Gibson DB, Zambon RA, Hairston WD, Hughes JD, Krystal A and Nichols AS (2015) Traumatic brain injury detection using electrophysiological methods. *Front. Hum. Neurosci.* 9:11. doi: 10.3389/fnhum.2015.00011

This article was submitted to the journal *Frontiers in Human Neuroscience*.

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