

Practice Guideline: Use of quantitative electroencephalography (qEEG) for the diagnosis of mild traumatic brain injury (mTBI)

Report of the Guideline Committee of the American Clinical Neurophysiology Society

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INTRODUCTION

The traditional visual review of electroencephalogram (EEG) waveforms focuses on assessment of normal brain rhythms and detection of pathological, including epileptiform, activity. However, visual unassisted precise quantification of various frequencies is difficult. Likewise, visual analysis cannot resolve inter-related brain network oscillations or how a signal might relate to normal or abnormal cognition or consciousness.¹ Over the last several decades, investigators have tried to address these limitations using computer-driven algorithms which have broadly been referred to as quantitative EEG (qEEG).²

One application of qEEG has been in the field of mild traumatic brain injury (mTBI). This is defined as a physical injury to the brain causing compression or tearing of the tissue. Initial clinical symptoms related to mTBI may be minimal but cognitive and psychiatric symptoms may become chronic and last for weeks or months.³ The rapid and accurate identification of mTBI is an important issue for populations such as the military and sports athletes and its correct diagnosis and prognosis has many medico-legal consequences.⁴ qEEG technology has become a promising, yet controversial tool within this field since it has been felt that it can provide a rapid way to detect pathological brain patterns after mTBI.

A review of qEEG was completed by the American Clinical Neurophysiology Society (ACNS) and the American Academy of Neurology (AAN) in 1996 as part of a joint guideline to assess the clinical usefulness of the technique.⁵ At that time, it was reported that qEEG had Class I (one or more well designed, prospective, blinded, controlled clinical studies) and II (one or more well designed clinical studies such as case control, cohort, etc.) evidence, Type A (strong positive recommendation, based in Class I or overwhelming Class II evidence) and B (positive recommendation, based on Class II evidence) recommendation for use as an adjunctive tool in epilepsy and OR/ICU monitoring. Most other uses of qEEG had Class II and III (expert opinion, non-randomized historical controls, or case reports of one or

more) evidence, Type D recommendation (negative recommendation, based on inconclusive or conflicting Class II evidence), including in patients with post-concussion syndrome and mild/moderate head injury.

Since the original guidelines were published over 20 years ago there has been a great deal of advancement in the field of qEEG, particularly in the areas of Critical Care monitoring and spike/seizure detection in Epilepsy Monitoring Units. The prior guideline addressed a wide variety of clinical and investigational uses. Subsequently, a recent American Academy of Neurology Assessment updated the use of qEEG in the assessment of patients with possible Attention Deficit Hyperactivity Syndrome.⁶ This guideline is focused on qEEG as related to the diagnosis of mTBI because of its important medico-legal ramifications.

This guideline addresses the following primary aim: For patients with or without post-traumatic symptoms (abnormal cognition or behavior), does qEEG either at the time of injury or remote from the injury, as compared to current clinical diagnostic criteria, accurately identify those patients with mild traumatic brain injury (TBI) (i.e., concussion)? Secondary aims included differentiating between mTBI and other diagnoses, detecting mTBI in the presence of medications, and relevant statistical methods for measurements.

Despite extensive research, controversy regarding the utility of qEEG for the accurate diagnosis of mTBI remains. The guidelines presented below are meant to assist clinicians by providing an expert review of the clinical usefulness of qEEG techniques for the diagnosis of mTBI.

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DESCRIPTION OF THE REVIEW PROCESS

The development of this guideline follows the 2011 American Academy of Neurology (AAN) clinical process guideline development manual.⁷ All author conflict of interests (COIs) were reviewed and in compliance with AAN policy. An experienced methodologist (D.G.) supported the design of the project.

Multiple databases (Medline, EMBASE, Science Citation Index) were initially searched by a medical research librarian using the following terms: EEG OR qEEG OR quantitative EEG AND mild traumatic brain injury OR concussion. The literature search based on these criteria yielded 598 abstracts, which were then reviewed independently by two authors (J.T., R.A.); 68 abstracts were determined to meet the inclusion/exclusion criteria. The full text of these articles was then reviewed independently by the authorship group and from these, 29 articles met criteria for data extraction and grading. Nine articles were graded Class III and were included in this review (Figure 1).

Risk of bias was ascertained using the latest version of the AAN guideline development manual for risk of bias evaluation.⁷ Due to the wide diversity of methods and outcome measures in this literature, results were accepted from the included manuscripts without further group-wise statistical synthesis. This was not decided *a priori* in hopes of not inadvertently excluding evidence.

Literature Inclusion and Exclusion Criteria:

The following inclusion criteria were used (1) all languages, (2) dates January 1, 1996 (time of the last published guideline) to December 31, 2017, (3) human subjects, (4) randomized controlled trials (RCTs), case control studies, or retrospective case series, (5) studies related to use of qEEG as a diagnostic tool for mTBI with outcomes related to frequency analysis, monitoring/trend analysis, source localization, topographic analysis, statistical analysis, comparison to normative values, or other signal analysis (i.e., coherence). The exclusion criterion was (1) case series with the number of participants less than 10.

ANALYSIS OF EVIDENCE

Diagnosis of mTBI

There has been no agreement in the literature concerning the choice of qEEG analysis method.⁸⁻
¹² Spectral analysis involving signal power quantification from delta to gamma bands is most commonly used. Five Class III studies utilized spectral power as the qEEG method to assess mTBI.⁸⁻¹² Increased beta power was reported in only the left occipital head region for mTBI patients during NREM sleep [sleep cycle 1 ($F = 4.454$; $p = 0.039$), sleep cycle 2 ($F = 3.761$; $p = 0.047$), sleep cycle 3 ($F = 7.455$; $p = 0.008$)] in one study⁸ whereas another demonstrated increased beta asymmetry in only the frontal regions [control ($\mu = 1.12 \pm 0.33$), concussion ($\mu = 2.38 \pm 0.26$), $p = 0.01$]¹¹. Decreased alpha power for mTBI patients was reported in three of the studies.^{9,11,12} One of these studies reported that athletes with a history of concussion had decreased alpha power asymmetry compared to controls [control ($\mu = 4.28 \pm 0.46$), concussion ($\mu = 3.02 \pm 0.22$), $p = 0.01$]¹¹, while another showed those with mTBI and moderate-severe neuropsychological impairment had decreased global alpha power compared to those with mTBI and mild impairment ($\chi^2 = 6.47$, $p < 0.05$)⁹. Another study during REM sleep showed lower delta power at two electrodes for patients with mTBI [C3 electrode (mTBI = $0.07 \mu V^2$, controls = $0.77 \mu V^2$, $p = 0.03$); O2 electrode (mTBI = $0.56 \mu V^2$, controls = $0.69 \mu V^2$, $p = 0.02$)] and higher beta and gamma power during stage 2 NREM sleep [beta (mTBI = $0.07 \mu V^2$, controls = $0.06 \mu V^2$, $p = 0.04$); gamma (mTBI = $0.03 \mu V^2$, controls = $0.02 \mu V^2$, $p = 0.03$)].¹⁰ Similarly, increased delta power (percent of total electrode power) was reported for patients with mTBI (mTBI = $3.7 \pm 0.2\%$, controls = $2.8 \pm 0.2\%$, $p = 0.002$) but a decrease in alpha power only for those with mTBI who had developed post-traumatic epilepsy (mTBI = $2.1 \pm 0.1\%$, controls = $2.9 \pm 0.2\%$, $p = 0.005$).¹² Studies utilizing spectral power measurements were not done using diagnostic study designs, two of these included sleep recordings only^{8,10}, and another did not clearly correct for multiple comparisons¹¹.

Two Class III studies utilized a proprietary handheld frontal recording device (Brainscope®, Brainscope Company Inc, Bethesda, MD).^{13,14} One of the studies processed the collected EEG data offline to create a “TBI-index”.¹⁴ This measurement was compared with the New Orleans Criteria (NOC) to predict which patients would have a positive head CT finding. The TBI-index had improved specificity over NOC (49.4% vs 23.5% respectively) to predict head CT findings. Although the TBI-index was compared with “age expected normal values”, no controls were used in this study and the lowest risk mTBI group, without head imaging ordered, was excluded. The other Class III study utilizing the same recording technique used an offline multivariate analysis of 7 qEEG features.¹³ These were found to be abnormal for patients with mTBI at days 0 (controls $F = 0.52$, mTBI $F = 2.5$, $p < 0.05$) and 8 (controls $F = 0.56$, mTBI $F = 3.3$, $p < 0.05$), relative to the injury, but not at day 45 (controls $F = 0.86$, mTBI $F = 1.5$).

Three of the Class III studies used a variety of other analysis techniques including EEG microstates, standardized low-resolution brain electromagnetic tomography (sLORETA) activation, wavelet entropy, and graph theory measures.^{9,15,16} It was reported that patients with mTBI had durations of microstates which decreased linearly with the degree of neuropsychological impairment ($\rho = -0.541$, $p < 0.01$; $r = -0.573$, $p < 0.01$) and had reduced sLORETA activation in mTBI with moderate-severe neuropsychological impairment compared to patients with mTBI and no impairment ($F = 3.901$, $p = 0.036$).⁹ Wavelet entropy was reduced at day 7 post-mTBI and a recovery to baseline was slower after a second mTBI [occipital ($F = 179.18$, $p < 0.001$), parietal ($F = 181.98$, $p < 0.001$), temporal ($F = 98.17$, $p < 0.001$)].¹⁵ In this study, there was a comparison to an individual baseline but not against healthy controls. Graph theory measures have been reported with no small world topology differences between mTBI and control groups but regional increases in betweenness centrality [F4 electrode ($p = 0.05$), F10 electrode ($p = 0.02$)] and mixed regional increases [F10 electrode ($p = 0.01$)] and decreases (Fpz electrode ($p = 0.01$)] in degree for patients with mTBI.¹⁶ These were group-level but not individual patient differences.

Evidence Synthesis

The evidence does not support the use of qEEG to accurately identify patients with mTBI either at the time of injury or remote from the injury.

Differentiation of mTBI from related diagnoses

Some of the studies attempted to differentiate mTBI from healthy controls as well as sub-groups such as those with/without pain or with/without post-traumatic epilepsy.^{10,12} However, none of the Class III studies compared patients with mTBI to other related neuropsychiatric disorders also likely to have altered qEEG measures such as depression, autism, attention deficit hyperactivity disorder (ADHD), and migraine, so specificity for the mTBI diagnosis could not be determined. Low amplitude alpha also is considered to be a normal variation.¹⁷

Evidence Synthesis

The evidence does not support the use of qEEG to correctly differentiate mTBI from other disorders.

Presence of medications

It is possible that a variety of medications as a covariate could have altered qEEG measures and acted as a confounder. None of the included Class III studies used a wash out period for medications or included their use in the analysis. Only one of the studies specifically excluded patients for “use of psychotropic medication or other drugs known to influence sleep or motor behavior”.¹⁰

Evidence Synthesis

The evidence does not support the use of qEEG to reliably identify patients with mTBI in the presence of medication.

Differentiation between mTBI and state (drowsiness)

The patient's state of alertness (e.g., awake, drowsy, asleep) is another potential confounder to consider for qEEG measurements since it can change spectral power in specific frequency bandwidths. Six of the nine Class III studies included here reported and controlled for wakefulness. Four studies were completed while awake in an eyes closed state^{11,13,14,16} and two were done during sleep because the primary outcome was sleep-related^{8,10}. None of the studies compared qEEG measurements with the patient both awake and drowsy or asleep.

Evidence Synthesis

The evidence does not support the use of qEEG to differentiate between drowsiness and mTBI.

Statistical considerations

There is no agreement in the literature related to the statistical measures for qEEG analyses. Many times, given the number of participants, time points, electrodes, and frequency bins it is preferable to have a correction for multiple comparisons. The included Class III studies presented here used a variety of statistical analysis tools including analysis of variance (ANOVA) or multivariate analysis of variance (MANOVA) with Tukey post-hoc analysis, non-parametric Kruskal-Wallis test, receiver operating curve

(ROC), Mann-Whitney U test, or software packages with built-in statistical function (Brain Connectivity Toolbox).¹⁸ Two of the studies specifically discussed the use of multiple comparison corrections.^{11,16} It is noted that testing in 4-6 frequency bands, at 21 scalp electrodes, in 2-6 measurements each, and coherence across 21x20 electrode sites can generate many thousands of individual statistical comparisons. When judged at a likelihood of $p < 0.05$, hundreds of false positive results can occur. When performing group-level analyses, these electrodes cannot be treated as independent observations but require the use of mixed models.

Evidence Synthesis

The evidence does not demonstrate that suitable statistical methods exist when using qEEG to identify patients with mTBI.

Neurophysiological considerations

Since the neurophysiological studies reviewed here used heterogeneous methods for measurement of qEEG and neuropsychological evaluations, there are multiple sources of possible bias. This can include differences in acquisition hardware and practices such as conventional electrodes versus whole head caps and whether the technician ensures adequate impedance before recording. Other potential sources of bias could include recording techniques, amplifier properties, and whether data is down sampled prior to analysis.

Clinical Context

Identification of individuals with acute or remote mTBI is an important goal, as it is a widespread health problem in both civilian and military populations with important medico-legal ramifications. Altered brain rhythms following mTBI have been purported to occur and are a possible neurophysiologic biomarker to explore. Rapidly evolving and numerous qEEG methods with no associated clinical guidelines have led to significant controversy which exists in the field.

This review reveals a diverse dearth of evidence-based qEEG diagnostic techniques for the identification of individuals with mTBI. The best studies utilized multiple different qEEG techniques but even the most commonly used technique of spectral analysis had variations among studies with regards to recording parameters and analysis methods. There is also no standardization in regards to qEEG acquisition which can lead to inadequately performed recordings that could contain artifact inadvertently interpreted as an abnormality. It is recommended that qEEG studies be performed by a qualified EEG technician to ensure high quality data is acquired.

The identified literature does not inform about considerations regarding qEEG as a clinical diagnostic tool such as specificity for mTBI, effects of potential confounders such as patient state and medications, and appropriate statistics. The evaluation of any new diagnostic EEG test must evaluate several specific issues which have previously been outlined if it is to be deemed clinically valuable to clinicians and is clinically relevant for patients.¹⁹

CONCLUSIONS AND RECOMMENDATIONS

Practice Recommendations

For patients with or without symptoms of abnormal cognition or behavior, the evidence at this time does not support the clinical use of qEEG either at the time of injury or remote from the injury to identify patients with mTBI (Level U). Based upon the current literature, qEEG remains investigational for clinical use as a diagnostic tool for mTBI (Class III evidence).

Suggestions for Further Research

There have been no well-designed studies of qEEG-related methods for the diagnosis of mTBI. Optimal trials to validate qEEG as a tool for mTBI diagnosis would use well-accepted standards to initially define the disease population. The criteria to define a possible “abnormality” for a qEEG method should also be specified in advance before data are collected. While many qEEG measures may classify a measure as abnormal based on comparison to normative values, the test should be validated on participants different from the original cohort or normative database. Also, although qEEG methods may be able to discriminate between patients with mTBI and healthy controls, to be clinically useful, it should also be able to differentiate between mTBI patients and other conditions in the differential diagnosis.

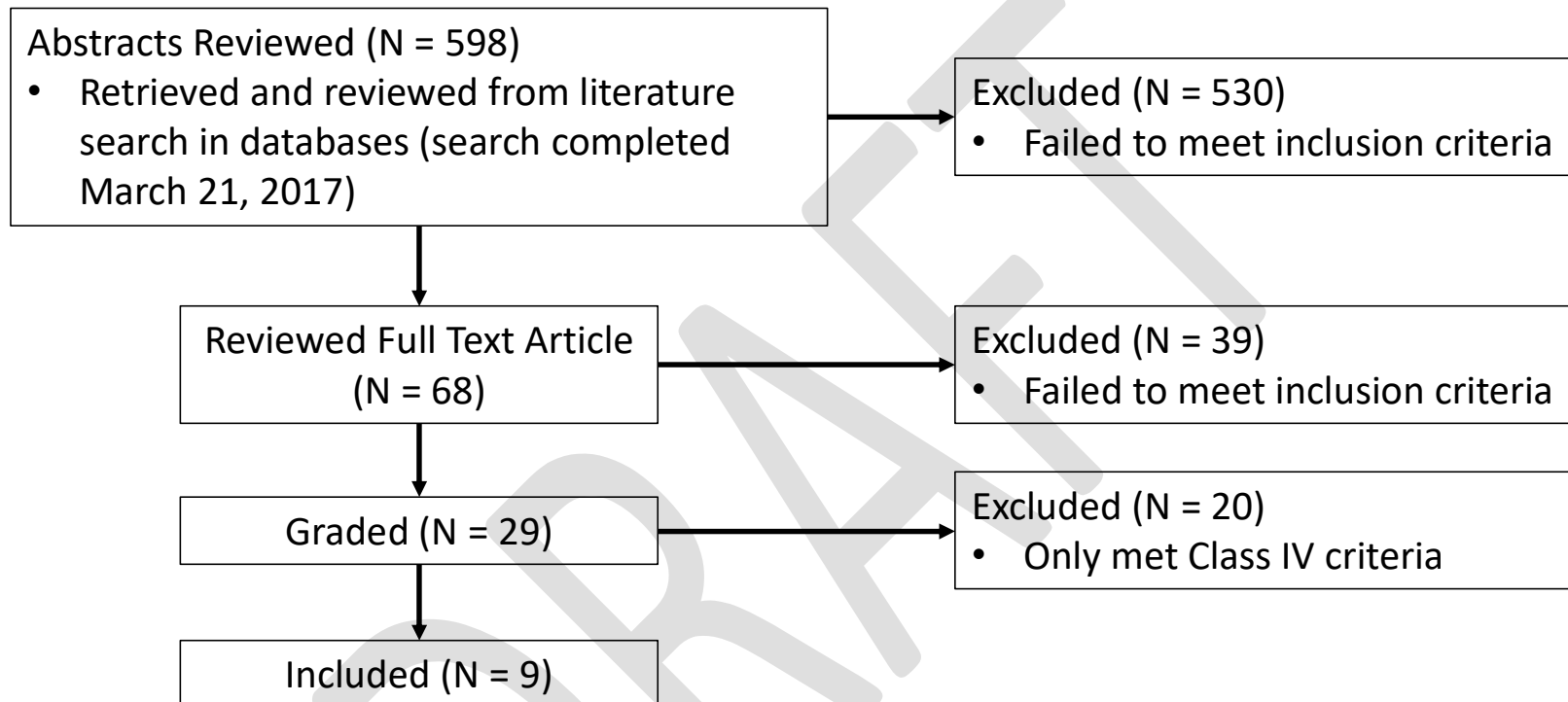
To summarize, there are 4 important issues which would need to be addressed if a clinical practice change is to occur in patients with mTBI using qEEG: (i) definition of a gold-standard against which diagnostic performance of any qEEG modality could be measured, (ii) consensus on methods for data acquisition, (iii) analysis of multiple qEEG measures representing different neurophysiological aspects, and (iv) inclusion of these metrics and use of appropriate statistical methods to develop a predictive, as opposed to merely an explanatory model.

Like standard EEG, it is important that the qEEG interpreters be blinded to the clinical status of the participants. The effect of potential qEEG signal confounders also needs to be understood and

controlled for, including patient state and medications. Lastly, there is a need for careful statistical considerations given the number of measures that are typically necessary for qEEG acquisition, analysis, and interpretation. Any group level differences would also need to be validated on an individual patient basis for it to be a clinically useful tool.

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FIGURE 1



Author Year	Class	Blind	Cohort Size	Controls Type	qEEG Method	Results	Notes
Arbour 2015⁸	III	No	34	Yes Previous database	Spectral Power	1) Higher beta power for mTBI in O1 in NREM 2) No other qEEG differences	1) No diagnostic study design 2) No awake qEEG
Corradini 2014⁹	III	No	26	Yes Newly acquired	Spectral Power Microstates sLORETA activation	1) Lower alpha power in mTBI with mod-severe impairment 2) Decreased duration of microstates for mTBI with mod-severe impairment 3) Reduced sLORETA activation for mTBI with mod-severe impairment	1) Not controlled 2) No diagnostic study design
O'Neil 2012¹⁴	III	No	119	No	Brainscope (handheld frontal recording)	1) TBI-index with improved specificity than New Orleans Criteria (NOC) to predict positive head CT	1) Not controlled 2) Excludes lowest risk mTBI group (without head CT ordered)
Khoury 2013¹⁰	III	No	24	Yes Newly acquired	Spectral Power	1) Lower delta power for mTBI 2) Higher beta and gamma power for mTBI 3) No differences for mTBI without pain	1) No diagnostic study design 2) No awake qEEG
McCrea 2010¹³	III	No	28	Yes Newly acquired	Brainscope (handheld frontal recording)	1) Multivariate analysis of 7 qEEG features were abnormal for mTBI at days 0 and 8 but not at day 45	1) Narrow spectrum of persons with and without disease
Moore 2016¹¹	III	No	52	Yes Newly acquired	Spectral Power (High density EEG)	1) Decreased alpha and increased beta frontal asymmetry for mTBI	1) No correction for multiple comparisons
Slobounov 2009¹⁵	III	No	21	No	Wavelet entropy	1) Entropy was reduced at 7 days post-mTBI 2) Recovery to baseline was slower after 2 nd mTBI	1) No diagnostic study design 2) Comparison to baseline but not controls

Tomkins 2011¹²	III	Yes	22	Yes Newly acquired	Spectral Power	1) Increase in delta power for mTBI 2) Decrease in alpha power for mTBI + PTE only	1) Diagnostic study for PTE
Virji-Babul 2014¹⁶	III	No	9	Yes Newly acquired	Graph theory	1) No small world topology differences 2) Regional increase in betweenness centrality 3) Regional mixed increases and decreases in degree	1) No diagnostic study design 2) Group level but not individual analyses

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