Is a diagnosis of "mild traumatic brain injury" a category mistake?

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BACKGROUND: Efforts to produce definitions and diagnostic standards for mild traumatic brain injury (TBI) have a long and complex history. The diagnosis of TBI must be considered in the larger context of neuropsychiatric diagnosis. A major reconceptualization of diagnosis is now underway in which the classical syndrome conceptualization is being discarded. We address the question, what are the implications of this revision of thinking in the specific context of TBI?

METHODS: A recent literature on logical structures for neuropsychiatric disorders was reviewed. The symptom pattern of TBI was identified, and a literature survey determined the frequency of these symptom patterns in other disorders and in healthy control populations.

RESULTS: The frequency of symptom endorsement in populations without a history of TBI can be equal to endorsement frequencies in populations with a history of mild TBI. In some studies, the frequency of symptom endorsement in healthy controls having no history of head injury actually exceeded the endorsement rates in a comparison group with a history mild TBI.

CONCLUSION: The heterogeneity of this clinical population and their clinical presentations, the absence of a unitary etiology of postinjury deficits, and the complex idiosyncratic time course of the appearance of these deficits argue against the valid implementation of the classical model of diagnosis. In addition, the accepted criteria of diagnostic utility are not satisfied. TBI is not a disease; it is an event. More precisely, TBI is an event or a sequence of events that can, in some instances, lead to a diagnosable neurological or psychiatric disorder.
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Arguably, the diagnosis of traumatic brain injury (TBI), and in particular mild TBI (MTBI), is an example of what Ryle[1] would have called a category mistake. A category mistake occurs when a property is associated to an object that cannot meaningfully possess that property or when a process is implemented in a context where it cannot be meaningfully implemented. For example, the statement "all asteroids are philosophers" is a category mistake. Similarly, a classification of asteroids according to philosophical school is a category mistake.

Diagnosis is a process that can be meaningfully associated with a disease. A TBI is not a disease. It is an event. More precisely, TBI is an event or a sequence of events that can, in some instances, lead to a diagnosable neurological or psychiatric disorder. Although acute and chronic neurological and psychological deficits that follow brain injury can be assessed, the diagnosis of TBI as a discrete clinical entity is not a logical possibility. An analogy can be made with a myocardial infarction (MI). An MI is not a disease; atherosclerosis is the disease, and an MI is the acute event related to the disease and may result in a host of complications or resulting disabilities.

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PATIENTS AND METHODS

The analysis presented here is constructed on a review of the recent literature on neuropsychiatric diagnosis. The assessment of MTBI and postconcussion syndrome (PCS) is significantly complicated by marked population heterogeneity, different pathophysiological processes that can be initiated by different injury events, and lack of pathognomonic signs and symptoms. Rather, MTBI is characterized and defined by a whole host of nonspecific symptoms that are commonly observed in a wide variety of other disorders. In addition, postconcussion symptoms may not be present in the immediate postinjury period. Delayed-onset disorders that can follow TBI include major depressive disorder, posttraumatic stress disorder (PTSD), and anxiety disorders. Although the probability of progression to severe neuropsychiatric disorders after MTBI may be low, by definition the diagnosis of severe psychiatric disorders requires the presence of symptoms for a specified minimum period. They cannot therefore be diagnosed immediately after injury. However, is a diagnosis of, for example, PTSD meaningful? There is a deeper issue to be considered that extends beyond the immediate context of TBI to a larger consideration of neuropsychiatric diagnosis. A major revision in our conceptualization of diagnosis is now underway. As summarized by Smith and Oltmanns,[2] the "classical syndrome conceptualization is being discarded for a description along dimensions of function." Similarly, Persons[3] argued for the study of "psychological phenomena rather than psychiatric diagnoses." The driving motivation for this reconceptualization has been presented with clarity by Kupfer et al,[4] "the goal of validating these syndromes and discovering common etiologies has remained elusive." Despite many proposed candidates, not one laboratory marker has been found to be specific in identifying any of the syndromes defined in the

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Diagnostic and Statistical Manual of Mental Disorders (*DSM*). Epidemiologic and clinical studies have shown extremely high rates of comorbidities among the disorders, undermining the hypothesis that the syndromes represent distinct etiologies." Kupfer is chair and Regier is vice-chair of the DSM-V Task Force.

What can be said about the psychological validity of the syndrome conceptualization in neuropsychiatry and specifically to TBI? Smith et al[5] have provided the following generic summary (italics in the original): "Empirical data have been quite consistent with the possibility that terms that are routinely used in clinical inquiry, from *neuroticism* and *extraversion* to *depression* and *posttraumatic stress disorder*, do not in fact represent meaningful cohesive psychological constructs." These authors emphasize the critical importance of identifying homogeneous constructs in the characterization of psychological disorders. Hierarchical organizations of such constructs, they argue, might be useful descriptively, but these "higher order composites do not refer to definable psychological processes." Although Smith et al[5] are writing specifically about psychopathology, their arguments generalize to a composite structure, such as TBI, that is associated with a profoundly heterogeneous patient population and nonspecific diagnostic criteria.

Historically, a diagnosis of TBI and a severity classification of injury have been based on a physical examination and patient report. The development of criteria for diagnosis has a long and contentious history. When considering diagnostic and assessment criteria, a distinction must be made between the severity classification at the time of injury, the itemization of current postconcussion symptoms, and the severity classification of current postconcussion symptoms. Among the most commonly used classifications of severity at injury are those of Arlinghaus et al,[6] Greenwald et al,[7] and Rao and Lyketsos.[8] Cantu[9] summarized eight grading systems, and Anderson et al[10] reported that there are at least 41 guidelines for grading mild head injury. In addition, the *Mayo Classification of Mild Traumatic Brain Injury*[11] was published after the Anderson et al[10] review. Several instruments for the itemization of current postconcussion symptoms are available, including the Rivermead Post-concussion Symptom Questionnaire,[12] the Postconcussion Syndrome Checklist,[13] the Postconcussion Checklist,[14] and the Postconcussion Symptom Scale Revised.[15] Severity classification scales for current postconcussion symptoms can be constructed by assigning cut points (minimal, mild, moderate, and severe) based on the aggregate scores of current symptom scales. This has been performed, for example, using the Rivermead aggregate scores by Potter et al.[16]

The complication of nonspecificity of symptoms (elaborated in the next paragraph) reduces the accuracy of these instruments. Donnelly et al[17] investigated the Veterans Traumatic Brain Injury Screening Tool, a structured diagnostic interview for TBI. They found that "the presence of significant PTSD symptoms, however, reduces the accuracy of the measure." Studies have investigated the validity of TBI instruments where the internal validity was assessed by the Rasch model,[18] and the external consistency was assessed by comparison with another instrument.[19] It should be stressed, however, that an assessment of construct validity does not ensure the test-retest reliability that is essential for clinical use. The limited test-retest reliability testing has been performed, and the results obtained are not encouraging. Acting in response to a specific recommendation from the US Government Accountability Office,[20] Van Dyke et al[21] measured the test-retest reliability of the Traumatic Brain Injury Screening Instrument[22] and found "poor test-retest reliability of the screening tool with regard to type of event, injuries sustained and resulting sequelae."

The validity of a diagnosis based on a physical examination and patient report requires using a standardized screening instrument that uses diagnostic criteria specific to the disease being diagnosed. Is this criterion met in the case of TBI? Arguably not. The nonspecificity of diagnostic criteria for TBI can be established by examining the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) diagnostic criteria for PCS[23] and the *DSM-IV* research criteria for postconcussion disorder.[24] Boake et al[25] studied 178 adults with mild to moderate TBI. Although the concordance of *DSM-IV* and *ICD-10* symptom criteria was high ($\kappa = 0.78$, indicating "substantial" agreement[26]), the concordance of diagnosis was low ($\kappa = 0.13$). In a subsequent study, Boake et al[27] applied *ICD-10* and *DSM-IV* diagnostic criteria to the previously examined group of patients with mild to moderate TBI and 104 adults with extracranial injury. They found that 64% of the population with a history of TBI and 40% of the extracranial injury population met *ICD-10* criteria for PCS. In addition, 11% of the TBI group and 7% of the patients with extracranial trauma met *DSM-IV* criteria for postconcussion disorder, emphasizing both the low diagnostic concordance and their nonspecificity.

RESULTS

The frequency of common postconcussion symptoms in populations without a history of TBI is summarized in Table 1 (modified from McCrea[28]). Table 1 indicates that the frequency of symptom endorsement in populations without a history of TBI can be equal to endorsement frequencies in the population with a history of MTBI. Indeed, in some studies, the frequency of symptom endorsement in healthy controls without a history of head injury exceeded the endorsement rates in a comparison group with a history of MTBI. The population showing the highest frequency of TBI symptoms was composed of personal injury claimants who did not have a history of TBI.

An examination of the details provided in the studies summarized in Table 1 further argues against the validity of MTBI as a diagnostic entity. Trahan et al[29] examined 496 participants with no history of head injury or depression, 56 neurologically normal individuals with both a history of depression and a current Beck Depression Inventory score greater than 20, and 40 participants who had experienced a mild brain injury. Individuals scoring positive for alcohol abuse or the use of recreational drugs were excluded from the study. The percentages in Table 1 are the percentages of subjects reporting symptoms twice a week or more. The postconcussion index scores or the MTBI group were higher than those observed in the control group, but notably, the depressed participants, who did not have a history of head injury, exhibited substantially

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TABLE 1. Frequency of Postconcussion Symptoms in MTBI and Comparison Populations

Study	Population	Headache, %	Dizziness, %	Irritability, %	Memory Problems, %	Concentration Problems, %
Trahan et al[29]	MTBI	19	7	21	25	30
Ingebrigtsen et al[34]	MTBI	42	26	28	36	25
Gouvier et al[13]	Moderate/Severe TBI	Not reported	Not reported	29	38	29
Hawley et al[39]	Mild-severe pediatric TBI	15.6–27.7	2.9–6.4	18.2–36.2	9.4–23.2	14.1–29.2
Dunn et al[30]	Head trauma or toxic exposure	57	28	31	21	34
Radanov et al[35]	Soft tissue injury cervical spine	80	67	49	33	63
Trahan et al[29]	Clinically depressed	37	20	52	25	54
Chakraborty et al[42]	Clinically depressed	24	8	Not reported	Not reported	Not reported
Dunn et al[30]	PI claimants Non-TBI	77	41	63	46	71
Lees-Haley and Brown[33]	General medicine controls	62	26	38	20	26
Trahan et al[29]	Healthy controls	13	4	9	12	18
Dunn et al[30]	Healthy controls	50	21	27	12	21
Gouvier et al[13]	Healthy controls	Not reported	Not reported	31	20	6
Wong et al[32]	Healthy controls	43	33	Not reported	47	Not reported
Bardel et al[43]	General population women >64 years old	35.4	16.8	30.5	Not reported	Not reported
Hawley et al[39]	Pediatric controls	4.4	0	2.2	2.2	2.2
Zolog et al[40]	School-based adolescent controls	10.2	4.8	Not reported	Not reported	Not reported
Vila et al[41]	School-based adolescent controls	13	12	Not reported	Not reported	Not reported

higher endorsement of postconcussion symptoms compared with the MTBI group.

Dunn et al[30] included 113 subjects with no history of head trauma or toxic exposure, 68 participants with a history of head trauma or toxic exposure, and 156 personal injury claimants with no history of toxic exposure or head trauma who received a psychological examination for emotional distress. As shown in Table 1, personal injury claimants report neurological symptoms with a higher frequency compared with patients in the head trauma/toxic exposure group. In addition to comparing healthy controls and self-reports of patients with severe TBI, Gouvier et al[31] also asked a close relative of the patients to report participant symptoms (self-reports are shown in Table 1). The symptom frequencies reported by relatives were consistently higher than self-report frequencies for both uninjured controls and participants with TBI. The control population studied by Wong et al[32] was composed of 88 university undergraduates in an introductory psychology class. On reviewing their results, they concluded that "this suggests that some 'classic' symptoms of head injury have very high base rates at least among certain segments of the normal population." In the study of Lees-Haley and Brown,[33] comparison data were collected from 50 outpatients recruited from a family practice clinic. The controls presented symptoms commonly seen in a family practice: sore throat, respiratory complaints, flu, hypertension, fatigue, and headache. Because this comparison population was recruited form a medical practice, it might be supposed that the incidence of headache endorsement would be greater than that seen in the general population. Endorsement rates for other symptoms were, however, also similar to those seen in populations with a history of TBI.

Ingebrigtsen et al[34] studied 100 patients with MTBI with normal findings on CAT scans 3 months after injury at the time of the study. No association was found between the Rivermead Post-concussion Symptom Scale and the severity of injury, duration of amnesia, cause of injury, sex, or age. Radanov et al[35] examined 51 patients who had experienced comparable injury mechanisms (at least hyperextension of the neck due to impact trauma), leading to soft tissue injury of the cervical spine. No neurological symptoms were found, and none of the participants in this study had a previous injury or disease of the central nervous system (CNS). Eighty-eight percent of the participants were injured in traffic accidents and 5.9% in sports activities. Although not identified as patients with TBI in this report, it is recognized that TBI is probably a confounding variable. In a related study, Sawchyn et al[36] studied 326 undergraduates who were recruited from a university population. Twenty-four percent of the sample reported a head injury resulting in a loss of consciousness. Results from the groups with and without TBI were not reported separately. They state, however, that there was no effect of head injury on the endorsement frequency of any of the postconcussion symptoms.

The incidence of postconcussion symptoms in populations with and without a history of TBI has also been assessed by Dean et al.[37] In this study, the presence of MTBI was determined using the *ICD-10* criteria. Participants had to report one or more loss of consciousness for 30 minutes or less and dizziness, confusion, or posttraumatic amnesia for less than 25 hours. PCS was established by *ICD-10* criteria. Symptom endorsement was determined by administering the Rivermead Post-concussion Symptom Questionnaire. In the case of participants with MTBI, PCS was diagnosed if three or more of the symptom categories in the *ICD-10* criteria were more severe after head injury. PCS was assessed in the population without a history of TBI using a modified version of the Rivermead Post-concussion Symptom Questionnaire.[38] The standard version of the Rivermead questionnaire begins with "Compared with before the accident…" In the revision, this is replaced

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with "Compared with your peers…." Thus, a within-person comparison is changed to a between-person comparison. The authors report that the equivalence of the two versions of the Rivermead questionnaire was assessed with a multidimensional scaling analysis of the two instruments. No significant differences in latent structure were observed. Using this procedure, it was found that 34% of the control participants met the *ICD-10* diagnostic criteria for PCS. Using the conventional Rivermead questionnaire, 31% of the participants with MTBI met the PCS diagnostic criteria. Dean et al[39] concluded that "persistent PCS, as currently defined, is not specific to MTBI." Similar patterns of symptom endorsement have also been observed in pediatric populations,[39–41] in depressed patients,[42] and in the general population.[43]

Because TBI and PTSD have symptoms in common, the diagnosis of TBI may be particularly complex in cases where PTSD may also be present.[44,45] Indeed, there has been considerable debate about the possible existence of TBI/PTSD comorbidity in the case of patients with TBI who experienced retrograde or anterograde amnesia.[46] Studies indicate that individuals with PTSD can be misdiagnosed with TBI,[47] and conversely, individuals with TBI can be misdiagnosed with PTSD.[48] In part, this diagnostic uncertainty results from the sensitivity of PTSD diagnosis to the diagnostic procedure. The use of questionnaires results in a high incidence of positive PTSD diagnosis, whereas comprehensive clinical interviews result in a low incidence.[49] The results of Harvey et al[49] were confirmed by Sumter and McMillan.[50,51] In a population of patients with severe TBI, questionnaires indicate that 59% had PTSD, whereas a structured clinical interview had a 2.9% (one patient) incidence.

The continuing disappointment with questionnaire/interview diagnostic instruments for TBI has encouraged the search for imaging technologies and for physiological measures of postinjury pathology. Although it is not the purpose of this contribution to present a systematic review of this research, several encouraging recent results warrant brief consideration.

Most patients with MTBI have normal findings on computed tomography (CT) and structural MRI scans.[52,53] In contrast, diffusion tensor imaging (DTI) studies have identified abnormalities in this patient population. Fractional anisotropy is the most frequently reported measure in diffusion tensor imaging studies. This number varies from zero (free diffusion in a sphere) to one, indicating maximal anisotropic diffusion. Elevated or reduced fractional anisotropy values are associated with different white matter abnormalities.[54] In a study that included patients with MTBI as well as patients who are moderately and severely injured, Kraus et al[55] found decreased fractional anisotropy in the corticospinal tract, sagittal stratum, and superior longitudinal fasciculus of the MTBI participants. All severities of TBI resulted in quantifiable axonal damage. Irreversible myelin damage was only seen after moderate or severe injury. Importantly, these investigators found that white matter load (an index of global white matter damage) was correlated with cognitive deficits as assessed by neuropsychological testing. Wilde et al[53] conducted a diffusion tensor imaging study of the corpus callosum of adolescents who had sustained an MTBI (Glasgow Coma Scale score of 15 and a negative finding on CT scan). Increased fractional anisotropy and decreased apparent diffusion coefficient were observed in the population with a history of MTBI. The magnitude of a patient's departure from the anisotropy scores obtained from matched controls correlated with the severity of postconcussion symptoms scored using the Rivermead Post-concussion Symptom Questionnaire. A diffusion tensor imaging study published by Mayer et al[56] is particularly valuable in being a longitudinal study. The clinical imaging and neuropsychological assessments of the MTBI group were negative, although the patients did report postinjury deficits. Clinical participants were initially assessed within 21 days of injury (mean, 12 days after injury). When compared with controls, the patients showed a greater fractional anisotropy resulting from reduced radial diffusion. A partial normalization of the DTI was observed longitudinally (3–5 months). In aggregate, the emerging evidence suggests that diffusion tensor imaging may become an important technology for quantifying postinjury CNS damage.

The investigation of physiological markers includes studies of biomarkers, quantitative electroencephalogram (qEEG), evoked potentials, event-related potentials (ERPs), and eye tracking. Biomarkers are defined here as measureable changes in an organism that can be measured at the level of cellular chemistry. The development of new technologies for the identification of biomarkers is accelerating.[57–61] The utility of these marker in the assessment of MTBI requires further investigation.

Can a quantitative analysis of free-running EEGs (qEEG) reliably diagnose MTBI? This is an unfortunately controversial question. The earlier literature was reviewed by Gaetz and Bernstein[62] and by Wallace et al,[63] who recommended caution. In a foundational study conducted between 1983 and 1989, Thatcher et al[64] examined 608 patients with MTBI and 108 age-matched controls. They reported diagnostic sensitivity based on a quantitative analysis of EEG signals of 96.6% and specificity of 89.1%. In a follow-up study, Thatcher et al[65] used qEEG metrics to construct an EEG-based Severity Index of Traumatic Brain Injury to discriminate between mild and severe TBI. The classification accuracy was 96.3% with a sensitivity of 95.5% and a specificity of 97%. The Thatcher et al results have not received universal acceptance. Nuwer[66] concluded, "On the basis of the current clinical literature, opinions of most experts, and proposed rationales for their use, qEEG remains investigational for clinical use in PCS, mild or moderate head injury, learning disability, attention disorders, schizophrenia, depression, alcoholism and drug abuse…." He further stated, "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." These views were rebutted by Thatcher et al[67] and Hoffmann et al.[68] Court action followed the 1997 Nuwer paper (County Court at Law No. 1. Travis County Texas. Cause No. 227, 520). The outcome of this action was reported by Thatcher and Biver.[69] In a subsequent evaluation, Nuwer et al[70] concluded that "overall, the disadvantages of qEEG panels and diagnostic discriminants presently outweigh the advantages of these studies for the diagnosis of MTBI." A great deal has happened since the court action, and a reassessment is clearly warranted.

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Naunheim and Casner[71] have reported a case history in which a quantitative evaluation of the EEG indicated an abnormality in a patient who presented an epidural hematoma after a TBI. In the immediate postinjury period, the findings on the patient's neurological examination was normal, with a Glasgow Coma Scale score of 15. An epidural hematoma was identified in the CT scan. A qEEG examination was then performed with a handheld portable device that measures potentials at five frontal sites (BrainScope, Bethesda, Md). The qEEG assessment indicated the presence of a brain abnormality with a probability of 99%. The portability of the equipment suggests that qEEG evaluations may be particularly valuable in TBI assessments in circumstances where a CT scan is not immediately available. In a subsequent study using the same device, Naunheim et al[72] assessed 153 patients admitted to a tertiary hospital with headaches or altered mental status. A clinician, blinded with respect to the qEEG assessment, reviewed the patients' history, the physical examination results, and the results of imaging studies. On the basis of this evidence, the clinician predicted if the qEEG evaluation would assign the patient to the normal or abnormal group. The device replicated this assignment with a sensitivity of 96% and a specificity of 87%. Using the BrainScope system, Naunheim et al[73] collected data from 105 emergency department patients with head injury (53 positive and 52 negative CT scan findings) and from 50 emergency department controls. Using an analysis of the eyes closed resting EEG, a discriminant score representing the probability of belonging to the TBI-CT scan-positive group was constructed. The discriminant scores for the TBI-CT scan-positive group, TBI-CT scan-negative group, and controls were 80.4, 38.9, and 24.5, respectively; 92.5% of the TBI-CT scan-positive patients were classified as brain injured, and 34.6% of the TBI-CT scan-negative patients and 10% of the controls were classified as brain injured.

Studies using the BrainScope system have also been published by McCrea et al[74] and by Barr et al.[75] The McCrea et al[74] study was a prospective study of high school and college athletes. EEGs were recorded at preseason baseline on the day of injury, 8 days after injury, and 45 days after injury. The study examined records from 28 participants who sustained a concussion and from 28 matched controls drawn from the same preseason cohort. The injured participants had lower neurocognitive test scores on the day of injury. There were no test score differences at day 8 or at day 45. In contrast, injured-control differences in the qEEG were observed on day 8. Between-group qEEG differences were not, however, observed on day 45. In an expansion of the McCrea et al[74] study, Barr et al[75] again found that injured versus control differences were observable in the qEEG at day 8, but not at day 45. The divergent time courses of EEG recovery and neurocognitive test recovery suggests that physiological recovery may extend beyond the period identified by neuropsychological testing. As will be reported presently, evidence indicates that ERPs can identify postinjury CNS abnormalities for significantly longer periods.

When considering qEEG results, it should be noted that these studies applied a qEEG discriminant function, which was derived to maximally separate a normal population from patients with TBI. It is possible that the alterations of brain electrical activity observed in the population with a history of TBI are also observable in other neuropsychiatric populations, for example, depression and schizophrenia. The generalization of this algorithm beyond an immediate consideration of traumatic brain injury is uncertain.

A quantitative analysis of evoked potentials and of ERPs as distinct from EEGs may provide important additional classification power, where it is stressed that EEGs, evoked potentials, and ERPs can be combined in the same clinical evaluation. Evoked potentials are electrical potentials recorded in response to a well-defined punctate stimulus. They are therefore distinct from spontaneous EEG potentials analyzed in qEEG. The term *evoked potential* is typically reserved for short latency responses that assess the patency of afferent pathways. In most applications, the average response to multiple presentations of an identical stimulus is examined. Several investigators have used brain stem auditory-evoked potentials (BAEPs) to examine MTBI. The results have been mixed. Rizzo et al[76] found interpeak intervals in BAEPs to be abnormal in 10 of 57 patients with TBI assessed. Schoenhuber and Gentillini[77] found abnormal BAEPs in 60 of 30 patients. Werner and Vanderzandt[78] and Haglund and Persson[79] reported no abnormal BAEPs recorded from the confirmed patients with TBI participating in their studies. Reviewing evidence available at the time, Gaetz and Bernstein[62] concluded that evoked potentials were of limited diagnostic efficacy in TBI. However, these conclusions should be reconsidered in the light of subsequent research. Arciniegas and Topkoff[80] reviewed the application of the P50-evoked response in the evaluation of cognitive impairments after TBI. They concluded,

> "The P50 ERP may be a useful marker of cholinergic dysfunction among individuals with persistent attention and memory impairment after TBI. As such, it is possible that the P50 ERP may be useful as a measure with which to identify patients whose posttraumatic cognitive disturbances are associated with neurophysiologic evidence of cholinergic dysfunction and who might respond to treatment with cholinergic augmentation strategies (i.e. cholinesterase inhibitors). The limitations of the present data are substantial, however, and must be addressed before the P50 ERP can be applied usefully to the clinical evaluation and treatment of patients with posttraumatic cognitive impairments."

An ERP is distinguished from an evoked potential by having a longer latency and in being altered by the cognitive significance of the stimulus to the subject. Evoked potentials are called exogenous and are strongly dependent on the physical properties of the stimulus (e.g., auditory versus visual stimulation). ERPs are called endogenous and are formed by higher level cognitive processes. They are less dependent on stimulus modality. Can ERPs characterize MTBI? Although several studies of ERPs obtained from patients with TBI have been published, our literature search identified 90 articles showing differences in ERPs obtained from patients with TBI and healthy controls, the collective experience does not provide a definitive answer to this question. In their review of electrophysiology procedures for the assessment of MTBI, Gaetz and Bernstein[62] concluded,

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"3. 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.

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

Given the dependence of ERPs on cognitive processes, Lew et al[81] also suggested that "longer latency ERP components hold promise in predicting recovery of higher cognitive functions." Deficits in emotional processing can be an element in the clinical presentation of TBI. ERP investigations of patients with TBI using emotionally valenced stimuli[82–84] may be particularly informative with this patient population.

ERPs may show a greater postinjury sensitivity than qEEGs. Recall that the results of McCrea et al[74] and Barr et al[75] did not find significant qEEG differences between concussed athletes and controls at 45 days after injury. Some results suggest that ERPs are more sensitive and show statistically significant differences between TBI and control populations during greater postinjury periods. In a study where participants were 9 to 81 months after injury, DeBeaumont et al[85] found significantly suppressed P3 amplitudes in athletes with multiple concussions compared with those with single concussion and without concussion. Broglio et al[86] found persistent alterations in the ERP correlates of attentional allocation in a population that was on average 3.4 years after injury. In a study of older athletes who were 30 years old after concussion, DeBeaumont et al[87] found attenuated P3 amplitudes and increased P3 latencies.

To date, the examination of ERPs obtained from patients with TBI has, with few exceptions, been limited to reports of differences in amplitude and latencies of identified components of the ERP. We suggest that a dynamical analysis of ERPs, particularly event-related synchronization and desynchronization, causality analysis, and small world modeling will result in significant improvements in clinical utility.

For some patients, tests of eye movement and visually guided arm movement may also provide quantitative physiological measures of deficit after MTBI that are observable in the absence of deficits in neuropsychological tests. Heitger et al[88,89] found that mild closed head injury was associated with deficits in saccades and impaired upper limb visuomotor function although no oculomotor or visuomotor deficits were found in a standard clinical examination. The greatest between-group discrimination (controls versus mild closed head injury) was seen in errors in a visuomotor control test that also required memory (memory-guided sequences of the fixation point). After controlling for sampling dependent differences in verbal IQ, no differences were found in the assessed neuropsychological measures (Paced Auditory Serial Addition Test, California Verbal Learning Test, Symbol Digit Modalities Test, and Trail Making Test). They conclude that "These results indicate that multiple motor systems can be impaired after mild CHI (closed head injury) and that this can occur independently of neuropsychological impairment." These measures were used longitudinally at 1 week, 3 months, 6 months, and 12 months after injury.[90] At 12 months, residual deficits in visuomotor and arm motor function persisted in the absence of cognitive impairments as assessed by neuropsychological tests. In a subsequent study, Heitger et al[91] compared head injury patients who had made a good recovery with equivalently injured patients who presented PCS as defined by World Health Organization guidelines. The PCS group performed worse on antisaccades, self-paced saccades, memory-guided sequences, and smooth pursuit. Importantly, poor performances included measures beyond conscious control suggesting subcortical impairment. The indication of subcortical involvement is consistent with the earlier results of Suh et al,[92] suggesting a disruption of cerebellar-cortical connections. It should also be noted that they found measures of predictive eye movement to be more sensitive than target tracking. A predictive paradigm assays oculomotor integrity and cognitive deficits. A study by Caeyenberghs et al[93] included both diffusion tensor imaging and an upper limb visuomotor task that required predictive control. The TBI group displayed poor tracking performance and a decreased fractional anisotropy due to increased diffusivity parallel and perpendicular to the axonal fiber direction. A discriminant analysis that combined both classes of measures (diffusion tensor imaging and visuomotor tracking) was more effective in separating the clinical and control populations than discriminations using a single class of measures.

In two studies of exceptional interest, Contreras et al[94,95] measured smooth pursuit eye movement as participants tracked a circularly moving target. The tracking accuracy was assessed quantitatively by computing the synchronization index.[96,97] Phase synchronization is a particularly effective measure for characterizing circular tracking because most saccades are normal to the orbit. Phase is insensitive to normal displacements. In the discussion of Contreras et al,[94] the authors note that an analysis could be constructed by determining the x-axis and y-axis phases separately by computing the Hilbert transform of each function's time series. The phase synchronization can then be calculated separately for the horizontal and vertical axis. Because these two components of eye movement are controlled by different regions of the cerebellum, this would allow a more highly resolved characterization of corticocerebellar integrity. As discussed in the following paragraphs, this alternative was implemented in their 2011 study. The 2008 study showed that phase synchronization was dependent on age. In their population, the synchronization index of older healthy participants was less than that observed in both young and older TBI participants. In addition, fatigue had a significant effect on the synchronization index in both populations, where the authors note that fatigue as measured by their method incorporates fatigue, as the term is conventionally understood, and boredom. The sensitivity of the synchronization index to participant motivation may have significant implications for the measure's clinical utility. In the subsequent study, Contreras et al[95] combined smooth pursuit eye movement tracking of a circularly moving target with a cognitive task.

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Before beginning the visual task, the experimenter read one word (one-word task) or a list of five words (five-word task) to the participant with the instruction that the words are to be remembered and that the participant will be asked to recall the words at the end of the eye movement recording. A control zero-word task was included in the protocol. The synchronization index values were larger for the healthy controls than those for the TBI participants. The between-group differences were statistically significant on the horizontal axis for the five-word task and on the vertical axis for the one- and five-word tasks. Velocity error and number of saccades and conventional measures of eye movement were greater for the TBI participants.

The 2011 study of Contreras et al[95] showed the discriminative value of combining an eye movement task with a demanding cognitive task. It should be noted that with an integrated data acquisition platform, it is possible to measure eye movement, heart rate variability, and ERPs during a neuropsychological assessment. We suggest that this simultaneous multidimensional investigation will provide a more sensitive characterization of MTBI.

When considering the progress made in identifying physiological correlates of MTBI, cautionary observations should be made concerning specificity and test-retest reliability. Although the current literature suggests that ERPs can be a sensitive indicator of MTBI, it should be recognized that similar alterations of ERPs have been observed in other clinical populations including bipolar disorder, dementia, depression, PTSD, and schizophrenia. Similarly, eye movement smooth-pursuit deficits have been observed in schizophrenia, autism, PTSD, alcoholism, and substance abuse. Alterations in heart rate variability, a noninvasive measure of autonomic nervous system function, have been observed after TBI, but they have also been observed in schizophrenia, PTSD, depression, and anxiety. Although the lack of specificity must be clearly recognized, the value of a sensitive albeit nonspecific measure should not be underestimated. The classical example of a sensitive but nonspecific clinical measure is body temperature. A temperature of 104°F is nonspecific but highly significant. Like body temperature, the value of measures of CNS integrity lies in their longitudinal use. Is the patient improving or deteriorating? Therefore, although physiological measures will be clinically important, given nonspecificity, these measures alone will not provide a diagnosis.

Enthusiasm for the use of these measures in longitudinal assessment must, however, be tempered by considerations of test-retest reliability. Inconsistency in performance is a characteristic of the injured CNS. This was indicated in the 19th century by Hughlings-Jacksons's case histories[98] and explicitly reported by Henry Head in 1926[99]: "An inconsistent response is one of the most striking results produced by a lesion of the cerebral cortex." This inconsistency has been observed in neuropsychological testing after TBI.[100,101] When considering the longitudinal neuropsychological assessment of TBI with the Automated Neuropsychological Assessment Metric (ANAM), a computer-administered neurocognitive assessment tool developed by the US Department of Defense, the contribution of Bleiberg et al[102] is of particular interest. In a study with 12 subjects (6 patients with TBI and 6 controls), investigators measured within-day and across-day variation in ANAM performance. A subset of ANAM tests was administered 30 times during 4 days, and the performance patterns between TBI and control subjects were compared. Control subjects showed consistent improvement, presumably the results of a practice effect. Patients showed "erratic and inconsistent performance" across days. Bleiberg et al[102] made the following important point: "Inconsistent performance was observed even in those subjects with TBI whose initial performance was equal to or better than that of the control subjects. Deficits in dynamic performance may explain why some patients with TBI who have excellent neuropsychological test performance nonetheless complain of functional decrement from premorbid ability." Previous studies of test-retest reliability of ERPs in healthy controls present variable results. Depending on the ERP component assessed, reliabilities are good to excellent.[103–106] To date, we have located only one study of ERP test-retest reliability after TBI.[107] The Lew et al[107] study compared 19 healthy participants against 7 clinical participants with a history of moderate to severe TBI. The retest interval ranged from 2 days to 2 months. Latencies and amplitudes were measured for four components in the averaged ERP wave form. A measure was deemed to be reliable if the corresponding interclass correlation coefficient was greater than 0.6. In the case of controls, four amplitude and three latency measures met the stability criterion. In the population with a history of TBI, only the amplitude and latency of the N1 was stable.

Lew et al[107] found the amplitudes of defined components to be more reliable than component latencies. This emphasizes the importance of making a distinction between amplitude and latency reliability. In their studies for healthy participants, Walhovd and Fjell[103] and Sinha et al[108] also found amplitude measures to be more reliable than latency measures. The functional significance of ERP amplitude is not well understood. It is generally argued that latency reflects the efficiency of information processing. Thus, of the two measures examined, the measure that relates most directly to the assessment of cognitive deficits shows poor reliability. A potential resolution of this problem may lie in expanding the class of quantitative measures used to characterize ERPs. Most studies examine average ERP wave forms and limit quantification to estimating amplitudes and latencies of identified components. It is possible that greater reliability will be obtained by applying additional analytical procedures. In addition, it should be noted as was noted in Lew et al[107] that the lack of temporal stability of ERPs in the population with a history of TBI may itself be a useful clinical indicator.

When evaluating the unquestionably encouraging results from imaging studies and from physiological research, three points should be made.

1. TBI is not, we contend, a distinct disease entity. Qualitatively (mechanistically) different pathophysiological processes may be initiated by different injury events. In addition, more than one pathological process may be initiated by a single event. Therefore, there will never be a single imaging or physiological test for TBI.
2. Although the results obtained with imaging and physiological measures are very encouraging, a great deal of

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research is still required to established sensitivity and test-retest reliability. The nonspecificity of the symptoms, as argued earlier, indicates that sensitivity may be achieved, whereas specificity will quite probably be unobtainable.

3. The physiological and imaging results should not deflect focus from the central argument of this article. The physiological characterization of postinjury deficits does not confer logical meaning to a diagnostic treatment of an event as a disease.

If a diagnosis of TBI is not epistemologically valid, might it nonetheless be useful? After all, as observed by Kendell and Jablonsky,[109] "it is crucial to maintain a clear distinction between the validity and utility" of a diagnostic process (see also Mullins-Sweatt and Widiger[110]). Although the preceding analysis argues against diagnostic validity, we must ask as a separate question, is it useful? Kendell and Jablonsky[109] have provided the following criterion for diagnostic utility, "We propose that a diagnostic rubric may be said to possess utility if it provides nontrivial information about prognosis and likely treatment outcomes and/or testable propositions about biological and social correlates." Have these criteria been met in the case of MTBI? Arguably not. The heterogeneity of the population with a history of MTBI and their clinical presentation, the absence of a unitary etiology of postinjury deficit, and the complex, idiosyncratic time course of the appearance of these deficits precludes satisfying this criterion of utility. A similar conclusion has been reached by Smith[111] in the letter "Postconcussional Symptoms not a Syndrome" in the journal *Psychosomatics*: "It is my view that symptoms typically attributed to postconcussion are so nonspecific and are associated with such a wide variety of other conditions that they do not meet the definition of a syndrome." Smith cites several studies in support of this conclusion, which show that the symptom collections of PCS are not unique to the head injury population and have a high baseline prevalence in the general population.[32,34,112,113]

If not useful, can we at least be assured that this diagnosis is not harmful? Usually, but not always. The mischief of a false-positive identification should not be underestimated. McCrea[28] has written about the potential iatrogenic effects of either misdiagnosing or making an accurate assessment of MTBI that is followed by an ill-considered or imperfectly communicated prognosis that suggests the likelihood of a poor outcome and long-term disability. An effective summary is provided by Tukey,[114] a mathematician noted for clarifying statistical issues concerning false-positive results in his essay emphasizing the importance of both accuracy and relevance, "It's often much worse to have a good measurement of the wrong thing,… than to have a poor measurement of the right thing."

DISCUSSION

It would follow that the diagnosis of MTBI is not valid, not useful, possibly harmful, and proceeds from the imprecise use of language. This said, what is the alternative? The 1986 article of Persons[3] provides guidance. Persons argued for a focus not on diagnostic categories but on the symptoms leading to an investigation of the underlying processes of a specified symptom. In a major contribution, Halbauer et al[115] have provided a systematic implementation of Persons' conceptualization by arguing for a clinical approach to TBI based on five groups of symptom clusters (cognitive dysfunctions, neurobehavioral disorders, somatosensory disruptions, somatic symptoms, and substance dependence). We would add that in the ideal case, the observed symptom should be as proximal as possible to the underlying pathophysiological lesion and that the search for underlying processes should be a search for the symptom's physiological substrate. Again, the heterogeneity of the population and the nonspecificity of the symptoms remain a formidable obstacle. In any case, our present level of understanding potentially precludes a physiologically based investigation. Recent advances with CSF and serum biomarkers as well as functional and structural imaging investigations have yet to rise to the level of acknowledgment as evidence-based "gold standards." Although some imaging studies may be considered gold standard within certain communities, these procedures are, at present, inappropriate for assessing MTBI and are only useful as a screening tool for moderate or severe injury. This is especially true of subtle cognitive deficits after MTBI. Imaging studies are nondisclosing of these deficits, although they may have a profound effect on the patient's quality of life. The physiological measures discussed earlier are, in some instances, disclosing of cognitive deficits and show promise, but as previously argued, because TBI is not a single disease, no single measure will be clinically disclosing.

Persons and others have emphasized the examination of psychological processes. Investigations of this type can be conducted in the absence of detailed knowledge of the underlying physiology. The power of this form of analysis should not be underestimated as, for example, in the research of Wylie et al[116,117] on interference control during action selection in Parkinson's disease and in recent quantitative studies of patterns in patient-therapist communication in psychotherapy after TBI.[118]

The search for mechanisms and processes, physiological or psychological, is demanding. As previously observed, different injury events can initiate different pathophysiological processes, and a single injury event can initiate more than one pathophysiological process. These processes may have different time courses, and they may interact. Therefore, there will never be a single measure for the characterization of TBI. In response to this, we propose the development of an integrated imaging, biomarkers, examination, neuropsychology, and neurophysiology assessment that combines all elements into the assessment. This development process will be a formidable task. The identification of homogeneous, or approximately homogeneous, participant groups has been and will remain perhaps the biggest single challenge, but the effort is essential. Logically ill-posed diagnostic exercises are not sufficient. Much has been accomplished already through the study of football, rugby, and soccer players, yet these groups cannot address the unique mechanisms of injury faced by combatants or civilians in wars or terrorism, or the unique anatomic and physiological characteristics of children or the elderly. The closing observation is provided by Tukey[114]: "If what is really needed is harder to measure or harder to explain, we still need to measure and explain it."

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Following the completion of an earlier draft of this article, our attention was directed to the article "Traumatic Brain Injury: A Disease Process not an Event," by Masel and DeWitt.[119] This is a valuable contribution to the TBI literature. We concur in concluding that TBI can, in some instances, result in a chronic disorder. In response to Masel and DeWitt, we would like to make two additional observations. First, in the case of MTBI, the postinjury population is exceptionally heterogeneous. As Masel and DeWitt recognize, progression to a chronic disorder will be limited to a subset of that population. Identifying these individuals in the immediate postinjury period is an important, unresolved challenge. Second, although a chronic disorder may follow from a TBI, describing an injury event as a disease cannot be logically substantiated.

AUTHORSHIP

P.E.R and K.C.C. designed the study. P.E.R. conducted the literature search and constructed the table. Both authors participated in writing, revising and editing the manuscript.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Ryle G. *The Concept of Mind*. Chicago: University of Chicago Press; 1949.
2. Smith GT, Oltmanns TF. Scientific advances in the diagnosis of psychopathology: introduction to the special section. *Psychol Assess*. 2009;21:241–242.
3. Persons JB. The advantages of studying psychological phenomena rather than psychiatric diagnoses. *Am Psychol*. 1986;41:1252–1260.
4. Kupfer DJ, First MB, Regier DE. Introduction. In: Kupfer DJ, First MB, Regier DE, eds. *Research Agenda for DSM-V*. Washington, DC: American Psychiatric Association; 2002:xv–xxiii.
5. Smith GT, McCarthy DM, Zapolski TCB. On the value of homogeneous constructs for construct validation, theory testing and the description of psychopathology. *Psychol Assess*. 2009;21:272–284.
6. Arlinghaus KA, Shoaib AM, Price TRP. Neuropsychiatric assessment. In: Silver JM, McAllister TM, Yudofsky SC, eds. *Textbook of Traumatic Brain Injury*. Washington, DC: American Psychiatric Publishing, Inc.; 2004:59–78.
7. Greenwald BD, Burnett DM, Miller MA. Congenital and acquired brain injury. 1. Brain injury: epidemiology and pathophysiology. *Arch Phys Med Rehabil*. 2003;84:S3–S7.
8. Rao V, Lyketsos C. Neuropsychiatric sequelae of traumatic brain injury. *Psychosomatics*. 2000;41:95–103.
9. Cantu RC. Concussion classification: ongoing controversy. In: Slobunov S, Sabastianelli W, eds. *Foundations of Sports-Related Brain Injuries*. New York: Springer; 2006:87–110.
10. Anderson T, Heitger M, Macleod AD. Concussion and mild head injury. *Pract Neurol*. 2006;6:342–357.
11. Malec JF, Brown AW, Leibson CL, Flaada JT, Mandrekar JN, Diehl NN, Perkins PK. The Mayo classification system for traumatic brain injury. *J Neurotrauma*. 2007;24:1417–1424.
12. King NS, Crawford S, Wenden FJ, Moss NE, Wode DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *J Neurol*. 1995;242:587–592.
13. Gouvier WD, Cubic B, Jones G, Brantley P, Cutlip Q. Postconcussion symptoms and daily stress in normal and head injured college populations. *Arch Clin Neuropsychol*. 1992;7:193–211.
14. Oddy M, Humphrey M, Uttley D. Subjective impairment and social recovery after closed head injury. *J Neurol Neurosurg Psychiatry*. 1978; 41:611–616.
15. Lovell MR, Collins MW. Neuropsycholgoical assessment of the college football player. *J Head Trauma Rehabil*. 1998;13:9–26.
16. Potter S, Leigh E, Wade D, Fleminger S. The Rivermead Post Concussion Symptoms Questionnaire: a confirmatory factor analysis. *J Neurol*. 2006;253:1603–1614.
17. Donnelly KT, Donnelly JP, Dunnam M, Warner GC, Kittleson CJ, Constance JE, Bradshaw CB, Alt M. Reliability, sensitivity, and specificity of the VA traumatic brain injury screening tool. *J Head Trauma Rehabil*. 2011;26:439–453.
18. Andrich D. *Rasch Models for Measurement*. London: Sage; 1988.
19. Eyres S, Carey A, Gilworth G, Neumann V, Tennant A. Construct validity and reliability of the Rivermead Post Concussion Symptoms Questionnaire. *Clin Rehabil*. 2005;19:878–887.
20. US Government Accountability Office. *VA Health Care: Mild Traumatic Brain Injury Screening and Evaluation Implemented for OEF/OIF Veterans but Challenges Remain (GAO-08-276)*. Washington, DC: US Government Accountability Office; 2008.
21. Van Dyke SA, Axelrod BN, Schutte C. Test-retest reliability of the traumatic brain injury screening instrument. *Mil Med*. 2010;175: 947–949.
22. Department of Veterans Affairs. *Veterans Health Administration Directive VHA: 2007-013: Screening and Evaluation of Possible Traumatic Brain Injury in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) Veterans*. Washington, DC: Department of Veterans Affairs, Veterans Health Administration; 2007.
23. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems. Tenth Edition. Geneva*. Switzerland: World Health Organization; 1992.
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
25. Boake C, McCauley SR, Levin HS, Contant CF, Song JX, Brown SA, Goodman HS, Brundage SI, Diaz-Marchan PJ, Merritt SG. Limited agreement between criteria-based diagnoses of postconcussional syndrome. *J Neuropsychiatry Clin Neurosci*. 2004;16:493–499.
26. Viera AJ, Garrett JM. Understanding interobserver agreement: the Kappa statistic. *Fam Med*. 2005;37:360–363.
27. Boake C, McCauley SR, Levin HR, Pedroza C, Contant CF, Song JX, Brown SA, Goodman H, Brundage SI, Diaz-Marchan PJ. Diagnostic criteria for postconcussional syndrome after mild to moderate traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2005;17:350–356.
28. McCrea MA. *Mild Traumatic Brain Injury and Postconcussion Syndrome*. Oxford: Oxford University Press; 2008.
29. Trahan DE, Ross CE, Trahan SL. Relationships among postconcussional-type symptoms, depression and anxiety in neurologically normal young adults and victims of mild brain injury. *Arch Clin Neuropsychol*. 2001;16:435–445.
30. Dunn JT, Lees-Haley PR, Brown RS, Williams CW, English LT. Neurotoxic complaint base rates of personal injury claimants: implications for neuropsychological assessment. *J Clin Psychol*. 1995;51:577–584.
31. Grouvier WD, Uddo-Crane M, Brown LM. Base rates of post-concussive symptoms. *Arch Clin Neurol*. 1988;3:273–278.
32. Wong JL, Regennitter RP, Barrios F. Base rate and simulated symptoms of mild head injury among normals. *Arch Clin Neuropsychol*. 1994;9: 411–425.
33. Lees-Haley P, Brown RS. Neuropsychological complaint base rates

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of 170 personal-injury claimants. *Arch Clin Neuropsychol*. 1993;8: 203–209.
34. Ingebrigtsen T, Waterloo K, Marup-Jensen S, Attner E, Romner B. Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients. *J Neurol*. 1998;254:609–612.
35. Radanov BP, Dvorak J, Valach F. Cognitive deficits in patients after soft tissue injury of the cervical spine. *Spine*. 1992;17:127–131.
36. Sawchyn JM, Burlot MM, Straus E. Note on the use of the postconcussion syndrome checklist. *Arch Clin Neuropsychol*. 2000;15:1–8.
37. Dean PJA, O'Neill D, Sterr A. Post-concussion syndrome: prevalence after mild traumatic brain injury in comparison with a sample without head injury. *Brain Inj*. 2012;26:14–26.
38. Sterr A, Herron KA, Hayward C, Montaldi D. Are mild head injuries as mild as we think? Neurobehavioral concomitants of chronic post-concussion syndrome. *BMC Neurol*. 2006;6:7 doi: 10.1186/1471-2377-6-7.
39. Hawley CA, Ward AB, Magnay AR, Long J. Outcomes following childhood head injury: a population study. *J Neurol Neurosurg Psychiatry*. 2004;75:737–742.
40. Zolog TC, Jane-Ballabriga MC, Bonillo-Martin A, Canals-Sans J, Hernandez-Martinez C, Romero-Acosta K, Domenech-Llaberia E. Somatic complaints and symptoms of anxiety and depression in a school based sample of preadolescents and adolescents. Functional impairment and implications for treatment. *J Cogn Behav Psychother*. 2011;11:online prepublication.
41. Vila M, Kramer T, Hickey N, Dattani M, Jefferis H, Singh M, Garralda E. Assessment of somatic symptoms in British secondary school children using the Children's Somatization Inventory (CSI). *J Pediatr Psychol*. 2009;34:989–998.
42. Chakraborty K, Avasthi A, Kumar S, Grover S. Psychological and clinical correlates of functional somatic complaints in depression. *Int J Soc Psychiatry*. 2012;58:87–95.
43. Bardel A, Wallander MA, Wedel H, Svärdsudd K. Age-specific symptom prevalence in women 35–64 years old: a population based study. *BMC Public Health*. 2009;9:37.
44. Sbordone RJ, Ruff RM. Re-examination of the controversial coexistence of traumatic brain injury and posttraumatic stress disorder. Misdiagnosis and self-report measures. *Psychol Inj Law*. 2010;3:63–76.
45. Ruff RL, Riechers RG, Ruff SS. Relationships between mild traumatic brain injury sustained in combat and posttraumatic stress disorder. *F1000 Med Rep*. 2010;2:64 (doi: 10.3410/M2-64).
46. Sbordone RJ, Liter JC. Mild traumatic brain injury does not produce post-traumatic stress disorder. *Brain Inj*. 1995;9:405–412.
47. Hickling EJ, Gillen R, Blanchard EB, Buckley T, Taylor A. Traumatic brain injury and post traumatic stress disorder: a preliminary investigation of neuropsychological test results in PTSD secondary to motor vehicle accidents. *Brain Inj*. 1998;12:265–274.
48. McMillan TM. Post-traumatic stress disorder following minor and severe closed head injury: 10 single cases. *Brain Inj*. 1996;40:749–758.
49. Harvey AG, Brewin CR, Jones C, Kopelman MD. Coexistence of post-traumatic stress disorder and traumatic brain injury: towards a resolution of the paradox. *J Int Neuropsychol Soc*. 2003;9:663–676.
50. Sumpter RE, McMillan TM. Misdiagnosis of post traumatic stress disorder following severe traumatic brain injury. *Br J Psychiatry*. 2005; 186:423–426.
51. Sumpter RE, McMillan TM. Errors in self-report of post-traumatic stress disorder and severe brain injury. *Brain Inj*. 2006;20:93–99.
52. Belanger HG, Vanderploeg RD, Curtiss G, Warden DL. Recent neuroimaging techniques in mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2007;19:5–20.
53. Wilde EA, McCauley SR, Hunter JV, Bigler ED, Chu Z, Wang ZJ, Hanten GR, Troyanskaya M, Yallampalli R, Li X, Chia J, Levin HS. Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology*. 2008;70:948–955.
54. Bigler ED, Bazarian JJ. Diffusion tensor imaging. A biomarker for mild traumatic brain injury. *Neurology*. 2010;74:626–627.
55. Kraus M, Susmaras T, Caughlin BP, Walker CJ, Sweeney JA, Little DM. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*. 2007;130:2508–2519.
56. Mayer AR, Ling J, Mannell MV, Gasparovic C, Phillips JP, Doezema D, Reichard R, Yeo RA. A prospective diffusion tensor imaging study in mild traumatic brain injury. *Neurology*. 2010;74:643–650.
57. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *J Neurotrauma*. 2008;25:279–290.
58. Kobeissy FH, Sadasivan S, Oli MW, Robinson G, Larner SF, Zhang Z, Hayes RL, Wang KKW. Neuroproteomics and systems biology-based discovery of protein biomarkers for traumatic brain injury and clinical validation. *Proteomics Clin Appl*. 2008;2:10–25.
59. Papa L, Robinson G, Oli M, Pineda J, Demery J, Brophy G, Robicsek SA, Gabrielli A, Robertson CS, Wang KK, Hayes RL. Use of biomarkers for diagnosis and management of traumatic brain injury patients. *Expert Opin Med Diagn*. 2008;2:937–945.
60. Wagner AK, McCollough EH, Niyonkuru C, Ozawa H, Loucks TL, Dobos JA, Brett CA, Santarsieri M, Doxon CE, Berga SL, Fabio A. Acute serum hormone levels: characterization and prognosis after severe traumatic brain injury. *J Neurotrauma*. 2011;28:871–888.
61. Hayes RL, Jeromin A, Mondello S, Muller U, Streeter J, Wang KKW. Blood based diagnostics of traumatic brain injuries. *Expert Rev Mol Diagn*. 2011;11:65–78.
62. Gaetz M, Bernstein D. The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. *J Head Trauma Rehabil*. 2001;16:386–405.
63. Wallace BE, Wagner AK, Wagner EP, McDeavitt JT. A history and review of quantitative electroencephalography in traumatic brain injury. *J Head Trauma Rehabil*. 2001;16:165–190.
64. Thatcher RW, Walker RA, Gerson I, Geisler F. EEG discriminant analyses of mild head trauma. *Electroencephalogr Clin Neurophysiol*. 1989;73: 93–106.
65. Thatcher RW, North DM, Curtin RT, Walker RA, Birer CJ, Gomez JF, Salazar AM. An EEG severity index of traumatic brain injury. *J Neuropsychiatry Clin Neurosci*. 2001;13:77–87.
66. Nuwer M. Assessment of digital EEG, quantitative EEG, and EEG brain mapping: report of the American Academy of Neurology and the American Clinical Neurophysiology Society. *Neurology*. 1997;49: 277–292.
67. Thatcher RW, Moore N, John ER, Duffy F, Hughes JR, Krieger M. QEEG and traumatic brain injury: rebuttal of the American Academy of Neurology 1997 report by the EEG and Clinical Neuroscience Society. *Clin Electroencephalogr*. 1999;30:94–98.
68. Hoffmann DA, Lubar JF, Thatcher RW, Sterman MB, Rosenfeld PJ, Striefel S, Trudeau D, Stockdale S. Limitations of the American Academy of Neurology and American Clinical Neurophysiology Society paper on QEEG. *J Neuropsychiatry Clin Neurosci*. 1999;11:401–407.
69. Thatcher RW, Biver CJ, North DM. Quantitative EEG and the Frye and Daubert standards of admissibility. *Clin Electroencephalogr*. 2003;34: 39–53.
70. Nuwer MR, Hovda DA, Schrader LM, Vespa PM. Routine and quantitative EEG in mild traumatic brain injury. *Clin Neurophysiol*. 2005;116: 2001–2025.
71. Naunheim RS, Casner T. Novel method for detecting brain abnormality in a patient with epidural hematoma: a case report. *Am J Emerg Med*. 2010;28:386e1–386e2.
72. Naunheim RS, Treaster M, English J, Casner T. Automated electroencephalogram (EEG) identifies abnormalities in the emergency department. *Am J Emerg Med*. 2010;29:845–848.
73. Naunheim RS, Treaster M, English J, Casner T, Chabot R. Use of brain electrical activity to quantify traumatic brain injury in the emergency department. *Brain Inj*. 2010;24:1324–1329.
74. McCrea M, Prichep LS, Powell MR, Chabot R, Barr WB. Acute effects and recovery after sports-related concussion: a quantitative brain electrical activity study. *J Head Trauma Rehabil*. 2010;25:283–292.
75. Barr WB, Prichep LS, Chabot R, Powell MR, McCrea M. Measuring brain electrical activity to track recovery from sport-related concussion. *Brain Inj*. 2112;26:58–66.
76. Rizzo PA, Pierelli F, Pozzessere G, Floris L, Morocutti C. Subjective posttraumatic syndrome: a comparison of visual and brainstem auditory evoked responses. *Neuropsychobiology*. 1983;9:72–82.
77. Schoenhuber R, Gentilini M. Auditory brain stem responses in the prognosis

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of late postconcussional symptoms and neuropsychological dysfunction after minor head injury. *Neurosurgery.* 1986;19:532–534.
78. Werner R, Vanderzandt C. Multimodality evoked potential testing in acute mild closed head injury. *Arch Phys Med Rehabil*. 1991;72:31–34.
79. Haglund Y, Persson HE. Does Swedish amateur boxing lead to chronic brain damage. 3. A retrospective clinical neurophysiological study. *Acta Neurol Scand*. 1990;82:353–360.
80. Arciniegas DB, Topkoff JL. Applications of the P50 evoked response to the evaluation of cognitive impairments after traumatic brain injury. *Phys Med Rehabil Clin N Am*. 2004;15:177–203.
81. Lew HL, Poole JH, Castenada A, Salerno RM, Gray M. Prognostic value of evoked potentials and event-related potentials in moderate to severe brain injury. *J Head Trauma Rehabil*. 2006;21:350–360.
82. Catani C. *Affective Stimulus Processing Following Traumatic Brain Injury.* [doctoral dissertation]. Konstanz, Germany: Universität Konstanz; 2003.
83. Lew HD, Poole JH, Chiang JYP, Lee EH, Date ES, Warden D. Event related potential in facial affect recognition: potential clinical utility in patients with traumatic brain injury. *J Rehabil Res Dev.* 2005;42:29–34.
84. Solbakk AK, Reinvang I, Svebak S, Nielsen CS, Sundet K. Attention to affective pictures in closed head injury: event-related brain potentials and cardiac responses. *J Clin Exp Neurospychol*. 2005;27:205–223.
85. De Beaumont L, Brisson B, Lassonde M, Jolicoeur P. Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj*. 2007;21:631–644.
86. Broglio SP, Pontifex MB, O'Connor P. The persistent effects of concussion on neuroelectric indices of attention. *J Neurotrauma*. 2009;26:1463–1470.
87. De Beaumont L, Théoret H, Mongeon D, Messier J, Leclerc S, Tremblay S, Ellenberg D, Lassonde M. Brain function decline in healthy retired athletes who sustained their last concussion in early adulthood. *Brain*. 2009;132:695–708.
88. Heitger MH, Anderson TJ, Jones RD. Saccade sequences as markers for cerebral dysfunction following mild closed head injury. *Prog Brain Res*. 2002;140:433–438.
89. Heitger MH, Anderson TJ, Jones RD, Dalrymple-Alford JC, Frampton CM, Ardagh MW. Eye movement and visuomotor arm movement deficits following mild closed head injury. *Brain*. 2004;127:575–590.
90. Heitger MH, Jones RD, Dalrymple-Alford JC, Frampton CM, Ardagh MW, Anderson TJ. Motor deficits and recovery during the first year following mild closed head injury. *Brain Inj*. 2006;20:807–824.
91. Heitger MH, Jones RD, Macleod AD, Snell DL, Frampton CM, Anderson TJ. Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. *Brain*. 2009;132:2850–2870.
92. Suh M, Kolster R, Sarkar R, McCandliss B, Ghajar J. Deficits in predictive smooth pursuit after mild traumatic brain injury. *Neurosci Lett*. 2006;401:108–113.
93. Caeyenberghs K, Leemans A, Geurts M, Taymans T, Vander Linden C, Smits-Engelsman BCM, Sunaert S, Swinnen SP. Brain-behavior relationships in young traumatic brain injury patients: fractional anisotropy measures are highly correlated with dynamic visuomotor tracking performance. *Neuropsychologia*. 2010;48:1472–1482.
94. Contreras R, Kolster R, Voss HU, Ghajar J, Suh M, Bahar S. Eye-target synchronization in mild traumatic brain-injured patients. *J Biol Phys*. 2008;34:381–392.
95. Contreras RJ, Ghajar J, Bahar S, Suh M. Effect of cognitive load on eye-target synchronization during smooth pursuit eye movement. *Brain Res*. 2011;1398:55–63.
96. Rosenblum MG, Pikovsky AS, Kurths J. Phase synchronization of chaotic oscillators. *Phys Rev Lett*. 1996;76:1804–1807.
97. Rosenblum MG, Pikovsky AS, Kurths J. From phase lag to phase synchronization in coupled chaotic oscillators. *Phys Rev Lett*. 1997;78: 4193–4196.
98. Hughlings-Jackson J. On some implications of dissolution of the nervous system. In: Taylor J, ed. *Selected Writings of John Hughlings-Jackson*. Reprint of the 1982 Edition, Volume 2. New York: Basic Books; 1958: 29–45.
99. Head H. *Aphasia and Kindred Disorders of Speech*. Cambridge, UK: Cambridge University Press; 1926.
100. Stuss DT, Stethem LL, Hugenholtz H, Picton T, Pivik J, Richard MT. Reaction time after head injury. Fatigue, divided and focused attention and consistency of performance. *J Neurol Neurosurg Psychiatry.* 1989;52: 742–748.
101. Hetherington CR, Stuss DT, Finlayson MA. Reaction time and variability 5 and 10 years after traumatic brain injury. *Brain Inj*. 1996;10:473–486.
102. Bleiberg J, Garmoe WS, Halpern EL, Reeves DL, Nadler JD. Consistency of within-day and across-day performance after mild brain injury. *Neuropsychiatry Neuropsychyol Behav Neurol*. 1997;10:247–253.
103. Walhovd KB, Fjell AM. One-year test-retest reliability of auditory ERPs in young and old adults. *Int J Psychophysiol*. 2002;46:29–40.
104. Weinberg A, Hajcak G. Longer term test-retest reliability of error-related brain activity. *Psychophysiology.* 2011;48:1420–1425.
105. Rentzsch J, Jockers-Scherübl MC, Boutros NN, Gallinat J. Test-retest reliability P50, N100 and P200 auditory sensory gating in healthy subjects. *Int J Psychophysiol*. 2008;67:81–90.
106. Fuerst DR, Gallinat J, Boutros NN. Range of sensory gating values and test-retest reliability in normal subjects. *Psychophysiology.* 2007; 44:620–626.
107. Lew HL, Gray M, Poole JH, Chow E, Salerno RM, Date ES. Test-retest reliability of ERPs in TBI and healthy individuals. *J Head Trauma Rehabil*. 2007;21:430.
108. Sinha R, Bernardy N, Parson OA. Long-term test-retest reliability of event-related potentials in normals and alcoholics. *Biol Psychiatry.* 1992;32:992–1003.
109. Kendall R, Jablonsky A. Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry.* 2003;160:4–12.
110. Mullins-Sweatt SN, Widiger TA. Clinical utility and DSM-V. *Psychol Assess*. 2009;21:302–312.
111. Smith DH. Postconcussional symptoms not a syndrome. *Psychosomatics*. 2006;47:271–272.
112. Chan RCK. Base rate of post-concussion symptoms among normal people and its neuropsychological correlates. *Clin Rehabil*. 2001;15: 266–273.
113. Iverson G, McCracken LM. Post-concussive symptoms in persons with chronic pain. *Brain Inj*. 1997;11:783–790.
114. Tukey JW. Methodology and the statistician's responsibility for both accuracy and relevance. *J Am Stat Assoc*. 1979;74:786–793.
115. Halbauer JD, Ashford W, Zeitzer JM, Adamson MM, Lew HL, Yesavage JA. Neuropsychiatric diagnosis and management of chronic sequelae of war-related mild to moderate traumatic brain injury. *J Rehabil Res Dev.* 2009;46:757–796.
116. Wylie SA, van den Wildenberg WPM, Ridderinkhof KR, Bashore TR, Powell VD, Manning CA, Wooten GF. The effect of Parkinson's disease on interference control during action selection. *Neuropsychologia*. 2009;47:145–157.
117. Wylie SA, van den Wildenberg WPM, Ridderinkhof KR, Bashore TR, Powell VD, Manning CA, Wooten GF. The effect of speed-accuracy strategy on response interference control in Parkinson's disease. *Neuropsychologia*. 2009;47:1844–1853.
118. Rapp PE, Cellucci CJ, Gilpin AK, Jiménez-Montaño MA, Korslund KE. Communication patterns in a psychotherapy following traumatic brain injury: a quantitative case study based on symbolic dynamics. *BMC Psychiatry.* 2011;11:119.
119. Masel BE, DeWitt DS. Traumatic brain injury: a disease process not an event. *J Neurotrauma*. 2010;27:1529–1540.

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